COLLEGE OF MEDICINE AND LIFE SCIENCES

THE UNIVERSITY OF TOLEDO

LANCE DWORKIN

2023

MEDICAL RESEARCH SYMPOSIUM

Dr. Lance Dworkin: A Pioneer in Medicine and Research

Robert E. McCullumsmith, MD, PhD[1*]

[1]Professor and Chair, Department of Neurosciences, Department of Psychiatry,
The University of Toledo, Toledo, OH 43614

*Corresponding author: Robert.Smith@utoledo.edu

Published: 14 December 2023

This past year, the annual Department of Internal Medicine Research Symposium was renamed after Dr. Lance Dworkin. As the Mercy Professor & Chair of the Department of Medicine at the University of Toledo College of Medicine & Life Sciences since 2016, Dr. Dworkin has transformed the research footprint within his department and at the University of Toledo College of Medicine and Life Sciences. His program building efforts span all levels of research trainees, including undergraduates, medical students, residents, fellows, postdoctoral fellows, and early career faculty. One particular highlight is the medical student research program that he built from scratch, focused on getting interested students connected with clinical and basic research faculty.

Dr. Dworkin's direct contributions during his career as a researcher also warrant special mention. His research spans key areas, notably exploring the hemodynamic basis for the progression of chronic kidney disease. Dr. Dworkin's pioneering studies provided a groundbreaking hypothesis on glomerular capillary hypertension, fundamentally influencing strategies for aggressive blood pressure reduction in chronic kidney disease. Dr. Dworkin's has also studied hepatocyte growth factor in chronic kidney disease, revealing its multifaceted effects as an antifibrotic and anti-inflammatory factor. His work identified downstream mediators, including glycogen synthase kinase 3β. His studies on small molecule inhibitors of GSK 3β point to transformative potential in ameliorating inflammation and injury, offering new avenues for kidney therapeutics.

In a significant contribution to clinical practice, Dr. Dworkin played a pivotal role in the CORAL trial, conclusively demonstrating the efficacy of medical therapy over renal artery stenting in atherosclerotic renal-artery stenosis. This landmark trial has reshaped clinical decisions and interventions for patients with this condition.

In addition to his impactful leadership and research in chronic kidney disease, Dr. Dworkin has been a driving force in international nephrology organizations. Serving on the Nominating Committee and North American Regional Council of the International Society of Nephrology (ISN), he actively contributes to shaping the future of nephrology on a global scale. Dr. Dworkin has been deeply involved in the ISN Global Outreach programs. As a key leader and ISN ambassador, he has established several exemplary and impactful ISN Regional Sister Renal Center programs in China and Kenya.

Further, as the President of University of Toledo Physicians since 2019, Dr. Dworkin's impact on healthcare administration is profound. His prior role as Vice President from 2017 to 2019 laid the

https://dx.doi.org/10.46570/utjms.vol11-2023-1213

foundation for his influential leadership. Dr. Dworkin's illustrious career is marked by exceptional leadership in healthcare administration and groundbreaking contributions to medical research.

Dr. Dworkin's enduring commitment to advancing medical knowledge, coupled with his international influence, highlights his outstanding contributions. His leadership, mentorship, transformative research, and dedication to improving patient outcomes underscore his pivotal role in shaping the future of medicine and nephrology. For the second year in a row, *Translation*, the Journal of Medical Sciences for the University of Toledo, is honored to publish the meeting abstracts for the Dr. Lance D. Dworkin Department of Medicine Research Symposium.

Acknowledgements

Special thanks to Rujun Gong, PhD, David Kennedy, PhD and Chris Cooper, MD for assistance in the preparation of this editorial.

Dr. Lance D. Dworkin Department of Medicine Research Symposium

Persistent Skin Eruption in a Renal Transplant Patient

Omar Abdul-Aziz[1*], Safa Habib[1], Ambika Sood[1], Michael W. Ellis, MD[2],
[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Omar.Abdul-Aziz@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Renal transplants are the most common transplant surgery performed in the United States and pose a significant challenge in post-operative care due to the need for strict immunosuppression management. These immunosuppressive medications increase the risk of opportunistic infections, including nocardial infections. Nocardia are Gram-positive, partially acid-fast, aerobic, catalase-positive, non-motile branching rod-shaped bacteria. They are considered ubiquitous and are isolated from multiple environmental sources such as soil, decomposing vegetation, and water. Due to its ability to mimic other diseases, nocardial infections pose a diagnostic challenge and often result in a delay in diagnosis and therapy.

Case Presentation: A 72-year-old man with a past medical history for renal transplantation done in 2020 for end stage renal disease secondary to focal segmental glomerulosclerosis (FSGS) presented to the Infectious Diseases clinic with a non-healing left forearm lesion. Three months prior to evaluation, the patient reported that he had cut his forearm while working on a golf cart. Over weeks, the patient developed an ulcerative and crusting wound on his forearm. After topical management with antibacterial and antifungal ointments, and brief courses of cephalexin for common skin and tissue infection he underwent skin biopsy. On physical examination, vital signs were normal as were pulmonary and neurological examination. Skin examination was remarkable for an approximately 5 x 7 cm ulcerated and crusted lesion without surrounding erythema, and slight tenderness. He had no lymphadenopathy. His laboratory studies showed slight lymphopenia and normal renal function with serum creatinine of 1.2 mg/DL. Skin biopsy culture yielded Nocardia abscessus complex. Antibiotic susceptibilities performed at an academic reference lab demonstrated susceptibility to amikacin, doxycycline, tobramycin, imipenem, ceftriaxone, and TMP-MX. To exclude pulmonary or central nervous system involvement, the patient underwent computed tomography (CT) of his chest and magnetic resonance imaging (MRI) of his brain, both of which showed no evidence of infection.

Outcomes: The patient was treated with ceftriaxone during admission along with reduction in mycophenolate sodium. He was discharged on TMP-SMX DS twice daily with a plan for 6 months duration. During follow-up, he was noted to have asymptomatic hyperkalemia and his regimen was changed to doxycycline 100 mg twice daily for a 6-month duration. Within one month of treatment, his arm lesion began to improve.

https://dx.doi.org/10.46570/utjms.vol11-2023-899

Conclusion: Cutaneous Nocardiosis usually occurs in immunocompromised individuals who experience bacterial infiltration of the skin via abrasions. Treatment for cutaneous nocardiosis typically involves a single drug regimen based on susceptibilities. This case highlights that opportunistic infections like Nocardia pose a significant challenge to those undergoing immunosuppressive therapy for organ transplantation and that early detection is vital to avoid dissemination.

Characterization of Human Colon Tissue for Harmful Algal Bloom Exposure in Cancer and Non-Cancer Patients

Bella Khatib-Shahidi[1*], John Najjar[1], Anish Sharma[1], Sara Kazmi[1], Apurva Lad, PhD[1], Benjamin W. French[1], Bivek Timalsima[1], Caitlin Murphy[1], Julissa Vargas[1], Humza Bashir[1], David Kennedy, PhD[2], Steven Haller, PhD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: bella.khatibshahidi@rockets.utoledo.edu

Keywords: Harmful algal blooms, Cyanobacteria, Internal Medicine, Family Medicine, Emergency Medicine, Medicine, Microcystin, Oncology, Gastroenterology, Enterology

Published: 14 December 2023

Introduction: Harmful algal blooms (HABs) are emerging not only in the Great Lakes region, but also globally. HABs release cyanotoxins, which present public health concerns and significant health risks. Cyanotoxins may enter humans through water ingestion, aerosol inhalation, or direct skin contact. We have previously demonstrated that cyanotoxins exacerbate pre-existing liver and inflammatory bowel disease in mice. However, the effects of cyanotoxin exposure in humans with colon disease and colon cancer is poorly understood.

Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) colon tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in colon cancer.

Methods: Using an optimized extraction/purification protocol designed for FFPE samples, DNA and RNA were extracted from colon tissues of invasive adenocarcinoma (n=5) and age- and sex-matched non-adenocarcinoma controls (n=5). The presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.

Results: Cyanobacteria levels were elevated in colon cancer tissues compared to non-cancer (1.0±0.27 vs 1.3±0.66), although this was not statistically significant. Interestingly, while markers of tissue remodeling were not significantly correlated with cyanobacterial load in both cancer and non-cancer samples, cyanobacterial load was negatively correlated with transforming growth factor-beta (r=-0.6121, p=0.0334) and matrix metalloprotease isoform 9 (r=-0.6272, p=0.0261) in the invasive adenocarcinoma samples.

Conclusion: Our results suggest that cyanobacteria may be increased in the setting of invasive adenocarcinoma and may impact the expression of key tissue remodeling genes within these tumors.

This data agrees with clinical and experimental evidence, suggesting an association between cyanobacteria and cancer progression in other settings. The data also supports the need to investigate the potential role of cyanobacteria in colon cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

The Evaluation of a Pharmacist-Led Multidisciplinary Quality Committee in a General Internal Medicine Outpatient Clinic

Marilee Clemons[1*], Sarah Aldrich Renner[1], William Barnett, MS, MA[3],

[1]Division of Pharmacy Practice, College of Pharmacy, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: marilee.clemons@utoledo.edu

Keywords: Quality, Survey, Pharmacist, Quality Improvement

Published: 14 December 2023

Background: Two embedded pharmacists in the outpatient general internal medicine clinics developed and lead a division-wide quality committee. The committee consists of division leadership and select quality champion members including other providers and staff who meet to review and implement clinic-wide processes to improve Accountable Care Organization (ACO) quality measures. Three quality metrics have been the focus of improvement: Hemoglobin A1c < 9%, blood pressure (BP) < 140/90 mmHg, and improved documentation of immunizations.

Objective: To use the perceptions of the clinic team members to evaluate the effectiveness of pharmacist-led quality committee aimed to develop, implement, and facilitate standardized clinic-wide processes to improve ACO quality measures.

Methods: A 32 question survey, including 27 Likert-scale questions and 5 free response questions was created to review the committee members' perspectives on the pharmacist-led committee. The survey was sent to all members of the committee (18 participants). Survey results were evaluated using Winsteps 5.4 Rasch analysis and a variance map was constructed to understand how the items/respondents interacted – this allowed the creation of 4 domains.

Results: Eighteen participants were invited to complete the survey with a 50% response rate. The survey was found to demonstrate high reliability and the Likert scale was appropriate. Based on the variable map, 2 of 9 respondents did not agree with all the questions specifically surrounding effectiveness and engagement of the committee. The results indicate that most committee members agreed with the effectiveness of the pharmacist-led quality committee.

Conclusion: The survey was worded well and appropriate for the study objective. The development of this committee resulted in quality success and the pharmacists are well suited to lead these efforts.

https://dx.doi.org/10.46570/utjms.vol11-2023-821

Mycobacterium goodii Associated with Breast Tissue Expanders

A. Sood[1*], V. Starnes, D. Chu, N. Hubbard, MD; C. Hollingshead, MD
[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo,

Toledo, OH 43614

*Corresponding author: Ambika.sood@rockets.utoledo.edu

Published: 14 December 2023

Introduction: *Mycobacterium goodii*, a non-tuberculous mycobacterium (NTM), is associated with implanted medical devices. Due to the rise of nosocomial infections, *M. goodii* presents a challenge due to unique resistance patterns. We present a case of bilateral breast tissue expanders infected with *Mycobacterium goodii*.

Case Description: A 52-year-old woman with a history of hypertension, type 2 diabetes mellitus, infiltrating ductal carcinoma of the left breast, and a history of previous Group B Strep (GBS) infection associated with breast tissue expanders. The patient underwent a delayed bilateral breast reconstruction due to the breast expanders needing removal. There was also a placement of tissue expanders and bilateral biosynthetic mesh along with a left periprosthetic capsulectomy and excision of right chest subcutaneous cyst in December 2021. She was noted to have increased drain output post-operatively, which prompted aspiration from her bilateral breast expander ports and initiation of empiric doxycycline. Due to doxycycline being a broad-spectrum antibiotic and typically being used in skin, mucosa, and similar infections, it was chosen as initial treatment.

Three days after initiating doxycycline, the patient was in a high-speed motor vehicle collision and presented at our hospital. The patient had severe injuries such as a right orbital blow out fracture, dental avulsion, cervical fracture, rib fracture, and left wrist fracture which required surgical intervention with orthopedics. Following surgery, the patient remained afebrile without leukocytosis but continued to have 10-15mL of drain output bilaterally. Infectious diseases were consulted to specifically investigate and understand which bacteria was inflicting the patient. Cultures drawn from her bilateral breast expander ports became positive for a beaded, gram-positive rod that was modified acid-fast positive which signified a nosocomial, opportunistic infection. Meropenem and trimethoprim-sulfamethoxazole (TMP-SMX) were initiated due to concern for rapidly growing mycobacterial infection. She was discharged after about two weeks after the MVC with a PICC line and a follow-up with ID. The organism was found to be positive for M. *goodii*. The organism was found to be sensitive to TMP-SMX, and meropenem was discontinued. She tolerated therapy with TMP-SMX well and had no allergic reactions or other adverse side effects. About two weeks after being discharged, her breast expanders were removed, and cultures at this juncture were negative. On follow-up, she had completed 3 months of

https://dx.doi.org/10.46570/utjms.vol11-2023-824

TMP-SMX post-removal of implants and had a delayed bilateral deep inferior epigastric perforator (DIEP) free flap procedure without any signs of recurrence of infection.

Discussion: Mycobacterium goodii is a rapidly growing non-tuberculous mycobacterium (NTM) that was originally associated with traumatic wound infections, particularly osteomyelitis following open fractures1. Since its original description, M. goodii has emerged as a challenging infectious pathogen of implantable medical devices. M. goodii is naturally resistant to rifampin and macrolides, which are often the empiric treatment of choice in NTM infections. If the infection involves a medical implant, removal of the device is usually pursued, though there have been cases of successful cure with retention of the implant3. As with other mycobacterial infections, duration of antibiotics is prolonged, ranging from 1-12 months2. We found in our review that there has been one other documented case of M. goodii infection due to a breast implant, in which the patient required reoperation and a prolonged course of antibiotics4. Therapy should ultimately be targeted based on culture sensitivities and patient tolerance with likely explantation of the infected hardware and prolonged duration of antimicrobials.

References:

1. Brown, B.A., B. Springer, V.A. Steingrube, R.W. Wilson, G.E. Pfyffer, M.J. Garcia, M.C. Menendez, B. Rodriguez-Salgado, K.C. Jost, Jr., S.H. Chiu, G.O. Onyi, E.C. Böttger, and R.J. Wallace, Jr., *Mycobacterium wolinskyi sp. nov. and Mycobacterium goodii sp. nov., two new rapidly growing species related to Mycobacterium smegmatis and associated with human wound infections: a cooperative study from the International Working Group on Mycobacterial Taxonomy.* Int J Syst Bacteriol, 1999. **49 Pt 4**: p. 1493-511.

2. Pennington, K.M., A. Vu, D. Challener, C.G. Rivera, F.N.U. Shweta, J.D. Zeuli, and Z. Temesgen, *Approach to the diagnosis and treatment of non-tuberculous mycobacterial disease.* J Clin Tuberc Other Mycobact Dis, 2021. **24**: p. 100244.

3. Marchandin, H., P. Battistella, B. Calvet, H. Darbas, J.M. Frapier, H. Jean-Pierre, S. Parer, E. Jumas-Bilak, P. Van de Perre, and S. Godreuil, *Pacemaker surgical site infection caused by Mycobacterium goodii.* J Med Microbiol, 2009. **58**(Pt 4): p. 517-520.

4. Salas, N.M. and N. Klein, *Mycobacterium goodii: An Emerging Nosocomial Pathogen: A Case Report and Review of the Literature.* Infect Dis Clin Pract (Baltim Md), 2017. **25**(2): p. 62-65.

5. Pandita A., Thomas S., Granato P., Sharma A., Eranki A. and T. Fazili. *Mycobacterium goodii related breast implant infection: First case and literature review*. Clin Microbiol Infect Dis, 2017. **2**(1):1-3.

Histoplasmosis of the left wrist in an immunosuppressed host with myasthenia gravis

Noor Abdulhameed[1*], Omar Abdul-Aziz[1], Meghan Sawyer[1], Caitlyn Hollingshead, MD[2], Salman Arif, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: noor.abdulhameed@rockets.utoledo.edu

Keyword: Fungal Infection

Published: 14 December 2023

Introduction: Myasthenia gravis (MG) is an NMJ disorder targeting acetylcholine receptors. Symptomatic treatment inhibits acetylcholinesterase, while long-term therapies target immune system overactivation. Prednisone inhibits antibodies; mycophenolate mofetil decreases T&B lymphocyte proliferation. Immunosuppressants pose opportunistic infection risks, such as histoplasmosis due to Histoplasma capsulatum spores.

Case Presentation: A 55-year old male with MG on prednisone 40mg/daily and mycophenolate mofetil 1,500mg/daily presented with left wrist pain and forearm swelling one month prior, following a gardening injury. Cellulitis treated with trimethoprim-sulfamethoxazole and doxycycline without improvement, and started on IV vancomycin. CT revealed olecranon bursitis and soft tissue inflammation. Patient underwent debridement; serous fluid was cultured. Patient discharged after 5 days on trimethoprim-sulfamethoxazole 800mg-160mg twice/daily. Fluid histoplasma antibodies tested positive. CXR unremarkable for pulmonary histoplasmosis.

Patient was prescribed itraconazole 100mg/twice daily for 9 months. After 6 weeks, patient reported open left foot wound, without underlying trauma. MRI revealed soft tissue swelling consistent with cellulitis. The patient underwent debridement due to cutaneous histoplasmosis history. Cultures revealed Streptococcus agalactiae. Patient prescribed amoxicillin- clavulanate 875-125mg BID and foot healed. 16 months post-itraconazole therapy, patient revealed no cyanosis nor edema with a left sporotrichoid scar along the ulnar lymphatics from resolved infection.

Conclusion: Corticosteroids are vital for rheumatological therapies but involve diabetes, avascular necrosis, osteoporosis, and CVD. Their anti-inflammatory properties contribute to lymphocytopenia and pose dose-dependent infectious risks. Opportunistic pathogens should be evaluated in MG patients including VZV, tuberculosis, PJP, aspergillosis, candidiasis, and cryptococcosis. This case is a rare example of isolated extrapulmonary histoplasmosis in an immunocompromised patient. Immunosuppressed MG patients should be

educated on risk of infections. Lower corticosteroid dosages decrease infection risk. PJP prophylaxis should be offered in appropriate patients. Vaccinations and lifestyle modifications reduce infectious complications. This case highlights the importance of early detection and the challenges opportunistic infections pose to patients undergoing immunosuppressive therapy.

Dr. Lance D. Dworkin Department of Medicine Research Symposium

Fungal Prosthetic Joint Infection: A Case Series and Review of the Literature

Victoria Starnes[1*], Caitlyn Hollingshead, MD[2], Joan Duggan, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: victoria.starnes@rockets.utoledo.edu

Keywords: Fungal Joint Infection, Fungal Infection

Published: 14 December 2023

Background: The most effective treatment for fungal prosthetic joint infections remains unclear. Most cases are treated with two-stage revisions combined with systemic antifungal medications. To date, the largest studies of total hip arthroplasty and total knee arthroplasty fungal infections have included 37 and 45 patients, respectively.

Objective: The goal of this study is to examine reported cases to determine trends in management and outcomes.

Methods: A retrospective record review of patients admitted in two health systems between January 1, 2007 and December 31, 2018 with prosthetic joints and a deep culture of the joint positive for fungal organisms was performed as well as a review of the literature. A Pubmed and Embase search of the English-language literature from Jan 1, 1980 to Jan 1, 2023 was performed with review of the pertinent references for cases meeting the following case definition: individual with prosthetic joint and positive deep tissue culture for fungus.

Results: 159 patients fit criteria. 73 patients had knee replacements, 62 patients had hip replacements, and 5 had other joint involvement. 52% were female. 137 patients had yeast involvement, with Candida species being predominant, while 11 had mold and 11 with dimorphic infections. 55 patients were treated with two-stage revisions, 44 received one-stage revisions, 32 received debridement only or Girdlestone procedure, and 1 required amputation. 141 reported details on antifungal therapy. After performing multivariate analysis, polyene treatment was found to be associated with higher rate of recovery, p=0.042. However, there was a trend towards recurrence requiring surgical intervention in patients treated with polyenes, p=0.067. 22.6% had a poor outcome, including recurrence, amputation, or death.

Conclusion: Surprisingly, polyenes did not underperform when compared to other antifungal therapy. Prospective research assessing optimal surgical treatment modality and antifungal therapy is needed as this infection is associated with high morbidity and mortality.

The Negative Consequences of False Negative Lung Cancer Screenings

Hoda Shabpiray, MD[1*], Mani Khorsand Askari, MD, FACP[1], Jerrin George[2]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614
[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: Hoda.Shabpiray@utoledo.edu

Keywords: Lung Cancer Screening, LDCT, Negative Lung Cancer Screening

Published: 14 December 2023

Introduction: Lung cancer is the leading cause of cancer death in the United States of America (1). The US Preventive Services Task Force recommends an annual low-dose computed tomography scan (LDCT) for 50- to 80-year-old adults with a 20 pack-year smoking history or more who are current smokers or have quit smoking within the past 15 years (2). Although it has been shown to be effective in reducing mortality rates (3), LDCT screening tests have false-negative rates of up to 15% (4). We present a patient with a negative lung cancer screening who was diagnosed with advanced lung cancer seven months after negative screening results.

Case Presentation: An LDCT scan for a 61-year-old female, with a past medical history significant for Chronic Obstructive Pulmonary Disease (COPD) and a 40 pack-year smoking history, revealed a benign screening result. LDCT in October 2021 revealed calcified granulomas and a 3mm lingular lung nodule consistent with Lung RADS category 2. Seven months later the patient was admitted to the hospital with shortness of breath, and a productive cough. Chest X-ray revealed patchy infiltration in the left upper lobe consistent with lobar pneumonia. The patient received a full course of antibiotics for community acquired pneumonia. Ten days later, following worsening symptoms, A CT scan of the chest demonstrated a left upper lobe mass suspicious for neoplasm. Subsequent Lung biopsy revealed small cell carcinoma. Bone scan also demonstrated possible osseous metastasis. Chemotherapy started for the patient with carboplatin/etoposide, A positron emission tomography (PET) scan was obtained due to severe pain in her spine, mid- and lower-back, and a compression fracture in L3 which demonstrated significant disease progression in the skeleton with foci of increased activity in the thoracic, lumbar, and sacral portions of the spine worrisome for metastasis. Palliative radiation therapy started to help with pain.

Conclusion: Lung cancer screening requires a shared decision-making visit. Required elements of this visit that must be documented include false positive rates, overdiagnosis and possible further evaluations5. However, there is no requirement to discuss false negative results or the possibility of interval diagnosis of lung cancer between annual screenings in a shared decision-making visit (5).

Those with negative results may be less likely to present in the event of developing symptoms or may interpret their symptoms as insignificant and believe they are unlikely to develop lung cancer. It may also cause false reassurance for health care workers, causing a delay in appropriate testing (4). Furthermore, a negative test may result in a reluctance to change detrimental health-related behaviors, such as smoking (4). Providers should educate their patients that LDCT can have false negative results and this discussion about possible false negative results and the possibility of a tumor developed de novo after the negative screening test should be added to the requirements of a shared decision-making visit.

References

1. American Cancer Society. *Facts & Figures 2023*. American Cancer Society. Atlanta, Ga. 2023.

2. US Preventive Services Task Force; Krist, A.H, Davidson, K.W., Mangione, C.M., Barry, M.J., Cabana, M., Caughey Donahue, K.E., Doubeni, C.A., Kubik, M., Landefeld, C.S., Li, L., Ogedegbe, G., Owens, D.K., Pbert, L., Silverstein, M., Steve Wong, J.B. *Screening for Lung Cancer: US Preventive Services Task Force Recommendation Statement*. JAMA, 2021 Mar 9. **325**(10): pp. 962-970.

3. Cheung, L.C., Katki, H.A., Chaturvedi, A.K., Jemal, A., Berg, C.D. *Preventing lung cancer mortality by computed to The effect of risk-based versus U.S. Preventive Services Task Force Eligibility Criteria, 2005–2015*. Annals of Internal Medicine, 2018. **168**(3): p. 229. doi:10.7326/m17-2067

4. Bartlett, E.C., Silva, M., Callister, M.E., Devaraj, A. False-negative results in lung cancer screening—evidence a Journal of Thoracic Oncology, 2021. **16**(6):912-921

5. https://www.acr.org/-/media/ACR/NOINDEX/Advocacy/CT-LCS-shared-decision-making_fillable.pdf

Are intravenous steroids better than oral steroids in treating COPD exacerbations in hospitalized patients? A systematic review and meta-analysis

Rabbia Siddiqi, MD[1*], Nasir Shivani, MD[2], Nezam Altorok, MD[3],

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Junior Clinical Fellow, Bedford Hospital, National Health System Trust, Bedford, England, United Kingdom

[3]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: rabbia.siddiqi@utoledo.edu

Keywords: Steroids, COPD, COPD Exacerbation, Meta-Analysis

Published: 14 December 2023

Introduction: Systemic steroids are routinely used in the inpatient management of chronic obstructive pulmonary disease (COPD exacerbations and may be administered orally (PO or intravenously (IV. IV steroids are often pursued as a more aggressive approach although there is no clear evidence of their superiority over PO route, and may increase the risk of hyperglycemic events. Here we compare the effectiveness of IV versus PO steroids in COPD exacerbations.

Methods: PubMed/MEDLINE, EMBASE, and Cochrane databases were searched for randomized controlled trials (RCTs comparing IV versus PO administration of steroids in patients admitted for COPD exacerbation. Primary outcome was mortality during the study follow-up period. Secondary outcomes included: mean change in forced expiratory volume in 1 second (FEV1 from baseline to end of steroid course; length of hospital stay; treatment failure; and readmission rate. Effect estimates were pooled using a random-effects model and reported as mean differences (MD or relative risks (RR with the corresponding 95% confidence interval (CI.

Results: A total of 3 RCTs were included, comprising 296 patients (IV group=150, PO group=146. Study treatment duration varied between 7-10 days, and median follow-up was 1-3 months. Our meta-analysis showed no statistically significant difference between the two groups in risk of death (RR 1.45 [0.34-6.29]) by the end of the study follow-up. Both groups (IV versus PO) had a similar mean change in FEV1 from baseline (MD -0.06 liters [-0.19-0.07]) and similar length of hospital stay (MD 1UTJMS 2023 December 14; 11(3):e1-e2.88 days

https://dx.doi.org/10.46570/utjms.vol11-2023-835

[-3.07-6.83]). There was no statistical difference in treatment failure rate (RR 0.96 [0.55-1.66]) or readmission rate (RR 0.93 [0.54-1.61]).

Conclusion: Our study showed that IV steroids have no benefit over PO steroids in patients admitted with COPD exacerbations. This suggests that IV steroids and their associated risks may be unnecessary and can be avoided in many patients.

Multiple Sclerosis anti-CD20 (Ocrelizumab) therapy inducing hypogammaglobulinemia

Nora Abdul-Aziz[1*], Noor Abdulhameed[1], Amulya Marellapudi[1], Haroon Shah, DO[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Nora.Abdul-Aziz@rockets.utoledo.edu

Keywords: Multiple Sclerosis, Hypogammaglobulinemia
Published: 14 December 2023

Introduction: Multiple sclerosis (MS) is a progressive autoimmune demyelination of the central nervous system. Therapies used in clinical practice encompass anti-CD20 agents such as Ocrelizumab and Rituximab that selectively target CD20+ B-cells to suppress the inflammation of the disease pathway. However, B-cell deficiency contributes to a heightened risk for infection. Anti-CD20 mAb drug-induced hypogammaglobulinemia puts patients at risk for various complications such as reactivation of latent infections, respiratory tract infections, and neutropenia.

Case Presentation: A 58-year old female with past medical history of MS and recurrent sinopulmonary infections, presented with persistent fatigue, fevers, and chest discomfort upon inhalation. Chest CT was notable for ground glass opacities in right upper lobe. Labs were ordered for viral respiratory panel, viral culture, fungal culture, and serum immunoglobulins. Bronchoalveolar lavage isolated mold and oral voriconazole was administrated when isolate identified Penicillum sp. fungus. Patient is on Ocrelizumab, twice yearly infusions for the past 5-6 years. Diagnosis of pulmonary fibrosis secondary to bronchiolitis on 6/20/2023 and patient was referred to immunology for intravenous immunoglobulin injections or other therapy to support immune system.

Conclusion: Diagnosis of penicilliosis is through microscopy, histology, and culture of the fungus from bone marrow, skin lesions, and blood. Therapy is extrapolated from Talaromyces marfenii guidelines (formerly Penicillium). Preferred treatment is induction therapy with amphotericin B for 2 weeks followed by consolidation therapy with itraconazole for 10 weeks. There is no guidance on routine secondary prophylaxis.

Patient has anti-CD20 mAb drug-induced hypogammaglobulinemia contributing to her chronic lung disease bronchiectasis due to low IgA and IgM levels which is causing recurrent infections due to patient's immunosuppressed state, resulting in organized pneumonia. Frequent measurement of immunoglobulin levels, immunoglobulin transfusions, and immunologist check-ins are vital for immunocompromised individuals on these anti-CD20 therapies.

Hyperinsulinemic milieu elicits glomerular podocyte impairment and dysfunction via inducing GSK3β hyperactivity

Mengxuan Chen[1*], Yan Ge[1], Lance D. Dworkin, MD[1], Rujun Gong[1]

[1]Division of Nephrology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: mengxuan.chen@utoledo.edu

Keywords: Hyperinsulinema, GSK3beta hyperactivity, Podocyte Injury

Published: 14 December 2023

Background: Epidemiological evidence suggests that hyperinsulinemia or insulin resistance is a significant risk factor for the development of diabetic complications such as DKD. However, whether hyperinsulinemia per se plays a causative role in the development of diabetic kidney injury is unknown and was explored here.

Methods: Pre-diabetic db/db mice were examined for serum insulin levels, urinary albumin to creatinine ratios and renal histology. Conditionally immortalized mouse podocytes were cultured under non-permissive conditions and exposed to high ambient insulin conditions, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with a small molecule GSK3β inhibitor tideglusib. Podocyte injury was assessed and signaling pathways examined.

Results: In pre-diabetic db/db mice, hyperinsulinemia was evident and associated with microalbuminuria and early signs of podocyte impairment, including diminished expression of homeostatic marker proteins like synaptopodin, as compared with db/m littermates. In vitro, prolonged exposure of differentiated podocytes to high ambient insulin induced podocytopathic changes, including cellular hypertrophy, loss of synaptopodin, and disruption of actin cytoskeleton integrity. This was associated with a desensitized insulin signaling and diminished inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In pre-diabetic db/db mice, GSK3β hyperactivity was confirmed in glomerular podocytes, correlating with the level of hyperinsulinemia or microalbuminuria. In cultured podocytes, ectopic expression of S9A caused podocyte hypertrophy and podocytopathic changes, reminiscent of the harmful effect of the hyperinsulinemic milieu. Conversely, GSK3β knockdown mitigates podocyte injury elicited by hyperinsulinemic milieu. This protective effect was mimicked by the small molecule inhibitor tideglusib.

Conclusion: GSK3β hyperactivity is required and sufficient for Hyperinsulinemic milieu-elicited glomerular podocyte impairment and dysfunction.

Carfilzomib induced Alveolar Hemorrhage

Zachary Holtzapple, MD[1*], Andrew Campbell, MD[1], Konrad Katterle[2], Fadi Safi[3]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Zachary.Holtzapple@utoledo.edu

Keywords: Carfilzomib, Alveolar Hemorrhage, Multiple Myeloma

Published: 14 December 2023

Background: Multiple myeloma is a malignancy characterized by an abnormal accumulation of clonal plasma cells in bone marrow. Carfilzomib is commonly used as a medication for relapsed and refractory multiple myeloma. It is well known to cause a myriad of side effects including pulmonary toxicity.

Case Report: Our patient presented with severe shortness of breath, nausea, diarrhea without signs of hemoptysis that started the evening after chemotherapy infusion 3 days prior to admission, which included carfilzomib, pomalidomide, and dexamethasone. She was found to be severely hypoxemic and required high flow oxygen in the emergency room. Computerized tomography (CT) scan of the patient's chest showed findings concerning for pulmonary hemorrhage.

Conclusion: Carfilzomib has multiple known side effects including peripheral neuropathy, herpes zoster reactivation, hepatotoxicity, thrombocytopenia, neutropenia, pulmonary toxicity, and heart failure. Unfortunately, there are limited treatment options in patients with pulmonary hemorrhage outside of reducing inciting factors and limiting hypercoagulability. In our case, we suspect carfilzomib induced alveolar hemorrhage in the setting of ongoing multiple myeloma resulted in this patient's severe anemia and acute hypoxic respiratory failure on admission. Our case report represents an uncommon pulmonary side effect of carfilzomib with limited prior documentation.

Chemotherapy Induced Pulmonary Fibrosis

Konrad Katterle[1*], Zachary Holtzapple, MD[2], Abdulmajeed Alharbi, MD[2], Youngsook Yoon, MD[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614
[3]Division of Pulmonary and Critical Care, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: konrad.katterle@rockets.utoledo.edu

Keywords: FOLFOX, Pulmonary Fibrosis, Pneumothorax

Published: 14 December 2023

Background: FOLFOX (Oxaliplatin, 5-Fluorouracil, and Leucovorin) is one of the most commonly used first-line chemotherapies for metastatic colorectal cancer in the USA, and its efficacy has been repeatedly demonstrated by numerous trials. However, it has many side effects that affect numerous organ systems including myelosuppression, neuropathy, hepatotoxicity, and pulmonary toxicity. This case describes an 81-year-old male who developed pulmonary fibrosis after receiving FOLFOX chemotherapy, a late and rarely documented adverse affect.

Case Report: Our patient was an 81-year-old male who underwent 12 cycles of adjuvant FOLFOX chemotherapy for metastatic colon cancer. Patient is a nonsmoker, has no industrial exposure to pulmonary toxic agents, no past medical history of autoimmune diseases, and was on medications for hypertension, diabetes mellitus type 2, GERD, Benign Prostatic Hyperplasia, and hypothyroidism, none of which have any known pulmonary toxicity. The patient developed shortness of breath and dyspnea over the next two years, and serial CT scans of the chest showed progressive fibrosis of the lungs. Patient was originally admitted on 2 liters of oxygen via nasal canual with follow up imaging revealing bilateral pneumothoracies secondary to pulmonary fibrosis, five years after initiating FOLFOX treatment.

Conclusion: FOLFOX is known to have many adverse effects, including myelotoxicity, neurologic toxicity, diarrhea, and cardiopulmonary toxicity. In this case report, it is our belief that this patient developed bilateral pneumothoraces secondary to pulmonary fibrosis, which in turn was likely to have been caused by the patient's 12 cycles of FOLFOX therapy. Our case report represents an uncommon pulmonary side effect of FOLFOX and a unique manifestation with limited prior documentation.

Newly Diagnosed Severe AIDS with Recovery of CMV Retinitis with concurrent Cryptococcal Meningitis

Zachary Holtzapple, MD[1*], Ayman Salih, MD[1], Cassidy Eby, MD[1], Mitchell Salke, MD[1], Caitlyn Hollingshead, MD[2]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo,

Toledo, OH 43614

[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo,

Toledo, OH 43614

*Corresponding author: Zachary.Holtzapple@utoledo.edu

Keywords: HIV, AIDS, Cryptococcus Meningitis, CMV Retinitis

Published: 14 December 2023

Background: With modern medicine, human immunodeficiency virus (HIV) has become easily manageable for patients and the feared complication of acquired immunodeficiency syndrome (AIDS) has become relatively uncommon. This condition leads as a pathway to multiple illness not commonly seen in healthy individuals, including but not limited to pneumocystis pneumonia, disseminated histoplasmosis, cytomegalovirus infections, and extrapulmonary cryptococcosis. When these patient are critical ill, communication can be limited by pain, delirium, and intubation, which severely limits our ability to evaluate patients.

Case Report: Our patient presented to the hospital with generalized fatigue and shortness of breath. Further workup revealed severe HIV with CD4 count being < 50. Follow up CT Chest was initially concerning for pneumocystis pneumonia which was later ruled out with a bronchoscopy lavage. Lumbar puncture revealed cryptococcus meningitis and fundoscopic exam revealed findings consistent with CMV retinitis. In our patient, intubation for repeat lumbar punctures provided a barrier to the patient's communication and led to progressing CMV retinitis that briefly led to full loss of vision. Patient was appropriately treated with antifungals and antivirals throughout the hospital course.

Conclusion: With modern medicine, new onset HIV presented with an AIDS defining illness is exceedingly rare. With cryptococcus meningitis, the prolonged lumbar punctures and variable septic like presentation likely leads to intubation. This case cements why broad treatment and prophylaxis is important in individuals that are immunocompromised, specifically in the population of severe HIV and AIDS.

Validation of Airway Epithelial Cell TP53 Biomarker for Lung Cancer Risk

Daniel J. Craig, MD[1], Erin L. Crawford[2], Heidi Chen, Eric L. Grogan, Steven A. Deppen, Thomas Morrison, Sanja L. Antic, Pierre P. Massion, James C. Willey[3]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[3]Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: daniel.craig@rockets.utoledo.edu

Keywords: Molecular Oncology, Biomarker, Lung Cancer

Published: 14 December 2023

Background: There is a need for biomarkers that reliably detect those at highest risk for developing lung cancer, thereby enabling more effective screening by annual low-dose CT. We previously discovered a biomarker for lung cancer risk characterized by an increased prevalence of TP53 somatic mutations in airway epithelial cells (AEC)1. Here we present results from a blinded retrospective case-control validation study.

Methods: AEC genomic (g)DNA specimens were collected at Vanderbilt University in collaboration with the National Cancer Institute (NCI) Early Detection Risk Network (EDRN) according to a University of Toledo IRB-approved protocol. Synthetic DNA internal standards (IS) were prepared for 3 exons in TP53 spanning 193 base pairs and mixed with each AEC genomic DNA specimen prior to competitive multiplex PCR amplicon NGS library preparation. These competitive IS molecules enable the determination of site-specific sequencing error and thus lower the limit of detection for detecting somatic mutations (1,2).

Results: TP53 mutation prevalence was significantly associated with cancer status. The lung cancer detection receiver operator characteristic (ROC) area under the curve (AUC) for the TP53 biomarker was 0.845 (0.749-0.942) with sensitivity: 60.0%, and specificity: 96.7%. In contrast, TP53 mutation prevalence was not significantly associated with age or smoking status among non-cancer subjects. The combination of TP53 mutation prevalence and Brock Risk Score significantly improved the association with lung cancer compared with either factor alone.

Conclusion: These results support the validity of the TP53 mutation prevalence biomarker and justify taking additional steps to assess this biomarker in AEC specimens from a prospective cohort and in matched nasal brushing specimens as a potential non-invasive surrogate specimen.

References:

1. Craig DJ, Morrison T, Khuder SA, Crawford EL, Wu L, Xu J, Blomquist TM, Willey JC. *Technical advance in targeted NGS analysis enables identification of lung cancer risk-associated low frequency TP53, PIK3CA, and BRAF mutations in airway epithelial cells*. BMC Cancer, 2019. **19**(1): p 1081.

2. Blomquist T, Crawford EL, Yeo J, Zhang X, Willey JC. *Control for stochastic sampling variation and qualitative sequencing error in next generation sequencing*. Biomol Detect Quantif, 2015. **5**: pp. 30-37.

Rituximab in Kidney-Limited Microscopic Polyangiitis: A Case Report

Madhavaram, Anvitha R.[1*], Nezam, Altorok MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Anvitha.Madhavaram@rockets.utoledo.edu

Keywords: Microscopic Polyangiitis, Rituximab

Published: 14 December 2023

Background: Microscopic polyangiitis (MPA) is an immune complex mediated necrotizing vasculitis. The diagnosis is based on symptoms, including rapidly progressive glomerulonephritis, peripheral nerve disorder, lung abnormalities, and positive MPO-ANCA findings (1). The pathophysiology involves formation of neutrophil extracellular traps in the kidneys, which correlate with ANCA affinity for MPO and disease activity (2). Rituximab has been used in cases where conventional cyclophosphamide therapy may not be suitable (3).

Case Presentation: A 78-year-old white male with a past medical history of gout and type 2 diabetes mellitus, presented with general weakness. Laboratory testing revealed serum creatinine of 5.2 mg/dl (normal <1.3 mg/dl) on presentation. He underwent kidney biopsy which demonstrated crescentic pauci-immune glomerulonephritis. He was treated with two doses of rituximab 1 gram, two weeks apart every 6 months for the past year. Upon presentation, he underwent dialysis for 2 months. After two years of treatment, laboratory evaluations reveal a stable creatinine of 1.77 and MPO antibody titers persistently elevated above 8. The patient responds well to Rituximab treatment, with stable renal function and no signs of extrarenal organ involvement. The plan is to continue treatment for a minimum of five years due to his consistently elevated MPO titer.

Discussion: Rituximab, a monoclonal antibody against CD20, is used as monotherapy for MPA to induce remission or alongside prednisone in severe MPA [4]. Given the patient's age, his remarkably kidney-limited disease, and favorable side effect profile, rituximab infusions were initiated over conventional chronic corticosteroids and cyclophosphamide therapy.

This case report highlights the kidney-limited form of MPA, and aims to underscore the utility of rituximab as a treatment option for kidney-limited MPA. Further research is needed to understand long-term outcomes, optimize management, and establish guidelines for management of similar cases.

References

1. Yoshida, M., Yamada, M., Sudo, Y., Kojima, T., Tomiyasu, T., Yoshikawa, N., Oda, T., Yamada, M. *Myeloperoxidase anti-neutrophil cytoplasmic antibody affinity is associated with the formation of neutrophil extracellular traps in the kidney and vasculitis activity in myeloperoxidase anti-neutrophil cytoplasmic antibody-associated microscopic polyangiitis*. Nephrology, 2016. **21**(6): pp. 624-629. doi:10.1111/nep.12736

2. Tamei, N., Sugiura, H., Takei, T., Itabashi, M., Uchida, K., Nitta, K. *Ruptured arterial aneurysm of the kidney in a patient with microscopic polyangiitis*. Intern Med, 2008. **47**(6): pp. 521-526. doi:10.2169/internalmedicine.47.0624

3. Moiseev, S., Bossuyt, X., Arimura, Y., Blockmans, D., Cxernok, E., Damoiseaux, J., Emmi, G., Flores-Suarez, L.F., Hellmich, B., Jayne, D., Jennette, J.C., Little, M.A., Mohammad, A.J., Moosig, F., Novikov, P., Pagnoux, C., Radice, A., Sada, K.-E., Segelmark, M., Shoenfeld, Y., Sinico, R.A., Specks, U., Terrier, B., Tzioufas, A.G., Vaglio, A., Zhao, M.-H., Tervaert, J.W.C., European Study Group. *International Consensus on ANCA Testing in Eosinophilic Granulomatosis with Polyangiitis*. Am J Respir Crit Care Med, 2020. **202**(5): p. 1628SO. doi:10.1164/rccm.202005-1628SO

4. Allena N, Patel J, Nader G, Patel, M., Medvedovsky, B. *A Rare Case of SARS-CoV-2-Induced Microscopic Polyangiitis*. Cureus, 2021. **13**(5): p. e15259. doi:10.7759/cureus.15259

Pulmonary tuberculosis infection in the setting of Interstitial Lung Disease

Safa Habib[1*], Rebecca Asher[1], Salman Arif, MD[2], Hend Elsaghir, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: safa.habib@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Tuberculosis (TB) is a contagious airborne infection with many undiagnosed cases. Here we present a case of pulmonary tuberculosis that was treated in a 9-month course in a patient with a history of ILD.

Case Presentation: A 78-year-old man has a past medical history significant for idiopathic pulmonary fibrosis, hypothyroidism, coronary artery disease, hypertension, and obstructive sleep apnea. The patient was diagnosed with progressive idiopathic pulmonary fibrosis in 2013 and developed hypoxic respiratory failure. He was intolerant to Nintedanib and deemed unfit for a lung transplant. Therefore, the patient was instructed to use the albuterol inhaler and attend pulmonary rehab. In July 2021, he presented with cough, fatigue, dyspnea, and a decreased appetite. Treatment with amoxicillin-clavulanate was ineffective and his COVID-19 test was negative. Imaging showed a left upper lobe infiltrate and his chest CT (Computed Tomography) displayed left upper lobe consolidation with necrotic changes concerning for severe pneumonia. He was treated with IV ceftriaxone, oral azithromycin, and discharged with a 5-day course of cefdinir. After no improvement, he returned, and Tuberculosis was diagnosed with bronchoscopy with positive acid-fast staining and TB PCR (Polymerase Chain Reaction). The patient completed a 9-month treatment course with infectious disease follow-ups afterward. He had a negative acid-fast bacilli since September 2021.

Conclusion: Diagnosing a TB infection in ILD patients can be difficult due to the presence of interstitial processes and fibrosis masking the infection. In this case, atypical radiological patterns initially led to a misdiagnosis of pneumonia. Once TB was confirmed, the treatment regimen was successful. Clinicians managing ILD patients must rule out mycobacterial infections, such as TB, through a comprehensive diagnostic approach.

Prolonged Diabetic Ketoacidosis with Hyperammoniemia in the setting of Normal Liver Function

Zachary Holtzapple, MD[1*], Mohammad Al Azzawi, MD[1], Harith Al-Ataby, MD[1], Rayna Patel, MD[1], Ayman Salih, MD[1], Andrew Abrahamian, MD[1], Fadi Safi, MD[2]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Division of Pulmonology and Critical Care Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: zachary.holzapple@utoledo.edu

Published: 14 December 2023

Background: Acute encephalopathy in the setting of diabetic ketoacidosis is typically metabolic in origin, but less pursued are other causes including hepatic encephalopathy, namely hyperammonemia. These cases are less common in the setting of diabetic ketoacidosis and more so associated with cirrhotic pathology, however they should not be excluded in the differential diagnosis of patients with altered mentation in the setting of normal liver function.

Case Report: 37-year-old female patient presented to the emergency department with a chief complaint of confusion and nausea/vomiting over the past few days prior to admission. She has past medical history of type 1 diabetes mellitus, and she had intermittently taken her insulin over the past year. On initial presentation, patient was found to be in acute respiratory distress and ill-appearing. She was oriented to person but not place nor time.

On initial lab works, the patient had severe metabolic acidosis with pH less than 7 on venous blood gas and bicarb of 2 with anion gap of 30 and glucose elevated 581. Beta hydroxybutyrate was elevated on admission. Patient required emergent intubation given her severe respiratory distress. Surprisingly, her ammonium was elevated at 138 with normal liver function test.

Throughout her hospital course diabetic ketoacidosis protocol was followed and patient's anion gap closed within the three days. Patient was safely transitioned to subcutaneous long-acting insulin along with close follow-up with outpatient endocrinology. Liver function tests continue to remain stable throughout the hospital course.

Conclusion: This case highlights a rare manifestation of hyperammonemia in the setting of a young patient with normal liver and kidney function. It also highlights the molecular mechanisms behind diabetic ketoacidosis along with how they applied a clinical practice. Often overlooked are the protein catabolic reactions and their bioproducts that are underlying patients with prolonged ketosis, as seen in this case.

Dr. Lance D. Dworkin Department of Medicine Research Symposium

Pseudo-Thrombotic Microangiopathy by Vitamin B12 deficiency

Prajwal Hegde[1], Jennifer Kim[1], Caleb Spencer[2*],

[1]College of Medicine and Life Sciences, University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo,

Toledo, OH 43614

*Corresponding author: caleb.spencer@utoledo.edu

Keywords: Hemolytic Anemia, Vitamin B12, TTP
Published: 14 December 2023

Introduction: Vitamin B12 is a water-soluble vitamin primarily obtained from dairy and animal products. It is essential for several key enzymatic processes in the body, including DNA production. Vitamin B12 deficiency can manifest as pseudo-thrombotic microangiopathy (PTMA), which is an unusual clinical presentation of B12 deficiency. PTMA mimics primary thrombotic microangiopathies (TMAs) such as TTP, DIC, and HUS, with features like thrombocytopenia, schistocytes, and hemolytic anemia. In contrast to the aggressive treatment required for primary TMAs, PTMA can be effectively treated with B12 supplementation.

Case Presentation: A 73-year-old Caucasian male with a history of gout, hypertension, and hyperlipidemia presented with new-onset shortness of breath, bilateral leg pain, dizziness, tinnitus, and peripheral neuropathy. Physical examination revealed bilateral lower extremity edema, scleral icterus, and jaundice. Laboratory findings indicated normal folate levels, decreased vitamin B12 levels, elevated homocysteine, and elevated markers of hemolysis, including LDH (3137 U/L) and reticulocyte index (2.3). A peripheral blood smear exhibited macrocytic normochromic anemia with schistocytes and hypersegmented neutrophils. The patient began intramuscular and sublingual vitamin B-12 therapy, and substantial improvement in blood counts and reduced hemolytic markers were observed during a one-week follow-up.

Conclusion: PTMA is a crucial consideration in the differential diagnosis of TMA. A review by Fahmawi et al. in 2019 documented 41 cases of PTMA since 1971, suggesting that this remains a rare and potentially underdiagnosed condition. In contrast to true TMA, PTMA shows an excellent response to B12 supplementation alone, setting the standard for treatment. Physicians must remain vigilant about PTMA to prevent misdiagnosis and mistreatment. In fact, a review by Tran et al. demonstrated several adverse outcomes associated with unnecessary plasmapheresis, including anaphylaxis, hemothorax, and cardiac arrest. Recognizing PTMA could spare patients from unnecessary and risky treatments that are, at best, inefficacious and, at worst, life-threatening, when a significantly more feasible approach is available.

References

1. Ventura, P., Panini, R., Tremosini, S., Salvioli, G. *A role for homocysteine increase in haemolysis of megaloblastic anaemias due to vitamin B12 and folate deficiency: results from an in vitro experience*. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 2004. **1739**: pp. 33–42. doi:10.1016/j.bbadis.2004.08.005

2. Durmaz, A., Dikmen, N. *Homocysteine effects on cellular glutathione peroxidase (GPx-1) activity under in vitro conditions*. Journal of Enzyme Inhibition and Medicinal Chemistry, 2007. **22**(6): pp. 733–738. doi:10.1080/14756360601164929

3. Tran, P. N., Tran, M.-H. *Cobalamin deficiency presenting with thrombotic microangiopathy (TMA) features: A systematic review*. Transfusion and Apheresis Science: Official Journal of the World Apheresis Association: Official Journal of the European Society for Haemapheresis, 2018. **57**(1): pp. 102–106. doi:10.1016/j.transci.2018.01.003

4. Walter, K., Vaughn, J., Martin, D. *Therapeutic dilemma in the management of a patient with the clinical picture of TTP and severe B12 deficiency*. BMC Hematology, 2015. **15**: p.16. doi:10.1186/s12878-015-0036-2

5. Hassouneh, R., Shen, S., Lee, O., Hart, R. A., Rhea, L. P., & Fadden, P. *Severe Vitamin B12 Deficiency Mimicking Microangiopathic Hemolytic Anemia*. Journal of Hematology, 2021. **10**(4); pp. 202–205. doi:10.14740/jh889

6. Chiasakul, T., Cuker, A. *Clinical and laboratory diagnosis of TTP: An integrated approach*. Hematology, 2018. **2018**(1): pp. 530–538. doi:10.1182/asheducation-2018.1.530

7. Favaloro, E. J., Pasalic, L., Henry, B., Lippi, G. *Laboratory testing for ADAMTS13: Utility for TTP diagnosis/exclusion and beyond*. American Journal of Hematology, 2021. **96**(8), 1049–1055. doi:10.1002/ajh.26241

8. Tun, A. M., Myint, Z. W., Rojas Hernandez, C., Guevara, E., Thein, K. Z., Oo, T. H. *Vitamin B12 Deficiency-Related Pseudo-Thrombotic Microangiopathy Might be Misdiagnosed and Treated with Plasma Product Therapy: Review of the Literature and Analysis of the Reported Cases*. Blood, 2017. **130**(Supplement 1): p.5576. doi:10.1182/blood.V130.Suppl_1.5576.5576

9. Fahmawi, Y., Campos, Y., Khushman, M., Alkharabsheh, O., Manne, A., Zubair, H., Haleema, S., Polski, J., Bessette, S. *Vitamin B12 deficiency presenting as pseudo-thrombotic microangiopathy: A case report and literature review*. Clinical Pharmacology: Advances and Applications, 2019. **11**: pp.127–131. doi:10.2147/CPAA.S207258

10. Ankar, A., & Kumar, A. (2023). *Vitamin B12 Deficiency*. StatPearls Publishing, 2023. http://www.ncbi.nlm.nih.gov/books/NBK441923/

11. Rao, V.R. *Vitamin B12 deficiency presenting with hyperpigmentation and pancytopenia*. Journal of Family Medicine and Primary Care, 2018. **7**(3): pp. 642–644. doi:10.4103/jfmpc.jfmpc_347_16

12. Abdalla, Elm., Al-Sadi, A., Fadul, A., Ahmed, A. H., & Musa, M. (n.d.). *Non-immune Intravascular Hemolytic Anemia, an Unusual Presentation of Severe Vitamin B-12 Deficiency*. Cureus, 2022. **14**(7): p.e26507. doi:10.7759/cureus.26507

Improvement of in-office Blood Pressure targets in an Academic primary care setting

Mani Khorsand Askari, MD[1*], Hoda Shabpiray, MD[1], Sadik Khuder, PhD[1], Anand Mutgi, MD, Ken Vellequette[2], Cheryl Growden[2], Lisa Heyman[1], Dawn Lennard[1], Sarah Aldrich, PharmD[1], Marilee Clemons, PharmD[1], Jenni Gilmore[1], Brenda Joyce[1], Basil Akpunonu, MD[1]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Community Care Clinics, The University of Toledo, Toledo, OH 43614

*Corresponding author: mani.askari@utoledo.edu

Published: 14 December 2023

Background: Accurate blood pressure (BP) measurement in an office-based setting is essential for diagnosis and management of hypertension. Staff education on proper blood pressure measurement technique and recording is a focus of recent hypertension guidelines. Compared with other methods, unattended Automated Office Blood Pressure (AOBP) devices reduce measurement errors and improve BP Management. The addition of AOBP to staff education needs to be assessed objectively.

Objectives: To determine the effect of staff education on proper BP measurement and addition of AOBP devices on BP targets in an academic general internal medicine clinic.

Methods: Education was provided to the medical staff on how to appropriately check BP in general and on the proper use of the AOBP devices. Education was repeated in several intervals to ensure consistency in practice. Six AOBP Hillrom (Welch Allyn spot 4400) devices were deployed for the clinic. Devices allowed for three automated readings 1 minute apart eliminating the first reading and keeping the other 2 readings. Staff were instructed to document two blood pressure readings into the electronic medical record. The number of patients who completed two BP measurements documented in the EMR over time.

Results: Our results showed timely education with refresher, increased BP measurement protocol and improved BP recordings. Adherence to 2 BP checks increased from 40% in Dec-2021 to 99% in Jun-2023. The percentage of patients with improved BP increased from 40% to 76% after staff education and addition of AOBP.

Conclusion: Timely education of medical staff and the addition of AOBP could increase the accuracy of in-office BP measurement.

References

1. Unger T, Borghi C, Charchar F, et al. *2020 International Society of Hypertension Global Hypertension Practice Guidelines*. Hypertension, 2020. **75**(6): pp. 1334-1357. doi:10.1161/hypertensionaha.120.15026
2. Pappaccogli M, Di Monaco S, Perlo E, et al. *Comparison of Automated Office Blood Pressure With Office and Out-Off-Office Measurement Techniques*. Hypertension, 2019. **73**(2): pp. 481-490. doi:10.1161/hypertensionaha.118.1207
3. Stergiou G, Kollias A, Parati G, O'Brien E. *Office Blood Pressure Measurement: The Weak Cornerstone of Hypertension Diagnosis*. Hypertension, 2018. **71**(5): pp. 813-815. doi:10.1161/hypertensionaha.118.10850
4. Landgraf J, Wishner SH, Kloner RA. *Comparison of automated oscillometric versus auscultatory blood pressure measurement*. Am J Cardiol. 2010, **106**(3): pp. 386-388. doi:10.1016/j.amjcard.2010.03.040

Effects of reminder systems in reducing No-Show Rate in an academic general internal medicine clinic

Mani Khorsand Askari, MD[1], Hoda Shabpiray, MD[1], Sadik Khuder, PhD[1], Anand Mutgi MD, Ken Vellequette, MD[2], Cheryl Growden[2], Lisa Heyman[2], Dawn Lennard[2], Brenda Joyce[1], Basil Akpunonu, MD[1]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Community Care Clinics, The University of Toledo, Toledo, OH 43614

*Corresponding author: mani.askari@utoledo.edu

Published: 14 December 2023

Background: A No-show (NS) is defined as a failure to keep a face-to-face or virtual outpatient appointment without notice. A High no-show rate (NSR) affects continuity of care. The mean NSR in US is 18.8% with the highest rate seen in primary care offices (1). There are several reasons for NS including transportation issues, concurrent admission on the day of appointment, with the most reported reason being "forgetting the time of appointment"(2-4). Interventions are designed based on the main reason of NS. Some interventions to decrease NSR include automated reminder systems (ARS) by texts, emails, and staff calls to patients 24hrs before visit. The effect on NSR reduction with these measures in our setting is unclear.

Objectives: This prospective study was conducted to assess the effect of ARS on NSR in an academic general internal medicine (GIM) clinic.

Methods: Data on NSR was collected in the academic GIM clinic after initiating ARS by telephone, text, or email. ARS delivered before the appointment time and was consistent throughout the study. We also collected data on actual reasons for NS by random telephone calls to NS patients. The second intervention was a direct call from staff members to the patients 24 hours before the appointment as a direct reminder.

Results: The total number of visits for the year was 18640. NSR was around 19% at the introduction of ARS, Nov 2022, and over 6 months of using ARS dropped to 15% by end of May 2023 (P=0.001). There was a significant further reduction from June to the end of July with the use of direct staff calls (P=0.0000005).

Conclusion: We conclude the ARS reduces the NSR in this academic GIM clinic. Moreover, the addition of direct staff calls to the patient could further reduce the NSR.

References

1. Kheirkhah P, Feng Q, Travis LM, Tavakoli-Tabasi S, Sharafkhaneh A. *Prevalence, predictors and economic consequences of no-shows*. BMC Health Serv Res. 2016; **16**: pp. 13. doi:10.1186/s12913-015-1243-z

2. Kaplan-Lewis E, Percac-Lima S. *No-show to primary care appointments: why patients do not come*. J Prim Care Community Health, 2013. **4**(4): pp. 251-255. doi:10.1177/2150131913498513

3. Mohamed K, Mustafa A, Tahtamouni S, Eshraga T, Reham H. *A Quality Improvement Project to Reduce the 'No Show' rate in a Paediatric Neurology Clinic*. BMJ Open.Quality, 2016. **5**: pp. u209266.w3789. doi: 10.1136/bmjquality.u209266.w3789

4. Johnson BJ, Mold JW, Pontious JM. *Reduction and management of no-shows by family medicine residency practice exemplars*. Ann Fam Med, 2007. **5**(6): pp. 534-539. doi:10.1370/afm.752

Current Legislative Status of Pharmacy-driven PEP in the US

Katherine Esser[1*], Joan Duggan, MD[2], Kaylee Scarnati[1], Eric Sahloff, Pharm D[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Pharmacy Practice, College of Pharmacy and Pharmaceutical Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: kesser@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Non-occupational post-exposure prophylaxis (nPEP) to prevent HIV infection is highly effective and consists of initiation of antiretroviral medications (ART) ideally within 2 – 24 hours after HIV exposure and continued for 28 days: it is a medical emergency requiring rapid ART access. Rapid access problems have hindered its widespread usage. Pharmacy-initiated PEP access was first trialed in New York City in 2017, allowing pharmacists to prescribe a seven-day supply of PEP without a prescription for consumers at high risk for HIV infection. The provision of PEP by pharmacists – ie, pharmacy-driven PEP (PDP) – may improve access to this time-sensitive HIV prevention strategy in the US but the current status of PDP nationwide is not known. We assessed the current legal status of PDP nationally since its initiation in 2017.

Objective: To assess the current legislative status of pharmacy-driven PEP in the US.

Methods: A review of the status of current state legislation/guidance related to PDP was performed.

Results: As of July 31, 2023, 12 states allow pharmacists to furnish HIV PEP through specific legislative initiatives. The authority for pharmacist prescribing or furnishing nPEP is defined primarily through state government-defined protocols, standing orders, prescriptive authority or collaborative practice agreements (California, Colorado, Illinois, Maine, Missouri, New Mexico, New York, Nevada, North Carolina, Oregon, Utah, Virginia). Multiple states have legislation pending specifically for nPEP (Massachusetts, New Jersey, Florida, and Maryland).

Conclusion: The lifetime risk of contracting HIV among Black MSM (men who have sex with men) is 1 in 2. nPEP is currently rapidly accessible through pharmacies for patients at risk in 12 states but is accessible only through physicians and physician extenders in 38 states. Analysis of barriers to widespread implementation of pharmacy-driven PEP nationwide should be undertaken to improve rapid access to nPEP for communities at risk.

References

1. *HIV Surveillance*. Volume **28**(3). Centers for Disease Control and Prevention, May 23, 2023. Accessed June 6, 2023. https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-28-no-3/index.html.

2. *HIV declines among young people and drives overall decrease in new HIV infections*. Centers for Disease Control and Prevention, May 23, 2023. Accessed June 6, 2023. https://www.cdc.gov/media/releases/2023/p0523-hiv-declines-among-young-people.html.

3. Centers for Disease Control and Prevention. About Ending the HIV Epidemic Initiative, September 2021.https://www.cdc.gov/endhiv/about.html

4. "*Post-Exposure Prophylaxis*." HIV.gov, www.hiv.gov/hiv-basics/hiv-prevention/using-hiv-medication-to-reduce-risk/post-exposure-prophylaxis.

5. *Public Health Service Guidelines for the Management of Health-Care Worker Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR, May 15, 1998. **47**(RR-7);1-28

6. Joyce MP, Kuhar D, Brooks JT. *Notes from the Field: Occupationally Acquired HIV Infection Among Health Care Workers — United States, 1985–2013*. MMWR, January 9, 2015. **63**(53);1245-1246

7. Beymer MR, Kofron RM, Tseng CH, Bolan RK, Flynn RP, Sayles JM, Perez MJ, Jordan WC, Landovitz RJ. *Results from the post-exposure prophylaxis pilot program (P-QUAD) demonstration project in Los Angeles County*. Int J STD AIDS, 2018 May. **29**(6): pp. 557-562.

8. *Unknown*. United States Office of Safety and Health Administration. https://www.osha.gov/laws-regs/standardinterpretations/2020-08-19-1

9. *Unknown*. United States Office of Safety and Health Administration. https://www.osha.gov/laws-regs/standardinterpretations/2013-11-27-0

10. John SA, Quinn KG, Pleuhs B, Walsh JL, Petroll AE. *HIV Post-Exposure Prophylaxis (PEP) Awareness and Non-Occupational PEP (nPEP) Prescribing History Among U.S. Healthcare Providers*. AIDS Behav, 2020 Nov. **24**(11): pp. 3124-3131. doi:10.1007/s10461-020-02866-6.

11."*HIV Diagnoses*." Centers for Disease Control and Prevention, Centers for Disease Control and Prevention, 24 Oct. 2022, www.cdc.gov/hiv/statistics/overview/diagnoses.html.

12. Reif S, Safley D, McAllaster C, Wilson E, Whetten K. *State of HIV in the US deep South*. 2017, 42: pp. 844-853.

13. Lewis, C.F., Lekas, HM., Rivera, A. et al. *Pharmacy PEP Access Intervention Among Persons Who Use Drugs in New York City: iPEPcare Study—Rethinking Biomedical HIV Prevention Strategies*. AIDS Behav, 2020. **24**: pp. 2101–2111. https://doi.org/10.1007/s10461-019-02775-3

14. Goode JV, Owen J, Page A, Gatewood S. *Community-Based Pharmacy Practice Innovation and the Role of the Community-Based Pharmacist Practitioner in the United States*. Pharmacy (Basel), 2019 Aug 4. **7**(3): p.106. doi:10.3390/pharmacy7030106.

15. Berenbrok LA, Tang S, Gabriel N, Guo J, Sharareh N, Patel N, et al. *Access to community pharmacies: a nationwide geographic information systems cross-sectional analysis*. Journal of the American Pharmacists Association, 2022. **62**: pp.1816-1822. https://doi.org/10.1016/j.japh.2022.07.003

16. Mitchell, Travis. "*Views of Problems Facing Urban, Suburban and Rural Communities*." Pew Research Center's Social & Demographic Trends Project, Pew Research Center, 30 May 2020. www.pewresearch.org/social-trends/2018/05/22/views-of-problems-facing-urban-suburban-and-rural-communities/

17. National Alliance of State and Territorial AIDS Directors (NASTAD). "*Pharmacist- Initiated PrEP and PEP" Information Sheet*. NASTAD.org, 2021. https://nastad.org/sites/default/files/2021-11/PDF-Pharmacist-Initiated-PrEP-PEP.pdf Accessed June 15, 2023.

18. Tung EL, Thomas A, Eichner A, Shalit P. *Implementation of a community pharmacy-based pre-exposure prophylaxis service: a novel model for pre-exposure prophylaxis care*. Sex Health, 2018 Nov. **15**(6): pp. 556-561.

19. Havens JP, Scarsi KK, Sayles H, Klepser DG, Swindells S, Bares SH. *Acceptability and feasibility of a pharmacist-led HIV pre-exposure prophylaxis (PrEP) program in the Midwestern United States*. Open Forum Infect Dis, 2019 Aug 14. **pii**: ofz365.

20. Lopez MI, Cocohoba J, Cohen SE, Trainor N, Levy MM, Dong BJ. *Implementation of pre-exposure prophylaxis at a community pharmacy through a collaborative practice agreement with San Francisco Department of Health*. J Amer Pharm Assoc, 2019. **60**: pp.138-144.

21. *SB 159. HIV: pre-exposure and post-exposure prophylaxis*. California Legislative Information. https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201920200SB159. Accessed August 1, 2023.

22. *HBj20-1061. Human Immunodeficiency Virus Infection Prevention Medications*. Colorado General Assembly. https://leg.colorado.gov/sites/default/files/2020a_1061_signed.pdf. Accessed August 1, 2023.

23. *CCR 719-1 Appendix C. Colorado State Board of Pharmacy Statewide Protocol. Pre-Exposure and Post-Exposure Prophylaxis of HIV*. Code of Colorado Regulations. https://drive.google.com/file/d/10vcW8Pq-1rjBjQ3Uvm1ZZPGmHiEOPgWB/view. Accessed August 1, 2023.

24. *Full Text of HB4430. 102nd general assembly*. Illinois General Assembly. https://www.ilga.gov/legislation/fulltext.asp?DocName=&SessionId=110&GA=102&DocTypeId=HB&DocNum=4430&GAID=16&LegID=&SpecSess=&Session=. Accessed August 1, 2023.

25. *LD 1115. An Act to improve access to HIV prevention medications*. Maine Legislature. https://legislature.maine.gov/bills/getPDF.asp?paper=SP0378&item=1&snum=130. Accessed August 1, 2023.

26. *HB 476*. Missouri General Assembly. https://house.mo.gov/billtracking/bills191/hlrbillspdf/1034H.01I.pdf. Accessed August 1, 2023.

27. Missouri Department of Commerce and Insurance. Division State Board of Pharmacy. *20 CSR 2220-6.025 HIV Post-Exposure Prophylaxis*. https://dci.mo.gov/proposed-rule/20CSR2220-6.025.pdf. Accessed August 1, 2023.

28. New Mexico Administrative Code. *NMAC 16.19.26. Occupational and Professional Licensing Pharmacist Prescriptive Authority*. https://www.srca.nm.gov/parts/title16/16.019.0026.html. Accessed August 1, 2023.

29. New Mexico Regulation and Licensing Department. *Protocol for pharmacist prescribing HIV post-exposure prophylaxis (PEP) therapy in conjunction with point-of-care testing (POCT)*. https://www.rld.nm.gov/uploads/files/PEPProtocolALONE.pdf. Accessed August 1, 2023.

30. New York State Department of Health. *The licensed pharmacist's role in initiating HIV post-exposure prophylaxis: overview and frequently asked questions*. Published August 2022. https://www.health.ny.gov/diseases/aids/general/pep/docs/pharmacists_role.pdf. Accessed August 1, 2023.

31. Nevada Electronic Legislative Information System. *SB 325*. https://www.leg.state.nv.us/App/NELIS/REL/81st2021/Bill/7959/Text. Accessed August 1, 2023.

32. Nevada State Board of Pharmacy. *LCB File No. R039-21*. https://www.leg.state.nv.us/Register/2021Register/R039-21AP.pdf. Accessed August 1, 2023.

33. North Carolina General Assembly. *HB 96*. https://www.ncleg.gov/Sessions/2021/Bills/House/PDF/H96v5.pdf. Accessed August 1, 2023.

34. *North Carolina State Health Director's Standing Order for Post-Exposure Prophylaxis (PEP) for Human Immunodeficiency Virus*. North Carolina Department of Health and Human Services, March 28, 2022. https://www.dph.ncdhhs.gov/docs/PEP-StandingOrder-March2022.pdf. Accessed August 1, 2023.

35. Oregon State Legislature. *HB 2958*. 2021. Accessed August 1, 2023. https://legiscan.com/OR/text/HB2958/2021

36. Oregon Secretary of State. *OAR 855-020-0110: Prescribing Practices*. Pharmacist Prescriptive Authority. https://oregon.public.law/rules/oar_855-020-0110. Accessed August 1, 2023.

37. Oregon Board of Pharmacy. *Preventative Care: HIV Post-Exposure Prophylaxis. Statewide drug therapy management protocol for Oregon pharmacists*. https://www.oregon.gov/pharmacy/Documents/PrevCare_PEP_Protocol_v.6.2023.pdf. Accessed August 1, 2023.

38. Utah State Legislature. *HB 178*. Pharmacy practice modifications. https://le.utah.gov/~2021/bills/hbillenr/HB0178.pdf. Accessed August 1, 2023.

39. Utah Division of Occupational Professional Licensing. *Utah guidance for pre-exposure and post-exposure prophylaxis of HIV*. Published September 2021. https://www.dopl.utah.gov/wp-content/uploads/2022/09/utah-guidance-for-pre-exposure-and-post-exposure-prophylaxis-of-hiv.pdf. Accessed August 1, 2023.

40. Virginia General Assembly. *HB 2079. Pharmacists: initiation of treatment with and dispensing and administering drugs and devices*. http://leg1.state.va.us/cgi-bin/legp504.exe?212+ful+HB2079ER. Accessed August 1, 2023.

41. Virginia Department of Health Professionals. *Virginia Board of Pharmacy. HIV Post-Exposure Prophylaxis (PEP) Statewide Protocol*. https://www.dhp.virginia.gov/pharmacy/docs/protocols/PEPCombinedProtocol12-22-2021.pdf. Accessed August 1, 2023.

42. Bellman R, Mohebbi S, Nobahar N, Parizher J, Apollonio DE. An observational survey assessing the extent of PrEP and PEP furnishing in San Francisco Bay Area pharmacies. J Am Pharm Assoc, 2022 Jan-Feb. **62**(1): pp. 370-377.e3. doi: 10.1016/j.japh.2021.08.001. Epub 2021 Aug

The Impact of Sickle Cell Disease on Acute Coronary Syndrome Outcomes: A Retrospective Observational Study in the United States for the Year 2020

Abdulmajeed Alharbi, MD[1*], Clarissa Pena, MD[2], Caleb Spencer, MD[2], Masharib Bashar, MD[1], Michelle Cherian[3], Mohammed Siddique, MD[1], Ragheb Assaly, MD[1]

[1]Division of Pulmonary and Critical Care, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: abdulmajeed.alharbi@utoledo.edu

Published: 14 December 2023

Introduction: Sickle cell disease (SCD), a multisystem disorder resulting from a single gene mutation, has been recognized as a global health issue, affecting more than 300,000 infants every year with an expected rise to 400,000 by the year 2050 (1). The influence of Sickle Cell Disease (SCD) on Acute Coronary Syndrome (ACS) outcomes have been the focus of a number of previous studies.

Objective: In this current study, we investigated the clinical characteristics and outcomes of SCD patients admitted with ACS and assessed the impact of SCD on ACS patient outcomes.

Methods: This was a retrospective observational study of a large cohort of adult patients who died with a primary diagnosis of SCD and a secondary diagnosis of ACS within the United States in the year 2020. The focus of our study was on in-hospital mortality, length of stay, and total hospital charges which were compared between the two cohorts. Procedure Classification System (ICD-10-CM) codes were used to identify codes for diagnosis with the final study sample of patients admitted with ACS comprising 779,895. Of the patients admitted with ACS, 23085 also had established diagnosis of SCD.

Results: Our findings revealed that firstly, SCD patients admitted with ACS demonstrated a heightened prevalence of hypertension, drug abuse, and chronic lung diseases, further highlighting the association between SCD and these co-morbidities. Secondly, among patients admitted with STEMI, SCD patients exhibited higher inpatient mortality rates, although this disparity did not reach statistical significance. Lastly, among SCD patients admitted for ACS who underwent PCI, the study revealed a statistically significant elevation in the risk of coronary dissection. Additionally, there were notable increases in the occurrences of atrial fibrillation and acute heart failure in this group; however, these associations did not reach statistical significance.

Conclusion: These findings provide valuable insights into the outcomes of SCD patients in the context of ACS and PCI, particularly in regard to the increased risk of coronary dissection posed to these patients. However, future studies are warranted to explore the underlying mechanisms and potential implications between SCD and ACS.

References:

1. Piel FB, Steinberg MH, Rees DC. *Sickle Cell Disease*. NEJM, Apr 20 2017. **376**(16): pp. 1561–73. doi: 101056/NEJMra1510865. 2017

Characterization of a Novel IQGAP1-ADRα2 axis as a Target of Norepinephrine in Lung Cancer

Tatiana B. De Souza[1*], Yusuf Barudi[1], Mahasin A. Osman[2],

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: tatiana.desouza@rockets.utoledo.edu

Keywords: IQGAP1, ADRα-2, Norepinephrine, Lung Cancer, Adrenergic Receptor α-2a

Published: 14 December 2023

Background: Lung cancer is a leading cause of cancer death worldwide with few personalized treatment options. IQGAP1 is a signaling oncoprotein implicated in lung cancer, but its mechanism is poorly defined. In a yeast screen, the neurotransmitter/hormone norepinephrine (NE) was identified as an inhibitor of IQGAP1 in cell proliferation. As the GPCR Adrenergic Receptor α-2a (ADRα-2a) is a known NE target, its link to IQGAP1 and NE utility in lung cancer therapy was investigated.

Objectives: Decipher the NE-IQGAP1-ADRα2 interplay in human lung cancer.

Methods: Western Blot was used to quantify ADRα-2a and IQGAP1 protein levels in several lung cancer cell lines. MTT assay was used to determine proliferation inhibition of lung cancer cell line and identify the NE IC50 dose. qRT-PCR was employed to measure NE effects on IQGAP1 and ADRα-2a mRNA levels in human cancer cell lines and WT and iqgap1-/- mouse embryonic fibroblasts (MEFs). Wound healing assays were used to measure the NE effects on cell migration capacity of lung cancer cells.

Results: ADRα-2 and IQGAP1 were differentially expressed in the different lung cancer cell lines. NE significantly reduced the ADRα-2 mRNA in normal but not lung cancer cells and insignificantly affected its level in WT MEFs. By contrast, in iqgap1-1- MEFs, NE appeared to increase ADRα-2 mRNA levels, suggesting that IQGAP1 influences ADRα-2a mRNA expression and that NE effects require IQGAP1. Interestingly, NE significantly reduced IQGAP1 mRNA in WT MEFs explaining the lack of effect on ADRα-2a. NE affected migration differently among lung cancer cell lines, suggesting a more individualized approach to developing future NE-based therapy.

Conclusion: IQGAP1 appears to negatively regulates ADRα-2a expression and can serve as an NE target in lung cancer.

Association between autoimmune diseases and glioblastoma: results from national inpatient database

Nahshon A. Puente[1*], Mahasin Osman[2], Sadik A. Khuder, PhD[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614
[3]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Sadik.Khuder@utoledo.edu

Published: 14 December 2023

Background: Glioblastoma multiform (GBM) is the most frequent malignancy among primary brain tumors in adults and has one of the worst 5-year survival rates among all human cancers. Certain autoimmune diseases (AID) and their treatments may increase the risk of cancer. Studies report conflicting data about the effects of AID on the risk of GBM.

Objectives: To evaluate the effect of AID on the risk of GBM.

Methods: Discharge data for 2020 Nationwide Inpatient Sample, Healthcare Cost and Utilization Project (HCUP), which approximates a 20% stratified sample of all US hospitalizations, were analyzed. Cases of AID and GBM were identified using the ICD10 codes. Autoimmune comorbidity index was used for the combined autoimmune diseases. Weighted Multivariable logistic regression was used to examine the association between GBM and AID and adjusting for sociodemographic characteristics. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) were calculated using SAS survey logistic regression procedure.

Results: Among 6,471,165 admissions, 178,254 patients were identified with AID. The prevalence of GBM in patients with AD was 0.07% compared to 0.12% in patients without AID (AOR = 0.653, CI= 0.546-0.782, p = 0.0016). Significant reduction was found for rheumatoid arthritis (RA), lupus, and scleroderma. The highest reduction in the risk of GBM was for scleroderma. No significant differences were found for Sjogren's syndrome, psoriasis, sarcoidosis, thyroiditis, multiple sclerosis, or other AID.

Conclusion: In the US, among hospitalized adults diagnosed with AID, patients with RA, lupus, and scleroderma are significantly less likely to have GBM. This reduction could be attributed to the effect of anti-AID drugs administered to the patients, or the nature of the activated pathways in AID that naturally antagonize neoplastic activation.

Acute exacerbation of bronchiectasis secondary to Achromobacter xylosoxidans in a patient with Mycobacterium-Avium Intracellulare infection

Kashvi Patel[1], Sree Jambunathan[1], Faraz Badar MD[2], Muzdah Anwar[3], Zaid Zakaria[4], Amna Al-Tkrit MD[2], Fadi Safi MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Pulmonary and Critical Care, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Khyber Girls Medical College, Pakistan
[4]An-Najah National University

*Corresponding author: kashvi.patel@utoledo.edu

Published: 14 December 2023

Introduction: We report the rare case of a patient with known history of Mycobacterium-avium intracellulare (MAI) presenting with bronchiectasis exacerbation due to multidrug resistant organism (MDRO) Achromobacter xylosoxidans.

Case Presentation: A 79-year-old female with history of acquired bronchiectasis secondary to MAI infection presented with worsening dyspnea and pleuritic chest pain for 1 month duration. Chest auscultation revealed coarse breath sounds bilaterally and CT chest showed diffuse bronchiectasis with multifocal bronchial opacification bilaterally and diffuse bronchial wall thickening.

Laboratory testing showed normal immunoglobulins, cyclic citrullinated peptide, antinuclear antibody and alpha-1-antitrypsin levels. Flexible fiberoptic bronchoscopy with bronchoalveolar lavage showed copious amounts of mucopurulent secretions. Respiratory culture was negative for acid fast bacilli and fungal smear but positive for Achromobacter xylosoxidans.. Sensitivity testing showed resistance to multiple antibiotics including cephalosporins, penicillin, fluroquinolones, aztreonam, and aminoglycosides. Patient received trimethoprim/sulfamethoxazole for 1 week and reported improvement in symptoms.

Conclusion: A 79-year-old female with history of acquired bronchiectasis secondary to MAI infection presented with worsening dyspnea and pleuritic chest pain for 1 month duration. Chest auscultation revealed coarse breath sounds bilaterally and CT chest showed diffuse bronchiectasis with multifocal bronchial opacification bilaterally and diffuse bronchial wall thickening.

Laboratory testing showed normal immunoglobulins, cyclic citrullinated peptide, antinuclear antibody and alpha-1-antitrypsin levels. Flexible fiberoptic bronchoscopy with bronchoalveolar lavage showed

copious amounts of mucopurulent secretions. Respiratory culture was negative for acid fast bacilli and fungal smear but positive for Achromobacter xylosoxidans.. Sensitivity testing showed resistance to multiple antibiotics including cephalosporins, penicillin, fluroquinolones, aztreonam, and aminoglycosides. Patient received trimethoprim/sulfamethoxazole for 1 week and reported improvement in symptoms.

References:

1. Swenson, C. E., R.T. Sadikot. Achromobacter respiratory infections. Annals of the American Thoracic Society, 2015. **12**(2): pp. 252–258. https://doi.org/10.1513/AnnalsATS.201406-288FR

2. Polverino, E., Goeminne, P. C., McDonnell, M. J., Aliberti, S., Marshall, S. E., Loebinger, M. R., Murris, M., Cantón, R., Torres, A., Dimakou, K., De Soyza, A., Hill, A. T., Haworth, C. S., Vendrell, M., Ringshausen, F. C., Subotic, D., Wilson, R., Vilaró, J., Stallberg, B., Welte, T., Rohde G., Blasi F., Elborn S, Almagro M, Timothy A., Ruddy T., Tonia T., Rigau D., and J.D. Chalmers. *European Respiratory Society guidelines for the management of adult bronchiectasis*. The European respiratory journal, 2017. **50**(3): p. 1700629. https://doi.org/10.1183/13993003.00629-2017

Role of IQGAP1-Estrogen Receptorα-AMPK Axis in the Sex Differences of Type 2 Diabetes

Rawan Moussa[1*], Alice Lu[1], Mahasin A. Osman, PhD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: alice.lu@utoledo.edu

Keywords: Sex differences in Type 2 Diabetes, IQGAP1, Estrogen receptor alpha, AMPK

Published: 14 December 2023

Type 2 diabetes (T2D) is a 2-hit chronic metabolic disorder arising from defects in insulin secretion from pancreatic -cells and insulin sensitivity in peripheral tissues. Population studies indicated that T2D affects more men than women. The mammalian target of rapamycin (mTOR) and its downstream key energy sensor AMPKα have been largely implicated in T2D. Strong evidence suggests that the estrogen receptor α (ERα) influences AMPK activity and T2D sex disparity, but the molecular mechanisms remain unclear. The scaffold signaling protein IQGAP1 binds AMPKα and ERα and regulates insulin secretion in pancreatic -cells. Here, we aim to test the novel hypothesis that an IQGAP1-ERα-AMPKs signaling axis plays a role in the disparity of T2D and exerts its effects in the pancreas. Preliminary results revealed significant metabolic differences in male and female mice lacking IQGAP1 (KO) and fed a high-fat diet (HFD) compared to control groups. While all KO mice exhibited significant decreases in body weight, the female mice were much leaner and ate less food. Furthermore, metabolic analyses indicated a significant reduction in insulin levels in KO male mice on HFD while the female mice displayed improved glucose homeostasis likely due to enhanced insulin secretion. Insulin, gene expression levels and co-localization of the pathway components in the pancreas are being investigated in treated and control mice groups. Overall, the study likely will provide important new insights into the determinants of sex-differences of T2D and reveal potential diagnostic biomarkers for future therapies.

Dr. Lance D. Dworkin Department of Medicine Research Symposium

Recurrent Bilateral Pleural Effusion Secondary to Idiopathic Pleuritis in a Young Female Patient

Muzdah Anwar[1], Sree Jambunathan[2], Kashvi Patel[2], Zaid Zakaria[3], Faraz Badar MD[4], Amna Al-Tkrit MD[4], Fadi Safi MD[4], Mohamed Omballi MD[4]

[1]Khyber Girls Medical College, Khyber Pakhtunkhwa, Pakistan

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[3]An-Najah National University, Nablus, West Bank, Palestine

[4]Division of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: muzdah420@gmail.com

Published: 14 December 2023

Introduction: We present a rare case of a 38-year-old female patient with recurrent bilateral pleural and pericardial effusion and Primary Raynaud phenomenon.

Case Presentation: A 38-year-old female presents with bilateral recurrent exudative pleural effusions requiring drainage six times in the past five months. She has complaints of discoloration of the fingers (Raynaud phenomenon), dry cough, and bilateral leg swelling. She denies joint pain, upper extremity swelling, fever, or chills. She has no history of cancer and no new medications. She had extensive rheumatology work-up due to primary Raynaud's phenomenon. Work-up revealed negative cyclic citrullinated peptide, antinuclear antibody, rheumatoid factor, anticentromere, and anti-scl 70. Her TSH was elevated at 6.7 being controlled with levothyroxine 88 mcg daily. She does not have other clinical features of connective tissue disease or autoimmune inflammatory disease such as Familial Mediterranean Fever. CT abdomen revealed bilateral pleural effusion, pericardial effusion, ascites, and no ovarian masses. Liver ultrasound showed normal echotexture and no cirrhosis. Urinalysis showed no proteinuria. Cardiac MRI showed no infiltrative disease. No pulmonary hypertension. Cytology from the pleural fluid has been negative. Patient underwent fluoroscopy with pleural biopsy and pleurx catheter placement. Pleural biopsy showed pleuritis. She received empiric prednisone with plan for right-sided heart catheterization to rule out constrictive pericarditis or restrictive cardiomyopathy.

Conclusion: There are many causes of pleural effusions including congestive heart failure, malignancy, pneumonia, pulmonary emboli, and liver or renal failure. Non-specific pleuritis, defined as fibrinous or inflammatory pleuritis without a specific etiology, can also cause recurrent pleural effusions (1). Thoracoscopic pleural biopsy is valuable in investigating patients with exudative pleural effusions, especially when pleural fluid analysis is uninformative (2). Thus, with pleural effusions of unknown etiology, it is important to include pleuritis, constrictive pericarditis, and restrictive cardiomyopathy.

References

1. Janssen J, Maldonado F, Metintas M. *What is the significance of non-specific pleuritis? A trick question*. Clin Respir J, 2018 Sep. **12**(9):2407-2410. doi: 10.1111/crj.12940. PMID: 30004629.

2. Davies HE, Nicholson JE, Rahman NM, Wilkinson EM, Davies RJ, Lee YC. *Outcome of patients with nonspecific pleuritis/fibrosis on thoracoscopic pleural biopsies*. Eur J Cardiothorac Surg, 2010 Oct. **38**(4):472-7. doi: 10.1016/j.ejcts.2010.01.057. Epub 2010 Mar 12. PMID: 20219385.

Perihepatic abscess secondary to Sphingobacterium spiritivorum

Victoria Soewarna[1*], Kada Williams[1], Salman Arif [3], Hend Elsaghir, MD

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: victoria.soewarna@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Sphingobacterium spiritivorum is a gram-negative rod belonging to the Sphingobacterium species, previously classified as Flavobacterium species (1). The genus is comprised of S. spiritivorum and S. multivorum. It is commonly found in nature, primarily in water and soil (2). Human infections are rare and predominantly impact immunocompromised or elderly individuals. We present a case of a perihepatic abscess secondary to Sphingobacterium spiritivorum.

Case Presentation: A 65-year-old male with a history of pulmonary embolism on Eliquis, hyperlipidemia, anxiety, depression, and thyroid disease presented to the hospital as a level 1 trauma due to motor vehicle accident with multiple orthopedic fractures. On admission, computed tomography (CT) of the abdomen and pelvis revealed mild degree of diffuse hepatic steatosis with no gross focal hepatic lesion. On hospital day two, CT of the abdomen and pelvis revealed a subcapsular lesion in the right liver, concerning for hemangioma or cyst. On day eleven, hospitalization was complicated by a lower extremity wound infection positive for Bacillus species and Acinetobacter baumannii complex. The patient was treated with Vancomycin and Unasyn for 7 days with resolution of symptoms. On hospital day sixteen, CT abdomen/pelvis revealed an increase in subcapsular fluid accumulation along the right hepatic lobe now measuring 7 cm by 5 cm. The perihepatic abscess was drained by interventional radiology on hospital day 17 and sent for cultures. Cultures were positive for Sphingobacterium spiritivorum. The patient completed a course of IV ceftriaxone 2 grams daily for 6 weeks via PICC line, metronidazole 500 mg every 8 hours for 14 days, and repeated imaging of the liver in 4 weeks.

Conclusion: Currently, there are no standard treatments for *Sphingobacterium* spp. Based on previously reported cases and antibiotic susceptibility, *Sphingobacterium spiritivorum* is susceptible to carbapenems, quinolones, trimethoprim-sulfamethoxazole, and ceftazidime. This patient was successfully treated with ceftriaxone and metronidazole, which supports these susceptibilities.

References

1. Yabuuchi E., Kaneko T., Yano I., Moss C.W., Miyoshi N. *Sphingobacterium gen. nov., Sphingobacterium spiritivorum comb. nov., Sphingobacterium multivorum comb. nov., Sphingobacterium mizutae sp. nov., and Flavobacterium indologenes sp. nov.:Glucose*

Nonfermenting Gram-Negative Rods in CDC Groups IIK-2 and IIb. International Journal of Systemic Bacteriology, July 1983. p. 580-598.

2. Hibi A, Kumano Y. *Sphingobacterium spiritivorum bacteremia due to cellulitis in an elderly man with chronic obstructive pulmonary disease and congestive heart failure: a case report*. J Med Case Rep, 2017 Sep 30. **11**(1): p.277. doi:10.1186/s13256-017-1445-6. PMID: 28962584; PMCID: PMC5622497.

Into the unknown: Navigating orbital cellulitis to reveal retinal metastasis of a hidden primary tumor

Mohammed Abu-Rumaileh, MD[1], Kashvi Patel[2], Fahham Asghar[1]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614
[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: mohammed.abu-rumaileh@utoledo.edu

Published: 14 December 2023

Introduction: This is a rare patient presentation of retinal metastasis with an unknown primary tumor.

Case Presentation: A 65-year-old woman with a past medical history of left breast carcinoma stage 1 status post left mastectomy in 2014, iron deficiency anemia, anxiety, and depression presented to the emergency department with 1-2 weeks of worsening lower abdominal pain and left-sided chest pain. She also complained of right eye pain, blurry vision, and painful eye movement. Ocular examination demonstrated edema, mild proptosis, conjunctival chemosis, and conjunctival injection. Patient was started on bacitracin ointment and ceftriaxone due to concerns of orbital cellulitis. Ophthalmology was consulted, and their assessment was suggestive of bilateral metastatic neoplastic lesion in retina of both eyes, more pronounced in the right than the left eye. Left supraclavicular lymph node biopsy showed metastatic adenocarcinoma, likely of gastrointestinal or pancreaticobiliary primary. MRI brain was suspicious for calvarial metastatic disease, MRI abdomen showed multiple nodules in the liver suggesting metastases, and NM bone scan whole body suggested possible metastases in the hemithorax and bilateral femurs. After several goals of care discussions, the decision was made by the patient and her family to pursue comfort measures only and she was discharged home with home hospice.

Conclusion: Retinal metastasis is a rare condition due to the absence of lymphatic system in the eye (1). The most common primary tumors to metastasize to the eye are from breast (47%), lung (21%), and the gastrointestinal tract (4%) (2). In some cases, patients may have no other symptoms (1). Thus, retinal metastasis is important to include in the differential diagnosis, especially for patients with a history of treated primary cancer.

References

1. Cohen V. M. *Ocular metastases*. Eye (London, England), 2013. **27**(2), 137–141. doi:10.1038/eye.2012.252

2. Shields, C. L., Shields, J. A., Gross, N. E., Schwartz, G. P., & Lally, S. E. *Survey of 520 eyes with uveal metastases*. Ophthalmology, 1997. **104**(8), 1265–1276. doi:10.1016/s0161-6420(97)30148-1

Dr. Lance D. Dworkin Department of Medicine Research Symposium

A case of palindromic rheumatism and literature review

Dharmindra Dulal[1*], Bashar Kahaleh, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: dharmindra.dulal@rockets.utoledo.edu

Keywords: Palindromic Rheumatism, Episodic Arthritis
Published: 14 December 2023

Introduction: Palindromic rheumatism (PR) is an autoimmune condition characterized by transient migratory arthritic attacks involving one or multiple joints. Although any joints are vulnerable to attack, the wrist, knee, and fingers are commonly involved. PR attacks are associated with debilitating pain with joint stiffness, swelling, and warmth, but do not result in residual damage. PR is a commonly misdiagnosed condition due to the lack of established diagnostic guidelines, and it often presents with standard inflammatory and autoimmune markers.

Case Presentation: The patient is a 36-year-old white female who was first presented to the rheumatology clinic on November 8th, 2022, complaining of migratory joint pain over multiple days. However, the patient denied any swelling, erythema, or morning stiffness. The patient was noted to have an elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) over the past two years. All other inflammatory and autoimmune markers were found to be in the normal range. Evaluation of the sacroiliac joint and cervical spine via X-rays did not reveal any significant abnormalities. The trial of 5mg prednisone for two weeks failed to show improvement in symptoms.

Conclusion: After multiple follow-ups over a year, the patient was diagnosed with PR based on recommendations proposed by Pasero and Barbieri, which include: 1) six months history of brief, sudden, and recurrent episodes of mono-arthritis or polyarthritis; 2) the physician must observe at least one attack; 3) PR must involve three or more joints; 4) radiographic findings are normal; 5) it is a diagnosis of exclusion. Although there haven't been any FDA-approved medications to treat PR, the clinician has been using conventional therapy to treat other rheumatic conditions as a mainstay treatment. Among traditional treatments, hydroxychloroquine (HCQ), corticosteroid, methotrexate (MTX), and biologics (such as rituximab) have shown the most significant therapeutic benefits in limited case studies. Therefore, our patient was offered HCQ, MTX, and biologics as treatment options. Although, our patient hasn't decided on specific therapy to pursue yet, we will be continuously monitoring the disease progression and effects of therapy once started.

Late angina due to anomalous Right Coronary Artery

Nahush R. Bansal, MD[1*], Catalin Dragomirescu[2], Mona Mahmoud, MD[1]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[3]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: nahush096@gmail.com

Keywords: Anomalous Coronary Arteries

Published: 14 December 2023

Introduction: Anomalous origin of the right coronary artery arising from the left coronary sinus and taking an interarterial course between the great vessels is a rare diagnosis, with a reported incidence between 0.026% and 0.250%. While most cases are asymptomatic, the anomalous right coronary artery is typically diagnosed incidentally. However, this abnormal anatomy of the right coronary artery renders it vulnerable to compression between the right ventricular outflow tract or pulmonary artery and the aorta. This compression can potentially manifest as angina, arrhythmias, and sudden cardiac death. We report a case with this rare diagnosis that presented atypically with angina, mainly at rest, and had a late presentation at an older age.

Case Presentation: A 46-year-old female presented to the Emergency department (ED) with a year-long history of intermittent episodes of nocturnal retrosternal chest pain, radiating to the jaw, neck and arm that were severe enough to disrupt her sleep. These episodes worsened progressively over time, leading to multiple office and ED visits for the patient. Notably, the patient did not report any symptoms with exertion or activity. The cardiac workup, including ECG, troponins and echocardiogram, yielded benign results. The patient also underwent a nuclear stress test with low-risk result. The coronary CT angiogram revealed an anomalous right coronary artery arising from the left coronary sinus, with compression of the proximal right coronary artery occurring between the right ventricular outflow tract/proximal pulmonary artery and the aorta.

Conclusion: This case adds to the spectrum of atypical presentations occurring from the anomalous right coronary artery. A concrete understanding of the symptomatology and signs will raise the suspicion of this rare diagnosis among physicians. This will eventually help them to make an early diagnosis and intervene early to prevent malignant arrythmias and sudden cardiac death among these patients.

Differential Expression of Organic Anion Transporting Polypeptides in the Liver and Common Comorbidities: Implication for Toxicity of Microcystins and other Xenobiotics

Margo Bush[1*], James Bassett[1], Alexander Luna[1], K Helminiak[1], Joshua D. Breidenbach[1], Benjamin W. French[1], David Kennedy[2], Steven Haller, PhD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: margo.bush@rockets.utoledo.edu

Keywords: Liver, Harmful Algal Blooms, Xenobiotics

Published: 14 December 2023

Background: Organic Anion Transporting Polypeptides (OATPs) are a family of transporters found throughout the body and encoded by Solute Carrier Organic Anion Transporter (SLCO) genes. The role of OATP in the transport of xenobiotics has gained increased attention due to harmful algal blooms (HABs) and the subsequent release of cyanotoxins like Microcystin-LR (MC-LR) that can harm humans. Exposure is known to cause acute illness including liver injury, however the extent of illness and susceptibility of individuals with common liver disease comorbidities is unknown.

Objectives: We used a differential expression analysis to determine levels of SLCO expression in both healthy individuals and those with common pre-existing liver diseases to understand how hepatic comorbidities may impact susceptibility to HAB cyanotoxin exposures.

Methods: We examined RNA expression levels of OATP related SLCO genes in hepatic tissue across a variety of comorbidities. Differential gene expression data was obtained from the National Center for Biotechnology Information (NCBI), Gene Expression Omnibus (GEO). Search queries in the GEO browser were formatted as "(Disease) AND tissue." Datasets which did not fulfill "disease vs. healthy" criteria were omitted. Differential Expression Analysis was performed using NCBI's integrated GEO2R software.

Results: Liver tissue exhibited high expression levels of several SLCO isoforms. When compared to non-diseased control liver samples, SLCO expression was decreased in cirrhotic liver, while liver samples obtained from hyperglycemic and diabetic patients as well as patients with

hepatocellular carcinoma demonstrated increased expression of SLCO compared with non-diseased controls.

Conclusion: This data supports the hypothesis that disease states impact the expression level of SLCOs. Decreased expression in cirrhosis suggests a downregulation of OATP as a response to damaged hepatic tissue. Increased expression in hyperglycemic, diabetic, and hepatocellular carcinoma patients aligns with previous studies from our lab and others indicating that these disease states confer increased susceptibility to cyanotoxin exposure.

Hypocomplementemic-urticarial vasculitis syndrome (hvus): A diagnostic dilemma

Masharib Bashar, MD[1*], Aqsa Farooqui, MBBS[2], Halah Al-Fatlawi

[1]Division of Rheumatology, Department of Medicine, The University of Toledo,

Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH

43614

*Corresponding author: masharib.bashar@utoledo.edu

Keywords: Rheumatology, Vasculitis, Urticaria, Hypocomplementemia, Bradykinin

Published: 14 December 2023

Introduction: HVUS Is an extremely rare debilitating condition with reported incidence of 0.5/100000. Presence of recurrent and chronic urticarial rash is the dominant clinical finding in HVUS. Exact pathophysiology is unknown, however, it has been demonstrated that immune-complex mediated injury is the predominant mechanism leading to systemic manifestations just like in SLE. It can involve multiple systems and pulmonary involvement is the leading cause of mortality and morbidity in HVUS. This article serves to create more awareness about this rare condition among clinicians and specifically highlights the appropriate diagnostic strategies and treatment options available, with special emphasis on the latest advancements in management as well as ongoing or recent clinical trials regarding treatment of this condition.

Case Presentation: Our patient was a 47-year-old Caucasian female whose initial symptoms started with episodic urticaria which gradually progressed to respiratory symptoms such as hoarseness, chest wall and laryngeal edema. Patient's symptoms occurred gradually and progressed stubbornly over the past 2 years. Her personal and family history was also unremarkable for any autoimmune or rheumatological conditions. She became increasingly resistant to conventional treatment with antihistamines and steroids. During frequent ED visits, her symptoms were partially responsive to fresh frozen plasma, epinephrine and high-dose steroid therapies given together. Outpatient, medications targeting complement and bradykinin-mediated pathways failed to produce any significant improvement. Blood tests were only significant for low complement levels and positive p-ANCA. She suffered immense stress along with delayed diagnosis and multiple failed treatments and multiple negative skin biopsies, before finally a 3rd skin biopsy, clinched the above diagnosis.

Conclusion: This case serves to highlight the insidious and non-specific nature of this morbid condition along with the common mimics for this condition. The role of skin biopsy is extremely important in the diagnosis along with the utility of multiple skin biopsies. Even after initial negative biopsies, the finding of low complement along with recurrent urticarial rash, should have alerted the clinicians much earlier about this rare condition and would had allowed earlier treatment. Lastly, this case also highlights the

experimental nature of most drugs which are currently employed in treating HVUS. Treatment of HVUS currently usually employs different types of immunosuppressants and nowadays, biologics are being increasingly used to block functionality of different cytokines.

A Case of Bullous Systemic Lupus Erythematosus

Matthew Niedoba[1], Sahithi Chinnam[1*], Alborz Sherafati[2], Andrew Teletnick, Natalie Tuttle, and Anu Garg[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614
[2]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614
[3]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: schinna@rockets.utoledo.edu

Keywords: Bullous Lupus

Published: 14 December 2023

Introduction: Bullous systemic lupus erythematosus (BSLE) is a rare manifestation of systemic lupus erythematosus (SLE) with an incidence of 3.4 cases per million per year. (1) It primarily affects females, and adults between 20 and 40. BSLE manifests with vesicles and bullae that affect the trunk, head, neck, arms, legs, and mucosal membranes (2). Most lesions resolve with hyper/hypo-pigmentation without scarring or milia, but milia occurs in 21% of cases and scarring occurs in 16% of cases. The criteria for diagnosis of BSLE:

1. Acute onset of vesicles and/or bullae on normal or erythematous skin

2. Histopathology of subepidermal blistering with neutrophil-dominant infiltrate in superficial dermis

3. Direct immunofluorescence of linear or granular immunoglobulin at basement membrane

4. Elevated antinuclear antibody

5. Exclusion of other causes (3)

Prior diagnosis of SLE is supportive of but not required for diagnosis of BSLE since it may be the first manifestation of SLE. First-line treatment for BSLE is dapsone which has an efficacy of 90%. Second-line treatment for patients unresponsive or who cannot tolerate dapsone include: glucocorticoids, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, methotrexate, and rituximab (2).

Case Presentation: A 19-year-old female with a history of systemic lupus erythematosus, lupus nephritis, anemia of chronic disease, chronic impetigo, and history of septic shock secondary to Streptococcus pyogenes two months ago presents with bilateral lower extremity swelling with bullous lesions. The patient's symptoms started one week ago and have progressively worsened. The patient reports her bullous lesions begin as fluid-filled blisters that leave scars when they reduce. The patient was on prednisone, mycophenolate mofetil, and hydroxychloroquine for systemic lupus erythematosus

prior to admission. The patient's SLE has manifested with diffuse joint pain and skin rash. The patient is positive for antinuclear antibody, anti-chromatin IgG, anti-dsDNA, anti-RNP, and anti-Smith with low complement levels. Skin punch biopsies were performed on the left anterior thigh. Histopathology shows vacuolar interface dermatitis with subepidermal splitting with lymphocyte infiltrate in superficial dermis. Direct immunofluorescence was negative for IgG, IgG4, IgM, and IgA and showed discontinuous weak granular deposits of C3 at the basement membrane and non-specific deposits of fibrinogen in connective tissue. Patient was treated with dapsone, which provided significant improvements in skin lesions.

Conclusion: Bullous systemic lupus erythematosus is a rare manifestation of SLE that should be considered as a differential diagnosis for vesiculobullous lesions in patients with SLE. BSLE must be

differentiated from other cutaneous bullous skin lesions including bullous pemphigoid, linear IgA dermatosis, pemphigoid gestationis, and epidermolysis bullosa acquisita. While scarring is not a sequela for most cases of BSLE, it should not be considered a cause for ruling out. In this case presentation, a diagnosis of BSLE was made based on patient history, clinical presentation, antibodies, and histopathology in the setting of negative direct immunofluorescence. Criteria for diagnosis of BSLE should consider reassessment for patients with this presentation.

This may be the first manifestation of SLE in patients who have not been diagnosed.

References

1. Bernard, P., Vaillant, L., Labeille, B., Bedane, C., Arbeille, B., Denoeux, J.P., Lorette, G.,

Bonnetblanc, J.M., Prost, C. *Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group*. Arch Dermatol, Jan 1995. **131**(1): pp. 48-52. https://doi.org/10.1001/archderm.1995.01690130050009

2. de Risi-Pugliese, T., Cohen Aubart, F., Haroche, J., Moguelet, P., Grootenboer-Mignot, S., Mathian, A.,
Ingen-Housz-Oro, S., Hie, M., Wendremaire, N., Aucouturier, F., Lepelletier, F., Miyara, M., Bader-Meunier, B., Rémy, P., Fabien, N., Francès, C., Barete, S., Amoura, Z. *Clinical, histological, immunological presentations and outcomes of bullous systemic lupus erythematosus: 10 New cases and a literature review of 118 cases*. Semin Arthriti Rheum, 2018 Aug. **48**(1): pp. 83-89. Doi: 10.1016/j.semarthrit.2017.11.003

3. Odonwodo, A., Vashisht, P. *Bullous Systemic Lupus Erythematosus*. 2023 May 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.

Unveiling the Silent Constrictor: A Case Report of Takayasu Arteritis Manifesting as a Vascular Enigma

Vanessa Pasadyn, BA[1*], Samantha Davis, MD[2], Rawish Fatima, MD[3], Nezam Altorok, MD[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: vanessa.pasadyn@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Takayasu arteritis (TKA) is a rare large vessel vasculitis, most prevalent in Asia and affecting females ages 10-40 years. Through unclear etiology, it triggers chronic granulomatous inflammation leading to vessel wall thickening, stenosis, and occlusion. Manifestations vary from mild malaise to severe ischemic complications. Diagnosis hinges on clinical criteria, including angiography, and exclusion of mimicking conditions like giant cell arteritis, fibromuscular dysplasia, or atherosclerosis. Treatment necessitates immunosuppression and anti-inflammatories to curb disease progression and limit complications.

Case Presentation: A 61-year-old Caucasian female presented with claudication of the upper extremities upon using the shower. She reported episodes of headache, myalgia, fever and chills of several months. She reported fatigue with overhead reaching and difficulty finding her pulse on her upper extremities. Labs were notable for elevated ESR and CRP. MRA chest showed smoky thickened appearance of the descending aorta wall, some missing wall thickening in origins of the left common carotid and left subclavian arteries. PET scan revealed diffuse hypermetabolic activity involving the bilateral common carotid arteries, peripheral aortic arch and descending thoracic aorta.

With these ongoing symptoms and characteristic features on imaging, we established the diagnosis of TKA. She was started on 5mg oral prednisone daily and methotrexate 10mg weekly with daily folic acid.

Conclusion: This case highlights the diagnosis and treatment of a rare condition, Takayasu arteritis, the pulseless disease. TKA is a challenging condition to study and understand fully, but advancements in medical knowledge, imaging, and management are gradually improving our understanding and ability to diagnose and treat this condition. With increased awareness of this condition, earlier detection and monitoring will serve to benefit future patient populations.

https://dx.doi.org/10.46570/utjms.vol11-2023-889

Polyarteritis Nodosa Presenting With Abdominal Pain and Mesenteric Stenosis

Jerrin George[1*], Avish Persaud[1], Nezam Altorok, MD[2], Nathaniel Gilbert, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Allergy, Rheumatology, and Immunology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: jgeorge17@rockets.utoledo.edu

Keywords: Polyarteritis Nodosoa
Published: 14 December 2023

Introduction: Polyarteritis nodosa (PAN) is a rare medium-vessel vasculitis that occurs in about 0.003% in the United States annually (1). Mesenteric vasculitis due to PAN presents as an atypical but life-threatening cause of bowel ischemia and acute abdomen (2). We present a unique case of PAN with several complications and unusual findings on imaging.

Case Presentation: Our patient is a 43-year-old female who presented to the emergency department with abdominal pain. She had persistently elevated blood pressures in the range of 200/100. Computerized tomography (CT) of the abdomen demonstrated segmental occlusion of the proximal celiac artery, small intimal dissection flap of the superior mesenteric artery (SMA), a 6mm focal pseudoaneurysm that had enlarged in size over 3 months, high-grade luminal narrowing of the SMA, right hepatic artery occlusion, right renal artery occlusion, and a small infrarenal aortic dissection. Laboratory workup was negative for antineutrophilic cytoplasmic antibody. In addition, she had an elevated C-reactive protein of 2.8 (units), an erythrocyte sedimentation rate of 50 (units), and proteinuria of 0.5 grams daily. PET CT scan confirmed metabolic activity in the vasculature described above. She was started on a prednisone taper at 20 mg for 15 days for concerns of PAN with reduction in her pain that was previously refractory to opioids. The patient was treated successfully with a tapering dose of dexamethasone starting at 6 mg twice daily and azathioprine 150 mg daily.

Conclusions: Treated PAN has a five-year survival of 80%, while untreated PAN has a survival of 13% (3), making the workup and diagnosis of PAN urgent to reduce mortality (4). Life-threatening complications and poor indicators of prognosis for untreated PAN include ischemia, dissection, or pseudoaneurysm of multiple arteries, as well as hypertensive urgency and proteinuria (5). Early detection and treatment for PAN is essential to improve health outcomes, reduce complications, and improve mortality.

References:

1. Stanton M, Tiwari V. Polyarteritis Nodosa. 2023 Feb 22. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.

2. Asti E, Pogliani L, Tritella S, Bonavina L. *Polyarteritis nodosa and acute abdomen: A role for laparoscopy?* Int J Surg Case Rep, 2015. **17**: pp.161-3. doi: 10.1016/j.ijscr.2015.11.007

3. Springer JM, Byram K. *Polyarteritis nodosa: an evolving primary systemic vasculitis*. Postgrad Med, 2023 Jan. **135**(sup1): pp. 61-68. doi: 10.1080/00325481.2022.2088940

4. Levine SM, Hellmann DB, Stone JH. *Gastrointestinal involvement in polyarteritis nodosa (1986-2000): presentation and outcomes in 24 patients*. Am J Med, 2002 Apr 1. **112**(5): pp.386-91. doi: 10.1016/s0002-9343(01)01131-7

5. Matsuo S, Hayashi K, Morimoto E, Kato A, Sada KE, Watanabe H, Takano-Narazaki M, Sunahori-Watanabe K, Kawabata T, Wada J. *The Successful Treatment of Refractory Polyarteritis Nodosa Using Infliximab*. Intern Med, 2017. **56**(11): pp. 1435-1438. doi: 10.2169/internalmedicine.56.8235

Differential Expression of Organic Anion Transporting Polypeptides in the Kidney: Implication for Cyanotoxins Toxicity

Margo Bush[1*], James Bassett, Alexander Luna[1], Kathryn Helminiak[1], Joshua D. Breidenbach[1], Benjamin W. French[1], Steven Haller[2], David Kennedy[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: margo.bush@rockets.utoledo.edu

Keywords: OATPs, Microcystins, HABs, SLCO, Renal

Published: 14 December 2023

Background: Organic Anion Transporting Polypeptides (OATPs) are a family of transporters found throughout the body and encoded by Solute Carrier Organic Anion Transporter (SLCO) genes. The role of OATP's has gained increased attention due to harmful algal blooms (HABs). We have previously demonstrated the kidney is a major target organ of HAB cyanotoxins, however the impact of common kidney comorbidities on OATP transporters is unknown.

Objectives: We used a differential expression analysis to determine levels of SLCO expression in both healthy individuals and those with common pre-existing kidney disease to understand how renal comorbidities may impact susceptibility to HAB cyanotoxin exposures.

Methods: We examined expression levels of OATP related SLCO genes in renal tissue from 230 participants across a variety of comorbidities. Differential gene expression data was obtained and analyzed through the National Center for Biotechnology Information (NCBI), Gene Expression Omnibus (GEO). Search queries in the GEO browser were formatted as "(Disease) AND tissue." Datasets which did not fulfill "disease vs. healthy" criteria were omitted.

Results: Renal tissue exhibited a similar pattern of expression of SLCO isoforms to other major organs with the highest level of expression for SLCO isoforms 2A1, 2B1, and 4C1. When compared to non-diseased controls, patients with diabetic nephropathy demonstrated significant ($p<0.01$) increases in glomerular expression of SLCO isoforms 1B1, 2B1, and 4C1 as well as tubulointerstitial increases in expression of SLCO3A1. There was also mild downregulation of SLCOs 1A2, 1C1, 2B1, and 5A1.

Conclusion: This data supports the hypothesis that disease states impact the expression level of key transporters for cyanotoxins in the kidney. Increased expression in both the glomerular and tubulointerstitial expression of OATP transporters in patients with diabetic nephropathy agrees with experimental evidence suggesting an increased susceptibility to renal injury after cyanotoxin exposure in diabetic models.

Bridging Health Gaps in Central America: Identifying Prevalent Diagnoses Across University of Toledo Medical Missions for Improving Targeting of Treatment

James Bassett[1*], Jennida Chan[1], Jennifer Kim[1], Richard Paat[2],

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: jbasset@rockets.utoledo.edu

Keywords: Medical Missions, Health Outcomes, Centers for Disease Control and Prevention

Published**:** 14 December 2023

Introduction: International medical mission trips commonly have a goal to provide care to underserved populations in developing countries. Despite the recent increase in the number of international medical mission trips and the services they provide, there is limited literature outlining the impact of the mission trips and how it aligns with the needs of the countries they serve.

Objectives: The main objective of this study was to determine the top diagnoses during recent medical mission trips and compare them with the most prevalent health concerns reported within that country. A secondary objective is to inform preparation for future medical mission trips.

Methods: Volunteers from the medical triage team collected basic patient health information on paper print-outs, noting vitals and reason for visit. Care teams updated each patient print-out with diagnose(s), treatment plan, and any relevant prescriptions. Students uploaded each patient record, removing patient identifiers.

Results: From January 2022 to July 2023, University of Toledo students collected data on two mission trips to Guatemala and one to Honduras. 2,740 patients were treated in total. In Guatemala, top diagnoses included headache (8.8%), dental conditions (7.5%), parasites (7.4%), and arthritis (7.2%) (ICD-10 codes R51, Z98, B89, and M13.80). As a result, the top treatments focused on pain and inflammation including ibuprofen (11.6%) and acetaminophen (10.3%). In Honduras, pain and GERD easily led the group (18.8% and 17.1%, respectively) with allergies (11.2%) and headache (10.2%) also common (ICD-10 codes M79, K21.9, J30.2, and R51).

Conclusion: Our data indicates a high prevalence of disease in Central America that is treatable and amenable to short-term mission-oriented intervention. However, there was little overlap of the most common diagnoses when compared to the CDC's top five priority health conditions listed for Central

America: anemia, Chagas disease, mental health, obesity, and parasite infection. Further studies should explore these differences to address the country's needs more effectively from within and on future medical missions.

Dr. Lance D. Dworkin Department of Medicine Research Symposium

Comparison of TP53 mutation prevalence in human blood cells from lung cancer patients and control subjects

Patrick T. Gorman[1], Erin L. Crawford, MD[2], Daniel J. Craig, MD[2], and James C. Willey, MD[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Pulmonary and Critical Care, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: patrick.gorman2@rockets.utoledo.edu

Keywords: Lung Cancer, TP53, Biomarker

Published: 14 December 2023

Early detection and diagnosis of lung cancer is a crucial component of treatment and increasing survival odds. Our previous research demonstrated the utility of mutation prevalence of the TP53 gene in bronchial epithelial cells as an indicator of lung cancer risk. The purpose of our research was to determine if TP53 mutation prevalence in peripheral blood cells is a useful marker for determining lung cancer status. We used genomic DNA (gDNA) extracted from blood cells to examine TP53 mutation status and prevalence in lung cancer and non-cancer (control) groups. Samples from cases and controls were selected as pairs based on age, sex, race, smoking status, and smoking history expressed in pack-years. gDNA was extracted from buffy coat samples, target sequences were amplified via PCR, and two sequencing libraries were created. Both libraries have been sequenced: Approximately 28 million reads were obtained from each library with approximately 94.4% %Q30. Bioinformatic analysis is in progress to enable a comparison of TP53 mutation prevalence in cancer and non-cancer groups. If TP53 mutations are more common in the cancer group, it may suggest that mutation prevalence in gDNA collected from peripheral blood can be used as a marker of lung cancer status.

A Case of Nivolumab-induced Hypophysitis in a 72-year-old Female with Metastatic Melanoma

Vikhyathi Pallerla, MS[1*], Avish Persaud, MS[1], Divya Vijendra, MD[2],

[1]College of Medicine and Life Sciences The University of Toledo, Toledo, OH 43614

[2]Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: vikhyathi.pallerla@rockets.utoledo.edu

Keywords: Hypophysitis, Hematology/Oncology, Melanoma, Metastatic Cancer, Complications of Immunotherapy

Published: 14 December 2023

Introduction: Hypophysitis is a rare condition in which inflammation in the suprasellar region leads to pituitary gland insufficiency, affecting both its hormonal activity as well as potentially causing mass effect on surrounding structures (1). There are various etiologies of this condition including lymphocytic, granulomatous, IgG4-related, and xanthomatous, but it has been commonly confused for other pituitary conditions such as pituitary adenomas due to its similar presentation (2).

Case Report: We present a case of a 72-year-old female with metastatic melanoma of the lower extremity undergoing Nivolumab immunotherapy. She presented to her oncologist with notable hypotension and one week history of severe fatigue and dizziness, prompting an emergent workup. An MRI was performed and read as a pituitary adenoma, but the high suspicion of immunotherapy-related toxicity led to a CMP showing severe hyponatremia reaching 124 mmol/L, low cortisol, and low ACTH. These findings led to the rare diagnosis of Nivolumab-induced hypophysitis. She was started on prednisolone while in the hospital, but was switched to a tapering dose of hydrocortisone and referred to endocrinology upon discharge to further manage her adrenocortical insufficiency. Eventually, her dose of hydrocortisone was tapered down to physiologic dose and she was educated on the importance of adjusting her dose in the case of acute illness.

Conclusion: Immunotherapy has revolutionized the treatment of cancer over time, but with its remarkable improvements come immune-mediated side effects. Due to the immune-mediated nature of hypophysitis, it can be reasonably deduced that immunomodulation can predispose to its development. The long-term hormonal and systemic complications outlined in this case are severe enough to require hospitalization. The severity of complications highlights the importance of developing a high level of suspicion for treatment-related toxicity and in this case, an irreversible effect such as pituitary failure. However, identifying this complication early allowed for our patient to resume her treatment with

Nivolumab along with the supplementation of pituitary hormones, effectively treating both her pituitary dysfunction and her melanoma while reducing both morbidity and mortality.

References

1. Gubbi S, Hannah-Shmouni F, Verbalis JG, Koch CA. *Hypophysitis: An update on the novel forms, diagnosis and management of disorders of pituitary inflammation*. Best Practice & Research Clinical Endocrinology & Metabolism. 2019; **33**(6): p. 101371. doi:10.1016/j.beem.2019.101371

2. Imga NN, Yildirim AE, Baser OO, Berker D. *Clinical and hormonal characteristics of patients with different types of hypophysitis: a single-center experience*. Arch Endocrinol Metab. 2019; **63**(1): pp. 47-52. doi:10.20945/2359-3997000000102

A Case of Enterococcus Infective Endocarditis Following Parasitic Gastroenteritis in a Previously Healthy 20-Year-Old Male

Marwa Hassan[1*], Vikhyathi Pallerla, MS[1], Adeel Tausif[1], Mona Mahmoud, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Marwa.Hassan@rockets.utoledo.edu

Keywords: Infective Endocarditis, Enterococcus, Cardiology, Gastroenterology

Published: 14 December 2023

Introduction: Infective endocarditis is a life-threatening condition stemming from various bacterial and viral origins, presenting most commonly in hospital settings. The most common bacterial pathogens contributing to the development of infective endocarditis include staphylococci and streptococci, with Enterococcus faecalis being the third most common cause (1). Enterococcus faecalis is a part of normal gastrointestinal and genitourinary flora but can sometimes extravasate into the bloodstream following damage to the gut mucosa due to trauma, malignancy, or infection (2). The resultant Enterococcus bacteremia predisposes patients to infective endocarditis (3). Enterococcus faecalis contributes to the development of about 5-10% of infective endocarditis cases, and presents predominantly in elderly males as a subacute illness (1).

Case Report: We present a rare case of a 20-year-old male patient with a history of parasitic gastroenteritis six months prior to presenting with symptoms of infective Enterococcus faecalis endocarditis involving the atrial surface of the anterior leaflet of the mitral valve. The gastroenteritis was preceded by a history of travel to Cancun and consumption of octopus, which was suspected to be the source of the gastrointestinal infection.

Conclusion: Enterococcus faecalis tends to lead to infective endocarditis and septicemia primarily in elderly males or patients with in-hospital procedures that can introduce the bacteria into the bloodstream (4). Our case illustrates an exception in which a previously healthy, young male experienced gut mucosal damage allowing Enterococcus faecalis to invade and spread hematogenously to his heart.

References

1. Liesman RM, Pritt BS, Maleszewski JJ, Patel R. *Laboratory Diagnosis of Infective Endocarditis*. J Clin Microbiol, 2017 Sep. **55**(9): pp.2599-2608. doi: 10.1128/JCM.00635-17. Epub 2017 Jun 28. PMID: 28659319; PMCID: PMC5648697. https://pubmed.ncbi.nlm.nih.gov/28659319/

2. Dubin K, Pamer EG. *Enterococci and Their Interactions with the Intestinal Microbiome*. Microbiol Spectr, 2014 Nov. **5**(6): pp. 10.1128/microbiolspec.BAD-0014-2016. doi: 10.1128/microbiolspec.BAD-0014-2016. PMID: 29125098; PMCID: PMC5691600. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5691600/

3. Berge, A., Krantz, A., Östlund, H., Nauclér, P., Rasmussen, M. *The DENOVA score efficiently identifies patients with monomicrobial Enterococcus faecalis bacteremia where echocardiography is not necessary*. Infection, 2019. **47**: pp. 45–50. https://doi.org/10.1007/s15010-018-1208-3

4. Megran DW. *Enterococcal endocarditis*. Clin Infect Dis, 1992 Jul. **15**(1): pp. 63-71. doi: 10.1093/clinids/15.1.63. PMID: 1617074. https://pubmed.ncbi.nlm.nih.gov/1617074/

Dr. Lance D. Dworkin Department of Medicine Research Symposium

A Case of a 25-year-old Male with Pituitary and Hypothalamic Extension of Recurrent Anaplastic Astrocytoma

Avish Persaud, MS[1*], Vikhyathi Pallerla, MS[1], Dr. Divya Vijendra MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Hematology and Oncology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: avish.persaud@rockets.utoledo.edu

Keywords: Astrocytoma, Pituitary Dysfunction, Hematology/Oncology, Endocrinology

Published: 14 December 2023

Introduction: Although brain tumors are most commonly metastatic, primary brain tumors can present due to various local cellular etiologies. Astrocytoma is a type of glioma comprising of astrocytes, which are cells responsible for assisting various essential neuronal processes but also proliferate in response to cellular insults, occasionally leading to pathologic growth (1). These gliomas can range from low-grade pilocytic astrocytoma to high-grade, rapidly-growing glioblastomas and anaplastic astrocytoma (2). Anaplastic astrocytoma most commonly present in the 40s, have a dismal prognosis, and can be distinguished from glioblastoma due to lack of endothelial proliferation or surrounding necrosis (3).

Case Report: We present a unique case of a 25-year-old male with history of recurrent WHO grade three primary CNS anaplastic astrocytoma of the right parietal lobe. The tumor has an IDH1-R132H mutation present, ATRX mutation, unmethylated MGMT promoter, and no deletion of 1p and 19q. Patient had a right frontal craniotomy in 2016, followed by chemoradiation with temozolomide for six months. In 2021, he had a recurrence that presented with seizures, prompting treatment by radiation and temozolomide for 11 months with the seizures being controlled. MRIs done in 2023 showed a new expanding mass at the floor of the anterior third ventricle/prepontine cistern, corpus callosum, pituitary infundibulum and hypothalamus. The extension into the pituitary infundibulum led to a concern for hypopituitarism, prompting testing of pituitary hormone levels which revealed low FSH and LH, testosterone, and cortisol.

Conclusion: Although there have been rare instances of anaplastic astrocytoma coexisting with pituitary macroadenomas, there have not been many reported cases of an anaplastic astrocytoma spreading to the suprasellar region (4). This case illustrates a novel, important factor to consider in evaluating astrocytoma and other base of skull tumors which includes considering the possibility of pituitary dysfunction.

References

1. Sofroniew MV, Vinters HV. *Astrocytes: biology and pathology*. Acta Neuropathol, 2010. **119**(1): pp. 7-35. doi:10.1007/s00401-009-06198 https://pubmed.ncbi.nlm.nih.gov/20012068/

2. Perkins A, Liu G. *Primary Brain Tumors in Adults: Diagnosis and Treatment*. Am Fam Physician, 2016. **93**(3):211-217. https://pubmed.ncbi.nlm.nih.gov/26926614/

3. Grimm SA, Chamberlain MC. *Anaplastic astrocytoma*. CNS Oncol, 2016. **5**(3): pp.145-157. doi:10.2217/cns-2016-0002 https://pubmed.ncbi.nlm.nih.gov/27230974/

4. Naik H, Vernon V, Gade P, Bhople L, Guha A. *Anaplastic astrocytoma and pituitary macroadenoma within the same patient: A rare case of intracranial collision tumor*. Neurol India, 2018. **66**(3): pp. 857-860. doi:10.4103/0028-3886.232341 https://pubmed.ncbi.nlm.nih.gov/29766961/

Epigenetic Repression of eNOS in Scleroderma (SSc) Microvascular Endothelial Cells (MVECs) is Related to the Downregulation of MicroRNA-152 by Enhanced DNA Methyltransferase 1 (Dnmt1) Expression.

Yongqing Wang[1*], Bashar Kahaleh, MD[2]

[1]Division of Rheumatology , Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author:

Keywords:
Published: 14 December 2023

Objectives: Alteration in Scleroderma (SSc)-microvascular endothelial cells (MVEC) is related to epigenetic influences on gene expression level. Nitric oxide synthase gene (NOS3) repression is a prime example of epigenetic alteration of SSc-MVEC phenotype. The underlying mechanism of epigenetic imprinting in SSc-MVEC remains unknown. MicroRNAs (miRNAs), which are noncoding RNAs that regulate gene expression, are involved in diverse biological functions, including epigenetics regulation. It has been reported that downregulation of microRNA-152 induces aberrant DNA methylation by targeting the maintenance methyl transferase Dnmt1. In this study, we investigated miRNA-152 expression levels in SSc-MVEC and whether it is involved in the regulation of epigenetic imprinting in SSc.

Methods: MVEC cells were isolated from skin biopsies of SSc patients and matched control subjects. The NOS3, Dnmt1, and miR-152 expression levels in normal and SSc-MVEC were checked by real-time PCR. The epigenetic regulation of NOS3 was examined by the addition of DNA methyltransferase and histone deacetylase inhibitors to MVEC cultures and by analysis of CpG site methylation in the NOS3 promotor region. The effect of Dnmt1 on NOS3 mRNA expression was examined by transfecting SSc- MVEC with Dnmt1-specific siRNA and irrelevant control siRNA. The effect of miR-152 on Dnmt1 mRNA and NOS3 expression was examined by transfecting hsa-miR-152 into SSc-MVEC and transfecting miR-152 inhibitor into control- MVEC.

Results: A significant increase in Dnmt1 expression levels and a significant decrease in NOS3 expression levels were noted in SSc-MVEC. The addition of 2-deoxy-5-azacytidine and Trichostatin A to SSc-MVEC cultures normalized NOS3 expression levels. CpG sites in the NOS3 promoter were methylated in SSc-MVEC but not in control-MVEC. Transfection of SSc-MVEC with siRNA specific

for Dnmt1 resulted in an 80% decrease in the expression levels and an increase in the NOS3 expression level. Since DNMT1 is one of the predicted direct targets of miR-152, we investigated the expression levels of miR-152 in SSc and control MVEC. Levels were significantly down-regulated in SSc-MVEC and were inversely correlated to DNMT1 expression levels. Forced expression of miR-152 in SSc-MVEC led to a reduction in DNMT1 expression at the mRNA level in comparison with the negative control, while inhibition of miR-152 expression in control-MVEC enhanced DNMT1 expression levels in association with reduced NOS3 expression level.

Conclusion: *NOS3* expression level is down-regulated in SSc-MVEC and correlated with its promoter methylation. Dnmt1 expression is up-regulated in SSc-MVEC and inversely correlated to *NOS3* expression levels. miR-152 expression is downregulated in SSc-MVEC and inversely correlates with DNMT1 and relative correlates with *NOS3* expression levels. miR-152 may play a causal role in DNA methylation changes in SSc-MVEC through targeting Dnmt1.

References:

1. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. *Arthritis Rheum*, 2013 Aug. **65**(8):1953-62. Doi:10.1002/art.37988

2. Altorok, N., & Kahaleh, B. Epigenetics and systemic sclerosis: An answer to disease onset and evolution? *European journal of rheumatology*, 2020. **7**(Suppl 3), S147–S156. Doi: 10.5152/eurjrheum.2020.19112

PAVER: Pathway Analysis Visualization with Embedding Representations

William Ryan[1*], Ali Sajid Imami, MD[1], Hunter Eby[1], Robert McCullumsmith, MD, PhD[2,3], Rammohan Shukla, PhD[2]

[1]College of Medicine and Life Sciences, University of Toledo, Toledo, OH 43614
[2]Department of Neurosciences, The University of Toledo, Toledo, OH 43614
[3]Department of Psychiatry, The University of Toledo, Toledo, OH 43614

*Corresponding author: wryan3@rockets.utoledo.edu

Keywords: Bioinformatics, Pathway Analysis, Gene Ontology, Omics
Published: 14 December 2023

Interpreting pathway analysis often poses a significant challenge due to the extensive lists of gene ontology (GO) terms that require meticulous manual curation to identify underlying themes. We developed PAVER, a novel R software package, to address this issue by automating theme generation and clustering of GO terms. By utilizing embedding representations and advanced machine learning techniques, PAVER discerns patterns within the GO terms, creating an intuitive visual landscape of clusters for ease of functional interpretation. This method significantly minimizes the time and effort traditionally required for manual curation. We applied PAVER to a previously published dataset, where it demonstrated robustness by generating themes that closely mirrored those produced by manual curation. With PAVER, we present a powerful tool that not only enhances the efficiency of pathway analysis but also broadens its accessibility across various fields, including disease pathway modeling, drug target identification, and comparative genomics. Our work with PAVER marks a significant step towards simplifying the pathway analysis interpretation process in bioinformatics research.

Cyanobacterial Detection in Human Kidney Formalin-Fixed Paraffin Embedded Specimens from Cancer and Non-Cancer Populations

Anish Sharma[1], Sara Kazmi[1], Bella Khatib-Shahidi[1], John Najjar[1], Caitlin Murphy[1], Humza Bashir[1], Julissa Vargas[1], Bivek Timalsina[1], Apurva Lad, PhD[1], David J. Kennedy, PhD[2], Steven T. Haller, PhD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: asharma26@rockets.utoledo.edu

Keywords: Cyanotoxin, Renal Cell Carcinoma, Microcystin, Inflammation

Published: 14 December 2023

Introduction: Harmful algal blooms (HABs) are uncontrolled outbreaks of cyanobacterial growth that thrive in warm waters. HABs pose a serious health risk to humans due to the release of cyanotoxins produced by cyanobacteria. We and others have demonstrated that the kidney is a key target organ for cyanotoxin induced injury and that these cyanotoxins are capable of activating key oncogenic genes in renal cells in vitro. However, the effects of cyanotoxin exposure in humans with renal cancer is poorly understood.

Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) kidney tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in renal cell carcinoma (RCC).

Methods: DNA and RNA were extracted using an optimized extraction/purification protocol designed for Formalin-fixed paraffin-embedded (FFPE) kidney tissues from RCC (n=13) and age and sex matched non-RCC controls (n=3). Presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.

Results: Cyanobacteria levels were elevated in RCC compared to non-RCC (1.0±0.34 vs 1.3±.26) although this was not statistically significant. Interestingly, while markers of inflammation and angiogenesis were not significantly correlated with cyanobacterial load overall in both cancer and non-

cancer samples, cyanobacterial load was positively correlated with Transforming Growth Factor-beta in all patients (r=0.5452, p=0.0013) as well as within the RCC cohort (r=0.5320, p=0.0052).

Conclusion: Our results suggest that cyanobacteria may be increased in the setting of RCC and impact the expression of key tissue remodeling genes within these tumors. This data is in agreement with clinical and experimental evidence suggesting an association between cyanobacteria and cancer progression in other settings and supports the need to investigate the potential role of cyanobacteria in renal cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

Treprostinil inhibits functional activation of scleroderma (SSc) vascular smooth muscle cells (vSMCs) by inhibiting Yap and activating PPARG signaling.

Yongqing Wang[1*] and Bashar Kahaleh, MD[1]

[1]Division of Allergy, Rheumatology, and Immunology, Department of Medicine,
The University of Toledo, Toledo, OH 43614

*Corresponding author: yongqing.wang2@utoledo.edu

Keywords: Vascular Smooth Cells, Scleroderma Vascular Disease

Published: 14 December 2023

Background: Progressive vascular wall thickness and fibrosis are the hallmarks of SSc vasculopathy. Overexpression of TGFB1 in SSc and activation of vSMCs are important steps in the pathogenesis of SSc vascular disease.

Objectives: In this study, we examined the expression levels of COL1, PCNA, PFKP, IP, EP2, IP, and PTGIS in SSc skin, the effects of Treprostinil (prostacyclin analog) on cell proliferation, TGFB1-induced collagen expression in SSc-vSMCs, PPARG expression and Yap nuclear translocation.

Methods: SSc and control skin biopsies were fixed and 10uM serial sections were cut for histological examination. vSMCs were isolated from involved skin and matched healthy subjects. The expression and distribution of collagen, PCNA, PFKP, IP, EP2, PTGIS, PPARG, and Yap were measured by immunohistochemical staining or immunofluorescent staining. Cell proliferation was measured by MTT assay. The mRNA expression levels were detected by qPCR.

Results: The protein expression levels of collagen, PCNA, PFKP, and EP2 were increased, while the expression levels of PTGIS and IP were decreased in vSMCs of SSc-skin, compared to the control. These results suggested that defective PGI2-IP signaling in SSc-vSMCs may contribute to vessel wall thickness and vascular fibrosis in SSc. Treprostinil inhibited vSMCs proliferation, COL1A1, and PFKP mRNA expression in SSc-vSMCs in a dose-dependent fashion. Treprostinil also inhibited TGFB1-induced COL1A1 mRNA expression in SSc-vSMCs via engagement of EP2. The PPARG expression was significantly increased in treprostinil-treated SSc-vSMCs. Treprostinil decreased the nuclear location of YAP which is induced by 10%FBS and TGFB1.

Conclusion: Defective PGI2-IP signaling in SSc-vSMCs is associated with enhanced expression of collagen, PCNA, and PFKP in SSc vessel walls. The antiproliferative and antifibrotic activity of treprostinil is mediated through the inhibition of YAP nuclear translocation and enhanced PPARG expression. YAP and PPARG might be promising therapeutic targets for the treatment of SSc-related vasculopathy.

Restoration of Immune Imbalance in Type 1 Diabetes with Simultaneous Notch and eIF5a Inhibition

Shafiya Imtiaz Rafiqi[1*], Ahmad Aldasouqi[1], Sarah Faisal[2], Salauddin Qureshi[1], Sandesh Dewan[1], Aneeba Farooqi[1], Asif Mahmood[1], Shahnawaz Imam[1]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo,

Toledo, OH 43614

[2]Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine,

The University of Toledo, Toledo, OH 43614

*Corresponding author: shafiya.rafiqi@utoledo.edu

Keywords: Autoimmune disorders, Notch signaling, eIF5a signaling, immunomodulation, immune cell plasticity

Published: 14 December 2023

Immune cell plasticity is the ability of immune cells to switch between functional states in response to cytokine milieu. In Type 1 diabetes (T1D), T effector cells attack pancreatic β-cells while T regulatory cells fail to contain this immune attack. The present study explores immune cell plasticity in response to simultaneous treatment with eIF5a (eukaryotic translation initiation factor 5A) inhibitor N1-Guanyl-1-7-diaminoheptane (GC7) and Notch inhibitor anti-DLL4 in human peripheral blood. Delta-like-ligand-4 (DLL4), in the Notch signaling pathway, is a key regulator of cell fate decisions and modulates immune cell behavior, while eIF5a regulates gene expression. Peripheral blood mononuclear cells (PBMCs) were isolated from patients with T1D (n=3-4) and healthy controls. To evaluate the plasticization of these cells into Tregs, Treg deficient CD4 (CD4+CD25-) cells were cultured with GC7(100µM) + anti-DLL4(10µg/ml) + rhGAD65(4µg/ml) for 7 days. Cells were quantified using flow cytometry and compared with conventional stimulation by anti-CD3/CD28 dyna beads. We observed that 60-70% of CD4+CD25- cells were plasticized into T regulatory cells (CD4+CD25+). We also investigated the functional stability of plasticized Tregs compared to freshly isolated naïve T regulatory cells from the same patient. The plasticized T regulatory cells were co-cultured with T-effector cells in Treg: T-effector ratios of 0:1, 1:1, 1:2, and 1:0, and suppression/proliferation was accessed after 5 days. Flow cytometry revealed that plasticized cells expressed regulatory phenotype (CD4+CD25+FoxP3+) and suppressed T-effector cells. We further evaluated GC7+ anti-DLL4 for adverse effects on cell viability for 7 days, demonstrating no significant difference between control and GC7+anti-DLL4 treated groups in terms of live, dead, and apoptotic cells until 48 hrs. However, a significant increase in dead cells post 48 hours in the treated group was observed, and the cellular signature of cells confirmed increased plasticized Tregs (CD4+CD25+FoxP3+) (2-fold) killing T effectors. This experiment provides a means by which previously committed CD4 T cells or intermediate subsets can be pushed to acquire a T regulatory cell phenotype to restore immune imbalance in autoimmune disorders, particularly T1D. This approach of immunomodulation is novel and may, in the future, find its way to clinical trials once confirmed with a larger patient sample dataset.

GELCC Phenotype Database: Familial Lung Cancer Data Across Families

Matthew Orchard[1*], Colette Gaba [2], Erin L. Crawford, MD[2], Christopher I. Amos[3], Uma Ramamurthy[3], James C. Willey, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Baylor College of Medicine, Houston, TX

*Corresponding author: matthew.orchard@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Lung cancer is the leading cause of cancer mortality in the USA while having the second highest incidence rate. Often presenting with aggressive development and rapid lethality, lung cancer is influenced by several environmental factors, including tobacco and arsenic. Furthermore, prior studies illustrate the genetic influences in lung cancer linked to specific genes, such as TP53, RB1, and PARK2 (1, 2). The Genetic Epidemiology of Lung Cancer Consortium (GELCC) is a collective study of data and bio-samples from individuals with strong family history of lung cancer. The data was compiled into a phenotype database.

Results: GELCC features 10 different participating sites with [n = 10,624] database entries: the University of Toledo accounts for [n = 1,951] entries. Prior comparison between sequenced data and pedigrees from the GELCC database (e.g., multipoint linkage analysis) found significant linkages on 6q , which uncovered susceptible genes, such as RGS17, through targeted sequencing analysis (3). Subsequently, it is probable that other genes impacting the incidence of familial lung cancer have yet to be discovered, which the GELCC aims to achieve. To facilitate this aim with the latest and accurate information, numerous records and data were validated and updated in the GELCC database. Five UToledo families, including [n = 729] individuals and 3 new lung cancer cases, were updated or added into the database. Furthermore, family pedigrees were generated for each of these families, and multisite linkage analysis will be completed at the Baylor College of Medicine.

Conclusion: Overall, these pertinent updates alongside performing further linkage analysis can help elucidate and characterize the underlying causes, pathways, and mechanisms influencing familial lung cancer incidence. The characterization can potentially aid in screening at-risk individuals with the goal of increasing early diagnoses that corresponds with better clinical outcomes.

References

1. George, J., Lim, J.S., Jang, S.J., Cun, Y., Ozretić, L., Kong, G, Leenders, F., Lu, X., Fernández-Cuesta, L., Bosco, G., Müller, C., Dahmen, I., Jahchan, N.S., Park, K.S., Yang, D., Karnezis, A.N., Vaka, D., Torres, A., Wang, M.S., Korbel, J.O., Menon, R., Chun, S.M., Kim, D., Wilkerson, M.,

Hayes, N., Engelmann, D., Pützer, B., Bos, M., Michels, S., Vlasic, I., Seidel, D., Pinther, B., Schaub, P., Becker, C., Altmüller, J., Yokota, J., Kohno, T., Iwakawa, R., Tsuta, K., Noguchi, M., Muley, T., Hoffmann, H., Schnabel P.A., Petersen, I., Chen, Y., Soltermann, A., Tischler, V., Choi, C.M., Kim, Y.H., Massion, P.P., Zou, Y., Jovanovic, D., Kontic, M., Wright, G.M., Russell, P.A., Solomon, B., Koch, I., Lindner, M., Muscarella, L.A., la Torre, A., Field, J.K., Jakopovic, M., Knezevic, J., Castaños-Vélez, E., Roz, L., Pastorino, U., Brustugun, O.T., Lund-Iversen, M., Thunnissen, E., Köhler, J., Schuler, M., Botling, J., Sandelin, M., Sanchez-Cespedes, M., Salvesen, H.B., Achter, V., Lang, U., Bogus, M., Schneider, P.M., Zander, T., Ansén, S., Hallek, M., Wolf, J., Vingron, M., Yatabe, Y., Travis, W.D., Nürnberg, P., Reinhardt, C., Perner, S., Heukamp, L., Büttner, R., Haas, S.A., Brambilla, E., Peifer, M., Sage, J., Thomas, R.K. *Comprehensive genomic profiles of small cell lung cancer*. Nature, 2015. **524**(7563): pp. 47-53.

2. Xiong, D., Wang, Y., Kupert, E., Simpson, C., Pinney, S.M., Gaba, C.R., Mandal, D., Schwartz, A.G., Yang, P., de Andrade, M., Pikielny, C., Byun, J., Li, Y., Stambolian, D., Spitz, M.R., Liu, Y., Amos, C.I., Bailey-Wilson, J.E., Anderson, M., You, M. *A recurrent mutation in PARK2 is associated with familial lung cancer*. The American Journal of Human Genetics, 2015. **96**(2): pp. 301-308.

3. You, M., Wang, D., Liu, P., Vikis, H., James, M., Lu, Y., Wang, Y., Wang, M., Chen, Q., Jia, D., Liu, Y., Wen, W., Yang, P., Sun, Z., Pinney, S.M., Zheng, W., Shu, X.O., Long, J., Gao, Y.T., Xiang, Y.B., Chow, W.H., Rothman, N., Petersen, G.M., de Andrade, M., Wu, Y., Cunningham, J.M., Wiest, J.S., Fain, P.R., Schwartz, A.G., Girard, L., Gazdar, A., Gaba, C., Rothschild, H., Mandal, D., Coons, T., Lee, J., Kupert, E., Seminara, D., Minna, J., Bailey-Wilson, J.E., Amos, C.I., Anderson, M.W. *Fine mapping of chromosome 6q23-25 region in familial lung cancer families reveals RGS17 as a likely candidate gene*. Clinical cancer research, 2009. **15**(8): pp. 2666-2674.

A prolonged presentation of cyclic vomiting syndrome in an adult

Audrey Ballard[1*], Andrew Campbell, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: audrey.ballard@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Intractable nausea and vomiting are symptoms commonly encountered in the clinical setting. Patients often experience weight loss, nutritional and electrolyte abnormalities, and emotional stress due to inability to eat, work, or socialize. Cyclic vomiting syndrome (CVS) is defined as recurrent episodes of intense nausea and vomiting episodes that can last anywhere from hours or days. It is a diagnosis by exclusion and there is often a negative workup for infectious or functional causes. Most commonly, it is diagnosed in children but occasionally can manifest in the adult population.

Case Summary: A 44-year-old African American male presented with intractable nausea and vomiting and 42 lbs weight loss for several months. Past medical history included GERD, DVT, AVMs and Morbid Obesity. Patient denied use of marijuana and family history included hypertension, diabetes, and migraines. Initial labs showed hypernatremic at 149, hypokalemic at 3.1, chloride at 107, bicarb at 29. Patient was complaining of dizziness and vertigo accompanying the nausea and vomiting. Patient initially improved following intubation for MRV Brain but returned a few days later. A diagnosis of neuromyelitis optica (NMO) was investigated and the patient was given five days of high dose steroids. However, aquaporin 4 antibody titers were negative and an MRI cervical spine/orbits did not show any signs of NMO. GI workup revealed no obstruction seen on CT enterography and EGD showed grade D esophagitis with erythematous gastric mucosa. No improvement was seen with PPI therapy and primary differential diagnosis was assumed to be intractable nausea and vomiting due to cyclic vomiting syndrome. The patient was started on 25 mg amitriptyline daily which was titrated up to 75 mg daily over a few weeks. With the increasing dose, the patient's nausea and vomiting began to improve and was able to tolerate food by mouth. Patient was discharged after 6 weeks in the hospital with plans for GI follow-up.

Discussion: Cyclic vomiting syndrome is most commonly a pediatric disorder but can occasionally manifest in adults. The cause of CVS is somewhat unknown but is considered to be related to migraines. Other causes have been found to be related to cannabis use, excessive hypothalamic-pituitary-adrenal axis activation, autonomic dysfunction, and mitochondrial DNA mutations (1). Multiple case reports of CVS in adults suggest patients typically have a family history of migraines and episodes begin in early adulthood. Episodes are often triggered by infections, stress, sleep deprivation, menstrual cycles, food allergies, or cannabis use (2). CVS has been described as commonly having four phases: interepisodic,

prodromal, emetic, and recovery. During the interepisodic phase the patient is often symptom free for weeks to months. The prodromal phase is categorized by the patient sensing the start of an episode. Similar to a migraine aura, symptoms during this period include nausea, sweating, abdominal pain, temperature intolerance, food aversion, and irritability. Once an episode begins patients experience the extreme nausea and vomiting that can last from days to weeks. Finally, during the recovery phase, the patient's nausea diminishes as this slowly increases their tolerance for oral intake (3). While it is often a diagnosis of exclusion, there are several diagnostic criteria that can be used to consider the diagnosis such as the Rome IV Criteria which includes 1) stereotypical episodes of vomiting that have an acute onset and a set duration, 2) three or more episodes within a year, and 3) absence of vomiting between episodes. The presence of all three criteria supports the diagnosis of CVS. Management of CVS is typically either prophylactic, abortive and/or supportive (4). Due to the hypothesis of the etiology being related to migraines, standard prophylactic treatment is low-dose amitriptyline. Other studies have shown that topiramate, cyproheptadine, propranolol and erythromycin can also be used as alternative prophylactic treatment (5,6). Supportive medication during an episode is typically intravenous fluids and anti-nausea medications like ondansetron or prochlorperazine. Sumatriptan has been shown to be effective as an abortive agent that can be used during the prodromal phase or during an acute episode (7). Cyclic vomiting syndrome is a minimally understood disorder especially in the adult population and more studies and research are needed to understand the etiology and presentation to hopefully one day minimize the impact on a patient’s health and lives.

References

1. Fleisher DR, Gornowicz B, Adams K, Burch R, Feldman EJ. *Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management*. BMC Med, 2005 Dec 21. **3**: p. 20. doi:10.1186/1741-7015-3-20

2. Al-Mahrouqi T, Al Busaidi SA, Al Alawi AM. *Cyclic Vomiting Syndrome: A Case Report and Mini Literature Review*. Cureus, 2020 Nov 25. **12**(11): p. e11695.

3. Pareek N, Fleisher DR, Abell T. *Cyclic vomiting syndrome: what a gastroenterologist needs to know*. Am J Gastroenterol, 2007. **102**(12): pp. 2832–2840.

4. Davis A, Bryant JH. *Cyclic Vomiting Syndrome*. [Updated 2022 June 21]. In: *StatPearls* [Internet]. 2023, Treasure Island (FL): StatPearls Publishing.

5. Venkatesan T, Levinthal DJ, Tarbell SE, Jaradeh SS, Hasler WL, Issenman RM, Adams KA, Sarosiek I, Stave CD, Sharaf RN, Sultan S, Li BUK. *Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association*. Neurogastroenterol Motil, 2019 Jun. **31**(Suppl 2): p. e13604.

6. Bagherian Z, Yaghini O, Saneian H, Badihian S. *Comparison of the Efficacy of Amitriptyline and Topiramate in Prophylaxis of Cyclic Vomiting Syndrome*. Iran J Child Neurol, 2019 Winter. **13**(1): pp. 37-44.

7. Benson J, Zorn S, Book L. *Sumatriptan in the treatment of cyclic vomiting*. Ann Pharmacother, 1995. **29**(10): pp. 997–999.

Polymyalgia Rheumatica Treated with Sarilumab: A Case Report

Madhavaram, Anvitha R[1*], Bashar, Kahaleh, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Anvitha.Madhavaram@rockets.utoledo.edu

Keywords: Polymyalgia Rheumatica, Sarilumab

Published: 14 December 2023

Background: Polymyalgia rheumatica (PMR) is characterized by bilateral subacute-to-chronic pain and stiffness of the shoulders and hip girdle with an elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein (CRP), and a normal creatinine kinase. Typically, rapid improvement is shown in PMR upon treatment with oral glucocorticoids. However, prolonged use can lead to significant side effects. Methotrexate is often used as a steroid-sparing agent, but some patients may not respond to or tolerate it. This case highlights the potential of sarilumab as a therapeutic option in PMR refractory to both methotrexate and glucocorticoids.

Case Presentation: A 74-year-old white male with chronic PMR presented to the office with continued consistent breakthrough 7/10 PMR pain (with 10 being the most severe) despite treatment with 20 mg prednisone and 20 mg methotrexate for the past six years. Upon presentation three months ago, his prednisone dosage was weaned from 20 mg to 5 mg and methotrexate was discontinued due to increasing breakthrough PMR pain, skin thinning, and decreased wound healing.

Vitals and physical exam findings were within normal limits outside of decreased range of motion of shoulders bilaterally. His latest labs showed an elevated ESR of 37 and CRP level of 15.3 consistent with ongoing PMR. Due to the refractory nature of his symptoms and prolonged steroid use, treatment with sarilumab was initiated.

Conclusion: Sarilumab is a human IgG1 monoclonal antibody that binds to IL-6 receptors, inhibiting IL-6 signaling. Several clinical trials have demonstrated the safety, efficacy, and tolerability of Sarilumab in RA patients (1). Furthermore, studies comparing Sarilumab with Tocilizumab in terms of safety and tolerability found no clinically meaningful differences (2). Sarilumab has a greater affinity to IL-6 than that of tocilizumab, which may even suggest a potential superiority (3).

References

1. Dejaco C, Singh YP, Perel P, Hutchings, A., Camellino, S.M., Abril, A., Bachta, A., Balint, P., Barraclough, K., Bianconi, L., Buttgereit, F., Carsons, S. Ching, D., Cid, M., Cimmino, M.,

Diamantopoulos, A., Docken, W., Duftner, C., Fashanu, B., Gilbert, K., Hildreth, P., Hollywood, J., Jayne, D., Lima, M., Maharaj, A., Mallen, C., Martinez-Taboada, V., Maz, M., Merry, S., Miller, J., Mori, S., Neill, L., Nordborg, E., Nott, J., Padbury, H., Pease, C., Salvarani, C., Schirmer, M., Schmidt, W., Spiera, R., Tronnier, D., Wagner, A., Whitlock, M., Matteson, E.L., Dasgupta, B., European League Against Rheumatism, American College of Rheumatology. *2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative*. Ann Rheum Dis, 2015. **74**(10): pp. 1799-1807. doi:10.1136/annrheumdis-2015-207492

2. Pelechas, E., Voulgari, P.V., Drosos, A.A. *Clinical evaluation of the safety, efficacy, and tolerability of sarilumab in the treatment of moderate to severe rheymatoid arthritis.* Ther Clin Risk Manag, 2019. **15**: pp. 1073-1079. doi:10.2147/tcrm.s167452

3. Devauchelle-Pensec, V., Berthelot, J.M., Cornec, D., Renaudineau, Y., Marhadour, T., Jousse-Joulin, S., Querellou, S., Garrigues, F., De Bandt, M., Gouillou, M., Saraux, A. *Efficacy of first-line tocilizumab therapy in early polymyalgia rheumatica: a prospective longitudinal study*. Ann Rheum Dis, 2016. **75**(8): pp. 1506-1510. doi:10.1136/annrheumdis-2015-208742

Exposure to Microcystin-LR Induces Differential Gene Regulation in Primary Human Keratinocytes

Shereen G. Yassine[1*], Benjamin W. French[1], Steven T. Haller, PhD[2], David J. Kennedy, PhD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: shereen.yassine@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Harmful algal blooms (HABs) are on the rise globally, including in Lake Erie near Toledo. HABs are composed of blue-green algae, or cyanobacteria, which produce cyanotoxins, like microcystins, anatoxins, and saxitoxins, among others. Over 270 congeners of microcystin exist, but microcystin-LR (MC-LR) is most prevalent and potent. Dermal contact represents one of the most common exposure routes to MC-LR and dermal lesions account for a significant majority of HAB exposure symptoms. Despite this, almost no work has been published on the toxicity of microcystins in the skin.

Objectives: Determine potential health impacts in human keratinocytes after exposure to MC-LR, looking at inflammatory markers and structural barrier proteins

Methods: Primary keratinocytes were cultured in 12 well-plates and exposed to 1 or 10 µM MC-LR for 6, 12, and 24 hours (n=3/group). After the exposure periods, cells were subjected to RT-PCR, assessing inflammatory markers and key structural barrier proteins.

Results: 1 uM MC-LR exposure caused a time-dependent increase in the expression of structural barrier proteins involucrin (IVL), loricrin (LOR), and filaggrin (FLG), with this trend reaching significance at 24 hours post-exposure (IVL $p = 0.0007$; LOR $p = 0.0276$; FLG $p < 0.0001$). Similarly, the 10 uM MC-LR exposure induced a stepwise increase in the expression of interleukin 1-beta (IL-1B), with significance increases at 12 ($p = 0.0138$) and 24 hours ($p = 0.001$). The 10 uM exposure additionally caused an initial spike in Tumor Necrosis Factor a expression at 6 hours ($p = 0.0286$), followed by a decrease in expression at 24 hours ($p = 0.0072$).

Conclusions: Our results suggest that MC-LR exposure induces significant activation of key proteins involved in inflammation and the structural integrity of primary human keratinocytes. These findings suggest that microcystins are capable of inducing inflammation in underlying skin lesion phenotypes associated with dermal HAB exposure.

Natural history of type 1 diabetes in humanized mouse model

Ahmad Aldasouqi[1,2], Shafiya Imtiaz Rafiqi DVM, PhD[3,4], Shahnawaz Imam DVM, PhD[3,4*]

[1]College of Natural Sciences and Math, The University of Toledo, Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[3]Division of Diabetes, Endocrinology, and Metabolism, Department of Medicine, The University of Toledo, Toledo, OH 43614

[4]Center for Diabetes and Endocrine Research (CeDER), University of Toledo, Toledo, OH 43614

*Corresponding author: Shahnawaz.imam@utoledo.edu

Keywords: T1D, Type 1 Diabetes, Humanized Mouse Model, T1D Pathophysiology

Published: 14 December 2023

Type 1 diabetes (T1D) is an autoimmune disease caused by an imbalance in T-regulatory and T-effector cells characterized by the destruction of insulin-producing beta cells by diabetogenic T-effector cells, leading to insulin deficiency and complexities like diabetic nephropathy, retinopathy, and neuropathy. Researchers at The University of Toledo have developed a humanized mice model that spontaneously develops T1D at 3-5 weeks and mimics human T1D. This study aims to monitor blood glucose levels before the onset of T1D (pre-weaned stage mice) and track the dynamics of immune cells using flow cytometry throughout the progression of the disease. Our results show that T-regulatory cells constitute 4.773% ± 0.81% cells at preweaning, which significantly ($p<0.05$) drops to 2.60± 0.35 (%) in males and 1.78 ± 0.58 (%) in females at the 10th week, while CD8+ T cells produce interferon-gamma (cytotoxic lymphocytes, CTLs) constitute 3.32 ± 0.60 (%) at preweaning, which increased significantly ($p<0.05$) to 27.625± 1.43 (%) in males and 21.13± 2.87 (%) in females as the disease progresses. This reduction in T-regulatory cells and enrichment of CD8s and CTLs leads to the destruction of beta cells, as seen in humans. Dysregulation of immune responses can be correlated with the progression of diabetes in terms of blood glucose levels, which increased from 147mg/dl (preweaning), which significantly ($p<0.05$) peaked at 373mg/dl in 5th week, and was observed in partial remission stage around the 8th week as observed in human T1D 'honeymoon period.' This study will help us to understand the immune dynamics in the progression of T1D as it helps us to present a better picture of the status of immune cells in a human-like immune system and provides benchmark data of the interplay of the immune system.

Short-term Exposure to Nanoplastic – containing Aerosol Causes Immunodmodulation in Healthy Human Primary Airway Epithelium

Benjamin French[1*], Joshua Breidenbach, PhD[1], Shereen Yassine[1], James Willey[2], Jeffery R. Hammersley, MD[2], Erin Crawford[3], Deepak Malhotra[4], Steve Haller, PhD[1], David Kennedy, PhD[1]

[1]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Division of Pulmonary and Critical Care, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Nephrology, Department of Medicine, The University of Toledo, Toledo, OH 43614

[4]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: bfrench4@rockets.utoledo.edu

Keywords: Pulmonology, Immunology

Published: 14 December 2023

Introduction: As an environmental pollutant, nano-plastics (NP) have been detected in ocean and freshwater ecosystems. NPs are used in a variety of commercial and industrial processes, and larger plastics released into the environment will inevitably break down into NPs. Recent evidence suggests that NP particles become airborne in aerosols generated by natural water body motion. Occupational exposure to various NPs suggest airway irritation, neutrophilic inflammation, translocation, increased risk of lung carcinoma and chronic respiratory disease such as asthma, and even respiratory failure.

Objectives: Determine how a 3-dimensional cell culture model of airway epithelial cells responds to aerosolized NP particles.

Methods: A 3-dimensional cell culture model was constructed using cells pooled from 14 donor patients using a 24 well plate transwell insert format. Each set of cells was exposed to nanoplastic aerosol (2.5% w/v, 0.05 µm mean diameter) or vehicle for 3 minutes per exposure, 3 exposures per day, for 3 days total. Tissue integrity, mucociliary clearance, protein secretion, and chemoattractant potential were all measured post exposure.

Results: No changes to tissue integrity or mucociliary clearance were detected after exposure. However, protein secretion of IL-21, IL-2, IL-15, CXCL10, and TGFß were all significantly decreased after exposure to NP-containing aerosol vs. control (all $p<0.05$)l, while MIP-1a showed a significantly higher secretion from the NP-containing aerosol exposed cells vs. control ($p<0.05$). Additionally, a Boyden

Chamber assay revealed that aerosol exposed cells caused a significantly higher migration of neutrophils.

Conclusion: Aerosolized micro- and nanoplastics are a potential threat to human health, inducing immunomodulatory effects even after short term exposures in healthy human airway epithelium. Those living in areas with high levels of pollution, and those with pre-existing conditions may be at higher risk for inhalation toxicity, which warrants further study.

Dynamics of Peripheral Artery Disease and Influencing Factors in the United States and the World (1999-2020)

Taryn Hibshman[1*], Sishir Doddi[1], Oscar Salichs[1], Rabbia Siddiqi, MD[2]

[1]College of Medicine and Life Sciences, University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo,

Toledo, OH 43614

*Corresponding author: taryn.hibshman@rockets.utoledo.edu

Keywords: Peripheral Artery Disease (PAD), Epidemiology, Incidence, Prevalence, Global Burden of Disease, Public Health, Healthcare Disparities, Disability-Adjusted Life Years (DALYs), Global Heath Diseases Database

Published: 14 December 2023

Introduction: This research explores the evolving epidemiology of Peripheral Artery Disease (PAD) from 1990 to 2019, analyzing trends in global incidence, prevalence, disability-adjusted life years (DALYs), and their variations in the United States (US) and across different socio-demographic contexts. This study provides a comprehensive analysis of PAD's impact on public health, utilizing the Global Burden of Disease (GBD) framework.

Objectives: Our research advances existing knowledge by headlining the unique pattern of PAD trends, as well as emphasizing the higher burden of PAD in high-income countries. Additionally, this study indicates PAD's growing impact on health, irrespective of socio-demographic context, as all countries, regardless of Socio-Demographic Indexes (SDI) status, experience increases in DALYs.

Methods: Data on peripheral artery disease mortality, incidence, prevalence, and DALYs from 1990 to 2019 were sourced from the Global Health Data Exchange (GHDx) database. The Joinpoint Regression Program was used to compute annual percent changes (APC) and overall average annual percent change (AAPC) over the given time period. Confidence intervals for APC were determined using the Grid Search Method with permutation and parametric tests. Identification of significant differences in AAPC trends among groups was conducted through parallel pairwise comparison tests.

Results: Our findings reveal significant upward trends in worldwise PAD prevalence, incidence, and DALYs, paralleling a growing global burden of the disease over this period. In the US, analysis reveals an increase in DALYs, paired with a decrease in both incidence and prevalence. Overall, the US exhibits higher rates of all measured variables attributed to PAD compared to the global population.

Conclusion: Overall, our study enhances the understanding of PAD's epidemiology by contextualizing global and national trends of PAD between 1999 and 2019. By providing a holistic assessment of PAD's advancing burden, this research emphasizes the need for further intervention to address the widespread challenge posed by PAD.

Fecal microbiota transplant is associated with lower risk of mortality, hepatic encephalopathy, ascites, and infection patients with severe alcohol-associated hepatitis: A systematic review and meta-analysis

Zohaib Ahmed[1], Andrew Kelly[1]; Joyce Badal[2], Wade M. Lee-Smith[3], Manesh Gangwani[1], Yaseen Alastal[1], Mona Hassan[1].

[1]Division of Gastroenterology, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[3]College of University Libraries, The University of Toledo, Toledo, OH 43614

*Corresponding author: zohaib.ahmed@utoledo.edu

Keywords: FMT, Alcoholic Hepatitis, Alcoholism

Published: 14 December 2023

Introduction: Severe alcohol-associated hepatitis (SAH) is an acute, inflammatory liver disease that results in disruptions of the gut microbiome leading to bacterial translocation which drives systemic inflammation and end-organ damage. Despite high risk of mortality, treatment options are limited. Fecal microbiota transplant (FMT) may help restore the balance of healthy bacteria in patients with disrupted gut microbiomes due to SAH, which may decrease systemic inflammation, infection, and mortality. As the role of FMT in the treatment of SAH is not yet established, we conducted a systematic review and meta-analysis to evaluate the currently available literature regarding the impact of FMT on outcomes in patients with SAH.

Methods: A comprehensive search strategy was used to identify studies that reported outcomes of patients with SAH receiving FMT compared to no FMT in Embase, MEDLINE (PubMed), Cochrane Library, Web of Science Core Collection, and Korean Journal Index, and Global Index Medicus. Outcomes of interest included 1-, 3-, and 6- month mortality, overall mortality, and risk of HE, ascites, upper GI bleeding, and infection. RevMan software was used for statistical analysis.

Results: 7 studies with a total of 384 patients were included in the final meta-analysis. Patients who received FMT had significantly lower risk of 1-month mortality (RR: 0.51, 95% CI: 0.29-0.91, p=0.02), 3-month mortality (RR: 0.61, 95% CI: 0.38-0.98, p=0.04), and overall mortality (RR: 0.58, 95% CI: 0.38-0.87, p=0.009) compared to those who did not receive FMT, although the difference in 6-month mortality did not reach statistical significance (RR: 0.73, 95% CI: 0.18-2.89, p=0.65). Patients who

received FMT also had significantly lower risk of hepatic encephalopathy (RR: 0.27, 95% CI: 0.16-0.46, p< 0.00001), ascites (RR: 0.47, 95% CI: 0.33-0.67, p< 0.0001), noncritical infections (RR: 0.36, 95% CI: 0.21-0.6, p=0.0001), and critical infections (RR: 0.28, 95% CI: 0.17-0.48, p< 0.00001). There was no significant difference in risk of upper gastrointestinal bleeding (RR: 0.77, 95% CI: 0.48- 1.24, p=0.28).

Discussion: FMT for SAH is associated with significantly lower risk of 1-month, 3-month, and overall mortality, as well as lower risk of hepatic encephalopathy, ascites, and both critical and non-critical infections. Further studies, particularly large randomized controlled trials, are needed to establish the role of FMT in the treatment of patients with SAH.

A Rare Case of Localized Colonic Amyloidosis Identified During a Screening Colonoscopy

Sami Ghazaleh, MD[1]; Chmsalddin Alkhas, MD[2]; Ali Heif[3]; Muhannad Heif, MD[1,4]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]St. John's Jesuit High School, Toledo, OH, USA

[4]Department of Gastroenterology and Hepatology, ProMedica Toledo Hospital, Toledo, OH, USA

*Corresponding author: sami.ghazaleh@utoledo.edu

Keywords: Colonoscopy, Amyloidosis

Published: 14 December 2023 **Introduction:** Amyloidosis is an abnormal accumulation of amyloid protein in different organs and tissues, which typically results in nephropathy, cardiomegaly, hepatomegaly, and neuropathy. We report a rare case of localized amyloidosis that was identified during a screening colonoscopy.

Case Presentation: A 73-year-old male patient was referred to the gastroenterology clinic for a screening colonoscopy. Past medical history was significant for essential hypertension, type 2 diabetes mellites, gastroesophageal reflux disease (GERD), and myasthenia gravis.

Screening colonoscopy revealed one 12 mm flat polyp in the ascending colon. The polyp was removed with endoscopic mucosal resection (EMR) and retrieved successfully. Biopsy of the polyp showed amorphous deposits in the submucosa, suggestive of amyloid deposits. Congo red stain was performed, and stain was suggestive of amyloidosis. Liquid chromatography tandem mass spectrometry was later performed on the biopsy, which detected a peptide profile consistent with AL (kappa)-type amyloid deposition. In addition, seven other sub-centimeter tubular adenomas were seen in the transverse and sigmoid colons, which were removed with cold snare and cold biopsy forceps.

The patient was referred to hematology to rule out systemic amyloidosis. Workup by hematology was negative for systemic amyloidosis. The only abnormal finding was a slightly elevated kappa/lambda light chain ratio at 1.69. In addition, fat pad biopsy showed no evidence of Congo red/amyloid deposits, cardiac MRI showed no evidence of amyloidosis, and bone marrow biopsy showed no evidence of plasma cell dyscrasia and was negative for amyloid stain. It was concluded that the patient had localized amyloidosis without evidence of systemic disease.

Conclusion: Gastrointestinal amyloidosis is a common finding in systemic amyloidosis, especially AA amyloidosis. However, localized gastrointestinal amyloidosis without evidence of systemic amyloidosis

is uncommon. Management consists of observation or removal of the localized deposition. Patients have a good prognosis and they do not typically transition to systemic amyloidosis.

Trends of Renal Failure Mortality from 1999 to 2020 in the United States by Demographics

Oscar Salichs[1*], Sishir Doddi[1], Taryn Hibshman[1], Puneet Sindhwani, MD[2], Rabba Siddiqi, MD[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Department of Urology, The University of Toledo, Toledo, OH 43614

[3]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: oscar.salichs@rockets.utoledo.edu

Keywords: Renal Failure, Mortality Rates, Affordable Care Act, Healthcare Disparities, Disease Management, Healthcare Policy, Centers for Disease Control and Prevention, CDC Wonder, Joint Regression Program

Published: 14 December 2023

Introduction: Renal failure, encompassing both acute and chronic forms, stands as a formidable public health challenge with far-reaching consequences for individual well-being and healthcare systems. This study delves into the mortality rates of renal failure in the United States over two transformative decades, from 1999 to 2020. Renal failure's significance arises from its escalating prevalence, substantial healthcare costs, and the imperative to understand the multifaceted factors that influence its outcomes.

Objectives: The primary objectives of this research are to analyze temporal trends in renal failure mortality rates, explore the impact of the Affordable Care Act (ACA) and advancements in renal care practices on mortality rates, and assess demographic disparities in mortality outcomes.

Methods: Utilizing CDC WONDER's multi-cause mortality data, we assessed mortality due to renal failure (ICD-10 Codes: N17-N19). Age-adjusted mortality rates (AAMR) were collected, stratified by sex and race. The Joinpoint Regression Program analyzed trends, calculating annual percent change (APC) and significant average annual percent change (AAPC) from 1999 to 2020. Segmented line regression models were employed for parallel pairwise comparisons.

Results: Renal failure mortality rates decreased for both sexes during the late 2000s. The ACA's enactment in 2010 coincided with improved access to healthcare, possibly contributing to the decline. Demographic disparities highlighted variations in mortality rates across racial and gender groups. Advancements in renal care practices were evident, driven by innovations in treatment modalities and disease management. Significant temporal trends were observed by race, with varying periods of decrease or uptrend.

Conclusion: The decline in renal failure mortality rates during the late 2000s was potentially influenced by the ACA and advances in renal care practices. Demographic disparities emphasize the need for equitable healthcare access and interventions. These findings underscore the significance of healthcare policies and medical advancements in reducing renal failure mortality rates and addressing disparities. Persistent efforts to mitigate challenges such as healthcare access, cost barriers, and disparities remain crucial to enhancing renal failure outcomes.

Acute Cerebral Edema and Hyperammonemia After Transjugular Intrahepatic Portosystemic Shunt Placement in a patient with chronic liver disease.

Anas Renno, MD[1], Sara Stanley, DO[1], Tetyana Kulish[2], Ali Heif[1], Thomas Sodeman, MD[4]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: anas.renno@utoledo.edu

Keywords: Acute Cerebral Edema, Transjugular Intrahepatic Portosystemic Shunt, Chronic Liver Disease, TIPS, Hyperammonemia

Published: 14 December 2023

Introduction: Transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients results in porto-systemic encephalopathy in approximately 30-35%, usually apparent 2-3 weeks post TIPS. Cerebral edema and intracranial hypertension are known complications of acute liver failure, however are rarely seen in chronic liver disease. We describe a patient with cirrhosis who had physical exam findings of cerebral edema 24 hours post TIPS.

Case Report: A 71-year-old male with newly diagnosed liver cirrhosis who initially presented to the ED with profound hematochezia. He became hypotensive requiring pressor support and massive transfusion protocol. Patient also became altered requiring intubation. Nasogastric tube was placed, and aspirate revealed no evidence of blood. His pH was 6.8 and ammonia level was 43. A flexible sigmoidoscopy revealed an actively bleeding rectal varix. The varix was treated with 6 ml sodium tetradecyl sulfate for varix eradication without success (Fig. 1). Patient required an emergent TIPS for ongoing bleeding with successful embolization of the distal inferior mesenteric vein perirectal varices. The portal pressure gradient was reduced from 20 mmHg to 6 mm Hg. He remained intubated. The following day, the patient developed scleral edema and conjunctival hemorrhage, concern for cerebral edema and brain compression. 24 hours post TIPS the ammonia level 507. The patient was clinically unstable to undergo a CT brain. Hypertonic saline was started, however his clinic status continued to decline, and the patient expired.

Discussion: This case demonstrates the development of acute cerebral edema caused by hyperammonemia as a complication of TIPS in a patient with chronic liver disease. The development of hepatic encephalopathy after TIPS is common, however development of cerebral edema in patients with

chronic liver disease undergoing TIPS is rare. Cerebral edema should be recognized as a potential complication of TIPS to avoid permanent neurologic injury. Although elevations in serum ammonia are expected after a TIPS procedure, there is a mistaken impression that cerebral edema is not seen in chronic liver disease. We hypothesize that the serum ammonia level increased after the patient's TIPS because the TIPS shunted ammonia-containing blood to the systemic circulation and away from the liver. Prompt consideration should be given to reversing or downsizing the TIPS as early as possible in the clinical course if warranted.

Prophylactic Pancreatic Stent Placement to Prevent Post-ERCP Pancreatitis: A Systematic Review and Meta-analysis

Wasef Sayeh; MD[1], Sudheer Dhoop; MD[1], Sahithi Chinnam; DO[1], Rayna Patel; MD[1], Azizullah Beran; MD[2], Sami Ghazaleh; MD[3], Sara Stanley; DO[3], Yaseen Alastal; MD[3]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo,

Toledo, OH 43614

[2]Division of Gastroenterology, Indiana University, Indiana, United States

[3]Division of Gastroenterology, Department of Medicine, The University of Toledo,

Toledo, OH 43614

*Corresponding author: wasef.sayeh@utoledo.edu

Keywords: ERCP, Pancreatitis, Pancreatic Stent,

Published: 14 December 2023

Introduction: Post-ERCP pancreatitis (PEP) is considered a common complication that can sometimes be fatal. Studies showed that the incidence of PEP averages around 9.7% with a 0.7% mortality rate. Many strategies were presumed to prevent PEP including periprocedural aggressive hydration with Intravenous fluids, the periprocedural administration of non-steroidal anti-inflammatory medications (NSAIDS), or pancreatic duct stent placement. We conducted a meta-analysis to study the effectiveness of the prophylactic placement of a stent in the pancreatic duct in the prevention of PEP.

Methods: We performed a comprehensive search of the databases: PubMed/MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception through May 15th, 2023. We considered randomized controlled trials. The primary outcome was the occurrence of PEP. Also, we did a subgroup analysis based on the severity of PEP. The random-effects model was used to calculate the risk ratios (RR) and 95% confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I2 index.

Results: Fifteen randomized controlled trials involving 1,850 patients were included in the meta-analysis. All studies compared the occurrence of PEP which was significantly lower in the pancreatic stent placement group (5.9% vs 16.8%, RR 0.40, 95% CI 0.30-0.54, p<0.001, I2 = 0%). Subgroup analysis based on the severity of PEP showed that prophylactic pancreatic stent placement was associated with lower occurrence of mild-moderate PEP (5.6% vs 13.9%, RR 0.46, 95% CI 0.34-.064, p <0.001, I2 = 0%). Also, prophylactic pancreatic stent placement significantly lowered the occurrence of severe PEP (0% vs 1.6%, RR 0.26, 95% CI 0.09-0.76, p =0.01, I2 =0%).

Discussion: Our meta-analysis demonstrated that the prophylactic placement of a stent in the pancreatic duct decreases the occurrence of PEP. It was especially helpful in significantly lowering the occurrence of severe PEP.

Whipple's Endocarditis, a blood culture-negative endocarditis

Alyssa Lange[1*], Mona Mahmoud, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: alyssa.lange2@Rockets.utoledo.edu

Keywords: Endocarditis, Whipple's Disease, Cardiology

Published: 14 December 2023

Introduction: Whipple's disease is rare systemic disease caused by Tropheryma whipplei, a gram-positive rod-shaped bacterium widespread in the general population (1,2). The classic course of Whipple's disease includes intermittent arthralgias and fever, weight loss, gastrointestinal symptoms, and neurological symptoms (1-3). Blood culture negative endocarditis accounts for 2.5 – 31.0 % of all cases of endocarditis (4). The incidence rate of T. whipplei among blood culture negative endocarditis cases has not been well established. In this case report, we describe a 63-year-old patient with a past medical history of refractory seronegative rheumatoid arthritis and a newly discovered aortic valve vegetation.

Case Presentation: Our patient presented to the emergency department experiencing increasing non-radiating, sharp, severe abdominal pain with watery diarrhea for a month. After an unremarkable colonoscopy, the pain subsided. An echo showed an aortic vegetation. The TEE showed a 0.7 cm x 0.7 cm vegetation attached to the right coronary cusp of aortic valve.

Two months later, the patient was readmitted after losing thirty pounds since last admission. The EGD showed thickened folds and scalloped mucosa in the duodenum which were biopsied. The results were positive for T. whipplei. A blood culture was performed which was negative. A repeat echo showed a mobile mass on the right side of the interatrial septum, small sessile mass fixed to the right coronary cusp, and now severe atrial valve regurgitation. The patient was treated with six weeks of ceftriaxone and scheduled for a valve replacement.

Conclusion:
We report a typically subacute presentation of infective endocarditis due to *T. whipplei* with a pertinent past medical history of inflammatory, seronegative rheumatoid arthritis and gastrointestinal symptoms. This case highlights the need to consider *T. whipplei* in the differential with infective endocarditis with negative blood cultures especially in the setting of refractory inflammatory arthritis history and recent GI symptoms.

https://dx.doi.org/10.46570/utjms.vol11-2023-931

References

1. Dolmans, R.A., et al., *Clinical Manifestations, Treatment, and Diagnosis of Tropheryma whipplei Infections.* Clin Microbiol Rev, 2017. **30**(2): p. 529-555.
2. Kucharz, E.J., et al., *Clinical manifestations of Whipple's disease mimicking rheumatic disorders.* Reumatologia, 2021. **59**(2): p. 104-110.
3. Hannachi, N., et al., *A Massive Number of Extracellular Tropheryma whipplei in Infective Endocarditis: A Case Report and Literature Review.* Front Immunol, 2022. **13**: p. 900589.
4. Fenollar, F., et al., *Tropheryma whipplei endocarditis.* Emerg Infect Dis, 2013. **19**(11): p. 1721-30.

The Effect Of SGLT-2 Inhibitors on Improving Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis

Wasef Sayeh; MD[1], Sudheer Dhoop; MD[1], Sahithi Chinnam; DO[1], Rayna Patel; MD[1], Azizullah Beran; MD[2], Megan Karrick; MD[3], Anas Renno; MD[3], Ali Nawras; MD[3]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo,

Toledo, OH 43614

[2]Division of Gastroenterology, Indiana University, Indiana

[3]Division of Gastroenterology, Department of Medicine, The University of Toledo,

Toledo, OH 43614

*Corresponding author: wasef.sayeh@utoledo.edu

Keywords: SLGT-2, NAFLD

Published: 14 December 2023

Introduction: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease, and its prevalence continues to increase worldwide. Approximately 80% of patients with Type 2 Diabetes Miletus (T2DM) have NAFLD. SGLT-2 inhibitors are novel oral antihyperglycemic that work by inhibiting the absorption of glucose from the renal tubules which also causes a minor diuretic effect. They also showed huge benefits in managing T2DM, Chronic kidney disease and heart failure. Many clinical trials reported that SGLT-2 inhibitors can improve NAFLD.

Methods: We performed a comprehensive search of the databases from inception through May 15th, 2023. The primary outcome was the improvement of liver enzymes (ALT, AST). The secondary outcome was the improvement in the fibrosis index score (FIB-4). The random-effects model was used to calculate the mean differences (MD) and 95% confidence intervals (CI). A p value <0.05 was considered statistically significant. Heterogeneity was assessed using the Higgins I2 index.

Results: Eleven randomized controlled trials involving 589 patients were included in the meta-analysis. All studies compared the levels of ALT between the SGLT-2 inhibitors group and the control group which showed a significant reduction in the enzyme level in the treatment group (MD -5.02, 95% CI -7.89- -2.15, p=0.0006, I2 = 89%).Ten studies compared the AST levels which also showed a significant reduction in the enzyme level in the SGLT-2 inhibitors group compared to the control group (MD -2.51, 95% CI -3.37 - -1.65, p <0.00001, I2 = 43%). Only, four studies compared the improvement in FIB-4 and the reduction in FIB-4 was significantly lower in the SGLT-2 inhibitors group compared to the control group (MD -0.07, 95% CI -0.08- - 0.05, p <0.00001, I2 =0%).

Discussion: Our meta-analysis demonstrated that the use of SGLT-2 inhibitors can be beneficial in patients with NAFLD in terms of lowering the level of liver enzymes (ALT and AST) and lowering the fibrosis index score (FIB-4).

Interstitial Lung Disease with Autoimmune Features Successfully Treated with Mycophenolate Mofetil: Case Report

Sabrina S. Khuder[1*], Samantha Davis, MD[2], Nathan Gilbert, MD[2], Nezam Altorok, MD[3]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: sabrina.khuder@rockets.utoledo.edu

Keywords: Interstitial Lung Disease, Mycophenolate Mofetil, Autoimmune, Autoimmune Diseases

Published: 14 December 2023

Introduction: Interstitial lung disease (ILD) is a broad term used to describe a group of lung disorders characterized by fibrosis of the lungs. ILD is classified into known factors including occupational and environmental exposures, as well as idiopathic cases. ILDs can be associated with connective tissue disease including systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, or limited autoimmune features1. Patients will often present with dyspnea and non-productive cough. Mycophenolate mofetil (MMF) is an immunosuppressive drug that has shown to be well tolerated in ILD patients and restore pulmonary function2. Efficacy is not established yet in ILD with autoimmune features.

Case Presentation: Patient is a 58-year-old male who presented with shortness of breath at rest. Medical history was significant for hypertension and chronic obstructive pulmonary disease (COPD). His pulmonary function testing shows diffusing capacity of the lungs for carbon monoxide (DLCO) of 30 (normal > 70%), forced vital capacity (FVC) of 67% of age predicted, and forced expiratory volume (FEV1) of 66% (normal between 70-80%). Initial CT scan performed demonstrated mediastinal lymph nodes with upper lobe fibrotic changes. His lung biopsy showed inflammation and evidence of non-specific ILD (NSIP). Laboratory results were positive for anti-nuclear antibodies (ANA) and elevated erythrocyte sedimentation rate (ESR) while negative for other immunological markers. The patient did not have any known occupational exposure. On physical exam, he had evidence of nail clubbing. The patient met criteria for diagnosis of interstitial lung disease with autoimmunity. He was started on treatment with 1000 mg of MMF twice daily as well as oral prednisone 2.5 mg daily. The patient was found at follow up appointments to be responding well to treatment.

Discussion: The case highlights a unique presentation of ILD in a patient with features of an autoimmune process including a positive ANA titer. Although there is not much data in the literature to delineate treatment of ILD with autoimmune features, we believe this case may support use of MMF in larger clinical trials.

References:

1. Morice, A.H., Millqvist, E., Bieksiene, K., Birring, S.S., Dicpinigaitis, P., Domingo Ribas, C., Hilton Boon, M., Kantar, A., Lai, K., McGarvey, L., Rigau, D., Satia, I., Smith, J., Song, W.J., Tonia, T., van den Berg, J.W.K., van Manen, M.J.G., Zacharasiewicz, *A. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children*. Eur Respir J, 2020 Jan 2. **55**(1):p. 1901136. doi: 10.1183/13993003.01136-2019

2. Cully, M. *Interstitial lung disease treated with mycophenolate mofetil*. Nat Rev Rheumatol, 2013. **9**(198). Doi:10.1038/nrrheum.2013.42

An Unusual Presentation of Granulomatosis with Polyangiitis (GPA): A Case Report

Sabrina Khuder[1*], Caleb Gerber[1], Samantha Davis, MD[2], Nathan Gilbert, MD[2], Rawish Fatima, MD[2], Nezam Altorok, MD[3],

[1]College of Medicine and Life Sciences, University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: sabrina.khuder@rockets.utoledo.edu

Keywords: Granulomatosis with Polyangiitis, Vasculitis, Autoimmune Disease
Published: 14 December 2023

Introduction: Granulomatosis with polyangiitis (GPA) is a small vessel necrotizing vasculitis that involves the upper and lower respiratory tracts and the kidneys. Patients commonly present with symptoms such as sinusitis, otitis media, hemoptysis, and features of glomerulonephritis, such as microscopic hematuria and renal dysfunction1. In this report, we describe an unusual case of GPA, with the patient initially presenting with fever and jaw claudication, which are more commonly associated with other vasculitides like giant cell arteritis (GCA), Takayasu arteritis, and polyarteritis nodosa.

Case Presentation: A 66-year-old Middle Eastern male was admitted to the hospital with a 2-week history of bilateral severe headache, jaw claudication, blurry vision, sinus congestion and feverish sensation. Medical history was significant for essential hypertension and type 2 diabetes. Sedimentation rate (ESR) was 83. The patient's symptoms were initially suspicious of giant cell arteritis (GCA); however, temporal artery biopsy was normal. CT scan of the sinuses showed complete opacification of the left frontal and left maxillary sinuses (image 1). The patient's urinalysis revealed microscopic hematuria with proteinuria and protein creatinine ratio was elevated at 1.5. Labs further revealed elevated ESR, positive C-ANCA, and proteinase-3 antibodies. A kidney biopsy showed evidence of focal segmental pauci-immune glomerulonephritis. Overall, kidney biopsy findings along with CT scan results align most consistently with GPA. The patient was started on Rituximab infusions and prednisone. On follow up visits, the patient has had complete resolution of his sinus congestion, jaw claudication, and blurry vision with decreasing ANCA and PR3 titers, and resolution of proteinuria.

Discussion: This case demonstrates an unusual presentation of GPA with the patient initially presenting with features of headache, blurry vision, and jaw claudication that mimics presenting symptoms of other vasculitides. It is important to highlight unique cases such as this one to increase awareness to all primary care physicians, including rheumatologists, of how GPA may present to prevent delays that could affect patient outcomes.

Effects of Fentanyl Exposure during Mechanical Ventilation: A Retrospective Study

Rachel Ko[1], Dan Wright[1], Jonathan Irvin[1], Anna Guo[1], Saira Khan[1], Zachary Holtzapple, MD[2], Andrew Abrahamian, MD[2], William Barnett, MS[2], Brian Kaminski, DO[3], Ragheb Assaly, MD[4]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Department of Emergency Medicine, ProMedica, Toledo, OH 43615

[4]Division of Pulmonary and Critical Care, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: rachel.ko@rockets.utoledo.edu

Keywords: Internal Medicine, Critical Medicine, Quality Improvement

Published: 14 December 2023

Background: Analgesics and sedation are often administered to ensure the comfort and safety of patients receiving mechanical ventilation (1). Patients are commonly treated with fentanyl, an opioid, to provide both pain control and sedation while mechanically ventilated. As opposed to benzodiazepines or propofol, fentanyl results in better pain control but is associated with risks such as chest wall rigidity, that may negatively impact outcomes of patients placed on mechanical ventilation (1, 2).

Objective: To assess the impact of fentanyl exposure on the outcomes of patients who undergo mechanical ventilation.

Methods: This study was a retrospective cohort study of 1191 patients from a tertiary care center. Data was gathered for all mechanically ventilated patients that survived to discharge from 2019-2022. The cumulative dose of fentanyl was quantified throughout the patient's hospital stay. Outcomes including ICU and total length of stay were ascertained upon review of the patient's medical record.

Results: Greater fentanyl exposure was associated with a longer duration of ICU and total hospital length of stay. ICU length of stay increased by 1.09 days when exposed to low doses of fentanyl and 8.78 days with higher exposure. High-dose fentanyl exposure increased total hospital length of stay by 9.71 days.

Conclusions: Higher levels of fentanyl exposure while on ventilator support significantly increased ICU and total hospital length of stay. Longer length of stay is associated with negative health outcomes such as hospital-acquired infection and cardiac arrythmias. High doses of fentanyl in critically ill patients predisposes them to serious and life-threatening medical complications.

References

1. Tedders, K.M., McNorton K.N., and Edwin S.B. Efficacy and safety of analgosedation with fentanyl compared with traditional sedation with propofol. Pharmacotherapy, 2014. **34**(6): p. 643-7.

2. McGreevy, J.L., Piraino, S.T., and Sandhu, G. Fentanyl-Associated Serotonin Syndrome and Chest Wall Rigidity in an Intensive Care Unit Patient. Am J Ther, 2019. **26**(5): p. e612-e614.

Safety and Efficacy of Anti-Hypertensive Medications in Patients with Heart Failure with Preserved Ejection Fraction: A Systematic Review and Meta-analysis

Mohammad Alqadi, MD[1*]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: mohammad.alqadi@utoledo.edu

Key Words: HFpEF, Hypertension, Antihypertensive agents, Outcomes

Published: 14 December 2023

Introduction: Hypertension (HTN) is a co-morbidity that is commonly associated with heart failure (HF) with preserved ejection fraction (HFpEF). This meta-analysis aims to evaluate the association of anti-hypertensive medications (AHM) therapy with cardiovascular (CV) outcomes in patients with HFpEF.

Objectives: Treatment of HTN in HFpEF patients is associated with improved CV outcomes.

Methods: Performed a database search (OVID Medline, Web of Science, and Embase) for studies reporting the association of AHM with CV outcomes in patients with HFpEF. The primary endpoint was all-cause mortality. Secondary endpoints include CV mortality, worsening HF, CV hospitalization, and major adverse CV events (MACE).

Results: A total of 15 studies with 17507 HFpEF participants (8732 treated with medical therapy vs 8775 treated with placebo) met inclusion criteria. Use of AHM was not associated with lower all-cause mortality or CV mortality compared to treatment with placebo (OR 1.01, 95% CI 0.80-1.27; p=0.95, OR 0.97, 95% CI 0.86-1.08; p=0.53). Use of AHM was associated with a statistically significant lower risk of MACE and CV hospitalization (OR 0.90, 95% CI 0.83-0.97; p<0.01, OR 0.89, 95% CI 0.81-0.97; p<0=0.04). Subgroup analysis demonstrated this to be primarily driven by studies with mixed HFpEF patients with or without HTN, not HFpEF patients with HTN. There was a non-significant trend toward lower risk of worsening HF in patients treated with AHM, and was driven by HFpEF patients with or without HTN, not HFpEF patients with HTN (OR 0.87, 95% CI 0.78-0.97; p=0.02 versus OR 0.57, 95% CI 0.18-1.86; p=0.35).

Conclusion: While treatment with anti-hypertensives was not associated with lower risk of all-cause mortality, their use may be associated with reduced risk of adverse CV outcomes in patients with HFpEF regardless of whether they have HTN. Further studies are needed to clarify this association and determine the effect based classes of medications.

Subcutaneous Immunoglobulin (SCig) for Maintenance Therapy in Severe POTS: A Case Report.

Tahrima Ferdous, MD[1*]

[1]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Tahrima.Ferdous@utoledo.edu

Published: 14 December 2023

Introduction: Introduction: Postural Orthostatic Tachycardia Syndrome (POTS) is a multisystem disorder involving the nervous and cardiovascular systems. POTS diagnosis requires an increase in heart rate of at least 30 beats per minute upon standing, in the absence of orthostatic hypotension (1).

There have been multiple theories suggesting a possible autoimmune pathogenesis of POTS, as multiple autoantibodies have been identified in patients with POTS such as ganglionic acetylcholine receptor (gAChR) and voltage-gated potassium channel complex, (Watari et al., 2018) .Moreover patient with POTS tend to have high prevalence of ANA antibodies and co-occurrence of other autoimmune conditions such as systemic lupus (Blitshteyn, 2015).

The use of immunomodulator therapy such IVIG has been reported in multiple case reports with encouraging results, in this case we report significant improvement POTS symptoms with SCig in a patient with debilitating symptoms.

Case Presentation: A 42-year-old female with a past medical history significant for Ehlers-Danlos Syndrome complicated by multiple vertebral and disc issues was evaluated in the rheumatology clinic for sever debilitating POTS that was refractory to standardized treatment. The patient had repeated hospital admissions for syncopal episodes. The decision was made to start intravenous immunoglobulin and following an initial positive response, she developed aseptic meningitis. Intravenous therapy was discontinued, and the patient was started on subcutaneous immunoglobulin. At the time of this case report, the patient had been on subcutaneous Ig for more than 3 years. She has reported significant improvement in her symptoms with less hospitalization. The patient used an apple watch to measure and record her daily heart rate, summary of average HR reported over 3 years is summarized in the graph below.

Conclusion: This case highlights a case of debilitating POTS that showed a clinical subjective and objective response to subcutaneous immunoglobulin. which suggests a possible autoimmune pathway of disease. Further studies are needed to assess the efficacy and safety of Scig in the treatment of refractory POTS.

References

1. Sheldon, R.S., Grubb, B.P. II, Olshansky, B., Shen, W.K., Calkins, H., Brignole, M., Raj, S.R., Krahn, A.D., Morillo, C.A., Steward, J.M., Sutton, R., Sandroni, P., Friday, K.J., Hachul, D.T., Cohen, M.I., Lau, D.H., Maygua, K.A., Moak, J.P., Sandhu, R.K., Kanjwal, K. *2015 Heart Rhythm Society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope*. Heart Rhythm, 2015 Jun. **12**(6): pp. e41-63. doi: 10.1016/j.hrthm.2015.03.029

2. Ballow, M. *Safety of IGIV therapy and infusion-related adverse events*. Immunol Res, 2007. **38**(1-3): pp. 122-32. doi:10.1007/s12026-007-0003-5

3. Ruzieh, M., Batizy, L., Dasa, O., Oostra, C., Grubb, B. *The role of autoantibodies in the syndromes of orthostatic intolerance: a systematic review*. Scandinavian Cardiovascular Journal, 2017. **51**(5): pp. 243-247, doi:10.1080/14017431.2017.1355068

Protocol Development for Yielding High Quality DNA and RNA from Archived Formalin-Fixed Paraffin Embedded Tissues

Sara Kazmi, BA[1*], Bella Khatib-Shahidi, BS[1], John Najjar, BS[1], Anish Sharma, BS[1], Caitlyn Murphy, BS[1], Humza Bashir, BS[1], Benjamin W. French, BS[1], Apurva Lad, PhD[1], David J. Kennedy, PhD[1], and Steven T. Haller, PhD[1]

[1]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Sara.Kazmi@rockets.utoledo.edu

Key Words: DNA Extraction, RNA Extraction

Published: 14 December 2023

Introduction: While genetic analysis of archived formalin-fixed paraffin embedded (FFPE) tissue specimens would be a significant research resource, extraction of high-quality DNA and RNA from these specimens is a significant challenge. Storage duration, tissue handling and tissue preservation processes as well as their interactions with the nucleic acids could influence the quality and integrity of the DNA or RNA required for genetic analysis.

Objectives: The goal of this study was to establish a protocol to extract high quality DNA and RNA from the FFPE tissues for further use in quantitative PCR analysis.

Methods: For the purposes of this study, human FFPE biopsy tissues from lung, liver, colon and kidney were obtained from a single center biorepository. GeneJET Genomic DNA Purification Kit (Catalog # K0722) obtained from Thermo Fisher Scientific and RecoverAll Total Nucleic Acid Isolation Kit obtained from Life Technologies were modified and used for extraction of DNA and RNA, respectively. Briefly, modifications involved extending reagent incubation times, increasing sample volumes and wash steps, and increased final nucleic acids recovery and concentration steps. Eight sections around 8-10 µm thick were microtomed for each tissue sample and used for extraction. The purity of the nucleic acids obtained was verified using Nanodrop Spectrophotometer.

Results: The average DNA yield from eight sections for each of the tissues was 270±184 ng/µl and for RNA was 296±188 ng/µl. Nucleic acid quality was assessed by measuring the 260nm/280nm absorbance ratio for protein contamination as well as the 260nm/230nm absorbance ratio for salt contamination. Both were found to be within acceptable ranges. RNA was reverse transcribed to cDNA and qPCR was successfully performed on both DNA and cDNA samples.

Conclusion: These results indicate that protocols using the silica-based membrane technology can yield high quality DNA and RNA that can be successfully used for downstream genetic analysis.

Dr. Lance D. Dworkin Department of Medicine Research Symposium

Characterization of Human Liver Tissue for Harmful Algal Bloom Exposure in Cancer and Non-Cancer Patients

John Najjar[1*], Anish Sharma[1], Sara Kazmi[1], Bella Khatib-Shahidi[1], Caitlin Murphy[1], Humza Bashir[1], Julissa Vargas[1], Bivek Timalsina[1], Apurva Lad[1], David Kennedy[2], Steve Haller[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiology, Department of Medicine, The University of Toledo, Toledo, OH 43614

Keywords: Cyanotoxin, Harmful Algal Blooms, Microcystis, Microcystin, Hepatocellular Carcinoma, Liver

*Corresponding author: jnajjar@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Harmful algal blooms (HABs) are occurring more frequently not only in the Great Lakes region but also globally. HABs release cyanotoxins, which present public health concerns and significant health risks including associations with hepatocellular carcinoma. Cyanotoxins may enter humans through water ingestion, aerosol inhalation, or direct skin contact. We have previously demonstrated that cyanotoxins exacerbate pre-existing liver and inflammatory bowel disease in mice. However, the effects of cyanotoxin producing cyanobacteria in humans with liver cancer is unknown.

Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) liver tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in hepatocellular carcinoma (HCC).

Methods: DNA and RNA were extracted using an optimized extraction/purification protocol designed for Formalin-fixed paraffin-embedded (FFPE) liver tissues from HCC (n=4) and age and sex matched non-HCC controls (n=4). Presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.

Results: Cyanobacteria levels were elevated in liver cancer tissues compared to non-cancer (1.0±0.23 vs 2.8±1.0, p=0.06) although this was not statistically significant. Interestingly, while markers of tissue remodeling were not significantly correlated with cyanobacterial load overall in both cancer and non-cancer samples, within the HCC samples, cyanobacterial load was positively correlated with tissue inhibitor of metalloproteinases isoform 1 (TIMP-1, r=0.9103, p=0.0008).

Conclusion: Our results suggest that cyanobacteria may be increased in the setting of hepatocellular carcinoma and may impact the expression of key tissue remodeling genes within these tumors. This data is in agreement with clinical and experimental evidence suggesting an association between cyanobacteria and cancer progression in other settings and supports the need to investigate the potential

role of cyanobacteria in liver cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

The impact of libman-sacks endocarditis on inpatient outcomes of patients with systemic lupus erythematosus: A retrospective study

Halah Alfatlawi[1*]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: Halah.Alfatlawi@utoledo.edu

Published: 14 December 2023

Introduction: Libman-Sacks endocarditis (LSE) is recognized as the hallmark cardiac manifestation in individuals with the autoimmune disease of systemic lupus erythematosus (SLE). The existing literature offers limited insights into the influence of LSE on inpatient outcomes in individuals with SLE. This study was conducted to explore the characteristics and prognosis of SLE patients with LSE and the impact of LSE in patients with SLE on inpatient outcomes including: inpatient mortality, length of stay, acute heart failure, atrial fibrillation, and cerebrovascular accidents (CVA).

Methods: This study followed a retrospective observational design and included adult patients who were hospitalized with SLE between the years 2019 and 2020, using the National Inpatient Sample (NIS) database. NIS is one of the largest available databases in United States and consists of discharge data from a 20% stratified sample of US hospitalizations. There is a possibility that our data utilizing NIS does not include the entire population that otherwise fits the inclusion crtieria. Data was expressed as percentages for categorical variables and mean ±SD for continuous variables. All p values were 2-sided, with 0.05 as a threshold for statistical significance.

The total number of patients with a diagnosis of SLE in the 2019 and 2020 in the NIS database was 150,411. Of those, 349 had a diagnosis of LSE.

The study population was divided into two groups: one group with SLE and LSE, and another group with SLE but without LSE.

Results: Caucasians made up 54.9% of the patients with a diagnosis of SLE in our patient population, while African Americans made up 26.9% and the Hispanics accounted for 12.2%. Of patients with LSE, Caucasians and African Americans made up 42.9% each.

Patients with a diagnosis of LSE had a higher inpatient mortality than those with SLE without LSE (aOR: 9.74 CI 1.12-84.79, p 0.04). Patients with SLE with LSE were more likely to have acute heart failure than those without LSE, although this was not statistically significant (aOR 1.18 CI 0.13-11.07, p

0.88). Similarly, patients with SLE with LSE were more likely to have atrial fibrillation than those without LSE (aOR 4.45 CI: 0.77- 25.57, p 0.10). CVAs were significantly higher in SLE patients with LSE than those without LSE (aOR 141.43 CI 16.59-1205.52, p <0.01).**Discussion:** Findings from this study underscore the significance of conducting further studies to explore the relationship between systemic lupus erythematosus and Libman-Sacks endocarditis. Particularly, patients who develop LSE were found to have significantly higher risks of inpatient mortality and cerebrovascular accidents. Early and precise detection of LSE in such patients may ensure timely intervention and prevention of the associated adverse outcomes. Further studies may attempt to develop screening methods for detection of LSE to effectively reduce morbidity and mortality associated with SLE.

Conclusion: Findings from this study underscore the significance of conducting further studies to explore the relationship between systemic lupus erythematosus and Libman-Sacks endocarditis. Particularly, patients who develop LSE were found to have significantly higher risks of inpatient mortality and cerebrovascular accidents. Early and precise detection of LSE in such patients may ensure timely intervention and prevention of the associated adverse outcomes. Further studies may attempt to develop screening methods for detection of LSE to effectively reduce morbidity and mortality associated with SLE.

Characterization of Human Colon Tissue for Harmful Algal Bloom Exposure in Cancer and Non-Cancer Patients

Bella Khatib-Shahidi[1*], John Najjar[1], Anish Sharma[1], Sara Kazmi[1], Apurva Lad, PhD[1], Benjamin W. French[1], Bivek Timalsima[1], Caitlin Murphy[1], Julissa Vargas[1], Humza Bashir[1], David Kennedy, PhD[2], Steven Haller, PhD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: bella.khatibshahidi@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Harmful algal blooms (HABs) are emerging not only in the Great Lakes region, but also globally. HABs release cyanotoxins, which present public health concerns and significant health risks. Cyanotoxins may enter humans through water ingestion, aerosol inhalation, or direct skin contact. We have previously demonstrated that cyanotoxins exacerbate pre-existing liver and inflammatory bowel disease in mice. However, the effects of cyanotoxin exposure in humans with colon disease and colon cancer is poorly understood.

Objectives: We sought to identify the presence of cyanobacteria in Formalin-Fixed Paraffin Embedded (FFPE) colon tissue obtained from patients residing in the Great Lakes region. We hypothesized that the levels of cyanobacteria correlate with markers of tumor severity in colon cancer.

Methods: Using an optimized extraction/purification protocol designed for FFPE samples, DNA and RNA were extracted from colon tissues of invasive adenocarcinoma (n=5) and age- and sex-matched non-adenocarcinoma controls (n=5). The presence of cyanobacteria and markers of tumor severity were determined using quantitative PCR analysis.

Results: Cyanobacteria levels were elevated in colon cancer tissues compared to non-cancer (1.0±0.27 vs 1.3±0.66), although this was not statistically significant. Interestingly, while markers of tissue remodeling were not significantly correlated with cyanobacterial load in both cancer and non-cancer samples, cyanobacterial load was negatively correlated with transforming growth factor-beta (r=-0.6121, p=0.0334) and matrix metalloprotease isoform 9 (r=-0.6272, p=0.0261) in the invasive adenocarcinoma samples.

Conclusion: Our results suggest that cyanobacteria may be increased in the setting of invasive adenocarcinoma and may impact the expression of key tissue remodeling genes within these tumors. This data agrees with clinical and experimental evidence, suggesting an association between cyanobacteria and cancer progression in other settings. The data also supports the need to investigate the potential role of cyanobacteria in colon cancer progression. Analysis of additional samples is ongoing to establish this relationship in an expanded cohort.

Response to aerobic training reveals key differences in cardiovascular adaptation in an adenine diet induced model of chronic kidney disease

Vinicius Guzzoni[1,2], Samantha J. McKee[2], Emma J. Verkley[2], Nicholas J. Kesler[2], Prabhatchandra R. Dube[3], Apurva Lad[3], Bivek Timalsina[3], Tatiana Sousa Cunha[4], Dulce Elena Casarini[5], Steven T. Haller[3], David J. Kennedy[3], Lauren G. Koch[2]

[1]Department of Medicine, School of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, Brazil;

[2]Department of Physiology and Pharmacology, The University of Toledo College of Medicine and Life Sciences;

[3]Department of Medicine, The University of Toledo College of Medicine and Life Sciences;

[4]Institute of Science and Technology, Department of Science and Technology, Federal University of São Paulo (UNIFESP), São José dos Campos, Brazil;

[5]Department of Medicine, Nephrology Division, School of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, São Paulo, Brazil.

*Corresponding author: vinicius.guzzoni@unifesp.br

Published: 14 December 2023

Background: Rat models generated by selective breeding for low (LRT) or high (HRT) response to aerobic training closely embody human phenotypes and can be used to understand the exercise-disease linkages. Aerobic endurance training has been proposed as a model of exercise intervention capable of improving or minimizing the negative consequences of chronic diseases including chronic kidney disease (CKD).

Objectives: We hypothesized that resistance to aerobic training induces kidney damage in CKD settings.

Methods: Male and Female LRT and HRT rats (~ 17 months of age; n = 30) were freely fed with rodent chow supplemented with 0.75% of adenine for the induction of CKD.

Results: At the beginning of the experimental study, LRT rats showed greater body weight and lower arterial blood pressure (systolic, diastolic, and mean pressures) than HRT rats. Following two weeks of adenine diet, body weight of LRT rats remained higher in comparison to HRT rats, consequently both heart and kidney weight / body weight ratio were reduced in LRT (*vs.* HRT) after two weeks of adenine diet. However, after indexing heart weight to tibia length, which avoids biases because of disease-induced body weight changes, we noted that the heart weight / tibia length ratio was significantly increased in LRT vs HRT rats (2.51±0.58 vs 2.13±0.28, $p<0.027$). Kidney weight / tibia length unchanged between the groups.

Conclusion: Our preliminary findings show a better response of HRT rats in terms of cardiovascular adaptations after diet induced CKD. Molecular analyses are being currently performed to further investigate the impact of resistance to exercise induced aerobic training on inflammatory response, renin angiotensin system, pro-inflammatory signaling, and kidney fibrosis.

Machine Learning Analysis of Identifies Polyunsaturated Fatty Acid Metabolites Predictive of Adverse Outcomes In Heart Failure with Preserved Ejection Fraction Patients

Dhilhani Faleel[1*], Ahmed Elzanaty, MD[2], Vaishnavi Aradhyula[1], Rohit Vyas[1], Prabhatchandra Dube[1], Steven T. Haller,PhD[1], Rajesh Gupta, PhD[1], David J. Kennedy, PhD[1], Samer J. Khouri, MD[1]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Cardiology Fellow, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: fmohamm4@rockets.utoledo.edu

Keywords: Machine Learning, Polyunsaturated Fatty Acid (PUFA) Metabolites, Heart failure with preserved ejection fraction (HFpEF), Cardiovascular Health, Lipidomics Framework

Published: 14 December 2023

Background: Pulmonary hypertension (PH) in heart failure with preserved ejection fraction (HFpEF; PH-HFpEF) is associated with adverse clinical outcomes; however, the pathophysiology of disease is unknown. The development of PH is a continuum of disease processes initiated by HFpEF, where patients initially develop isolated postcapillary PH (ipc-PH) which can transform to combined pre and postcapillary PH (cpc-PH). This transformation of PH does not occur in all patients, is not explained by traditional risk factors alone, and is associated with significant morbidity and mortality suggesting the need to examine novel regulatory mechanisms. Polyunsaturated Fatty Acid (PUFA) metabolites play a vital role in cardiovascular health by regulating balance between anti-inflammatory and pro-resolutory lipid mediators and imbalances have been previously shown to predispose PH.

Objective: We sought to characterize PUFA-derived mediators that can serve in cardiovascular risk stratification in patients with HFpEF.

Methods: Venous serum samples were collected from 88 HFpEF patients without PH (control, n=40), HFpEF with ipc-PH (ipc-PH-HFpEF, n=30), and HFpEF with cpc-PH (cpc-PH-HFpEF, n=18). 143 PUFA metabolized were analyzed using mass spectroscopy with Multiple Reaction Monitoring. A machine learning model (Anaconda v2022.05) was conducted after ANOVA feature selection to assess

which molecules were associated with future risk of either all cause death or a combined adverse outcome of death or rehospitalization in the setting of HFpEF.

Results: In patients with HFpEF, increased levels of 9(10)-Epome, 15(R)-PGE1, 17-oxoRvD1, TXB3, RvD3, 5(S),15(S)-DiHETE, and 11dh-2,3-dinor TXB2 at baseline were predictive of all cause mortality (all $p<0.05$). Increased baseline levels of 8-oxoRvD1, MaR1(n-3DPA), PGE3, and 5,6-DiHETrE were predictive of the combined adverse outcome of death or rehospitalization (all $p<0.05$).

Conclusion: These findings support the hypothesis that distinct PUFA metabolites play a significant role in mediating cardiovascular disease in HFpEF. Our study introduces a novel lipidomics framework for the diagnostic and prognostic assessment of cardiovascular risk in HFpEF patients.

Durvulumab-induced rheumatoid arthritis

Masharib Bashar[1*], Aqsa Farooqui, MD, Divya Vijendra[2]

[1]Division of Rheumatology, Department of Medicine, The University of Toledo,

Toledo, OH 43614

[2]Division of Hematology and Oncology, Department of Medicine, The University of

Toledo, Toledo, OH 43614

*Corresponding author: masharib.bashar@utoledo.edu

Keywords: Oncology, Checkpoint Inhibitors, Immunotherapy, Durvulumab, Rheumatoid Arthritis

Published: 14 December 2023

Introduction: Durvulumab is a type of checkpoint inhibitor used in cancer immunotherapy and approved to treat different types of cancers including lung, bladder and biliary tract cancers. It inhibits a human immunoglobin monoclonal antibody which blocks the interaction between programmed cell death ligand (PD-L1) with the PD-1 (CD279).

Case Presentation: Our patient was a 70 year old female patient who was diagnosed with biopsy-proven Stage 3A (T1N2M0) non-small cell lung cancer of left upper lobe. She initially underwent radiation therapy as well as induction chemotherapy with combination of cisplatin and premetrexed. Patient then received initial consolidation immunotherapy with durvalumab and only after its first dose, she developed incapacitating migratory arthalgias and myalgias, within a week. She presented to ER and her labs were only significant for elevated acute-phase reactants ESR and CRP, along with concernful elevation of anti-CCP and RF levels. She had never been diagnosed with rheumatoid arthritis before. After review of symptoms and lab findings and evaluation by rheumatologist, she was diagnosed as case of rheumatoid arthritis, secondary to durvulumab. She was started on methotrexate and tapered dose of steroids which resolved her symptoms to a great extent. Not surprisingly, her immunotherapy regimen was switched to osimertinib (an epidermal growth factor tyrosine kinase inhibitor).

Conclusion: As per our literature review, this is the first-ever reported case of rheumatoid arthritis caused by durvulumab.

Recurrent Salmonellosis Complicating Ofatumumab Therapy for Multiple Sclerosis

Justin Franco[1*], Makoto Ibaraki[1], Basmah Khalil[2], Joel A. Kammeyer, MD,[3] Komal Masood, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Cardiovascular Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614

[3]Division of Infectious Diseases, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: justin.franco@rockets.utoledo.edu

Keywords: Multiple Sclerosis, Ofatumumab, Salmonella

Published: 14 December 2023

Introduction: Multiple Sclerosis (MS) is an autoimmune disease characterized by destruction of neural myelin sheaths. Treatment involves anti-CD20 monoclonal antibodies, such as Ofatumumab. Anti-CD20 therapeutics function by reducing autoreactive B-cell populations. Although anti-CD20 therapeutics are associated with infection risk, the occurrence of recurrent Salmonella infection is novel.

Case Presentation: A 41-year-old male presents with watery diarrhea occurring over 10-days. Past medical history includes depression, MS, and Salmonella infection. Initial Salmonella infection was reported 12-weeks prior, while the patient was taking Ofatumumab for MS. Salmonella infection was resolved following 2-weeks of IV-ceftriaxone. Ofatumumab was discontinued 7-weeks prior to hospital admission due to leukopenia. Physical exam was unremarkable, with mild abdominal tenderness. Laboratory findings revealed decreased antibody titers and positive Salmonella cultures.

Patient underwent EGD and colonoscopy, with biopsies indicating infectious colitis. He was diagnosed with recurrent non-Typhi Salmonella (NTS) infection. For treatment, the patient underwent a cholecystectomy and was discharged on a 14-day course of Azithromycin.

Discussion: Anti-CD20 therapies are mainstays of MS treatment. However, anti-CD20 medications are associated with increased risk for moderate infection (e.g., respiratory tract infection or UTIs). Rare infections associated with anti-CD20 therapeutics include HBV reactivation and progressive multifocal leukoencephalopathy.

The development of recurrent NTS in response to anti-CD20 therapy has not been reported in the literature. Gastroenteritis caused by NTS is self-limiting in immunocompetent patients. Major risk

factors for recurrent NTS include young/old age, contaminated food, and immunosuppression. Although our patient discontinued Ofatumumab 7-weeks prior to admission, he presented with reduced antibody titers (i.e., hypogammaglobulinemia). B-cell reconstitution following termination of Ofatumumab takes 24 to 36-weeks, during which time patients are immunosuppressed. One of the side effects of anti-CD20 therapy is reduced antibody titers, which can increase the patient's risk for NTS. This case highlights anti-CD20 therapy as a novel risk factor for recurrent NTS.

Into the unknown: Navigating orbital cellulitis to reveal retinal metastasis of a hidden primary tumor

Mohammed Abu-Rumaileh[1*], Kashvi Patel[2], Fanham Asghar[1], Anu Garg[1]

[1]Division of Internal Medicine, Department of Medicine, The University of Toledo, Toledo, OH 43614
[2]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

*Corresponding author: Mohammed.Abu-Rumaileh@UToledo.Edu

Published: 14 December 2023

Introduction: This is a rare patient presentation of retinal metastasis with an unknown primary tumor.

Case Presentation: A 65-year-old woman with a past medical history of left breast carcinoma stage 1 status post left mastectomy in 2014, iron deficiency anemia, anxiety, and depression presented to the emergency department with 1-2 weeks of worsening lower abdominal pain and left-sided chest pain. She also complained of right eye pain, blurry vision, and painful eye movement. Ocular examination demonstrated edema, mild proptosis, conjunctival chemosis, and conjunctival injection. Patient was started on bacitracin ointment and ceftriaxone due to concerns of orbital cellulitis. Ophthalmology was consulted, and their assessment was suggestive of bilateral metastatic neoplastic lesion in retina of both eyes, more pronounced in the right than the left eye. Left supraclavicular lymph node biopsy showed metastatic adenocarcinoma, likely of gastrointestinal or pancreaticobiliary primary. MRI brain was suspicious for calvarial metastatic disease, MRI abdomen showed multiple nodules in the liver suggesting metastases, and NM bone scan whole body suggested possible metastases in the hemithorax and bilateral femurs. After several goals of care discussions, the decision was made by the patient and her family to pursue comfort measures only and she was discharged home with home hospice.

Conclusion: Retinal metastasis is a rare condition due to the absence of lymphatic system in the eye (1). The most common primary tumors to metastasize to the eye are from breast (47%), lung (21%), and the gastrointestinal tract (4%) (2). In some cases, patients may have no other symptoms (1). Thus, retinal metastasis is important to include in the differential diagnosis, especially for patients with a history of treated primary cancer.

References

1. Cohen V.M. *Ocular metastases*. Eye (London, England), 2013, **27**(2): p. 137–141. https://doi.org/10.1038/eye.2012.252

2. Shields, C.L., Shields, J.A., Gross, N.E., Schwartz, G.P., & Lally, S.E. *Survey of 520 eyes with uveal metastases*. Ophthalmology, 1997, **104**(8): p. 1265–1276. https://doi.org/10.1016/s0161-6420(97)30148-1

The effects of MC4R activation on behavioral activity in transgenic mice

Joseph Dale II[1*], Mitchell Harberson[2], Jennifer W. Hill, PhD[1]

[1]Department of Physiology and Pharmacology, The University of Toledo, Toledo, OH 43614

[2]Department of Biology, Cellular and Molecular Biology, College of Natural Sciences and Mathematics, The University of Toledo, Toledo, OH 43614

*Corresponding author: joseph.dale@rockets.utoledo.edu

Keywords: PVH, Grooming, MC4R

Supporting agencies: NIH T-32 Program-TRAINING IN TRANSLATIONAL AND MOLECULAR CELL DYNAMICS (TMCD) #T32GM144873

Published: 14 December 2023

Background: Melanocortin receptors are a family of 5 classical GPCRs that activate the adenylyl cyclase pathway in cells leading to production of the secondary messenger cAMP. The melnocortin-4 receptor (MC4R) is abundantly expressed in the hypothalamus. The MC4R has been implicated in regulating various physiological processes, including energy homeostasis, cachexia, cardiovascular function, glucose and lipid homeostasis, reproduction, and sexual function. Drugs have been developed to treat eating conditions as well as sexual hypoactivity disorders, although the full role of melanocortin signaling in behavior is.

Objectives: The objective of this study was to characterize how an exogenous melanocortin affected grooming behavior and potential signaling pathways involved.

Methods: Wildtype mice were treated with the MC4R agonist bremelanotide and its impact on grooming behavior was studied. We administered i.p. bremelanotide at 0.01mg/kg, 0.1mg/kg, 1mg/kg and 10mg/kg or vehicle was administered, and grooming was recorded for 1 hour for blinded analysis. In situ hybridization was used to determine whether x- expressing neurons colocalize with the melanocortin receptor in the PVH and SON of the hypothalamus.

Results: Bremelanotide treatment induced an increase anogenital grooming and total time spent grooming in the 1mg/kg treatment group and the 10mg/kg treatment group. Vasopressin neurons were found to colocalize with the MC4R in the PVH and the SON.

Conclusion: Bremelanotide induces a dramatic increase in grooming behavior that correlates with dosage. This effect could be mediated through the MC4R expressed in vasopressin neurons of the PVH. Additional studies to test the receptor type and location that induces bremelanotide's grooming effects are needed. A future study will test the effects of the knocking out MC4Rs present on arginine vasopressin neurons on grooming and other behaviors.

Mesenteric Lymphadenopathy: a Rare Case of Rosai-Dorfman Disease

Amy Waters[1*], Joan Gekonde, MD[2], Nathaniel Gilbert, MD[2], Nezam Altorok, MD[2]

[1]College of Medicine and Life Sciences, The University of Toledo, Toledo, OH 43614

[2]Division of Rheumatology, Department of Medicine, The University of Toledo, Toledo, OH 43614

*Corresponding author: amy.waters@rockets.utoledo.edu

Published: 14 December 2023

Introduction: Rosai-Dorfman Disease (RDD) is rare with approximately 100 new cases annually in the United States and a mean age of 20.6 years (1). RDD is characterized by massive lymphadenopathy and sinus histiocytosis (1). Bilateral cervical lymphadenopathy is the typical presentation, however extra nodal sites have been noted (1). This case discusses manifestations of a rare disease state.

Case Presentation: A 19-year-old male with a history of eczema and juvenile rheumatoid arthritis presented to the emergency room with four days of diffuse abdominal pain localized to the left upper quadrant, radiation to the right lateral ribs with nausea and diarrhea. He reported an unintentional weight loss of 30 pounds in the last three months. Physical exam revealed generalized abdominal tenderness and rebound. Computed tomography of the abdomen and pelvis (CTAP) along with routine labs were ordered. CTAP showed retroperitoneal lymphadenopathy up to two centimeters in the short axis and mesenteric adenopathy with a 15 millimeter lymph node in the right lower quadrant. Histopathology reported necrotizing granulomatous lymphadenitis with benign sinus histiocytes. Referral to rheumatology was made and treatment was initiated with prednisone 20 milligrams daily with plans for repeat abdominal imaging to evaluate for reduction of adenopathy.

Discussion: RDD coexists with immunologic disease in 10% of cases.3 It has been associated with systemic lupus erythematous, idiopathic juvenile arthritis, autoimmune hemolytic anemia,24 and one case of RAS-associated autoimmune leukoproliferative disease (1). The prognosis for RDD is indolent, 50% of patients experiencing resolution, one third with residual asymptomatic adenopathy and 17% with persistent symptomatology (2). Our case highlights our patient's associated history of juvenile rheumatoid arthritis now presenting with histological findings of RDD. A methodical approach to assessing patients with diffuse abdominal pain and ensured collaboration amongst different medical specialists will ensure favorable treatment outcomes.

References

1. Abla, O., Jacobsen, E., Picarsic, J., Krenova, Z., Jaffe, R., Emile, J.F., Durham, B.H., Braier, J., Charlotte, F., Donadieu, J., Cohen-Aubart, F., Rodriguez-Galindo, C., Allen, C., Whitlock, J.A., Weitzman, S., McClain, K.L., Haroche, J., Diamond, E.L. *Consensus recommendations for the*

https://dx.doi.org/10.46570/utjms.vol11-2023-902

diagnosis and clinical management of Rosai-Dorfman-Destombes disease. Blood, Jun 28 2018. **131**(26): pp.2877-2890. doi: 10.1182/blood-2018-03-839753

2. Sodhi, K.S., Suri, S., Nijhawan, R., Kang, M., Gautam, V. *Rosai-Dorfman disease: unusual cause of diffuse and massive retroperitoneal lymphadenopathy*. Br J Radiol, Sep 2005. **78**(933): pp.845-7. doi: 10.1259/bjr/23127241

