

Case Report of Vocal Cord Palsy and Neutropenia due to B-12 Deficiency

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Abstract

This case presents an interesting combination of vitamin B12 deficiency and cefepime use, both isolated causes of neutropenia, occurring together. A 67-year-old male presented to the Emergency Department with severe leukopenia after six weeks of cefepime for osteomyelitis. On arrival, he endorsed pharyngitis, dyspnea, cough productive of clear sputum, and headaches for five days. The next day, he developed new onset dysphagia with thick, white oral secretions requiring suctioning with a strong productive cough. He then reported breathy, gravelly voice changes, present days prior to admission. Laryngoscopy demonstrated acute left true vocal cord immobility with right hypomobility, dysphonia, and dysphagia. Hematology cited both vitamin B12 deficiency and cefepime course were likely causing his neutropenia. Vitamin B12 deficiency commonly causes megaloblastic anemia and rarely pancytopenia. Manifestations may include gastrointestinal and neurological symptoms, such as dysphagia and vocal cord paralysis, as in this case. These complications can persist if not treated immediately. Antibiotics, such as cephalosporins, are also a known cause of neutropenia. This case highlights the broad spectrum of manifestations of vitamin B12 deficiency and emphasizes the importance of keeping this disorder on the differential diagnosis with a variety of clinical presentations.

Keywords: Vitamin B12, vocal cord palsy, severe neutropenia, cefepime, pancytopenia

1. Introduction

Vitamin B12 is an essential component of DNA synthesis and blood cell formation. Severe deficiency of Vitamin B12 causes megaloblastic anemia and may also result in thrombocytopenia and leukopenia (neutropenia) (1-3). Inadequate intake of animal products and pernicious anemia (loss of intrinsic factor due to autoimmune atrophic gastritis) are the most common causes of severe vitamin B12 deficiency worldwide in pediatric and adult populations, respectively (4,5). Vitamin B12 deficiency may contribute to different hematological and neurological diseases including reversible megaloblastic anemia as well as demyelinating central nervous system disease. Though the causation remains unknown, the severity of megaloblastic anemia in vitamin B12-deficient individuals is inversely correlated with the extent of neurological dysfunction (4).

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2. Case Presentation

Patient is a 67-year-old male who presented to the Emergency Department after receiving results from follow-up lab work demonstrating severe leukopenia. The lab work was subsequent to a 6-week-course of cefepime for osteomyelitis. His medical history was significant for coronary artery disease, hypertension, type 2 diabetes mellitus, abdominal aortic aneurysm status-post rupture and repair, QTc prolongation, peripheral artery disease, below-knee-amputation of right lower extremity and amputation of the 1st, 3rd, and 4th digits on left lower extremity. On presentation, he presented with sore throat, shortness of breath, cough productive of clear sputum, and headache for five days. He denied any sick contact or fever and was fully vaccinated against COVID-19. His social history was significant for tobacco use of 1

pack of cigarettes per day for 40 years, without smokeless tobacco use or vape use, and alcohol consumption on social occasions. On physical exam, an obese body habitus was appreciated, and his vitals were stable, except for mild sinus tachycardia. He was awake and in no acute distress. Examination of the throat demonstrated oral thrush, coarse breath sounds were appreciated on lung auscultation, and his abdomen was soft, nondistended and nontender. Physical exam of the extremities was consistent with past medical history, demonstrating a prior below-knee-amputation of the right lower extremity, as well as amputation of the 1st, 3rd, and 4th digits of the left lower extremity.

Following the initial workup, his WBC count was 2.2 with an Absolute Neutrophil Count of 0 (Figure 1). Other results included: Procalcitonin 0.14 (normal <0.5), Sodium 125 (normal 135-145), and an elevated D-dimer 392. To further assess the isolated and severe neutropenia, the following tests were ordered: sputum culture, blood cultures, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), HIV polymerase chain reaction (PCR), respiratory pathogens panel (RPP), folate level, B12 level, copper level, and peripheral blood smear. He was initiated on Fluconazole for the oral thrush and was placed on neutropenic precautions. Infectious disease and Hematology were consulted. The patient's hyponatremia was later found to be hypovolemic in nature and was corrected with normal saline. Later that evening, the patient underwent and failed a bedside swallow evaluation after describing difficulty swallowing.

The next day, the patient was experiencing dysphagia with thick, white oral secretions that required oral suctioning and had a strong productive cough. Due to concerns for underlying bone marrow disorder, as evidenced by neutropenia with agranulocytosis, a bone marrow biopsy was obtained. Other etiologies, including

Day of Admission:	6 Months Prior	1	2	3	4	5	6	7	8	Day of Discharge
WBC	6.6	2.2(L)	0.6(L)	0.7(L)	1.2(L)	2.2(L)	10.2	10.8	13.9(H)	12.7(H)
RBC	3.29(L)	3.81(L)	3.74(L)	3.54(L)	3.3(L)	3.47(L)	3.48(L)	3.53(L)	3.62(L)	3.52(L)
HBG	10.8(L)	13.0(L)	12.9(L)	11.8(L)	11.0(L)	11.7(L)	11.8(L)	11.9(L)	11.8(L)	11.8(L)
HCT	32.3(L)	37.6(L)	37.2(L)	35.6(L)	33.4(L)	35.4(L)	36.3(L)	35.6(L)	36.6(L)	35.5(L)
MCV	98	99	100	101(H)	101(H)	102(H)	104(H)	101(H)	101(H)	101(H)
PLT	288	--	245	233	241	269	256	230	224	214
ANC	3.7	0.0(L)	--	0.0(L)	0.0(L)	1.0(L)	5.8	6.8(H)	8.3(H)	8.0(H)

Figure 1. Complete Blood Count Trend

B12 deficiency and the extended course of cephalosporin antibiotics (cefepime) were being continuously assessed by the Hematology team. A new video swallow study demonstrated severe impairment of pharyngeal swallow with gross aspiration. Otolaryngology was then consulted for the patient's new onset dysphagia, in the context of a prior tracheostomy following a ruptured abdominal aortic aneurysm. He also complained of breathy and gravelly voice changes which had started a couple of days prior to admission. Subsequently, laryngoscopy demonstrated acute left true vocal cord immobility and right vocal cord hypomobility, dysphonia, and dysphagia.

The patient's blood culture, sputum culture, and RPP had all come back within normal limits. Other results yielded elevated inflammatory markers (ESR and CRP) and low Vitamin B12 (135). For continued investigative purposes, a thyroid-stimulating hormone (TSH), urinalysis (UA), antinuclear antibody (ANA) and fungal blood culture were ordered, and the patient was started on B12 and folic acid replacement. Due to continued neutropenia, Filgrastim was then initiated in companion with daily B12 repletion. Neurology simultaneously conducted work-up for concerns of Myasthenia Gravis after observation of acute dysphagia, nasal twang in voice, ptosis, in combination with diurnal variation in symptoms; however, the Myasthenia Gravis panel was negative. Overnight, the patient was noted to be febrile (38.3°C). Thus, he was initiated on antibiotic

therapy with Piperacillin-Tazobactam (renally dosed) and Acetaminophen.

Bone marrow biopsy demonstrated hypocellular bone marrow with myeloid hyperplasia, likely from B12 deficiency and other factors. Filgrastim was stopped and daily B12 replacement continued.

On the sixth day of admission, the patient's WBC improved to 10.2 (Figure 2) and his Absolute Neutrophil Count reached 5.8 (Figure 3). He was able to communicate well and reported improving dysphagia and dysphonia. After the neutropenia was corrected, overlaying concerns for retropharyngeal fluid abscess resolved, all cultures remained negative with no growth. Piperacillin-Tazobactam was discontinued. To ascertain etiology of the B12 deficiency, intrinsic factor blocking antibodies (negative) and anti-parietal cell antibodies (negative) were ordered. At this point, flow cytometry analysis of the bone marrow biopsy was negative for phenotypic abnormalities, increased blasts or monoclonality of granulocytic or lymphoid populations which suggested no underlying primary bone marrow disorder, but consistent with vitamin B12 deficiency as the most probable cause of the neutropenia.

By day 7 of admission, a repeat Video Swallow Study demonstrated only mild oral and pharyngeal phase dysphagia. The patient's diet was advanced to complete oral intake without restrictions. Shortly thereafter, the patient medically stabilized and was discharged home with

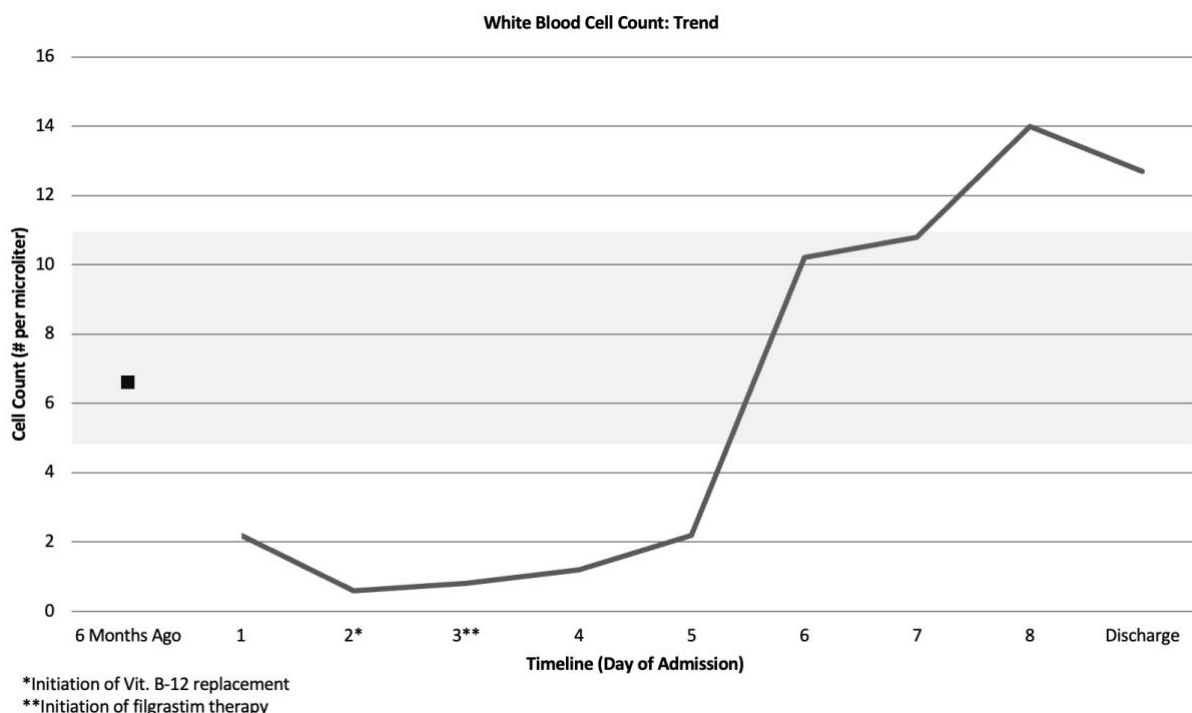


Figure 2. White Blood Cell Count: Trend

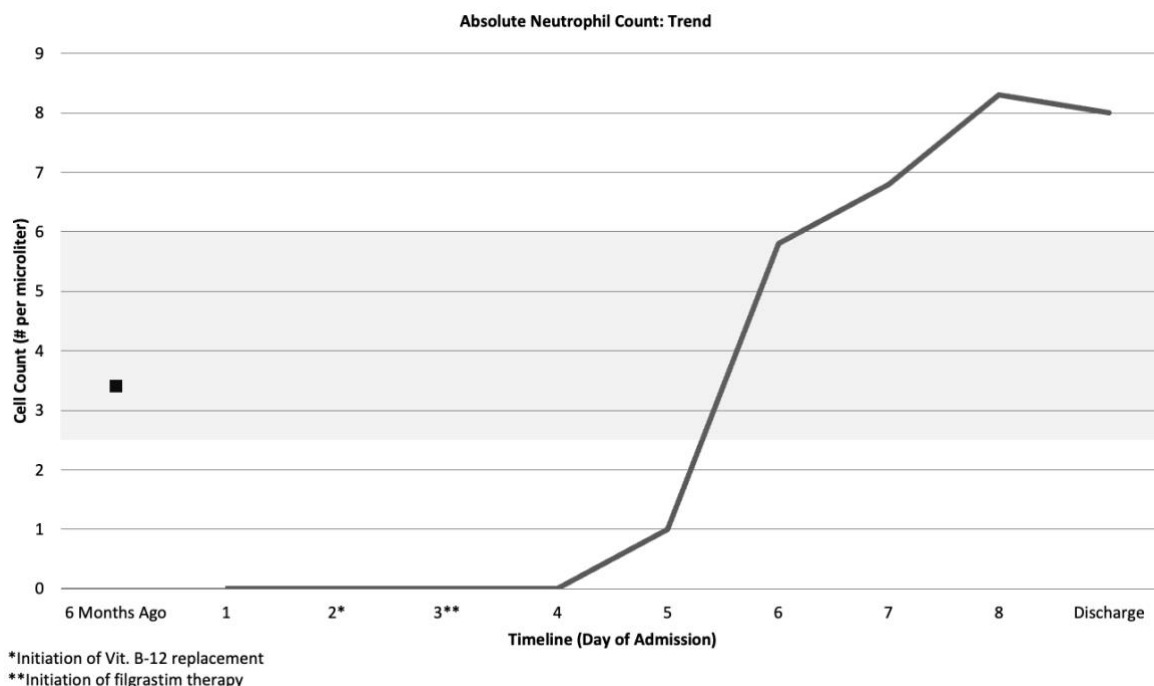


Figure 3. Absolute Neutrophil Count: Trend

home healthcare and primary diagnoses of neutropenia with neutropenic fever, acute severe dysphagia, fixated left vocal cord and hypomobile right vocal cord.

3. Discussion

Vitamin B12 deficiency can be caused by inadequate intake or the inability to absorb the vitamin (6). Since Vitamin B12 cannot be synthesized naturally, it is absorbed through various foods and supplements. Eggs and other animal-derived products are the primary dietary sources of vitamin B12, rather than fruits and vegetables (7).

In humans, vitamin B12 is a required cofactor for two biological reactions: methyl cobalamin is the cofactor for the cytoplasmic enzyme, methionine synthase, and adenosyl cobalamin is the cofactor for the mitochondrial enzyme, methyl malonyl coenzyme A mutase. Thus, vitamin B12 deficiency leads to an accumulation of homocysteine and methyl malonic acid. Cobalamin is an essential component for DNA synthesis, hematopoiesis and myelination (4,5,8). The most common cause of B12 deficiency is inadequate consumption due to dietary restriction or lack of access to animal-sourced food (5). B12 stores last for several years after restriction of intake or malabsorption (4). Serum B12 level is the primary method of investigation for vitamin B12 deficiency,

but an increase in serum levels of methylmalonic acid and homocysteine are also indicative (9).

Vitamin B12 deficiency commonly results in megaloblastic anemia and rarely, pancytopenia. However, vitamin B12 deficiency may also lead to leukopenia and thrombocytopenia in later stages (4). This serves as an explanation for this patient's pancytopenia. Common signs indicating B12 deficiency include oral symptoms, such as glossitis and recurrent oral ulcers. In this case, however, the patient presented with severe neutropenia, macrocytosis, and esophageal candidiasis partly also attributed to his neutropenic state and long-term antibiotic use (5).

Although most vitamin B12-deficient individuals present with only mild hematological findings, approximately 10% of patients have life-threatening conditions, as reported in literature: symptomatic pancytopenia, severe anemia (hemoglobin level < 6 g/dl), and hemolytic anemia (5). In a study including 201 adults with well-documented B12 deficiency, approximately 10% of the patients were found to have life-threatening hematological manifestations. Among these manifestations were pancytopenia (5%), severe anemia (hemoglobin level <6.0 g/dl, 2.5%) and hemolytic anemia (1.5%) (10).

Vitamin B12 deficiency can result in serious complications in developing infants as well. Honzik et al. describe failure to thrive, hypotonia, irritability, lethargy, developmental

delay/regression, epilepsy and movement disorders to be associated with vitamin B12 deficiency (11). They also report associations with brain atrophy, delayed myelination, polyneuropathy, and abnormal evoked responses. However, there is a wide spectrum of variation between studies. One study consisting of 27 patients with vitamin B12 deficiency found failure to thrive in 63%, hypotonia in 66.7%, refusal to wean in 81.3%, and absence of eye contact/social retardation in 51.9% (12). This highlights the broad spectrum of manifestations of vitamin B12 deficiency and emphasizes the importance of keeping this disorder on the differential diagnosis with a variety of clinical presentations.

Another manifestation of B12 deficiency includes neurological changes. B12 is vital for the development and myelination of the central nervous system, as well as the maintenance of its normal function. The most common neurological findings are symmetric parathesis due to subacute combined degeneration of the dorsal and lateral columns of the spinal cord. Cerebellar dysfunction and cranial neuropathies other than optic nerve involvement have been rarely reported (13). The first case of B12 deficiency-associated vocal cord palsy was documented in 2011 (14). This patient presented with acute onset vocal cord palsy in the setting of mild megaloblastic anemia. It is difficult to establish definitive diagnosis in any case but, given the patient's presentation in the setting of abnormal key lab values and clinical manifestations, a diagnosis of vitamin B12 deficiency-associated vocal cord palsy can be made.

Long-lasting neurological consequences due to vitamin B12 deficiency have been documented even after sufficient supplementation. One case involving a 14-month-old with vitamin B12 deficiency complications continued experiencing cognitive and language developmental delay at two years of age despite resolution of cerebral atrophy after 10 weeks of supplementation (15). Another four-month-old patient with acute encephalopathy and seizures from vitamin B12 deficiency sustained moderate mental developmental disability at seven years of age (16). Conversely, other studies found B12 supplementation to result in significant improvement in both physical growth and neurological complications. One study including 27 infants demonstrated clinical and hematological improvements in all infants after supplementation (12). Furthermore, a review of five patient cases found normalization of neurological outcomes by

13 months to seven years of age (17). In adults, there can also be longstanding neurologic symptoms due to B12 deficiency including paresthesia, sensory loss, ataxia, dementia, and psychiatric disorders (13).

Imaging modalities, like MRI, may be helpful in evaluating neurological manifestations of B12 deficiency, as demyelination has been reported to be associated with vitamin B12 deficiency (18). Accumulated homocysteine levels result in endothelial dysfunction and neuronal damage because of increased mitochondrial dysfunction and apoptotic cell death (19). After starting vitamin B12 supplementation, there seems to be some variability regarding the resolution of MRI findings. Some studies report complete resolution of structural anomalies on MRI after 10 weeks of treatment (15). However, at seven-month follow-up of three infants, structural abnormalities remained present on computerized tomography, as well as abnormal electroencephalograms (20).

4. Conclusion

B12 deficiency may manifest in a variety of patient presentations. Clinicians should be aware of diverse hematological and neurological presentations secondary to B12 deficiency including neutropenia and dysphagia. Though more rare, vocal cord paralysis, as in this case, may also indicate B12 deficiency if in conjunction with abnormal lab values. Another interesting feature of this case is the combination of vitamin B12 deficiency and cefepime use, both known isolated causes of neutropenia, occurring together. This case highlights the broad spectrum of manifestations of vitamin B12 deficiency and emphasizes the importance of keeping this disorder on the differential diagnosis with a variety of clinical presentations.

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