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CASE REPORT

A Profound Vitamin B12 Deficiency in a Patient with Lofgren's Syndrome

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Abstract: Lofgren's syndrome is a unique manifestation of sarcoidosis presenting with erythema nodosum, bilateral hilar lymphadenopathy and migratory polyarthritis. A concurrent vitamin B12 deficiency is not well described and may be related to a rare gastrointestinal manifestation of sarcoid and Lofgren's syndrome. We describe a case of a 57-year-old male presented with migratory polyarthritis, erythemic nodules, edema of his legs and fever. His laboratory tests showed anemia with a profound vitamin B12 deficiency. Imaging demonstrated bilateral hilar adenopathy. Pathology revealed non-necrotizing granulomas consistent with sarcoidosis. The patient was started on prednisone and vitamin B12 supplements with improvement of his complaints and vitamin B12 levels. Sarcoidosis can manifest in many extrapulmonary organs, including the gastrointestinal tract, resulting in nutritional deficiencies, such as vitamin B12 deficiency. Treatment of these nutritional deficiencies includes treatment with steroids, as well as vitamin supplementation. We suggest this case to be a rare manifestation of gastrointestinal involvement in Lofgren syndrome; however, a biopsy from the GI tract was not performed to confirm the diagnosis. An informed consent was obtained from the patient. An institutional approval was not required for the publication of this case.

Keywords: vitamin B12, sarcoidosis, Lofgren's syndrome, gastrointestinal tract

Introduction

Sarcoidosis is a multisystem granulomatous disease characterized pathologically by the presence of noncaseating granulomas in involved organs.[1] The etiology of sarcoidosis remains unknown, characterized by the accumulation of T lymphocytes, mononuclear phagocytes, and noncaseating granulomas in involved tissues. The most common manifestation of sarcoidosis is pulmonary disease; however, skin and articular manifestations are not rare.[2,3] Gastrointestinal (GI) involvement is rare, occurs in less than 1% of patients, and is often silent and under-diagnosed. GI sarcoidosis is often masquerading as an infection, an inflammatory bowel disease, a peptic ulcer disease, a malignancy or even a foreign body, depending on the GI organ involved.[4,5] Lofgren's syndrome (LS) is a unique form of sarcoidosis, and it is characterized by the triad of acute onset of erythema nodosum, bilateral hilar lymphadenopathy and migratory polyarthritis.[3,6] Treatment of LS is typically supportive and prognosis is excellent, with a greater than 90% chance of spontaneous remission within 2 years.[6,7] However, GI involvement and especially symptomatic GI involvement in LS is poorly described in the literature. There are many etiologies which can cause vitamin B12 deficiency. A few mechanisms are thought to cause severe vitamin B12 deficiency including severe malabsorption, food cobalamin malabsorption, pernicious anemia, bariatric surgery, and intestinal malabsorption. Vitamin B12 deficiency may lead to hematological disorders including anemia, and neurological disorders. Treatment includes vitamin B12 replacement and treatment of the underlying disease.[8]

This case report will describe a rare manifestation of LS presented with a profound vitamin B12 deficiency.

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Case Description

A 57-year-old male presented with complaints of migratory joint pain mainly in his lower limbs. His medical history was positive for vitamin B12 deficiency, gastrointestinal (GI) reflux disease, and fatty liver. Initial evaluation demonstrated an elevated erythrocyte sedimentation rate of 93 mm\hour, X-rays of the vertebra were normal. He was started on prednisone 40 mg daily with improvement of his complaints. While tapering down prednisone doses, symptoms reoccurred. The patient reported of peripheral edema, night sweats and weight loss, with no fever. He noticed a nodular and sensitive to touch lesion on his palms and bilateral non-purulent conjunctivitis. Physical examination revealed bilateral leg edema and erythemic nodules at the palms of his hands. He had mild normochromic normocytic anemia with hemoglobin level of 13.1 g\dL and a normal red blood cell distribution width. C-reactive proteins was elevated 14.5 mg\dL. Inquiry for anemia demonstrated a profound vitamin B12 deficiency – levels of 75 pmol\dL, folic acid and TSH were within the normal range, there was no evidence of iron deficiency – iron levels were 79 µg/dl, transferrin levels were 272 mg/dl, ferritin levels were 188ng/mL, intrinsic factor antibodies and anti-parietal cell antibodies were negative, rheumatic panel was negative. Blood cultures and infectious panel were negative. Chest X-ray showed bilateral hilar adenopathy. Ultrasound of the swollen ankle did not demonstrate a collection or abscesses; abdominal ultrasound showed hepatic steatosis with no enlargement of liver or spleen. A fundus examination showed no signs of uveitis. A skin biopsy from the erythemic nodules on his palms demonstrated no signs of vasculitis, with non-specific inflammatory infiltrates. A positron emission tomography–computed tomography (PET-CT) demonstrated bilateral hilar adenopathy with pathologic fluorodeoxyglucose (FDG) uptake, as well as pathologic FDG uptake at pulmonary nodules. Another finding was thickening throughout the ascending colon. Bronchoscopy with endobronchial ultrasound was performed, the pathology report indicated lymphatic tissue and non-necrotizing granulomas consistent with sarcoidosis.

Discussion

This case is an example of a rare manifestation of Lofgren's syndrome (LS), with a concurrent profound vitamin B12 deficiency. Limited data are available regarding nutritional deficiencies and the association to LS or sarcoidosis. This patient presented a profound and resistant vitamin B12 deficiency, even though his diet was not vegan or vegetarian. His vitamin B12 levels throughout the years ranged from 111 to 250 pmol\L alternately, without a significant response to supplemental therapy. In this current hospitalization vitamin B12 levels were measured as low as 75 pmol\L, the lowest value recorded throughout his entire medical history. These coinciding events raise the suspicion that there is a relation between vitamin B12 deficiency and the diagnosis of LS.

Several mechanisms are suggested to be attributed to the relationship between vitamin B12 deficiency and LS. The first is sarcoid GI involvement. The process of absorbing vitamin B12 involves a few sites in the GI tract – vitamin B12 is bound first to Haptocorrin in the saliva, then in the stomach Haptocorrin is dissolved, and the cobalamin is bound to intrinsic factor (IF) until this complex reaches the terminal ileum where it is absorbed to the blood stream.[9] Any disruption of the gastric or terminal ileum mucosa could potentially cause vitamin B12 deficiency. Sarcoid in the GI tract is relatively rare; however, gastric sarcoid is considered the most frequent form of sarcoid in the GI tract. It usually presents with epigastric pain, nausea, vomiting and weight loss, although 10% of patients can be asymptomatic. Microscopically, the most frequent lesion observed is diffuse infiltration of the gastric wall,[5] with the assumption that such infiltrations will reduce levels of IF and therefore vitamin B12 malabsorption. There are a few case reports describing gastric sarcoidosis with concomitant severe vitamin B12 deficiency.[10,11] In both cases, the patients presented with a megaloblastic anemia, unlike this patient, presented with normocytic anemia, that can be explained by a combined etiology, such as vitamin B12 deficiency with a concurrent chronic disease.[12] Ileal sarcoidosis is infrequent, usually presents in the terminal ileum, and occurs with a concomitant sarcoid gastric involvement.[5] A case report published in 1992 described a woman with a persistent folate deficiency and proven ileal sarcoidosis preceding systemic manifestations of sarcoidosis in years.[13]

A second proposed mechanism is pernicious anemia. There are several case reports describing sarcoidosis with vitamin B12 deficiency, atrophic gastritis, and positive anti-parietal cell antibodies.[14,15] Although sarcoidosis with the

combination of other immune mediated disorders exists,[16] pernicious anemia with sarcoidosis is not well documented and it is not more prevalent in patients with sarcoidosis than in the general population.[14,17] Also, pernicious anemia in this patient is less likely as the relevant antibodies were negative.

A third proposed mechanism is food-cobalamin malabsorption (FCM), which is characterized by the inability to release cobalamin from food or intestinal transport proteins. This syndrome is more prevalent among the elderly and is usually related to atrophic gastritis.[18] There are few reported cases of FCM in relation to Sjogren syndrome.[19] Another study reported vitamin B12 deficiency in patients with systemic lupus erythematosus with a proposed underlying cause of FCM.[20] The relation between FCM and autoimmune diseases is unknown. However, we assume that the same mechanism may possibly be related to LS.

We suggest a possibility that this patient has sarcoidosis involvement of the GI tract, and more specifically gastric involvement. Vitamin B12 deficiency might have been the first and early manifestation of LS, although extrapulmonary involvement in LS is approximately 12%.[7] To confirm gastric sarcoid, endoscopic investigation should be performed with biopsies demonstrating typical pathological findings of sarcoidosis.[10] To note, PET-CT demonstrated an accidental finding of thickening of the ascending colon, which will require further investigation with a colonoscopy to rule out a rare colonic involvement.[5]

After the initiation of steroid and vitamin B12 replacement therapy, vitamin B12 levels were >1476 pmol\L. It can be debated whether the replacement therapy of vitamin B12 alone elevated vitamin B12 levels, or steroid therapy improved the disease status and therefore also the vitamin B12 levels. However, supplemental treatments did not resolve the B12 deficiency throughout the years, until steroid treatment was initiated. Furthermore, during follow-up and initiation of tapering down of steroids regimen, the patient relapsed and developed vitamin B12 deficiency while taking supplemental vitamin B12.

Although the patient has no GI symptoms, it is possible that vitamin B12 deficiency is the sole manifestation of GI sarcoidosis. Additional tests are warranted and were recommended to the patient, to diagnose GI involvement, mainly gastroscopy and colonoscopy with biopsies.

In conclusion, sarcoid involvement of the GI tract is suggested to be the cause of vitamin B12 deficiency in this patient, responsive mainly to steroid treatment with partial response to supplemental vitamin B12. An informed consent was obtained from the patient for the publication of their case details and any accompanying images.

Disclosure

The authors report no conflicts of interest in this work.

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