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Atypical sarcoidosis masquerading as neutropenia

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Abstract. Sarcoidosis is a systemic granulomatous disease of unknown etiology. Gastrointestinal involvement in sarcoidosis is rare and so are its hematological manifestations. We report an unusual case of sarcoidosis with isolated gastric involvement and concomitant B12 and iron deficiency, leucopenia and severe neutropenia. The diagnosis of GI tract sarcoidosis is difficult and other causes of GI tract granulomas should be excluded. Patients can have unusual manifestations like B12 deficiency and one should be aware of this possibility. Careful follow-up and frequent reevaluation of the patient may be a sound strategy in equivocal cases with unusual presentation. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 160-163)*

Key words: sarcoidosis; gastrointestinal; neutropenia; leucopenia; B12 deficiency

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology, which most commonly manifests with pulmonary findings. It is rare to find an isolated extrapulmonary disease (less than 10 % of patients) of hollow organs.(1). Gastric sarcoidosis, particularly involving the antrum, affects approximately 10 % of patients with systemic disease (2). Gastrointestinal (GI) tract sarcoidosis commonly occurs subclinically, with clinical manifestations present in only 0.1 to 0.9 % of patients with the disease (3). Sarcoidosis with B12 deficiency and hematological abnormalities which may include mild anemia, neutropenia, lymphopenia, eosinophilia and thrombocytopenia are extremely uncommon. We report a rare case of isolated gastric sarcoidosis presenting with leucopenia, neutropenia, iron and B12 deficiency.

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Case

A 58 -year old- African-American male with no significant past medical history was referred to our clinic for evaluation of leucopenia and severe neutropenia discovered on routine blood work by his primary care physician. He complained of generalized fatigue, early satiety and an unintentional weight loss of 20 pounds over a period of 6 months. Physical examination was unremarkable. His white count was 2200/l with absolute neutrophil count of 670 cells/μl, hemoglobin was 14.1 g/dl and hematocrit 42.3%, with a mean corpuscular volume of 84 fl and platelet count was 175,000 /l. Peripheral smear was unremarkable except for rare elliptocytes and 1+ poikilocytosis. His workup at our office included B12 and folate levels, iron studies, rheumatology panel including ANA and rheumatoid factor, viral and autoimmune hepatitis panel, serum protein electrophoresis as well as urine protein electrophoresis to rule out multiple myeloma. Results were significant

for a B12 level of 172 pg/ml normal range (211-946 pg/ml), and a ferritin level of 14 ng/ml normal range (30-400 ng/ml). Anti-parietal antibody was negative. His counts didn't recover with oral B12 and iron replacement. Bone marrow biopsy revealed normocellular marrow with 1.2% blasts, normal myeloid: erythroid ratio and normal megakarocytes .Myeloid maturation appeared orderly and complete. There was no evidence of granulomas. Further investigation included a computed tomography scan (CT) abdomen which revealed diffuse thickening of the wall of the gastric antrum and innumerable enlarged mesenteric lymph nodes. There was no evidence of splenomegaly. Upper GI endoscopy revealed gastritis and an isolated gastric polyp. Biopsies of the gastric antrum and gastric polyp revealed severe acute and chronic inflammation with non-necrotizing granulomas (fig. 1). There was no evidence of H. pylori, acid fast bacilli, or fungi. CT chest did not show any evidence of pulmonary sarcoidosis. Pulmonary function tests showed normal lung volume and flow and a normal diffusion capacity. Angiotensin converting enzyme (ACE) level was elevated at 95. Initial oral supplement with B12 and iron did not improve his white blood cell count or B12 or ferritin level but after starting him on oral prednisone for the treatment of gastric sarcoidosis along with supplementation of iron and vitamin B12, he started gaining weight with improvement in his energy levels. Repeat blood work revealed a white count of 4300/l with an absolute neutrophil count of 2460 cells/µl within 2 weeks of initiation of therapy. Repeat B12 level was 787 pg/ml, ferritin was 188ng/ml and ACE level was 24.

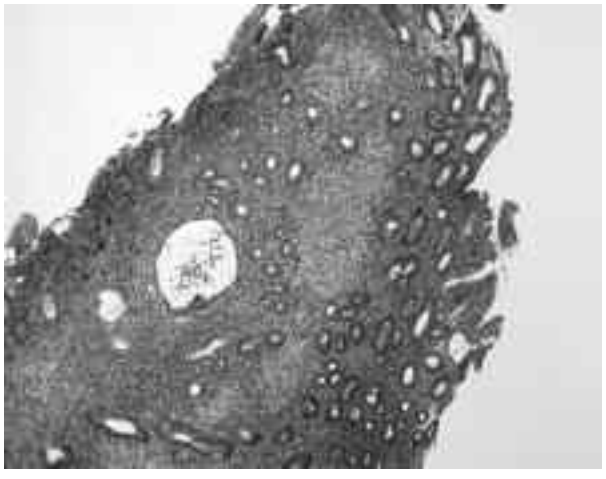

Fig. 1. Non-necrotizing granulomas in the lamina propria with accompanying acute and chronic inflammation.

Discussion

This case is an example of some rare manifestations of sarcoidosis that posed a huge diagnostic challenge. Sarcoidosis, a disease of unknown etiology characterized by noncaseating granulomas, produces varied symptoms depending upon the major sites of involvement (4). GI sarcoidosis is extremely rare, and being symptomatic from it is even rarer. In fact the true incidence is unknown since most patients are asymptomatic and sarcoidosis is only found on autopsy (5). Several autopsy studies found no GI involvement (6, 7) while another reported intestinal and gastric disease in 3.4% and 2.5 % respectively (8). Various hematological abnormalities described in sarcoidosis include anemia which may be hemolytic or non-hemolytic, leucopenia, monocytosis, eosinophilia, and thrombocytopenia, however, the most frequent hematological abnormality secondary to the disease is lymphopenia. Sarcoidosis patients as a group have a lower mean total lymphocyte count than normal controls; especially in those with active disease (9). Hematological abnormalities in sarcoidosis occur independently of, and are probably no more frequent in association with the splenomegaly of sarcoidosis than with any other forms of splenomegaly. There are few data on the incidence of bone marrow involvement in sarcoidosis. Some clinical and autopsy series report that non-caseating granulomas in the bone marrow were encountered in 20-30% of sarcoidosis patients. The incidence of bone marrow involvement is higher in patients who have abnormalities in any of their hematological parameters.

Clinical presentation of gastric sarcoidosis varies depending on the intensity of granulomatous inflammation and anatomic location of the gastric involvement. When gastrointestinal sarcoidosis is symptomatic, it is usually related to granulomatous organ infiltration or as an effect of mechanical compression by enlarged lymph nodes (10). Gastric sarcoid usually manifests as gastric ulcer or diffuse infiltration of gastric mucosa with granulomas causing secondary fibrosis and luminal narrowing. Gastric

polypoid is a rare, early phase and atypical appearance of diffuse type gastric sarcoidosis. Single and multiple gastric polypoid lesions have been reported in the literature as well (11-13). Gastric sarcoid manifests as postprandial epigastric pain, nausea, vomiting, weight loss and upper GI bleeding (14-16). Extrinsic compression from lymphadenopathy can occur throughout the gastrointestinal tract. In some patients, malabsorption has resulted, and a megaloblastic anemia due to malabsorption of vitamin B12 has been documented. This was explained by terminal ileal disease in one patient (17) and achlorhydria in another (18), and in a third patient was attributed to achlorhydria secondary to gastric sarcoidosis (19). Teichman et al reported a case of isolated gastric sarcoidosis complicated by pernicious anemia. Other possible mechanism for cytopenias in sarcoidosis could be granulomas directly affecting the bone marrow (20). However, there is no relationship between the presence or absence of cytopenias and bone marrow granulomas (14). Local inflammation can lead to sequestration of cells, particularly lymphocytes, the most likely reason for lymphopenia in this disease. Furthermore, splenomegaly can cause sequestration of various cells. Although often noted on CT scans, splenomegaly seems to have few, direct clinical sequelae. Finally, sarcoidosis can cause immunologic, antibody-mediated destruction of certain blood components, notably platelets. Anemia, which is often mild and can be seen in many persons with sarcoidosis, likely, occurs because of the effect of chronic inflammation in the bone marrow, as seen in the classic "anemia of chronic disease."

Diagnosis of sarcoidosis is generally based upon a compatible history, demonstration of granulomas in at least two different organs, negative staining and culture for acid fast bacilli, absence of occupational or domestic exposure to toxins, and lack of drug-induced disease (21, 22). ACE levels are elevated in 60% of patients and have been shown to correlate with the level of disease activity (23).

Although there are no data available from clinical trials, corticosteroid therapy seems to be effective in GI tract sarcoidosis. The decision to treat gastrointestinal tract sarcoidosis is based upon the activity and extent of the disease. Overall prognosis is good. Corticosteroid therapy produces a dramatic clinical response in about 66% of patients with systemic gastric sarcoidosis (15). Prednisone 20-40 mg/d can be started with gradual dose reduction. Although the duration of therapy depends on clinical response, rapid reduction of prednisone may result in recurrence of the symptoms. The disease is monitored clinically, radiographically, and by serum ACE levels. Methotrexate, chlorambucil, azathioprine, infliximab, and cyclosporine are alternative agents that can be used in refractory cases to prednisone but initial therapy with these agents can be challenging in the presence of neutropenia.

Conclusion

Our case underscores an unusual presentation of sarcoidosis with isolated gastric involvement and concomitant B12 and iron deficiency, leucopenia and severe neutropenia. We do not believe that nutritional deficiency was contributing to the patient's severe neutropenia as there were no other hematological manifestations of B12 or iron deficiency like anemia or megaloblastoid changes in the bone marrow. Prolonged achlorhydria, the mechanism of which is unclear in sarcoidosis, can cause malabsorption of both B12 and iron. B12 deficiency could be further explained by impaired production of intrinsic factor. Severe neutropenia with gastric sarcoidosis is rarely described and we believe that the mechanism of severe neutropenia in our case was immune mediated which nicely responded to the steroid therapy. It is also important to replace iron and vitamin B12 in addition to sarcoidosis therapy in this type of cases to prevent future hematological manifestations. Isolated gastrointestinal sarcoid can be challenging diagnosis to make. In equivocal cases, clinicians should be cautious in making a diagnosis of GI tract sarcoidosis before excluding other alternative diagnoses. Careful follow-up and frequent follow up of the patient may be a sound strategy in these difficult cases.

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