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Sarcoidosis, Celiac Disease and Deep Venous Thrombosis: a Rare Association

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ABSTRACT

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology and it may rarely be associated with a second disorder. Celiac disease is an immune-mediated enteropathy characterized with malabsorption caused by gluten intolerance, and several reports indicate an association between celiac disease and sarcoidosis. In addition, although celiac disease is associated with several extraintestinal pathologies, venous thrombosis has been rarely reported. Herein we present a rare case report of a patient with a diagnosis of sarcoidosis, celiac disease and deep venous thrombosis because of the rare association of these disorders. The patient was admitted with abdominal pain, weight loss, chronic diarrhea and a 5-day history of swelling in her right leg. A diagnosis of deep venous thrombosis was achieved by doppler ultrasonographic examination. The diagnosis of celiac disease was made by biopsy of duodenal mucosa and supported with elevated serum level of anti-gliadin IgA and IgG, and a diagnosis of sarcoidosis was achieved by transbronchial needle aspiration from the subcarinal lymph node during flexible bronchoscopy.

Key Words: Sarcoidosis, celiac, venous thrombosis

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Introduction

Sarcoidosis is characterized by granulomatous inflammation in any part of the body, usually in more than one area (1). Rare manifestations of sarcoidosis include unusual patterns of organ involvement, or are the result of granulomatous inflammation developing in unusual locations for sarcoidosis. In other rare cases, sarcoidosis is associated with a second disorder. Celiac disease (CD) is a chronic, autoimmune inflammatory disease of the small intestine mostly characterized by malabsorption caused by gluten intolerance, and in several reports it has been reported that CD may be associated with sarcoidosis (2, 3) and both sarcoidosis and CD may be the result of a related defective antigen handling process. Moreover, although CD is associated with several extraintestinal conditions, venous thrombosis is an uncommon presentation of CD. The probable reasons for venous thrombosis in CD that have been reported are hyperhomocysteinemia and protein S deficiency and the site of venous thrombosis is predominantly an intraabdominal localization, which is different from the presented case.

Case Report

A 78 year old female patient was admitted with abdominal pain, weight loss and chronic diarrhea of one year duration, and a 5-day history of swelling in her right leg. On physical examination, the patient appeared fatigued, the temperature was 36.8°C, the respiratory rate 14/min, heart rate 87/min and blood pressure was 110/60 mmHg. Lung and cardiac examinations were normal. The right leg showed marked swelling with edema and Homan's sign was positive. The white blood cell count was $8.5x10^3/mm^3$, hemoglobin was 10.5g/dL, platelet count was $410x10^3/mm^3$ and erythrocyte sedimentation rate was 66 mm/h. The total serum protein and albumin levels were 5.7g/dL (N:6.4-8.3) and 2.1g/dL (N:3.5-5.2) respectively. The 24-hour urine protein level was 364 mg (N:<140 mg). Arterial blood gas analyses were as follows: PaO_2: 71.9 mmHg, $PaCO_2$: 32.7 mmHg and pH: 7.45 when breathing ambient air. Autoantibodies including ANA, Anti ds-DNA, RF and ANCA were negative. Microscopic examination of feces was normal and pathogenic microorganisms were not detected in the culture of feces. Pulmonary function tests were normal. The protein C, protein S and antithrombin III levels were 57.8% (N:70-140), 57.6% (N:76-135) and 61.9% (N: 84-120) respectively. In doppler ultrasonographic examination, there was evidence of acute thrombosis in the right common femoral, deep femoral and popliteal veins. Thorax computed tomography (CT) revealed multiple mediastinal, bilateral hilar lymphadenopathy and no paranchymal infiltration (Figure 1). A flexible bronchoscopy was performed and the cytology of transbronchial needle aspiration from the subcarinal lymph node revealed non-necrotizing granulomatous inflammation and a diagnosis of radiological stage I sarcoidosis was made. Cervical ultrasonography revealed enlarged lymphadenopathies. There was no eye or other organ involvement. While no treatment was

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given for sarcoidosis, enoxaparin 1mg/kg bid subcutaneously was started for deep venous thrombosis (DVT). Because of the history of chronic diarrhea associated with signs of malnutrition, the patient was serologically tested for CD.An elevated serum level of anti-gliadin IgA and IgG was found. The levels of anti-gliadin IgA and IgG were >100U/mL (N: 0-10) and 178U/mL (N:0-10) respectively. During upper gastrointestinal (GIS) endoscopy, atrophic gastritis and duodenitis was observed. Biopsy of duodenal mucosa revealed villous atrophy and an increase in intraepithelial lymphocytes (Figure 2). According to these findings, the diagnosis of CD was made and a gluten-free diet was started. After the gluten-free diet, a considerable improvement in her GIS complaints was observed.

Discussion

CD is a gluten-sensitive enteropathy characterized by chronic inflammation of the small intestinal mucosa that gradually leads to the development of villous atrophy. Several case reports and European studies have suggested an association between sarcoidosis and CD (2-6).

Several investigators have demonstrated an association between sarcoidosis and human leucocyte antigen (7, 8). In particular, the class II haplotype, HLA-DR3, DQ2, has been shown to be increased in several sarcoid populations. This haplotype has also been linked with a number of other immunopathological conditions including the autoimmune disorders. It has been reported that CD may be associated with sarcoidosis, and suspectibility to CD has also been strongly linked to HLA-DQ2, which in Northern Europeans is linked to DR3 or the much rarer DR5/DR7 in well over 90% of cases (9), suggesting that both sarcoidosis and coeliac disease may be the result of a related defective antigen handling process. In contrast to these previous reports, DQ5, DQ6, DR15 and DR16 was detected in the presented case.

Rutherford et al. compared 102 sarcoid patients and 105 healthy, ethnically matched controls for CD and found that, 12 (12%) patients and four (4%) controls had elevated anti-gliadin IgA (2). They also showed an increased prevalence of biopsy-proven CD in patients with sarcoidosis (4% prevalence compared with 1% in the controls) which did not reach statistical significance (p=0.21). In contrast, Papadopoulos et al. found an increased frequency of gliadin antibodies but no actual increase in the diagnosis of CD in patients with sarcoidosis (3). Hwang et al. studied 866 biopsy-proven CD patients and found that 10 patients had a comorbid diagnosis of sarcoidosis (4). They concluded that, in patients with CD, there was a significantly increased risk of sarcoidosis. Bianconcini et al. reported a 42 year-old patient with a diagnosis of CD and sarcoidosis (5). Douglas et al. reported 5 patients with sarcoidosis and CD (6). In their three cases the GIS symptoms of CD preceded those of sarcoidosis and in the other two patients symptoms of both diseases appeared at the same time. In contrast, Hwang et al. reported that most of the patients in their study were diagnosed with sarcoidosis before CD (4). In our case the GIS symptoms preceded those of sarcoidosis.

Since undetected CD predisposes to osteoporosis, and patients with CD have an increased risk of GIS malignancy,

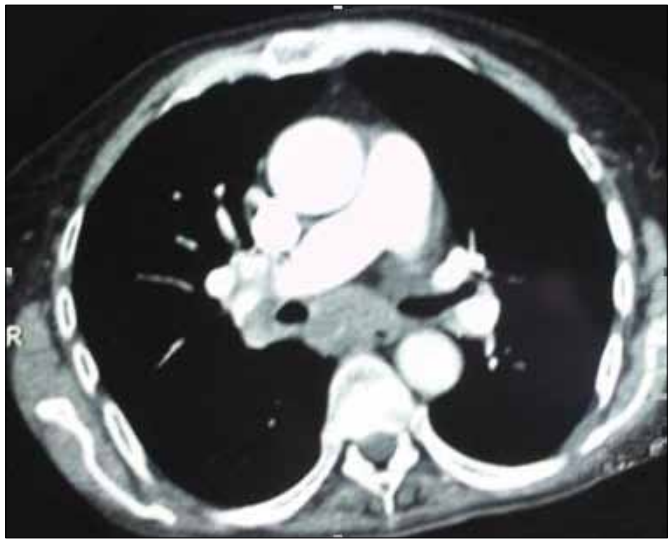

Figure 1. Thorax CT of patient revealing subcarinal and hilar lymphadenopathy

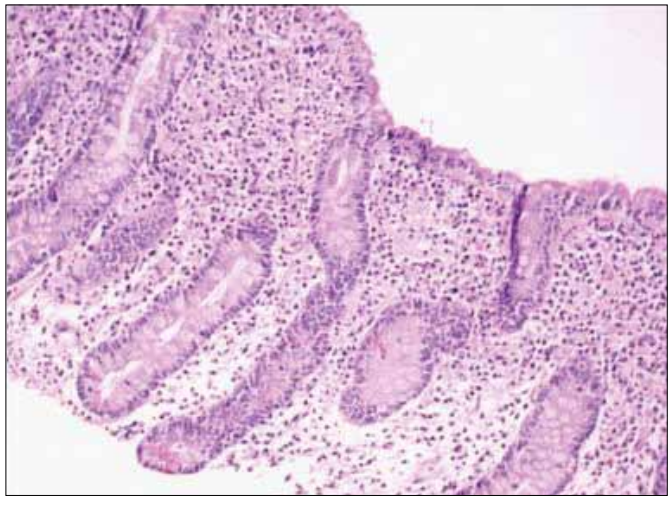

Figure 2. Villous atrophy and focal increase in intraepithelial lymphocytes in duodenal mucosa, H.E X400

and gluten avoidance may significantly attenuate the risk of these complications in patients with CD, we suggested that patients with sarcoidosis should be evaluated for an early diagnosis of CD.

Venous thrombosis is an uncommon presentation of CD. While Budd-Chiari syndrome associated with intraabdominal venous thrombosis represents the majority of reported cases, venous thrombosis in other localization has more rarely been reported. In the presented case the site of venous thrombosis was the extremity as an extremely rare localization. The study by Ludvigsson et al. had shown a significant, positive association between CD and venous thromboembolism (10). The exact causes of thrombosis in patients with CD are yet unknown, but in some cases thrombosis has been attributed to acquired hyperhomocysteinemia as a concequence of folic acid and vitamin B12 deficiency (11). Saibeni et al. reported that hyperhomocysteinemia is more frequent in patients with CD than in a healthy control group (12). Protein S deficiency is another reported possible cause of venous thrombosis. Bahloul et al. re-

ported a patient with CD and cerebral venous thrombosis and the etiologic investigation revealed protein S deficiency (13). Similarly, Kallel et al. reported a patient with CD, deep venous thrombosis and protein S deficiency (14). However, Kchaou et al. reported a case of a 28-year-old woman who presented with CD associated with Budd-Chiari syndrome for which no cause could be found (15). In our case, while serum homocystein level was normal, we detected antithrombin III, protein C and protein S deficiency as the cause of DVT and to our knowledge, this combination has never been reported previously. Although the patient was an elderly subject with a chronic inflammatory disease, there was no other risk factor for venous thrombosis except antithrombin III, protein C and protein S deficiency such as immobilization, a history of trauma or surgery. It is well known that heparin and oral anticoagulants can affect the serum levels of coagulation parameters. In the presented case, the protein C and protein S levels were measured while the patient was on heparin therapy and the antithrombin III level was measured after cessation of heparin and while the patient was on warfarin therapy.

In conclusion, in patients with CD or sarcoidosis, the rare association of these two disorders should be brought into mind. In additon, patients with CD should be carefully evaluated for venous thrombosis.

Conflict of Interest

No conflict of interest was declared by the authors.

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