

Limited form of Wegener's granulomatosis in a patient with Crohn's disease. A case report

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ABSTRACT

Wegener's granulomatosis (WG) is a multisystemic disease of unknown etiology characterized by necrotizing vasculitis and granulomatous inflammation. Although, the gastrointestinal tract can be involved in this vasculitis, the association between WG and Crohn's disease (CD) exists and was previously described. We report the case of a 29 year-old Tunisian white patient previously diagnosed with CD, presenting 3 years later with a perforated nasal septum, mucosal ulcers and sinusitis. He had also a skin ulcerative eruption of the trunk. There was no evidence of a flare of his CD. A computed tomography scan of the head showed nasal septal perforation, and maxillary pansinusitis. A biopsy from the nasal septum demonstrated nasal mucosa with extensive necrotizing granulomatous reaction associated with vasculitis. The patient was diagnosed as having limited form of Wegener's granulomatosis. He was treated with prednisone 60 mg/day and methotrexate 15 mg weekly. After Two months of treatment, he had no complaints, skin eruption and orofacial lesions were improved. Although, the gastrointestinal tract can be involved in patients with WG, the association with a CD exists and was previously described. The distinction between the two conditions and their possible coexistence is very important and requires histological examination of involved tissue.

Keywords: Crohn's disease, vasculitis; Wegener's granulomatosis, corticoid therapy

INTRODUCTION

Wegener's granulomatosis (WG) is a necrotizing vasculitis of the small to medium-sized arteries characterized by involvement of the upper and lower respiratory tract and the kidneys (1-3). Although, the gastrointestinal tract can be involved in 10%-24% of patients with WG (4-8), the association with a Crohn's disease (CD) exists and was previously described (9,10). The distinction between the two conditions and their possible coexistence requires histological examination of involved tissues. We describe a patient previously diagnosed with CD, presenting 3 years later with a perforated nasal septum and histological evidence of nasal granulomas and ultimately diagnosed as having WG.

CASE PRESENTATION

A 29-year-old Tunisian white man first developed a chronic profuse diarrhea with blood and mucus in 2008. He consulted in gastroenterology. The colonoscopy revealed multiple, deep, irregular ulcers of rectosigmoid mucosa. The rest of the colon was normal to the cecum. The ileal mucosa was ulcerated and very inflammatory. The histological diagnosis was consistent with CD, based on transmural inflammatory process including fissure ulcers and the finding of many lymphoid follicles in the subserosa with several non-necrotizing granuloma. He was subsequently treated for one year with mesalazine (2 g per day per os) with rapid resolution of the diarrhea. Intermittent bloody diarrhea had exacerbated

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in March 2010 and became more severe and was associated with abdominal pain. A 60 mg of prednisone for three weeks associated with azathioprine (150 mg/per day) were necessary to establish control.

In March 2011, he was hospitalized in gastroenterology for a subocclusive syndrome and abdominal pain. The plain abdominal X-ray showed multiple air fluid levels. Abdominal ultrasound revealed thickening of the last ileal loop associated with intraabdominal effusion. Colonoscopy revealed thickened and rigid mucosa of the ileocecal valve and stigma of active bleeding. An explorative laparotomy showed terminal ileitis, effusion in the Douglas pouch, blood throughout the colon and lower. An ileocecal resection was performed with an end to end ileocolic anastomosis. The histological examination of the resected specimens confirmed the diagnostic of Cohn's disease. There were no extraintestinal manifestations of CD. Thereafter, intermittent bloody diarrhea was improved and mesalazine alone was used to maintain surgically induced remission and to prevent relapses.

In April 2011, the patient presented a nasal obstruction, rhinorrhea, and epistaxis. He had consulted in otolaryngology. The exams showed a nasal septum deviation. A septoplasty was performed. The evolution wasn't good and the patient developed a perforation of the septoplasty due to a delayed epithelial healing. Two others attempts of transplantation; rhinoplasty and septoplasty with graft materials from the ear, were failed. Histopathological studies had revealed a granulomatous leukocytoclastic vasculitis compatible with WG.

In November 2011, the patient was transferred in our Department of Internal Medicine. He has no personal or family history of tuberculosis. He didn't consume alcoholic beverage but he smoke 20-30 cigarettes per day for 15 years. On admission, he complained of sinus pain, of green sputum and epistaxis. He had no abdominal pain or diarrhea or fever. There were no apparent extra-intestinal manifestations of inflammatory bowel disease. Physical examination demonstrated normal vital signs. His body height was 160 cm and he weighed 65.7 kg. His blood pressure was 133/ 74 mmHg, and her pulse rate was 100/min. His abdomen was soft and non-tender. There were no significant neurological findings. The nose was tender, and the anterior portion of the nasal septum was perforated with a typical aspect of saddle nose deformity (Figure 1). The otolaryngologist examination revealed multiples ulcerated lesions of oral and nasal mucosa. He presented two perforations of the ear cartilage and large oropharynx ulceration. He had also a skin ulcerative lesion of the trunk (Figure 2). Ophthalmologic examination revealed a chronic conjunctivitis due to a dacrocystitis.

Laboratory tests showed normocytic normochromic anemia with hemoglobin at 11.9 g/dL. The white blood cell count was 8,600/mm³, and platelets count was 431,000/mm³. The erythrocyte sedimentation rate was 130 mm/hour and C-reactive pro-

tein was 20 mg/dL. Glucose, blood urea nitrogen, creatinine, sodium and potassium were all normal. Urinalysis on repeated testing was normal. Serological testing for HIV and syphilis, as well as sputum cultures for tuberculosis were negative. Skin test tuberculosis was negative. Serological testing for anti-nuclear antibodies (ANA), anti-DNA antibodies and rheumatoid factor were negative. The C3 level was 1,3 g/L and the C4 level 0.29 g/L. Indirect immunofluorescence for both c-ANCA and p-ANCA was negative.

A computed tomography (CT) scan of the head showed nasal septal perforation, and maxillary pansinusitis (Figure 3). A chest



Figure 1. a,b. saddle nose deformity caused by bony destruction of the nasal cavity in our patient with Wegener's granulomatosis. Before treatment with corticosteroid and Methotrexate (a). After 2 months of treatment (b).



Figure 2. a,b. Skin ulcerative lesion of the trunk. Before treatment (a); after treatment (b).

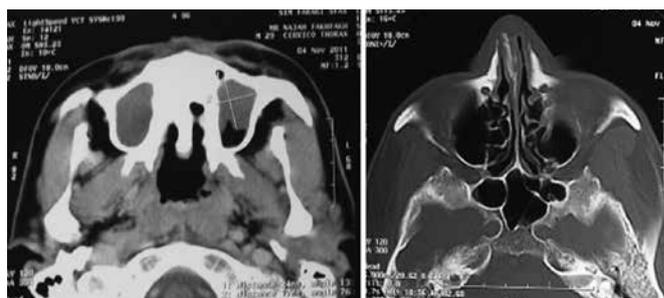


Figure 3. Computed tomography (CT) scan of the head showing nasal septal perforation and maxillary pansinusitis consisting with the diagnosis of Wegener's granulomatosis.

CT scan was normal. A skin biopsy revealed no specific inflammation. Another biopsy from the nasal septum, taken under local anesthesia, demonstrated nasal mucosa with extensive necrotizing granulomatous reaction associated with vasculitis. According to the criteria proposed by the American College of Rheumatology (1990 ACR criteria for the classification of WG) (11), the diagnosis of a limited form of WG was made based on the following evidence: the nasal destructive lesion, mucosa ulceration, pansinusitis, dacryocystitis and histological findings of granulomatous and vasculitis together. There were no pulmonary or renal involvements. Birmingham Vasculitis Activity Score (BVAS) was 14 points: Cutaneous (4), Mucous Membranes and Eyes (4), ENT (6). In another hand, there were no clinical, biological or endoscopic evidence of active CD.

The patient was treated with methotrexate (15 mg weekly), trimethoprim-sulfamethoxazole (2 cp/day) and prednisone (60 mg/day), which was reduced to 20 mg/day over a 2 month period and gradually tapered down. After Two months of treatment, he had no complaints, skin eruption and orofacial lesions were improved (Figures 1, 2).

DISCUSSION

The patient we describe had been diagnosed with CD 3 years prior to his present admission. The diagnosis had been based on the clinical presentation and pathological finding following surgical resection. The patient's disease responded very well to treatment with mesalazine and for the previous year, his disease was in complete remission.

The patient has developed recently a limited form with biopsy-verified WG. This was supported by the combination of a nasal destructive lesion, mucosa ulceration, pansinusitis and dacryocystitis and histological findings of granulomatous vasculitis. There aren't any pulmonary or renal involvements.

The co-existence of inflammatory bowel diseases (ulcerative colitis (UC) or CD) and WG has been reported (9,10,12-14). Their association in the same patient raises the question of a common etiologic basis including immunologic defect. Colitis may be the initial presentation of WG in some cases, while in others, chronic inflammatory bowel disease is complicated by extra-intestinal manifestations and/or secondary (immune complex-mediated) vasculitis (9,15). Demonstration of typical Crohn's epithelioid cell granulomas in one location and necrotizing palisading granulomas of WG can be an argument for the association between two granulomatous diseases (16).

First described by Friedrich Wegener in 1936 (17), WG is a form of vasculitis that affects various organs. Its incidence is 10 cases per million per year, and it mainly occurs among the middle aged. Definitive diagnosis of WG is based on tissue biopsy. Histopathological findings include the classic triad of vasculitis, granulomatous inflammation (with or without giant cells) and tissue necrosis; however, the full picture may not be seen in

one specimen (1,7,18). The disease has a predilection to involve upper and lower respiratory tract and the kidneys. In the clinical course of the illness, most patients show multisystemic disease (19). Only 6% of patients with WG present oral manifestations, however the majority appear during an advanced stage of the disease; oral symptoms are rarely an early indicator (20). The oral lesions may be either mucosal ulcers on the tongue, jugal mucosa, gums or palate, or gingival hyperplasia with a "bruised" coloring. It may also manifest in the eyes, causing epiphora due to involvement of the nasolacrimal duct (21,22). Otorhinolaryngologic manifestations are more frequent during the course of the disease (23). Nasal involvement consists of rhinitis with a feeling of nasal obstruction, hemorrhagic or purulent nasal discharge and sinusitis. These nasal manifestations may be a predicting sign of disease activity and of relapse (24). Perforation of the nasal septum and saddle nose deformity may occur during the evolution, although it does not necessarily imply disease activity (25). Although CD can also involve the oropharynx (nasal septal perforation, mucosal ulcers, sinusitis) (26), the presence of granulomatous vasculitis, the extensive necrosis, the type of granulomata, and the lack of intestinal inflammation indicate that our patient developed WG rather than an extra-intestinal complication of CD. A pathologic review of the surgically resected colonic tissue did not reveal evidence of vasculitis or granulomas typical of WG.

In the other hand, and although involvement of the gastrointestinal tract can occur in WG, it remains an uncommon and rare manifestation and usually detected in autopsy studies (4,7,5). It is also likely that intestinal manifestation in WG occurs during active phases of the disease which may explain that intestinal symptoms in our patient are related to the CD and not to WG. It is suggested that the use of corticosteroid therapy may be an etiological factor for the development of intestinal manifestations in this vasculitis (27). In some reported cases, the main problem is to determine the causative agent for intestinal involvement (16). Classical descriptions of intestinal pathology of WG have been based on the study of surgically resected specimens. Pathological findings include multiple small ulcerations, and intestinal perforation (28). Histological examination usually shows marked mixed inflammatory infiltrate associated with necrotizing and granulomatous vasculitis of small-medium sized vessels. The small bowel is the most common site (29,30). In our case, the histological examination showed transmural inflammatory process including fissure ulcers and the finding of many lymphoid follicles in the subserosa with several non-necrotizing granuloma. CD was the major possibility and the diagnosis was confirmed by histological finding.

5-aminosalicylic acid (5-ASA) preparations are well-established preparations used in the management of inflammatory bowel disease (31,32). Medical therapy outcomes and clinical trials of these medications are often categorized by their ability to achieve induction of response or remission during a period of active disease, to maintain medically induced remission, or to

maintain surgically induced remission (32). These drugs are most useful for the treatment of mild to moderate flares of ulcerative colitis and, especially, for maintenance of remission (31). However, there is conflicting evidence regarding the efficacy of oral 5-ASA in active CD and their use in mild to moderate CD has been debated. Mesalazine has not been shown to be superior to placebo for maintaining medically induced remission, however, it may have a modest effect in surgically induced remission for patients without risk factors for recurrent surgery (such as mucosal ulceration, smoking, or predictors of disabling course) (32). Recently, the American and the British National Gastroenterology Associations have recommended the use of high-dose 5-ASA for the first-line treatment of mild ileal, ileocolonic or colonic CD (31). In our case, patient's bowel symptoms were improved by surgical resection of the obstruction and mesalazine was used as a preventive therapy after surgery.

Three years later, our patient developed orofacial manifestation including mucosal ulcers and a perforated nasal septum with a difficulty in cicatrization. Some of the authors suggested that in order to establish the diagnosis of intestinal WG there should be histological evidence of vasculitis (6). Inflammatory and infective bowel diseases were considered a major differential diagnosis. The American College of Rheumatology criteria distinguish patients with WG from other patients with a different vasculitis on the basis of criteria with high level sensitivity and specificity. The four criteria for WG include abnormal urinary sediment, abnormal findings on chest X-ray, oral ulcers or nasal discharge, and granulomatous inflammation on biopsy. The presence of two or more of these four criteria is associated with a sensitivity of 88.2% and a specificity of 92.0% (11). Although the c-ANCA are not considered a diagnostic criterion according to "The American College of Rheumatology", they have a 96% specificity and a 92% sensitivity (24). If the c-ANCA are negative, they don't necessarily exclude disease; in fact, in early stages, the analytical results of c-ANCA may be negative, especially if there is no renal involvement. In any case, they play an important role in the diagnosis and monitoring of the regression of the disease once treatment has been initiated (20,25). The current treatment of WG and do not have contraindications, methotrexate and glucocorticoids can induce and maintain remission. For patients with severe disease, options include glucocorticoids combined with either cyclophosphamide or rituximab (33). Methotrexate is an alternative in patients with less severe disease and has been used with good results in limited forms such in the present case.

In summary, while the association between CD and WG appears to be extremely rare, it should be considered a diagnostic possibility in patients with either disease who present new symptoms that are not typical of the existing diagnosed disease. The distinction between the two conditions and their possible co-existence requires histological examination of involved tissue.

Although, the gastrointestinal tract can be involved in patients with WG, the association with a CD exists and was previously described. The distinction between the two conditions and their possible coexistence is very important and requires histological examination of involved tissue.

Conflicts of Interest: No conflict of interest was declared by the authors.

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