Wegener's Granulomatosis in a Patient with Crohn's Disease*

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Wegener's granulomatosis and Crohn's disease are two distinct chronic inflammatory diseases that may involve various organ systems, including the alimentary tract and the oropharynx. In both diseases there is an association with different types of anti-neutrophil cytoplasmic antibodies. We describe a patient previously diagnosed with Crohn's disease, presenting 13 years later with a perforated nasal septum and histological evidence of nasal granulomas and ultimately diagnosed as having Wegener's granulomatosis.

Case Description

A 36-year-old man was admitted to our hospital because of severe nasal pain, difficulty in nasal breathing, repeated epistaxis during the 2 months prior to his admission, and profound fatigue. There was no history of facial trauma.

Twelve years previously he had been admitted because of a fistula to his right groin. An explorative laparotomy revealed terminal ileitis, and a right hemicolectomy was performed. The histological diagnosis was Crohn's disease, based on transmural inflammatory process including fissure ulcers and the finding of many lymphoid follicles in the subserosa with several non-necrotizing granulomata. He was subsequently treated for one year with 5-amino salicylic acid with good response. A follow-up colonoscopy performed 3 years prior to his present admission was normal.

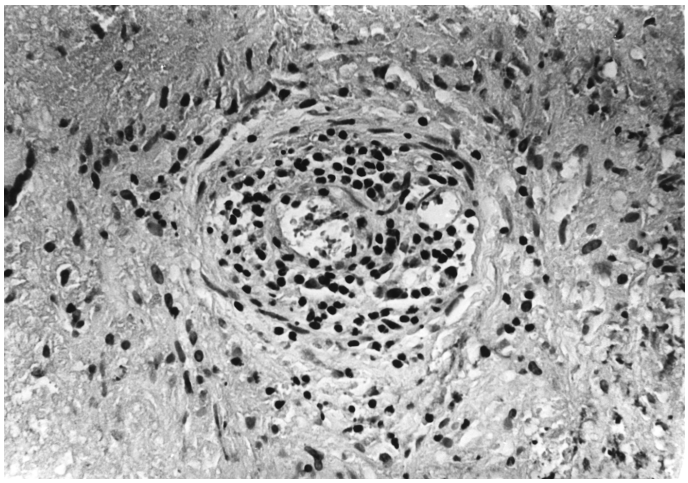
At the present admission, he had no abdominal pain or diarrhea and was not taking any medication. Physical examination demonstrated normal vital signs. The nose was tender, and the anterior portion of the nasal septum was perforated. Examination of the heart, lungs, abdomen and neurological system was normal. There were no apparent extra-intestinal manifestations of inflammatory bowel disease. Laboratory tests showed normocytic normochromic anemia of hemoglobin 12.9 g/dl. The white blood cell count was 8,360/L, and platelets 431,000/L. The erythrocyte sedimentation rate was 130 mm/60 minutes. Glucose, blood urea nitrogen, creatinine, sodium and potassium were all normal. Urinalysis on repeated testing was normal. Testing for fecal occult blood was negative. Serological testing for HIV and syphilis, as well as sputum cultures for tuberculosis were negative. Serological testing for anti-nuclear antibodies, anti-DNA antibodies and rheumatoid factor was negative. The C3 level was 145 mg/dl and the C4 level 32 mg/dl. Indirect immunoflorescence for both c-ANCA and p-ANCA was positive. The chest X-ray was normal. A computed tomography scan and magnetic resonance imaging study of the head demonstrated a proliferation of soft tissue in the left naris of the nose, with nasal septum deviation due to local pressure. The paranasal sinuses were normal. A chest CT scan was normal.

A biopsy from the nasal septum, taken under local anesthesia, demonstrated nasal mucosa with extensive necrotizing granulomatous reaction [Figure 1] associated with vasculitis. Deep mucosal fissures or small non-caseating granulomata were not demonstrated. The patient was diagnosed with limited Wegener's granulomatosis. He refused treatment with methotrexate and was initially treated with trimethoprim-sulfamethoxazole and prednisone 60 mg/day, which was reduced to 30 mg/day over a 2 month period and gradually tapered down. The patient's fatigue and facial pain disappeared within a short time.

His symptoms recurred when the prednisone dose was 15 mg/day. He developed severe serous otitis media with right ear deafness, pansinusitis and extreme headaches. CT scan showed nasal septal perforation, proliferation of soft tissue in the nasal cavity, and pansinusitis. A repeated biopsy from his nose demonstrated granulomatous vasculitis. Two weeks later the patient presented with symptoms of right eye redness and pain and numbness in both legs. Ophthalmologic examination revealed severe episcleritis. A nerve conduction test was consistent with axonal degeneration of the left sural and peroneal nerves. The prednisone dosage was raised to 60 mg/day and the patient consented to therapy with methotrexate 20 mg/week. Three weeks later he was suffering fewer headaches and had started to regain his strength. Within 2 months the episcleritis had markely ameliorated

* See also review by Lambrecht et al. on page 621

ANCA = anti-neutrophil cytoplasmic antibodies



Blood vessel showing transmural vasculitis (hematoxylin & eosin. x400).

and no neurological deficit was observed.

Comment

There have been few reports of an association between inflammatory bowel disease, mainly ulcerative colitis, and Wegener's granulomatosis [1]. Crohn's disease and Wegener's granulomatosis share several clinical features: both can present as a gastrointestinal tract disease, both can involve the oropharynx, the extraintestinal manifestations of Crohn's disease can mimic common symptoms of Wegener's granulomatosis such as arthralgia, fever, skin abnormalities and weight loss, and both are associated with ANCA [2].

The patient we describe had been diagnosed with Crohn's disease 13 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 5-ASA and for the previous 8 years his disease was in complete remission. The present positive p-ANCA result might provide further corroboration for the diagnosis of Crohn's disease [3].

The patient was recently diagnosed as suffering from limited Wegener's granulomatosis. This was supported by the combination of a nasal destructive lesion, pansinusitis, otitis, subsequent development of episcleritis and the finding of c-ANCA. The histological findings of granulomatous vasculitis together with the lack of demonstrable pulmonary or renal abnormalities define the limited nature of this patient's disease.

Although nasal septal perforation has been reported in patients with Crohn's disease [4], the presence of granulomatous vasculitis, the extensive necrosis, the type of granulomata, the presence of c-ANCA and the lack of intestinal inflammation indicate that our patient developed Wegener's granulomatosis rather than an extraintestinal complication of Crohn's disease. A pathologic review of the surgically resected colonic tissue did not reveal evidence of vasculitis or granulomas typical of Wegener's granulomatosis.

C-ANCA are antibodies directed primarily against proteinase-3 in neutrophil azurophilic granules. The reported sensitivity of c-ANCA for Wegener's granulomatosis is between 32% and 92% with a pooled sensitivity of 66%, and the reported specificity 88–100% with a pooled specificity of 98% [5]. Other conditions in which positive c-ANCA results have been reported include tuberculosis, Hodgkin's lymphoma, HIV infection, microscopic polyangiitis and monoclonal gammopathies. It has been suggested that c-ANCA might be essential in the pathogenesis of Wegener's granulomatosis, however in about 30% of patients with the active limited form of the disease c-ANCA might not be detectable. Whether c-ANCA has a primarily pathogenic role or whether it may augment the immunoinflammatory process is unclear.

Inflammatory bowel diseases are associated with p-ANCA, more commonly in ulcerative colitis (50–80%) than in Crohn's disease (10–40%) [3]. In these cases, ANCA is specific for myeloperoxidase only in the minority of cases. ANCA specific for elastase, lactoferrin, cathepsin G and other neutrophil antigens has been reported in patients with inflammatory bowel diseases. Whether any of these ANCA have a role in the mucosal inflammation or in the clinical manifestations of patients with inflammatory bowel diseases is unknown.

In summary, while the association between Crohn's disease and Wegener's granulomatosis 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 coexistence requires histological examination of involved tissue.

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