

Granulomatosis with Polyangiitis in Patient with Crohn's Disease

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Abstract

Granulomatosis with polyangiitis 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 20 years later with a rapidly progressive glomerulonephritis and histological evidence of crescentic glomerulonephritis and surrounded by severe interstitial inflammatory infiltrate, ultimately diagnosed as having granulomatosis with polyangiitis.

Keywords: Granulomatosis; Inflammation; Glomerulonephritis; Lymphoma

Introduction

Granulomatosis with polyangiitis (GPA) called Wegner granulomatosis [1] 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 GPA and Crohn's disease (CD) exists and was previously described. We report the case of a 50-year-old Moroccan white female previously diagnosed with CD, presenting 20 years later with a rapidly progressive glomerulonephritis and histological evidence of renal granulomas and ultimately diagnosed as having GPA. There was no evidence of a flare of her CD.

Case Report

A 50-year-old woman was admitted to our hospital because of severe acute kidney injury, and profound fatigue. 20 years previously she had been admitted because of a fistula to her right groin. An explorative laparotomy revealed terminal ileitis, and a right hemicolectomy was performed. The histological diagnosis was CD, based on transmural inflammatory process including fissure ulcers and the finding of many lymphoid follicles in the subserosa with several non-necrotizing granulomata. She was subsequently treated for two years with Mesalazine (2 g per day per os) with good response and resolution of the diarrhea. A follow-up colonoscopy performed 5 years prior to her present admission was normal.

At the present admission, she had no abdominal pain or diarrhea and was not taking any medication. Physical examination demonstrated normal vital signs. 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 9.3 g/dL. The white blood cell count was 9,760/mL, and platelets 460,000/mL. The erythrocyte sedimentation rate was 78 mm/h. Glucose 0.86 g/L, urea 2.1 g/L, creatinine 470 umol/L, sodium 133 mmol/L and potassium 5.8 mmol/L, alkaline reserve 14 mmol/L. Urinalysis on repeated testing showed microscopic hematuria 69 000/ml and proteinuria 1.9 g/24 h.

Testing for fecal occult blood was negative. Serological testing for HIV and syphilis. Serological testing for anti-nuclear antibodies, anti-DNA antibodies and rheumatoid factor was negative. The C3 level was 122 mg/dl and the C4 level 34 mg/dl. Indirect immunofluorescence for both c-ANCA was positive. The paranasal sinuses were normal. A chest CT scan was normal.

The renal biopsy demonstrated involvement of essentially all glomeruli by necrosis. Approximately 80% of glomeruli had cellular crescents (Figure 1). There was focal disruption of Bowman's capsule. Most glomeruli had prominent adjacent periglomerular inflammation, including occasional multinucleated giant cells. Arteries and arterioles had moderate sclerosis as well as focal necrotizing vasculitis (Figure 2). Immunofluorescence demonstrated positivity with antibody to fibrinogen (Figure 3).

The patient was diagnosed with systemic GPA. She was initially

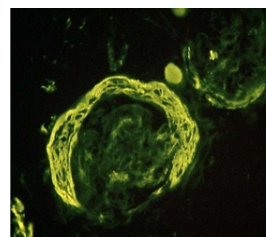


Figure 1: Immunofluorescence micrograph of a glomerulus demonstrates positivity with antibody to fibrinogen. The glomerular damage is so severe that fibrinogen leaks into Bowman's space, leading to proliferation of the epithelial cells and formation of the bright crescent. (Fluorescence microscopy 400x).

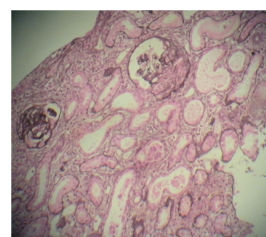


Figure 2: Arteries and arterioles had moderate sclerosis as well as focal necrotizing vasculitis.

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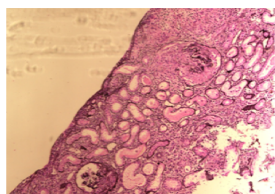


Figure 3: Well-developed cellular crescent with collapse of small amount of remaining glomerular tuft with segmental fibrinoid necrosis and extracapillary fibrin and necrosis (Jones silver stain; original magnification 200x).

treated with cyclophosphamide IV 500 mg/m² (J1, J15, J30,) and prednisone 60 mg/day after 3 bolus 750 mg, which was reduced to 30 mg/day over a 3 month period and gradually tapered down. Plasma exchange was not indicated [2,3]. Amelioration of renal function creatinine at 180 umol/L after 30 days. The patient's fatigue disappeared within a short time.

Discussion

There have been few reports of an association between inflammatory bowel disease, mainly ulcerative colitis, and GPA [4]. CD and GPA share several clinical features: both can present as a gastro-intestinal tract disease, both can involve the oropharynx, the extra- intestinal manifestations of CD can mimic common symptoms of GPA such as arthralgia, fever, skin abnormalities and weight loss, and both are associated with ANCA [5].

The patient we describe had been diagnosed with CD 20 years prior to her 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 6 years her disease was in complete remission. The present positive p-ANCA result might provide further corroboration for the diagnosis of CD [6].

The patient was recently diagnosed as suffering from GPA. Crescentic glomerulonephritis and severe interstitial inflammatory infiltrate, subsequent development of episcleritis and the finding of c-ANCA supported this. The histological findings of granulomatous vasculitis renal define the systemic nature of this patient's disease.

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 GPA 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 GPA.

C-ANCA are antibodies directed primarily against proteinase-3 in neutrophil azurophilic granules. The reported sensitivity of c-ANCA

for GPA is between 32% and 92% with a pooled sensitivity of 66%, and the reported specificity 88% to 100% with a pooled specificity of 98% [7]. 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 GPA, 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 immune inflammatory process is unclear.

Inflammatory bowel diseases are associated with p-ANCA, more commonly in ulcerative colitis (50% to 80%) than in CD (10% to 40%) [5]. 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.

Conclusion

In summary, while the association between CD and GPA 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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