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Case Report

Henoch-Schönlein purpura with IgG PR3-ANCA in a PiZZ alpha 1-antitrypsin deficient patient

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We report the case of a PiZZ α_1AT-deficient patient who presented with a chronic obstructive pulmonary disease (panlobular emphysema and chronic bronchitis) (COPD) and HSP with biopsy proved IgAN. The occurrence of IgG PR3-ANCA in this patient raises the question of the pathophysiological relevance of these antibodies in IgA-related diseases.

Introduction

Henoch-Schönlein purpura (HSP) is a clinical syndrome that includes arthralgias, purpuric lesions, abdominal pain and nephropathies. It is histopathologically characterized by widespread leukocytoclastic vasculitis with skin IgA deposits and mesangioproliferative IgA glomerulonephritis. Renal lesions closely resemble those of Berger's disease, the renal limited form of HSP [1].

Anti-neutrophil cytoplasmic antibodies (ANCA) are essentially found in two types of vasculitides. Those which give a cytoplasmic pattern (c-ANCA) and react with proteinase 3 (PR3-ANCA) are sensitive and specific markers of Wegener's granulomatosis (WG) [2]. On the other hand, p-ANCA mostly directed against myeloperoxidase (MPO) are generally encountered in microscopic polyangiitis. The incidence of ANCA is variable in other types of vasculitis including HSP, and their pathogenic significance in HSP and IgA nephropathy (IgAN) remains unclear. IgA-ANCA have been found in patients with HSP and more occasionally in those with IgAN [3]. The finding of IgG PR3-ANCA in HSP has rarely been mentioned [4].

Since alpha 1-antitrypsin (α_1AT) is a natural inhibitor of PR3, the target antigen of c-ANCA antibodies, α_1AT deficiency might explain the high PR3-ANCA concentration and the severity of inflammatory process in some patients with systemic vasculitis [5]. Circulating α_1AT levels depend on proteinase inhibitor Z (PiZ) allele and are only 10% of the normal value in homozygous individuals (PiZZ) [6].

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Case

A 47-year-old man with no previous renal or systemic disease was admitted to our nephrology unit with a 1-week history of migratory arthralgia and joint swellings. At the same time, he noticed pinpoint purpuric rash spread over the lower part of his body and dark brown urine 2 days before admission. He was a smoker, presented mild systemic hypertension and suffered from COPD. He mentioned no alcohol abuse and was not known to have liver or pancreatic diseases. Usual medication included salbutamol, ipratropium bromide, beclometasone, enalapril and hydrochlorothiazide. Two weeks before admission, the patient had presented with an upper respiratory tract infection that spontaneously resolved. On admission he was well hydrated and febrile at 38.7°C. Cardiac pulse was 88/min, and respiration 24/min. Blood pressure was 155/95 mmHg in supine position. Multiple palpable purpuric lesions were scattered over his knees, thighs and hands. They formed coalescent patches over his buttocks, and extended over the whole body during the next few days. His ankles and his knees were swollen and painful. The rest of the physical examination, including the ears, nose, and throat was unremarkable. White-cell count was normal. Hepatic and pancreatic enzyme levels were in normal range. Neither clinical manifestations nor histological (liver biopsy) findings related to hepatic cirrhosis were found. No antibodies against hepatitis B, C or HIV were detected. Serum polyclonal IgA was 540 mg/dl (normal 50–350 mg/dl). Complement was normal and antistreptolysin O, rheumatoid factor (RF) of IgA, IgG and IgM isotypes, anti-nuclear antibodies,

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anti-ribonucleoprotein antibodies, anti-cardiolipin (IgG, IgM) antibodies and cryoglobulins were not detected. Positive ANCA were demonstrated by indirect immunofluorescence giving a cytoplasmic pattern (titre 1 : 320; control < 1 : 20). Commercially available enzyme-linked immunosorbent assay (ELISA; INOVA®, Inova Diagnostics, San Diego, CA, USA) kit confirmed the presence of IgG anti-PR3 antibodies with a titre of 35 kU/l (control < 20 kU/l). Anti-MPO antibodies and IgA-ANCA (anti-PR3 specific ELISA) were not detected. Alpha 1-antitrypsin level was 0.27 g/l (normal 0.72–1.44 g/l) associated with homozygous PiZZ phenotype, which was determined by isoelectric focusing. Urinalysis showed 10 WBC/μl, 75 RBC/μl, without casts. Urine and throat cultures were negative. Urinary protein excretion was 1500 mg/24 h. Plasma creatinine was 1.1 mg/dl (97 μmol/l). Chest radiograph and thoracic CT showed hyperinflation resulting from panlobular emphysema with patchy opacities in both right and left lower zones but without mass or consolidation. The sinus CT scan showed pseudo-polyps in both left and right maxillary sinus and in the left sphenoidal sinus. Pulmonary functions demonstrated a severe obstructive syndrome (FEV_1: 0.99 l – 30% predictive value). Transbronchial biopsies showed neither vasculitis, nor necrosis, nor granuloma. A small amount of tissue available in biopsy specimen from the right maxillary sinus demonstrated no pathological feature of WG.

A skin biopsy of recent lesions showed a leukocytoclastic vasculitis with neutrophil granulocytes in and surrounding the walls of small arterioles (light microscopy), and deposits of IgA and complement (immunofluorescence) in the dermal vessel walls. A renal biopsy was performed two days after admission. Twelve glomeruli were present in the specimen for light microscopy. All glomeruli showed mesangial hyperplasia of various importance and nine glomeruli presented proliferative segmental lesions (Figure 1). Immunofluorescence-staining showed diffuse granular deposits of IgA (Figure 2A) and C3 (Figure 2B) in the mesangium. No IgG was found in the renal tissue. The glomerular basement membranes and the foot processes did not show ultrastructural modification by electron microscopy. Mesangial areas were massively enlarged by an increase in matrix material containing fine, granular, electron-dense deposits.

Our final diagnosis was HSP and IgAN in a patient with IgG PR3-ANCA and PiZZ α_1AT. Because the clinical presentation and the serological data were considered as risk factors for further severe renal impairment, oral prednisone (1 mg/kg/24 h) and cyclophosphamide (0.2 g/m^2/24 h) were given. Six weeks later, the patient was asymptomatic and the ulcerative skin lesions had healed. At that time the IgG PR3-ANCA concentration, the IgA titre and the α_1AT level were 35 kU/l, 537 mg/dl and 0.26 g/l respectively. Six months later the IgG PR3-ANCA and the IgA titres decreased to 13 kU/l and 127 mg/dl respectively. α_1AT remained low (0.19 g/l). The renal function remained normal (creatinine clearance measured by Cockcroft-Gault formula before treatment was 86 ml/min *vs* 89 ml/min 6 months later), proteinuria resolved (30 mg/24 h) and haematuria disappeared. At this time the blood pressure was 145/85 mmHg.

Discussion

This case report describes a COPD patient who presented with a systemic small-vessel vasculitis. The clinical and pathological features, in the absence of liver or pancreatic disease or other systemic illness, fulfil the American College of Rheumatology criteria for the diagnosis of HSP with IgAN [1]. Enzymatic measurement revealed low levels of α_1AT (0.19 to 0.27 g/l) and phenotyping showed the patient to be a PiZZ homozygote for α_1AT deficiency.

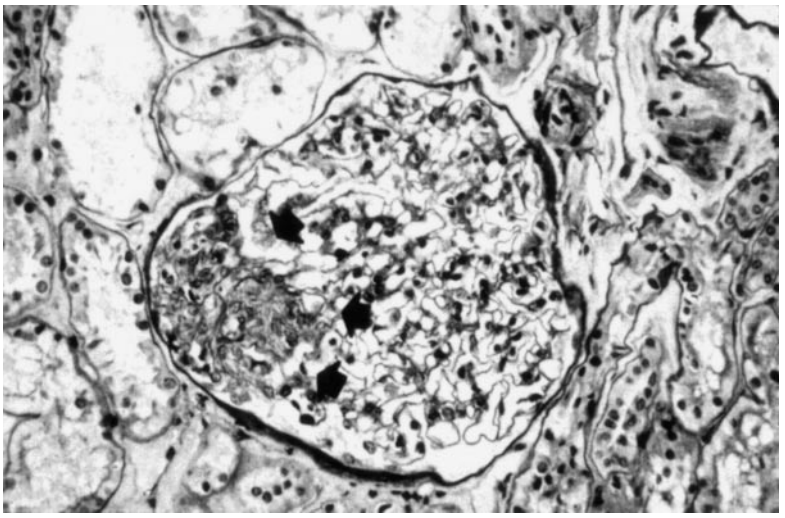

Fig. 1. Histology of a glomerulus showing some hyperplasia of the glomerular mesangium with segmental endocapillary proliferation. (Periodic acid-Schiff stain. Original magnification × 280.)

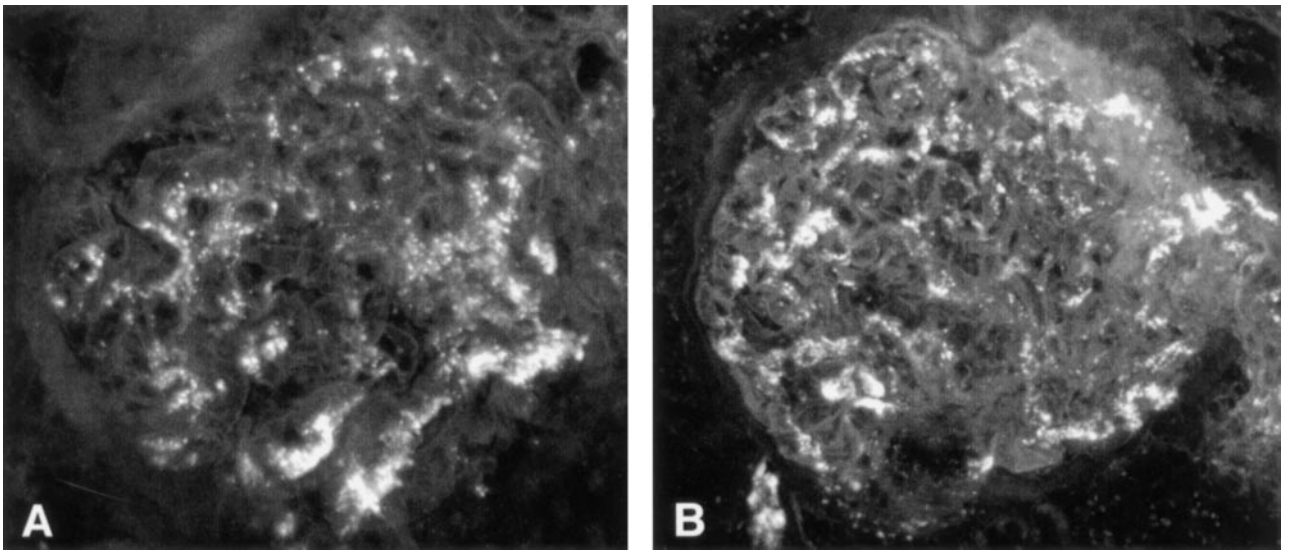

Fig. 2. (**A**) Direct immunofluorescence staining for IgA within a glomerulus showing typical mesangial distribution of granular deposits. (**B**) Direct immunofluorescence staining of a glomerulus for C3 complement showing intense mesangial distribution of granular deposits. (Original magnification × 300.)

Although this patient presented anti-PR3 c-ANCA of IgG isotype associated with pseudo-polyps in the sinus, he did not meet the criteria for WG. The absence of IgA-ANCA in the IgA-related disease (HSP and IgAN) of our patient is in keeping with a previous report which mentioned the presence of IgA-ANCA in only 28–79% of patients with HSP [3]. The occurrence of cross-reacting IgA RF has also been demonstrated in patients with HSP or IgAN [7], but was not found in our patient. The literature reports some cases of HSP and IgAN associated with p-ANCA [8,9]. Our case and those reported by Ramirez *et al.* [4] and Rollino *et al.* [10] indicate that *de novo* IgA-related disease can be associated with IgG-ANCA although a causality link remains to be established.

In addition, our patient was found to have a severe α_1AT deficiency with PiZZ phenotype, but neither liver cirrhosis nor hepatic artery aneurysm as a consequence of severe α_1AT deficiency. In the absence of liver disease, glomerular IgA deposits can be attributed to HSP. Increased incidence of α_1AT phenotype associated with dysfunctional α_1AT or low serum levels of α_1AT as well as PiZZ α_1AT deficiency have been reported in patients with anti-PR3 antibodies [5,6]. α_1AT is known to be the main natural inhibitor of neutral serine proteinases including PR3, a proteinase of polymorphonuclear leukocytes expressed in α granules [11]. α_1AT deficiency may lead to increased levels of PR3, which would be more accessible to the immune system. The absence of α_1AT may also favour the uncontrolled development of inflammatory activity.

The incidence of deficient α_1AT phenotype in ANCA-positive patients is probably low, but the clinical relevance of searching for anti-proteinase deficiency is emphasized by the poor outcome of anti-PR3-positive patients with the deficient PiZZ phenotype [6]. As reported in a recent review [12], which included two cases of HSP, vasculitis patients with severe α_1AT deficiency show a more widespread disease, an unusually severe course and a worse prognosis. Another important feature of systemic vasculitis linked with α_1AT deficiency is the association with panlobular emphysema. In agreement with recent studies [12,13], rather than being an etiological risk factor, α_1AT deficiency may have an adverse accelerative effect on the vasculitic process even in HSP. Detecting severe α_1AT deficiency may have implications for both treatment and clinical response [14]. In our case, the skin lesions healed and haematuria resolved with both steroids and cyclophosphamide. In more severe manifestations (severe skin vasculitis, rapidly progressive glomerulonephritis associated with HSP) plasma exchange might be used.

Our case report suggests a link between α_1AT deficiency, HSP with IgAN, and the presence of PR3-ANCA. The enhancing of IgG PR3-ANCA in HSP and IgAN remains to be demonstrated. However, we recommend to search for α_1AT deficiency in patients with lung disease and HSP because this anomaly may entail a poor outcome and justify a more aggressive treatment.

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