Rheumatol Int (2013) 33:493–496
DOI 10.1007/s00296-010-1608-x

CASE REPORT

Adult-onset Henoch–Schonlein purpura with positive c-ANCA (anti-proteinase 3): case report and review of literature

Eman Boulis · Vikas Majithia · Robert McMurray

Received: 22 February 2010 / Accepted: 3 October 2010 / Published online: 21 October 2010

Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) have two common patterns detected by indirect immunofluorescence test (IIF test). The cytoplasmic pattern (c-ANCA) that is strongly associated with antibodies against proteinase-3 (PR3) and the perinuclear pattern (p-ANCA) that is mostly directed against myeloperoxidase (MPO). Anti-proteinase 3 and anti-MPO are characteristic for pauci-immune small vessel vasculitis like Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome and idiopathic crescentic glomerulonephritis [1]. In Wegener's granulomatosis (WG), the combination of c-ANCA with anti-PR3 antibodies has a sensitivity of 58% and a specificity of 99% [2]. On the other hand, the presence of c-ANCA (anti-PR3) in immune-complex-mediated vasculitis such as Henoch–Schonlein purpura (HSP) is very unusual. We report a case of biopsy proven HSP associated with IgG c-ANCA (anti-PR3).

Case report

A 51-year-old white man presented with a 2-week history of diarrhea, abdominal pain, arthralgia and skin rash that started on his legs then spread to the rest of his body. His past medical history was unremarkable with no history of sinusitis, otitis or asthma. He was on no medications (whether over the counter or prescribed). He did not smoke or drink alcohol. His family history was non-contributory. Vital signs were stable. Exam revealed palpable purpuric rash on the legs (Fig. 1), mild epigastric tenderness and edema at the dorsum of his hands and feet. Abnormal laboratory studies included elevated WBC count, liver transaminases, alkaline phosphatase and bilirubin as well as hematuria (urinary RBCs 50/HPF) and pyuria (urinary WBCs 20/HPF) without casts. Urinary protein was 413 mg/24 h. A positive c-ANCA was detected by indirect immunofluorescence assay (IIFA) and was confirmed to be IgG anti-PR3 by enzyme-linked immunosorbent assay (ELISA) at 14 U/ml (negative <6 U/ml). Remaining studies including chemistries, renal functions, blood counts, coagulation tests, p-ANCA, ANA, hepatitis serology, cryoglobulins and complements were normal. Blood and urine cultures showed no growth. Chest X-ray was normal and transthoracic echocardiogram showed no vegetations or intracardiac source of emboli. Gall bladder ultrasound was consistent with acute cholecystitis. Skin biopsy showed leukocytoclastic vasculitis (Fig. 2) with IgA and C3 deposition by immunofluorescence.

A diagnosis of adult-onset Henoch–Schonlein purpura and acute cholecystitis was made. He was treated with intravenous antibiotics, ERCP guided papillotomy and oral prednisone 1 mg/kg/day. Upon follow-up at six weeks, he had complete resolution of his rash and recovery of his systemic symptoms. His renal functions remained stable, while his hematuria, pyuria and liver functions were improving.

Discussion

Henoch–Schonlein purpura is a systemic immune-complex-mediated vasculitis, more common in children, but well documented in adults [3]. It is characterized by a tetrad of purpuric skin lesions, arthralgia, abdominal pain and

E. Boulis (✉) · V. Majithia · R. McMurray
Division of Rheumatology, Department of Medicine,
University of Mississippi Medical Center, Jackson, MS, USA
e-mail: erboulis@yahoo.com

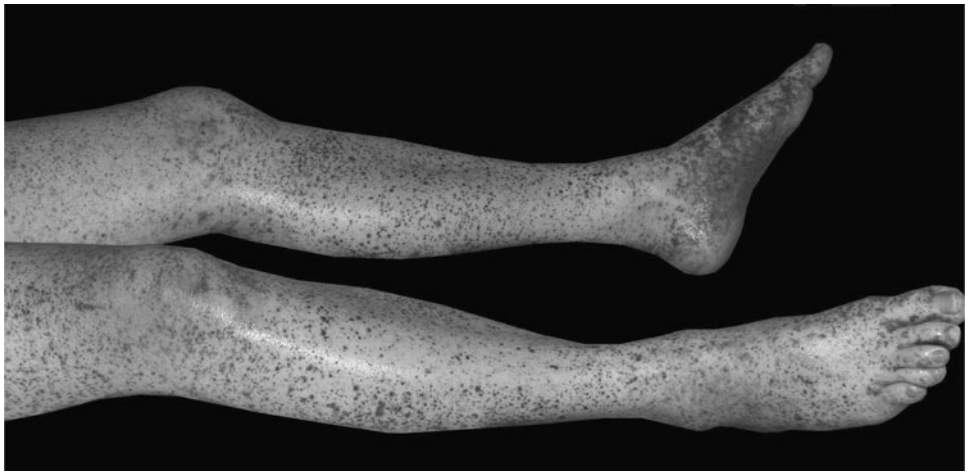

Fig. 1 Multiple palpable purpuric lesions with coalescent patches over the foot sole

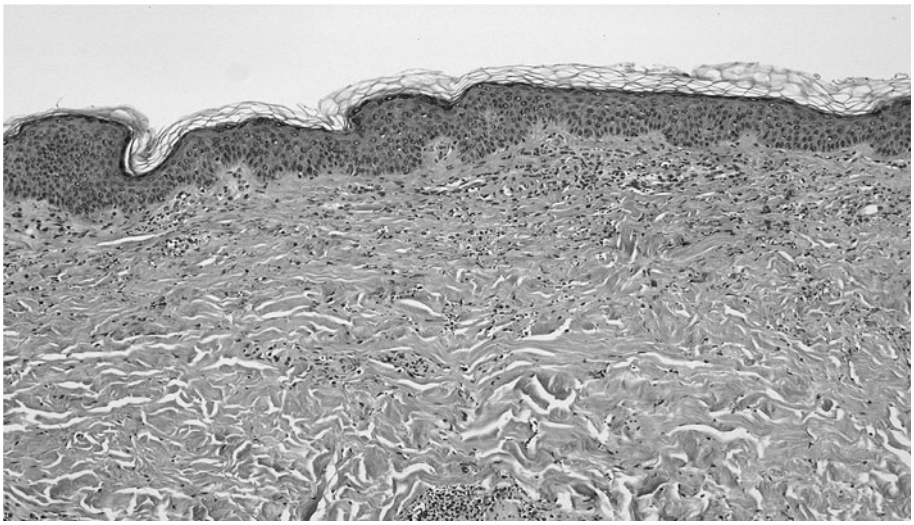

Fig. 2 Skin biopsy revealed dermal inflammatory infiltrate centered on vessels with prominent nuclear debris typical of leukocytoclastic vasculitis (*H* and *E*)

nephropathies. Histopathologically skin biopsy characteristically shows leukocytoclastic vasculitis with IgA deposits. It must be distinguished from clotting disorders, sepsis and other systemic vasculitic diseases.

Anti-neutrophil cytoplasmic antibodies (ANCA) are a group of autoantibodies directed against proteins in the granules of neutrophils and in peroxidase-positive lysosomes of peripheral blood monocytes. Studies so far indicate that ANCA are predominantly of the IgG isotype, but other isotypes also exist, including IgA and IgM [4]. Different target antigens for ANCA were identified and include proteinase 3, myeloperoxidase, elastase, cathepsin G, lactoferrin and lysozyme [5]. The presence of ANCA in patients with vasculitis was first observed in 1982 by Davies [6]. As ANCA has been well documented in pauci-immune vasculitis as Wegener's granulomatosis and microscopic polyangiitis [1], its presence in immune-complex-mediated vasculitis, specifically HSP, remains controversial. Whereas some authors have not been able to demonstrate either IgG or IgA isotypes of ANCA in HSP patients [7, 8], others have shown IgA ANCA in HSP [9–12] and some thought these were false-positive results attributed to the following: (a) the presence of IgA rheumatoid factor [13], (b) IgA binding to crude granulocyte extracts but not to purified ANCA antigens [14], (c) the occurrence of different lectinic interactions rather than an antigen–antibody reaction due to abnormal arrangements of IgA carbohydrate side chains [15]. IgG ANCA was generally found to be negative in HSP [9, 10]. IgG c-ANCA (anti-PR3) has been reported in only two cases of HSP [16, 17] (Table 1).

Our case highlights that HSP can be associated with IgG PR3-ANCA, confounding the diagnosis and making it difficult to distinguish from Wegener's granulomatosis and other pauci-immune vasculitis due to the similarities in clinical presentation. Management of Wegener's granulomatosis and HSP is also different; Wegener's granulomatosis usually require immunosuppressive agents (e.g. cyclophosphamide, methotrexate, azathioprine), whereas HSP in most cases resolve spontaneously with or without the use of corticosteroids unless there is severe renal or bowel involvement.

Table 1 Characteristics of previously reported cases with HSP associated with IgG c-ANCA (anti-PR3)

Author	Age (sex)	Clinical picture	Serology	Renal involvement	Pathology	Treatment	Outcome
Meier [16]	47 years (male)	URTI* followed by arthralgia and purpuric rash. (patient also had alpha 1 antitrypsin deficiency)	IIFA*: cytoplasmic pattern of ANCA ELISA*: IgG anti-PR3 antibodies	Urine analysis: 10 WBCs/µl, 75 RBCs/µl without casts. Urinary protein of 1,500 mg/24 h Plasma creatinine was 1.1 mg/dl	Skin biopsy: Leucocytoclastic vasculitis with vascular IgA and complement deposition Kidney biopsy: Mesangial IgA and C3 deposits (no IgG) with mesangial hyperplasia	Prednisone (1 mg/kg/day) and Cyclo–phosphamide (0.2gm/m2/day)	Good
Ferraz-Amao [17]	60 years (male)	URTI* followed by arthralgia and palpable purpura	IIFA*: perinuclear and cytoplasmic patterns of ANCA ELISA*: IgG and IgA antibodies each react to both PR3 and MPO	Benign urinary sediment. Urinary protein of 3,140 mg/24 h Plasma creatinine was normal	Skin biopsy: Leucocytoclastic vasculitis with vascular IgA deposition Kidney biopsy: Mesangial IgA, C3 and IgG deposits with mesangial proliferation	Prednisone (1 mg/kg/day)	Good

IIFA indirect immunofluorescence assay, *ELISA* enzyme-linked immunosorbent assay, *URTI* upper respiratory tract infection

Even though the IgG anti-PR3 was positive in our patient, he had no upper or lower respiratory tract involvement or granulomatous vasculitides suggestive of Wegener's granulomatosis; we so felt that he had primarily HSP and chose to treat him with steroids only with a good outcome.

ANCAs of the IgG isotype are associated with rapidly progressive glomerulonephritis, and there has been reports suggesting an association between ANCA-associated diseases and fulminant IgA nephropathy, the renal-limited form of HSP [18]. This raises the question of the clinical and pathological significance of IgG c-ANCA (anti-PR3) in the setting of HSP and whether identification of these antibodies maybe a potential marker for more aggressive HSP. This in turn could have potential implications for therapy in patients with HSP and a positive IgG c-ANCA; for instance, aggressive treatment of such a variant with pulse steroids and cyclophosphamide, the regimens used in classic ANCA-mediated diseases, may decrease the potential of serious complications.

We conclude that although IgG c-ANCA (anti-PR3) is highly specific for pauci-immune vasculitis, specifically Wegener's granulomatosis [1], it can occur in immune-complex-mediated diseases as HSP. Further studies may establish the causality link between IgG PR3-ANCA and HSP patients and help tailor management and follow-up recommendations.

Conflict of interest None.

References

1. Kallenberg CG, Brouwere, Weening JJ et al (1994) Antineutrophil cytoplasmic antibodies: current diagnostic and pathophysiological potential. Kidney Int 46:1–15 (Review)
2. Hagen EC, Daha M, Hermans J et al (1998) The diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies (ANCA) in idiopathic systemic vasculitis: results of an international collaborative study. Kidney Int 53:743–753
3. Cream JJ, Gumpel JM, Peachey RDG (1970) Schönlein-Henoch purpura in the adult: a study of 77 adults with anaphylactoid or Schönlein-Henoch purpura. QJM 39:461–484
4. Jayne DR, Jones SJ, Severn A et al (1989) Severe pulmonary hemorrhage and systemic vasculitis in association with circulating anti-neutrophil cytoplasm antibodies of IgM class only. Clin Nephrol 32:101–106
5. Hauschild S, Schmitt WH, Csernok E et al (1993) ANCA in systemic vasculitides, collagen vascular diseases, rheumatic disorders and inflammatory bowel diseases. Adv Exp Med Biol 336:245–251
6. Davies DJ, Moran JE, Niall JF et al (1982) Segmental necrotizing glomerulonephritis with antineutrophil antibody: possible arbovirus aetiology? Br Med J 285(6342):606
7. Robson WL, Leung AK, Woodman RC (1994) The absence of anti-neutrophil cytoplasmic antibodies in patients with Henoch-Schönlein purpura. Pediatr Nephrol 8(3):295–298
8. O'Donoghue DJ, Nusbaum P, Noel LH et al (1992) Antineutrophil cytoplasmic antibodies in IgA nephropathy and Henoch-Schonlein purpura. Nephrol Dial Transplant 7:534–538

9. Ozaltin F, Bakkaloglu A, Ozen S et al (2004) The significance of IgA class of antineutrophil cytoplasmic antibodies (ANCA) in childhood Henoch-Schönlein purpura. Clin Rheumatol 23(5):426–429
10. Ronda N, Esnault VL, Layward L et al (1994) Antineutrophil cytoplasm antibodies (ANCA) of IgA isotype in adult Henoch-Schönlein purpura. Clin Exp Immunol 95(1):49–55
11. Hong SM, Chen YC, Hsueh S et al (2009) Adult-onset perinuclear antineutrophil cytoplasmic antibody-positive Henoch-Schönlein purpura in diabetic nephropathy. J Nephrol 22:164–170
12. Van der Wall Bake AWL, Lobatto S, Jonges L et al (1987) IgA antibodies directed against cytoplasmic antigens of polymorphonuclear leukocytes in patients with Henoch-Schoenlein purpura. Adv Exp Med Biol 216:1593–1598
13. Saulsbury FT, Kirkpatrick PR, Bolton WK (1991) IgA antineutrophil cytoplasmic antibody in Henoch-Schonlein purpura. Am J Nephrol 11:295–300
14. Sinico RA, Tadros M, Radice A et al (1994) Lack of IgA antineutrophil cytoplasmic antibodies in Henoch-Schonlein purpura and IgA nephropathy. Clin Immunol Immunopathol 73:19–26
15. Coppo R, Cirina P, Amore A et al (1997) Properties of circulating IgA molecules in Henoch-Schonlein purpura nephritis with focus on neutrophil cytoplasmic antigen IgA binding (IgA-ANCA): new insight into a debated issue. Italian group of renal immunopathology collaborative study on Henoch-Schonlein purpura in adults and in children. Nephrol Dial Transplant 12:2269–2276
16. Meier P, Dayer E, Lemoine R et al (2001) Henoch-Schönlein purpura with IgG PR3-ANCA in a PiZZ alpha 1-antitrypsin deficient patient. Nephrol Dial Transplant 16(9):1932–1935
17. Ferraz-Amaro I, Herrero MJ, Jurado A et al (2004) Dual positivity for cytoplasmic and perinuclear anti-neutrophil antibodies in a patient with Henoch-Schönlein purpura. Clin Exp Rheumatol 22(2):233–234
18. Ramirez SB, Rosen S, Niles J et al (1998) IgG antineutrophil cytoplasmic antibodies in IgA nephropathy: a clinical variant? Am J Kidney Dis 31(2):341–344