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Original article

IgG and IgA classes of anti-neutrophil cytoplasmic autoantibodies in a 13-year-old girl with recurrent Henoch-Schonlein purpura

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Abstract. We describe a 13-year-old girl with recurrent Henoch-Schonlein purpura whose symptoms were precipitated by upper respiratory tract infections. Her serum was positive for both IgG and IgA classes of anti-neutrophil cytoplasmic autoantibodies by immunofluorescence. The titers of both autoantibodies correlated with disease activity. The immunopathology underlying these findings is discussed.

Key words: Anti-neutrophil cytoplasmic autoantibodies – Henoch-Schonlein purpura – Vasculitis

Introduction

Anti-neutrophil cytoplasmic autoantibodies (ANCA) have been described in some patients with systemic vasculitides. There are different immunoglobulin classes of ANCA. According to the location of immunostaining in the neutrophils, ANCA can be cytoplasmic pattern (cANCA) or perinuclear pattern (pANCA). IgG-ANCA are mainly described in Wegener's granulomatosis (WG) [1, 2], microscopic polyarteritis nodosa [3], necrotizing crescentic glomerulonephritis [4], and recently in Henoch-Schonlein purpura (HSP) [5, 6]. IgA-ANCA are described in 28%–79% of patients with HSP [5–8]. A correlation between the titers and the disease activity has been reported for IgG-ANCA in WG [2] and for IgA-ANCA in HSP [5], but not in the same patient. This report is of a patient whose clinical and pathological findings were consistent with HSP and whose serum was positive for both IgG and IgA classes of cANCA. In addition, the titers of both autoantibodies correlated with disease activity.

Case report

A 13-year-old white female developed multiple pinpoint purpuric rash on both ankles while receiving penicillin for streptococcal pharyngitis. Shortly after completion of the treatment, dark brown urine, intermittent abdominal pain, and arthralgia over the ankles developed. Cefadroxil was prescribed because the throat culture remained positive for group A β-hemolytic streptococci. Over the next few days, the skin rash and arthralgia extended to the lower legs and elbows. There was no history of travel, recent immunization, weight loss, respiratory symptoms, transfusion, or drug ingestion prior to the illness. The past medical history was unremarkable. A maternal aunt had "nephritis" during adolescence.

She was referred to us 3 weeks after onset of the illness. Positive physical findings were limited to a limp, a multiple nonconfluent palpable purpuric rash with lesions 0.2–2 cm in diameter present on her elbows, buttocks, and lower legs, and tenderness and mild edema over both ankles. Urinalysis showed a specific gravity of 1.015 with 1+ protein, 10–15 white blood cells (WBC), 5–10 red blood cells (RBC), and a few granular casts per high power field. Urine and throat cultures were negative. Erythrocyte sedimentation rate (ESR) was 115 mm/h (control <20 mm/h). Serum streptozyme was more than 800 STZ units (normal <200 units). WBC count was 11,000/mm^3 with a normal differential count. Blood smear showed normal RBC morphology. Serum creatinine, C3, C4, electrolytes, and liver function test were within the normal range. Serum IgA was 211 mg/dl (normal 85–450 mg/dl). Rheumatoid factor (RF, IgG and IgM), anti-nuclear antibodies (ANA), and cryoglobulins were not detected. Creatinine clearance was 91 ml/min per 1.73 m^2. Urinary protein excretion was 675 mg/24 h. Renal ultrasound examination was unremarkable. Our diagnosis was HSP and/or a resolving poststreptococcal glomerulonephritis. She was followed as an outpatient without additional treatment; during the following month the symptoms persisted. Urine protein excretion (24-h) and ESR decreased to 75 mg/24 h and 79 mm/h, respectively.

On 23 June 1991, she was admitted to our hospital because of gastrointestinal bleeding. Blood smear showed normal morphology and the coagulation profile was normal. Urinalysis was negative, ESR was 116 mm/h. Serum electrolytes, creatinine, C3, C4, and anti-DNase antibodies (measured by enzyme-linked immunosorbent assay) where within the normal range. RF, ANA, anti-Ro, anti-La, anti-Smith, anti-RNP, and anti-glomerular basement membrane antibodies were not detected. IgG-ANCA detected by immunofluorescence showed a cytoplasmic pattern at 1:32 dilution (Fig. 1 A). This was performed by consecutive additions of the patient's serum (1:8 dilution) and fluorescein isothiocyanate conjugated anti-human IgG (anti-human IgA for IgA-ANCA) to alcohol-fixed neutrophils (2×10^5/ml) [9]. She received a blood transfusion, prednisone 50 mg daily, and ranitidine 75 mg b.i.d. Gastrointestinal bleeding and abdominal pain ceased within a few days. The skin rash and arthralgia gradually improved. She was discharged in 1 week. Prednisone was gradually tapered by 10 mg each week and was discontinued after 6 weeks. Two months after discharge, she was asymptomatic.

At the beginning of October, following an upper respiratory tract infection, abdominal pain, skin rash, and arthralgia reappeared. On 26 November 1991 she was admitted again because of gastrointestinal bleeding. IgG-cANCA were detected at a 1:128 dilution. A cytoplasmic pattern of IgA-ANCA was positive at a 1:32 dilution. ANA were not

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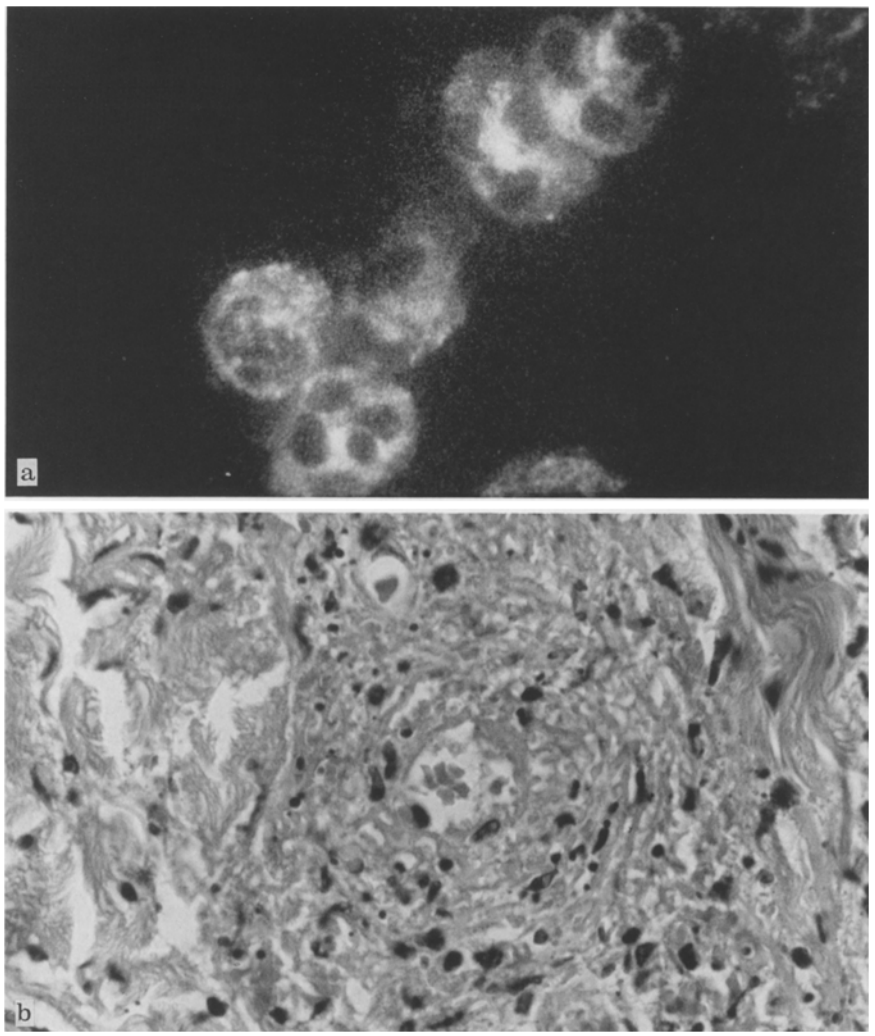

Fig. 1. A Immunofluorescence of IgG-anti-neutrophil cytoplasmic autoantibodies (ANCA) showing a cytoplasmic pattern (× 2.500, kindly provided by Dr. Frederick Miller). **B** Light micrograph of uninvolved skin showing a leukocytoclastic vasculitis (hematoxylin and eosin stain, × 1,800)

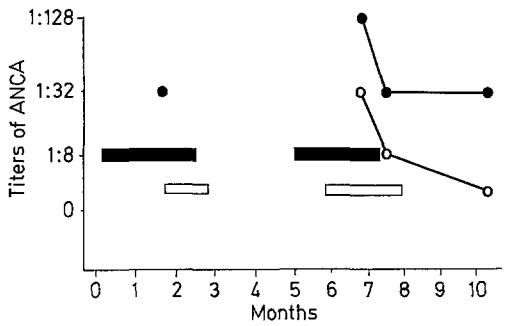

Fig. 2. Titers of ANCA since onset of the illness. ■, Presence of symptoms; □, prednisone therapy; ●, IgG-ANCA; ○, IgA-ANCA

detected. The serum IgA level was 189 mg/dl (normal 85–450 mg/dl). ESR was 89 mm/h. Urinalysis was normal. Biopsy of the uninvolved skin showed a leukocytoclastic vasculitis (Fig. 1 B) with deposits of IgA, C3, IgM, IgG, and fibrin in the dermal vessel walls. She was transfused and prednisone 60 mg daily, ranitidine 75 mg b. i. d., and 6 mg/kg of iron supplement daily were initiated. Three weeks later she was asymptomatic. IgG-cANCA was positive at a 1 : 32 dilution and IgA-cANCA was positive at a 1 : 8 dilution. Hepatitis B surface antigen was not present. ESR was 10 mm/h. Urinalysis was normal. During the next 4 months of follow-up, prednisone was gradually tapered and discontinued in 2 months. She remained asymptomatic. IgG-ANCA remained positive at a 1 : 32 dilution while IgA-ANCA was negative at a 1 : 8 dilution (Fig. 2).

Discussion

Other than HSP and microscopic polyarteritis nodosa, small vessel leukocytoclastic vasculitis without granuloma or nodule formation can occasionally be seen in serum sickness, systemic lupus erythematosus, rheumatoid arthritis, essential mixed cryoglobulinemia, subacute bacterial endocarditis, hypocomplementemic vasculitis, and malignancies such as Hodgkin's disease or leukemia [10, 11]. These possibilities can be excluded in our patient by the history, serological, and clinical findings. Lack of renal impairment and musculoskeletal symptoms make the diagnosis of microscopic polyarteritis nodosa unlikely, according to Savage et al. [12]. On the other hand, the history and presentation of this patient fulfill the criteria for HSP [13]. The demonstration of IgA deposits in dermal vessel walls supports this diagnosis [14].

IgG-ANCA have been described in 3 of 14 HSP patients by Ronda et al. [5] and in 6 of 18 patients by Li et al. [6]. We found that the titer of IgG-cANCA in this patient correlated with the extrarenal manifestations, similar to the

Table 1. Titers of anti-neutrophil cytoplasmic autoantibodies since onset of the illness[a]

	1 month	6 months	7 months	11 months
IgG-ANCA	1:32	1:128	1:32	1:32
IgA-ANCA	NA	1: 32	1: 8	–[b]
ERS[c]	+	+	–	–

ERS, Extrarenal symptoms; NA, not available

[a] Maximal dilutions for positive immunofluorescence reaction

[b] Negative at 1:8 dilution

[c] Including gastrointestinal symptoms, joint complaints, and skin rash

findings in patients with WG [2]. The role of IgG-ANCA in the pathophysiology of the systemic vasculitis is unclear. IgG-ANCA can induce the respiratory burst and degranulation of neutrophils [15], and injure the endothelial cells in vitro [16]. It has been proposed that as a result of chronic antigen(s) exposure [17] and/or dysregulation of T-cells [18], cANCA might directly bind to and activate granulocytes resulting in local tissue injury [19]. This could explain the recurrent presentations of our patient. However, such an immunopathological role for IgG-ANCA in HSP has been questioned by other investigators because they could not detect IgG-ANCA in HSP patients in association with declining renal function, rash, or gross hematuria, suggesting that the development of these manifestations does not require the presence of IgG-ANCA [20].

It has been suggested that, upon stimulation, mucosal B-cells oversynthesize polymeric IgA in the absence of normal T-cell regulation. The circulating IgA forms complexes with IgG and other proteins, activating the alternate complement pathway. Deposition of these IgA-containing complexes then produces local tissue injury [21]. This could explain the symptoms of our patient, since the deposition of IgA in her skin and the presence of IgA-cANCA suggest that there was an increased IgA production. We can not exclude the possibility that our observation of IgA-ANCA in this patient was due to the presence of IgA RF, as indicated by Saulsbury et al. [8]. However, their findings were from HSP patients with no IgA-ANCA detected by immunofluorescence. In contrast, our findings are compatible with those of Ronda et al. [5] who found that IgA-ANCA levels correlated with disease activity in two HSP patients with no IgA RF.

Coexistence of IgG- and IgA-ANCA in patients with HSP has been recently reported [5, 6]. In addition, we found in our patient the titers of both autoantibodies correlated with the extrarenal but not with the renal manifestations (Fig. 2). These two classes of ANCA recognize different antigens in neutrophils [5, 22]. Whether they have a synergistic effect on the patient's symptoms or interact in another way is yet to be determined. Microbial agents have been suggested to be responsible for the development of HSP [21] and the production of IgG-ANCA [23]. Our observations in this patient are compatible with this hypothesis. However, the coexistence of both classes of ANCA in this patient could simply be an epiphenomenon, secondary to the increased IgA and IgG production seen in HSP patients [14], as is the case for IgA RF [24].

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Ask the expert*

What is the current recommendation in the management of covert (significant) bacteriuria in infants and preschool children?

Key words: Covert bacteriuria – Management

The urinary tract is normally sterile but up to 2.7% of infants and preschool children have been shown to have asymptomatic bacteriuria as a result of screening programmes [1–4]. In contrast, in clinical practice asymptomatic bacteriuria is only detected when urine is collected and cultured from asymptomatic healthy children, usually following a previous urinary tract infection. Whilst the benefits of early treatment are clearcut for symptomatic infection, both in terms of eradicating symptoms and minimising the risk of renal damage [5], there is no evidence of comparable benefits from treatment of asymptomatic infection. In addition, there is evidence that successful treatment which eradicates an established and relatively benign organism may facilitate colonisation with a new more virulent organism which is more likely to cause symptoms [6, 7], and changes in organism were more often associated with scar formation in the Cardiff/Oxford Bacteriuria Survey [8].

After the first few weeks of life, infection of the urinary tract occurs via the urethra, with the reservoir of infecting organisms in the gut in females and under the foreskin in males. Symptoms develop when the invading bacteria stimulate the host's inflammatory response. Work in animals shows that after resolution of inflammation, scarring is more likely to develop in the young, in association with a delay in treatment and where there is an abnormal urinary tract [9, 10]. Clinical observations in symptomatic children have tended to confirm this view [5], however, there are no animal models for asymptomatic bacteriuria. Because asymptomatic bacteriuria is normally found by chance, it must be deduced that it may have been present for a long time and the opportunity for early treatment of acute inflammation has already passed (if indeed there ever was any acute inflammation).

Evidence from clinical studies in girls shows that although scarring is common amongst those with asymptomatic bacteriuria, progression of scarring is rarely seen [11], particularly in girls with normal urinary tracts. However, Savage et al. [12] showed that many of the children detected had urinary symptoms that had been overlooked and that these symptoms improved with treatment. He also showed that the children with scarred kidneys were shorter than those with normal kidneys. There is much less information about the risk of renal damage from asymptomatic infections in preschool children. However, Wettergren et al. [13] undertook an important prospective study of asymptomatic bacteriuria in Swedish infants. Although 2 infants went on to develop symptoms and were treated, in many infants bacteriuria either resolved [14] or persisted with no adverse effect on the kidneys detectable at 6-year follow-up.

There is no evidence that screening and treatment for bacteriuria in completely healthy infants and children is beneficial. However, there is good evidence that early detection and treatment of symptomatic infection, even when symptoms are non specific, is important in preventing renal scar formation with the long-term risk of hypertension and renal failure. Clinical effort should be focussed on the important task of improving the diagnosis and management of symptomatic infection in infancy rather than persuing the treatment of asymptomatic bacteriuria which is of doubtful value.

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* The editors invite questions for this section