For antinucleosome testing, at the 10 IU threshold suggested by the manufacturer, 109/270 (40%) sera were positive, including 51/114 (45%) rheumatoid arthritis (RA) and 20/34 (59%) spondyloarthropathy (SpA). However at the 20 IU threshold only 4% were still positive, including 2/33 (6%) unclassified arthritis, 5/105 (5%) RA, 2/52 (4%) SpA, 1/5 (20%) sicca syndrome, and only 1/5 (20%) patients later diagnosed as having SLE. Moreover for this single patient, the diagnosis was already firmly established, especially as the antinuclear antibody titre was 1/1000 and anti-dsDNA were positive. Hence the positive predictive value for SLE of antinucleosome testing was 1/11, and the sensitivity 1/5.

These low sensitivities do not support the working hypothesis that systematic screening for IIF-ANCA and antinucleosome antibodies is useful for the diagnosis of vasculitides in early arthritis and of SLE in patients with "naked" arthritis. Such results were somewhat expected, given that systemic vasculitis or SLE with arthritis as precursor are quite uncommon events. However, they confirm that determination of ANCA and antinucleosome antibodies should not be carried out in the absence of clinical extra-articular manifestations, especially as low ANCA titres have already been demonstrated in a large percentage of more benign conditions like early RA and early SpA.[6–9] We would therefore quite agree with the conclusion of Merkel *et al*, that instead of systematic screening for ANCA by IIF, only those patients with features atypical for RA, SpA, or undifferentiated arthritis should be tested for ANCA, using an ELISA for anti-PR3 and anti-MPO together with IIF-ANCA.[9]

Likewise in our cohort, antinucleosome antibodies were positive at low values at baseline in several conditions other than SLE and in only 1/5 patients with SLE. There are few reports on antinucleosome antibodies and SLE, and thus definite conclusions cannot be reached about the overall additional value of this test to support the diagnosis of SLE.[10] However, our results strongly suggest that systematic testing for antinucleosome antibodies should not be a substitute for a careful search for all visceral signs suggestive of lupus in a patient presenting with seemingly "naked" arthritis.

ACKNOWLEDGEMENT

Funding was provided by the Centre Hospitalier de Nantes and the Programme Hospitalier de Recherche Clinique 1995.

Authors' affiliations

J-M Berthelot, Rheumatology Unit, Nantes University Hospital, 44093, CHU, Nantes, France
A Saraux, P Le Goff, Rheumatology Unit, Brest University Hospital, 29629, CHU, Brest, France
M Audrain, J-Y Muller, Laboratory of Immunology, Nantes University Hospital, 44093, CHU, Nantes, France
M Hamidou, Internal Medicine Unit, Nantes University Hospital, 44093, CHU, Nantes, France
P Youinou, Laboratory of Immunology, Brest University Hospital, 29629, CHU, Brest, France

Correspondence to: Dr J-M Berthelot, Rheumatology Unit, CHU Nantes, Hôtel-Dieu, 44093, Nantes-Cedex 01, France; jeanmarie.berthelot@chu-nantes.fr

Accepted 4 February 2002

REFERENCES

1 **Berthelot JM**, Saraux A, Maugars Y, Prost A, Le Goff P. The taxonomy-nosology of arthritis: the experience of early-arthritis clinic. Semin Arthritis Rheum 2001;30:354–65.
2 **Soubrier M**, Le Seaux S, Dubost JJ, Mizony MH, Ristori JM, Bussière JL. Polyarthrite, manifestation inaugurale d'une polyangéite microscopique. A propos de deux observations. Rev Med Interne 2000;21:78–82.
3 **Choi HK**, Liu S, Merkel PA, Colditz GA, Niles JL. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: metaanalysis with a focus on antimyeloperoxidase antibodies. J Rheumatol 2001;28:1584–90.
4 **Wiik A**. Anti-neutrophil cytoplasmic antibodies tests: which tests should be used in practice? Intern Med 2001;40:466–70.
5 **Bruns A**, Blass S, Hausdorf G, Burmester GR, Hiepe F. Nucleosomes are major T and B cell autoantigens in systemic lupus erythematosus. Arthritis Rheum 2000;43:2307–15.
6 **De Bandt M**, Meyer O, Haim T, Kahn MF. Antineutrophil cytoplasmic antibodies in rheumatoid arthritis patients. Br J Rheumatol 1996;35:38–43.
7 **Vittecoq O**, Jouen-Beades F, Krzanowska K, Bichon-Tauvel JF, Menard JF, Daragon A, *et al*. Prospective evaluation of the frequency of clinical significance of antineutrophil cytoplasmic and anticardiolipin antibodies in community cases of patients with rheumatoid arthritis. Rheumatology (Oxford) 2000;39:481–9.
8 **Locht H**, Skogh T, Kihlstrom E. Anti-lactoferrin antibodies and other types of anti-neutrophil cytoplasmic antibodies (ANCA) in reactive arthritis and ankylosing spondylitis. Clin Exp Immunol 1999;117:568–73.
9 **Merkel PA**, Polisson RP, Chang Y, Skates SJ, Niles JL. Prevalence of antineutrophil cytoplasmic antibodies in a large inception cohort of patients with connective tissue disease. Ann Intern Med 1997;126:866–73.
10 **Amoura Z**, Koutouzov S, Chabre H, Cacoub P, Amoura I, Musset L, *et al*. Presence of antinucleosome autoantibodies in a restricted set of connective tissue diseases. Arthritis Rheum 2000;43:76–84.

Cogan's syndrome with antineutrophil cytoplasmic autoantibody

M Ikeda, H Okazaki, S Minota

Ann Rheum Dis 2002;**61**:761–762

Cogan's syndrome is a rare disease characterised by non-syphilitic interstitial keratitis with vestibuloauditory dysfunction, including loss of hearing, tinnitus, and vertigo.[1] We report here a case of Cogan's syndrome positive for antineutrophil cytoplasmic antibody (ANCA). This case is interesting in consideration of the pathogenesis of this syndrome.

CASE REPORT

In May 1999 a 61 year old man was admitted to our hospital with fever and myalgia localised to the lower part of both legs. He had a history of lung tuberculosis at 22 years old, chronic sinusitis at 30, and bilateral otitis media at 53. On admission, laboratory tests showed a white blood cell count of 11.2×10^9/l and a CRP level of 63 mg/l. Serum levels of creatine kinase, alanine aminotransferase, and aspartate aminotransferase, and a urinary examination were normal. A serological test was positive for perinuclear ANCA (pANCA) and myeloperoxidase ANCA (MPO-ANCA; 105 EU/ml (normal <10 EU/ml)), but negative for syphilis and cytoplasmic ANCA (cANCA). Electromyographic findings were normal. Although the pathological change of vasculitis was not detected in the biopsied muscle, the presence of microscopic polyangiitis was

highly suspected based on the high titre of MPO-ANCA. Prednisolone (30 mg/day) was given at once, and after one month the levels of C reactive protein (CRP) and MPO-ANCA decreased to 5 mg/l and 12 EU/ml, respectively, with clinical improvement.

While receiving continuous prednisolone treatment, in August 2000, the patient suddenly developed severe frontotemporal headache and vertigo. The CRP level increased to 43 mg/l. Two weeks later, complete hearing loss of his left ear developed. Immediate administration of betamethasone (10 mg/day) for three days did not improve his hearing.

In January 2001 myalgia and weight loss developed and continued, and the levels of CRP and MPO-ANCA were raised at 68 mg/l and 46 EU/ml, respectively. In February 2001 redness of both eyes due to keratouveitis suddenly occurred, which improved after treatment with corticosteroid eye drops. Cyclophosphamide (50 mg/day) was also given together with betamethasone (1.5 mg/day), and complete clinical and serological remission was obtained (CRP 5 mg/l, MPO-ANCA 10 EU/ml). A diagnosis of Cogan's syndrome was made based upon the clinical constellation of keratouveitis, sensorineural hearing loss, and suspected systemic vasculitis.

DISCUSSION

Previously, Cheson *et al* reviewed 53 cases of Cogan's syndrome[2]; 10/18 vessel or muscle biopsy specimens showed inflammatory vascular changes, of which four were considered to be diagnostic of polyarteritis in large and medium sized arteries. ANCA is widely used as a useful diagnostic marker for small vessel vasculitis, including Wegener's granulomatosis, microscopic polyangiitis, pauci-immune necrotising crescentic glomerulonephritis, and Churg-Strauss syndrome, although this test is occasionally positive in various other conditions. Recently, it has been reported that the combination of immunoassays for anti-MPO and indirect immunofluorescence for pANCA is highly specific for the diagnosis of systemic vasculitis.[3] Until now, five cases of Cogan's syndrome associated with ANCA have been reported, including ours,[4–7] and two of them also showed ANCA related glomerulonephritis. In our case, pANCA and MPO-ANCA were positive, and audiovestibular abnormalities and keratouveitis were present, but other manifestations of systemic vasculitis were not noted. We speculate, therefore, that all sizes of arteries may be affected in Cogan's syndrome.

The cause of Cogan's syndrome is still unknown. Interestingly, upper respiratory tract infections have been reported to precede the onset of Cogan's syndrome in 40% of cases,[8] suggesting that one of the triggering factors may be upper respiratory infection. Our patient also had a history of upper respiratory infections. The research group in the National Institute of Health found that patients with Cogan's syndrome had significantly high titres of antibodies to *Chlamydia trachomatis*.[9] Ljungstrom *et al* reported a patient with Cogan's syndrome who had a fourfold increase in serum IgG antibody titre to *Chlamydia pneumoniae*.[10] Furthermore, it has been reported that *Chlamydia* infections are related to vascular injury, such as arteriosclerosis and vasculitis. A relationship between previous *Chlamydia* infection and coronary artery disease is supported by seroepidemiological studies. It is suggested that the bacteria adhere to endothelial cells, because *Chlamydia pneumoniae* is detected in atherosclerotic plaques by both polymerase chain reaction and culture. In our case, the IgG titre to *Chlamydia pneumoniae* was negative, but the IgA titre was positive (2.23, cut off point 0.9). We suggest that the IgG titre might have been negative in our case because the titre was measured several months after treatment with corticosteroid and cyclophosphamide.

This case suggests a possibility that antinuclear antibodies are related to the pathogenesis of Cogan's syndrome, although further studies are required to confirm this hypothesis.

Authors' affiliations
M Ikeda, Health Science Centre, Utsunomiya University, Tochigi, Japan
H Okazaki, S Minota, Division of Rheumatology and Clinical Immunology, Jichi Medical School, Tochigi, Japan

Correspondence to: Dr M Ikeda, Health Science Centre, Utsunomiya University, Utsunomiya City, Tochigi 321–8505, Japan; ikedam@cc.utsunomiya-u.ac.jp

Accepted 7 January 2002
M Hamidou, Internal Medicine Unit, Nantes University Hospital, 44093, CHU, Nantes, France
P Youinou, Laboratory of Immunology, Brest University Hospital, 29629, CHU, Brest, France

Correspondence to: Dr J-M Berthelot, Rheumatology Unit, CHU Nantes, Hôtel-Dieu, 44093, Nantes-Cedex 01, France; jeanmarie.berthelot@chu-nantes.fr

Accepted 4 February 2002

REFERENCES

1 **Cogan DS**. Syndrome of nonsyphilic interstitial keratitis and vestibuloauditory symptoms. Arch Ophthalmol 1945;33:144–9.
2 **Cheson BD**, Bluming AZ, Alroy J. Cogan's syndrome: systemic vasculitis. Am J Med 1976; 60:549–55.
3 **Choi HK**, Liu S, Merkel PA, Colditz GA, Niles JL. Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitis: metaanalysis with a focus on antimyeloperoxidase antibodies. J Rheumatol 2001;28:1584–90.
4 **Yamanishi Y**, Ishioka S, Takeda M, Maeda H, Yamakido M. Atypical Cogan's syndrome associated with antineutrophil cytoplasmic autoantibodies. Br J Rheumatol 1996;35:601–3.
5 **Cohen Tervaert JW**, Mulder L, Stegeman C, Elema J, Huitema M, The H, *et al*. Occurrence of autoantibodies to human leukocyte elastase in Wegener's granulomatosis and other inflammatory disorders. Ann Rheum Dis 1993;52:115–20.
6 **Suzuki M**, Arimura Y, Minoshima S, Fukuoka K, Miyake N, Ishizuka S, *et al*. A case of myeloperoxidase-specific antineutrophil cytoplasmic antibody (MPO-ANCA)-related glomerulonephritis associated with Cogan's syndrome. Jpn J Nephrol 1996;38:423–7.
7 **Brijker F**, Magee CC, Tervaert JW, O'Neill S, Walshe JJ. Outcome analysis of patients with vasculitis associated with antineutrophil cytoplasmic antibodies. Clin Nephrol 1999;52:344–51.
8 **Vollertsen RS**, McDonald TJ, Younge BR, Banks PM, Stanson AW, Ilstrup DM. Cogan's syndrome: 18 cases and a review of the literature. Mayo Clin Proc 1986;61:344–61.
9 **Haynes BF**, Kasier-Kupfer MI, Mason P, Fauci AS. Cogan syndrome: studies in thirteen patients, long-term follow-up, and a review of the literature. Medicine (Baltimore) 1980;59:426–41.
10 **Ljungstrom L**, Franzen C, Schlaug M, Elowson S, Viidas U. Reinfection with Chlamydia pneumoniae may induce isolated and systemic vasculitis in small and large vessels. Scand J Infect Dis 1997;104{suppl):37–40.