Anti-cyclic citrullinated peptide antibodies (CCP2) in patients with psoriatic arthritis

Sirs,

Psoriatic arthritis is a chronic inflammatory joint disease whose extremely pleomorphic presentation combines variable degrees of peripheral arthritis, axial joint involvement, and enthesitis.

Antibodies to cyclic citrullinated peptides detected by second-generation ELISA (anti-CCP2) have been proven highly specific of rheumatoid arthritis (RA) (1). Anti-CCP2 are markers for severe erosive disease in patients with rheumatoid arthritis. Few studies have evaluated the prevalence of anti-CCP2 in patients with PA.

The objective of this study was to determine the prevalence of anti-CCP2 in patients with PA.

One hundred and two Caucasian patients admitted to the rheumatology department of the Bichat-Claude Bernard Teaching Hospital, Paris, France, from January 1997 to June 2005 were studied retrospectively. All patients met the McGonagle classification criteria (2). The presence of psoriasis was confirmed by a dermatologist. Presence of rheumatoid factors (RF) was not an exclusion criterion. The following data were abstracted from the medical charts: medical history, findings from a thorough physical examination, results of tests for RF and anti-CCP2 routinely performed without particular consent, and findings from radiographs of the hands and feet and from a posteroanterior radiograph of the lumbar spine in the standing position. Abnormalities on radiographs of the hands and feet met the CRDO classification criteria developed by Fournié *et al*. (3).

Anti-CCP2 antibodies were assayed in serum using a second-generation ELISA (Immunoscann RA Eurodiagnostica, Arnheim, The Netherlands). Titers greater than 50 U/ml were considered positive.

IgM RF were assayed in serum using nephelometry in a BN2 analyzer (N Latex RF, Dade Berhing, Marburg, Germany). Titers greater than 20 IU/ml were considered positive.

Table I reports the clinical, radiological, and laboratory features in the study patients. Of the 102 patients, 2 (2%) had positive anti-CCP2 antibodies; titers were 179 and 76 U/ml, respectively. One of these two patients had erosive distal polyarthritis and positive RF, whereas the other had oligoarthritis and negative RF. Table II reports the features in these two patients. In 3 (3%) patients, anti-CCP2 titers were between 25 and 50 IU/ml and remained unchanged upon re-assay 3 months later.

RF was present in 3 patients (3%). One of these patients had axial PA and a past history of hepatitis C. The other 2 patients had predominantly peripheral joint involvement. Bilateral sacroiliitis was a feature in all 3 patients. The mean RF titer was 145 IU/ml (range, 61-305).

Among the 102 patients with PA, 2 (2%) tested positive for anti-CCP2. One of these 2 patients also tested positive for RF; the clinical pattern in this patient was symmetric polyarthritis with joint destruction reminiscent of RA. The other patient had oligoarthritis and negative tests for RF.

Although the presence of citrullinated peptides is not specific of rheumatoid synovium (10), the production of serum anti-CCP2 is associated with the presence of one or two HLA DR B1*04 or *01 alleles (4). High specificity of anti-CCP for rheumatoid arthritis has been reported (2); in one study, specificity was 98% and sensitivity 68% (2).

Recently, the prevalence of anti-CCP2 was investigated in patients with juvenile arthritis (5), primary Sjögren syndrome (2) or systemic lupus erythematosus (6). A few studies looked for anti-CCP2 in patients with psoriatic arthritis and found far lower prevalences compared to patients with RA (5.8% to 15%) (7-10). Most of these studies found that presence of anti-CCP2 was significantly correlated with polyarticular involvement (often symmetric), presence of erosions, and presence of the shared epitope (10).

PA is widely recognized as raising major diagnostic challenges (12). A number of distinctive clinical and/or radiological features can be used to differentiate PA from RA. In a study by Vander Cruyssen B *et al*. of 192 patients with PA, 5 of the 15 patients with anti-CCP had a presentation reminiscent of RA, and 4 of these 15 patients tested positive for RF (7). The differences across the study populations and the classification criteria used (Moll and Wright criteria in most studies) undoubtedly constituted major sources of bias. Thus, patients with RA and psoriasis may have been misclassified as having PA, thereby artificially increasing the prevalence of anti-CCP2 in studies of PA. According to the Moll and Wright criteria, arthritis in a patient with psoriasis is classified as PA (1). The absence of validated diagnostic or classification criteria suitable for universal use may explain the discrepancies among studies. We used the McGonagle classification criteria, which rely on a decision tree to ensure high specificity and sensitivity (1). This ensured rigorous selection of patients with PA for our study. The 2% prevalence of anti-CCP2 in our population may therefore be more reliable than the higher prevalences in earlier studies. The long disease duration in our patients (mean, 122 months, *i.e*., about 10 years) and the recruitment at a single site to ensure patient homogeneity militate against misclassification of RA with psoriasis as PA in our study population.

However, large prospective studies should be undertaken from very early stages of the disease and following the patients for years in order to evaluate the disease evolution, especially looking at the shifts of patients from one subgroup to the other.

Anti-CCP2 are rare in patients with PA. The most common pattern of PA in anti-CCP2-positive patients is erosive polyarthritis with positive tests for RF and HLA DR B1*04 or *01, which may indicate RA combined with psoriasis. Nevertheless, oligo- or polyarticular PA with positive anti-CCP2 can occur. The significance of anti-CCP2 in this situation remains to be determined in a prospective study.

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Table I. Patient characteristics.

	n (%)	
Sex: male	59	(57.8)
female	43	(42.1)
Mean age (years)	50.82	[range, 2 -76]
Mean disease duration (months)	122	[range, 5-456]
Current pattern of joint involvement		
Cervical spine	41	(40.1)
Enthesitis	14	(13.7)
Predominantly peripheral involvement	90	(88.2)
Predominantly axial involvement	12	(11.7)
Psoriasis		
Previous	56	(54.9)
Concomitant	16	(15.7)
Subsequent	20	(19.6)
No skin involvement	10	(9.8)
Radiographic findings		
Sacroiliitis	30	(29.4)
CRDO criteria	33	(32.3)
Laboratory findings		
Latex-WR - positive	3	(2.9)
anti-CCP2 - positive	2	(1.9)

Table II. Clinical features in the patients with positive tests for anti-cyclic citrullinated peptide.

Sex	age (yrs)	Duration (mo)	Psoriasis	Sub-group	Erosions	Titer (Anti-CCP2) (U/ml)	RF	specific involvement (IU/ml)
F	72	108	patient	polyarthritis	yes	238	305	symmetric, sacroiliitis and DIP
F	53	72	family	oligoarthritis	no	76	no	enthesitis

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Treatment of Schnitzler's syndrome with anakinra

Sirs,

Schnitzler's syndrome is a rare disorder characterized by chronic urticaria, bone pain, monoclonal immunoglobulin M gammapathy and intermittent fever (1). Treatment is usually very disappointing, and only high-dose corticosteroids can improve the skin lesions, but they rapidly induce adverse effects. Recently, an interleukin 1 receptor antagonist (IL1Ra), anakinra, has demonstrated prolonged efficacy in some case reports (2, 3).

We report on a new case of a patient with Schnitzler's syndrome treated with anakinra, which was able to achieve a rapid and persistent remission of clinical and laboratory abnormalities.

This patient was a 72-year-old man without any particular medical history. He had been chronically ill for over a year, suffering from fever reaching 39°C, fatigue, weight loss and lower back pain. Examination revealed chronic urticaria affecting the back, chest and abdomen. This was associated with elevated C-reactive protein (180 mg/l), and leukocytosis ($25x10^9$/l). Serum protein electrophoresis revealed a monoclonal IgM kappa component (total IgM 2.55 g/L). A skin biopsy identified urticarial changes. Bone radiographs and CT-scan films evidenced condensations on the iliac bone and L4 vertebrae.

This led us to make a diagnosis of Schnitzler's syndrome (1). First-line therapy was based on full-dose corticosteroids (prednisone 1 mg/kg/day), but steroid dependency was observed when the daily dosage was tapered to 30 mg. Adding methotrexate did not ameliorate his dependency on prednisone.

A course of subcutaneous anakinra at a dose of 100 mg/day was then considered. Following the first injection, the urticaria immediately resolved and laboratory features of inflammation normalized over a few days. Remission still persisted after 6 months of follow-up, at which point, the injections of anakinra were maintained but reduced to 100 mg every two days. This change was followed by a relapse of urticaria, fever, leukocytosis and inflammatory syndrome. Reintroduction of the initial dosage of 100 mg/day enabled a complete regression of clinical and biological abnormalities. At the time of writing (12 months of follow-up), CRP and leukocytes remain normal, and urticaria and fever have not recurred. The concentration of the monoclonal component remains unchanged. Anakinra injections are well-tolerated, with only moderate skin dryness and pain at the injection sites.

Schnitzler's syndrome is a rare disease consisting chiefly of chronic urticaria, together with monoclonal IgM. Other symptoms include fever, joint and bone pain, enlarged lymph nodes, bone condensations, leukocytosis, and elevated CRP levels.

Dependency on high doses of corticosteroids is the rule, entailing steroid toxicity. Immunosuppressive drugs are mostly ineffective. The disease evolves to chronicity and affects the patient's quality of life (1).

The pathophysiology of Schnitzler's syndrome remains unclear. Anakinra is an interleukin 1 (IL-1) receptor antagonist. Its effectiveness in this syndrome evokes a key role for IL-1 (2, 3). It has been suggested that anti-IL1α IgA antibodies are more frequent in Schnitzler's syndrome than in controls (4).

In previous case-reports, the clinical benefits of anakinra were very rapid, observed within a few hours on urticaria, and within a few days on CPR and leukocytosis (2). We observed the same response, and showed that a reduction in dosage was followed immediately by a clinical and biological relapse of symptoms. However, anakinra only "suspends" the symptoms of this syndrome. It could perhaps be proposed as a diagnostic test. Nonetheless, the use of anakinra should be studied at a larger scale in order to confirm its efficacy and to evaluate the benefit/risk ratio in Schnitzler's syndrome (5).

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