

Letters to the Editor

Gastric Crohn's disease and SAPHO syndrome

Sirs,

The association between SAPHO (Synovitis, Acne, Pustolosis, Hyperostosis, Osteitis) syndrome and inflammatory bowel disease (IBD) is well known and firmly established (1). Nevertheless, to the best of our knowledge the association of primary gastric Crohn's disease and SAPHO syndrome has never been reported (1-5); we describe such a case here.

In October 1996, a 59-year-old Caucasian woman presented with fixed symmetrical arthritis of the wrists and metacarpophalangeal joints. Biochemical investigations only showed an increased erythrocyte sedimentation rate (ESR) (75 mm/hr) and C reactive protein (CRP) (11.5 mg/dL; normal values <0.8). Serum rheumatoid factor, antinuclear antibodies, anti-double stranded DNA, anti extractable nuclear antibodies, hepatitis B and C virus, Chlamydia and human immunodeficiency virus serology, serum complement and immune-complexes were in the normal range. A diagnosis of seronegative rheumatoid arthritis was made and she was placed on treatment with an oral non-steroidal anti-inflammatory drug (NSAID).

The patient remained well until January 1997, when the development of non-psoriatic palmo-plantar pustolosis and severe pain in the right costo-clavicular and costosternal joints, along with x-ray evidence of synovitis, osteitis and sacro-iliitis, strongly suggested SAPHO syndrome (Table I). NSAID did not control the symptoms and she started oral deflazacort 30 mg/day and cyclosporin A (CyA) 3 mg/kg/day. She was seen by a rheumatologist every 3 months; complete recovery was obtained and deflazacort was tapered and finally stopped in November 1998. CyA was reduced to 2 mg/Kg/day.

The patient was well until August 1999, when she presented with intermittent fever,

malaise, dyspepsia and weight loss that prompted hospitalization. Apart from the fever and sinus tachycardia, her physical examination was unremarkable; biochemical tests showed mild normochromic normocytic anemia, thrombocytosis, and an elevated ESR (121 mm/hr) and CRP (23 mg/dL). Repeated blood and urine cultures were sterile and stool examination for parasites, culture and blood was negative. Echocardiogram and x-ray chest were normal.

Esophagogastroduodenoscopy (EGDS) showed a 5 mm linear ulcer with nodularity of the surrounding mucosa located in the gastric antrum. Histologic examination disclosed chronic inflammatory changes with non-caseating granulomas and multi-nucleated giant cells; no acid-fast bacilli were found. A subsequent colonoscopy showed a normal mucosa, but scattered granulomas along with multi-nucleated giant cells were detectable in random bioptic specimens. The HLA haplotype was A2, A26 (10), B13 (W4), B35 (W6), CW4, DR7, DR53, DQ2. A tuberculin skin test and Histoplasma capsulatum, Chlamydia, Yersinia and Campylobacter serology were negative. Serum angiotensin I converting enzyme (ACE) was 28 mmol/dL (normal range 24-30).

A diagnosis of Crohn's disease associated with SAPHO syndrome was made and the patient restarted deflazacort 30 mg/day along with omeprazole 20 mg/day by mouth. This treatment was followed by disappearance of the symptoms and fever. An EGDS performed 3 months later showed complete ulcer healing with persistence of antral mucosa nodularity.

In this febrile immunosuppressed patient, the development of a granulomatous inflammatory gastrointestinal disorder mandated the exclusion of tuberculosis, cryptococcosis and histoplasmosis. Sarcoidosis is another rare cause of granulomatous gastritis, but the normal x-ray chests and serum ACE argued against this diagnosis. The spondyloarthropathies, whose spectrum probably includes SAPHO syndrome, are present in 2-6% of IBD patients, most of whom show the haplotype HLA B27 (6). In the same way many cutaneous conditions are associated with IBD, mainly erythema nodosum and pyoderma gangrenosum; interestingly, the last condition has been reported in a single patient with SAPHO syndrome (7) suggesting a common pathogenic link.

In conclusion, this is the first reported case of primary gastric Crohn's disease in a patient with SAPHO syndrome. We believe that studying the immunological and genetic status of patients with rare but clear-cut associations between IBD and extra-intestinal manifestations may be helpful in unrav-

eling the etiopathogenesis of these disorders.

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Transient hyperthyroidism in a patient with rheumatoid arthritis treated by etanercept

Sirs,

A 37-year-old woman presented with seropositive destructive rheumatoid arthritis (RA) meeting the revised American College of Rheumatology criteria (1), of 8 years' duration. Several disease-modifying drugs had been necessary for the management of her condition and she had been taking 50 mg of azathioprine per day and 7.5 mg of prednisone per day for 12 months.

A new attack of RA led to etanercept (25 mg subcutaneous twice weekly; Enbrel®, Wyeth-Lederlé) being added to the previous treatment. Her symptoms improved within a few weeks, with the disappearance of tenderness and joint swelling, the reduction of morning stiffness to 15 minutes and the nor-

Table I. SAPHO inclusion criteria [modified from Kahn *et al.*, (1)].

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| 1. Acne and osteoarticular involvement
or |
| 2. Palmoplantar pustolosis and
osteoarticular involvement
or |
| 3. Sternocostoclavicular hyperostosis
or |
| 4. "Sterile" osteomyelitis |

These features may be differently associated (i.e., acne + hyperostosis; acne + osteomyelitis; palmoplantar pustolosis + hyperostosis or osteomyelitis, etc.), but only one criterion is sufficient for inclusion.

malisation of acute phase reactants. Nevertheless, tachycardia and irritability occurred spontaneously 6 months later, while the patient was still taking this treatment. She had no diarrhoea or trembling. Weight and joints remained stable. Biological examination (Bayer Immuno-one; immuno-enzymatic procedure) detected hyperthyroidism: the ultrasensitive thyroid-stimulating hormone concentration was 0.05 mIU/l (normal: 0.6-6) and the free T4 concentration was 23 pmol/l (normal: 11-24). Clinical examination and scintigraphy showed the thyroid gland to be normal. We investigated possible autoimmunity: rheumatoid factor was as previously detected (ELISA: 20 IU - Normal < 10), but no significant quantities of anti-nuclear (50 IU) or anti-thyroglobulin or anti-peroxidase antibodies were detected.

Propranolol (40 mg/day) was introduced as a symptomatic treatment with success, and etanercept was continued. All clinical symptoms disappeared within a few weeks and one month later, thyroid function was normal (usTSH: 0.6 and fT4: 16.8).

We believe that this patient had transient mild hyperthyroidism with clinical and biological manifestations, possibly facilitated by tumour necrosis factor alpha antagonist. An association between autoimmune thyroiditis and RA has long been suspected, but remains a subject of debate (2). Tumour necrosis factor alpha (TNF- α) antagonists are an important new addition in RA treatment. Etanercept is a recombinant fusion protein consisting of the soluble TNF receptor (p75) linked to the Fc portion of human IgG1, produced in a hamster cell line. Safety analysis has demonstrated that this treatment is well tolerated. However, the production of non-neutralising antibodies directed against the etanercept molecule has been observed in 16% of patients taking the drug. In addition, antibodies against double-stranded DNA have been detected in 15% of treated patients and anti-nuclear antibodies in 11% (3). Furthermore, patients receiving etanercept may develop anti-animal antibodies that interfere with laboratory monoclonal antibody assays. Thyroid-stimulating hormone and T4 abnormalities, in particular, may have been underestimated for this reason (3). Similarly, autoimmunity may result from cross-reactive immunogenicity with these antibodies. The thyroid seems to be very sensitive to autoimmunity. Thus, thyroid dysfunction and thyroiditis have already been reported with various immunological treatments for multiple sclerosis, such as interferon beta-1a and pulses of humanised anti-CD52 monoclonal antibody (4), and also with the use of recombinant human TNF receptor: IgG chimera (rhu TNFR:Fc; Im-

mune) in combination with interleukin 2 for metastatic cancer (5).

This is the first report of a case of transient hyperthyroidism in a patient with rheumatoid arthritis treated by etanercept. Thyroid function should be taken into account in patients receiving this treatment.

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Minor but important symptoms and signs in primary hypertrophic osteoarthropathy

Sirs,

Hypertrophic osteoarthropathy (HOA) is a syndrome characterized by clubbing fingers and proliferative periostitis of the long bones. HOA may be classified as either primary (PHOA) or secondary, and is most often associated with neoplastic or infectious diseases. There are three incomplete forms of HOA: clubbing fingers, periostitis without clubbing fingers, and pachyder-

moperistosis with so-called "minor manifestations". Minor manifestations include synovial effusion, seborrhea, folliculitis, hyperhidrosis, hypertrophic gastropathy and acroosteolysis. Some of the minor signs and symptoms of PHOA are not included in present diagnostic criteria, but may be helpful in establishing the diagnosis of HOA. We present the results of our study regarding the prevalence of these symptoms and signs in patients with primary HOA.

At the Department of Rheumatology of the University Hospital "Sestre milosrdnice" in Zagreb-Croatia, during the period 1970-1996 we diagnosed primary HOA in 76 patients, 71 men (93.5%) and 5 women (6.5%). We followed up the majority of these patients for several years, and some of them for more than 2 decades (11 \pm 8.4 yrs). The patient history and results of clinical examinations were recorded in a simple chart designed in our department. The average age of the patients was 38.7 years (range 18-64 years). The disease started in childhood (up to age 14) in 62 patients and in adolescence in 14 patients.

The frequency of minor symptoms and signs are presented in Table I. Palmar and periungual erythema is accompanied by velvet-like and thickened skin, whilst excessive sweating is accompanied by a strong and penetrating odour. Changes regarding the angle between the nail and nail-bed region, and accordingly changes in shape are dependent on the phase of clubbing. Apart from changes in shape (convexity in all directions), the nails have longitudinal grooves and white dots. Stiffness in the hands and feet (lasting no longer than 30 minutes) were mainly present in the evening. Periarticular edema was present mostly in the ankle joints, and occasionally in the wrists and knees. Pathohistological

Table I. Minor symptoms and signs present in patients with primary hypertrophic osteoarthropathy (n = 76).

Symptoms and signs	No.	%
Fatigue	18	23.7
Palmar & periungual erythema	37	48.1
Enlarged fingers	52	68.4
Sense of warmth and burning in hands and feet	76	100.0
Deeper nasolabial fold	76	100.0
Loss of mimics	64	84.2
Leonine face	15	19.7
Cutis verticis gyrata	28	36.8
Arthralgia	30	39.5
Periarticular edema	40	52.6
Erythematous skin over joints	7	9.2
Gynaecomastia	3	3.9
Delayed sex development	51	67.1