Successful treatment of SAPHO syndrome with leflunomide. Report of two cases

Sirs,

SAPHO (Synovitis, Acne, Pustolosis, Hyperostosis, Osteitis) is characterized by aseptic bone and joint lesions, associated with skin involvement. Usually anterior chest pain is present at the early stage. Enthesis involvement was in most cases the first event leading to hyperostosis (1,2). We report two cases of SAPHO treated with leflunomide, with improvement of joint complaints and of skin lesions.

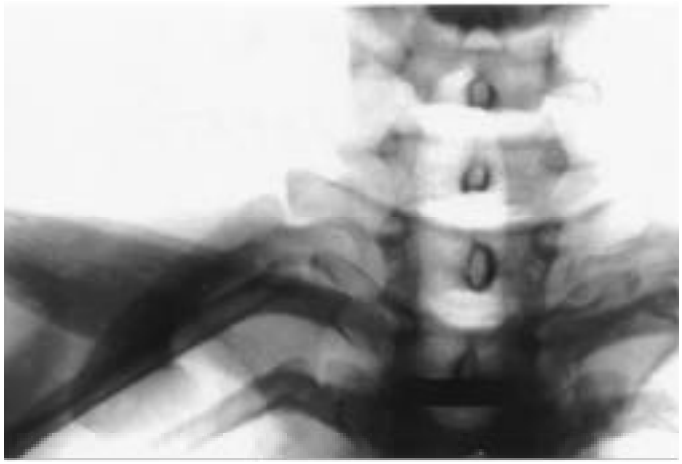
Case no. 1. A 17-year-old Caucasian boy with acne conglobata was admitted for fever, weight loss, swelling of right clavicle. His symptoms appeared one year ago. No history of psoriasis in his family. HLA typing was A3A9B7B35Cw4. Radiographs revealed hyperostotic changes of right clavicle with double track picture (Fig. 1), and right sacroiliitis. Bone scintigraphy showed increased uptake in right clavicle, manubriosternal, pubis and right sacro-iliac joint. A diagnosis of SAPHO syndrome was made and the patient was treated with diclofenac b.i.d. and injection of triamcinolone in sternal joints, with limited efficacy. Therefore, the patient was discharged on leflunomide (20 mg oad), diclofenac (100 mg) and rest. After 2 weeks the spine stiffness disappeared, after 1 month the swelling of right clavicle disappeared, the patient reported a total relief of cutaneous and osteoarticular symptoms, and diclofenac was withdrawn. At present, after 18 months the patient is in total remission with leflunomide 20 mg oad alone, which appears to be well tolerated. He presents only scars of acneic lesions.

Case no. 2. A 22-year-old Caucasian male was admitted for arthralgias, restricted spine movement, neck pain and anterior chest pain, swelling and tenderness of wrists, ankles, manubrio-sternal region. The onset of this symptomatology began 7 months ago. He suffered from acne conglobata. HLAtyping was not performed. Bone scintigraphy showed increased uptake in manubriosternal, condrosternal, sacro-iliac joints, ankles and knee. A diagnosis of SAPHO syndrome was made but the patient refused steroid therapy. Therefore he was discharged on leflunomide 20 mg oad and diclofenac 50 mg b.i.d. After 5 weeks the patient reported improvement of articular symptoms, with partial reduction of acneic lesions. Diclofenac was stopped. At present, after 9 months, the patient is in total remission. He complains only a mild nausea after taking leflunomide.

Wagner has demonstrated in histologic investigations of bone biopsy specimen in SAPHO patients an amounts of TNFα production (3).These findings provided several authors with a rationale for using TNFα blocking agents to treat successfully SAPHO patients (3-5). Leflunomide suppress pyrimidine synthesis, and recently significantly decreased expression of ICAM-1, TNFα and IL-1β was detected in synovial tissue samples from patients with RA after leflunomide treatment (6), accompanied by reduced cytokine synthesis by activated macrophages (7). The compound has recently been shown to be useful for the treatment of recalcitrant cases of psoriasis and psoriatic arthritis (8).

The young age, the severe course, the good compliance, the handling of dosage and the cost/benefit ratio oriented us to prefer leflunomide with respect other DMARDs, including TNFα-blocking agents. Leflunomide costs 904.87€ /year vs 12,984.81€ / year of Infliximab at dosage of 3 mg/Kg for each infusion for treatment of RA (9). Therefore, in our young patients we preferred leflunomide, with total remission of articular signs and good tolerance. At present the two patients are in good health, and our intention is to stop therapy with leflunomide after 2 years since remission, and then only to supervise periodically these patients.

Fig. 1. Periosteitis and hyperostosis of the right clavicle with double track picture.



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Anti-RNApolymerase antibodies in Korean patients with systemic sclerosis and their association with clinical features

Sirs,

In systemic sclerosis (SSc), serum autoantibodies such as anticentromere antibody (ACA) and anti-topoisomerase I antibody (anti-topo I) are helpful markers of certain clinical features. However, Korean SSc patients have shown different characteristics (1): (i) no association between autoantibodies and disease subsets; (ii) much lower ACAprevalence in limited subset (6.7% vs 44% in Caucasians and 37% in the Japanese) (2); and (iii) no significant difference in clinical characteristics between disease subsets, except for more frequent musculoskeletal involvement in limited subset. Therefore, we investigated the prevalence of anti-RNAP antibodies in Korean SSc patients and their association with clinical features.

Letters to the Editor

Table I. Clinical features according to anti-RNAP status*.

	Anti-RNAPI/III			Anti-RNAPII		
	positive n = 2	negative n = 57	p-value	positive n = 7	negative n = 52	p-value
Age at disease onset (yr)†	62.0 ± 5.7	41.1 ± 12.8	0.014	43.6 ± 13.6	41.6 ± 13.3	0.774
Symptom duration (yr)†‡	0.8 ± 0.4	3.9 ± 4.3	0.129	4.9 ± 7.2	3.7 ± 3.8	0.573
Sex (female)	1 (50)	50 (87.7)	0.255	6 (85.7)	45 (86.5)	1.000
Serological finding						
Anti-topo I	0	33 (57.9)	0.190	3 (42.9)	30 (57.7)	0.688
ACA	0	2 (3.5)	1.000	0	2 (3.8)	1.000
Clinical findings						
Diffuse subset	2 (100)	26(45.6)	0.221	5 (71.4)	23 (44.2)	0.240
Overlap syndrome	0	12 (21.1)	1.000	1 (14.3)	11 (21.2)	1.000
Raynaud's phenomenon	2 (100)	57 (100)	1.000	7 (100)	52 (100)	1.000
Digital pitting scar	1 (50)	39 (68.4)	0.544	4 (57.1)	36 (69.2)	0.670
Total skin score†	30.0 (n=1)	13.9 ± 10.2	0.208	12.8 ± 7.5	14.4 ± 10.7	0.974
Abnormal NC	1 (50)	42/43 (97.7)	0.088	5/6 (83.3)	38/39 (97.4)	0.252
Radiological ILD	0	39 (68.4)	0.111	4 (57.1)	35 (67.3)	0.679
FVC < 80 %	1 (50)	39 (68.4)	0.544	6 (85.7)	34 (65.4)	0.411
DLCO/VA< 80 %	1 (50)	23/55 (41.8)	1.000	7 (100)	17/50 (34.0)	0.001
Heart involvement	0	9 (15.8)	1.000	2 (28.6)	7 (13.5)	0.288
Renal crisis	1 (50)	0	0.034	0	1 (1.9)	1.000

*Values are presented as numbers (%), unless otherwise stated. † Mean ± SD. ‡ Symptom duration till diagnosis. ACA: anticentromere antibody; Anti-topo I: anti-topoisomerase I antibody; DLCO/VA: diffusing capacity of carbon monoxide over volume of alveoli; FVC: forced vital capacity; ILD: interstitial lung disease; NC: nailfold capillaroscopy; RNAP: RNApolymerase.

Fifty-nine Korean SSc patients who fulfilled ACR preliminary criteria and 59 controls (10 normal, 20 SLE, 10 RA, 19 SS) were included. Disease subset was classified as diffuse or limited based on cutaneous involvement (3). Clinical assessment was done as previously described (4), with further investigation by high resolution computed tomography (HRCT) and nailfold capillaroscopy. Anti-RNAPwas detected by immunoprecipitation using ^{35}S-methionine-labeled K 562 cells (5), and its clinical association was evaluated.

Twenty-eight patients had diffuse and 31 limited subset. Twelve patients (2 diffuse, 10 limited) had overlap syndrome with SLE (n = 7), polymyositis (n = 3), and SLE/ polymyositis (n = 2). Interstitial lung disease (ILD) was shown in 66.1% (39/59) by chest X-ray and/or HRCT. FVC < 80% or DLCO/VA < 80% were shown in 79.6% (47/59). Heart involvement was seen in 15.3% and renal crisis in 1.7%. No difference between disease subsets was found in clinical features or ACA and anti-topo I frequencies, except for more frequent overlap syndromes and digital pitting scars in limited subset compared with diffuse subset (32.3% vs. 7.1%, p = 0.017; 80.6% vs. 53.6%, p = 0.026, respectively).

Eight sera of SSc patients (13.6%) precipitated RNAP subunits. In controls, one SLE serum precipitated RNAPII subunits. Eight anti-RNAP SSc sera consisted of anti-RANP I/II/III (n = 1, diffuse), anti-RNAP I/III (n = 1, diffuse) and isolated anti-RNAP II reactivity (n = 6; 4 diffuse, 2 limited). Five isolated anti-RNAP II and one anti-RNAP I/II/III sera precipitated RNAP IIO subunit. Anti-RNAP I/III was associated with older age at disease onset and renal crisis (Table I), while anti-RNAP II with more frequent DLCO/VA < 80% (Table I) and lower DLCO/VA (61.1± 15.0% vs. 83.6 ± 22.6%, p = 0.004). Ground glass opacity (GGO) and fibrosis scores measured on HRCT (n = 24) according to Kazerooni *et al*. (6) tended to be higher in the anti-RNAP II positive group compared with the negative group, but they were not statistically significant (2.13 ± 0.42 vs. 1.52 ± 0.90, p = 0.354; 1.40 ± 0.92, vs. 0.92 ± 0.99, p = 0.354, respectively). The lack of statistical significance might be due to the small number of analyzed patients. However, GGO scores were negatively correlated with FVC (r = –0.466, p = 0.022) and the fibrosis scores with FVC and DLCO/VA (r = –0.461, p = 0.023; r = –0.469, p = 0.024, respectively).

Anti-RNAP I/III frequency of our patients, 3.4% (2/59), appears to be lower than those reported in Caucasian patients from Italy, UK, and the USA; 7.2% (9/125), 11.6% (18/155), and 15.9% (40/252), respectively (7-9). When compared with Japanese patients whose genetic background is similar to that of Korean patients, anti-RNAP I/III was comparable in frequency (3.4% vs. 5.1% in Japanese, p = 0.747), and showed similar SSc specificity, association with diffuse subset and renal crisis, and mutual exclusiveness with anti-topo I (5). On the other hand, association between anti-RNAP IIO and anti-topo I seen in Japanese patients (94%, 14/15) was not apparent in our patients (60%, 3/5) (10).

In conclusion, the prevalence of anti-RNAP in Korean patients was 13.6%, with 3.4% for anti-RNAP I/III and 11.9% for anti-RNAP II. Anti-RNAP I/III was associated with renal crisis and an older age at onset, whereas anti-RNAP II was associated with reduced DLCO/VA. Because clinical analysis was limited due to the low frequency of anti-RNAP, further study with a larger number of patients is warranted.

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