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Reply

Sir,

We thank Dr. Gerli *et al.* for their comments. They confirmed our observations in a larger series of SS patients. Interestingly, they further demonstrated that CD30+ cells are absent in both peripheral blood and minor salivary gland tissue from SS patients, and suggested that activated CD30+ cells are operating in other lymphoid organs.

Some of the discrepancies between Gerli's observations and our own, such as the serum sCD30 and RF levels in SS patients, will be explained by the number of patients and/or the patient population examined: in our 35 SS patients, anti-SS-A/Ro and SS-B/La antibodies were positive in 75.7% and 33.3%, respectively. RF were not frequently detected in our SS patients (34.3%), but significantly positive correlations were observed among anti-SS-A/Ro antibody, anti-SS-B/La antibody, RF and IgG levels.

In contrast to their previous observations, we did not detect any correlations between sCD-30 levels and clinical parameters of disease activity in RA and SLE patients. We believe in the validity of our observations in RA patients, since we examined a larger number of patients. In addition, the serum C-reactive protein (CRP) level is one of the most useful parameters of disease activity in RA. In our 69 RA patients, CRP levels correlated well with other parameters such as the erythrocyte sedimentation rate ($p < 0.0001$), painful and/or swollen joint counts ($p = 0.0005$), and the modified Lansbury's activity index ($p < 0.0001$), but not with serum sCD30 levels.

Y. ICHIKAWA*, *MD, PhD, Associate Professor*
M. YOSHIDA, *MT*
C. YAMADA, *MD*
T. HORIKI, *MD, PhD, Instructor*
Y. HOSHINA, *MD, PhD, Instructor*
M. UCHIYAMA, *MD, PhD, Asst. Professor*

Division of Rheumatology, Department of Internal Medicine 4, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, 259-1193, Japan.
** To whom all correspondence should be addressed.*

Remitting seronegative symmetrical synovitis with pitting edema syndrome associated with cryptogenic hepatocellular carcinoma

Sir,

McCarty reported the RS3PE syndrome as being a distinct form of seronegative rheumatoid arthritis-like polyarthritis characterized by late onset, symmetrical joint involvement, pitting edema of the hands and feet, and a benign course of the illness (1). Although polyarthritis is a symptom often associated with carcinoma (2), cases of RS3PE syndrome in association with carcinoma have rarely been reported. We herein report a case of RS3PE syndrome associated with a hepatocellular carcinoma (HCC).

A 69-year-old Japanese man, who had atrial fibrillation and abdominal aortic aneurysm, complained of sudden onset polyarthralgia. His wrists, metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints, and knees all exhibited bilateral, symmetrical polyarthritis associated with intense inflammatory joint signs. Pronounced pitting edema was also observed on the dorsa of both his hands and his feet.

Laboratory investigations showed a CRP of 4.9 mg/dl, an ESR of 52 mm/hr and a WBC count of 10,500/mm^3. Antinuclear antibody, anti-smooth muscle antibody, rheumatoid factor, and anti-human T cell lymphotropic virus type I antibody were all negative. In addition, hepatitis B surface (HBs) antigen and antibody and HBe antigen and antibody were also negative. The HBc antibody positive rate was 85 (normal 30 - 69). Hepatitis C virus (HCV) antibody and RT-PCR for GB virus C/hepatitis G virus (GBV-C/HGV) (3) were negative. Radiographs of the painful joints were normal. The HLA phenotype was A24, A2, B7, B62, Cw7, Cw3, DR2, and DR8. The disease was diagnosed as RS3PE syndrome.

Treatment with 20 mg/day of prednisolone was initiated, and rapid resolution of the joint pain and edema occurred within 48 hours. When he was seen at follow-up 7 days later, the polyarthralgia was absent and the edema had nearly disappeared. Laboratory data showed an ESR of 7 mm/hr and CRP of 0.9 mg/dl.

Abdominal ultrasonography to evaluate the patient's abdominal aortic aneurism at the same time disclosed a space-occupying lesion (SOL) in liver segment 8, which had not been detected six months earlier. Histology of the biopsy specimen of this lesion showed moderately differentiated hepatocellular carcinoma. Anterior segmentectomy of the liver together with resection and reconstruction of the abdominal aortic aneurysm were performed on June 19, 1998. In spite of the discontinuation of prednisolone, his polyarthralgia and edema never reappeared after the operation.

The interesting points in this case are that the HCC, which was an uncommon cryptogenic type, was detected in an RS3PE syndrome patient, and that the symptoms specific to this syndrome disappeared following resection of the HCC. The serum of this patient was negative for HBs antigen and anti-HCV antibody. In 95% of HCC cases persistent infection with HBV or HCV is considered to be the causative pathogenic factor (4). HBV DNA amplification by PCR of the genomic DNA extracted from the tumor cells was not observed. Koga has described 22 cases of non-B-non-C HCC (5). These comprised patients with alcoholic liver disease (16/22), autoantibody (17/22) and others. In the current case the specific histological findings of alcoholic liver disease were not detected in the non-cancerous portion of the resected liver, and no autoantibody was detected.

Polyarthritis is often associated with carcinoma (carcinoma polyarthritis syndrome) and 80% of woman with this syndrome suffer

from breast carcinoma. The onset of this type of polyarthritis is during old age and usually the polyarthritis is asymmetric (2). There have been 3 case reports of RS3PE syndrome associated with carcinoma, specifically involving endometrial adenocarcinoma (6), pancreas carcinoma (7), and gastric carcinoma (8). It is possible that alterations in immunity induced by malignancy could be the trigger of RS3PE syndrome.

H. NAKASHIMA T. OTSUKA
Y. TANAKA K. HAYASHIDA
H. SHIGEMATSU T. HORIUCHI
S. KANAYA Y. NIHO

First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, 812-8582 Japan.

Please address correspondence to: Hitoshi Nakashima, First Department of Internal Medicine, Faculty of Medicine, Kyushu University, Fukuoka, 812-8582 Japan.

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Treatment of thrombophlebitis of Behcet's disease with low dose cyclosporin A

Sir,

Recurrent thrombophlebitis (TP) of the lower limbs are the most common vascular manifestations of Behçet's disease (BD) (1, 2). Pulmonary embolization is rare (1, 3). Postphlebitic syndrome and leg ulcers are the most frequent complications of TP (4). The treatment of TP of BD is still controversial. Controlled studies demonstrating the efficacy of anticoagulants alone and/or of a single immunosuppressant drug are lacking. In recent years the important therapeutic role of cyclosporin A (CSA), through its selective action on helper T-cells, in BD has been demonstrated (5).

Considering the rarity of thromboembolic complications (1, 3), the absence of specific abnormalities of coagulation or fibrinolytic activity (6), the potentially dangerous role of anticoagulants in the treatment of TP in BD (7, 8), the evidence that venous immune-mediated vasculitis represents the prominent histological lesion and the central role played by T-cells in the pathogenesis of the disease (9), we decided to evaluate the efficacy of CSA, without adding anticoagulants, in the treatment of deep TP of the legs in a consecutive series of patients with BD.

Between January 1990 and December 1995, after approval by the appropriate local ethical committees and the patients' informed consent were obtained, we treated 9 episodes of deep TP of the lower limbs occurring in 7 consecutive patients meeting the ISG criteria for BD (10). All episodes of TP were diagnosed within 15 days from the onset. The demographic and clinical characteristics, including the site of venous occlusions, of the 7 patients are summarized in Table I. None of the patients had contra-indications for CSA therapy (high blood pressure, abnormal liver and renal function, or altered blood cell counts).

Patients 3 and 7 had a second episode of TP 2 years and 2 months after CSA withdrawal and were treated with CSA again. Three patients had TP at diagnosis and 4 during the course of the disease (mean interval from the diagnosis: 22 months; range: 2-36). The latter 4 were in treatment with colchicine, methylprednisolone (2 patients) and azathioprine.

The diagnosis of deep TP was made by clinical evaluation (local pain over the affected veins, dilatation and varicosity of the superficial veins with evidence of collateral circles, swelling and edema of the leg), doppler/ultrasonography and ^{99m}Tc red blood cell phleboscintigraphy (3 patients).

Previous therapy was interrupted and CSA was given at an initial dose of 5 mg/Kg/day, At clinical remission of TP the drug was reduced monthly by 1 mg/Kg/day to a maintenance dose of 2 mg/Kg/day for a further 6 months. If required, acetaminophen was given to control the symptoms during the first weeks.

Patients were examined at one-month intervals. Each visit included a physical examination, blood pressure measurement, blood samples to monitor the response to CSA therapy and doppler/ultrasonography. After 1 and 6 months phleboscintigraphy was repeated in 3 patients. After CSA withdrawal the patients were evaluated every 3 months. TP coexisted with erythema nodosum in 6/9 (66%) episodes, aphtous stomatitis in 5/9 (55%), uveitis in 4/9 (44%), arthritis in 3/9 (33%), mucocutaneous lesions in 1/9 (11%).

Table I. Demographic, clinical characteristics of the 7 patients with BD and deep TP of the lower limbs.

Clinical features	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6	Pt. 7
Sex/age (years)	M/49	M/26	F/21	F/30	M/25	M/25	M/45
HLA B5/51	-	+	+	+	+	-	-
Pathergy test	-	+	+	-	+	-	-
Aphtous stomatitis	+	+	+	+	+	+	+
Uveitis	-	+	+	+	+	+	-
Genital ulcers	+	-	+	-	-	-	+
Erythema nodosum	+	+	+	+	+	+	+
Cutaneous lesions	+	-	-	+	+	+	+
Arthritis	+	+	+	-	+	-	+
Colitis	-	-	-	-	-	-	-
CNS involvement	+	-	-	-	-	-	-
Arterial lesions	-	-	+	-	-	-	-
Thrombophlebitis	+	+	+	+	+	+	+
Leg involved	L	L	L/1st, R/2nd	L	R	R	R/1st, L/2nd
Vein occlusion	P	I-F	I-F-P/1st, F-P/2nd	I-F	I-F	P	P/1st, P/2nd

L = left, R = right, 1st = first episode, 2nd = second episode, I = iliac, F = femoral, P = popliteal