Soluble CD30 in primary Sjögren's syndrome

Sir,

We read with interest the paper by Ichikawa *et al.* reporting high serum levels of the soluble form of the CD30 molecule (sCD30) in primary Sjögren's syndrome (SS) (1). This finding is in line with the increased levels we described in other autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and systemic sclerosis (SSc) (2-4). Although the CD30 surface molecule is expressed not only by T lymphocytes and its significance as marker of a distinct T cell subpopulation secreting Th2-type cytokines is still controversial (5-8), it is not unreasonable to postulate that the high serum levels of sCD30 detected in autoimmune diseases may reflect an activation of CD30+ T cells at the sites of inflammation. This assumption is supported by the demonstration of T cells expressing the CD30 surface molecule in the synovial fluid of RA, in the ascitic effusion of SLE and in the skin of SSc patients (2, 3, 9). In SS, however, this conclusion is less straightforward.

In a large series of patients examined at the University of Perugia (60 females, 7 males), who fulfilled the Vitali's criteria for primary SS (10), we confirmed that sCD30 serum levels (Ki-1 antigen ELISA,Dako A/S, Glostrup, Denmark) are higher in SS (median, range: 46.5 U/ml, 10-252) than in sex- and age-matched controls (n. 58, 12 U/ml, 5-31 $p < 0.001$). However, we failed to find CD30+ cells in 22 peripheral blood samples (flow cytometry, FACS, Becton Dickinson, San José, CA) as well as in 6 minor salivary gland tissue specimens, analyzed by a described immunohistologic technique (11), in our SS patients. This negative finding may be due to the fact that activated CD30+ cells are operating in other sites, such as lymphoid organs. Alternatively, CD30+ cells may either lack adhesion molecules able to firmly anchor them to the inflamed tissue or rapidly lose the molecule from their surface by shedding.

In contrast to Ichikawa's data, in our study the sCD30 values correlated well with rheumatoid factor (RF, $p < 0.01$; $r = 0.42$), but not with IgG, IgA and IgM values (laser nephelometry). We confirmed, on the other hand, that SS patients positive for fluorescent antinuclear antibodies (ANA) display higher sCD30 levels compared to the group of ANA-negative SS patients ($p < 0.001$). In particular, patients with circulating anti-Ro (SSA) and anti-La (SSB) antibodies (counterimmunoelectrophoresis) showed the highest sCD30 values (Fig. 1). In our opinion, these findings are relevant for two reasons. First, RF, ANA and anti- Ro/La antibodies are able to distinguish those cases of SS in which T cells are actively involved (12). Second, anti-La antibodies represent the best marker of exocrine gland inflammation and are strictly associated with the degree of glandular lymphoid infiltration (13). Thus, higher serum levels of sCD30 in SS may actually reflect an involvement of CD30+ T cells in the course of the chronic inflammatory autoimmune process characterizing the disease.

The functional role exerted by this T cell subset in modulating the activity of systemic autoimmune disorders remains, however, unclarified. In contrast to our observations, Ichikawa *et al.* did not find any correlation between sCD30 levels and parameters of disease activity in RA and SLE. This is difficult to interpret in RA on the basis of the documented presence of CD30+ T cells in the joint effusion (3). The discrepancy with our SLE patients may be explained, at least in part, by different disease severity and organ involvement. In this setting, it is interesting to note that SLE patients with renal involvement usually have low levels of sCD30, as already reported (2) and confirmed by additional studies in a larger group of SLE patients followed for several months, while joint and skin involvement seems to be associated with high sCD30 values (unpublished observations).

In conclusion, we believe that our and Ichikawa's findings support an involvement of CD30+ T cells in systemic autoimmune diseases, even if they do not clarify their functional role in these disorders. Although the concept that Th1/Th2 cell balance plays a key role in determining activation or remission of autoimmune diseases is a fascinating possibility supported by several experimental findings (reviewed in refs. 14, 15), the relevance of sCD30 as marker of Th0/Th2 cell activation and/or disease activity in these diseases is still unproven and needs additional studies. A better understanding of the role of the CD30 molecule on the surface of T cells may provide new insight into the role exerted by CD30+ T cells in systemic autoimmune disorders.

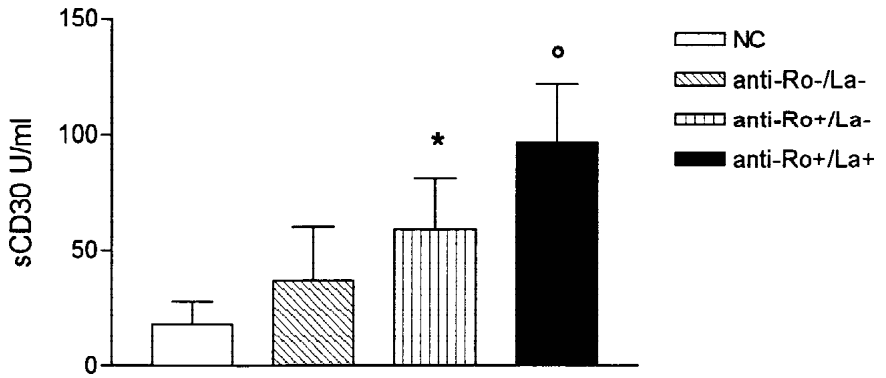

Fig. 1. Serum levels of sCD30 (mean ± SEM) in primary SS patients subdivided according to anti-Ro/La positivity evaluated by counterimmunoelectrophoresis (11) and in 58 age- and sex-matched normal controls (NC). * $p < 0.01$; ° $p < 0.001$ vs NC

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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.

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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