Low prevalence of ectopic germinal centre formation in patients with HTLV-I-associated Sjögren’s syndrome

Sir, We have proposed that HTLV-I infection can be a possible environmental factor for SS based on high prevalence of an anti-HTLV-I antibody in primary Sjögren’s syndrome (pSS) in Nagasaki [1–3], and recently confirmed that labial salivary glands (LSGs) of the HTLV-I-seropositive SS patients are less damaged in radiography [4]. Amt et al. [5] revealed the prominent expression of B cell-attracting chemokine 1 (BCA-1/CXCL13) on endothelial cells and lymphocytic aggregates in the ectopic germinal centre (GC) of LSGs in SS, speculating that ectopic GC is an environmental factor for SS based on high prevalence of an anti-SS-A/SS-B antibodies (Mesacup SS-A/Ro test and SS-B/La Test; Medical & Biological Laboratories, Nagoya, Japan) and IgG concentrations at the time of biopsy were not statistically significant irrespective of HTLV-I infection. Strikingly, ectopic GC was low in HTLV-I-seropositive SS patients (1/32, 3.1%) as compared with HTLV-I-seropositive pSS patients (6/32, 18.8%) (P = 0.045), and 0% in HAM–pSS.

Expression of CXCL13 was observed in 0–10% of mono-nuclear cells (MNCs) of HTLV-I-seropositive pSS without ectopic GC patients or HTLV-I-seropositive pSS patients (Fig. 1). In HTLV-I-seropositive pSS (n = 6) with ectopic GC patients, the expression of CXCL13 was found dominantly in the light zone of ectopic GC. All of the cases showed >50% of MNCs

![Image](https://academic.oup.com/rheumatology/article-abstract/48/7/854/1789133)

FIG. 1. Expression of CXCL13 and CXCL12 in HTLV-I-seropositive and HTLV-I-seronegative SS patients with SS. Immunohistochemical analysis of CXCL13 (BCA-1) in minor LSGs was demonstrated (A–D). After pre-treatment with microwave epitope retrieval, goat anti-CXCL13 polyclonal antibody was used to detect the expression of CXCL13. Expression of CXCL12 (SDF-1) was examined using mouse anti-CXCL12 monoclonal antibody (E–G). A and E Expression of CXCL13 and CXCL12 in minor LSG from an HTLV-I-seronegative SS patient with ectopic GC. B and F Expression of CXCL13 and CXCL12 in minor LSG from an HTLV-I-seropositive SS patient without GC. C and G Expression of CXCL13 and CXCL12 in minor LSG from an HTLV-I-seropositive SS patient without GC. These are representative of five patients with HTLV-I-seropositive SS with ectopic GC, HTLV-I-seronegative SS patients without ectopic GC and HTLV-I-seropositive SS patients without GC, respectively. D and H Expression of CXCL13 and CXCL12 in minor LSG from an HTLV-I-seropositive SS patient with GC. These are representative of five patients with HTLV-I-seropositive SS with ectopic GC, HTLV-I-seronegative SS patients without ectopic GC and HTLV-I-seropositive SS patients without GC, respectively. I and J Expression of CXCL13 and CXCL12 in minor LSG section from a normal subject, respectively. K and L Expression of CXCL13 in the light zone and CXCL12 in mantle zone of human tonsil tissue as a positive control, respectively. Haematoxylin and methyl green were used for counterstaining of CXCL13 and CXCL12, respectively (original magnification ×100).

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in the light zone of ectopic GC expressing CXCL13. One pSS in HTLV-I carrier showed a relatively small size of ectopic GC whose CXCL13 expression pattern was similar. However, interestingly, the MNCs of HAM–pSS patients demonstrated no expression of CXCL13. In contrast to CXCL13, CXCL12 was commonly expressed on ductal epithelial cells of all the pSS patients irrespective of anti-HTLV-I antibody. In a normal subject, no expression of CXCL13 was observed with positive expression of CXCL12 similar with pSS.

The lymphoid aggregates of LSGs are responsible for autoimmune production that locally occurs in ectopic GC [5, 7, 8]. Radiographic destruction of the ductal structure in HTLV-I-seropositive pSS occurs to a lesser extent than in HTLV-I-seronegative pSS, which is a unique characteristic of the former [4].

The chemokines have been found to regulate ectopic GC formation of SS [5]. Xanthou et al. [9] also demonstrated the significance of lymphoid chemokines for lymphoid structure formation in SS, while others have demonstrated an association of CXCL13 expression and ectopic GC formation in SS [7, 8]. Barone et al. [8] found a B cell-dominant expression pattern, whereas the selected expression in acinar and ductal epithelial cells was observed by Salomonsson et al. [7], although the exact roles of these results remain unclear.

Our data suggest an important interaction of CXCL13 and ectopic GC in sialadenitis in SS. The tendency towards low levels of radiographic damage in patients with HAM– pSS suggests that salivary-specific cytotoxicity is modified by HTLV-I infection. Due to even expression of CXCL12 irrespective of HTLV-I infection, HTLV-I presumably affects the CXCL13 expression of infected CD4+ T cells. Via inflammatory mediators modulated by HTLV-I tax protein, dysfunction of MNC-lineage cells due to HTLV-I infection is supposed to play an important role.

Rheumatology key message

- Low prevalence of ectopic GC is a characteristic of HTLV-I-associated SS with CXCL13 on MNCs.

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Monozygotic twins with distinct forms of idiopathic inflammatory myositis

Sir, A 56-year-old female (Patient A) presented with leg weakness of 4 years duration. Examination showed weakness of hip flexors and extensors, knee flexors and extensors and weakness of finger flexors confirmed with dynometry. Manual muscle testing showed that power was 3+/5 in finger flexors, 4/5 in forearm pronators and supinators and 4/5 in hip rotation. Investigations revealed: creatine kinase (CK), 605 U/l [normal range (NR)<150]; lactate dehydrogenase (LDH), 382 U/l (NR 115–200); CRP, 1 mg/l (NR<6); RF, 48 IU/l (NR<40); negative antibodies to ENAs; and negative ANA and ANCA. IgG antibodies directed to PL7, PL12, PMScl, Mi-2, Ku, Jo-1 and Ro52 were negative (Euroline Kit, ESL Biosciences, Parramatta, New South Wales, Australia). Muscle biopsy showed polyfocal, polyphasic muscle fibre necrosis, endomysial lymphocytic infiltration and rimmed vacuoles consistent with IBM (Fig. 1a and b). She was commenced on prednisolone 50 mg/day but showed gradual deterioration in power.

Her previously well monozygotic twin (Patient B) aged 56 years presented with 6 years of myalgia and dysphagia. Examination showed isolated weakness of neck flexors (dynomometry confirmed normal power elsewhere). Manual muscle testing showed that power was 3+/5 in neck flexors and normal elsewhere. Investigations showed: CK, 230 U/l (NR<150); LDH, 236 U/l (NR 115–200); ESR, 23 mm; CRP, 3 mg/l (NR<6); RF, 49 IU/l (NR<40); negative ANA; negative antibodies to ENA; and negative IgG antibodies to PL7, PL12, PMScl, Mi-2, Ku, Jo-1 and Ro52 (Euroline Kit). Muscle biopsy showed polyfocal, polyphasic muscle fibre necrosis, patchy endomysial lymphocytic infiltration, non-necrotic fibres infiltrated by lymphocytes and absence of rimmed vacuoles consistent with PM (Fig. 1c). She responded well to prednisolone 25 mg/day and MTX. At 8 years follow-up, Patients A and B are on 7.5 mg/day and 2.5 mg/day prednisolone, respectively. At 8 years follow-up, Patients A and B are on 7.5 mg/day and 2.5 mg/day prednisolone, respectively.

We present a case of disease disconcordant monozygotic twins, who developed idiopathic inflammatory myositis (IIM) with distinct clinical and histological features, and varied response to immunosuppressive treatment. Reports of IIM in monozygotic twins are sparse, with one report of childhood DM [1], and another of focal myositis [2] in monozygotic twin pairs.

Disease disconcordant monozygotic twins suggest that environmental factors play a critical role in determining disease phenotype. Neither twin had smoked cigarettes. Patient A was a former day-therapy coordinator, whereas Patient B had not been engaged in physical labour. Both twins have distinct phenotypic features of IIM, and the varied responses to treatment suggest that environmental factors are involved in the pathogenesis of IIM.