Unusual cause of lymphadenopathy in a patient with systemic sclerosis

Sirs,

We report a rare association between histiocytic necrotising lymphadenitis, also called Kikuchi-Fujimoto disease (KFD), and systemic sclerosis.

A 55-year-old female presented in the outpatient clinic with a self-diagnosed axillar lymphadenopathy. She also reported night sweats, weight loss and proximal interphalangeal synovitis during the last two months. A diagnosis of limited cutaneous systemic sclerosis was previously made at the age of 40 years. Review of her medical history also revealed a previous treatment for pulmonary tuberculosis during her infancy. Classic infectious causes were excluded and the buffy coat did not reveal any abnormalities. FDG-PET/CT confirmed the presence of cervical, axillary and abdominal lymphadenopathy. Surgical biopsy of an axillary adenopathy was performed and showed the preservation of the lymph node architecture, with hyperplastic follicles and germinal centres. Numerous tingible body macrophages were identified, together with geographic necrosis bounded with histiocytes and apoptotic cells (Fig. 1). Immunophenotyping demonstrated the predominance of T cells and few neutrophils. A diagnosis of KFD was made and the patient was treated with a short course of prednisolone, resulting in complete resolution of symptoms, and no recurrence.

KFD affects mostly women (sex ratio 4:1) and appears in most cases before the age of 40 years (1). In our review of the literature focused on KFD in the setting of autoimmune conditions (data not shown), we found an even stronger sex ratio of 6:1, and a mean age at onset of 30.7 years. The disease typically starts with lymphadenopathy, acute fever, and fatigue (2). Rash, arthritis, upper respiratory symptoms and weight loss are less frequently observed.

The usual clinical course of KFD is a spontaneous resolution within a few weeks or months, despite rare cases of relapses and a few fatal cases (3), usually associated with severe manifestations such as aseptic meningitis or pleural effusions (4). Favourable clinical responses are obtained in most cases with aspirin or NSAIDS. Low dose glucocorticoids or intravenous immunoglobulins are mainly used for more severe or recurrent cases (5).

Diagnosis of KFD must be confirmed by a lymph node biopsy, clinical features of KFD remaining aspecific and easily misdiagnosed as a malignant condition. Indeed, the relative risk of haematological cancer is higher in systemic sclerosis patients than in the general population, with over-representation of non-Hodgkin's lymphoma (6). Incomplete architectural disappearance with patent sinuses, presence of numerous reactive histiocytes, relatively low mitotic rates and absence of Reed Sternberg cells help the pathologist to differentiate KFD from lymphoma (5).

There is a timely association between the onset of KFD and the diagnosis of connective tissue disease. In particular, the co-occurrence of KFD and systemic lupus erythematosus (SLE) is well described, in 13 to 25% of connective tissue diseases (CTD) cases. Of note, KFD in the setting of a CTD is usually associated with a flare-up of disease activity (7). On the other hand, the differential diagnosis between KFD and CTD flares is difficult because the two diseases share the same symptoms, such as fever, skin rash or lymphadenopathy (8). It is therefore strongly recommended to perform ANA testing when a case of KFD is suspected, in order to exclude SLE.

Pathophysiological mechanisms underlying KFD remain elusive. Histopathological studies suggest the involvement of T cells and histiocytes in an immune response directed against viral pathogens, leading to T cell proliferation and apoptosis (9). In particular, apoptotic cell death mediated by cytotoxic CD8 T cells appears to be a major component of this immune reaction (9). In addition, Szturz *et al*. described that serum cytokines levels in patients with KFD and SLE are similar, suggesting common immune responses mediated by type 1 interferons (10).

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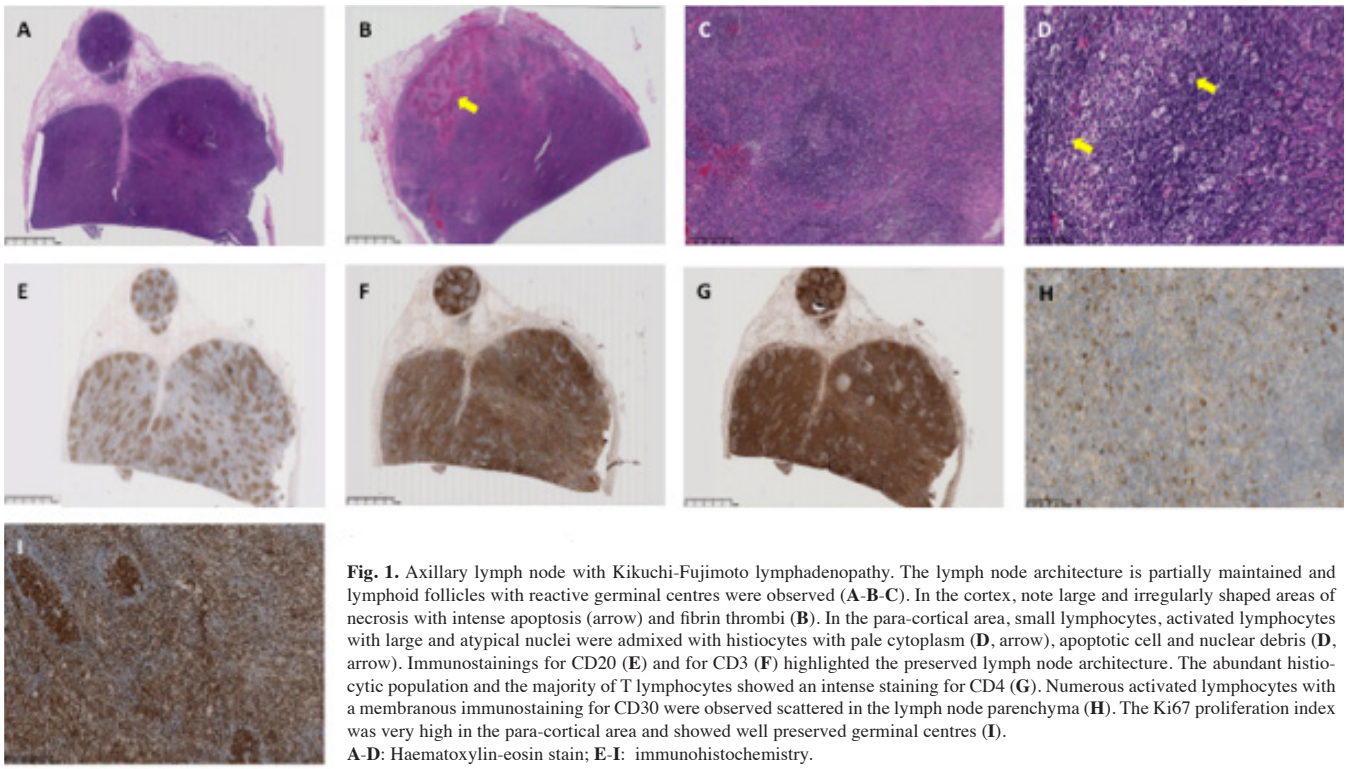

Fig. 1. Axillary lymph node with Kikuchi-Fujimoto lymphadenopathy. The lymph node architecture is partially maintained and lymphoid follicles with reactive germinal centres were observed (**A**-**B**-**C**). In the cortex, note large and irregularly shaped areas of necrosis with intense apoptosis (arrow) and fibrin thrombi (**B**). In the para-cortical area, small lymphocytes, activated lymphocytes with large and atypical nuclei were admixed with histiocytes with pale cytoplasm (**D**, arrow), apoptotic cell and nuclear debris (**D**, arrow). Immunostainings for CD20 (**E**) and for CD3 (**F**) highlighted the preserved lymph node architecture. The abundant histiocytic population and the majority of T lymphocytes showed an intense staining for CD4 (**G**). Numerous activated lymphocytes with a membranous immunostaining for CD30 were observed scattered in the lymph node parenchyma (**H**). The Ki67 proliferation index was very high in the para-cortical area and showed well preserved germinal centres (**I**).
A-**D**: Haematoxylin-eosin stain; **E**-**I**: immunohistochemistry.

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