A rare case of angioimmunoblastic T-cell lymphoma presenting with fever and late polyarthritis

Sir, A 71-year-old Caucasian male presented to our department with a 4-month history of generalized myalgias, arthralgias of the knees and small joints of the hands and high-grade fever. Three months prior to admission, the patient received a 2-week course of antibiotics for cervical lymphadenopathy. One month later he developed polyarthritis and low-grade afternoon fever (maximum 38.5°C) and received an intramuscular depot form of corticosteroids and oral MTX for possible RA with marked improvement.

Clinical examination on admission revealed an overweight patient and was remarkable for bilateral cervical lymphadenopathy (all <1 cm) and bilateral synovitis of the MCP, proximal phalangophalangeal joints and knees and a continuous fever (maximum 39.8°C) with no distinct pattern. Laboratory investigation revealed anaemia (haemoglobin 11.4 g/dl), high ESR (130 mm/h) and CRP (17.3 mg/dl). Urea, creatinine, electrolytes, liver function tests and urinalysis were normal, except for mildly elevated lactate dehydrogenase (LDH), Blood cultures, hepatitis B and C antibodies, serology for Brucella and Salmonella species, RF, ANA, ANCA and serum electrophoresis were negative. Chest X-ray, 24-h urine collection, immunoglobulins and complement levels were normal. Cervical ultrasound showed mild lymphadenopathy.

Because of the recent history of lymphadenopathy, increased LDH and the patient’s age, a cervical lymph node biopsy was performed and corticosteroids were added to MTX. The patient defervesced in 24 h and was discharged. The lymph node biopsy specimen revealed complete loss of normal architecture with infiltration by polymorphic lymphoid cells, composed mainly of CD3+/CD5+/CD4+/CD10−/L26− T cells and a significant B-cell population [CD79a+/L26+/CD10−/CD3−−], with foci of IgMk+ clonality. PCR for the TCR chain locus detected the presence of a clonal T-cell population establishing the diagnosis of high-grade angioimmunoblastic T-cell lymphoma [AILT-World Health Organization (WHO)].

At follow-up, the patient was asymptomatic and afebrile with no palpable cervical lymph nodes. An abdominal CT scan showed enlarged pelvic lymph nodes. Bone marrow biopsy revealed T-cell infiltration. Treatment with two cycles of cyclophosphamide/vincristine/prednisone (COP) was initiated, with regression of the lymphadenopathy. This was followed by six courses of Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine), Prednisolone (CHOP) therapy, with rituximab added in the last two courses, a decision based on the presence of the B-cell clone. CT re-evaluation after completion of the initial treatment showed no lymphadenopathy while bone marrow was free of T-cell infiltration. The patient continued to receive monthly infusions of rituximab. Two months later he presented with left axilar lymphadenopathy and biopsy confirmed a diffuse large B-cell non Hodgkin’s lymphoma (NHL). He received etoposide/methylprednisolone/cytarabine/cisplatin (ESHAP) and rituximab for two cycles followed by cyclophosphamide/mesna/vincristine/doxorubicin/dexamethazone (R-HyperCVAD) due to life-threatening myelosuppression. A repeat CT scan obtained after completion of treatment confirmed complete resolution of the lymphadenopathy.

In the ensuing months, the patient presented with recurrent pneumonias from resistant Enterococcus faecalis and Acinetobacter baumannii and a case of deep vein thrombosis of the right axillary vein. However, he was in complete remission in his next follow-up. He died 2 years after the initial diagnosis due to A. baumannii pneumonia.

AILT is a rare disease comprising 2% of all NHLs, characterized by generalized lymphadenopathy, hepatosplenomegaly, anaemia and hypergammaglobulinaemias [1], and shares many symptoms with CTDs, especially SLE and Still’s disease. It is estimated to be significantly underdiagnosed [2]. Lymph node histology is characterized by mixed lymphoid infiltration and a monoclonal T-cell population, whereas in some patients an expanded B-cell population is present [3]. Patients with AILT present in their sixth/seventh decade with systemic illness, often mimicking an infectious process, B symptoms, cutaneous involvement and generalized lymphadenopathy [3–5]. AILT has a waxing and waning course; however, as it progresses, symptoms persist. Autoimmune phenomena associated with AILT are polyarthritis

Rheumatology key message
- Tacrolimus is an effective therapeutic option in the inflammatory myopathies.

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(18% of the patients) [5, 6], autoimmune haemolytic anaemia [7], vasculitis [8] and autoimmune thyroid disease [5]. High levels of lymph node mRNA expression and serum levels of TNF-α and IL-6 have been reported [9, 10], suggesting a hypercytokinaemia commonly seen in CTDs. Frequently, considerable effort must be spent in order to differentiate this entity from adult onset Still’s disease, RA and SLE [3, 5, 6].

The clinical outcome of AILT remains poor (median survival <3 years, 5-year survival 30–35%) [5]. Combination chemotherapy may lead to complete remission (50%) but relapse rates remain high. Overall combination chemotherapy appears to be superior to glucocorticosteroids alone [5] but studies are limited. Furthermore, some patients develop secondary diffuse large B-cell lymphoma (DLBCL) [3]. Recognition of AILT is therefore important as the management of the differential diagnoses may lead to inappropriate treatment.

In summary, we present a rare case of AILT with clinical features of autoimmune disease. Rapid escalation and de-escalation of the lymphadenopathy, combined with more prominent symptoms from the joints, gave the strong impression of an underlying disorder like RA. AILT should be considered in the differential diagnosis of late-onset RA or Still’s disease in older patients presenting with a recent history of lymphadenopathy and fever. In such patients, sites of lymph-node involvement non-apparent by physical examination should be investigated.

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**Rheumatology key message**

- AILT should be suspected in patients with late-onset RA and recent history of lymphadenopathy.

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**The analysis of interleukin-6 in patients with systemic IgG4-related plasmacytic syndrome—expansion of SIPS to the territory of Castleman’s disease**

Sir, we continue to perform clinical and pathological analyses of systemic immunoglobulin (IgG4)-related plasmacytic syndrome (SIPS), which includes lacrimal and salivary gland enlargement, autoimmune pancreatitis and IgG4-related tubulo-interstitial nephritis (TIN) [1, 2]. The characteristics of this syndrome are as follows: (i) presentation with chronic and inflammatory sclerosis and pseudo-tumour lesions; (ii) dysfunction of organs due to formation of pseudo-tumours with less tissue destruction; and (iii) responsive to glucocorticoid therapy in many cases. These patients often present with enlarged lymph nodes, but without elevated levels of CRP. We recently encountered two cases of SIPS with continuous fever, systemic lymphadenopathy and elevated levels of serum IL-6 that resembled multicentric Castleman’s disease (MCD). We were troubled by the diagnosis in each of these cases. We present the cases herein, and discuss problems in this clinical entity.

A 56-year-old Japanese man suffered from swelling of bilateral upper eyelids in 1996. He went to an ophthalmologist and was diagnosed with dacryoadenitis following biopsy of the lacrimal gland. Treatment with prednisolone for 1 month resulted in resolution of symptoms. Right submandibular swelling developed in 2000, with continuous fever and cervical lymph node swelling in 2006. After seeing a local doctor, hypergammaglobulinaemia was identified (IgG, 53.4 mg/l). He was referred to us in April 2007. Bilaterally enlarged parotid and submandibular glands were noted. Enhanced CT revealed cervical and mediastinal lymph node swelling. Multiple lesions resembling pseudo-tumours were apparent in both kidneys. Gallium scintigraphy showed uptake in bilateral parotid and submandibular glands and mediastinal lymph nodes. Laboratory data on admission revealed slight inflammation (CRP, 11.7 mg/l) and hypocomplementaemia. ANA was detected, but anti-DNA and anti-SS-A antibodies were not. Concentration of serum IgG4 was elevated (19.2 mg/l; normal, <1.4 mg/l), and serum levels of soluble IL-2 receptor and IL-6 were 2160 U/ml (normal, 145–519 U/ml) and 184 pg/ml (normal, <40 pg/ml). Biopsy of a cervical lymph node and kidney was performed due to exclusion of haematological disorders. Lymph node specimens showed hyperplasia of lymphatic follicles and sheets of IgG4-positive plasmacytes in the interfollicular zone. Slight neovascularization into the germinal centre was identified, but activated B cells producing IL-6 and VEGF were not apparent. The renal specimen also showed abundant plasmacytes bearing IgG4 and fibrosis in the interstitium. We re-examined the initial lacrimal specimens, and found infiltration of plasma cells with IgG4 around the glands. SIPS was diagnosed, with preceding lacrimal lesions and complication to IgG4-related TIN. However, we could not confirm a diagnosis of MCD.

A 73-year-old Japanese man suffered from multiple skin lesions that had first appeared on his trunk 4 years earlier. He was admitted to the dermatology department of a general hospital for evaluation of the lesions. Reddish-brown, non-purpuritic plaques were noted on the chest, abdomen and back. Skin biopsy specimens showed severe infiltration of lymphocytes, plasma cells and eosinophils into the dermis and subcutaneous tissue. Monoclonality was not identified by immunostaining. Histological diagnosis was pseudolymphoma, but clinically the