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CORRESPONDENCE

Endomysial germinal centres in Hashimoto's thyroiditis with myopathic symptoms

Sir,

Hashimoto's thyroiditis (HT) is a common autoimmune disease characterised by inflammation and destruction of thyroid follicles, leading to the formation of tertiary lymphoid organs (TLOs).[1] TLOs are lymphoid cell collections in chronic inflammatory states that resemble lymph nodes in their cellular content, organisation and the presence of high endothelial venules and lymphatic vessels.[2] HT is only rarely associated with inflammatory myopathy.[3] We report one such patient whose clinical presentation was that of an inflammatory myopathy and muscle biopsy revealed TLOs, a finding not previously described in the literature.

A 24-year-old woman presented to our centre in March 2015 with a 9-month history of gradually progressive weakness. Initially, she noted difficulty in getting up from a sitting posture and in climbing stairs. Later, she developed weakness of both arms and could not lift them above the shoulders. There was no history of sensory symptoms, sphincter dysfunction, spasticity, ataxia, diurnal variation, fatigability, muscle pain, cramps, cola coloured urine, myotonia, second-wind phenomenon or fasciculations.

In 2011, the patient was diagnosed as HT based on mood swings, low serum T4 [2.51 μg/dL; reference range (RR) 4.5–12.6], elevated thyroid-stimulating hormone (TSH; 9.53 μIU/mL; RR 0.35–5.50) and anti-thyroid peroxidase (TPO) antibodies (>1300 IU/mL; RR 0–35). She was prescribed oral levothyroxine 75 μg per day. As there was a symptomatic relief, she discontinued the medication in mid-2012.

Examination revealed pure motor quadriparesis [Medical Research Council (MRC) grade 3] affecting muscles of the neck, proximal upper limb, and lower limb. The proximal upper limb extensors were most severely affected with a milder involvement of distal lower limb flexors. Other general, physical and systemic examinations were unremarkable. Immunological tests (antinuclear antibodies, anti-U1-RNP, SSA/SSB, Sm, Scl-70, PM-1 and RA factor) were negative. Tests for myositis-specific antibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-SRP and anti-Mi-2) were also negative. Serum creatine kinase was raised (5130 U/L; RR 26–380). She had persistently elevated anti-TPO antibodies. Nerve conduction studies were normal. Electromyography revealed spontaneous fibrillations and positive sharp waves with increased recruitment in the right vastus lateralis, deltoid, and iliopsoas, a pattern consistent with inflammatory myopathy.

An open biopsy of the left deltoid muscle was performed. It showed 26 fascicles. Many large and confluent TLOs measuring 0.2–0.3 mm were seen exclusively in the endomysium (Fig. 1A). The ratio of TLOs:fascicles was 1:2.5. The ratio of non-follicle-forming lymphoid aggregates:fascicles was 0.8:2.5. The TLOs displayed germinal centres with preserved light, dark and mantle zones (Fig. 1B). Alkaline phosphatase (ALP) stain showed intense staining of the capillaries and regenerating fibres (Fig. 1C). There was no significant variation in fibre size, shape or perifascicular atrophy. On immunohistochemistry, the germinal centre B-cells and the mantle zone cells expressed CD20 (Fig. 1D). The intrafollicular T-cells were highlighted by CD3 (Fig. 1E). Non-neoplastic nature of the TLOs was corroborated by CD10, Bcl-6 and Bcl-2 immunolabelling (Fig. 1F–H). Neutrophils, eosinophils, and plasma cells were not prominent. Immunostain for MHC class I highlighted the inflammatory cells (Fig. 1I). The membrane attack complex (MAC) immunostain showed staining in some of the endomysial capillaries, and within the TLOs (Fig. 1J). The capillaries did not reveal any rarefaction, obliteration or pipe-stemming. On electron microscopy, no endothelial cell inclusions, vacuoles or abnormal mitochondria could be discerned (not shown). Based on the above findings, the muscle biopsy was signed out as inflammatory myopathy, possibly related to HT.

Subsequently, the patient received intravenous methylprednisolone pulses of 1 g daily for 3 days every month and mycophenolate sodium (720 mg twice daily). Follow-up at 2 month intervals revealed significant improvement in well-being, power and dealing with daily activities.

TLOs often form at sites of inflammation in infectious, autoimmune or malignant disorders and in transplant rejection settings.[4] TLOs in various autoimmune diseases show predilections for specific sites. Cruickshank[5] described lymphoid aggregates in muscles of patients with rheumatoid arthritis that lacked zonation typical of a lymphoid follicle. Mashaly *et al.*[6] reported a case of polymyositis with lymphoid follicles in the muscle of a patient with gastric malignancy. The patient had positive antinuclear antibodies with a homogeneous pattern, normal creatine kinase and lactate dehydrogenase, and a monoclonal peak on serum electrophoresis. The lymphoid follicles were confined to the epimysium and perimysium with perifascicular atrophy. Hence, this possibly represents an overlap myositis rather than polymyositis. Inoue *et al.*[7] reported TLOs in a muscle biopsy from a patient with mixed connective tissue disease although the detailed histopathological description was lacking.

The most detailed descriptions of skeletal muscle-localised TLOs come from the study by Lopez De Padilla *et al.*[8] The follicle-like structures described by them in muscle biopsies of juvenile dermatomyositis patients displayed high levels of CXCL13 and lymphotoxins. It is pertinent to note that CXCL13, in concert with other cytokines, orchestrates tertiary lymphoid organogenesis in the thyroid gland in HT.[9] Our case also displayed TLOs in the muscle. Various studies have shown that complement system is activated due to anti-TPO antibodies in the thyroid gland of HT.[10,11] This could possibly explain the reason for MAC deposition in some of the endomysial capillaries and within the TLOs in our case. Hence, we speculate a similar pathogenetic mechanism for the TLO formation in the skeletal muscle. The development of quadriparesis 3 years after the onset of HT and the persistently elevated anti-TPO antibodies in our patient indicates an autoimmune process likely to be linked to HT (as the work-up for autoantibodies other than anti-TPO antibodies was negative). This is also corroborated by the subsequent response of quadriparesis to immunosuppression. Moreover, in our patient the clinical manifestations started

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