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LETTERS TO THE EDITOR

Muscle cramps and weakness secondary to graft versus host disease fasciitis

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Sir,

Uncommon manifestations of chronic graft versus host disease (GvHD) include a variety of neurological presentations (Bolger *et al*., 1986; Urbano-Marquez *et al*., 1986; Nelson and McQuillen, 1988; Tse *et al*., 1999; Takahashi *et al*., 2000; Ma *et al*., 2002; Nagashima *et al*., 2002) and sclerodermatous skin changes (Shulman *et al*., 1978; Chosidow *et al*., 1992; Janin *et al*., 1994; Penas *et al*., 2002). Here we report a case of chronic GvHD fasciitis presenting with progressive muscular cramps and weakness, not previously reported.

The patient was diagnosed with Hodgkin's disease in 1983 at the age of 19 years, suffering two relapses in 1987 and 1997. In 1999, he developed a plasmacytoma and severe auto-immune haemolytic anaemia which were treated with chemotherapy and cyclosporin, respectively, followed by a reduced intensity allogeneic bone marrow transplant. Two months later, he developed mild GvHD with skin and liver involvement, treated with oral steroids. Over the following year, he developed chronic skin changes requiring intravenous methylprednisolone followed by maintenance prednisolone and cyclo sporin A.

In 2001, he was referred to neurology with a 1-year history of painful muscular cramps particularly around his mouth and neck, across his stomach and in his legs and hands, as well as muscular stiffness and proximal weakness. Examination revealed mild wasting of the left interossei and mild bilateral hip flexion weakness. Tone and power were otherwise normal. Reflexes were absent apart from knee jerks. Plantars were flexor. There was mild reduction of pain and temperature sensation in the hands. Creatine kinase was normal.

By January 2002, his skin had become thickened and sclerodermatous, requiring PUVA therapy, which resulted in some improvement. He had no other features of GvHD and his steroid dose was reduced. However, the severe muscle cramps continued, failing to respond to baclofen or dantrolene. He also developed more proximal limb weakness. A vastus medialis muscle biopsy was performed.

The biopsy showed a moderate inflammatory cell infiltrate within a thickened perimysium, consisting predominantly of T lymphocytes and macrophages (Fig. 1a). There was perifascicular atrophy with occasional necrotic fibres at the periphery of fascicles. Following immunocytochemistry increased sarcolemmal expression of class 1 major histocompatibility antigen was noted in perifascicular fibres (Fig. 1b).

The cramps continued to progress in association with worsening, primarily proximal weakness, distal wasting and joint pains and stiffness, resulting in reduction in mobility and requiring increasing doses of opiates for pain control. Treatment with steroids, mycophenolate, intravenous immunoglobulin, methotrexate, clofazimine or infliximab failed to halt his progression. Symptomatic trials of phenytoin and gabapentin were unsuccessful.

Sclerodermatous chronic GvHD is a rare but well recognized form of GvHD (Van den Bergh *et al*., 1987; Chosidow *et al*., 1992; Penas *et al*., 2002). Muscular presentations are more rarely reported

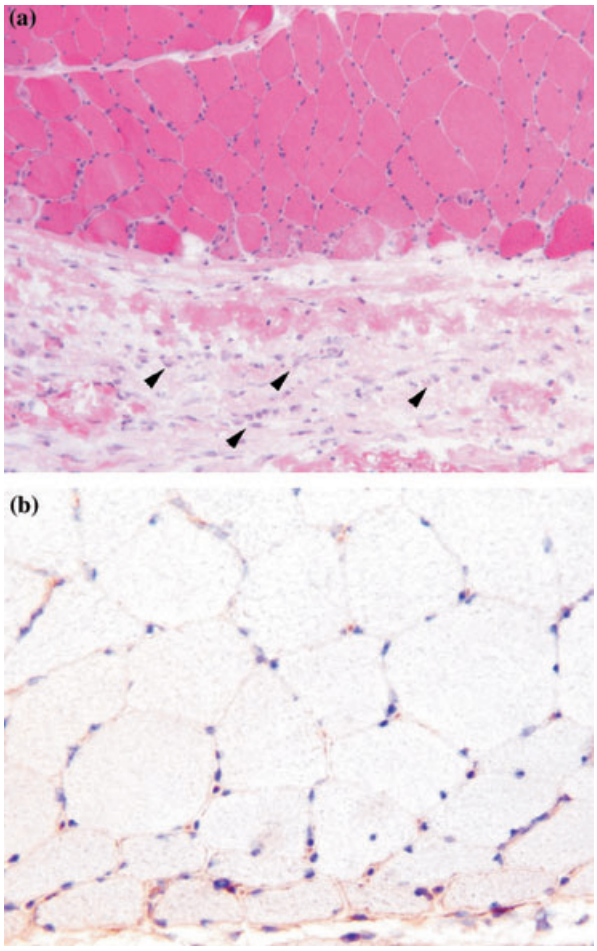

Figure 1 (a) Muscle showing scattered lymphocytes and macrophages (arrow heads) within a thickened perimysium and scattered atrophic fibres at the edge of the fascicle. (b) Following immunocytochemistry with an antibody to ß2-microglobulin, increased sarcolemmmal expression of Class 1 MHC antigen is noted in perifascicular fibres.

Table 1 Muscle biopsy findings in chronic fasciitis secondary to GvHD

Reference	Number who underwent muscle biopsy (total number in series)	Muscular symptoms	Underlying condition	Months from transplant (mean)	Subcutaneous tissue involvement	Response to therapy	Muscle biopsy pathology
Janin *et al.* (1994)	4 (14)	Myalgia	Aplastic anaemia (4); CML (4); ALL (3); AML (4)	12–123 (28)	Yes	Poor	Sparse lymphocytic infiltrate localised in perimysium, no myofibre necrosis or regeneration
Van den Bergh *et al.* (1987)	1	Painful limb movement	ALL	15	Yes	Good response to prednisolone and azathioprine	Mononuclear inflammatory cells throughout the muscular fascia with vascular cuffing of vessels in the epimysium. Diffuse infiltration in the perimysium with some spread into the endomysial connective tissue associated with moderate atrophy of some muscle fibres with some necrotic fibres
Chosidow *et al.* (1992)	1 (7)	None reported	Aplastic anaemia (1); CML (3); ALL (1); AML (2)	10–72 (24)	Yes	Unclear	Centripetal fibrosing process of the fascia (with rare mononuclear cells), interfascicular septa and endomysium
Current case	1	Cramps, weakness, wasting	Hodgkin's disease, plasmacytoma and haemolytic anaemia	15	Yes	None	Lymphocytes and macrophages in perimysium with perifascicular atrophy, necrosis and increased MHC expression

and include myositis (Urbano-Marquez *et al.*, 1986; Nelson and McQuillen, 1988; Takahashi *et al.*, 2000), occasionally in association with myasthenia gravis (Tse *et al.*, 1999). Muscle biopsy findings in chronic GvHD fasciitis have been reported previously and are summarized in Table 1. None of these patients developed the severe muscular cramps and progressive weakness and wasting which are the main features of the present case. We speculate that these symptoms are secondary to chronic inflammation and fibrosis of the perimysium causing muscular ischaemia. The present patient responded poorly to immunosuppressant therapy, in keeping with previously reported cases (Janin *et al.*, 1994), although other authors report more favourable treatment outcomes (Van den Bergh *et al.*, 1987; Penas *et al.*, 2002). This case represents a previously unreported neurological presentation of chronic GvHD and a rare cause of muscle cramps.

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Hyponatraemia and central pontine myelinolysis after elective colonoscopy

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A 79-year old lady was pre-treated with cathartics before undergoing elective colonoscopy. Soon she developed severe hyponatraemia, with seizures and coma. After rapid correction of sodium levels she regained consciousness but presented an impressive ataxic syndrome due to a by means of MRI verified Central Pontine Myelinolysis. We discuss the clinical and imaging features, as well as the possible pathogenetic mechanism of this rare neurological disease.

Central pontine myelinolysis (CPM) is a rare neurological disease of unknown aetiopathogenesis, characterized by demyelinating lesions localized mostly in the pons (Adams *et al.*, 1959; Sterns *et al.*, 1986). Some investigators have attributed it to rapidly corrected severe hyponatraemia (Sterns *et al.*, 1986; Laureno and Karp, 1997), whereas others strongly doubt this theory (Ayus *et al.*, 1985; Arieff, 1986).

We report the case of a 79-year-old lady with a history of hypertension treated with thiazides, normal sodium levels and no changes suggestive of extracellular fluid volume losses, who underwent elective colonoscopy after pre-treatment with cathartics. Six hours after the examination an increasing state of confusion followed by an epileptic seizure was observed. The patient remained thereafter comatose. At this time severe hyponatraemia (108 mmol/l) was detected. Brain-CT was normal. Although there were no signs of cerebral oedema anti-oedematous treatment with intravenous dexamethason was initiated. Almost 12 h later and after rapid correction of hyponatraemia (> 2 mmol/l/h) up to 132 mmol/l she regained consciousness but was unable to speak and swallow. This condition remained stable for 3 days, when external neurological evaluation was asked. On examination the patient was fully alert and orientated. However, she presented severe dysarthria and dysphagia. Due to a severe truncal ataxia she was unable to sit without support. There were no motor or sensory deficits. This combined cerebellar-pontine syndrome on the background of the electrolytic derangement suggested CPM. MRI was then performed. T2-weighted and Flair images demonstrated a large hyperintense central lesion without perifocal oedema respecting the surface of the pons. On T1-weighted images the lesion was hypointense without contrast enhancement (Fig. 1). Diffusion-weighted images showed high signal intensity in the borderzone between lesion and intact tissue, whereas MR spectroscopy disclosed a slight NAA reduction without lactate increase (Fig. 2). These imaging findings are typical for demyelination of osmotic aetiology and confirmed the clinical diagnosis of CPM (Laubenberger *et al.*, 1996; Ruzek *et al.*, 2004). Within 2 weeks the patient could eat, drink and walk with assistance. At follow-up 3 months later she

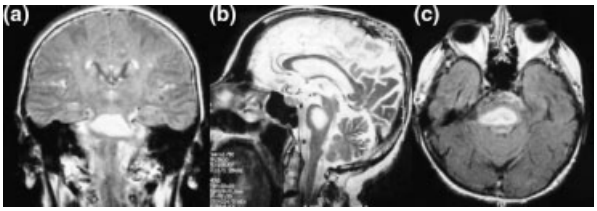

Figure 1 MRI scans showing in all three directions a large demyelinating lesion of the basis pontis (2×1.5×2.7 cm), respecting the pontine surface and partially affecting the cerebellar peduncles, with no contrast enhancement or perifocal oedema.

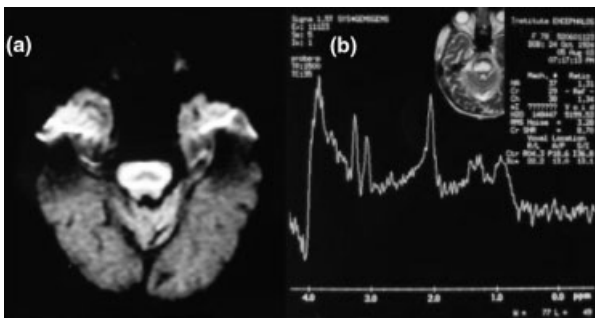

Figure 2 (a) Diffusion-weighted MR images demonstrate reduced tissue diffusion with high-intensity signal in the periphery of the lesion in the borderzone between intact and affected pontine tissue. (b) MR spectroscopy reveals a slight NAA reduction with slightly elevated lipid concentration as sign of cellular membrane lesion and excludes an ischaemic pathology by failing to detect lactate.