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Case report

Clinical, neuropathological and radiological evidence for a rare complication of rituximab therapy

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Abstract

We report a rare case of myofasciitis and meningitis with deafness caused by systemic enterovirus infection in the setting of hypogammaglobulinaemia induced by rituximab. Whilst effective and generally safe, anti- CD 20 antibody therapy is increasingly recognised to result in unusual infectious complications to be considered in a treated patient presenting with neurological symptoms. These cases may pose diagnostic difficulties and can have atypical presentations. We present this rare complication of rituximab therapy, with histopathological confirmation of myofasciitis. In the older literature, enterovirus associated myofasciitis may have erroneously been termed dermatomyositis and we review the literature to demonstrate this important nosological point.

Keywords: Rituximab; Echovirus; Hypogammaglobulinaemia; Myofasciitis; Meningitis

1. Introduction

Anti CD 20 therapy may result in unusual infections with atypical presentations, posing diagnostic difficulties. We highlight the long term immunomodulatory effects of rituximab by reporting the rare complication of myofasciitis, with clear documentation of the pathology of enterovirus myofasciitis for the first time.

2. Case report

A 36-year-old man was treated four years into his diagnosis of a grade 1 follicular lymphoma, with six cycles of R-CHOP chemotherapy. He achieved a complete metabolic remission on re-staging positron emission tomography (PET) scanning. Chemotherapy was complicated by two episodes of neutropenic sepsis and mild iatrogenic deafness with vestibular failure from aminoglycoside use. One year following treatment, whilst on maintenance therapy with rituximab for three months, he developed myalgia, shoulder pain, fatigue, weight loss and progressive hearing and balance impairment. There was no history of foreign travel or vaccination. General examination was unremarkable; in particular there was no skin rash, lymphadenopathy or splenomegaly. Neurological examination revealed subtle sensorineural hearing loss, upper limb fasciculations and present but reduced reflexes in the upper and lower limbs. A recurrence of lymphoma was excluded. Investigations showed panhypogammaglobulinaemia; IgG 6.91 g/L (normal: 7–16), IgA 0.54 g/L (0.7–4.0) and IgM 0.33 g/L (0.44–2.3). Creatine kinase was normal, 64 IU/L (38–204) and LDH was elevated 929 IU/L (240–480). CSF chemistry showed an elevated protein 2.55 g/L (0.13–0.40) and reduced glucose 2.0/5.7 mmol/L (3.9–5.8). There were 105 white blood cells per cubic mm of CSF, mainly lymphocytes, and examination by flow cytometry and PCR confirmed a reactive population with no clonality. Neurophysiological examination demonstrated a mild, predominantly sensory, sensorimotor neuropathy consistent with previous chemotherapy with mild myopathic changes only by electromyography with small polyphasic motor units with short duration and no spontaneous activity. The muscles were hard and 'woody' on needle insertion. Audiometry confirmed sensorineural deafness with vestibular and cochlear failure. MRI of the brain, spine and internal auditory meatus was normal. MRI axial imaging of the thighs showed florid myofascial high signal on STIR sequences, consistent with fasciitis (Fig. 1A).

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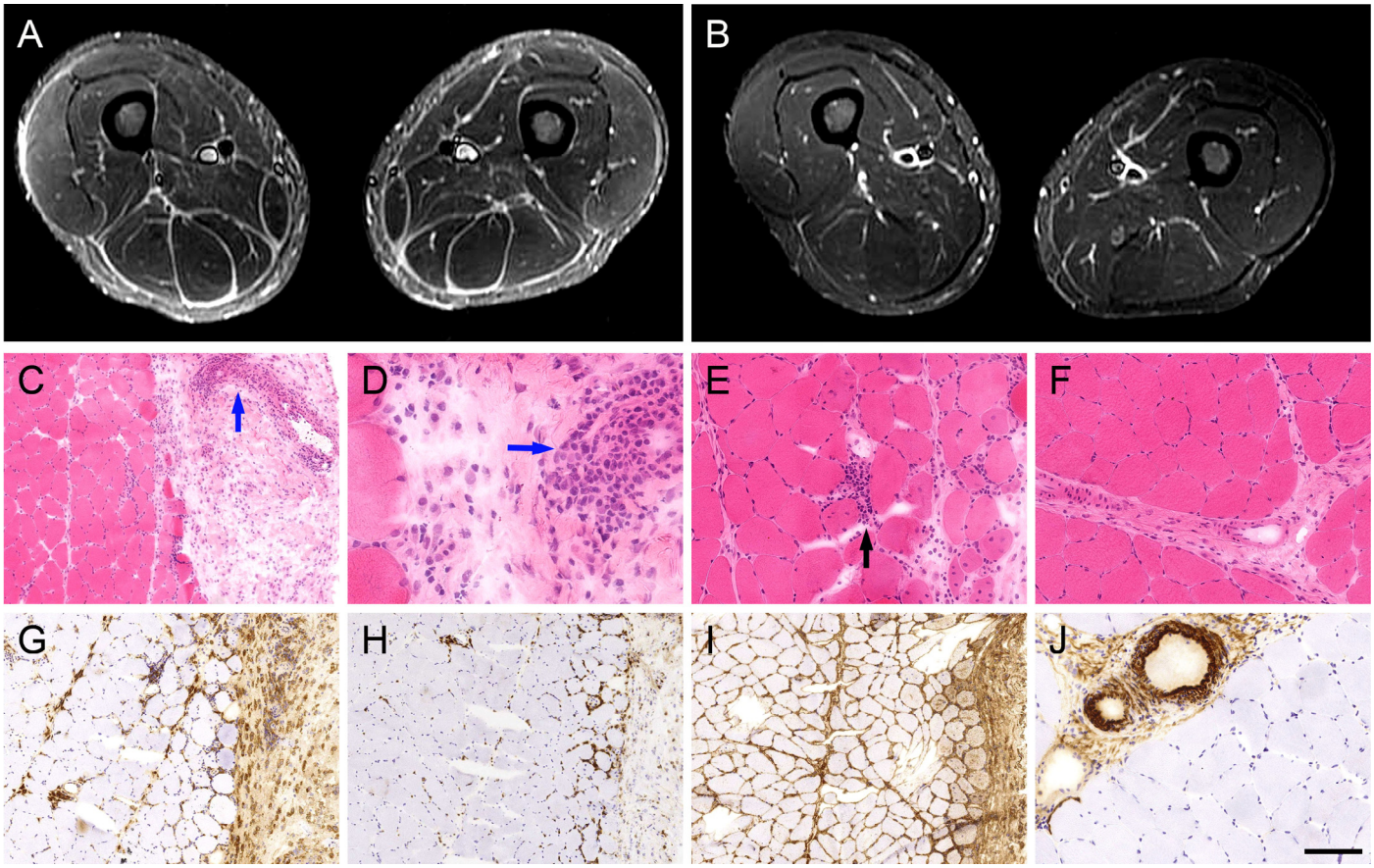

Fig. 1. MRI and muscle biopsy findings. Axial STIR imaging of the thighs showing diffuse inflammation within the inter-muscular spaces in the anterior, adductor and posterior compartments. The muscle signal is normal. There is fascial inflammation on the superficial enveloping fascia lata, fat and dermal tissue, overlying the anterior and posterior aspects of the thighs (A). Further axial STIR imaging after an interval of 3 months and IVIG therapy (same scanner and imaging protocol) shows complete resolution of the inflammation (B). Haematoxylin and eosin stained sections from a muscle biopsy of the left vastus lateralis (C–F) show marked inflammation centered on the epimysium and perimysial septa (C, D and F) with perivascular lymphocyte cuffing in the fascia (blue arrows in C and in D, at higher power). The inflammatory infiltrate extends minimally in to the peripheral of the fascicles, with scattered foci of lymphocytes which do not invade the fibres (black arrow in E). There is no perifascicular atrophy (F). Immunotyping shows strong positive staining with CD68 which highlights the presence of macrophages (G) and CD8+ T lymphocytes (H). HLA upregulation (antibody to MHC Class I) is strongest within the fascia and in fibres at the edge of fascicles (I) and labelling for complement (antibody to C5b-9) shows no abnormal deposits on the endomysial capillaries (J). The pathology is consistent with myofasciitis and there are no features of classical dermatomyositis. Scale bar: 200 μm (C, G, H and I); 100 μm (E and J); 50 μm (D).

A biopsy of the left vastus lateralis showed macrophages infiltrating the epimysium and perimysial septa, with accompanying perivascular lymphocytic cuffs (CD3+, CD8+ T cells), fewer CD4+ T cells and no CD20+ B cells. Minimal extension of the fascial inflammation was seen, limited to adjacent muscle fibres at the periphery of the fascicles. Perifascicular atrophy, endomysial capillary loss and capillary complement activation were absent. The pathology was of myofasciitis (Fig. 1C–J). PCR was performed on the serum and CSF, demonstrating high copy numbers of enterovirus, sequenced as echovirus type 9. Matching high copy number PCR was also demonstrated in blood. Additional infections were ruled out, including herpes viruses and fungal species. No virus was detected on PCR of the muscle and fascia sample. No viral particles or aluminium deposits were visualised. The diagnosis of systemic enterovirus infection due to rituximab induced panhypogammaglobulinaemia was made, with increasing deafness due to inflammatory meningitis and accompanying myofasciitis. The mild neuropathy was consistent with previous CHOP chemotherapy. Treatment with IVIG was commenced with an initial dose of 2 g/kg over 5 days, reduced to a standard dose of 0.4 g/kg every 4 weeks, resulting in a sustained rise in IgG levels with peak dose levels in the high normal range for IgG. Serum and subsequently CSF became negative for enterovirus by PCR at 6 and 10 weeks, however, the CSF remained active (70 lymphocytes/mm^3, protein 1.94 g/L, glucose normal). The muscle pain and fasciculations resolved, permitting gym exercise. Repeat MRI imaging of the thighs showed complete resolution of the fascial inflammation (Fig. 1B) at 16 weeks. Additional steroid treatment was initiated, in addition to the IVIG in an attempt to mitigate deafness at week 18. However, a sudden and rapidly progressive deterioration to total deafness occurred at week 20. Repeat CSF examination indicated an increasingly active CSF (200 WCC and protein 2 g/L) with reactivation of enterovirus and subsequent complete hearing loss. The dose of IVIG was