Nerve biopsy in T-cell lymphoma with neurolymphomatosis: where and when.

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Abstract

Peripheral T-cell lymphomas are rare heterogeneous haematological malignancies and in a very small subset of cases they may also involve peripheral nerves. We report a patient with a diagnostically challenging cutaneous T-cell lymphoma and multifocal mononeuropathies in whom a targeted nerve biopsy revealed lymphomatous infiltration of nerves and expedited combination treatment with chemotherapy and an autologous stem cell transplant. She showed an excellent response with a complete metabolic response on PET and significant clinical improvement which she maintained 5 years post-treatment.

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) account for 5-10% of Non-Hodgkin's lymphoid tumours.[1] Patients often have multi-system involvement at presentation including bone marrow, lymph nodes, skin and rarely the central and peripheral nervous systems. The long-term outcome of patients with PTCLs is poor with less than 50% alive at 3 years.[1,2] An initial presentation of PTCLs in the peripheral nervous system is very rare, and they more commonly involve peripheral nerves following presentation elsewhere, such as in our case. As well as direct nervous system infiltration, peripheral nerve involvement with PTCLs includes structural compression of nerves by enlarging lymph nodes, a demyelinating polyneuropathy and an axonal neuropathy due to non-specific inflammation and/or vasculitis.[3]

CASE PRESENTATION

A 43 year old white Caucasian woman, presented with a flu-like illness with low grade pyrexia, persistent arthralgia and myalgia. She subsequently developed painful joints and multiple small, painful, hard skin lumps predominantly in the limbs. Following negative serological tests and whole body CT imaging, she was treated with oral corticosteroids for a presumed seronegative inflammatory arthropathy which significantly improved the arthritis but the skin lesions remained unchanged. Over the following 4 months, she developed sequential symptoms suggesting multiple mononeuropathies including right anterior thigh shooting pains and weakness (femoral nerve), left facial weakness (facial nerve) and left foot drop (common peroneal). She lost 22kg of weight over her 9 month illness.

Examination confirmed the presence of hardened subcutaneous nodules but no lymphadenopathy or hepatosplenomegaly. Neurological and neurophysiological examinations (Supplementary Table 1) revealed evidence of post-ganglionic mononeuropathies including left facial, bilateral obturator, right sciatic, sural and saphenous and left deep peroneal nerves. A whole-body positron emission tomography-computed tomography (PET-CT) scan and lower limb MR neurography confirmed diffuse, multisystem uptake predominantly in somatic soft tissue nodules and involvement of specific nerves (Figure, A-H). Repeated serological and CSF examinations were non-diagnostic (Supplementary Table 2).

Multiple skin and two bone marrow biopsies had previously failed to achieve a conclusive diagnosis of a lymphoproliferative disorder. Although the bulk of the disease radiologically was in the proximal lower limb nerves we initially did a right sural nerve biopsy, as there was such extensive multifocal nerve involvement, and reserved a more proximal biopsy if this was unhelpful. This showed widespread, dense endoneurial and perineurial infiltration of atypical, mitotically active CD3+ T-lymphoid cells (Figure, I-N). The morphological and immunohistochemical features of the infiltrate in the nerve was similar to the dermal infiltrate from previous skin biopsies and in keeping with PTCL although skin biopsies alone were not diagnostic due to an insufficient number of infiltrating T-cells for adequate characterisation. In contrast, the sural nerve contained ample T-cells for immunophenotypic and genotypic characterisation to achieve the diagnosis.

She was treated with an intensive regimen incorporating high-dose methotrexate, cytarabine and Thiotepa and underwent consolidation with high-dose chemotherapy

with BCNU and thiotepa and an autologous stem cell transplant. The patient achieved a complete metabolic response on PET (Figure, D-F) and continuing clinical improvement. Three years after her treatment regimen, she remains in remission, with resolution of the left facial palsy, albeit with remnant aberrant reinnervation, minimal weakness in lower limb proximal muscles (right hip flexion and bilateral hip extension Medical Research Council grade 5-/5) and left ankle dorsiflexion (4+/5) and she can ambulate independently.

DISCUSSION

This patient presented initially with a systemic illness and subsequently multiple mononeuropathies, and a targeted nerve biopsy secured a histopathological diagnosis whereas multiple previous skin and bone marrow biopsies had been inconclusive. Although the absent right sural sensory action potential (SAP) (left sural SAP 33μV) could have been secondary to the documented (PET and MRI) proximal nerve infiltration, local sural nerve infiltration was also possible especially as PTCLs are known to be neurotropic. As a proximal nerve biopsy is more invasive we elected to do a right sural nerve biopsy first which was diagnostic. Alternative to the right sural nerve biopsy and before proceeding to a more proximal nerve biopsy, the left superficial peroneal nerve could have also been targeted for biopsy, as it showed an absent sensory response on the nerve conduction studies.

Previous reports have suggested that the peripheral nervous system and especially distal nerves are prone to invasion by T-cell lymphomas, with endoneurial and epineurial lymphomatous infiltration.[3–5] In all cases including ours, T-cell lymphocytes invaded the vessel walls concentrically without mural fibrinoid necrosis.

In a large retrospective study of neurological complications in 291 patients with T-cell lymphoma, the peripheral nervous system was involved in 7 cases (polyradiculopathy, distal axonal polyneuropathy, bilateral peroneal neuropathies, multifocal mononeuropathies).[6]

In conclusion, this report illustrates that in cases of PTCLs with peripheral nerve involvement, an early nerve biopsy should be considered and the neurotropic nature of the lymphoid tissue increases the likelihood of a positive yield from distal nerve biopsies which may expedite early diagnosis and treatment.

Key points

- Lymphomatous infiltration of peripheral nerves is a rare cause of multiple mononeuropathies
- The combination of avid skin involvement and multiple mononeuropathies should raise the index of clinical suspicion for a PTCL
- PET imaging and MR neurography are useful imaging modalities when PTCL with peripheral nerve involvement is suspected
- The neurotropic nature of PTCLs means that nerve biopsies may provide a sufficient amount of lymphomatous cells to achieve a histopathological diagnosis

Further reading

1. Vose J, Armitage J, Weisenburger D, *et al.* International peripheral T-cell and natural killer/T-cell lymphoma study: Pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26:4124–30.
2. Kaufman DK, Habermann TM, Kurtin PJ, *et al.* Neurological complications of peripheral and cutaneous T-cell lymphomas. *Ann Neurol*. 1994;36:625–9.

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Author Contributions

MP – major role in the acquisition of data, drafting, revising and finalising the manuscript for content.

ZJ, TM, SB, MPL – acquisition of data, interpretation and presentation of pathological findings, review and critique of the manuscript.

KC, ES, SD – acquisition of data, responsible consultants for patient's care and subsequent treatment, review and critique of the manuscript.

SS, DF – acquisition of data, interpretation and presentation of radiological and neurophysiological findings, review and critique of the manuscript.

GF, MMR – major acquisition of data, responsible consultants for patient's care, conceptualisation of the study, revising and finalising the manuscript for content.

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Disclosure

All authors report no relevant disclosures to the manuscript.

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Figure legend – Imaging findings illustrating multiple mononeuropathies and neuropathological findings from sural nerve biopsy.

Whole body PET imaging pre-treatment (A, B, C) and post-treatment (D, E, F), showing complete metabolic remission. Pre-treatment, there is FDG-avid uptake in multiple tissue nodules and along specific nerves: left peroneal (A, white arrowhead), right femoral (B, white arrowhead), and right sciatic (C, white arrowhead). MRI Neurography (G) of axial T1 fat suppressed post-GAD images of distal thighs showing avid and thickened right sciatic nerve (red arrow) and avid enhancement of left proximal common peroneal (green arrow). MRI axial STIR images (H) of proximal calves showing denervation changes in the right posterior muscular compartment (white arrowhead) and the left anterolateral muscular compartment (white arrow). Right sural nerve biopsy (I-N) shows a dense endoneurial and perineurial infiltrate of lymphoid cells (I, Haematoxylin & Eosin) with a high Ki67 proliferation index (J). The majority of lymphoid cells are CD3+ (K) and CD4+ (L) T lymphocytes with only rare CD8+ (M) T cells. A proportion of T lymphocytes show GranzymeB co-expression (N). Scale bar: 100μm in I-N. Immunostaining with antibodies Ki67 (1:200, MIB1, DAKO), CD3 (1:100, LN10, Leica), CD4 (1:200, 4b12, Leica), CD8 (1:100, C8/144B, DAKO) and GranzymeB (dilution RTU, 11F1, Leica) was performed on automated immunostainers (Roche Ventana Discovery or Leica BondMax) following manufacturer's guidelines.