An unusual extra-nodal T-cell non Hodgkin lymphoma

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A 32-year-old female was admitted to our Medical Admissions Unit in April 2015 with a two week history of back and loin pain, heaviness in her thighs, intermittent fever and rigors. Her past medical history included trigeminal neuralgia and pervasive anxiety, for which she had recently commenced quetiapine. On examination, her temperature was 39°C, but there were no other abnormal physical findings. The blood count and biochemical profile, including liver and renal function, were normal barring an elevated C-reactive protein (CRP) (118 mg/L, normal <4). With a provisional diagnosis of acute pyelonephritis, she received broad-spectrum intravenous antibiotics; however, urine and blood cultures were sterile and CT of the renal tract was normal. Considering a bacterial infection unlikely, we discontinued antibiotic therapy.

Due to continuing fever and increasing discomfort in her back and thighs, we undertook additional tests: an elevated serum creatine kinase (CK) level (1827 U/L, range 25-200) raised the possibility of quetiapine-associated neuroleptic malignant syndrome, but her clinical status remained unchanged despite discontinuing quetiapine. Repeat blood and urine analysis, throat swabs and cerebrospinal fluid failed to identify microorganisms including mycobacterial species. Chest X-ray, and echocardiogram were normal. Serum complement (C3/C4) levels were unremarkable and autoantibody screens negative. One week into admission, her haemoglobin decreased (93g/L, range 120-160) and she developed a mild neutropenia (0·9 x 10⁹/L, range 2·0-7·5) and thrombocytopenia (110 x 10⁹/L, range 150-400). Iron studies supported inflammatory co-morbidity, but serum ferritin was disproportionately raised (15,507µg/L, range 13-150) with marked fluctuation (nadir
2000 and peak 20,161) over the next week, corresponding to CK levels (445 U/L and 1429 U/L respectively). Serum lactate dehydrogenase (LDH) was also raised (632 U/L, range 120-246). Based on these results, we considered a myositis, possibly paraneoplastic, the likely cause of her symptoms despite undetectable anti-myositis antibodies. The hyperferritinaemia and cytopenias also prompted consideration of haemophagocytic lymphohistiocytosis (HLH), often secondary in adults.\(^1\)

\(^{18}\)F-FDG PET/CT imaging to identify malignancy showed no abnormalities in muscles or organs including lymph nodes, liver or spleen, but diffusely increased, non-homogeneous FDG up-take was observed in the axial skeleton (figure A). MRI of the spine revealed marrow signal abnormalities corresponding to FDG-avid areas; patchy muscle and fascial oedema was also identified within the iliopsoas and obturator externus muscles bilaterally. Needle electromyography of the hip adductors was abandoned due to pain; while no spontaneous activity was evident in the right quadriceps muscle, the presence of increased polyphasic motor unit potentials of short duration with refractory early recruitment suggested a myopathy. Muscle biopsy was technically challenging and showed non-specific small group atrophy, but no inflammatory, vasculitic, dystrophic, metabolic or mitochondrial myopathy. Bone marrow biopsy was also performed: the marrow was cellular with fibrotic changes, but without morphological or immunohistochemical feaures of malignancy. In addition, the absence of haemophagocytosis made the case for HLH less compelling (probability HScore 70%).\(^2\) With a provisional diagnosis of ‘idiopathic inflammatory myopathy’, we decided to immunosuppress her with intravenous methylprednisolone.
Prior to the first dose of steroids, unexpectedly, an abnormal karyotype - 43~45,XX,-5,-10,-15,add(15)(p10),-22,+mar1,+mar2,+mar3[cp8]/46,XX[18] was identified in 30% of marrow cells, suggesting an infiltrative neoplastic disorder. Therefore, 10 days after the initial biopsy, we undertook repeat marrow sampling to identify the malignant cell phenotype, but the morphological, immunohistochemical and cytogenetic features were unchanged. She commenced steroids with no clinical improvement; this, along with progressive pancytopenia (haemoglobin 80g/L, neutrophils 0.5 x 10^9/L and platelets 50 x 10^9/L) made us consider a non-lymphoid, myeloid malignancy as the likely diagnosis. Consequently, bone marrow was sampled for the third time in four weeks.

On this occasion, the marrow was unaspirable and the trephine biopsy showed near-total effacement of the marrow by a necrotic, high-grade tumour (figure B). The expression of CD2, cytoplasmic CD3, CD30, perforin and TIA-1 indicated a malignant T-cell phenotype. CD4, CD5, CD7, CD8, T-cell receptor (TCR)-gamma and ALK-1 were not detected, but TCR-beta F1 was expressed, which coupled with negative staining for TdT, excluded T-cell acute lymphoblastic leukaemia, and indicated a diagnosis of peripheral T-cell non Hodgkin lymphoma. We commenced her on multi-agent chemotherapy (CHOP) with rapid resolution of symptoms. Following three cycles, she achieved morphological and cytogenetic remission with normalisation of FDG signal on PET. Given the atypical presentation and steroid-insensitive disease, she was being considered for an allograft, but experienced disease-relapse that proved refractory to salvage chemotherapy. Sadly, she died in December 2015.
The frequency of ‘B-symptoms’ as paraneoplastic phenomena in lymphoma is well-recognized. In contrast, myositis, through unknown mechanisms is a rarer paraneoplastic occurrence with the potential to complicate the diagnostic process.

In our patient presenting with myositis, the diagnosis was additionally confounded by the anatomical restriction of non Hodgkin lymphoma (NHL) exclusively to the bone marrow, with no detectable disease at nodal or other extra-nodal sites even with sensitive PET/CT imaging. Thus, while bone marrow examination in nodal high-grade NHL is generally of prognostic, but not diagnostic utility, in our patient, the trephine biopsy proved to be most useful for the diagnosis. Through this report, we intend to increase awareness of the unique disease-distribution and clinical features of rarer primary extra-nodal NHL that could result in diagnostic delay despite a concerted multi-disciplinary approach.
Contributors

ADM, JTC and ST provided clinical care for the patient. PGR interpreted imaging studies. LMM performed cytogenetic analysis. NMK and JRG helped establish the pathological diagnosis. JC and ST wrote the report which was reviewed by all authors. Written consent to publish was obtained from the patient.

Conflicts of interest

None
References

Figure. Imaging and histopathological features of PTCL. A. A sagittal reconstruction of the PET component of the $^{18}$F-FDG PET/CT study shows widespread but non-homogeneous increase in tracer uptake within marrow. Representative areas shown are the T10 vertebra (red arrow) and sternum (blue arrow). Increased tracer uptake is also evident within the right anterior superior iliac spine (green arrow) in the axial image at the level of the pelvis (inset). B. Haematoxylin-eosin stained section of the bone marrow biopsy (under a 40x objective) shows extensive infiltration with high-grade tumour, and in the inset, the immunohistochemical expression of CD3 indicates a T-cell malignancy. The scale bars represent 0.1 mm.