CASE REPORT

Case of polyostotic primary bone lymphoma successfully treated with immunochemotherapy and consolidation radiotherapy

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Accepted 17 February 2017

SUMMARY

A 47-year-old woman presented with symptoms of sharp pain over the left anterior thigh with radiation from the groin to the knee. She subsequently developed numbness in that region and reduced motor strength in extensors of the left knee. Plain radiography of the spine and knee was normal. An MRI of the spine revealed an irregular extramedullary mass with intradural and extradural components, extending from the L3 to L5 vertebrae. She underwent a laminectomy and posterior spinal decompression based on a working diagnosis of nerve sheath tumour. Histopathology revealed a primary bone lymphoma. A positron emission tomography CT (PET-CT) performed as part of the staging workup revealed fluorodeoxyglucose avid lesions in the spine and left femur. She received immunochemotherapy (Rituximab-Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone) for eight cycles with an interim PET-CT revealing complete response. Subsequently, she received consolidation radiotherapy, 36 Gy in 20 fractions over 4 weeks to both lesions. She is now disease-free on follow-up for the past 1 year.

BACKGROUND

Primary bone lymphoma (PBL) is an uncommonly encountered malignancy that is usually not considered as a differential diagnosis when evaluating a bony lesion.^{1 2} Owing to its rarity, guidelines for treatment are extrapolated from retrospective reviews and a single prospective clinical trial.^{1 3–8} In this report, we describe a case of polyostotic PBL which was unusual in radiological appearance with both lesions at opposite ends of the radiological spectrum. We also present a brief review of the literature with an emphasis on imaging characteristics, staging and treatment of PBL.

CASE PRESENTATION

A 47-year-old woman presented to her physician with symptoms of sharp, self-resolving and poorly localised pain over the anterior aspect of the left thigh and knee. The pain was mild in intensity and radiated from the groin to the knee. On physical examination, there were no neurological findings and she was prescribed pain medication, to be taken on an as-needed basis. Over the next 2 months, she noticed the intensity of pain increasing along with diminished pain relief from medication. On returning to her physician, she was advised to undergo an X-ray of the knees and

spine, which were normal. She received stronger pain medication and was referred to an orthopaedic surgeon.

Over the next 2 weeks, she started noticing numbness over the left lower thigh and knee. On evaluation by the surgeon, she had reduced motor strength in the extensors of the left knee (3/5), sensory loss over the anterior half of the left lower thigh and knee, as well as a reverse straight leg raising (SLR) sign present. Straight and crossed SLR signs were absent.

INVESTIGATIONS

The surgeon recommended an MRI scan of the lumbosacral spine. It revealed an irregular extramedullary mass lesion with both intradural and extradural components, extending from the L3 to L5 vertebrae leading to central spinal canal stenosis and encroaching on the left neural foramina at L3-L4 and L4-L5 levels with consequent encasement of the L3 and L4 exiting nerve roots, respectively. Paravertebral extension of the lesion was seen along the left psoas muscle without definite invasion. All the lumbar vertebrae were of normal height and showed normal marrow signal intensity without any erosion or destruction of the cortex (*figure 1*). Routine blood investigations were normal.

Figure 1 Preoperative MRI. (A) T2-weighted axial image reveals the paraspinal mass (white arrow), displacement of the thecal sac (blue arrow) to the right and the intact cortex of the L3 vertebra (red arrow), (B) T2-weighted sagittal image showing the obliterated intervertebral foramina of L3-L4 and L4-L5 (white stars), whereas the L2-L3 foramina (red star) is uninvolved. (C) T1-weighted axial image reveals the mass abutting but not invading the left psoas muscle.

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To cite: Ahmad I, Chufal KS, Goyal N, *et al.* *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-218832

DIFFERENTIAL DIAGNOSIS

A differential diagnosis of nerve sheath tumour, meningioma or metastatic deposit was considered.

TREATMENT

On the basis of a preliminary diagnosis of spinal nerve sheath tumour, she underwent a laminectomy with posterior spinal decompression. Per-operative findings revealed a friable, vascular tumour, which could only be partially resected. The patient's postoperative recovery was uneventful and she noted a decrease in pain intensity. Her neurological examination was also normal.

Histopathological evaluation of tumour tissue revealed a small round cell tumour with involvement of associated bony tissue. Immunohistochemistry showed CD20+, CD10+, CD3- and Bcl-6 to be weak positive. Cerebrospinal fluid (CSF) sampled at the time of surgery was normal. The final histopathological diagnosis was that of an extranodal Non-Hodgkin's Lymphoma, diffuse large B-cell subtype (NHL-DLBCL) of the left paraspinal region.

The patient was then referred to our institution for further evaluation and management. After discussion in our tumour board, a staging workup appropriate for NHL was initiated and haematological investigations as well as a bone marrow examination were normal. Finally, she underwent a whole body ^{18}F Fluorodeoxyglucose positron emission tomography-CT (^{18}F FDG PET-CT) scan, which revealed significant uptake within the paraspinal soft tissue mass, posterior half of the body and pedicles of L2, L3, L4 vertebrae (figure 2A, B). Another FDG avid lesion was also seen in the head, neck and trochanteric region of the left femur with anterior cortical breach, permeative destruction of the cortex at the neck region and minimal adjacent soft tissue extension (figure 3A, B).

After completion of staging investigations, the results were discussed again in the tumour board. Owing to the absence of disease in any nodal region or elsewhere, secondary involvement of bone by NHL and disseminated NHL were excluded as possible diagnoses. On the basis of a literature review and discussion with the radiologist, both lesions (though radiologically distinct) were best explained by a diagnosis of polyostotic PBL. This was further supported by similar FDG avidity in both lesions. In order to prevent a fracture of the femur neck, excisional biopsy from that lesion was not performed.

The final diagnosis was polyostotic PBL, International Extranodal Lymphoma Study Group (IELSG) stage IVE and she received Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone (R-CHOP administered every 21 days) chemotherapy for four cycles.¹ An interim ^{18}F FDG PET-CT was performed for response evaluation and it showed complete response in both lesions. She then received four additional cycles of the same chemotherapy followed by consolidation radiotherapy to a total dose of 36 Gy in 20 fractions over 4 weeks to both sites.

Briefly, prechemotherapy PET-CT images were rigidly registered to the simulation CT and the prechemotherapy extent of disease was contoured as gross tumour volumes (GTV_Lumbar and GTV_Femur) at both sites. GTV_Lumbar was expanded isotropically by a 1 cm margin and was modified to include the entire postoperative bed as well as the left psoas muscle to generate the clinical target volume (CTV_Lumbar).³ GTV_Femur was also expanded similarly and modified to include the entire head, neck and greater trochanter of the left femur (CTV_Femur). Both CTVs were expanded by 5 mm to generate their respective planning target volumes (PTV) as per institutional protocols (figures 2C, D and 3C, D). In deciding the technique of irradiation for both PTVs, we chose Volumetric

Figure 2 (A, B) Axial and coronal images of prechemotherapy PET data fused with simulation CT. GTV_Lumbar (blue contour), CTV_Lumbar (green contour) and PTV_Lumbar (red contour) are shown. Note the FDG avidity of the pedicles of L3 and L4 vertebrae (black arrows) and the inclusion of the left psoas muscle in the CTV (white arrow). (C, D) Dose colour wash in axial and coronal planes achieved with VMAT planning (lower limit set to 95% of prescription dose). CTV, clinical target volume; FDG, fluorodeoxyglucose; PET, positron emission tomography; VMAT, Volumetric Modulated Arc Therapy.

Figure 3 (A, B) Axial and coronal images of prechemotherapy PET data fused with simulation CT. GTV_Femur (blue contour), CTV_Femur (green contour) and PTV_Femur (red contour) are shown. Note the FDG avid anterior and posterior cortical breach (white arrows). (C, D) Dose colour wash in axial and coronal planes achieved with conformal AP-PA fields (lower limit set to 95% of prescription dose). AP-PA, anteroposterior–posteroanterior; CTV, clinical target volume; FDG, fluorodeoxyglucose; PET, positron emission tomography.

Modulated Arc Therapy for the lumbar spine, as it minimised irradiation of normal tissue outside the PTV. For the femoral lesion, we used conformal anteroposterior–posteroanterior (AP-PA) fields, as it would irradiate any microscopic disease beyond the disrupted cortex of the femur. Treatment was delivered after performing daily setup verification with either kV planar imaging or cone beam CT.

Contouring and planning were performed on Eclipse V13.5 (Varian Medical Systems, Palo Alto, California, USA) and treatment was delivered on Varian Clinac 2100c (Varian Medical Systems, Palo Alto, California, USA).

OUTCOME AND FOLLOW-UP

The patient's RT course was uneventful and she is disease-free on follow-up for the past 1 year.

DISCUSSION

PBL is a rare malignancy and comprises <1% of all lymphomas.^{9–10} Most patients present with symptoms of pain or a palpable mass and are in the 40–60 year age group.^{10–11} Up to 80% of all bone lymphomas are of the DLBCL subtype with occasional reports of other subtypes of NHL.^{6–12} Since PBL comprises <7% of all malignant bone lesions, it may not be primarily considered prior to biopsy and this is the clinical scenario most often faced by physicians.² A concise algorithm to guide management, starting from a bone biopsy suggestive of NHL, is presented in figure 4.

Any lymphoma with involvement of bone can be classified as: (1) solitary PBL (a single bony lesion, with or without regional lymphadenopathy), (2) polyostotic PBL (multiple bony lesions exclusively involving the skeleton) and (3) disseminated lymphoma with secondary involvement of the bone.¹ Solitary PBL frequently affects the appendicular skeleton, and the polyostotic variant can involve both the axial and appendicular skeleton,

whereas preferential involvement of the axial skeleton is seen in disseminated lymphoma.¹³

Plain radiography features of PBL are variable and lesions can be lytic, mixed lytic-sclerotic, sclerotic or normal in appearance.^{13–15} CT evaluation is able to better characterise the lesion but is generally inferior to MRI in its ability to depict the full extent of the lesion.¹⁵ Details are provided in figure 5. ¹⁸FDG PET-CT is valuable in accurate staging as it upstages a significant number of patients with lymphoma with few false-positives.¹⁶

Interestingly, PBLs which demonstrate a near-normal pattern of bony involvement on plain radiography are often associated with a soft tissue mass on MRI, which has led some investigators to conclude that this combination is pathognomic for this tumour.^{14–17} The mechanism by which PBL traverses an apparently intact cortex is through cortical tunnelling, which was demonstrated by Hicks *et al*.¹⁸ In that study, MRI, histopathological and immunohistochemical correlation revealed cutting cones with marked osteoclastic activity and extensive bone resorption in the form of narrow channels through cortical bone, which were filled with tumour cells.

In our patient, MRI evaluation did not reveal any pathological marrow abnormality or cortical disruption in the spinal lesion (representing the near-normal pattern). However, the presence of disproportionate soft tissue component, FDG avidity in the vertebral bodies (including pedicles) and histopathological evidence representing bone involvement led us to a diagnosis of PBL. The presence of another lesion in the femur, which showed a lytic pattern, is interesting.

Recently, a new staging system for PBL was proposed by the IELSG which leads to better stratification of patients in terms of 5 years overall survival.¹ It overcomes the limitations of the Ann Arbor system, which does not account for the number of sites involved in those patients with only extranodal disease, as well

Figure 4 Management algorithm based on our institutional protocol for patients presenting with a bone biopsy suggestive of DLBCL. Prognosis is dependent on IELSG stage and treatment received.^{1 3-7} *Patients are considered high risk for CNS dissemination if there is involvement of bones close to the base of the skull and either MRI of the brain reveals meningeal lymphomatosis or CSF evaluation reveals the presence of lymphoma.^{1 19} **Patients are considered high risk for developing pathological fracture based on Mirel's score.²⁰ A patient with a score greater than eight first undergoes surgical stabilisation and then management as per stage group. CNS, central nervous system; CSF, cerebrospinal fluid; DLBCL, diffuse large B-cell lymphoma; FDG, fluorodeoxyglucose; IELSG, International Extranodal Lymphoma Study Group; PET, positron emission tomography.

as ignores the difference in prognosis between polyostotic PBL and disseminated lymphoma secondarily involving the skeleton (5 years OS: 74% vs 36%, respectively).¹⁹

Once a diagnosis of PBL has been established and staging workup is underway, attention has to be given to evaluate the skeletal integrity. Patients who present with a pathological fracture (or are at high risk for developing a fracture subsequently) should undergo surgical stabilisation with the intent of improving mobility and quality of life, without inadvertently prolonging time to start of chemotherapy.^{20 21} The reported rate of central nervous system (CNS) involvement with PBL is 2–5% and CNS prophylaxis should be offered to patients with high-risk features (CSF involvement, meningeal lymphomatosis on MRI or involvement of bones close to the skull base).¹⁹ The European Society for Medical Oncology recommends combined modality treatment (immunochemotherapy followed by consolidation radiotherapy) for the treatment of PBL IELSG Stage IE-IVE; however, the literature is equivocal about the role of rituximab and consolidation RT.²²

In a recent retrospective review by the MD Anderson group, addition of consolidation RT after R-CHOP chemotherapy in early and advanced PBL resulted in a significant benefit in 5-year PFS and OS irrespective of stage without any benefit in a dose exceeding 36 Gy.³ Another retrospective analysis, which

pooled patients with early and advanced PBL from nine trials conducted by the German High-Grade Non-Hodgkin's lymphoma Study Group (DSHNHL), also supports the addition of consolidation RT up to 36 Gy.⁵ In the only prospective trial conducted in patients with PBL, consolidation RT improved local control and, as a result, prevented pathological fractures (and associated disability) secondary to local recurrence.⁸ In contrast, the retrospective IELSG-14 study did not report any benefit from RT in early stage PBL.⁴ Another retrospective review from the British Columbia Cancer Agency (BCCA) found that consolidation RT resulted in 10 years OS significantly worse than those receiving immunochemotherapy alone.⁶

Interestingly, the analyses from DSHNHL and MD Anderson also differ from the analysis by BCCA with respect to the benefit of rituximab. Whereas the BCCA analysis found a significant benefit from the addition of rituximab, the other two analyses did not. Clearly, immunochemotherapy followed by consolidation radiotherapy may constitute overtreatment for a subgroup of patients with PBL. However, in the absence of a randomised trial or meta-analysis, this subgroup remains undefined and the use of rituximab/RT may vary with individual practice. For patients with PBL IELSG Stage IV, the role of RT is limited to those who do not achieve complete response to chemotherapy and/or had initial bulky disease.¹

Figure 5 Plain radiography and MRI features of PBL.^{13–15 17} PBL, Primary bone lymphoma.

Radiotherapy planning has evolved from irradiating the whole bone to using a 1 cm isotropic margin around the MRI/PET-CT-based GTV to create a CTV.^{1 3 7} The combination of a smaller target volume, conformal delivery techniques and modest dose will most likely limit morbidity associated with RT.

In conclusion, PBL is a rare entity with diverse clinical, radiological and pathological features. Multimodality management is essential for optimal treatment outcomes.

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Contributors IA is the treating senior resident (radiotherapy), author of the paper, responsible for drafting the manuscript and revising it. He is the guarantor. KSC is the supervising treating consultant (radiotherapy) and participated in article formulation, editing and oversight. NG is the radiologist and participated in interpreting and drafting the imaging-related portions of the paper. CPB is the physicist, responsible for generating the radiation treatment plan, performing quality assurance of the delivered plan and also participated in article editing.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Learning points

- ▶ Primary bone lymphoma (PBL) is a rare tumour and should be considered as a rare differential diagnosis in patients with a single or multiple bony lesions.
- ▶ PBL can present with diverse features on plain radiography (sclerotic, lytic, mixed lytic-sclerotic or near-normal) and additional imaging is often required to characterise the lesion.
- ▶ PBL is frequently diagnosed on the basis of biopsy and diffuse large B-cell subtype is the most common histological subtype.
- ▶ Staging should follow the International Extranodal Lymphoma Study Group classification for PBL and most patients should be offered immunochemotherapy (Rituximab, Cyclophosphamide, Hydroxydaunorubicin, Oncovin and Prednisone) followed by consolidation radiotherapy.
- ▶ Radiotherapy planning should use modern methods of treatment delivery and dose up to 36 Gy to minimise long-term morbidity.

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