CASE REPORT

Challenges of assessing response to therapy in non-Hodgkin's lymphoma of the bone

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SUMMARY

A 17-year-old male adolescent was diagnosed with diffuse large B cell lymphoma arising from the right humeral head. The lymphoma was found to be isolated to the bone, with a very small extraosseous component. After completion of a standard chemotherapy regimen, the Positron Emission Tomography-Computed Tomography (PET-CT) became PET negative but the CT and MRI appeared mostly unchanged in appearance, suggesting refractory disease. Repeat biopsy confirmed that no lymphoma remained, and he was in complete remission. Three months after completion of therapy, MRI continued to be abnormal. This case illustrates the unique challenges posed by the imaging characteristics of bone lymphoma, both during and after therapy. Biopsy is definitive but causes additional morbidity and may not be necessary. Imaging is done routinely to assess response to therapy, as with this patient, but in lymphomas of the bone imaging can be misleading and can lead to unnecessary procedures or follow-up imaging.

BACKGROUND

Diffuse large B cell lymphoma (DLBCL) is a mature B cell lymphoma that represents 10%–20% of paediatric non-Hodgkin's lymphomas (NHLs). Primary bone NHL comprises 1%–5% of all NHLs.¹ DLBCL is the most common NHL subtype

to arise in bone and has an excellent prognosis, particularly with Murphy stage I or II disease.² Most studies report a 5-year overall survival of over 90%.³ Relapsed patients are frequently salvaged successfully. Unlike nodal lymphoma, which quickly resolves on imaging, bone lymphomas may have persistent abnormal radiographic findings for years despite curative treatment response.

CASE PRESENTATION

A 17-year-old male adolescent without a significant medical history presented with a 10-month history of right shoulder pain. MRI demonstrated a heterogeneous lytic lesion centred in the humeral epiphysis extending into the metaphysis with lifting of the anterior humeral periosteum, as well as lateral cortical breakthrough with an associated soft tissue mass (figure 1). He underwent biopsy of the bony lesion. His diagnosis based on pathology was DLBCL. Disease evaluation was negative for any other sites of disease, making him Murphy stage I. PET-CT at diagnosis showed a hypermetabolic focus in the right humerus with an standardised uptake values (SUV) of 5.7, but no other sites of uptake (figure 2). Lactate dehydrogenase at diagnosis was 503 units/L which was within the normal range. He received chemotherapy on St Jude's Children's Research Hospital Consortium study protocol SJBC3, group B, consisting of a prephase (7-day cycle with cyclophosphamide, vincristine and prednisone) followed by two cycles of induction chemotherapy (21-day cycles with cyclophosphamide, vincristine, prednisone, doxorubicin and methotrexate with leucovorin rescue) and two cycles of consolidation chemotherapy (21-day cycles with cytarabine and methotrexate with leucovorin rescue). Intrathecal chemotherapy with methotrexate, cytarabine and/or hydrocortisone was given nine times during the treatment.

Rituximab was not used due to the low stage of the disease. In adult NHL treatment regimens, rituximab is commonly used to beneficial effect with the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy backbone. However, with the more intense backbone as described above used for paediatric NHL producing excellent survival outcomes in lower stage disease, both the Children's Oncology Group and St. Jude's Children's Research Hospital consortia have only added rituximab to the treatment protocols for advanced stage disease or disease with other poor response characteristics. Radiotherapy was not indicated or discussed as

Figure 1 MRI at diagnosis showing a heterogeneous lytic lesion centred in the humeral epiphysis extending into the metaphysis. The arrow refers to the small extraosseous component of the tumour.

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Figure 2 Left: PET at diagnosis. Right: PET at end of therapy.

part of his therapy as it would have been considered unnecessary for low stage disease.

His response to therapy was followed by MRI and PET-CT. Throughout the treatment as well as after completion of therapy, the MRI did not reflect treatment response and remained grossly abnormal with a persistent mass in the bone. In contrast, however, PET-CT showed complete resolution of hypermetabolic focus with no new lesions seen, consistent with complete treatment response (figure 2).

OUTCOME AND FOLLOW-UP

On the patient's end of therapy MRI, there was no change seen in the dominant mass in the proximal humeral epiphysis, but there was increased marrow signal more distally in the humerus. Internal and external radiological interpretations could not rule out progressive disease. Clinically, there was low suspicion by the treating oncology team for refractory or recurrent disease, but the parents and patient were uncomfortable with the ambiguity of the MRI. Therefore, an open biopsy was done of both the proximal and distal right humerus. Pathology of the biopsied sites was negative for viable lymphoma. He did not have any complications from the biopsy. Three-month post-therapy MRI remained grossly abnormal and very similar to the prior MRI. There was some decrease in the irregularity in the lateral

humeral epiphysis and metaphysis, however there was evolving T1 and T2 hypointensities in the medial humeral metaphysis that were felt to likely be subacute osteonecrosis (figure 3).

DISCUSSION

Standard of care for disease evaluation both during and after therapy for bone lymphoma includes imaging, typically MRI or CT, and more recently PET-CT. In paediatrics, MRI is usually favoured as it avoids radiation exposure. PET-CT is used as well to assess a metabolic response to therapy. There is no consensus regarding the disease evaluation of bone lymphoma when MRI fails to reflect treatment response. Biopsy can be done in select cases, especially if there is additional concern for refractory or relapsed disease. However, biopsy has potential drawbacks. While our patient had a relatively accessible site in the humeral head, lesions in the axial skeleton or adjacent to neurovascular bundles may pose greater risk of postsurgical complications. Inconclusive biopsy results can lead to repeat procedures, and negative biopsies are reassuring, but are always subject to sampling error. Resection of the abnormal bone is not usually desired due to potential for disfigurement and functional restriction, and does not contribute to curative therapy.

While imaging is the standard of care for disease evaluation and follow-up, it must be interpreted with caution. A growing body of evidence suggests that routine and frequent surveillance imaging does not improve patient care in primary bone lymphomas. MRI is sensitive and carries no radiation exposure, but MRI can remain abnormal for at least 2 years after disease resolution,³ which is the period when relapse is most often seen. By contrast, PET scans are positive at diagnosis in 98% of bone lymphomas,¹ and PET scans will show rapid decrease in fluorodeoxyglucose (FDG) activity with treatment response. The drawbacks of PET scans are radiation exposure and the relatively high false-positive rate due to bone remodelling and tumour necrosis. False positives can also occur with use of granulocyte colony stimulating factor (G-CSF) during treatment recovery.

In one cohort of primary bone lymphomas, frequent imaging often led to reimaging of incidental findings as well as biopsies of incidental findings, but did not demonstrate any improvement in outcome. Incidental findings were seen in 18% of PET-CTs, 19% of MRIs and 12% of CTs.³ This led the authors to recommend minimal follow-up imaging, using it for symptom evaluation only and not as surveillance. They recommend PET-CT over MRI.

Another cohort of six primary bone lymphomas was significant for 100% of patients having residual imaging abnormalities after end of therapy, in one case for up to 6 years. Similar to prior studies, all patients with PET-CT done before and after therapy had an appreciable decline in FDG uptake consistent with treatment response. They concluded that a single post-therapy PET-CT was the optimal imaging modality to assess treatment response.⁴

In the adult literature, the more recent Lugano criteria has redefined complete response when PET-CT is being used for response evaluation, such that a complete metabolic response is defined as complete response even when persistent masses remain.⁵ This is the situation our patient found himself in, but as these response guidelines were not yet incorporated into paediatric studies, biopsy of the residual lesions was still recommended. The most recent international paediatric NHL response criteria, published in 2015, concluded that there remains insufficient data regarding PET-CT for disease response evaluation in paediatric patients, and preserves the designation of complete response unconfirmed (CRu) which was removed from the Lugano criteria. CRu disease designation is reserved for those

Figure 3 Three-month post-therapy MRI demonstrating evolving T1 and T2 hypointensities in the medial humeral metaphysis that were felt to be subacute osteonecrosis.

Learning points

- ▶ The more recent Lugano criteria has redefined complete response when PET-CT is being used for response evaluation, such that a complete metabolic response is defined as complete response even when persistent masses remain.
- ▶ Paediatric criteria for non-Hodgkin's lymphoma (NHL) response remain in evolution, with the most recent international paediatric NHL response criteria considering patients with a residual mass after therapy that is FDG-PET negative as complete response unconfirmed. More studies are needed to evaluate the utility of FDG-PET specifically in the paediatric NHL population, and paediatric guidelines may change as these data become available.
- ▶ Lymphomas arising from bone are characterised by radiographic abnormalities for at least the first year after treatment and often for longer.
- ▶ PET-CT usually shows a hypermetabolic focus before therapy which quickly resolves with disease response. False positives can occur in PET-CT as a result of bone remodelling, tumour necrosis or use of growth factor.
- ▶ Frequent imaging after primary bone lymphoma therapy can lead to unnecessary follow-up imaging and procedures to evaluate ambiguous changes in the primary site or incidental findings.

who have a residual mass, which is negative by PET-CT. By this paediatric-specific criteria, our patient is CR biopsy which is reserved for those with a FDG-PEG negative residual mass with negative core biopsy.⁶

Our case lends additional supportive evidence illustrating the limits to MRI imaging in the evaluations of response to therapy and screening for relapse in paediatric bone lymphomas. In this patient, the PET-CT was more accurate than the MRI in evaluating the response to therapy, and following the response by the MRI led to him having undergone an additional biopsy.

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