CASE REPORT

Extramedullary CD20-positive B-lymphoblastic lymphoma in a 5-year-old child: A diagnostic challenge

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Abstract

Introduction: Lymphoblastic leukaemia/lymphoma may present as an isolated extramedullary mass, which includes the musculoskeletal region involvement with normal or near-normal blood counts. The tumour may be in the form of B or T-lymphoblastic leukaemia/lymphoma. The clinical features and histological morphology of extramedullary B-lymphoblastic lymphoma (B-LBL) may mimic mature B-cell neoplasms, thus posing a diagnostic challenge. Arriving at the right diagnosis is crucial because these two diseases differ in their prognosis and management. A high index of suspicion is therefore important so as not to miss the correct diagnosis. The diagnosis may be overlooked because the clinical presentation may not be typical of B-LBL or the blood counts do not show any abnormalities. In this report, we highlight one such case where the diagnosis of B-LBL was missed because of its atypical presentation.

Keywords: Extramedullary lymphoblastic lymphoma, CD20-positive, immunohistochemistry

INTRODUCTION

Primary extramedullary lymphoblastic lymphoma (LBL) is an uncommon disease where there is total lack or only minimal bone marrow infiltration by malignant cells. The revised 2016 WHO guideline defined lymphoblastic leukaemia/lymphoma entity as a precursor lymphoid cells neoplasm, which is committed to either B-cell or T-cell lineage. The term lymphoma is used when there are no or minimal blood and bone marrow involvement. In general, T-LBL, which constitutes 85% to 95% of cases is more common than B-LBL.

Although the natural history is not fully understood, lymphoblastic lymphoma has been reported to be more aggressive and carries a more unfavourable prognosis than lymphoblastic leukaemia. Morphologically, the blast cells in LBL may be small and homogenous resembling mature B-cell neoplasms and the diagnosis, if not thought of may be missed.

A high index of suspicion and adequate immunophenotyping is essential to prevent such misdiagnosis. We present a case of a five-year-old boy with multiple bone lesions in femur and pelvis that was initially diagnosed as diffuse large B-cell lymphoma (DLBCL) until the diagnosis was reviewed at the staging of the tumour.

CASE REPORT

A five-year-old boy was referred to our centre for further management of DLBCL. He first presented with left knee pain and fever for three months. Physical examination of his left knee and other systems were unremarkable. MRI revealed a multicentric bone tumour, involving the left triradiate bone, ilium, acetabulum and left distal femur suggestive of osteosarcoma (Fig. 1). Biopsy of the bone tumour from the referring hospital was diagnosed as DLBCL. The biopsy was described as consisting of tumour cells filling the marrow spaces. The cells were moderate to large, pleomorphic, round to oval, with vesicular nuclei and occasional prominent nucleoli. Limited immunohistochemistry (IHC) performed showed that the cells were positive for leucocyte common antigen (LCA), CD20, CD10 and focally for CD79a. They were negative for BCL6, MUM1 and CD3. Ki67 IHC was not performed. With this immunophenotyping, a diagnosis of DLBCL was made. He was then referred to our centre

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for the continuation of care and management of DLBCL.

At our centre, full blood counts showed a hemoglobin level of 9.2g/dL, normal white cell counts (4.9 x 10^9/L) and mild thrombocytosis with a platelet count of 533 x 10^9/L. Peripheral blood film showed normochromic normocytic anaemia with a leucoerythroblastic picture and no blasts or abnormal lymphoid cell present. A staging bone marrow aspiration performed at our centre showed a normocellular marrow. There is mild erythroid hyperplasia but with adequate granulopoiesis and megakaryopoiesis with no excess of blasts or abnormal lymphoid cells. Bone marrow aspiration was concluded as negative for malignant lymphomatous infiltration. However, the corresponding trephine biopsy (Fig. 2) revealed a focal area of

FIG. 1: MRI of the pelvis and bilateral femur showed (a) Multicentric lesions involving distal half of left femur, epiphysis and diaphysis, distal right femur (yellow arrows) and a focus in proximal right femoral diaphysis (red circle). (b) Left acetabulum (blue arrow). (c) Left ilium (red arrow). Courtesy of Dr Aina Khursiah Abdullah (Department of Radiology, Universiti Kebangsaan Malaysia).

FIG. 2: (H&E stain): (A) Trephine biopsy showed a focal area of infiltration by abnormal lymphoid cells (200x). (B) These cells were small with vesicular nuclei and prominent nucleoli (400x). These cells showed positive staining with (C) CD20 (200x) and (D) CD10 (200x) (E) CD79a (200x) and (F) TdT (200x).
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infiltration by abnormal lymphoid cells. These cells were small, exhibiting vesicular nuclei and inconspicuous nucleoli. IHC showed positivity for CD20, CD79a, CD10, BCL2 and terminal deoxynucleotidyl transferase (TdT) and negative for CD3. In view of the morphological features of the malignant cells and strong positivity for TdT, the trephine biopsy was diagnosed as B-acute lymphoblastic lymphoma.

Fluorescence in situ hybridization (FISH) analysis was performed on the trephine biopsy to exclude Burkitt lymphoma, by studying the status of the MYC gene. Using a break-apart probe, the FISH analysis showed no evidence of MYC gene rearrangement.

In view of these findings, the biopsy of the left distal femur from the referring hospital was requested for review and further IHC staining. The biopsy showed multiple fragments of bony trabeculae diffusely infiltrated by malignant lymphoid cells (Fig. 3). Unlike the small tumour cells seen in the trephine biopsy, these cells were moderately large, with pleomorphic vesicular nuclei and some showed conspicuous nucleoli. Numerous mitoses (27 per 10 high power field) were seen. In view of suspicion of B-LBL, further IHC; i.e. TdT and CD34 were performed in our laboratory on the unstained slide received from the referring hospital. The malignant cells showed positive expression for TdT and they were negative for CD34. This confirmed the diagnosis of B-LBL, which is similar to the diagnosis in the trephine biopsy.

In conclusion, the final diagnosis was B-LBL, involving multiple sites in the femur and pelvic bone as well as the bone marrow.

DISCUSSION

Extramedullary LBL is usually of T-cell origin and B-LBL accounts for about 10-15% of cases. It often poses a diagnostic challenge and a complete range of immunophenotyping is required for an accurate diagnosis. Besides musculoskeletal manifestations, it may present with renal masses, pleural effusion, skin lesions, tonsillar mass, oropharyngeal mass or multiple lymph nodes involving the cervical, supraclavicular or inguinal regions. In view of normal blood counts and unusual presentation, the haematological malignancy is always not thought of.

Extramedullary presentations made it unique and other differential diagnoses to be considered are DLBCL and Burkitt lymphoma. However, DLBCL is not common in a 5-year-old child. In children, it accounts for about 10% to 20% of non-Hodgkin lymphoma but it is more common in the 10 to 20 years age group, and not younger. It is important to exclude LBL or Burkitt lymphoma, which would be more common in the younger age group.

FIG. 3: (A) Femur biopsy showed diffuse infiltration of bony trabeculae by malignant cells (H&E, 40x). (B) The malignant cells were moderately large, with pleomorphic vesicular nuclei and some showed conspicuous nucleoli (H&E, 400x). They showed positive staining with (C) CD20 (400x), (D) CD79a (Focal positivity) (400x), (E) CD10 (400x) and (f) TdT (400x).
A careful study of the morphology and immunophenotype of the malignant cells are helpful for an accurate diagnosis. The immature lymphoblasts are usually morphologically distinct from mature lymphoid cells, but some cases can show relatively mature chromatin. In tissue biopsy, lymphoblasts of B-LBL are typically small to intermediate in size, with a high nuclear-cytoplasmic ratio, fine chromatin and inconspicuous to prominent nucleoli. In DLBCL, the cells are often large, with moderately abundant cytoplasm, oval to round, vesicular nuclei, fine chromatin and multiple nucleoli. In this case, however, the malignant cells in the femur biopsy were large and thus may have contributed to the misdiagnosis of DLBCL.

In most cases of B-LBL, immunophenotyping shows positivity for CD19, CD79a, CD10, PAX5 and TdT, and CD20 is usually negative. Interestingly, in this case, the tumour expressed CD20, with strong and uniform labelling. This has misled the pathologist to the diagnosis of DLBCL. It has been reported that CD20 is positive in only about 30% to 50% of B-LBL, compared to 80% to 90% of mature B-cell neoplasm. CD20-positivity reflects the stage of differentiation of the lymphoblasts. In the early precursor or pro-B and intermediate stage, the lymphoblasts do not express CD20 and it is positive only in the later stages of differentiation; ie pre-B stage. Conflicting data have been reported regarding the prognosis of CD20-positive in B-LBL. Some has reported more favourable prognosis while others associated CD20 expression with inferior survival rate.

Apart from this, surface/cyttoplasmic immunoglobulin is another marker which could be helpful in differentiating LBL from DLBCL. Surface/cyttoplasmic immunoglobulin (IgM>IgG>IgA) is present in 50% to 75% of DLBCL cases, in contrast to LBL, which usually shows negative expression.

A high index of suspicion of LBL is important, especially in a child so as not to miss the diagnosis since the clinical and histopathological presentation may not be typical or have overlapping features with other mature B-cell neoplasms. Expression of nuclear TdT, a highly specific marker for lymphoblastic lymphoma and absence of surface immunoglobulin expression is helpful to distinguish lymphoblastic lymphoma from the mature B-cell neoplasms. Other useful marker includes CD34, which is a marker for precursor cells.

CONCLUSION

This case illustrates that in extramedullary LBL, a high index of suspicion is important to guide the pathologist to perform appropriate immunohistochemical studies to ensure an accurate diagnosis. As morphology alone may sometimes be misleading, correlation with the patient’s age and clinical history is essential as not to miss the diagnosis.

Conflict of interest: The authors declare no conflict of interests.

REFERENCES