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### Primary lymphoma of bone, myeloma mimicker: a case report and review of literature

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#### ABSTRACT

Primary lymphoma of the bone (PLB) primarily arising from the medullary cavity is an extremely rare entity, with only limited number of studies and sporadic cases reported in the literature. The current study presents one case of PLB presented with unique presentation and treated with chemotherapy only. A 66 year old male presented with severe pain in the left hip that persisted for two months. Initial laboratory work up showed anemia, hypercalcemia and increase in free light chains kappa to lambda ratio, a diagnosis of multiple myeloma was suspected, magnetic resonance imaging of the vertebral spine extensive involvement of bone marrow of the vertebrae.

An 18F fluorodeoxyglucose positron emission tomography computed tomography (FDG PET CT) scan showed widely scattered moderate to intense uptake in multiple lytic of skeleton, Impression was : Image compatible with extensive multiple myeloma, No extra osseous involvement was found.

Bone marrow examination was performed confirmed a diagnosis of extensive bone marrow involvement by High grade B-cell neoplasm with areas of bone marrow necrosis.

The patient received six cycles of R-CHOP regimen (Rituximab, cyclo-phosphamide, Anthracycline, vincristine and prednisone) and achieved a complete response, as confirmed by FDG PET CT. At present, the patient is in a good condition. so this patient presentation mimicking multiple myeloma, which represent diagnostic dilemma.

Primary lymphoma of the bone is rare disease entity, there is no strong evidence supporting some diagnostic and therapeutic decisions, and therefore, case presentation of the rare disease may facilitate treatment of similar diseases. A review of the literature to elucidate the clinical, radiological, pathological phenotype and optimal treatment of PLB done.

**Key words:** Primary lymphoma of the bone, extra nodal, high grade B-cell lymphoma, multi focal lesions

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## Introduction

Primary lymphoma of bone (PLB) is a rare extra nodal lymphoma that accounts for less than 1 percent of all non-Hodgkin lymphomas (NHL) in adults, 3 to 7 percent of primary bone tumors and less than 5 percent of all extra nodal non-Hodgkin lymphomas. Usually, presented as solitary or multiple and destructive bone lesions. [1-3]

The vast majority of cases of PLB are pathologically diagnosed as diffuse large B cell lymphoma (DLBCL), Imaging features are usually non-specific. As PLB is a curable disease, it is important for it to be differentiated from other causes of lytic bone lesions, such as carcinomas and other primary bone tumors. [2] We report a 66-year-old male presented with hip pain, investigation revealed hypercalcemia and multiple lytic bone lesions mimicking multiple myeloma, which represent diagnostic dilemma.

## Case report

We report 66-year-old male presented to emergency department with severe pain in the left hip that persisted for two months, progressive, associated with weight loss 15 kg, but no fever or night sweats. No neurological manifestations. Physical examination revealed a bed-bound patient due to severe left hip pain. Bilateral hips tenderness with limited range of movement, otherwise unremarkable examination, no organomegaly.

Investigations showed white blood count 12.8 U/L (4-10,000 U/L), hemoglobin 11.5 g/dl (12-15g/dl), and platelets 353U/L (150-450U/L).

Peripheral smear showed moderate hypochromic microcytic anemia Mild neutrophilic leukocytosis.

Serum creatinine 57umol/L (64-110umol/L), calcium 2.97mmol/L (2.1-2.55mmol/L), albumin 26gm/L (35-50gm/L), protein 72 gm/L (64-83gm/L), LDH 438 U/L(125-220).

Beta-2 macroglobulin 3.64 mg/L(0.87-2.64), , KaFLC 99.4(3.3-19.4) LaFLC 24.9 (5.71-26), Ka/La FLC ratio of 3.98 [0.26-1.65], Urine negative for bence-Jones Protein, serum protein

electrophoresis showed no monoclonal band detected.

X-ray Pelvis and Left Hip showed diffuse osteoporosis of the bones, scattered sclerotic foci noted scattered in the visualized bones.

MRI thoracic lumbar spine showed extensive involvement of bone marrow of the vertebrae (Fig 1).

FDG-PET-CT:

Showed moderate to intense uptake in multiple lytic lesions associated with cortical breakdowns scattered widely in the imaged skeleton involving vertebrae, ribs, clavicles, scapulae, pelvic bones, and proximal 2/3 of humeri and both femora down to the knees. Impression: Image compatible with extensive multiple myeloma, No extra osseous involvement was found. Fig 2(A&B)

Bone marrow examination performed:

Peripheral blood shows mild hypochromic microcytic anemia, Hb (10.8 g/dl), mild thrombocytosis (Platelets:  $430 \times 10^3/\text{ul}$ ) and mild leukocytosis (WBCs:  $11.3 \times 10^3/\text{ul}$ ) with leucoerythroblastic picture. Bone marrow aspirate shows no particles and partially clotted and hemodilute with decreased shows relative increase in lymphocytes (52%) that appear mature looking, few (4%) looks atypical with blastoid morphology (relatively less condensed chromatin and one or more inconspicuous to prominent nucleoli). Flow cytometry on bone marrow aspirate shows a minute population of monotypic B cells comprises < 1% expressing CD19, CD20, CD10, FMC7, CD11c, cBCL2, partial CD43, IgM and show Kappa light chain restriction. The cells are negative for CD79b, CD5, CD23, CD103, CD200, IgD, IgG and IgA. Touch slides is hypercellular and stuffed with many medium to large cells with very high N/C ratio, irregular nuclear borders, some show blastoid morphology (less condensed chromatin and one or more inconspicuous to multiple nucleoli) (Fig 3).

Bone marrow biopsy is suboptimal with fragmentation and aspiration artifact. The

preserved areas appear hypercellular for age with ~ (75% to 85%) and extensively infiltrated by medium to large sized abnormal cells, with irregular nuclear contour, some with blastic morphology with marked depression of the trilineage hematopoietic cells (Fig 4A&B). These abnormal cells show diffuse positivity for CD20, PAX5, CD10, Bcl6, partial Bcl2 and shows >90% positivity for Ki67 and (20% to 30%) positivity for C-MYC (Fig 5), while negative for CD34, TdT, CD5 and CD23 with reactive increase in CD3 positive T- cells. There are areas of the biopsy show cellular necrosis with many ghost cells. There is significant increase in reticulin fibers (Grade 2/3) (Fig 6).

Patient diagnosed as Primary lymphoma of the bone and Started on R-CHOP regimen (Rituximab- Cyclophosphamide-Vincristine-Anthracycline-Prednisolone) chemotherapy protocol including CNS prophylaxis with intrathecal methotrexate.

Because of persistent pain and zero ambulation capability orthopedics were consulted again and X-ray pelvis and hips were repeated, diagnosed with Pathological Left trochanteric fracture and Left femur intramedullary nailing done.

After 6 cycles of R-CHOP chemotherapy, last FDG-PET- CT showed complete metabolic remission.



Figure 1: A: Sagittal T1 weighted images of the whole spine. B: Sagittal STIR images of the whole spine. There is extensive involvement of bone marrow of the vertebrae (involving vertebral bodies and posterior neural elements) with low signal in T1 WI and high signal in STIR images. Variable degree of vertebral collapse more marked at T7 and L4 (yellow arrows). No significant posterior displacement or neurological compression.

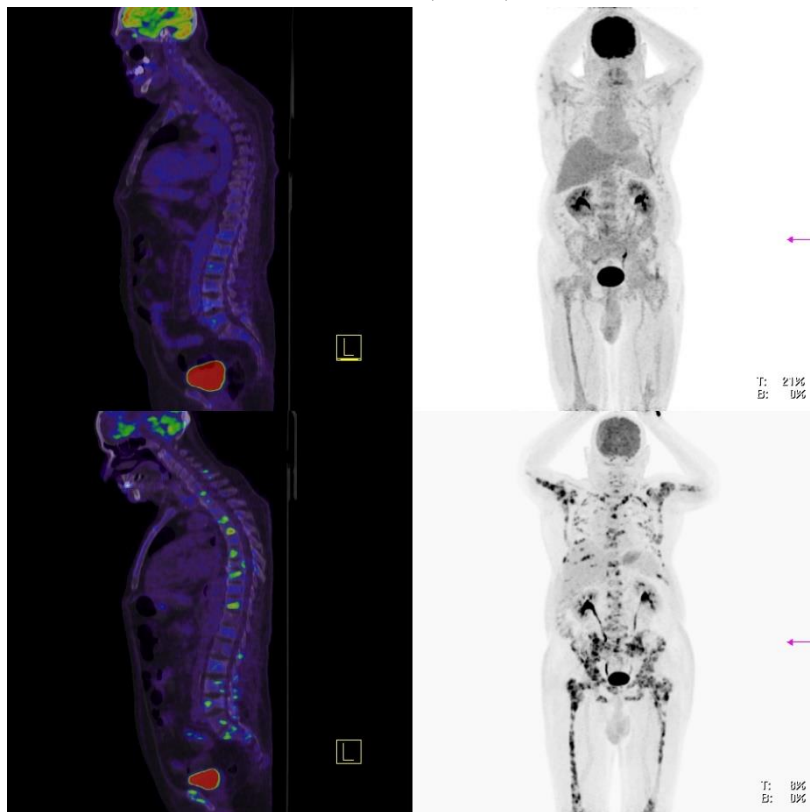


Figure 2,A

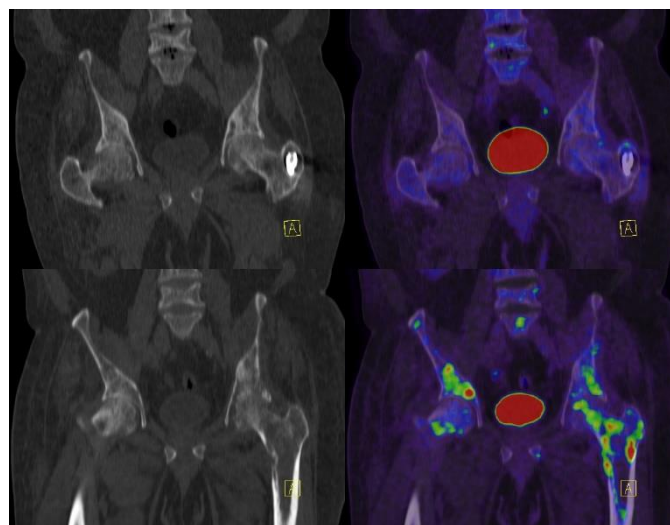
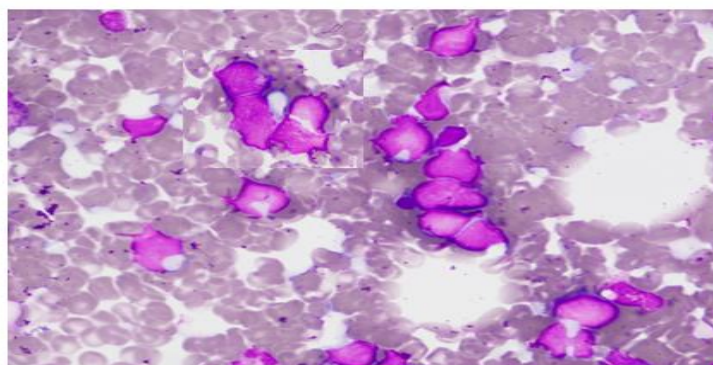


Figure 2,B



(Figure 3) x100 Touch slides is hypercellular and stuffed with many medium to large cells with very high N/C ratio, irregular nuclear borders, some show blastic morphology (less condensed chromatin and one or more inconspicuous to multiple nucleoli)



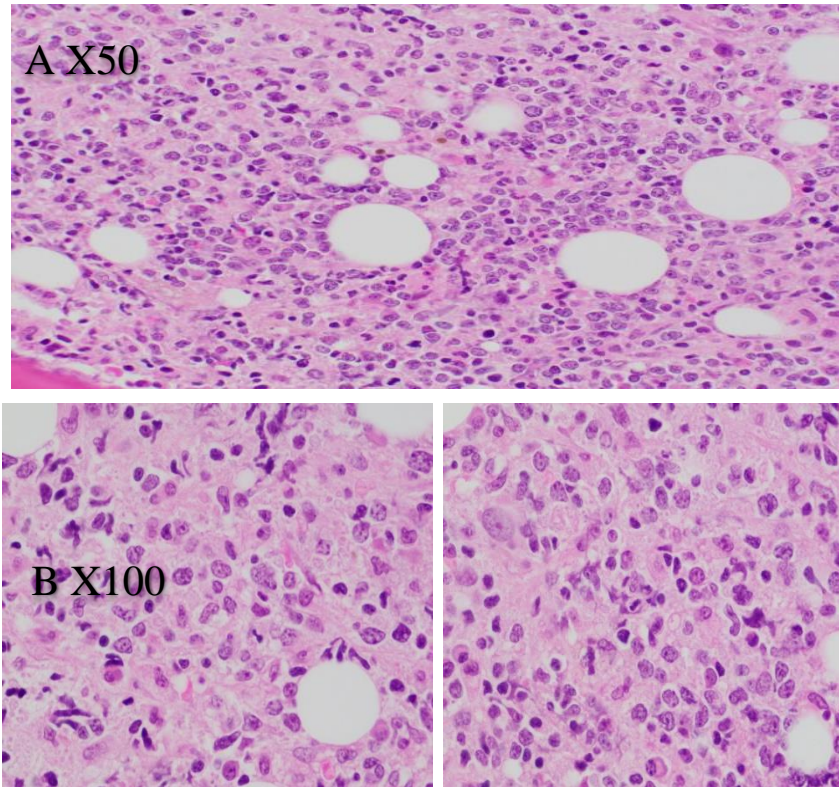


Figure 4 A & B Bone marrow biopsy is hypercellular with ~ (75% to 85%) and extensively infiltrated by medium to large sized abnormal cells, with irregular nuclear contour, some with blastic morphology with marked depression of the trilineage hematopoietic cells

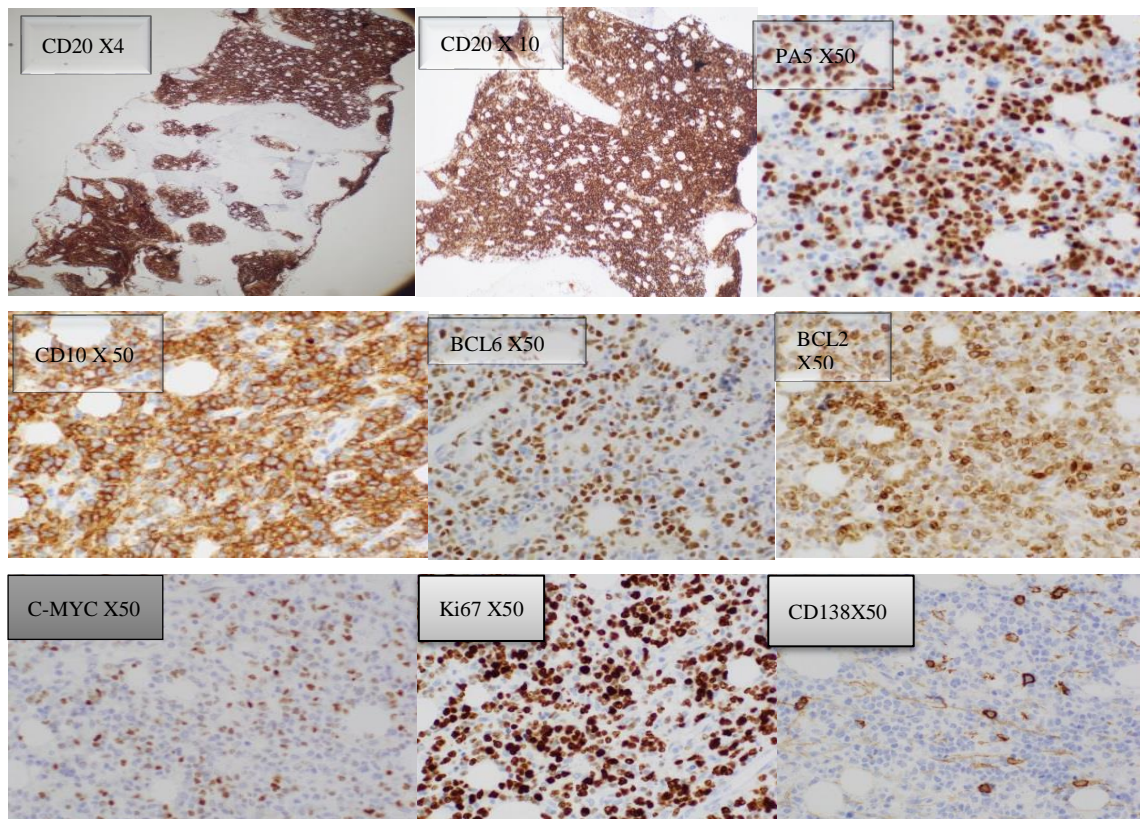


Figure 5 The abnormal cells show diffuse positivity for CD20, PAX5, CD10, Bcl6, Partial Bcl2 and shows >90% positivity for Ki67 and (20 to 30%) positivity for C-MYC, CD 138 X50 shows scattered plasma cells.



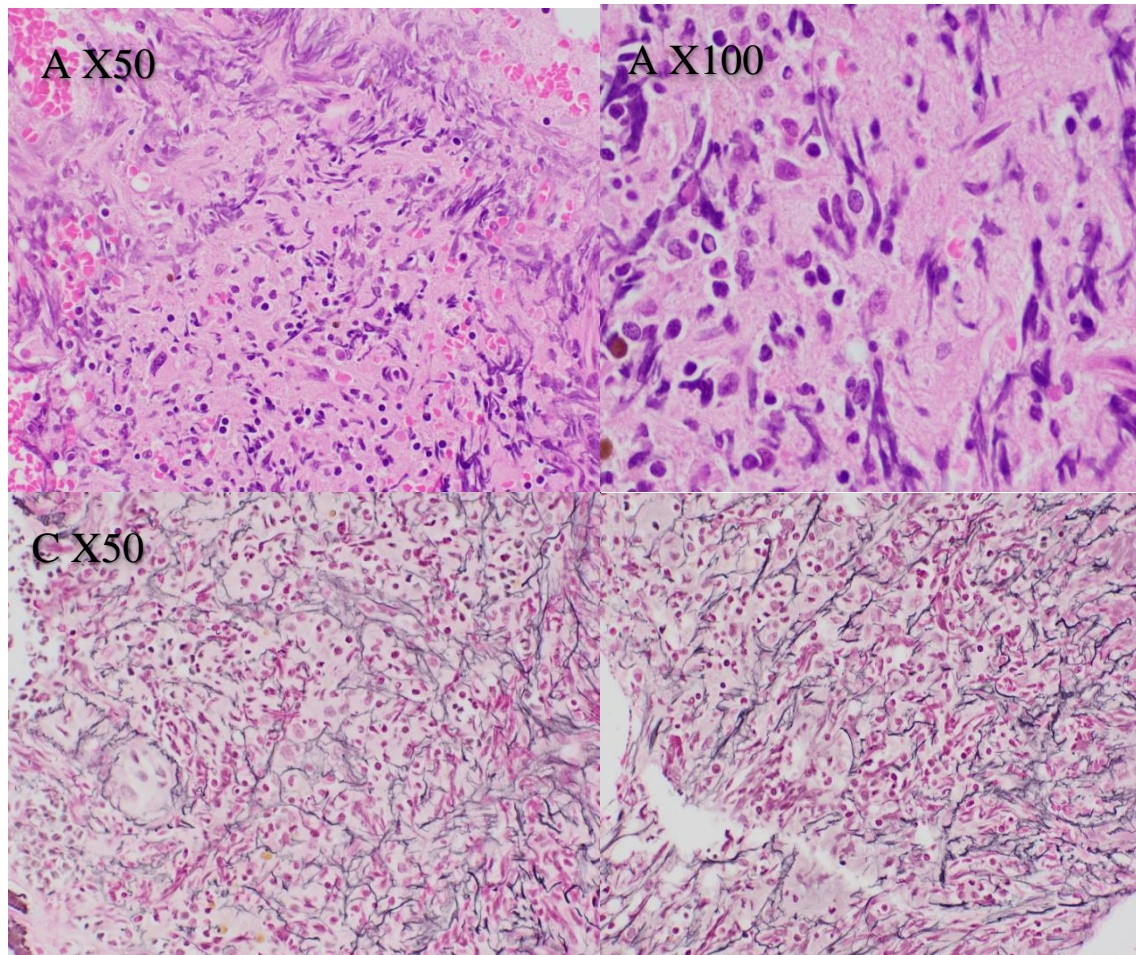


Figure 6. Increase in reticulin fibers (Grade 2/3) . H & E (A & B) Reticulin Stain (C)

Cytogenetic study revealed :abnormal karyotype 47,XY,+X,t(1;3)(q42;q12),add(14)(q32),add(19)(q13.3)[7]/46,XY[43]. G-banding chromosome analysis of 50 metaphase cells from bone marrow sample revealed an abnormal clone. The abnormal clone (7/50 cells) contains an extra copy of chromosome X, a reciprocal translocation between chromosomes 1 and 3 at cytogenetic bands 1q42 and 3q12, additional materials of unknown origin at 14q32 and 19q13. A normal clone (43/50 cells) was also present.

#### Discussion:

Primary bone lymphoma (PBL) is rare accounting for approximately 4-5% of extra nodal lymphoma and less than 1% of all Non-Hodgkin's lymphoma. Arising from medullary cavity. The cause of PLB is not well known and any part of the skel-eton can be involved [2].

Median age at diagnosis ranges between 45 and 60 years old with a male prevalence, while

pediatric cases have been also reported [8-10]. The vast majority of cases of PLB are pathologically diagnosed as diffuse large B cell lymphoma (DLBCL) in 60-80 percent, rarely indolent lymphomas may present as PLB. Highly aggressive subtypes, such as Burkitt or lymphoblastic lymphoma are rare.

Patients with PLB commonly present with local bone pain, soft tissue swelling, a mass or pathological fracture, or hypercalcemic crisis. 'B' symptoms are rare and are only observed in stage IV patients. Staging varies with different diagnosing criteria at different times [2].

Diagnosis of PBL depends on the combined clinical examination and imaging studies and is confirmed with immunohistochemically examination.

Radiologically bony lesions may be extensive, destructive or infiltrative [1]. The lytic destructive pattern is the most common radiographic appearance of PBL and it was reported in

approximately 70% of 237 cases reviewed by Mulligan et al [3]. Cortical breakthrough, pathological fracture and soft tissue masses represent a more aggressive pattern of involvement and poor prognosis [1]

Owing to its rarity, only a few retrospective studies have been published addressing the prognosis and treatment of primary bone lymphoma. As primary bone lymphoma is a highly curable disease, differentiation from other causes of lytic bone lesion such as secondaries from carcinomas and other primary bone tumors is important. Among PLBs, DLBCL is the most common subtype and accounts for 68-80% of the cases. The current standard chemotherapy for patients with DLBCL consists of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP with rituximab (R-CHOP). [11-13] Over the last two decades, chemotherapy (CHOP based) has become the standard treatment for PBL with or without consolidative irradiation. Traditionally, irradiation has been used alone or in combination with chemotherapy. [11-13] Irradiation alone in limited-stage disease has resulted in a poor five-year overall survival (OS) of around 45% even when patients have been carefully chosen for apparently limited-stage disease [9]

As regards the treatment outcome of PLB, combination chemotherapy with local radiotherapy has been reported to be superior to radiotherapy alone. Role of radiation in advanced stage PBL is controversial. [9]

Conversely, surgical resection, as a local treatment, has a limited indication only for spinal cases with progressive neurological disorder or cases with pathological fractures in the extremities. In the present case, chemotherapy with R-CHOP was given and the tumor exhibited a CR; therefore, these treatments were considered to be beneficial. Our case presented with hip pain and, on evaluation, the patient was diagnosed with primary bone lymphoma (DLBCL). The features included: serum hypercalcemia, multifocal osteolytic lesions present all over the body, and NHL presenting

as a primary bone tumor with multifocal disease is extremely rare. Primary bone lymphoma should be considered in the differential diagnosis of multiple osteolytic bony lesions.

## Conclusion

In conclusion, PLB is exceedingly rare and its radiological findings are variable and non-specific; therefore, diagnosis of PBL depends on the combined clinical examination, imaging studies, and confirmed with immunohistochemically examination.

Since PLB in the early stages is relatively curable by appropriate multimodal treatment using chemo and radiotherapy, correct diagnosis and staging by histological and imaging examinations are crucial. When radiologically diagnosing bone tumors clinicians should consider the possibility of PBL.

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