Case Report

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Pathology Section

# A Rare Case of Primary Bone Lymphoma Masquerading as Langerhans Cell Histiocytosis

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## ABSTRACT

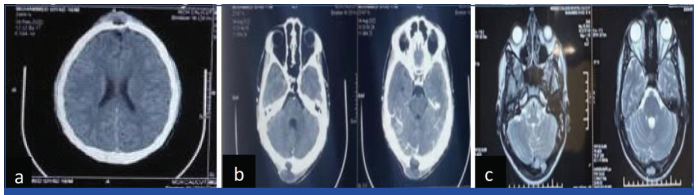
Anaplastic Large Cell Lymphoma (ALCL) is an uncommon type of Non Hodgkin Lymphoma (NHL). It commonly arises in lymph nodes and can also involve extranodal sites such as the skin, soft tissues, lungs, bones, and liver. Here, a case of Anaplastic Lymphoma Kinase (ALK)-positive ALCL in a 17-year-old male patient who presented with swelling in the frontal and occipital bones is presented. The patient was clinically and radiologically diagnosed with Langerhans Cell Histiocytosis (LCH), and excision of the occipital lesion was performed. Preoperatively, lymphoma was not considered a differential diagnosis. Detailed histopathological examination, immunohistochemistry, and Positron Emission Tomography (PET) scan confirmed the diagnosis of primary bone ALK-positive ALCL. This T-cell NHL is composed of large lymphoid cells with abundant cytoplasm and pleomorphic horseshoe or kidney-shaped nuclei, with characteristic ALK and CD30 positivity. An isolated presentation of ALCL as a primary lesion in the bone is extremely rare. Clinicians and pathologists should be aware of this rare presentation, as prompt diagnosis and proper treatment can lead to favourable outcomes.

**Keywords:** Anaplastic large cell lymphoma, Immunohistochemistry, Occipital bone

## CASE REPORT

A 17-year-old boy presented with a forehead swelling that had been present for two weeks. There was no history of fever, night sweats, associated pain, weight loss, or other swellings. On examination, there was a swelling measuring 3×2 cm, which was non tender and firm in consistency, located in the forehead. General and systemic examinations revealed no other abnormalities. He was evaluated by Ultrasonography (USG) and Computed Tomography (CT) scans. The USG of the forehead showed a well-defined hypoechoic area with erosion of the underlying bone, possibly of inflammatory granulomatous aetiology. The plain axial CT scan of the head revealed an extracranial soft-tissue swelling measuring 3.8×1.6 cm in the frontal region, midline, with underlying bone erosion and suspicious dural thickening, likely of inflammatory origin [Table/Fig-1a].

The surgical excision of the swelling was advised. The patient then noticed a gradual reduction in the size of the frontal swelling and revisited the doctor after three months. Following this, a Magnetic Resonance Imaging (MRI) scan and a CT scan were performed. The MRI of the brain showed a new irregular altered signal intensity lesion in the occipital area, raising suspicion of Langerhans Cell Histiocytosis (LCH) [Table/Fig-1c]. The repeat CT scan of the head also revealed a punched-out lytic lesion with an adjacent soft-tissue component in the occipital bone, measuring 3.4×2.7 cm, along with a lytic area in the frontal bone [Table/Fig-1b]. This led to considering LCH as the first differential diagnosis.



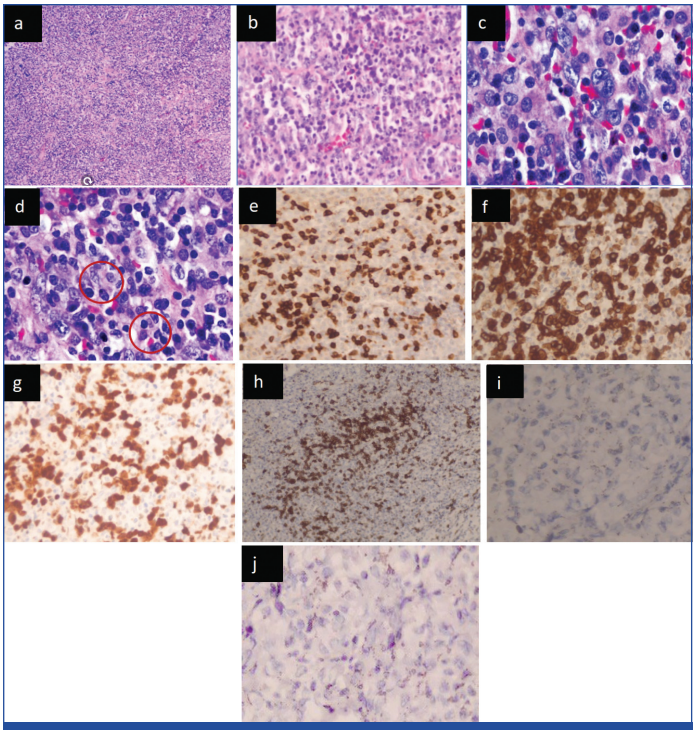

**[Table/Fig-1]:** a) CT head showing irregular lytic area in frontal bone in midline; b) CT head showing punched out lytic lesion in the lower part of the occipital bone in midline with adjacent soft-tissue compartment; c) MRI brain showing irregular altered signal intensity lesion in occipital bone in retro cerebellar location.

An excision biopsy of the occipital lesion was performed, and the sample was sent for histopathological examination. The specimen was received as multiple pieces of grey-white tissue, aggregate measuring 5×4×1 cm, with a rubbery consistency and areas of necrosis. Haematoxylin and eosin-stained sections revealed a lymphoid neoplasm with large atypical lymphoid cells arranged in sheets. These cells had indented kidney/horseshoe-shaped nuclei, a high nucleocytoplasmic ratio, coarse chromatin, and prominent nucleoli, admixed with numerous plasma cells and occasional eosinophils. No cells with nuclear grooves were noted. Mitosis was observed at a rate of >20 per 10 high-power fields. These findings raised suspicion of a high-grade non Hodgkin large cell lymphoma, possibly ALCL. An immunohistochemical study was conducted for confirmation. The tumour cells showed positivity for CD3, CD30, and ALK. CD20 positivity was noted in the reactive B lymphocytes in the background. Plasma cells in the background were positive for CD138. CD1a and S100 were negative in the tumour cells. These histopathological and immunohistochemical findings confirmed the diagnosis of ALK-positive ALCL [Table/Fig-2].

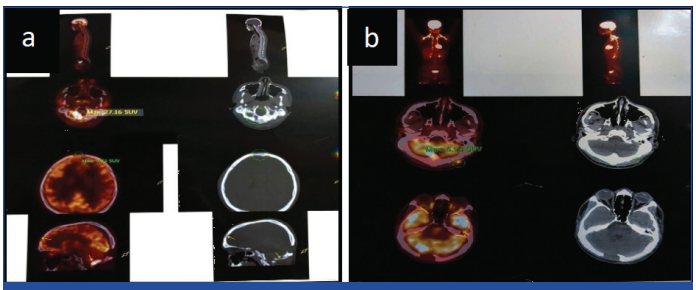
The peripheral smear and bone marrow examination were within normal limits. An 18-Fluoro-Deoxyglucose Positron Emission Tomography (FDG PET CT) scan was performed, which showed metabolically active lytic lesions involving the occipital and frontal bones. A suboccipital lymph node was also noted on the left-side. No other lymph nodes or extranodal sites were involved [Table/Fig-3]. Thus, a diagnosis of primary bone ALK-positive ALCL was confirmed. The patient underwent six cycles of the CHOP regimen (cyclophosphamide, doxorubicin [Adriamycin], vincristine, and prednisolone) chemotherapy, along with 28 fractions of radiotherapy. A repeat PET CT scan taken to assess treatment response showed a reduction in the size of both swellings, with findings suggestive of a favourable response to chemotherapy.

## DISCUSSION

The ALCL was originally designated as Ki-1 lymphoma in 1985 by Stein and his colleagues. The name is based on the Ki-1 or CD30 positivity of the tumour cells [1]. The understanding of this entity has evolved substantially over the years. In 2008, ALCL was divided into two provisional entities: ALK-positive ALCL and ALK-negative ALCL. It was considered as two distinct neoplasms in the revised 4th edition of the WHO classification of tumours of haematopoietic and lymphoid tissues [2].




**[Table/Fig-2]:** a) Sheets of large atypical lymphoid cells (H&E, x40); b) Lymphoid cells with indented nuclei in a background of small mature lymphocytes, histiocytes and plasma cells (H&E, x200); c) Cells with kidney shaped nuclei admixed with numerous plasma cells (H&E x oil immersion); d) Cells with horse shoe shaped nuclei (hallmark cell) (encircled) (H&E x oil immersion). Tumour cells are positive for CD3 (e), CD30 (f) and ALK (g) (H&E, x400). Background reactive B cells show CD 20 positivity (h) (H&E, x200). Tumour cells are negative for CD1a (i) and S100 (j) (H&E, x400).




**[Table/Fig-3]:** a) FDG avid lytic skeletal lesions involving frontal and occipital bones (Standardised Uptake Value (SUV) max 27.16); b) FDG avid suboccipital lymph node on left-side (SUVmax 6.9).

It is a T-cell lymphoma that accounts for 3% of adult NHL and 10-20% of childhood lymphoma. ALCL in bone is rare, but it is the most common primary T-cell lymphoma of bone [3]. The tumour consist of large lymphoid cells with abundant cytoplasm and pleomorphic horseshoe or kidney-shaped nuclei (hallmark cells).

In present case, the radiological diagnosis was LCH, but histopathological sections showed large lymphoid cells with kidney- or horseshoe-shaped nuclei in a background of plasma cells and occasional eosinophils. The absence of cells with nuclear grooves and negative Immunohistochemistry (IHC) for CD1a and S100 ruled out LCH. CD30, CD3, and ALK positivity in tumour cells confirmed the diagnosis of ALK-positive ALCL. A PET-CT scan showed no involvement of other sites, confirming the diagnosis of primary bone ALK-positive ALCL.

Only a very few cases of ALCL originating in bone have been reported so far. Nagasaka T et al., reported six cases of ALCL that presented primarily as osteolytic lesions in the radius, tibia, ilium, ribs, and vertebral bones. Out of the six cases, only one had cervical lymphadenopathy, while all others showed no extraskeletal involvement [4]. ALCL can present primarily as solitary or multiple bone lesions [5-7]. Barik S et al., reported primary ALCL in the calcaneum of a seven-year-old boy [8]. A case of primary maxillary bone ALK-positive ALCL was reported in a 15-year-old boy who later relapsed with rib metastasis [9]. Cheng L et al., reported another case of ALCL with primary bone involvement in a 47-year-old man who presented with multiple bony lesions, which were clinically misdiagnosed as multiple myeloma [10].

By definition, primary bone lymphoma is a neoplasm composed of malignant lymphoid cells producing one or more lesions within the bone, with no supra-regional lymph node involvement or other extranodal lesions. These tumours constitute 3-7% of primary bone tumours and less than 1-2% of all lymphomas [11]. The most common site is the femur (29% of all cases), followed by the pelvis, humerus, skull, and tibia, usually arising in the meta-diaphyseal region of the bone [12]. About 10-40% of cases are multifocal; some tumours produce multiple lesions in a single bone or involve multiple bones concurrently (polyostotic) [3]. The median age of presentation ranges between 45 and 60 years, with a slight male predominance. No geographic or racial preponderance has been demonstrated. Diffuse Large B Cell Lymphoma (DLBCL) constitutes more than 80% of the cases. Other lymphomas, such as follicular lymphoma, marginal zone lymphoma, lymphoblastic lymphomas, Hodgkin lymphoma, and ALK-positive and negative ALCLs, rarely arise primarily within the bone.

The most frequent genetic alteration observed in ALCL is the t(2;5)(p23;q35) translocation between the ALK gene on chromosome 2 and the Nucleophosmin 1 (NPM1) gene on chromosome 5. ALCL is most commonly seen in the first three decades of life. Extranodal sites of ALCL include the skin, soft tissue, lungs, bones, and liver. However, both primary and secondary involvement of bone in ALCL is a rare occurrence [13]. Patients with ALCL have good remission rates with chemotherapy. Most cases of ALCL in children are treated with high-grade B-cell NHL protocols, using a CHOP regimen due to the disease's high tendency for rapid progression and frequent B symptoms [14].

## CONCLUSION(S)

It is extremely rare for ALCL to manifest as a primary bone lesion. This case presented a diagnostic dilemma, as the patient's age, clinical features, and radiological findings favoured LCH, and the skull is an uncommon site for primary osseous lymphoma. These conditions can easily be misdiagnosed; therefore, a thorough evaluation of bone-limited lesions is crucial. This case report underscores the importance of considering primary bone lymphoma, and more specifically primary ALCL in bone, as a differential diagnosis for malignancies presenting with bone-limited lesions.

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