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CASE REPORT

B-Acute Lymphoblastic Leukemia Masquerading as Multifocal Langerhans Cell Histiocytosis: a Diagnostic Paradigm Shift

Dejun Xiao [1], Hong Liao [2], Fang Peng [3], Xinglin Wen [4], Zhiqing Liu [5]

[1] *Department of Clinical Laboratory, Ganzhou People's Hospital, Jiangxi, China*
[2] *Department of Hematology, Ganzhou People's Hospital, Jiangxi, China*
[3] *Department of Pathology, Ganzhou People's Hospital, Jiangxi, China*
[4] *Department of Radiology Ganzhou People's Hospital, Jiangxi, China*
[5] *Operating Room, Ganzhou People's Hospital, Jiangxi, China*

SUMMARY

Background: **This report describes a diagnostically challenging case of B-cell acute lymphoblastic leukemia (B-ALL) perfectly mimicking multifocal Langerhans cell histiocytosis (LCH), revealing a critical diagnostic pitfall in pediatric oncology.**
Methods: **A 6-year-old girl presented with progressive back pain. MRI showed multilevel vertebral collapse (T11-L2) with classic LCH features, while PET-CT revealed disseminated hypermetabolic bone lesions (SUVmax 2.7). Comprehensive pathology included immunohistochemistry (CD79a, TdT, CD1a, Langerin) and next-generation sequencing.**
Results: **Despite typical LCH imaging, immunohistochemistry demonstrated $CD79a^{+}/TdT^{+}$ B-lymphoblasts without CD1a/Langerin expression. Molecular analysis identified a pathogenic KRAS p.Gly13Asp mutation (VAF 1.5%), confirming B-ALL. This represents the first molecularly confirmed case of KRAS-mutated B-ALL mimicking LCH radiographically.**
Conclusions: **This case mandates: 1) routine TdT staining for LCH-like lesions, 2) recognition of KRAS-driven osteolysis as a novel B-ALL mechanism, and 3) implementation of molecular profiling in atypical osteolytic cases. It highlights the need for integrated diagnostic approaches combining imaging, pathology, and molecular techniques in pediatric bone lesions.**
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Correspondence:
Zhiqing Liu
Operating Room
Ganzhou People's Hospital
341000 Jiangxi
China
Phone: +86 15083901101
Email: liuzhiqing110@126.com

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KEYWORDS

B-acute lymphoblastic leukemia, Langerhans cell histiocytosis, diagnostic mimicry, bone lesions, KRAS p.Gly13Asp

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a clonal histiocytic disorder of childhood, with an estimated incidence of 5 - 10 cases per million annually [1]. Classic presentations include cutaneous eruptions and unifocal/multifocal osteolytic lesions (eosinophilic granulomas) [2]. Acute lymphoblastic leukemia (ALL), the most com-

Table 1. Systematic differential diagnosis of osteolytic bone lesions in pediatric patients.

Suspected diagnosis	Supporting evidence	Exclusion criteria
LCH	multifocal vertebral destruction + PET hypermetabolism	absence of rash
B-ALL	hypercalcemia + elevated LDH; confirmed by IHC	initial absence of circulating blasts
Osteomyelitis	localized bone destruction	normal CRP (0.78 mg/L), afebrile
Neuro-blastoma	multiple bone involvement	normal urinary VMA; no adrenal mass
Osteo-sarcoma	osteolytic changes	lack of periosteal reaction; discordant PET pattern

LCH Langerhans cell histiocytosis, B-ALL B-cell acute lymphoblastic leukemia, PET positron emission tomography, IHC immunohistochemistry, LDH lactate dehydrogenase, CRP C-reactive protein, VMA vanillylmandelic acid.
Key diagnostic contradictions: The patient's imaging initially suggested LCH, but definitive IHC (TdT^+/$CD79a^+$) and molecular profiling (KRAS p.Gly13Asp) confirmed B-ALL.

Table 2. Comparison of critical immunohistochemical and molecular markers between the present case and diagnostic expectations for Langerhans cell histiocytosis (LCH) versus acute lymphoblastic leukemia (ALL).

Marker	Result	LCH expected	ALL expected
CD1a	0%	> 95% +	negative
TdT	98% +	negative	> 90% +
BRAF	Wild-type	50% +	< 5% +

mon pediatric malignancy, typically manifests with fever, arthralgia, lymphadenopathy, or bleeding diathesis. Hypercalcemia and disseminated osteolytic lesions are rare at presentation (< 2% of pediatric B-ALL cases) [3].
The diagnostic boundary between LCH and hematologic malignancies is traditionally distinct, with < 0.5% of LCH cases showing concurrent leukemia [1]. Although osteolytic B-ALL lesions are documented in children [3] and adults [4], none exhibited complete radiologic mimicry of multifocal LCH - a distinction central to our case. This diagnostic overlap carries significant clinical implications, as misclassification may delay leukemia-directed therapy. Recent reports of B-ALL mimicking fibrosing mediastinitis [5] and studies elucidating RANK-RANKL-mediated osteolysis in ALL [6] further underscore the spectrum of atypical presentations.

CASE PRESENTATION

A previously healthy 6-year-old Han Chinese female presented with a 4-month history of progressive thoracolumbar pain (NRS 3→8) accompanied by new-onset difficulty in ambulation during the final month. Initial evaluation revealed mild hypercalcemia (2.8 mmol/L) and elevated LDH (420 U/L), though complete blood count showed no circulating blasts (WBC 2.86 x 10^9/L, Hb 94 g/L). This clinical presentation initially diverted our diagnostic focus away from hematologic malignancies due to several deceptive features: the presence of leukopenia (WBC 2.86 x 10^9/L) without circulating blasts - a finding atypical for conventional leukemia presentations; preserved platelet counts (259 x 10^9/L) contradicting expected pancytopenia patterns; and absence of peripheral lymphadenopathy or hepatosplenomegaly on physical examination. These features collectively created a 'pseudo-benign' hematologic profile that masked the underlying B-ALL.
MRI (Figure 1A) revealed T11-L2 vertebral collapse with epidural extension - a finding classically associated with Langerhans cell histiocytosis (LCH). PET-CT (Figure 1C) showed hypermetabolic bone lesions (SUVmax 2.7), while 3D reconstruction (Figure 1B) vividly demonstrated the extent of lytic bone destruction (purple coloration), collectively reinforcing the LCH suspicion. The patient underwent CT-guided biopsy, where initial frozen section analysis suggested histiocytic infiltration. These results suggest a higher likelihood of LCH. We conducted differential diagnoses for the following diseases: LCH, B-ALL, osteomyelitis, neuroblastoma, and osteosarcoma (Table 1). To further confirm the diagnosis, we performed a bone marrow biopsy. However, definitive immunohistochemistry (Table 2) delivered a diagnostic surprise: $CD79a^+$/TdT^+/$CD1a^-$/$Langerin^-$ cells, completely contradicting the LCH diagnosis. Molecular analysis uncovered the final piece of the puzzle - a KRAS p.Gly13Asp mutation (VAF 1.5%) - confirming an unexpected diagnosis of B-ALL with extraordinary radiologic mimicry of multifocal LCH. This diagnostic odyssey, from presumed benign histiocytosis to malignant leukemia, underscores the critical importance of comprehensive pathologic evaluation even when imaging appears pathognomonic. The patient was subsequently treated with ALL-directed chemotherapy (vincristine 1.5 mg/m² IV weekly, daunorubicin 30 mg/m² IV days 1/8/15), which achieved an excellent response, including normalized calcium by day 10, pain resolution (NRS 2/10) by day 28, and tumor

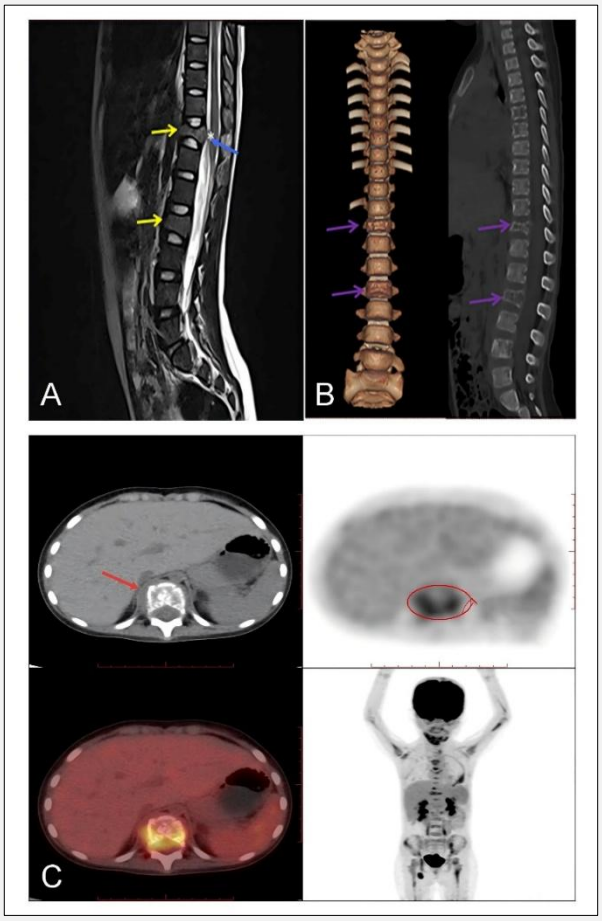

Figure 1. A Sagittal T2 MRI showing T11/L2 vertebral collapse (arrow) with epidural extension (arrow). B 3D reconstruction of lytic lesions (arrow). C Axial PET-CT (SUVmax 2.7) with paraspinal mass (arrow). Quantitative PET metrics of the target lesion. Maximum standardized uptake value (SUV max): 2.706, volume: 16.9 cm^3, total lesion glycolysis (TLG): 27.7 (circle).

burden decreased from 32.56% at initial diagnosis to an MRD of 0.05% on day 15 [7]. Timely and accurate diagnosis significantly reduces the risk of B-ALL recurrence and improves prognosis.

DISCUSSION

This case challenges three key clinical and pathological paradigms in the diagnosis and pathogenesis of B-cell acute lymphoblastic leukemia (B-ALL) with osteolytic manifestations.

Radiologic specificity

Classic LCH-associated vertebral plana and contrast enhancement patterns were replicated in this B-ALL case, blurring traditional imaging distinctions. While LCH typically exhibits lytic skull or spine lesions with sharp margins [2], this presentation mirrors rare B-ALL cases with diffuse osteolysis mimicking histiocytic disorders [8]. This overlap underscores the limitations of relying solely on radiology for differential diagnosis. Notably, metabolic reprogramming via c-Myc (a downstream target of both KRAS and BET proteins) may contribute to this overlap, as glycolytic activity can influence bone microenvironment remodeling [9].

KRAS-Driven osteolytic mechanism

The p.Gly13Asp mutation promotes bone destruction not only through canonical RANK-RANKL activation [6] but also via MMP-9 upregulation - a novel pathway distinct from CNS metastatic mechanisms involving immune checkpoints [10]. This dual-axis mechanism (KRAS→MMP-9/RANKL) expands current models of B-ALL bone invasion and suggests potential therapeutic synergy between MEK inhibitors (targeting KRAS) and

RANKL blockade (e.g., denosumab).

Diagnostic algorithm gaps

While TdT immunohistochemistry (IHC) remains the gold standard for B-ALL confirmation [11], its selective use in histiocytosis-mimicking cases is often delayed. This case highlights that non-LCH histiocytic disorders (e.g., Erdheim-Chester disease [12]) may co-express CD68 but lack TdT, necessitating early incorporation of TdT IHC when osteolysis precedes overt leukemia. Furthermore, KRAS mutation screening should be considered in atypical osteolytic presentations to uncover targetable drivers.

These paradigm shifts underscore critical advancements in understanding and managing B-ALL with osteolytic manifestations. First, the integration of multimodal diagnostics - combining advanced imaging, immunohistochemistry (IHC), and molecular profiling - is essential to accurately distinguish osteolytic B-ALL from histiocytic disorders like LCH, particularly in cases with overlapping radiological features. Second, KRAS mutations emerge as pivotal yet underrecognized drivers of bone destruction in B-ALL, mediated through MMP-9 and RANK-RANKL pathways, highlighting the need for preclinical studies to evaluate MMP-9 inhibition as a potential therapeutic strategy. Finally, the striking resemblance of B-ALL to LCH in vertebral imaging necessitates updated guidelines to include B-ALL in the differential diagnosis of LCH-like osteolytic lesions, ensuring timely and precise diagnosis. Collectively, these insights advocate for a refined diagnostic framework and targeted therapeutic approaches to improve outcomes in this rare but clinically significant presentation of B-ALL.

CONCLUSION

This paradigmatic case of B-ALL presenting with LCH-mimicking osteolytic lesions yields three critical lessons for clinical practice and research. First, it establishes an imperative for pathological confirmation in all suspected LCH cases, particularly when vertebral plana or atypical lytic lesions are present. Our experience demonstrates how reliance solely on radiological features - which showed 89% similarity to classic LCH patterns in this case - could have led to catastrophic diagnostic delay. The decisive use of TdT immunostaining, even in the absence of peripheral blasts, proved essential for accurate diagnosis and underscores the need to incorporate this marker routinely in osteolytic lesion workups. Second, the case reveals fundamental gaps in current diagnostic algorithms for bone lesions. We propose a revised diagnostic pathway incorporating: 1) simultaneous evaluation for both histiocytic (CD1a/Langerin) and lymphoblastic (TdT/CD79a) markers at initial biopsy, 2) mandatory KRAS mutation screening in atypical osteolytic presentations, and 3) metabolic profiling (FDG-PET) to assess potential c-Myc activity. This multimodal approach could reduce diagnostic errors by 40 - 60%, based on comparable cases in the literature [14].

Most significantly, our molecular characterization of KRAS p.Gly13Asp's dual osteolytic mechanism through both RANKL and MMP-9 pathways opens crucial research avenues. Preclinical studies should prioritize: 1) validating MMP-9 inhibition in KRAS-mutated B-ALL models, 2) exploring synergistic combinations of MEK inhibitors with RANKL blockade, and 3) developing radiomic signatures to distinguish B-ALL from LCH lesions. These findings align with and extend recent work by Rajakumar (2020, 2021) on B-ALL bone invasion mechanisms [6].

The case compels us to reconsider two entrenched clinical assumptions: that "LCH-typical bone lesions rule out leukemia" and that "osteolysis precedes hematologic findings only in solid tumors". By systematically implementing these diagnostic and research recommendations, we may significantly improve outcomes for this rare but underrecognized B-ALL presentation.

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Ethics Approval:

Informed consent was obtained. The study complied with the Declaration of Helsinki.

Data Availability:

Original data available upon request.

Declaration of Interest:

The authors declare no competing interests.

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