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Case Report

Atypical presentation of high-grade non-Hodgkin lymphoma in a child: A diagnostic challenge ☆,☆☆,★

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ABSTRACT

This case report describes an atypical presentation of high-grade Non-Hodgkin's Lymphoma (NHL) in a 10-year-old girl who presented to the emergency department with severe, unexplained flank pain and inability to walk, despite a lack of significant trauma history. Initial assessment revealed mild renal angle tenderness and a matted suprasternal lymph node, with laboratory results and preliminary imaging unremarkable. Persistent pain prompted advanced imaging, which identified a pathological spinal fracture and multiple masses consistent with aggressive NHL metastasis. Histopathological confirmation was achieved via lymph node biopsy. We highlight the diagnostic challenges posed by rare, atypical presentations of NHL in children, where symptoms may mimic benign conditions or minor trauma. Early suspicion and comprehensive diagnostic workup, including MRI and CT, were crucial for timely intervention. The patient was transferred to a pediatric oncology centre and achieved remission following chemotherapy. This report underscores the importance of maintaining a high index of suspicion for malignancy in children with unexplained pain or persistent symptoms, emphasizing the value of multidisciplinary collaboration and advanced imaging in early diagnosis.

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★ Ethical statement: All authors are accountable for the integrity of this work. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its amendments. Written informed consent was obtained from the patient's parent for publication of this case report and accompanying images. The report is sufficiently anonymized; ethical approval was not required for reporting a single case at our institution.

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Introduction

Non-Hodgkin's Lymphoma (NHL) represents a rare but significant malignancy in the pediatric population, accounting for 4% of all new cancers in the United Kingdom [1]. The typical pediatric presentation of NHL includes rapidly enlarging lymphadenopathy [2], systemic symptoms such as fever and weight loss, and sometimes mediastinal or abdominal masses [1]. However, where classic symptoms are absent or overshadowed by nonspecific complaints a considerable diagnostic challenge for clinicians occur, particularly in the fast-paced environment of emergency care. Vague symptoms such as persistent pain, fatigue, or impaired mobility may be mistakenly attributed to benign causes like minor trauma, musculoskeletal injury, or common infections. The complexity of pediatric pain perception [2,3], coupled with the frequent absence of classic red flag symptoms seen in adults, can further obscure the underlying pathology. This case report describes a 10-year-old girl who presented with severe, unexplained flank pain and an inability to walk, despite no history of significant trauma and unremarkable initial investigations. Her clinical course, characterized by subtle physical findings and persistent symptoms, ultimately led to the diagnosis of high-grade NHL with aggressive spinal metastasis. Through this case, we highlight the diagnostic challenges posed by atypical presentations of pediatric NHL and emphasize the need for vigilance, comprehensive assessment, and timely intervention to improve clinical outcomes in children with rare malignancies. In this context, careful attention to the child's verbal and nonverbal cues, as well as the concerns of caregivers, becomes paramount. Persistent expressions of pain, even after adequate analgesia, should prompt clinicians to consider more serious underlying conditions [2,3].

Case presentation

A previously well 10-year-old girl presented to the Emergency Department with an acute inability to ambulate beyond 3 steps. The onset of symptoms was traced to a minor incident 6 hours prior, during which the child jumped from a 0.5meters height while playing at a local park.

Thereafter, she had persistently reported right-sided flank pain, frequently expressing to her father, "dad, it still hurts", while localizing the discomfort predominantly at the flank. The pain was dull, nonradiating, 6/10 intensity, and relieved by rest. There were no associated fever, cough, chest pain, respiratory distress, urinary frequency, dysuria, incontinence, vomiting or bowel disturbance. There was no back pain, jaw swelling, facial swelling, history suggestive of constitutional symptoms such as weight loss or night sweats. Her developmental history, including antenatal, birth, and milestone achievements, were within normal limits. Immunisations were complete for age and nutrition unremarkable. There were no safeguarding concerns or notable family history of malignancy or chronic illness. Past medical history included a single admission for severe pneumonia; she was otherwise healthy and not on any regular medications. She had no known drug allergies. Her vital signs at triage were as follows: heart rate of 110 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 100/55 mmHg, temperature of 36.7°C, and oxygen saturation of 96% on room air. Initial assessment showed an alert, well-looking and interactive child with a patent airway, normal respiratory and cardiovascular examinations, and no neurological deficits. Cranial nerve function, gait, motor power, tone, reflexes, and sensation were all preserved. Abdominal examination revealed a soft, nondistended abdomen with no organomegaly or guarding. Pelvic and hip examinations were normal. She had right renal angle tenderness. In addition, no exact midline spinal tenderness or bony deformity, and no evidence of joint swelling or long bone tenderness were elicited during palpation. A 2 cm firm and matted suprasternal lymph node was palpated. The node was described by parent as an old and nonconcerning swelling for several months.

Differential diagnoses considered were muscular injury secondary to minor trauma, urinary tract infection, and vertebral fracture down the list. Urinalysis was positive for leukocytes, microscopic haematuria and nitrites, all suggestive of a urinary tract infection (UTI). A provisional diagnosis of UTI was considered, and antibiotics with adequate analgesia administered as per hospital protocol. However, her inability to weight bear after analgesia prompted re-evaluation and further escalation in management. Blood investigations including venous gas, full blood count, renal and liver panels, C-reactive protein, and clotting profile were all within normal range. Interferon Gamma Release Assays (IGRA) and viral screens were negative. Despite optimal analgesia, the child's pain worsened, creating a diagnostic dilemma. Focused thoraco-lumbar X-rays showed no convincing acute bony anomaly in the vertebrae.

Due to no response to opioids, an MRI spine was performed (Figs. 1–6), revealing a pathological fracture at T7 and T8, with radiological features suggestive of spinal metastasis. This finding triggered an urgent pediatric multidisciplinary team (MDT) discussion. A CT scan of the chest, abdomen, and pelvis revealed a bulky posterior mediastinal mass (Fig. 7). This was concerning for a lymphoproliferative malignancy. A neck ultrasound (Figs. 8 and 9) showed several shallow-seated left lymph nodes displaying varying degrees of peripheral hypervascularity, 1 measuring 35 mm x 20 mm and amenable for percutaneous biopsy. Cerebrospinal fluid analysis was unremarkable with no lymphoma cells detected. Microscopic examination of excised cervical node revealed infiltrate of large cells with irregular nuclei, vesicular chromatin, prominent nucleoli and large cytoplasm. Cells were strongly CD20 and CD79a positive, CD3 and CD10 negative, Ki-67 positive with assessed proliferation index of 83% and no evidence of MYC re-

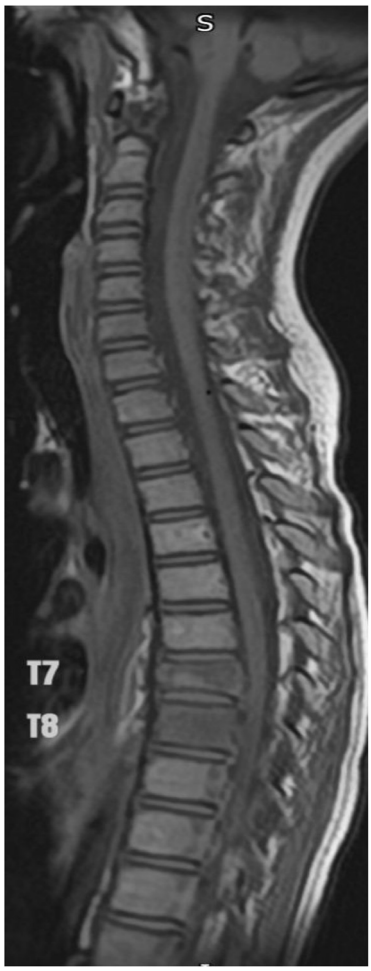

Fig. 1 – Sagittal MRI spine T1 sequence. Contrast-enhanced MRI image with T7 and T8 vertebral bodies exhibiting low signal intensity in keeping with pathological fractures.

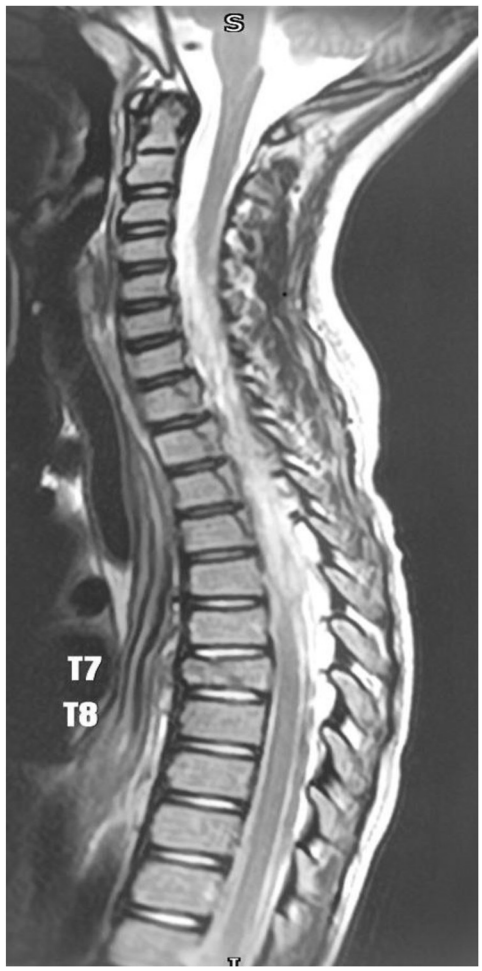

Fig. 2 – Sagittal MRI spine T2 sequence. T2 MRI image without fat suppression demonstrating high signal intensity within the T7 and T8 vertebral bodies, suggestive of acute bone marrow edema and possible marrow infiltration.

arrangement. Based on these findings and clinical staging (involvement of lymph nodes above and below the diaphragm), the diagnosis was confirmed as aggressive NHL, stage 3 (Ann Arbor classification). Overall histo-pathology consistent with diffuse large cell lymphoma (DLBCL), Activated B-cell (ABC) subtype.

The child was transferred to a tertiary pediatric oncology unit where a right-sided hickman line was inserted and commenced on a COP regimen (Cyclophosphamide, Oncovin, and Prednisolone) as per standard pediatric NHL protocols. Clinical improvement was rapid following chemotherapy. A repeat surveillance CT scan (Fig. 10) 4weeks postfirst chemotherapy cycle demonstrated near-complete radiological resolution of the mediastinal confluent mass. Further cycles and courses of COP regimen were established based on local guidelines with close outpatient follow up with pediatrics haemato-oncologist, spinal surgeons and pain team. Interval orthopaedic corset was applied to conservatively address pain and posture as appropriate. There was no development of spinal cord compression, gait abnormality or paralysis.

Discussion

Childhood NHL is a serious pediatric malignancy, with cryptic presentations that can pose considerable diagnostic challenges [1,2]. While NHL is uncommon in children, it remains the seventh most common cancer in the UK with 44% in females and 56% in males [1]. In the case described a child who presented with flank pain and an eventual compression fracture on imaging, which led to the diagnosis of Stage 3 NHL. This case highlights the critical importance of maintaining a broad differential diagnosis, even when initial symptoms appear minor or are associated with low-impact trauma, as in this instance following a negligible jump.

Children's perception and expression of pain are often nuanced and may not always correspond accurately to the underlying pathology or site [3]. Researchers have explored various synaesthetic descriptors, facial action codes and pain scales to understand how children respond to and describe noxious stimuli to guide appropriate diagnosis of the cause

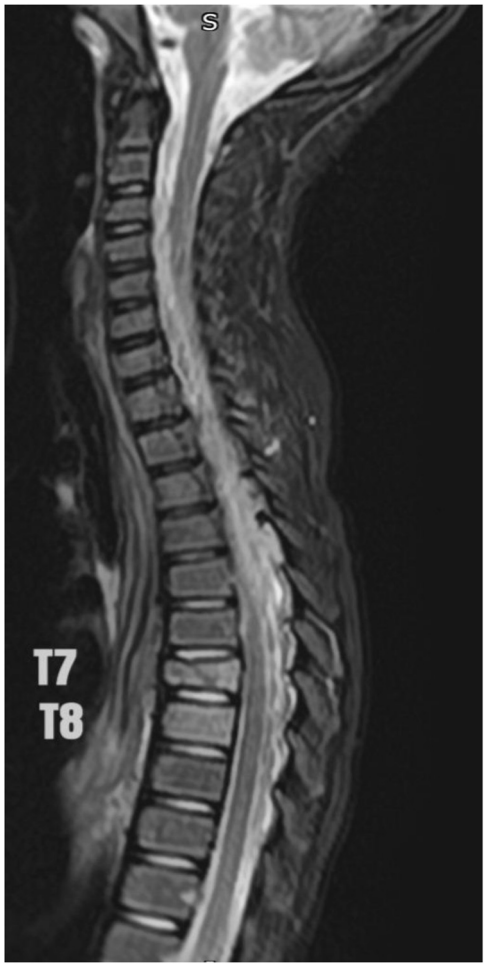

Fig. 3 – MRI spine STIR sequence. STIR MRI image with fat suppression showing markedly increased signal intensity at the T7 and T8 vertebral bodies, consistent with acute bone marrow edema and possible marrow infiltration.

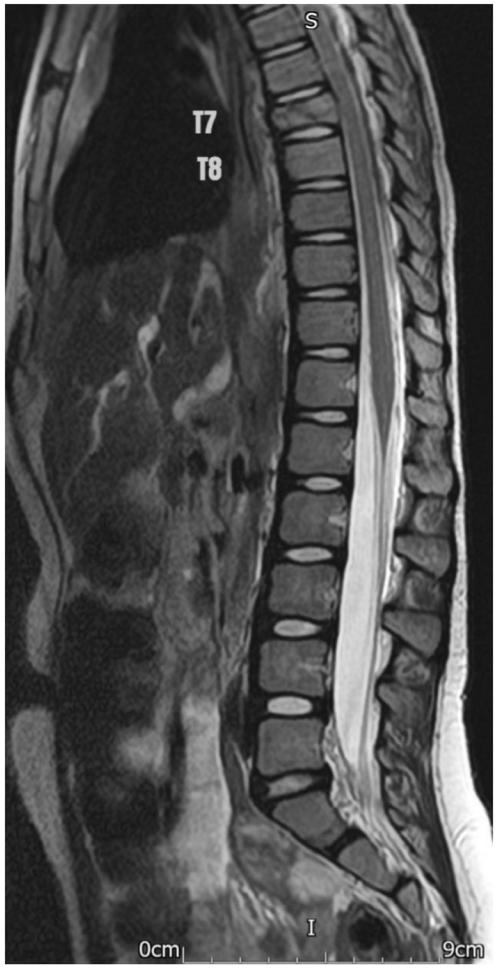

Fig. 4 – MRI sagittal T1-weighted sequence of the thoracic and lumbar spine. At the T7 vertebral level, there is loss of vertebral body height with disruption of the superior endplate, consistent with a compression fracture. The affected T7 and T8 vertebral bodies show reduced T1 signal intensity compared with adjacent levels, suggesting marrow edema and an acute rather than a chronic deformity. The posterior vertebral wall appears intact, and there is no significant retropulsion or spinal cord compression visible on this sequence.

and direct treatment [3,4]. Similarly, pain in this child was assessed by facial expressions and numeric pain rating scale. Ultimately, a consistently high index of suspicion is essential in identifying occult but serious disease processes, particularly in the pediatric population when pain is persistent [2]. Data gathering on such NHL occurrences within pediatric population may be challenging owing to the relative rarity of the disease and high incidence of atypical presentation leading to misdiagnosis. Britto et al. [5] systematic review examined the landscape of pediatric NHL in Bangladesh, highlighting gaps in epidemiological data and standardised treatment protocols.

The patient excised cervical lymph node appeared effaced and demonstrated diffuse proliferation of large, atypical B lymphoid cells that replaced normal tissue architecture. The cells had abundant cytoplasm with prominent mitotic figures in keeping with DLBCL (ABC subtype) NHL. Microscopically, NHL is characterized by the conspicuous absence of both Reed-Sternberg cells and starr-sky cells pattern, which distinguishes it from Hodgkin's lymphoma and Burkitt lymphoma respectively. Pediatric presentations of NHL often involve multiple organ systems and may include lymphadenopathy, mediastinal or retroperitoneal masses, and systemic features such as fever, night sweats, weight loss, pruritus, or fatigue. However, these symptoms may be subtle or absent in early stages, increasing the risk of diagnostic errors [1,2,5], a major worry in the case analyzed. Taneja et al. [6] reported precursor T-lymphoblastic NHL in a child presenting vaguely with persistent cough. The diagnostic challenge and aggressive management were relatable to our case report; however, it was a T cell NHL variant not DLBCL we reported. Moreso, there was absent of abdominal symptoms in this case submission unlike the review by Khan et al. [7]. The authors addressed diagnostic ambiguities between splenic NHL and abscesses in pediatric patients highlighting the fact intra-abdominal NHL disease could mimic surgical other nononcological emergen-

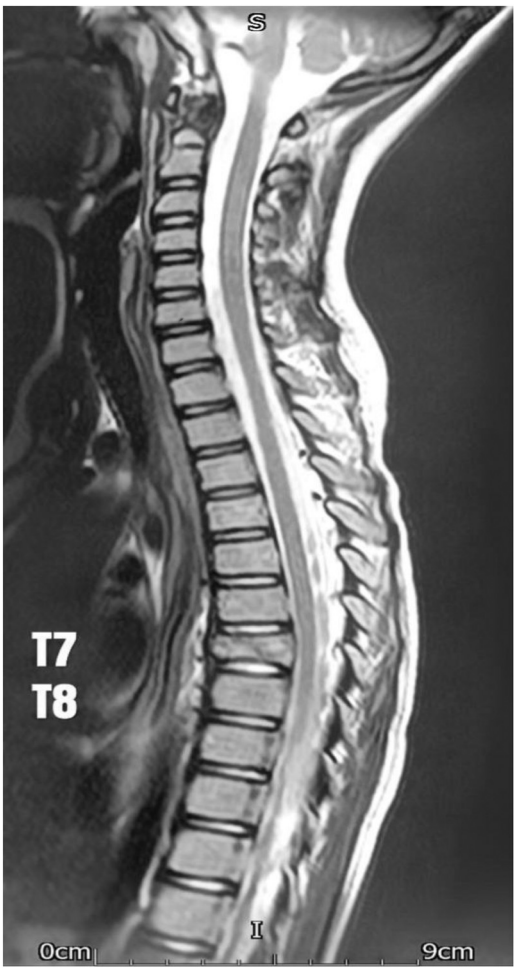

Fig. 5 – MRI sagittal T2 sequence. This sagittal T2 MRI sequence of the thoracic spine demonstrates diffuse high signal intensity within the T7 vertebral body, consistent with bone marrow edema secondary to an acute compression fracture. The superior endplate of T7 is depressed, indicating structural collapse. No evidence of retropulsion or significant spinal canal compromise.

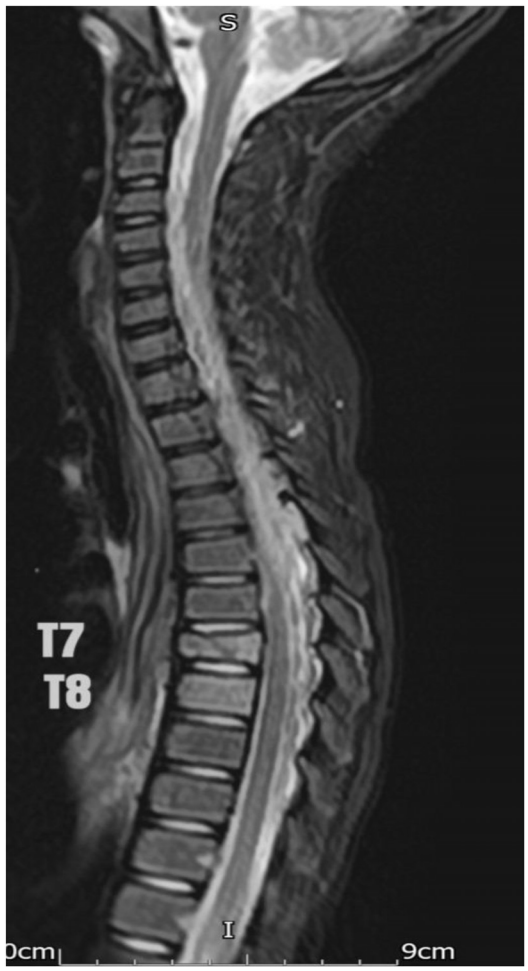

Fig. 6 – MRI spine STIR sequence. In this STIR sequence there is uniform suppression of fat with The T7 and T8 vertebral bodies showing focal marked hyperintensity intensity, coherent with bone marrow edema related to an acute compression fracture. The spinal cord and canal appear intact, with no evidence of significant retropulsion or compressive pathology.

cies [7]. A systematic review by Saatci et al. [8] consolidated presentation and staging data of B–cell NHL in under-19s. This provided valuable insights that patients often present with advanced stage disease and diagnostic delays. These findings accentuate the need for early recognition protocols across pediatric services regardless of their clinical presentations. In this clinical report, prompt escalation of care and advanced imagings, were pivotal in uncovering the diagnosis, particularly as the patient's flank pain became progressively debilitating despite optimal analgesia, unremarkable initial blood tests and X-rays. The absence of neurological signs or constitutional symptoms early in the disease should not dissuade clinicians from considering malignancy when the clinical course is atypical or pain is persistent and function-limiting [8,9]. As with our patient, initial presentations in some reported scenarios lacked overt systemic red flags but were later re-focused following escalation to imaging and MDT review [6,7,9,10]. In all these cases, as in this indexed 1, early consideration of malignancy in the differentials especially when symptoms persist despite conservative management was essential for timely diagnosis and favorable outcomes.

The patient reported herein underwent COP chemotherapy (as per local hospital guidelines) and follow-up imaging after the initial cycle demonstrated near-complete resolution of mediastinal, retroperitoneal, and supraclavicular disease, with the patient entering remission. Beyond traditional chemotherapy and stem cell transplants, there's a growing focus on targeted drug therapies and monoclonal antibodies (mAbs). In a multinational randomized trial led by Burke et al. [11], adding rituximab to standard chemotherapy improved 3–year event-free survival from 82% to 94% in high–risk B–cell NHL. Though associated with transient hypogammaglobulinemia, this marked the most significant advance in 3 decades in pediatric NHL treatment and has influenced

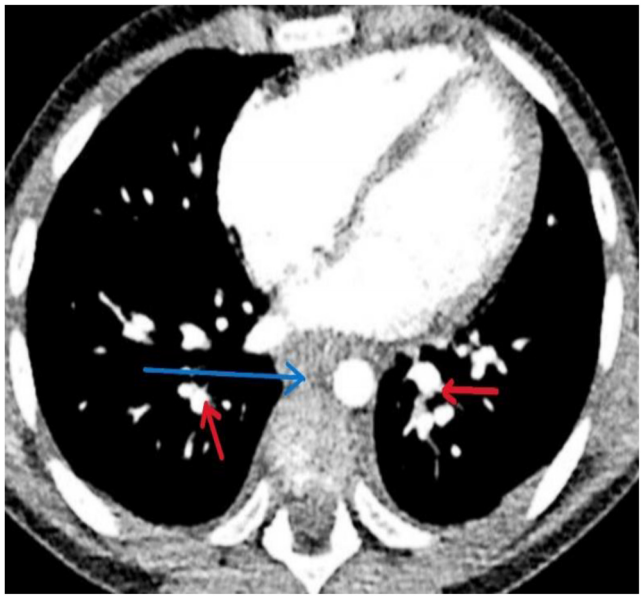

Fig. 7 – CT image prechemotherapy. Axial contrast-enhanced CT image of the chest reveals a large, confluent nodal mass located in the posterior mediastinum (blue arrow). Additionally, multiple distinct lung nodules are observed bilaterally within the pulmonary parenchyma (red arrows).

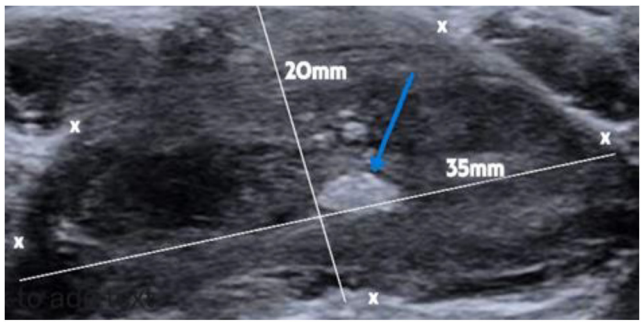

Fig. 8 – Ultrasound image of effaced cervical lymph node. Gray scale sonogram showing 35mm X 20mm lymph node with ill-defined capsule (marked x circumferentially) and hyperechoic centre (blue arrow).

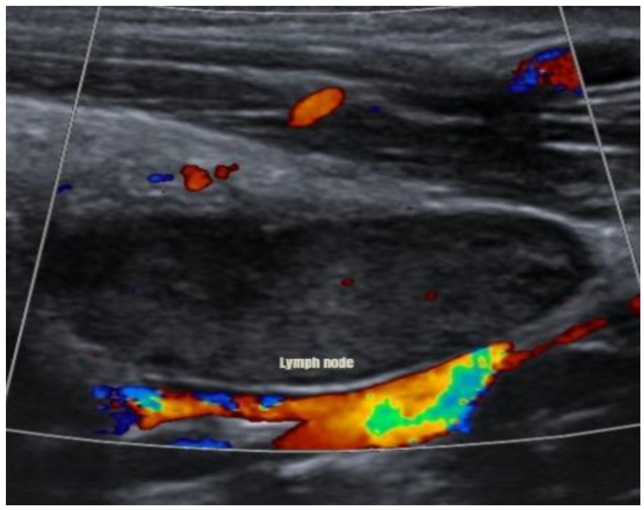

Fig. 9 – Doppler scan of a visualized cervical lymph node. Doppler ultrasound of a suprasternal lymph node demonstrated no internal vascular flow; however, there was marked peripheral hypervascularity surrounding the node.

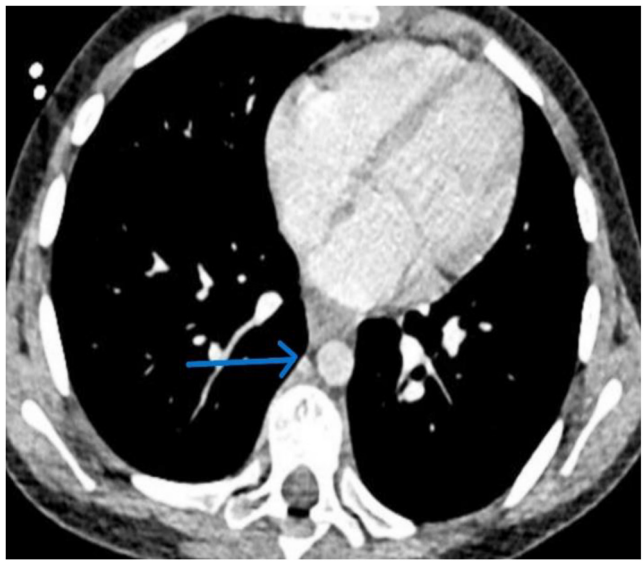

Fig. 10 – CT image postchemotherapy. This follow-up CT image demonstrates a significant reduction in the size of the previously noted confluent posterior mediastinal mass (blue arrow). Findings collectively indicate a favorable response to therapy for the underlying malignancy.

few guidelines. Newer generations of mAbs, including bispecific antibodies, are also being explored, with some like blinatumomab showing promise for relapsed or refractory B-NHL [12]. Antibody-Drug Conjugates (such as Brentuximab Vedotin), CAR T-cell therapy, and various targeted therapies like ALK inhibitors (Crizotinib, Ceritinib) and BCL-2 inhibitors (Venetoclax) have shown good potentials in NHL treatment [13,14]. These newer approaches are paramount for improving outcomes, especially in relapsed or refractory cases. Vigilance, holistic assessment, and appropriate use of imaging [15] and multidisciplinary specialists' input are essential tools in recognising serious underlying pathology early and improving prognoses in pediatric cancer patients [8,9]. The scenario thereby contributes to the body of clinical literature on varied NHL presentations among children.

Conclusions

This case highlights the diagnostic challenges posed by atypical presentations of high-grade Non-Hodgkin's Lymphoma in children. The patient's persistent, unexplained flank pain and

impaired mobility, in the absence of classic systemic symptoms or significant trauma, initially masked the underlying malignancy. Careful attention to the child's verbal and nonverbal cues, as well as the concerns of caregivers, was crucial in prompting further investigation. Advanced imaging and multidisciplinary collaboration are crucial for correct diagnosis and timely initiation of effective chemotherapy. This report underscores the importance of maintaining a high index of suspicion for malignancy in pediatric patients with persistent or unexplained symptoms, even when initial findings suggest benign conditions. Clinicians should remain vigilant, utilize comprehensive diagnostic approaches, and actively involve both the patient and their caregivers in the assessment process to ensure that serious underlying conditions are not overlooked.

Patient consent

Written parental consent was duly obtained for the materials about this patient to be used anonymously for publication purpose.

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