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Paediatric Castleman Disease: Diagnostic Challenges and Lessons from Two Rare Cases

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ABSTRACT

Castleman disease (CD) is a rare and heterogeneous lymphoproliferative disorder that affects both children and adults, typically presenting in young to middle-aged individuals. It is classified clinically as unicentric Castleman disease (UCD), which typically affects a single lymph node region and is often of the hyaline vascular subtype, or multicentric Castleman disease (MCD), which involves multiple lymph node stations and systemic inflammation. MCD includes HHV-8–associated MCD and idiopathic MCD (iMCD), each with distinct diagnostic and therapeutic profiles. CD can mimic various malignant, infectious, and autoimmune diseases, leading to frequent diagnostic challenges. Although paediatric cases are uncommon, they often exhibit overlapping clinical and histological features, necessitating a high index of suspicion for accurate diagnosis and management. Two rare paediatric cases of Castleman disease are reported, involving a 7-year-old and a 9-year-old male, each presenting with atypical symptoms and complex clinical profiles. The first case presented with progressive respiratory distress, cachexia, generalized lymphadenopathy, and a mediastinal mass initially suspected to be lymphoma. Although histopathology demonstrated hyaline vascular Castleman disease—a subtype typically seen in unicentric disease—the extent of lymphadenopathy and systemic compromise indicated a multicentric clinical behavior. Histopathology revealed hyaline vascular Castleman disease. The second case presented with prolonged fever, cough, pleural effusion, hepatosplenomegaly, nephropathy, and cardiac dysfunction. These widespread systemic abnormalities are more suggestive of multicentric Castleman disease (MCD), despite the hyaline vascular histologic findings. Extensive investigations excluded infectious and malignant causes, and lymph node biopsy confirmed hyaline vascular Castleman disease. Both cases required multidisciplinary evaluation and were subsequently referred for specialized tertiary management. Castleman disease, though rare in children, should be considered in cases of persistent lymphadenopathy and systemic illness unresponsive to conventional therapy. Early biopsy and histopathological confirmation remain essential for diagnosis, while timely referral and multidisciplinary management optimize outcomes. Increased awareness, improved diagnostic access, and expanded availability of immunomodulatory therapy are critical to improving prognosis in paediatric Castleman disease.

Keywords: Castleman disease, hyaline vascular type, paediatric lymphoproliferative disorder, lymphadenopathy, histopathology.

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INTRODUCTION

Castleman disease (CD) is a rare lymphoproliferative disorder affecting both children and adults, more commonly young to middle-aged adults.[1] It is classified based on the number of lymph node regions involved and histopathology: Unicentric CD (UCD) affects a single node, usually the hyaline vascular type, while Multicentric CD (MCD) involves multiple nodes and systemic symptoms, subdivided into HHV-8–associated and idiopathic (iMCD) forms.[2] Histologically, CD is divided into hyaline vascular (less aggressive, with "onion-skin" lymphocytes) and plasma cell types (systemic symptoms and multi-organ involvement).[3] Despite its rarity, CD holds significant clinical relevance because it can mimic malignant, infectious, and autoimmune diseases, often leading to diagnostic challenges.[4] Given its ability to resemble other pathological entities, maintaining a high index of suspicion is essential. Early recognition is crucial, as management strategies differ markedly between unicentric CD, which is typically curable by surgical excision, and multicentric CD, which often requires immunotherapy or antiviral treatment. [5]

First described by Benjamin Castleman in 1954, the disease was initially identified as a localized mediastinal lymph node enlargement characterized by numerous lymphoid follicles with germinal center involution, prominent capillary proliferation, and both follicular and interfollicular endothelial hyperplasia.[6] Castleman disease represents a heterogeneous group of disorders that vary widely in clinical presentation, histopathological features, and systemic involvement.[7] It most commonly presents in young adults and shows no clear predilection for sex or race.[8] Although rare in children, pediatric cases can occur, often presenting with systemic features such as fever, weight loss, fatigue, anemia, thrombocytosis, hepatosplenomegaly, lymphadenopathy, and pleural effusions.[9] Diagnosis requires a combination of clinical evaluation, imaging studies, and lymph node biopsy, which determines the histopathological subtype.[10] Pediatric cases may present clinically like idiopathic multicentric Castleman disease (iMCD) but histologically show hyaline vascular features, suggesting a possible mixed-type disease.[11]

Two rare cases of Castleman disease are presented in a 7-year-old and a 9-year-old child, both exhibiting atypical clinical manifestations that mimicked a broad spectrum of other diseases. Each case demonstrated distinct clinical and pathological profiles, highlighting the diagnostic complexity of the condition and the essential role of multidisciplinary evaluation in establishing an accurate diagnosis and guiding optimal patient management. The cases underscore the importance of maintaining a high index of suspicion, as well as the need for early recognition and prompt treatment to improve clinical outcomes.

To address diagnostic completeness, additional laboratory parameters crucial in distinguishing Castleman disease phenotypes were reviewed. Inflammatory markers including CRP and ESR were elevated in both children, supporting a systemic inflammatory process. Lactate dehydrogenase (LDH) levels were mildly elevated, raising suspicion for lymphoproliferative disorders. Renal indices (urea, creatinine) and hepatic enzymes (ALT, AST) were assessed, given the multi-organ involvement. IL-6 assay—although not available locally—is a key marker in Castleman disease and would have strengthened diagnostic classification, particularly for confirming idiopathic MCD.

Case 1

A 7-year-old male was admitted with a two-month history of reduced appetite and progressive weight loss, a three-week history of non-paroxysmal productive cough, and a two-week history of progressively worsening dyspnea. He had received treatment in two different hospitals prior to presentation without clinical improvement. On examination, he was acutely ill-looking and in severe respiratory distress, exhibiting flaring of the alae nasi, subcostal and intercostal retractions, and grunting respiration. He was febrile (temperature: 38°C), pale, and hypoxemic with an oxygen saturation (SpO_2) of 84% on room air. Capillary refill time was prolonged (>2 seconds). The patient appeared cachectic with prominent ribs and bony outlines, and visible engorged veins over the face, neck, and upper limbs. Generalized lymphadenopathy was noted, along with tender hepatomegaly measuring 6 cm below the right costal margin. Scarification marks were observed over the left chest wall and lumbar region. The anterior chest wall appeared bulged, with a dull percussion note and markedly reduced air entry over the right hemithorax. The patient's weight was 18.5 kg.

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The admitting diagnosis was superior vena cava (SVC) syndrome secondary to non-Hodgkin lymphoma. Full blood count demonstrated anemia and thrombocytopenia with derangement of two cell lines: packed cell volume (PCV) 22%, and platelet count (PLT) 65 × 10^9/L, however, the white blood cell count (WBC) 8,000/µL was normal. There was leukocytosis with marked lymphocytosis. Retroviral screening (RVS) was negative, and sputum GeneXpert assay was non-reactive for Mycobacterium tuberculosis. Chest radiography revealed a mediastinal mass extending into both lung fields, with associated right-sided pulmonary haziness. The patient underwent a lymph node biopsy in the cardiothoracic unit (CTU), which was complicated by significant intraoperative bleeding, necessitating transfusion with fresh whole blood. He was subsequently commenced on intravenous vitamin K, ondansetron, and frusemide.

Histopathological analysis of the lymph node biopsy revealed proliferation of T-immunoblasts with altered follicular architecture. There was marked hyalinization around blood vessels, with vascular proliferation within interfollicular areas and evidence of extra-nodular spread. The overall histopathologic features were most consistent with Castleman disease, hyaline vascular variant. The patient was subsequently referred to a tertiary hospital for specialized management.

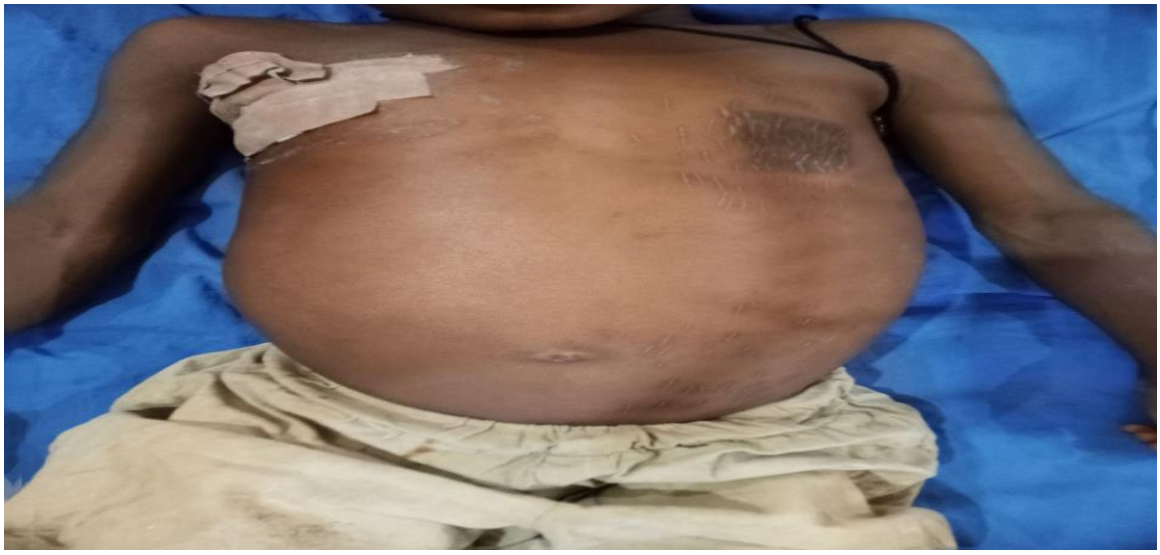

Fig 1: A child with Castleman disease.

Case 2

A 9-year-old male presented with a two-month history of high-grade intermittent fever, more pronounced at night, and a one-month history of a distressing nocturnal cough productive of whitish sputum, associated chest pain exacerbated by coughing, vomiting, and progressive weight loss. There was also a two-week history of tachypnea and bone pain. On examination, the patient was lethargic and in respiratory distress, with a respiratory rate of 38 breaths per minute and flaring of the alae nasi. He was febrile, pale, and exhibited bilateral digital clubbing (Grade 3). Multiple lymphadenopathies were noted, and the hair appeared brittle. The precordium was active, with visible scarification marks. The apex beat was displaced to the 5th left intercostal space, lateral to the midclavicular line. There was a mild anterior chest wall bulge, reduced tactile fremitus, dull percussion notes, and markedly reduced air entry over the left mid and lower lung zones. Coarse crepitations were audible bilaterally. The liver was palpable 4 cm below the right costal margin and tender, while the spleen was not enlarged.

Erythrocyte sedimentation rate (ESR) was elevated at 53 mm in the first hour. GeneXpert assays performed on sputum, stool, and pleural fluid samples were all negative for Mycobacterium tuberculosis. Hematological investigations revealed a packed cell volume (PCV) of 26%, hemoglobin concentration of 8.8 g/dL, platelet count of 513 × 10^9/L, and total white blood cell count of 6.3 × 10^9/L, with a differential count of neutrophils 57%, lymphocytes 40%, and monocytes 3%. Malaria parasite test was positive (++). Two weeks after initial discharge, the patient was readmitted with complaints of low-grade fever, bilateral leg swelling, facial puffiness, progressive dyspnea, generalized pallor, cough, passage of cola-colored urine, and reduced urine output.

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On presentation, the patient was in severe respiratory distress, with flaring of the alae nasi, intercostal and subcostal retractions. He was markedly pale (++), febrile, and exhibited facial puffiness as well as bilateral pitting pedal edema extending to the sacral region. The blood pressure was 130/90 mmHg (above the 95th percentile for age). The apex beat was displaced to the 6th left intercostal space, lateral to the midclavicular line, and a gallop rhythm was audible on auscultation. The liver and spleen were both enlarged and tender. Ascites was demonstrated by shifting dullness, and there was left renal angle tenderness with noticeable abdominal distension. Jugular venous pressure (JVP) was elevated at 6 cm. Malaria parasite test remained positive, and

A provisional diagnosis of anaemic heart failure secondary to nephropathy, with possible left-sided pyelonephritis, was made. Urinalysis revealed moderate leukocyturia, marked proteinuria (+++), large hematuria, and increased urobilinogen (+++), with a specific gravity of 1.025 and urine flow rate of 1–5 mL/kg/hr. Serum electrolytes were within normal limits. Testing for human herpesvirus 8 (HHV-8) was negative. Peripheral blood film showed no blasts. Retroviral screening was negative. Total serum protein was 5.8 g/dL, albumin 3.2 g/dL, and spot urine protein-to-creatinine ratio was elevated at 300. Mantoux test was non-reactive. Fasting lipid profile was within normal limits, and estimated glomerular filtration rate (eGFR) was 89.9 mL/min/1.73 m². Chest radiograph demonstrated left-sided pleural effusion and cardiomegaly of uncertain etiology.

Abdominal ultrasonography demonstrated increased parenchymal echogenicity with reduced corticomedullary differentiation. Two-dimensional echocardiography revealed features consistent with right ventricular dysfunction. A chest tube was inserted, draining 85 mL of serosanguinous fluid. Microbiological culture and sensitivity of the pleural fluid revealed numerous red blood cells and moderate growth of Staphylococcus species, which were sensitive to streptomycin, gentamicin, and ceftriaxone. Histological examination of a right axillary lymph node demonstrated matted lymph nodes measuring 0.5 cm and 1.5 cm in diameter. Microscopy revealed endothelial and vascular proliferation with hyalinization of vessel walls, atretic and hyalinized germinal centers, and lymphocytes arranged in concentric layers (“onion-skin” appearance). Scattered plasma cells and immunoblasts were also present. Based on these findings, a definitive diagnosis of Castleman disease (angiofollicular hyperplasia), hyaline vascular type was made. The patient was subsequently referred to a specialized tertiary institution for further management.

DISCUSSION

Castleman disease (CD) represents a heterogeneous group of rare, non-neoplastic lymphoproliferative disorders that pose significant diagnostic and therapeutic challenges due to their variable clinical manifestations and overlap with malignant, infectious, and autoimmune conditions.[1] Although the disease predominantly affects young to middle-aged adults, paediatric presentations, as seen in these two cases, are uncommon and frequently misdiagnosed due to their atypical and multisystem involvement.[13] Both patients in this report presented with constitutional symptoms such as fever, weight loss, and respiratory distress—features commonly associated with infectious or malignant etiologies.[14] The first case initially mimicked a mediastinal malignancy with superior vena cava (SVC) syndrome, while the second exhibited features suggestive of nephropathy, cardiac dysfunction, and systemic inflammation.[15] Such presentations highlight the protean nature of Castleman disease and its potential to masquerade as other severe paediatric conditions.[2]

Histopathological evaluation remains the cornerstone of diagnosis.[12] In both cases, the lymph node biopsies demonstrated classic features of the hyaline vascular subtype, including vascular proliferation, hyalinization of vessel walls, and the characteristic “onion-skin” arrangement of lymphocytes around atretic germinal centers.[17] Interestingly, both patients exhibited systemic features more consistent with multicentric Castleman disease (MCD), despite the histological diagnosis of the hyaline vascular (typically unicentric) variant. This discordance, increasingly recognized in paediatric CD, suggests that children may present with hybrid patterns where clinical behavior aligns with iMCD while histology appears hyaline vascular. Such mixed phenotypes further complicate diagnosis and highlight the need for comprehensive clinical-pathologic correlation.[9] This overlap suggests that paediatric cases may not always conform to classical adult subtypes, indicating possible mixed or transitional disease patterns.[18] The negative results for HHV-8 and HIV further support the diagnosis of idiopathic multicentric Castleman disease (iMCD), a form whose aetiology remains unclear but is hypothesized to involve dysregulated cytokine production, particularly interleukin-6 (IL-6).[19] Elevated IL-6 levels are known to drive

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many of the systemic manifestations seen in MCD, including anaemia, thrombocytosis, hepatosplenomegaly, and inflammatory responses—all present to varying degrees in the two patients.[4]

Management strategies differ based on disease classification.[3] Unicentric CD (UCD) typically responds well to complete surgical excision, while MCD requires systemic therapy, such as anti-IL-6 monoclonal antibodies (siltuximab or tocilizumab), corticosteroids, or antiviral therapy in HHV-8–associated cases.[12] Unfortunately, access to advanced immunotherapies remains limited in many low-resource settings, leading to delayed treatment and poorer outcomes.[15] Early referral to tertiary centres, as undertaken in these cases, is therefore crucial for accurate diagnosis and appropriate management.[13] These cases also underscore the importance of a multidisciplinary approach, involving paediatricians, pathologists, radiologists, and haematologists, in evaluating complex lymphoproliferative disorders. The integration of clinical, radiological, and histopathological data was essential to avoid misclassification and guide patient care effectively.

CONCLUSION

Castleman disease remains a rare but important differential diagnosis in children presenting with generalized lymphadenopathy, constitutional symptoms, and multisystem involvement. The presented cases demonstrate the wide clinical spectrum and diagnostic difficulty associated with this entity, particularly in pediatric populations where it may mimic malignancy or severe infection. Recognition of the hyaline vascular variant with systemic manifestations broadens the understanding of CD's presentation in children and emphasizes the potential for mixed subtypes. Early histopathological confirmation, coupled with prompt referral to specialized centers, is critical for guiding appropriate treatment and improving prognosis. Heightened awareness among clinicians is necessary to prevent diagnostic delays and ensure timely, targeted management.

RECOMMENDATIONS

The article emphasizes the critical importance of early recognition and comprehensive evaluation in the diagnosis and management of paediatric Castleman disease. Clinicians are urged to maintain a high index of suspicion in children presenting with unexplained lymphadenopathy, systemic symptoms, or organomegaly, particularly when infectious and malignant causes have been excluded. Accurate diagnosis relies on a multidisciplinary approach that integrates clinical findings with imaging, laboratory investigations, and, most importantly, histopathological confirmation through lymph node biopsy—the definitive diagnostic tool for Castleman disease. The article further highlights the need for efficient referral systems to tertiary centres equipped with specialized histopathological and immunological diagnostic facilities to facilitate timely and accurate diagnosis. It also underscores the necessity of improving access to IL-6–targeted and other advanced immunomodulatory therapies, especially in low- and middle-income countries where treatment options remain limited. Finally, it calls for ongoing research into the molecular and immunopathogenic mechanisms of paediatric Castleman disease, alongside long-term surveillance studies, to enhance understanding, refine treatment protocols, and ultimately improve patient outcomes.

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Disclosures and declarations

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