INTRODUCTION

Angiofollicular lymph node hyperplasia, known as Castleman disease (CD), is a group of histopathologically similar, non-clonal, lymphoproliferative disorders. CD is sub-typed as unicentric (UCD) or multicentric (MCD), depending on the number of lymph node regions involved and presence of systemic inflammatory symptoms. In MCD patients, testing for HHV-8 (a known association) needs to be performed and if negative, disease can be further classified as POEMS-associated MCD, TAFRO syndrome, or idiopathic MCD/not otherwise specified (iMCD/MCD-NOS).1,2 Given that CD largely affects the adult population, little is known regarding the clinical course in children.2,3 With informed consent obtained and documented, we present a pediatric case of Castleman disease.

CASE DESCRIPTION

A 12-year-old male presented with three weeks of persistent abdominal pain, emesis, and fever. Diagnostic testing revealed multi-organ system involvement and the diagnosis was ultimately made with tissue biopsy. Marked disease regression occurred after high-dose steroids and continued interleukin-6 inhibition.
abdominal tenderness, and distention, but clear lung fields and no cardiac murmur. Initial laboratory studies identified anemia (7.1 g/dL), thrombocytopenia (20x10^3/μL), neutrophilia (83%) without leukocytosis (11.3 x10^3/μL), hypocalcemia (5.8 mg/dL), elevated serum creatinine (1.52 mg/dL), and elevated inflammatory markers (erythrocyte sedimentation rate (ESR) 75 mm/hr, c-reactive protein (CRP) 31 mg/L). Abdominal computed tomography (CT) showed a 3.5 cm left adrenal mass, hepatosplenomegaly, colonic wall thickening, solitary lung nodule, and small pericardial effusion.

Empiric antibiotics were initiated but testing for bacterial, viral, and fungal infections, including HHV-8, remained negative. Laboratory results showed severe hypothyroidism with undetectable free thyroxine and negative thyroid antibody panel, arguing against a diagnosis of central hypothyroidism. Parathyroid hormone was elevated (79 pg/dL, RR 10–65 pg/dL), precluding hypoparathyroidism as the cause for hypocalcemia. He required titration of levothyroxine and aggressive supplementation with calcium gluconate injections, calcium carbonate, and calcitriol for refractory hypocalcemia.

Delirium improved with control of fever and correction of hypocalcemia and hypothyroidism. Throughout his admission, he developed hypertension and a pericardial effusion. Multiple antihypertensive medications (enalapril, labetalol, nifedipine, furosemide, and isradipine) were required to control hypertension. A renal biopsy was performed to evaluate proteinuria and hematuria but showed no significant abnormalities. Additional laboratory testing identified hyperuricemia (15 mg/dL, RR 2–7 mg/dL) and elevated lactate dehydrogenase (1437 U/L, RR 550–900 U/L). Hyperuricemia resolved after rasburicase and allopurinol treatment. Abdominal magnetic resonance imaging (MRI) showed a cystic, hemorrhagic adrenal lesion (Figure 1).

In addition to persistent thrombocytopenia and microcytic, hypochromic anemia, he also had prolonged prothrombin time (17.1 seconds) with normal activated partial thromboplastin time (31 seconds) and elevations in fibrinogen (864 mg/dL, RR 170–410 mg/dL), d-dimer (14.3 μg/mL, RR <0.5 μg/mL), and immature platelet fraction (16%, RR 1.1–8.5%). Peripheral smear showed spherocytes, polychromasia, schistocytes, and normal neutrophils. Peripheral blood flow cytometry showed no signs

![Image](image1.png)

**FIGURE 1** Initial abdominal and pelvic MRI. (A) Splenomegaly present with craniocaudal length of 14.3 cm and left adrenal gland with presence of a circumscribed lesion without additionally discerning features. (B) patchy confluent and geographic peripheral segmental T2 dark hypo-enhancing regions typical for splenic infarcts without discrete splenic mass. (C) Mildly enlarged lymph nodes present throughout abdomen most notably in the pelvis porta hepatis. (D) Left pelvic sidewall lymph node. (E) Left external iliac chain lymph node. Radiographic interpretation credit: Dr. Adam Bobbey
of myeloid neoplasm or lymphoma. Bone marrow biopsy demonstrated a hypercellular marrow (80–90%) with mild erythroid and megakaryocytic hyperplasia. These findings were largely attributed to reactive and regenerative responses to the anemia and thrombocytopenia but with slight concern for hemolytic anemia. ADAMTS13 activity was decreased (52% then 29%, RR >68%) with a negative ADAMTS13 antibody inhibitory titer (<0.5), inconsistent with thrombotic thrombocytopenic purpura. Blood product transfusions were given as needed for support.

Investigation for autoimmune disease identified a low positive antinuclear antibody (1:40), mildly positive anticyclic citrullinated peptide (anti-CCP) antibody, and mild hypocomplementemia, with negative testing for anti-neutrophil cytoplasmic antibody (ANCA) and cryoglobulins. Testing was also negative for antibodies to myeloperoxidase, proteinase 3, c, thidid, Sjögren’s syndrome-related antigen A and B, Smith, and ribonuclear protein. Notable elevations of soluble interleukin-2 (IL-2) receptor assay/soluble CD25 (2,029 U/mL, RR 137–838 U/mL), soluble IL-2 receptor-alpha (6500 pg/mL, RR 622–1619 pg/mL), ferritin (560 ng/mL, RR 7–142 ng/mL), and vascular endothelial growth factor (98 pg/mL, RR 9–86 pg/mL) were discovered with a normal serum interleukin-6 (IL-6, RR <5 pg/mL). Given these elevations in conjunction with evidence of fever, splenomegaly, pancytopenia, and hypocomplementemia, with negative testing for anti-neutrophil cytoplasmic antibody (ANCA) and cryoglobulins. The diagnosis of CD is both clinical and pathologic, often requiring extensive evaluation.1-3 Per the international, evidence-based consensus diagnostic criteria for MCD, there must be multilocentric lymphadenopathy with defined histopathology, two or more clinical or laboratory changes, and exclusion of MCD mimics, as delineated in Table 1.4 The patient presented had negative HHV-8 and HIV testing and meets both major diagnostic criteria and eight of the eleven minor diagnostic criteria for a diagnosis of MCD. Using the Japanese diagnostic criteria, this patient also meets criteria for iMCD-TAFRO syndrome. The diagnosis of CD is both clinical and pathologic, often requiring extensive evaluation.1-3 Per the international, evidence-based consensus diagnostic criteria for MCD, there must be multilocentric lymphadenopathy with defined histopathology, two or more clinical or laboratory changes, and exclusion of MCD mimics, as delineated in Table 1.4 The patient presented had negative HHV-8 and HIV testing and meets both major diagnostic criteria and eight of the eleven minor diagnostic criteria for a diagnosis of MCD. Using the Japanese diagnostic criteria, this patient also meets criteria for iMCD-TAFRO syndrome given his lymph node pathology (Figure 2), negative HHV-8 testing, and clinical evidence of thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly, absence of hypergammaglobulinemia, small volume lymphadenopathy, and hyperplasia of megakaryocytes in the bone marrow.5 Serum transaminases and alkaline phosphatase values were also WNL, and immunoglobulins were as follows: IgA 142 (WNL), IgE 99 (WNL), IgG 783 (WNL), IgD 2.2 (WNL), IgM 29 (low), all consistent with this diagnosis.6

Patients with MCD typically have profound systemic inflammatory disease, due to IL-6 predominant cytokine storm and resultant multi-organ dysfunction.7,8 The underlying trigger for the cytokine storm remains unknown. One hypothesis of pathogenesis involves an auto-antibody mediated IL-6 pathway in which auto-antibodies trigger self-perpetuating, pro-inflammatory cytokine release and dysregulate signaling in the antigen-presenting cells.

The diagnosis of CD is both clinical and pathologic, often requiring extensive evaluation.1-3 Per the international, evidence-based consensus diagnostic criteria for MCD, there must be multilocentric lymphadenopathy with defined histopathology, two or more clinical or laboratory changes, and exclusion of MCD mimics, as delineated in Table 1.4 The patient presented had negative HHV-8 and HIV testing and meets both major diagnostic criteria and eight of the eleven minor diagnostic criteria for a diagnosis of MCD. Using the Japanese diagnostic criteria, this patient also meets criteria for iMCD-TAFRO syndrome given his lymph node pathology (Figure 2), negative HHV-8 testing, and clinical evidence of thrombocytopenia, anasarca, fever, reticulin fibrosis, organomegaly, absence of hypergammaglobulinemia, small volume lymphadenopathy, and hyperplasia of megakaryocytes in the bone marrow.5 Serum transaminases and alkaline phosphatase values were also WNL, and immunoglobulins were as follows: IgA 142 (WNL), IgE 99 (WNL), IgG 783 (WNL), IgD 2.2 (WNL), IgM 29 (low), all consistent with this diagnosis.6

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The CDCN International Consensus Guidelines for treatment of iMCD were consulted to stratify our patient based on disease severity and choose the best therapeutic...
Treatment of CD is aimed at cytokine blockade, including high-dose steroids and IL-6 inhibition. Tocilizumab, a recombinant humanized monoclonal antibody directed against the IL-6 receptor, and siltuximab, a monoclonal antibody that binds IL-6, are two of the treatments used most frequently. Tocilizumab was used in this case due to equal effectiveness of both drugs and its availability on the formulary of our hospital. The IL-6 inhibitors can be efficacious even in the absence of elevated serum IL-6, as in this case. Additionally, current testing modalities may fail to recognize complexed IL-6 and provide falsely low IL-6 values on many commercial tests. As such, normal IL-6 levels should not preclude anti-IL-6 therapy. Further, novel therapies targeting upstream and downstream pathways such as Janus kinase/signal transducer activator of transcription 3 (JAK/STAT3), mitogen-activated protein kinase (MAPK), and phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) are currently under investigation and may have benefit.

Treatment response ranges from complete remission to refractory, progressive disease. Due to potential for repeated, dangerous flares, therapy is indefinite and clinical, laboratory, and radiographic indices must be closely trended, particularly if weaning immunosuppression. The necessary duration of immunosuppressive or immunomodulatory therapy to prevent disease relapse has not yet been defined.

Of note, on the primary immunodeficiency panel obtained for this patient, there was a pathologic variant in the primary immunodeficiency panel obtained for this patient, there was a pathologic variant in...
the MVK gene which has been associated with autosomal recessive mevalonate kinase deficiency, hyperimmunoglobulinemia D syndrome (HIDS), and periodic fever syndrome. While this patient's clinical presentation is not fully consistent with any of these diagnoses, the overlap between diagnostic clinical features is notable. The latter two syndromes are characterized by recurrent episodes of fever associated with lymphadenopathy, arthralgia, gastrointestinal dismay, and skin rash. To our knowledge, no previous associations between CD and MVK gene alteration have been reported.

CD remains a diagnostic challenge given the rarity of the condition in the pediatric population and its non-specific clinical, laboratory, and radiographic features impacting multiple organ systems. The importance of awareness of the clinical presentation in a pediatric patient to prevent delayed diagnosis and provide optimal care cannot be understated.

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CONFLICT OF INTEREST
All authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS
SD served as the lead and corresponding author, contributed to the conception and analysis of the case report, drafted the manuscript, gave final approval for publication, and agreed to be accountable for all aspects of the work. NK and CB both contributed to the conception and analysis of the case report, participated in drafting the manuscript, gave final approval for publication, and agreed to be accountable for all aspects of the work. SPA and SK contributed to the analysis of the case report, revised the manuscript, gave final approval for publication, and agreed to be accountable for all aspects of the work. MR served as the senior author on the project, contributed to the conception and analysis of the case report, revised the manuscript, gave final approval for publication, and agreed to be accountable for all aspects of the work.

ETHICAL APPROVAL
This case report conforms to recognized standards and was conducted in accordance with the Helsinki declaration as revised in 2013. This work was deemed exempt from formal review by Nationwide Children's Hospital's Institutional Review Board. Patient anonymity is preserved throughout.
CONSENT
Patient consent has been signed and collected in accordance with the journal's patient consent policy and can be provided upon request.

DATA AVAILABILITY STATEMENT
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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