UNICENTRIC CASTLEMAN DISEASE AND MICROCYTIC ANEMIA: A CHALLENGING DIAGNOSIS

Olayinka Okeleji[1], Kylie Holden[2], Miriam B. Garcia[1], Mary Austin[2], James You[3], and David McCall[1]

[1]The University of Texas MD Anderson Cancer Center Children's Cancer Hospital
[2]The University of Texas Health Science Center at Houston Department of Surgery
[3]The University of Texas MD Anderson Cancer Center Pathology Department

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Authors: Kylie Holden[1], Olayinka Okeleji[2] Miriam B. Garcia[2], Mary Austin[1], James You[3] and David McCall[2]

[1] Department of Surgery, McGovern Medical School at the University of Texas Health Science Center at Houston (UTHealth Houston) and Children's Memorial Hermann Hospital, Houston, TX

[2] Department of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX

[3] Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Corresponding author:

Olayinka Okeleji MD

Department of Pediatrics

The University of Texas MD Anderson Cancer Center

1515 Holcombe Blvd., Unit 87. Houston, TX 77030

Email: ookeleji@mdanderson.org

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Abbreviations: CD Castleman disease, HVV Hyaline-vascular variant, PET/CT Positron emission tomography/computed tomography, LDH lactate dehydrogenase, CBC Complete blood count, TIBC total iron binding capacity, MCV mean corpuscular volume, EBV Epstein-Barr virus, CMV cytomegalovirus, ANA antinuclear antibodies, RF rheumatoid factor, dsDNA double-stranded DNA, tTG-IgA Tissue Transglutaminase IgA, CRP C-reactive protein, ESR erythrocyte sedimentation rate, DAT direct antiglobulin test, MRI magnetic resonance imaging

BackgroundCastleman disease (CD) is an uncommon lymphoproliferative disorder characterized by hypervascular lymphoid hyperplasia. CD can be classified into two subgroups that differ in their pathogenesis, prognosis, and presentation: unicentric and multicentric.[1] Several histological variants are seen, including the hyaline vascular variant (HVV), plasma cell variant, and mixed variant[1]. Unicentric HVV, the most common variant, typically presents as a single enlarged lymph node that is most often found incidentally on radiographic studies or during surgical procedures and can be cured by surgery.[2,3]Approximately 5000 cases of unicentric CD occur in the United States annually, with few cases documented in pediatric patients.[3] In children, similar to adults, the most common subtype of CD is unicentric.[4] Here we discuss a delayed diagnosis of a case of unicentric HVV CD with an atypical presentation involving anemia.[5]

Case Description

A 12-year-old boy with recent poor weight gain and vague abdominal pain was found to have microcytic anemia during the work-up of his short stature. He denied fevers and night sweats. Blood work showed anemia (6.3 gm/dL), low MCV (61 fL), leukopenia ($2.5 \times 10^3/\mu L$), neutropenia ($0.5 \times 10^3/\mu L$), thrombocytosis ($401 \times 10^3/\mu L$), low serum iron (21 µg/dL), normal TIBC (298 µg/dL), normal ferritin (271 ng/mL), elevated haptoglobin level (347 mg/dL) and a negative IgG DAT. Hemoglobin electrophoresis was negative for hemoglobinopathy. Peripheral blood smear revealed reactive lymphocytes. EBV IgG and IgM were positive. Parvovirus, HIV, and CMV were negative. Chest x-ray and thyroid studies were normal. Baseline autoimmune workup (RF, dsDNA, ANA as well as tTG-IgA for celiac disease) was negative. Uric acid and LDH were normal. CRP (118 mg/L) and ESR (143 mm/h) were elevated.

He was referred to oncology after an ultrasonography of the patient's abdomen demonstrated an ill-defined abdominal mass. A subsequent MRI of the abdomen and pelvis revealed a solid, minimally enhancing $5 \times 3.6 \times 4.3$ cm retroperitoneal mass in the left para-aortic/mesenteric root region, just below the inferior border of the pancreas (**Figure 1)** . Fine-needle aspiration of the mass showed reactive/benign lymphoid proliferation with focal CD21-, CD35-, and D2-40+ dendritic meshwork, no immunophenotypic support for B-cell or T-cell neoplasia and Castleman disease could not be excluded. Positron emission tomography/computed tomography (PET/CT) scan demonstrated a unifocal, 4.5-cm lesion with a standardized uptake value of 8.5 (**Figure 1**). Given the concern for Castleman disease, the patient underwent laparoscopic resection of the mass. Pathology showed changes indicative of HVV CD (**Figure 2)** .

Within 2 months of the resection, the patient's IL-6 level decreased from 21 pg/mL to undetectable, hemoglobin level normalized, CRP level declined from 118 mg/L to 0.6 mg/L, and sedimentation rate decreased from 143 mm/h to 7 mm/h. PET/CT scan 1 month after excision showed no recurrence or new lesions. The patient's laboratory values remained normal (HB 11.2g/dL, MCV 82fL) at last follow-up, 24 months after resection.

Discussion

The infrequency with which CD is diagnosed in pediatric patients has hampered comprehensive clinical studies, leading to an incomplete understanding of the disease, its subtypes, and its prognosis.

Unicentric CD is more common than multifocal CD in children. It usually presents clinically with compressive symptoms, which are investigated with imaging, rather than abnormal labs or physical findings. Our patient's presentation was unique because microcytic anemia is more often seen in multifocal CD and in the absence of other significant symptoms. His presentation delayed diagnosis for several months. The patient's anemia likely resulted from IL-6–mediated hepcidin secretion, given his IL-6 level was elevated until removal of the mass[6]. Evaluation for short stature, abdominal pain with anemia in this case prompted the abdominal ultrasound that identified the mass. Although this mass was identified with abdominal ultrasonography, it is important to note that abdominal CT is more sensitive for the HVV due to the rich vascularization of these masses. Unicentric HVV CD is generally more common in the fourth decade of life[2], however, our patient was 12 years old at diagnosis.

As seen in this case, surgical excision is preferable to needle biopsy to properly analyze the architecture of

the entire germinal center and interfollicular zone[2]. Removal of the mass was curative in our patient, leading to normalization of the patient's laboratory values. However, unicentric CD is sometimes unresectable due to location or size and may require systemic therapy. While there is no standardized therapy, options include immunotherapy, corticosteroids, chemotherapy, or radiotherapy.[3]

Following excision, surveillance can be gradually spaced out as laboratory findings normalize; radiologic imaging may be considered 6 to 12 months later to verify cure and no recurrence[2]. Patients with systemic involvement must be monitored closely postoperatively, with regular laboratory tests and imaging studies[2]. However, since little data and few reported cases have described systemic symptoms in unicentric CD, the long-term monitoring plan for this patient was based on the normalization of his laboratory values and reassuring clinical examination.

Conclusion

CD is rare in children but should be considered in the setting of systemic inflammatory processes and associated anemia. Treatment depends on resectability and locations, and a multidisciplinary team involving surgery, pathology, hematology, and oncology is essential for an expeditious diagnosis and management.

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Ethics statement:

Informed parental consent was obtained to report these findings and pathology.

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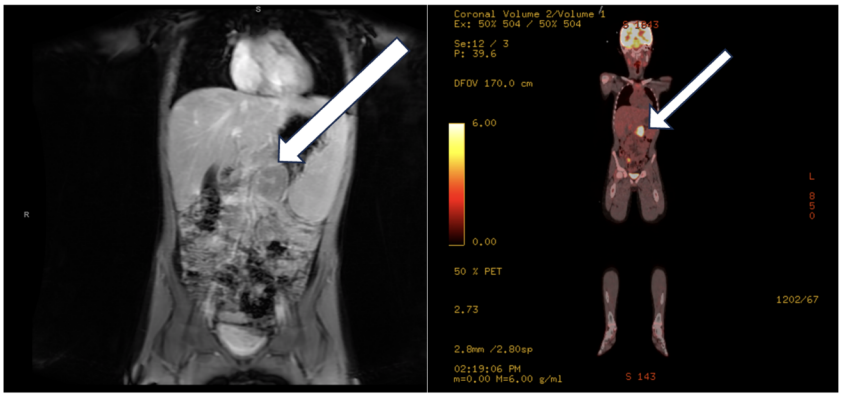

Figure 1. Pre-surgery MRI of the abdomen and pelvis (left) and PET/CT (right). White arrows indicate lesion later diagnosed as unicentric HVV CD.

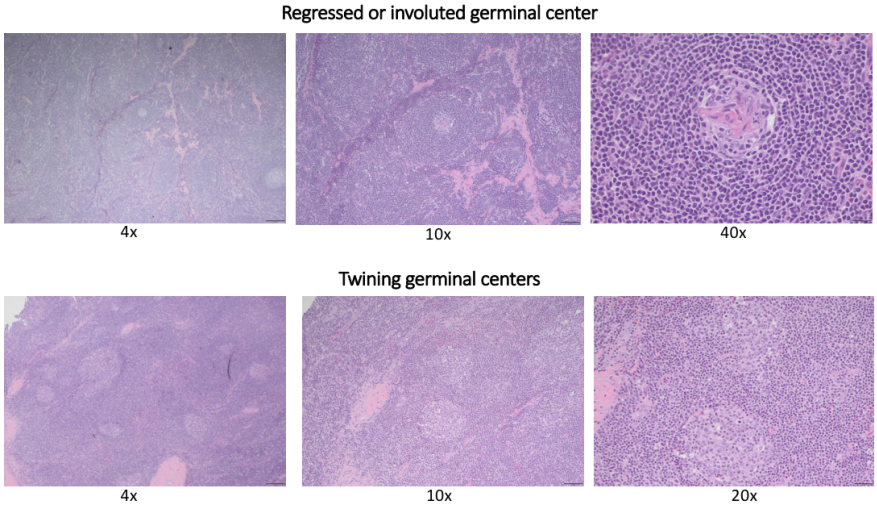

Figure 2: Pathologic images demonstrating progressive transformation of germinal centers, occasional large follicles with regressed (involuted) germinal centers, and some focal areas showing two or more germinal centers per follicle ("twinning"), suggestive of hyaline vascular variant Castleman disease.