Multicentric Castleman Disease Presenting with Fever

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Multicentric Castleman disease (MCD) is a rare lymphoproliferative disorder that usually manifests with nonspecific symptoms, including fever and lymphadenopathy. Treatment of pediatric MCD varies greatly. A 21-month-old child was diagnosed with MCD after presenting with fever. He had incomplete response to initial therapy directed at interleukin-6, but improved with subsequent chemotherapy. *(J Pediatr 2014;165:1261-5).*

Angiofollicular lymph node hyperplasia is a rare disorder first described by Castleman in 1954.[1] Fewer than 100 cases of pediatric Castleman disease (CD) have been reported, the vast majority of which have had a benign, unicentric pattern.[2-6] We report a young child with severe multicentric CD (MCD) of the hyaline vascular variant presenting as a challenging case of persistent fever.

Case Report

A previously healthy 21-month-old boy of Ashkenazi descent presented at the emergency department with fever of 5 days duration, irritability, and bruising. Physical examination revealed a temperature of 39.4°C, pallor, resolving ecchymoses on the abdomen and extremities, and scattered cervical and inguinal lymphadenopathy (all <1 cm). Initial laboratory test results are reported in Table I. Serum ferritin level was mildly elevated (205 ng/mL), and lactate dehydrogenase and uric acid levels were normal. The patient was admitted to the hospital on day of illness (DOI) 5 for evaluation of fever and initiation of empiric ceftriaxone therapy for suspected bacterial infection.

The patient's daily fever persisted (38.5-40.0°C), and lymphadenopathy became diffusely prominent. On DOI 7, abdominal computed tomography (CT) demonstrated enlarged mesenteric, aortocaval, pelvic, and inguinal lymph nodes and moderate ascites (Figure, A). Anasarca developed, despite albumin replacement and diuresis. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remained markedly elevated (Table I). Anemia and thrombocytopenia persisted, necessitating frequent transfusions. A direct Coombs test was negative. Bone marrow biopsy analysis on DOI 9 showed hypocellularity with no evidence of malignancy or hemophagocytosis. Cultures of blood, urine, and stool were negative. Doxycycline was initiated on DOI 10, and was discontinued when serology for Rocky Mountain spotted fever was negative. Serology, culture, and/or polymerase chain reaction for HIV, Epstein-Barr virus, cytomegalovirus, parvovirus, *Bartonella*, and West Nile virus were negative. Polymerase chain reaction of respiratory specimens was negative for respiratory viruses. A tuberculosis skin test was nonreactive. Serum IgG level was normal. Serology for autoimmune disorders, including C3/C4, antinuclear antibody, and double-stranded DNA antibody, was negative. An echocardiogram was normal.

On DOI 12, pulmonary edema, pleural effusions, and ascites led to respiratory distress requiring mechanical ventilation. Full-body magnetic resonance imaging showed severe anasarca and worsening generalized lymphadenopathy, consistent with a lymphoproliferative process. An inguinal lymph node was excised, and histology demonstrated reactive but atretic lymphoid follicles with small germinal centers and prominent reactive vascular endothelium within the sinuses (Figure, B). Some follicles contained "onion skin" circumferential arrangements of lymphocytes and vascular poles (Figure, C and D), features characteristic of the hyaline vascular variant of CD. Immunohistochemistry and serology for human herpesvirus (HHV)-8 was negative. Interleukin (IL)-6 level in serum was elevated at 88.4 pg/mL (normal 0.0-3.9 pg/mL), confirming the diagnosis of HHV-8–negative MCD of the hyaline vascular variant. Intravenous methylprednisolone (2-4 mg/kg/day) was initiated on DOI 13, but produced no change in fever, inflammatory markers, or hypoalbuminemia. Tocilizumab (10 mg/kg), a humanized monoclonal IL-6 receptor antibody, was administered on DOI 17, 22, and 36, after which gradual improvements in symptoms and decreases in inflammatory markers were seen (Table I). Corticosteroids

CD	Castleman disease
CRP	C-reactive protein
CT	Computed tomography
DOI	Day of illness
ESR	Erythrocyte sedimentation rate
HHV	Human herpesvirus
IL	Interleukin
MCD	Multicentric Castleman disease
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin, vincristine, and methylprednisolone

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Table I. Laboratory test results over time

Variables	Normal range	DOI 5	9	13	35	50	59	66	80
IL-6, pg/mL*	0.0-3.9	-	-	88.4	-	-			
	0.0-17.4						68	7.9	<7.6
CRP, mg/dL	0.0-1.0	17.2	24.0	19.7	1.2	17.1	4.1	<0.5	<0.5
ESR, mm/hr	0-15	128	113	71	41	105	5	-	-
WBC, per mm^3	5000-13 000	9500	7900	11 400	9900	22 100	11 300	32 400	4000
Hgb, g/dL	9.5-14.0	9.7	7.2	9.4	10.8	9.3	8.9	8.2	9.2
Platelets, per mm^3	150 000-500 000	25 000	17 000	29 000	37 000	33 000	20 000	58 000	115 000
Albumin, g/dL	3.4-4.2	3.2	2.0	2.5	3.7	3.0	3.0	2.3	3.2

Hgb, hemoglobin; *WBC*, white blood cell count.
*IL-6 levels were reported by 2 reference laboratories, National Jewish Health Advanced Diagnostics Laboratories, Denver, Colorado (normal, 0.0-3.9 pg/mL), and Viracor-IBT Laboratories, Lee's Summit, Missouri (normal, 0.0-17.4 pg/mL).

were discontinued on DOI 34. The patient was discharged on DOI 42 with plans for outpatient tocilizumab therapy.

On DOI 50, during a scheduled tocilizumab infusion, the patient developed angioedema, fever, hypotension, and hypoxia, and was readmitted to the intensive care unit for management of anaphylaxis. Ascites, pleural effusions, and diffuse lymphadenopathy had returned (**Figure**, E), requiring placement of pleural and peritoneal drains. ESR and CRP were again markedly elevated (**Table I**). Owing to concerns about lymphoma because of the rapid progression, repeat inguinal lymph node biopsy was performed; histology was identical to that of the previous biopsy specimen.

Chemotherapy was initiated on DOI 54 with six 21-day cycles of cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), vincristine (1.4 mg/m^2), rituximab (375 mg/m^2; one dose per week during the first cycle then one dose per each remaining cycle), and methylprednisolone (2 mg/kg/day for 5 days) (R-CHOP). After a complicated intensive care unit stay and a prolonged weaning off of corticosteroids, his condition steadily improved. Serum IL-6 level fell from 68 pg/mL on DOI 59 to 7.9 pg/mL on DOI 66 (normal, 0.0-17.4 pg/mL) (**Table I**). CT scan on DOI 70 revealed significant improvements in lymphadenopathy and ascites (**Figure**, F). Serum IL-6 level was undetectable on DOI 80 (**Table I**). The patient continued to improve 12 months after R-CHOP initiation, with no evidence of MCD by laboratory testing or CT imaging.

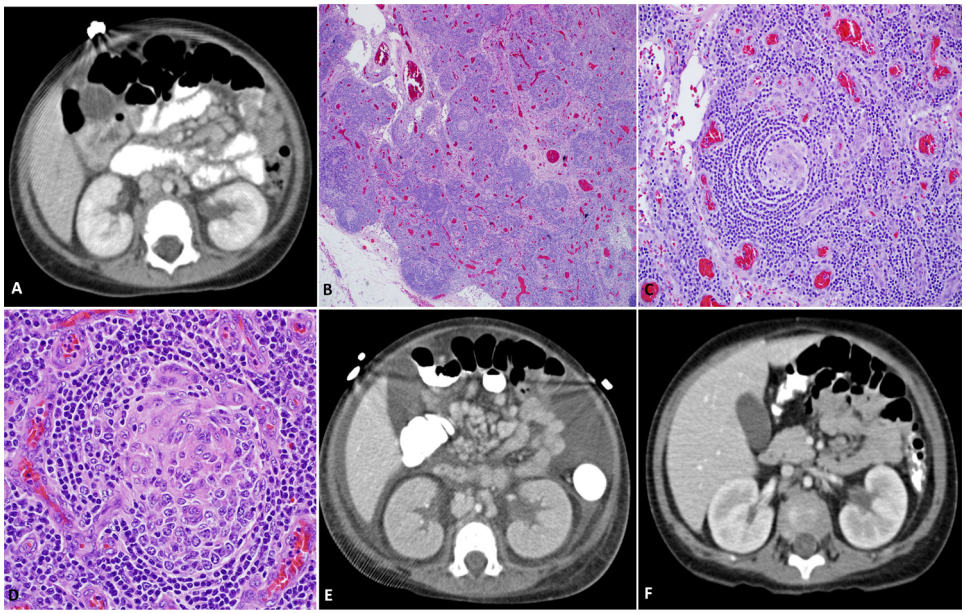

Figure. A, Initial abdominal CT revealed ascites and diffuse lymphadenopathy. **B-D,** Histological examination of a lymph node showed reactive lymphoid follicles, with an "onion skin" pattern of concentric lymphocytes surrounding atretic follicles with vascular poles in a so-called "lollipop" configuration. **E,** CT after anaphylaxis to tocilizumab showed increased size and conspicuity of lymph nodes in the upper abdomen, mesentery, and retrocrural area, large volume ascites, and pleural effusions. **F,** CT after 2 cycles of R-CHOP chemotherapy showed markedly decreased lymphadenopathy in the neck, mediastinum, retroperitoneum, and mesentery and resolution of pleural effusions and ascites.

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