Letter to the Editor

Castleman-Kojima Disease in a South Asian Adolescent

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TO THE EDITOR

Angiofollicular lymph node hyperplasia, with the eponym Castleman disease (CD) is a histomorphologic entity uniting a group of diseases with related and occasionally overlapping pathogenesis.1 Histologic variants of CD include the hyaline-vascular, plasmacytic, and mixed types and each of these may be clinically unicentric or multicentric.2,3 Recent reports describe a variant of idiopathic multicentric CD (MCD) in Japan4-10 provisionally labeled Castleman-Kojima disease.11 The characteristic features of the syndrome include thrombocytopenia, ascites, microcytic anemia, myelofibrosis, renal dysfunction and organomegaly (TAFRO syndrome); other distinguishing features of the syndrome include a lack of association with human herpesvirus (HHV)-8, good response to corticosteroid therapy and an indolent clinical course in many affected patients. We report the case of an adolescent boy with Castleman-Kojima disease treated with thalidomide.

A 14-years-old boy was seen in consultation at Mediciti Hospital in September 2012 with the chief complaints of recurrent episodes of fever, ascites, and anemia (Fig. 1). He had been in excellent health until September 2010 when he was seen elsewhere with the insidious onset of low-grade fever and distention of abdomen of three weeks’ duration. Physical examination showed pallor, marked ascites and splenomegaly. His hemoglobin (Hb) was 6.0 g/dL, mean corpuscular volume (MCV) 78 fl, white blood cell 10.8 × 109/L and the platelets 360 × 109/L. The serum bilirubin was 0.3 mg/dL, total serum proteins 6.7 g/dL, albumin 3.8 g/dL, serum iron 15 µg/dL, total iron binding capacity 266 µg/dL and the serum ferritin 560 ng/mL. A bone marrow biopsy showed normal morphology, adequate marrow iron and no ring sideroblasts; the reticulin stain showed grade I reticulin fibrosis (Modified Bauermeister scale). A Montoux test resulted in 3 mm induration. He was transfused a single unit of packed erythrocytes and a three-liter paracentesis was done. The fever and ascites resolved spontaneously over two weeks.

Six months later he was admitted to a separate hospital in March 2011 with abdominal distention, anasarca, and fever of several weeks’ duration. He had fever, bilateral cervical and axillary lymphadenopathy and tense ascites. A computed tomographic scan of abdomen showed splenomegaly and multiple retroperitoneal lymph nodes, the largest measuring 18 mm. A right axillary lymph node biopsy showed hyaline vascular type of CD (Fig. 2). Immunohistochemistry showed no evidence of clonal restriction. He was treated with diuretics and was given a single unit of packed erythrocyte transfusion and two units of human serum albumin. A two-liter paracentesis was done. The ascitic fluid was a transudate and a cytospin preparation showed mesothelial cells and a rare neutrophil. He received six cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy for reasons that are not clear, between March 2011 and July 2011. Following the chemotherapy there was resolution of ascites and anasarca but the organomegaly and lymphadenopathy remained unchanged. He had several episodes of fever and abdominal distention in the subsequent eight months that were treated symptomatically at different Clinics.

In October 2012 he was hospitalized with fever, abdominal distention and anasarca. His HB was 4.5 g/dL, MCV 77 fl, leukocytes 5.4 × 109/L and platelets 31 × 109/L. Serum creatinine was 1.3 mg/dL, total bilirubin 0.3 mg/dL, total serum proteins 5.1 g/dL, albumin 1.3 g/dL, aspartate amino-
transferase 9 U/L, alanine transaminase 15 U/L, alkaline phosphatase 227 U/L and lactate dehydrogenase 497 U/L (180-450 U/L). Serum was negative for HBs antigen and anti-HCV and HIV 1 & 2 antibodies. Anti-nuclear antibodies and a direct Coombs’ test result were negative. Urinalysis showed normal findings. Serum copper and ceruloplasmin levels, and 24-hr excretion of Copper were within normal limits. Echocardiography showed normal left ventricular function and mild pericardial effusion. He was discharged improved following treatment with packed erythrocyte transfusion, therapeutic paracentesis and diuretics. Remarkably, at follow-up in December 2012 he was well with no ascites or edema; the lymphadenopathy and hepatosplenomegaly remained unchanged. His Hb was 12.6 g/dL, MCV 81 fL, and the platelets 311 ×10^9/L. Total serum protein was 8.1 g/dL and albumin 4.8 g/dL.

In March 2013 he was re-admitted with fevers to 101ºF, abdominal distention and shortness of breath. He denied skin rash, paresthesiae, night sweats or weight loss. Bilateral posterior cervical and axillary lymph nodes were palpable, the largest measuring 1.5 cm. His Hb was 4.8 g/dL, MCV 77 fL, leukocytes 5.2 ×10^9/L and platelets 58 ×10^9/L. The total serum protein was 6.2 g/dL, albumin 2.2 g/dL, and alkaline phosphatase 330 U/L (60-160 U/L); serum protein electrophoresis shows no M-band. Computed tomographic scan of the abdomen showed hepatosplenomegaly, extensive retroperitoneal lymphadenopathy and fluid collection in the subhepatic space (Fig. 3). A liver biopsy showed minimal lobular hepatitis and no steatosis. An upper gastrointestinal endoscopy and duodenal biopsy showed normal findings. He was begun on treatment with 100 mg daily of thalidomide.

At his last evaluation on December 25, 2013, he was asymptomatic and looked well. He was normotensive with no ascites or edema. Bilateral posterior cervical lymphadenopathy and organomegaly remained unchanged. The serum creatinine was 0.3 mg/dL and urinalysis showed normal findings. An ultrasound examination of abdomen showed hepatosplenomegaly, retroperitoneal lymphadenopathy, and bilateral posterior cervical and axillary lymph nodes were palpable, the largest measuring 1.5 cm. His Hb was 4.8 g/dL, MCV 77 fL, leukocytes 5.2 ×10^9/L and platelets 58 ×10^9/L. The total serum protein was 6.2 g/dL, albumin 2.2 g/dL, and alkaline phosphatase 330 U/L (60-160 U/L); serum protein electrophoresis shows no M-band. Computed tomographic scan of the abdomen showed hepatosplenomegaly, extensive retroperitoneal lymphadenopathy and fluid collection in the subhepatic space (Fig. 3). A liver biopsy showed minimal lobular hepatitis and no steatosis. An upper gastrointestinal endoscopy and duodenal biopsy showed normal findings. He was begun on treatment with 100 mg daily of thalidomide.
eral nephromegaly with normal echo-structure and no hydronephrosis; the right kidney measured 125 mm \times 55 \text{mm} and the left kidney 138 \times 44 \text{mm}. Treatment with thalidomide was continued.

Thelymphnodebiopsyfindingstogetherwiththeclinical picture of fever, generalized lymphadenopathy, organomegaly, ascites, anasarca, microcytic anemia and thrombocytopenia establish the diagnosis of Castleman-Kojima disease in our patient. Our patient had the hyaline-vascular type of CD, which appears to be the dominant histologic pattern in the reported patients with Castleman-Kojima disease. The clinical picture of spontaneous remissions and exacerbations in disease activity in our patient is similar to that described by Frizzera. He described a group with "persistent" pattern (5 patients) and another group with "episodic" pattern (9 patients), among patients with MCD. In the latter group remissions occurred either spontaneously or following steroid therapy. Following the start of thalidomide treatment our patient has remained asymptomatic for over six months, with complete resolution of serositis and anasarca and has been attending school full-time. There has been no significant change in splenomegaly and retroperitoneal lymphadenopathy. Others have reported similar experience with the use of thalidomide.

![Fig. 2. Histological and immunohistochemical findings.](image)

**Fig. 2.** Histological and immunohistochemical findings. (2A) Follicle showing blood vessel radially penetrating the germinal center. Also seen is prominent vascularity of the interfollicular area (H&E stain, × 100). (2B) Compact follicle center surrounded by concentric circles of small lymphocytes (H&E stain, × 400). (2C & 3D) Lymph node section stained with antisera to \(\kappa\) light chain (2C) and \(\lambda\) light chain (2D) showing no evidence of clonal restriction (× 400).

![Fig. 3.](image)

**Fig. 3.** The finding of contrast enhanced computed tomography scan. Contrast enhanced computed tomography scan of abdomen (coronal reconstruction) shows hepatosplenomegaly, subhepatic fluid collection, and extensive retroperitoneal lymphadenopathy.
or lenalidomide in MCD.\textsuperscript{13-15} The nature of nephromegaly in our patient is undetermined.

Although rare, MCD has been reported in the pediatric age group and appears to have a favorable prognosis.\textsuperscript{16,17} It is still controversial whether Castleman-Kojima disease should be subsumed into the category of MCD or constitutes a distinct entity.\textsuperscript{11} Compared to idiopathic MCD, taken separately, no single feature (clinical or laboratory) is unique to Castleman-Kojima disease. It may be considered a unique subset of MCD characterized by serositis-dominant clinical presentation, the lack of association with HHV-8, thrombocytopenia and the chronic indolent clinical course. A prospective study of the natural history of idiopathic MCD presenting with an ascites/anasarca-dominant clinical picture among both Japanese and non-Japanese patients will help in advancing our understanding of MCD.

The patient was seen in the Clinic on August 14, 2014. He had been quite well with no intercurrent problems and had been taking 100 mg daily of thalidomide. He had bilateral axillary lymphadenopathy with the largest node measuring 2 cm. The spleen was palpable 2 cm below the costal margin. There was no edema or ascites. He was asked to continue taking thalidomide.

REFERENCES