Intestinal lymphangiectasia associated with angiofollicular lymph node hyperplasia (Castleman's disease)

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Abstract

A patient presenting with predominantly gastrointestinal symptoms and a history of myocardial infarction was found to have ascites, hepatosplenomegaly, para-aortic lymphadenopathy, thrombocytosis, and a para-proteinaemia. A jejunal biopsy specimen showed lymphangiectasia and histology of the spleen and lymph nodes showed angiofollicular hyperplasia or Castleman's disease of the hyaline vascular type. This association has not previously been described and, moreover, systemic symptoms are unusual in this variant of Castleman's disease.

Intestinal lymphangiectasia is an uncommon entity characterised by dilated lymphatics within the gut. It may be primary or secondary to lymphatic obstruction in a number of inflammatory or neoplastic conditions¹ or in right heart failure, where the lymphatic return from the intestine may be compromised. It may present with the consequences of protein losing enteropathy and is occasionally associated with immunodeficiency caused by the loss of T cells into the intestinal lumen.²

Castleman's disease, or angiofollicular lymph node hyperplasia, is a rare lymphoproliferative disorder of unknown aetiology. It usually occurs

as a solitary, symptomless, mediastinal mass characterised histologically by lymphoid follicle like structures with prominent proliferation of blood vessels.³ Two subtypes are described, probably representing the extremes of a spectrum of appearances.⁴ The hyaline vascular type is by far the more common, while the plasma cell variant is more likely to be associated with systemic symptoms, particularly when the condition is multicentric rather than solitary.

Case history

A 49 year old female teacher presented with a four year history of malaise and one year of nausea, abdominal swelling, and the passage of loose watery stools three times daily. Over this time she had lost 10 kg in weight. She also complained of numbness in both feet and of the symptoms of Raynaud's phenomenon affecting the left arm. Breathlessness prevented her from climbing more than two flights of stairs. Two years previously she had suffered an uncomplicated transmural inferior myocardial infarction. At this time she had a mild thrombocytosis with a platelet count of $600 \times 10^9/l$ but no other risk factors for ischaemic heart disease. She was taking aspirin (75 mg daily) and bumetanide with potassium.

On physical examination there were no signs

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Figure 1: High power magnification of jejunal mucosa showing lymphangiectasia. (Original magnification $\times 400$.)

Figure 2: High power magnification of lymph node showing follicle like structures. (Original magnification $\times 250$.)

of heart failure and no lymphadenopathy. There were ascites, moderate splenomegaly, and a sensory peripheral neuropathy in a glove and stocking distribution.

All haematological indices, including a bone marrow trephine, were normal except for a raised platelet count of $600 \times 10^9/l$. The alkaline phosphatase value was high at 176 iu/l but she had normal transaminase activities and total globulin concentrations. An IgA lambda paraprotein was detected in the serum by immunofixation, at a concentration of less than 1 g/l. The following investigations were either negative or within the normal range: urea and electrolytes, autoantibodies, cryoglobulin, complement, ferritin, protein electrophoresis, C reactive protein, and red cell and serum folate. Electromyograph showed a mixed demyelinating and axonal neuropathy.

Urinary protein excretion was 0.4 g/24 hours and Bence-Jones protein was not detected.

Abdominal paracentesis showed a straw coloured cellular exudate (protein 50 g/l and a cell count of $5.4 \times 10^9/l$, with 68% lymphocytes, 26% monocytes, and 4% neutrophils). Faecal fat excretion was slightly raised at 5.9 g/24 hours.

A jejunal mucosal biopsy specimen showed lymphangiectasia with a normal villous architecture (Fig 1). A reduced intraepithelial lymphocyte count of 8 per 100 epithelial cells (normal 18.0), was consistent with this diagnosis⁵ and the abnormal mucosa further excluded the possibility that the specimen had been taken from a localised lymphangiectatic cyst. In this condition, more often seen in older patients, the mucosa is normal.⁶

Computed tomogram confirmed the enlarged spleen and also showed mild hepatomegaly and para-aortic lymphadenopathy.

Because of the strong clinical suspicion of an intra-abdominal lymphoma, a laparotomy and

splenectomy were performed together with a liver biopsy.

Histology of the lymph nodes showed partial replacement of the normal architecture by structures comprising concentric rings of small lymphocytes surrounding small follicle centres containing hyalinised vessels that were occasionally seen to enter the follicle radially (Fig 2). The interfollicular areas showed proliferating blood vessels.

The spleen showed expansion of the white pulp with similar follicle like structures and the overall appearances were those of multicentric, hyaline vascular Castleman's disease. The liver biopsy was essentially normal.

After operation, the platelet count doubled to $1200 \times 10^9/l$ and hepatic alkaline phosphatase activity was 375 iu (normal <130).

Bone marrow examination now showed increased numbers of megakaryocytes and lymphocytes with a 7–10% eosinophilia.

T lymphocyte receptor gene rearrangement studies showed a discrete T cell clone in the ascitic fluid that was not seen in the peripheral blood. There was no evidence of an abnormal B cell clone.

Eight months later, the peripheral blood showed a persistent thrombocythaemia and also a raised haematocrit (0.5) and red cell volume (when corrected for plasma volume) consistent with polycythaemia. This was considered evidence of the development of a myeloproliferative process and in view of this and of the slowly progressive neurological symptoms, treatment with cyclophosphamide and prednisolone was begun.

Discussion

Our patient exhibited a number of systemic features usually associated with the plasma cell

variant of Castleman's disease, including weight loss, fever, thrombocythaemia,⁷ paraproteinaemia,⁷ peripheral neuropathy,^{7,8} and myocardial infarction.⁹ Other reported features include amyloidosis¹⁰ and anaemia (which may be due to circulating antierythrocyte antibody).¹¹

The pathogenesis of Castleman's disease is unknown but a number of lines of evidence point to it being an immunoproliferative condition. Monoclonal plasma cell populations have been shown in some cases of the plasma cell type^{12,13} and T cell gene rearrangements have been associated with Epstein-Barr virus incorporation.¹³ These abnormalities seem confined to the multicentric form of the disease. Moreover, production of the cytokine interleukin 6 by Castleman's nodes has been shown both in vitro¹⁴ and in vivo.¹⁵ Our patient had T cell gene rearrangement in the ascitic fluid though not in the peripheral blood.

One study reports a high rate of progression of the hyaline vascular form to angiomatous neoplasms¹⁶ but as the morphology of Castleman's nodes may resemble that seen in nodes draining malignant tumours, in autoimmune conditions, in HIV infection, and in Kaposi's sarcoma¹⁷ this association remains unproved.

Castleman's disease may present to the gastroenterologist in a number of ways – as hepatosplenomegaly, abdominal lymphadenopathy, or as a mass in the stomach or pancreas.^{18,19} However, intestinal lymphangiectasia secondary to this condition has not previously been described and in this patient is probably a result of the para-aortic and mesenteric lymphadenopathy of multicentric Castleman's disease.

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