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CASE REPORT

Splenectomy-induced long-term remission in a patient with multicentric Castleman's disease

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ABSTRACT

Castleman's disease (CD) is a rare lymphoproliferative disorder with a poorly understood pathogenesis. Multicentric CD can progress in different patterns, none of which can be cured with the current treatment options. We present a patient with multicentric CD in complete remission, eight years after a splenectomy without any other systemic treatment. We discuss the possible mechanism causing this long episode of complete remission in this patient.

KEYWORDS

Angiofollicular lymph node hyperplasia, Castleman's disease, human herpes virus type 8, lymphoproliferative disorders, splenectomy

What was known on this topic?
Multicentric CD can be either rapidly progressive and lethal or persistent as a chronic form. Patients are treated with corticosteroids, antiviral agents, anti-interleukin-6 antibodies, anti-CD20 antibodies (rituximab) or chemotherapy, none of which are curative. Splenectomy as a sole treatment for multicentric Castleman's has been described in only one patient with a follow-up of one year.

What does this add?
We present a patient with multicentric CD who is still in complete remission eight years after a diagnostic splenectomy without any other systemic treatment.

INTRODUCTION

Castleman's disease (CD) is a rare lymphoproliferative disorder of which the pathogenesis is still poorly understood. CD is associated with malignancies such as (non-)Hodgkin's lymphoma, Kaposi sarcoma and POEMS syndrome. The human herpes virus 8 (HHV-8) – with or without concurrent infection with the human immunodeficiency virus (HIV) – has been identified as a possible trigger of the immune activation associated with CD.[1,2]

In CD a disturbance of the lymph node architecture is seen that is both reactive and neoplastic. Three histopathological variants are recognised. Most common (±90%) is the hyaline vascular variant, characterised by a marked increase in abnormal follicles with regressed or atrophic germinal centres and broad mantle zones of small lymphocytes. The plasma cell variant (±10%) has hyperplastic germinal centres. Less common is the mixed type.[1,2]

CD comprises two different clinical presentations. Unicentric CD is an isolated benign lymphoproliferative disorder affecting young adults, which is initially asymptomatic. Surgical resection of the affected lymph node is usually curative; in case of incomplete resection radiotherapy is advised.[3,4] Patients with multicentric CD present with aspecific symptoms such as fever, weight loss, fatigue and night sweats and are usually middle-aged. Peripheral lymphadenopathy is common and can be accompanied by hepatomegaly and splenomegaly, high erythrocyte sedimentation rate (ESR), low haemoglobin and hypoalbuminaemia.[5] Multicentric CD can progress in different patterns. It can be rapidly progressive and lethal or persist as a chronic form. Treatment options are corticosteroids, antiviral agents, anti-CD20 antibodies (Rituximab), anti-interleukin-6 antibodies and chemotherapy.[6-8] None of these are curative. Splenectomy can temporarily result in improvement of symptoms.[9,10]

We present a patient with multicentric CD who is still in complete remission eight years after a diagnostic splenectomy without any other systemic treatment. The only other case ever describing splenectomy as a sole treatment for multicentric Castleman's disease was published in 1999, but follow-up was only one year.[11]

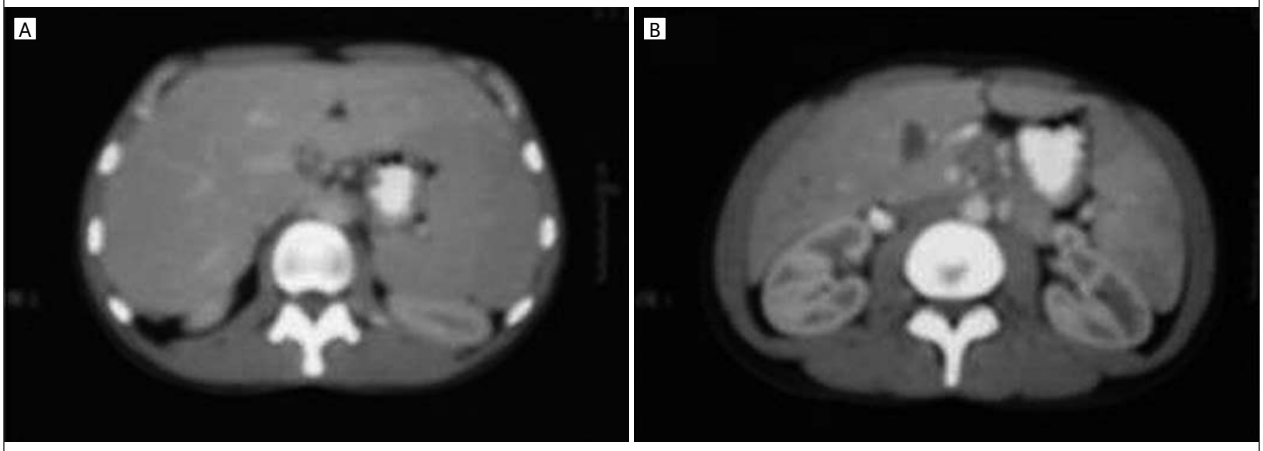
CASE REPORT

In 2001 a 29-year-old-man was first sent to our hospital because of abdominal pain, weight loss, ongoing fever and intermittent diarrhoea since a short holiday in Turkey, four weeks earlier. The previous medical history was not relevant. There were no risk factors for HIV. He did not smoke and was not using any medication. Physical examination showed a pale young man, not in distress, with a body mass index (BMI) of 21 kg/m^2. There were no palpable lymph nodes, but the liver was 1 cm palpable and the spleen reached the costal area.

Laboratory findings revealed an elevated ESR, a microcytic anaemia (mean corpus volume 57 fl), a normal leucocyte count and differentiation, a thrombocytosis (461 x 10^6/l) and macrothrombocytes in the blood smear. With an iron level of 1 µmol/l an iron deficiency was proven. Electrolytes, renal and liver function tests were normal, but a slightly elevated γ-glutamyl transpeptidase (56 U/l) and alkaline phosphatase (171 U/l) were present. The serum albumin level was low (31 g/l).

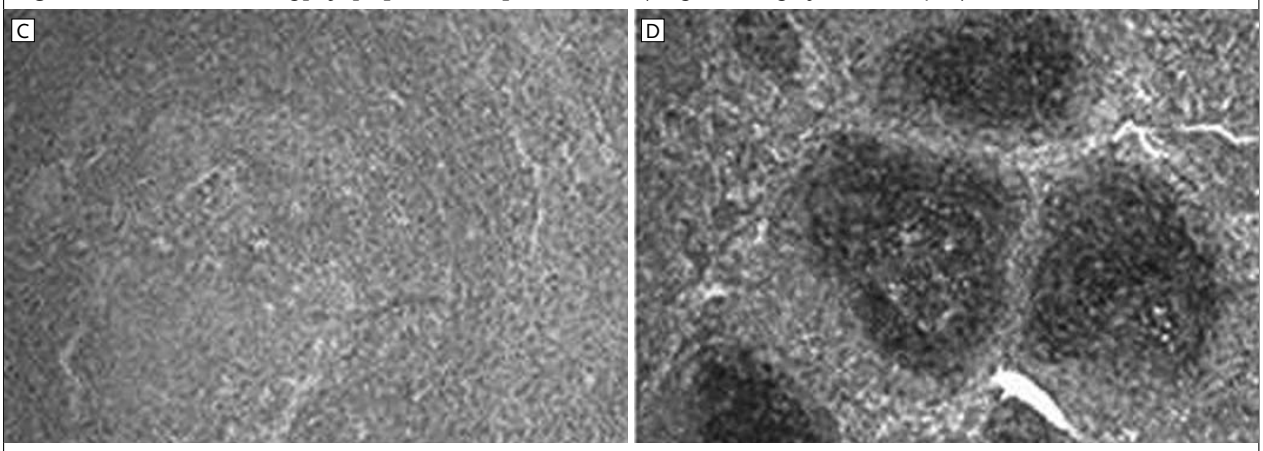
Serological tests for EBV, CMV and HIV were negative, as were stool examinations for *Giardia*, cysts and worms. Blood cultures and the tuberculin skin test were also negative. Endoscopic and radiographic examinations of the upper and lower digestive tract were within normal limits. A computed tomography (CT) scan of the abdomen showed multiple enlarged lymph nodes from the upper abdomen into the lower pelvic area, up to 5 cm in diameter. In addition, the liver (19 cm) and spleen (22 by 8 cm) were enlarged (*figures 1A* and *B*).

Figure 1A and B. *CT scan of the abdomen at presentation*



A) The spleen is enlarged measuring 8 cm transversally and 22 cm longitudinally. The liver is slightly enlarged but has a normal density.
B) Para-aortic lymph nodes (arrow) are enlarged up to 5 cm in diameter.

Figure 1C and D. *Pathology of lymph node at presentation (original magnification x 400)*



C) Enlarged lymphoid follicle with hyperplastic germinal centre and slight hyaline changes. Haematoxylin and eosin staining.
D) Immunohistochemistry with CD 23 showing compact enlarged germinal centres with compact organised dendritical cells.

Bone marrow examination showed an active haematopoesis without infiltration of malignant lymphoma or cytokeratine positive cells. At first an ultrasound-guided lymph node biopsy was performed. The pathology was suggestive but not decisive for a plasmocytic small-cell non-Hodgkin's lymphoma.

Because of the uncertainty of the diagnosis, the young age of the patient and the consequences for treatment and prognosis we decided to perform a diagnostic laparoscopic splenectomy. Both the spleen and a few enlarged para-aortal lymph nodes were removed. Particularly in the lymph nodes and to a smaller extent in the spleen, abnormal enlarged follicles with a compact and enlarged follicle centre with dendritical cells and occasionally hyaline changes were seen. Combined with interfollicular hypervascularity and a polyclonal plasmocytosis the diagnosis of multicentric plasmocellular CD was made (*figures 1C* and *D*). The pathology was reviewed by two independent pathology boards highly experienced in lymphoproliferative disorders. Serum tests for HHV8 (IgM, IgG and PCR) were negative.

Within weeks after the splenectomy our patient spontaneously recovered from his physical complaints. He gained 10 kg and the laboratory findings normalised, while the CT scan revealed a normalisation of all aspects of lymphadenopathy.

Now, eight years after the splenectomy, the patient is still without any signs of activity of Castleman's disease as proven by six monthly physical examinations, laboratory tests and a yearly CT scan.

DISCUSSION

The patient described here showed signs of malabsorption including a microcytic anaemia. After elaborate examination he was diagnosed with CD, meeting the criteria for multicentric CD (*table 1*).

Table 1. *Criteria for multicentric Castleman's disease in this patient*

Criteria for multicentric Castleman's disease	In this patient
Median age 52-64 years	-
Male sex	+
Symptoms of inflammatory illness (fever, night sweats, weight loss)	+
Peripheral lymphadenopathy	+
Hepatomegaly	+
Splenomegaly	+
Elevated ESR	+
Anaemia	+
Hypoalbuminaemia	+
Hypergammaglobulinaemia	+
Positive lymph node biopsy	+

In the treatment of multicentric CD anti-interleukin-6 antibodies, chemotherapy and steroids have been considered the mainstay, whereas lately rituximab (anti-CD-20 antibodies) is considered to be an alternative.[4,6,8,9,12,13] The disease progression in patients with multicentric CD varies from a rapid form with progression leading to death within a few weeks, an episodic relapsing form and a chronic persistent form. Regardless of the pattern, the median survival of patients with multicentric CD is 26 to 30 months.[6,9]

Our patient, meeting many criteria for multicentric CD, is still alive and well, eight years after diagnosis, without any systemic treatment. CT scans have been repeated yearly without showing significant lymphadenopathy or hepatomegaly.

This course suggests a beneficial effect of splenectomy. Previous research showed no benefit of any type of surgery in multicentric CD for the prognosis and disease progression.[9,10] In all reported cases chemotherapy was needed to improve the condition of the patient. This leaves us with the question why did splenectomy help our patient? Has the contribution of the spleen in the course of CD been underestimated until now, and/or did splenectomy result in an overall decline in interleukin-6 production due to the reduction of the tumour load? Earlier studies have linked overexpression of interleukin-6 to the systemic manifestations of CD.[14,15] Unfortunately, interleukin-6 levels were not measured in our patient. Alternatively, the beneficial outcome of this patient may at least in part be related to the fact that he is HIV and HHV8 negative. Of note, the presentation of this case of multicentric CD is atypical with regard to some aspects (*table 1*), e.g. most cases of MCD are HHV8- and HIV-related, whereas most HIV-negative patients with MCD are in their fifth to sixth decade of life.

Our patient presented with fever, abdominal pain and watery diarrhoea after a holiday abroad. Possibly, an unrecognised viral infection causing these symptoms triggered the immune system into the development of CD, similar to what has been described for HHV-8. Serology and PCR for HHV-8 were negative in this patient.

In our opinion, in a patient with multicentric CD and splenomegaly, a splenectomy could be reconsidered awaiting remission of the symptoms.

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