Obscure anaemia and hepatic dysfunction in Castleman’s disease

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Abstract
A case is reported illustrating a rare and puzzling cause of long standing anaemia and abnormal liver function tests. The diagnosis of Castleman’s disease came to light only after an adrenal mass was noted during ultrasound examination. Removal of the mass led to a rapid reversal of all the abnormalities.

With the increasing range of diagnostic techniques in liver disease few abnormalities of ‘liver function tests’ should remain undefined but occasionally unexplained anomalies can be challenging. The same can be said for anaemia. In the case we describe low grade chronic ill health associated with mild anaemia, abnormal alkaline phosphatase and gammaglutamyl transferase (γGT) activities, and a very high erythrocyte sedimentation rate (ESR) in a young woman defied diagnostic clarification for over 20 years.

Case report
The patient was first noted to be anaemic without obvious cause at the age of 14, and she was taking oral iron intermittently but frequently thereafter. She was otherwise totally well and there was no previous medical history or family history of relevance. In 1971, at the age of 19 and while a university student, she had an acute illness considered to be infectious mononucleosis, with a typical history, lymphocytosis in the peripheral blood, and a positive monospot test. The haemoglobin concentration was 8.5 g/dl, the ESR 85 mm in the first hour, and the serum alkaline phosphatase and γGT were both raised. After she was clinically well these four laboratory abnormalities persisted. The liver was then, and remained, mildly enlarged.

In 1978 when she moved to north east Scotland, she was reasonably well, with only minor symptoms of anaemia. The previous year she had had a spontaneous abortion at eight weeks’ gestation, at which time she was given intramuscular, followed by oral, iron. Soon after this she was given an oral contraceptive pill, but this was stopped after only six weeks, after an extremely heavy period. At no other time did she have a contraceptive drug.

Clinically, she was mildly anaemic and had just detectable hepatomegaly. The haemoglobin concentration was 10.4 g/dl, mean cell volume 78 fL, and ESR 110 mm in the first hour. The serum vitamin B-12 and folate concentrations were normal. She had hyperglobulinaemia: total protein was 83 g/l (normal 61–74 g/l), of which only 32 g/l was albumin, and the serum immunoglobulin showed an excess of polyclonal IgG, at 25.4 g/l (normal 7–15 g/l). Her serum alkaline phosphatase activity was 297 U/l (normal 30–100 U/l), γGT 70 U/l (normal <35 U/l), and the rest of the liver function tests were normal.

Concentrations of hepatitis B antigen, serum caeruloplasmin, α1 antitrypsin, and α fetoprotein and antismooth muscle, anti-DNA, and antimitochondrial antibodies were all negative. Ultrasonic scan, gallium scan, and technetium sulphur colloid (99mTc) scan all showed mild hepatomegaly and mild parenchymal disease without focal abnormality; mild splenomegaly was also noted. Cholecsintigraphy was normal. Liver biopsy results showed sinusoidal dilatation (Fig 1), and it was suggested at that time that the histology was compatible with an extrahepatic lymphoma, although no corroborative evidence was found. Hepatic arteriography showed no abnormality except the minor hepatospleno-megaly.

Over the next few years, many investigations added little, but merely confirmed the above findings, although a weakly positive antismooth muscle antibody developed. Anaemia persisted (Fig 2). The serum transferrin level was variably normal or low and haemoglobin electrophoresis normal; there was no evidence of haemolysis, but a jejunal biopsy specimen showed minor villous atrophy and an excess of iron laden macrophages (presumably due to continuing oral iron treatment). The ESR remained high—sometimes as high as 150 mm in the first hour.

The patient’s overall condition remained unchanged. She was never totally well, but was able to cope with her life. In 1984, after six first trimester abortions she finally delivered a normal live infant. Her condition remained unchanged.

Figure 1: The liver shows dilatation of the sinusoids especially in zone 3, whereas the portal tract is normal. (Haematoxylin and eosin ×160 original magnification.)
over the next two years except that her spleen gradually increased in size. In December 1986 it was easily palpable and an ultrasonic scan of the abdomen was therefore repeated. The spleen was uniformly enlarged, but more striking was the finding of a parasplenic mass medial to the spleen, which was thought to be of the left adrenal gland, especially as it contained flecks of calcification (Fig 3). The findings were confirmed with computed tomography (Fig 4).

Biochemical studies for evidence of a secreting adrenal tumour, including serum and urinary cortisol levels, short synacthen test, and metadiobenzylguanidine uptake were negative. A laparotomy was performed in February 1987 by Mr N A Matheson.

At operation the liver was noted to be large but otherwise normal. The gastroepiploic veins were grossly dilated and the spleen was markedly enlarged but there was no other evidence of portal hypertension (and no obvious abnormality of the portal vein). A mass could be felt in the region of the left adrenal gland. There were no other abnormal findings. The mass was removed along with the spleen and tail of the pancreas, with which it was in continuity, since its benign or malignant state was not clear at that stage.

The tumour mass was composed of lymphoid tissue with a normal follicular architecture and contained several hyaline vascular lesions surrounded by plasma cells (Fig 5). Immunohistochemical studies indicated the presence of both kappa and lambda light chains in the plasma cells, thus the plasma cell population was polyclonal. Lymph sinuses were partially preserved and there were many reactive germinal centres. Focal calcification and non-specific giant cell formation were seen near areas of irregular sclerosis. The spleen weighed 814 g (grossly enlarged), and showed only an increase in red pulp, with dilatation of the sinusoids. Liver biopsy again showed only mild dilatation of the sinusoids around the central vein. The picture was considered to be that of Castleman’s disease of localised plasma cell type.

Since her operation the patient’s general health has improved markedly. The haemoglobin has been normal, without anaematinics. The alkaline phosphatase and yGT activities reverted to total normality within three days of operation for the first time since 1971 (Fig 2). The ESR was 10 mm in the first hour. At the time of writing, she had just delivered a second normal infant. A recent ultrasonic scan showed only a well formed fetus in utero, and no other abnormality. In particular the liver appears normal.

Discussion

Castleman was the first to study in detail lymphoid tumours of the mediastinum which had characteristic histological features and had been previously mistaken for thymomas radiologically and histologically. In 1954 he described the first known case, and in 1956 reviewed the published reports, describing many cases. Popularly known as Castleman’s disease this form of lymph node hyperplasia has many synonyms including angiofollicular hyperplasia, giant lymphoid hyperplasia, lymphoid hamartoma, and follicular lymphoreticuloma.

It was soon evident that the disease developed in regions other than the mediastinum. In 1983 Tida et al reviewed 222 published cases, finding that the majority of Castleman tumours occurred in the mediastinum but some were found in other areas of the body where lymph nodes are present: 14% in the neck, 5% in the mesentery, and 4% in the pelvis and retroperitoneum.

The disease is a benign condition characterised by the presence of soft tissue lymphoid tumours which vary in size but are usually large, often arise along the tracheobronchial tree, and present as mediastinal or hilar masses on routine chest radiographs. In 1972 Keller, Hochholzer and Castleman divided the histological findings into two types: (i) hyaline-vascular form
characterised by prominent vascular proliferation and hyalinisation and absence of lymph sinuses; (ii) plasma cell form with sheets of mature plasma cells in the interfollicular tissue and a normal or large size follicular centre.

Ninety per cent are of the hyaline-vascular form, which tends to occur in otherwise healthy young people, 70% of whom are under 30 years of age. The plasma cell form is a rare variant of Castleman's disease (10%) and can occur at any age, and most of these patients present with general malaise or unexplained fever. Investigations disclose refractory anaemia, raised ESR, polyclonal hyperglobulinaemia with particularly high concentrations of IgG, and sometimes hypoalbuminaemia. It is remarkable that all these signs and symptoms remit soon after the Castleman tumour is excised, so that evidence of a causal relationship is very strong.

More recently, several reports have suggested the existence of a multicentric variant of Castleman's disease, featuring the involvement of multiple lymphoid sites. There are clinical and histological similarities to the plasma cell form of Castleman's disease. These patients often have hepatosplenomegaly. Several groups of superficial lymph nodes may be enlarged, although sometimes the enlargement appears mainly in one region, spreading to other areas later. There is invariably anaemia, polyclonal hyperglobulinaemia, and occasionally bone marrow plasmacytosis. Histologically there are concentric hyaline-vascular structures in some follicles, increased vascularity of interfollicular areas, and the presence of abundant plasma cells as well as reactive germinal centres of irregular outline, like those of the localised plasma cell variant. It is not clear whether these three forms of this condition represent different entities or variants of the same disorder.

There is no agreement as to the nature of this unusual disease. Focal hyperplasia secondary to chronic inflammation is thought by some to be its basic cause; while others suggest that the lesion is most likely a hamartomatous malformation. Thus the aetiology and pathogenesis should still be considered as uncertain, although in this case the essential lymph node architecture was partially preserved, indicating that the mass probably arose in a lymph node. However, there seems no doubt that complete excision of the lymphoid mass where possible is the treatment of choice in Castleman's disease. Radiotherapy has not proved to be of value in this condition. The anaemia and hyperglobulinaemia associated with the plasma cell forms have resisted all types of treatment except excision of the underlying mass, whereupon these abnormalities completely resolve.

Castleman's disease commonly presents as an incidental discovery of enlarged lymph nodes. In this patient a puzzling constellation of abnormalities persisted for many years accompanied by low grade ill health (and repeated spontaneous abortions). The diagnosis finally came to light by observant assessment of an abdominal ultrasonic scan leading to laparotomy and histological denouement.

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