Haematology Grand Rounds

Unusual response of lymphocytic lymphoma (not hairy cell leukaemia) to splenectomy without chemotherapy

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Summary

An unusual period of prolonged disease control after splenectomy without chemotherapy was achieved in 3 cases of B-cell lymphocytic lymphoma with pancytopenia, massive splenomegaly, minimal lymphadenopathy and circulating hairy cells. The finding of distinctive histopathological features in the bone marrow, lymph nodes and splenic tissue enabled this unusual condition to be characterized and differentiated from hairy cell leukaemia, which may have similar presenting features and in which response to splenectomy is generally good.

Case reports

Case 1

A 52-year-old man presented in August 1981 having lost 10 kg in weight and complaining of pain and a sensation of fullness in the left upper quadrant of the abdomen. The spleen was enlarged by 16 cm and the liver by 4 cm, and a large left-sided pleural effusion was present, but there was no superficial lymphadenopathy. The haemoglobin value was 7.5 g/dl, the white cell count 3 x 10⁹/1 and the platelet count 85 x 10⁹/1; the differential count showed 45% neutrophils, 3% band forms, 47% lymphocytes and 5% monocytes. Eighty per cent of the lymphocytes showed well-marked surface immunoglobulin with IgG-K monoclonal staining and a low percentage of mouse erythrocyte rosette formation. Ten per cent of the lymphocytes were T cells which formed sheep red cell rosettes and reacted with a pan-T monoclonal antibody. The helper/suppressor T-cell ratio was preserved, although both lymphocyte subsets were quantitatively suppressed. An attempt at bone marrow aspiration was unsuccessful, and trephine biopsy revealed numerous paratrabecular lymphoid aggregates made up of small cleaved cells (Fig. 1). Increased reticulin was demonstrable in the bone marrow and residual haematopoietic tissue was estimated as 60% of normal.

Splenectomy was performed to relieve the patient’s discomfort and reverse the pancytopenia. The spleen weighed 3.077 g and measured 25 x 21 x 12 cm. The capsular surface was studded with small white nodules measuring between 0.1 cm and 0.5 cm in diameter.

Disease progression in patients with hairy cell leukaemia is usually well controlled by removal of the spleen, and chemotherapy in the early stages may be detrimental.1 In contrast, patients with lymphocytic lymphoma generally respond to appropriate cytotoxic drugs and splenectomy is rarely indicated except to relieve discomfort due to the size of the spleen or the severe pancytopenia of hypersplenism. It was therefore of interest to encounter 3 patients who fulfilled the diagnostic criteria for B-cell lymphocytic lymphoma and in whom, contrary to expectations, prolonged control of the disease was achieved following splenectomy alone.

Although the combination of circulating atypical lymphoid cells with cytoplasmic projections, pancytopenia, massive splenomegaly and minimal lymphadenopathy is usually characteristic of hairy cell leukaemia or leukaemic reticulo-endotheliosis (LRE), these features may be associated with an unusual variant of lymphocytic lymphoma.1 In both conditions tartrate-resistant acid phosphatase, hairy projections and ribosomal lamellas may be noted when tumour cells are examined.1 The differentiation between hairy cell leukaemia and lymphoma is based on histopathological features in sections of the bone marrow,1 lymph nodes and spleen.1

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Fig. 1. Section of a trephine biopsy specimen of bone marrow obtained from the posterior superior iliac spine. The high-power view of the paratrabecular lymphoid aggregate shows a monomorphic, small, cleaved lymphoid population. A special stain shows increased reticulin in this area. No haematopoietic cells are recognizable (H and E x 600).
of the splenic substance. Histological examination showed expansion of the white pulp with some extension of atypical lymphocytes into the red pulp along the penicilliary arteries but with minimal infiltration of the splenic cords. Many hyalinized germinal centres were present.

Examination of a para-aortic lymph node specimen showed the structure to be partially effaced with loss of distinction between paracortex, cortex and medulla, partial obliteration of the sinus pattern, and sheets of small lymphocytes in the perinodal tissues. The infiltrating cells were small lymphocytes with round nuclei which had prominent cytoplasmic projections similar to those on lymphoid cells in the blood and the same surface immunoglobulin pattern.

The patient was still well 20 months after splenectomy, with no evidence of disease progression. The haemoglobin value was 13.7 g/dl, the white cell count 14 x 10^9/1 and the platelet count 477 x 10^9/1. The differential count was 61% neutrophils, 2% eosinophils, 31% lymphocytes and 6% monocytes.

**Case 2**

A 51-year-old woman who was otherwise asymptomatic was discovered to have a spleen which was palpable 16 cm into the abdomen. The haemoglobin value was 8.5 g/dl, the white cell count 6 x 10^9/1 and the platelet count 80 x 10^9/1; the differential count showed 50% neutrophils, 45% lymphocytes and 5% monocytes. Facilities for lymphocyte marker studies were not available at this time (December 1974). An attempt at bone marrow aspiration was unsuccessful and trephine biopsy revealed an extensive nodular infiltrate composed of small round lymphocytes. Elective splenectomy was undertaken to relieve the patient's discomfort and reverse the pancytopenia. The spleen weighed 802 g and measured 20 cm at its greatest diameter. The cut surface showed diffusely scattered pale nodules. Histological examination showed a marked increase in lymphoid tissue with expansion of the white pulp and some extension of lymphocytes into the red pulp along the penicilliary arteries (Fig. 2). Sections of a para-aortic lymph node specimen showed a normal sinus pattern with an intact capsule. The paracortex and medullary cords were expanded by a uniform infiltrate of small lymphocytes, which were arranged around the germinal centres in some areas. Some of the lymphocytes had distinct small nucleoli (Fig. 3). Liver biopsy revealed an increased number of lymphocytes in the portal tracts. Facilities for ultrastructural studies were not available.

**Case 3**

A 65-year-old man presented in November 1976 with a 2-month history of abdominal discomfort. Examination revealed a 6 cm firm splenomegaly. The haemoglobin value was 10.6 g/dl, the white cell count 2.1 x 10^9/1 and the platelet count 38 x 10^9/1. The differential count showed 40% neutrophils, 44% lymphocytes and 16% monocytes. Bone marrow aspiration and trephine biopsy revealed a nodular infiltration of lymphoma comprising small round lymphocytes with an admixture of less than 10% mature plasma cells. Splenectomy was undertaken to reduce the patient's discomfort and reverse the pancytopenia. The spleen weighed 1380 g and the capsular surface was unremarkable.

Histological examination showed a marked increase in lymphoid tissue with expansion of the white pulp and extension of lymphocytes around the penicilliary arteries into the red pulp. The infiltrate was mainly composed of small lymphocytes, occasional prolymphocytes and immunoblasts also being present. Examination of a para-aortic lymph node specimen showed the structure partially to be effaced with loss of distinction between paracortex and medulla and partial obliteration of the sinus pattern. Sheets of lymphocytes were present in the perinodal tissues. The infiltrating cells were small lymphocytes. Studies of lymphocyte membrane surface markers were not carried out on the node and the marrow. Examination of lymphocytes in a peripheral blood specimen showed monoclonal staining for IgM-κ surface immunoglobulin and preservation of the distribution of T-lymphocyte subsets.

The patient has remained well for 6 years. When he was last seen the haemoglobin value was 13 g/dl, the white cell count 9 x 10^9/1 and the platelet count 400 x 10^9/1. The differential leucocyte count was unchanged but the monoclonal abnormality of peripheral blood lymphocytes had persisted.

**Discussion**

Hairy cell leukaemia or LRE is an unusual but clinically well-defined lymphoproliferative disorder which was thought to be a distinct pathological entity for a long time. It is characterized by...
massive splenomegaly, pancytopenia, minimal lymphadenopathy, monocytopenia and circulating atypical lymphoid cells with cytoplastic projections. However, it has become clear that an unusual poorly differentiated diffuse lymphocytic lymphoma may simulate all these features. In both conditions tartrate-resistant acid phosphatase, ribosomal lamellae and hair-like projections may be found when tumour cells are examined.

In most cases of LRE the tumour cells are of B-lymphocyte origin, bearing monoclonal surface immunoglobulin which can be demonstrated by appropriate antibody studies, and have the capacity to synthesize immunoglobulin in vitro; 2 in other cases they may resemble monocytes 10 or, more rarely, express the T-lymphocyte phenotype. 11,12 The reason for these findings is not clear, but it has been suggested that the tumour cell may be a hybrid, expressing different antigenic determinants, and that the hairy cells may have the inherent capacity to differentiate along divergent cell lines; such a concept is consistent with tumour heterogeneity. Alternatively, distinct subgroups of LRE may exist. More recently, murine monoclonal antibodies have been used to examine these possibilities in greater detail and their wider application may help resolve this diagnostic dilemma. 13

Differential between LRE and B-cell lymphocytic lymphoma may also be based on histopathological features of the bone marrow, liver and spleen and lymph nodes. 14 The distribution of tumour cells in the bone marrow in lymphoma tends to be paratrabecular, and as a general rule the component cells are small cleaved lymphocytes. In hairy cell leukaemia, reticulin and mature collagen are prominent and there is diffuse infiltration of the bone marrow by round cells with slightly larger and more vesicular nuclei than those found in small cell lymphoma. Ultrastructural studies characteristically show the borders of these cells to have prominent interdigitating surfaces, whereas in lymphoma cell borders are smooth. In lymphocytic lymphoma the spleen is often macroscopically nodular and the white pulp is predominantly involved, with some inconspicuous extension into the medullary area. In contrast, there is extensive involvement of the red pulp in hairy cell leukaemia, and encroachment into the malpighian corpuscles is limited. In the lymph nodes lymphomatous infiltration is characteristically generalized with complete effacement of the structure, whereas in LRE involvement is usually sinusoidal or confined to the interfollicular area. When liver biopsy specimens are available the portal tract is found to be involved in lymphoma and sinusoidal invasion is characteristic of LRE.

Accuracy distinction between these two clinically similar conditions is of major importance because their management is different. It is generally agreed that patients with a definite diagnosis of hairy cell leukaemia should undergo splenectomy and then be subjected to a period of observation; chemotherapy is usually reserved for those with late-stage disease, when gradually expanding tumour mass impairs haemopoiesis and results in worsening pancytopenia. Infection resulting from neutropenia and monocytopenia rather than haemorrhage due to thrombocytopenia is the usual cause of death in such cases. In contrast, a symptomatic patient with a definite diagnosis of lymphocytic lymphoma would initially be managed with a combination of an alkylating agent and a corticosteroid or radiotherapy. Splenectomy would be reserved for those with persisting discomfort due to splenic enlargement or those in whom adequate therapy to control disease progression is prevented by splenomegaly and discomfort due to tumour mass.

At present splenectomy does not form part of the initial attempt simultaneously to decrease abdominal discomfort and reverse pancytopenia in patients with B-cell lymphocytic lymphoma. The remarkable results obtained in these 3 patients, who have not required additional chemotherapy, can be explained in two ways. It could be argued that these cases represent a forme fruste of LRE. We believe that the pattern of infiltration by the malignant cells does not support this theory, being consistent only with a diagnosis of B-cell lymphocytic lymphoma. Alternatively, these cases might represent a variant of lymphoma (the disease progressing very slowly because the patients were elderly), which can be managed by splenectomy alone.

We should like to make it clear that we are not suggesting that removal of the spleen routinely replace chemotherapy in cases of B-cell lymphocytic lymphoma but that it should be considered for patients with clinical features mimicking those of LRE.

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