Small cell variant of Ki-1 lymphoma associated with myelofibrosis and a novel constitutional chromosomal translocation t(3;4)(q13;q12)

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Abstract
An unusual case of small cell variant of Ki-1 non-Hodgkin’s lymphoma diagnosed one year after an original diagnosis of idiopathic myelofibrosis is reported. On the second occasion, the patient presented with fever, lymphadenopathy and hepatosplenomegaly. A lymph node biopsy specimen confirmed a diagnosis of small cell variant of Ki-1 lymphoma. A repeat bone marrow biopsy specimen showed myelofibrosis with no evidence of lymphomatous infiltration, but cytogenetic studies on blood, bone marrow and skin fibroblasts revealed a novel chromosomal translocation t(3;4)(q13;q12).

Keywords: Ki-1 lymphoma, myelofibrosis.

Small cell Ki-1 lymphoma is a variant of Ki-1 anaplastic large cell lymphoma (ALCL), which has been described recently. The specific chromosomal translocation t(2;5)(p23;q35) has been a consistent finding in association with both variants of Ki-1 lymphoma. The lymphoma is a recognised, albeit uncommon, cause of myelofibrosis. However, idiopathic myelo-
patient who subsequently developed the small cell variant of Ki-1 lymphoma and who has a previously unreported constitutional chromosomal translocation t(3;4)(q13;q12).

Case report
A 47 year old man presented in October 1993 with a two day history of fever, sore throat and swollen neck, and a four week history of weight loss and night sweats. In January 1993 he had been diagnosed as having idiopathic myelofibrosis, after a bone marrow biopsy was carried out for an incidental finding of anaemia. The patient remained transfusion dependent, and required blood transfusions every two months to maintain his haemoglobin level above 8 g/dl. On readmission to hospital, the patient was pyrexial, with a temperature of 38.5°C, and had enlarged tonsils with left-sided cervical swelling, lymphadenopathy of both axillae and the right groin, and hepatosplenomegaly. Ultrasound examination of the neck showed extensive cervical lymphadenopathy. Flexible endoscopy showed inflammatory swelling of the lateral pharyngeal wall extending to the piriform fossa. A computed tomography (CT) scan of the thorax was normal. Abdominal ultrasound and CT scan confirmed hepatomegaly with no focal lesion; the spleen was 13 cm long, and two small nodes associated with the porta hepatitis (0.9 cm) and coeliac axis (1.2 cm) were noted. The patient developed airway obstruction secondary to the pharyngeal cellulitis and required tracheotomy. The cellulitis responded to combined broad spectrum antibacterial, antiviral and antifungal agents, and the tracheotomy wound healed uneventfully. The bone marrow, left axillary node and right groin node were biopsied.

INITIAL LABORATORY INVESTIGATIONS
Peripheral blood count revealed a haemoglobin of 7.2 g/dl (normochromic normocytic picture), a white cell count of 1.1 x 10^9/l and a platelet count of 195 x 10^9/l. The peripheral blood smear was leukaerythroblastic with occasional atypical immature mononuclear cells. The erythrocyte sedimentation rate was 120 mm in the first hour. Renal function was normal but liver function was deranged: albumin, 19 g/l; total bilirubin, 32 µmol/l; alkaline phosphatase, 217 IU/l; alanine aminotransferase, 56 IU/l. The patient’s total protein concentration was 57 g/l, his IgG level was 20.4 g/l (normal range 5.3–16.3 g/l), IgA was 2.3 g/l (normal range 0.8–4.0 g/l) and IgM was 2.1 g/l (normal range 0.5–2.0 g/l). No paraprotein was detected. Viral serological studies showed that the antibody titre to Epstein–Barr virus (EBV) nuclear antigen was >2, IgG antibody titre to EBV viral capsid antigen (VCA) was 160, and IgM antibody to EBV VCA was negative. Serological markers for cytomegalovirus, hepatitis A and B, and HIV were negative.

Figure 1 (A) Lymph node histology showing polymorphic infiltrates with atypical lymphocytes and extramedullary haematopoeisis (haematoxylin and eosin, × 200); (B) bone marrow trephine biopsy specimen showing grade III myelofibrosis (mast reiculain stain)

Figure 2 Cytogenetics: metaphase chromosomes seen in peripheral blood showing 46XY, t(3;4)(q13;q12).

fibrosis is an extremely rare finding in association with lymphoma, with only three cases having been described previously. Here, we present a case of idiopathic myelofibrosis in a
**HISTOPATHOLOGICAL FINDINGS**

Histological examination of the lymph nodes (fig 1A) showed fragments of lymphoid tissue with noticeable paracortical and sinusaloid expansion and vascular proliferation. The sinusoids and perisinusoidal regions contained many blastic lymphocytes with large irregular nuclei and prominent nucleoli. The paracortical region contained mainly small lymphoid cells with irregular nuclei and clear cytoplasm. There was evidence of extramedullary haematopoiesis in the sinusoids (myeloid precursors and megakaryocytes) and numerous plasma cells and plasmablasts were seen. Immunocytochemistry showed the small T lymphocytes to be CD3+, CD43+, CD45RO+, CD20− and the large lymphoblasts to be mostly CD30+, CD3−, CD45RO+, CD45−. These findings were consistent with the small cell variant of Ki-1 lymphoma. Bone marrow biopsy specimens taken in November and December showed 50% cellularity, grade III reticulin myelofibrosis (fig 1B), trilineage haematopoiesis, and normal numbers of megakaryocytes. No myelodysplastic changes were noted and there was no evidence of lymphoma.

**CYTOGENETIC STUDIES**

Cytogenetic studies were done on short term synchronised cultures of unstimulated bone marrow and phytohaemagglutinin stimulated peripheral blood samples. The metaphase chromosomes obtained were stained for G bands using Wright’s stain and karyotyped according to ISCN 1991. Metaphase chromosomes seen in both bone marrow and peripheral blood samples showed 46XY, t(3;4)(q13;q12) (fig 2). No other abnormalities, and specifically no t(2;5) translocations could be identified and there were no normal metaphases. As there was no evidence of either bone marrow involvement or of circulating lymphoma cells, a constitutional chromosomal defect was suspected. Skin biopsy and analysis of metaphase chromosomes derived from the cultured skin fibroblasts confirmed an identical translocation in all metaphases examined.

**PROGRESS**

Fever persisted until chemotherapy with a standard CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) regimen commenced, when it resolved within 24 hours. Following the first cycle, further chemotherapy was delayed, initially because of prolonged pancytopenia and then because the patient declined further treatment and defaulted from follow up for four months. Subsequently, repeated admissions have been required for intravenous antibiotic therapy for septicemia, usually due to severe skin sepsis with cellulitis. Despite having received only one course of CHOP over 18 months ago, the lymphoma continues to run an indolent course. The lymphadenopathy has regressed, although both clinical examination and abdominal ultrasound confirm the persistence of hepatosplenomegaly. The intra-abdominal nodes have not increased in size. The patient has remained anaemic requiring intermittent red cell support. Repeat bone marrow examination six months after the only course of chemotherapy confirmed a hypocellular bone marrow with fibrosis and no evidence of lymphoma. The white cell count currently remains low, between 3-0 and 4-0 x 10^9/l, but the platelet count is normal. However, there is notably reduced bone marrow reserve, with severe pancytopenia developing rapidly following any infection.

**Discussion**

Small cell Ki-1 lymphoma accounts for approximately 10% of cases of Ki-1 ALCL. Small lymphoid cells predominate in the lymph node biopsy specimen with a minority component of large blastic lymphocytes. Ki-1 ALCL is classified as a high grade lymphoma but has a surprisingly variable clinical course, with episodes of apparent clinical remission, and prolonged survival despite multiple recurrences.

No specific association is known between primary myelofibrosis and lymphoma. In the two case reports describing three patients with concomitant or subsequent lymphoma associated with myelofibrosis, there was no bone marrow involvement with lymphoma. Bone marrow involvement in Ki-1 ALCL is in any case unusual, affecting approximately 10–15% of cases overall, and may be associated with histiocytosis rather than fibrosis. In a clinicopathological study of 41 patients with Ki-1 ALCL by Chott et al bone marrow involvement was described in seven patients, all of whom fell within a subgroup of patients with a monomorphic infiltrate of predominantly smaller cells. There was no distinctive pattern to the involvement in these cases, being either diffuse or focal, and ranging from a low degree of infiltration to complete effacement.

The specific chromosomal translocation t(2;5)(p23;q35) has been a consistent finding in association with Ki-1 ALCL. Of nine patients who were documented originally as having small cell Ki-1 lymphoma variant, one had cytogenetic studies performed on involved skin, and four had cytogenetic studies performed on bone marrow. The same translocation, together with multiple variable abnormalities affecting chromosome 7 and the sex chromosomes, was found in all cases. The translocation in our patient, 46XY t(3;4)(q13;q12) has not been described previously. The fact that it was isolated consistently in all metaphases examined from both blood and bone marrow, despite lack of evidence of morphological involvement by lymphoma, suggested that it was constitutional and this has been confirmed by chromosomal analysis of the patient’s skin fibroblasts.

The significance of this cytogenetic finding is unknown. However, the c-kit proto-oncogene that encodes the membrane tyrosine kinase receptor for stem cell factor, and the gene for platelet derived growth factor (PDGF) receptor A are localised to bands q11–13 of chromosome 4 in humans. Also, the small inducible gene family that encodes platelet factor 4, β-thromboglobulin and other related proteins which
are involved in the processes of coagulation, inflammation, immune response and wound repair, have been localised to chromosome bands 4q12–q13. It is intriguing to speculate that this constitutional genetic abnormality may have not only contributed to this patient's myelofibrosis by affecting PDGF production, but that it may have played a role in the development of his lymphoma and the pattern of his repeated septic episodes. The patient's atypical course and response to therapy may therefore reflect an unusual pattern of a rare disease modified by an unique underlying constitutional chromosomal aberration.

Addendum

Since the original submission of this article, a report has appeared of a non-constitutional (3;4) translocation occurring in association with a myeloproliferative disorder. (Myint H, Chacko L, Mould S, Ross F, Oscier DG. Karyotypic evolution in a granulocytic sarcoma developing in a myeloproliferative disorder with a novel (3;4) translocation. Br J Haematol 1995; 90:462–4.)

Langerhans cell histiocytosis forming an asymptomatic solitary nodule in the spleen

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Abstract

A case of solitary Langerhans cell histiocytosis (LCH) in the spleen of a 29 year old Chinese man, discovered incidentally at necropsy, is reported. This is the first documented case of LCH confined to the spleen and suggests that LCH should be included in the differential diagnosis of space occupying lesions in the spleen. (J Clin Pathol 1996;49:262–264)

Keywords: Langerhans cell histiocytosis, spleen.

The common denominator of all forms of Langerhans cell histiocytosis (LCH), formerly known as histiocytosis X, is the presence of histiocytes phenotypically similar to the Langerhans cell of the epidermis. The disease has a wide range of clinical and pathological presentations. Almost every organ in the body can be involved in LCH, the favoured sites being the skin, bone, lungs, and lymph nodes. While splenic infiltration is part of the multisystem disease in LCH, histiocytosis confined to the spleen, to our knowledge, has never been documented in the literature.

Case report

An otherwise healthy 29 year old Chinese man developed sudden onset retrosternal chest pain, shortness of breath and sweating. He then de-
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