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CLINICAL

Rare and fatal complications of an indolent disease – chronic lymphocytic leukaemia

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ABSTRACT Chronic lymphocytic leukaemia is often considered an indolent disease with a variable course, and patients with this disorder are monitored by general physicians and practitioners. The authors detail two cases of chronic lymphocytic leukaemia with very rare and fatal complications, namely haemophagocytic lymphohistiocytosis and Hodgkin's transformation. This is followed by a brief overview of these conditions.

KEYWORDS Chronic lymphocytic leukaemia, fatal complications, haemophagocytic lymphohistiocytosis, Hodgkin's transformation, immunosuppression, lymphoid malignancy

DECLARATION OF INTERESTS No conflict of interests declared.

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INTRODUCTION

Chronic lymphocytic leukaemia (CLL) has an extremely heterogeneous clinical course.[1] Modern chemotherapy and modulatory immunotherapy can help achieve excellent response rates,[2] yet the disease is not curable.[3] Patients can survive for decades with minimal or no treatment, whereas some succumb rapidly to the disease.[4] The following two cases illustrate the rare and fatal complications of chronic lymphocytic leukaemia. It is not the first time that they have been reported: our intention is to highlight that this indolent disease, which often presents to and is monitored by general physicians and practitioners, has some very uncommon and terminal complications.

CASE 1

A 63-year-old male with severe Parkinson's disease presented with a two-week history of fever and weight loss. Two years previously he had been diagnosed with non-progressive Binet and Rai stage A(O) chronic lymphocytic leukaemia, for which he had not required any treatment.

Clinically, he had no evidence of palpable lymphadenopathy or hepatosplenomegaly. Investigations revealed Hb 11.9 g/dl, a white cell count of 2.6 x 10^9/l, a platelet count of 80 x 10^9/l, prothrombin time 16 seconds, serum fibrinogen 0.5 g/l, serum bilirubin 38 micromol/l, serum triglycerides 3.3 mmol/l and serum LDH 1242 U/l, with normal activated partial thromboplastin time and serum creatinine levels. His blood and urine bacterial and viral cultures were negative.

A trephine biopsy and bone marrow aspirate showed a modest nodular infiltrate typical of chronic lymphocytic leukaemia with accompanying haemophagocytosis. Figure 1 illustrates a typical haemophagocyte, a mononuclear cell engulfing erythroid cells.

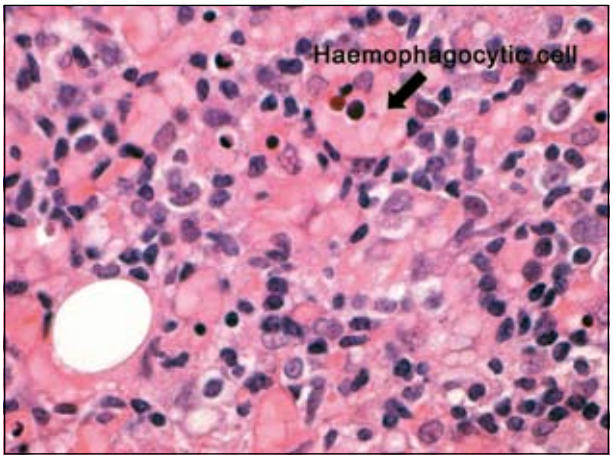

FIGURE 1 Bone marrow aspirate from a 63-year-old male, diagnosed with chronic lymphocytic leukaemia two years earlier. Stained with haematoxylin and eosin, it shows a modest nodular infiltration typical of chronic lymphocytic leukaemia accompanied by a haemophagocyte, a mononuclear cell engulfing erythroid cells.

In the absence of any identifiable infective cause, this pathology was attributed to the patient's underlying chronic lymphocytic leukaemia. Treatment including high-dose methylprednisolone, ciclosporin and intravenous immunoglobulins was considered. However, due to his severe debilitating co-morbidity with Parkinson's disease, he declined treatment and died over the next week.

CASE 2

A 57-year-old male presented with high-grade fever, weight loss, night sweats and cervical lymphadenopathy. Seven years earlier he had been diagnosed with Binet stage A(O) chronic lymphocytic leukaemia. Over this period he had immune thrombocytopenia, which was treated successfully with steroids and intravenous immunoglobulins, followed by a splenectomy. He had

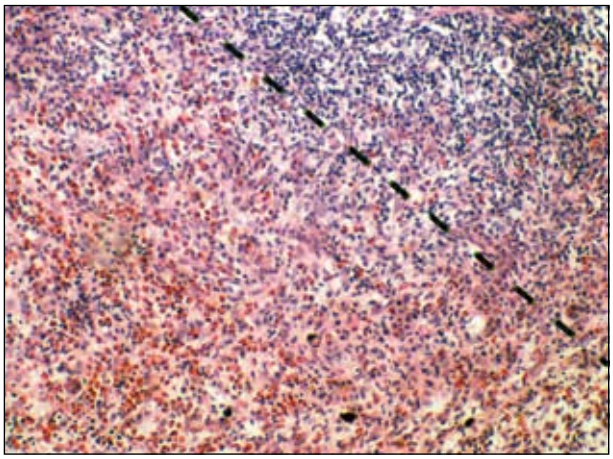

FIGURE 2 Section from the bone marrow trephine biopsy of a 57-year-old male diagnosed to have Binet stage A(O) chronic lymphocytic leukaemia seven years earlier. Stained with haematoxylin and eosin, the histology shows the nodular infiltrate of CLL in the right half and in the left half the eosinophilic infiltrate characteristic of Hodgkin's disease.

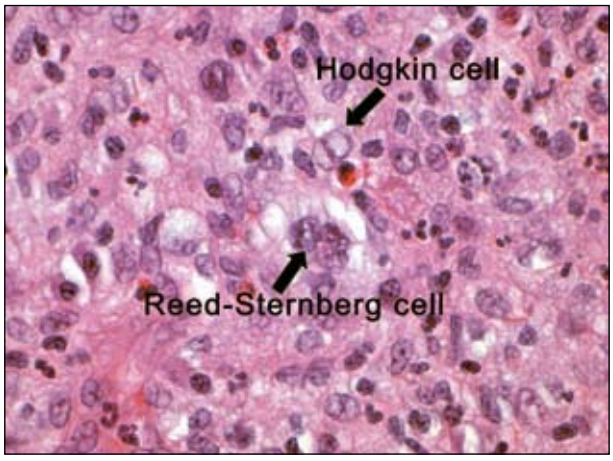

FIGURE 3 Lymph node section stained with haematoxylin and eosin shows the presence of a large mononuclear cell characteristic of Hodgkin's disease (Hodgkin cell) with a classical Reed-Sternberg cell.

also required chemotherapy for increasing lymphadenopathy. He had responded well to chlorambucil, followed by combination therapy in the form of fludarabine, cyclophosphamide and rituximab, and achieved a complete remission.

The patient was now found to have Hb 9 g/dl, a white cell count of 8.6 x 10^9/l, a platelet count of 181 x 10^9/l, normal renal and liver function tests, negative autoantibody screen and no growth on bacterial and viral cultures. His bone marrow aspirate and cervical lymph node biopsies showed nodular infiltrates of chronic lymphocytic leukaemia and the presence of large mononuclear cells, which morphologically and on immunophenotyping were consistent with classical Hodgkin's disease. Hence, a diagnosis of Reed-Sternberg (or Hodgkin's transformation) of chronic lymphocytic leukaemia was made. Figure 2 is an overview of the bone marrow trephine biopsy histology, illustrating the nodular infiltrate of CLL in the right half, and the eosinophilic infiltrate characteristic of Hodgkin's disease on the left. Figure 3 shows a lymph node section with a large mononuclear cell characteristic of Hodgkin's disease (Hodgkin cell) and a classical multinucleated Reed-Sternberg cell.

The patient was treated with ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine and dacarbazine) chemotherapy. Despite this, he deteriorated with *Escherichia coli* proven bacteraemia and died despite intensive antimicrobial, inotropic and ventilatory support.

DISCUSSION

Chronic lymphocytic leukaemia is a heterogeneous B-lineage lymphoid malignancy, wherein some cases may be asymptomatic and never require any treatment and others have aggressive disease. New therapeutic modalities have substantially improved response rates and outcomes, but the disease remains incurable.[6] Complications such as autoimmune haemolytic anaemia and immune thrombocytopenia are reported in a quarter of cases.[7] These usually respond to immunosuppression. The complications reported in this paper are rare and have a high mortality.

Case 1 was diagnosed with haemophagocytic lymphohistiocytosis. This life-threatening syndrome is caused by inappropriate activation of T-lymphocytes and histiocytes, and increased production of cytokines and haemophagocytosis.[8] Fever, pancytopenia, hypofibrinogenaemia, raised lactate dehydrogenase level and haemophagocytosis in the bone marrow, as seen in this case, are some of the cardinal features of this hyperinflammatory condition.[9] Hepatosplenomegaly, elevated liver enzymes, lymphadenopathy, thrombocytopenia and disseminated intravascular coagulation are commonly occurring features.[10] Awareness of the syndrome is important to enable prompt diagnosis.[9]

Haemophagocytic lymphohistiocytosis is associated with infections, neoplasms, collagen vascular diseases and immunodeficiency states.[11] In patients with CLL the haemophagocytosis is probably related to an underlying opportunistic viral infection, which may be a consequence of the immunesuppressed state.[12] Immunosuppressive and cytotoxic chemotherapy can induce remission in some patients, while others may require allogeneic bone marrow transplantation.[13] The reported mortality is 60%.[14]

Case 2 was diagnosed as Hodgkin's transformation of CLL. This again is a rare form of transformation of the rather indolent disease to an aggressive lymphoid malignancy. Up to 5% of CLL cases ultimately transform to a high-grade haematological malignancy, mostly to

high-grade B cell lymphomas. In a small minority of cases, the transformation is to Hodgkin's disease. Richter's syndrome is one of the other haematological malignancies that can arise from this leukaemia.[15] Hodgkin's transformation of CLL can occur at any site, is histologically of the mixed cellularity type and can arise up to 17 years after initial diagnosis.

It is known to be triggered by Epstein-Barr virus infection and is seen most often in patients treated with fludarabine chemotherapy in the past.[16] It has been suggested that its origin is restricted to those with evidence of somatic V(H) hypermutation (which relates to the cytogenetic characteristics).[17] Fever, weight loss, lymphadenopathy, hepatosplenomegaly, hypercalcaemia and infection are some of the presenting features of this condition. It is associated with a lower response rate to treatment as compared with *de novo* Hodgkin's lymphoma, and its median survival is reported as only 0.8 years.[15]

This clinical heterogeneity in CLL raises the issue of identifying those patients with high-risk disease, and tailoring treatment accordingly. Hence cytogenetics are now considered an essential prognostic factor. Unmutated IgV(H) genes and the expression of CD38 and ZAP-70 have emerged as the most useful biomarkers.[18] Genetic sub-groups with distinct clinical features have been identified, such as chromosome 11q deletion, associated with bulky lymphadenopathy and rapidly progressive disease, and 17q deletion, associated with a shorter survival time and resistance to the chemotherapeutic agent fludarabine.[19] However, further clinical trials and analysis are required to determine if these are prognostic markers for survival time or a type of therapy.[20]

The presentation of these two cases and discussion are an attempt to focus on the rare and often fatal complications of chronic lymphocytic leukaemia. This disease is often actively monitored by general physicians and practitioners, and it appears prudent that they are aware of the rare and aggressive course it can take.

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