Richter's Syndrome: A Case Report

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Key Words

Richter's syndrome • Chronic lymphocytic leukaemia •
Nigeria • Haematological malignancies

Abstract

Objective: To report a case of Richter's syndrome found in one of the teaching hospitals in Nigeria in the context of sparse earlier reports of Richter's syndrome in western Africa. **Clinical Presentation and Intervention:** A 52-year-old male had been diagnosed earlier as having chronic lymphocytic leukaemia (CLL) and treated for 6 months with chlorambucil, although compliance was poor and the patient eventually stopped treatment. He presented to our hospital 18 months later with clinical features in keeping with Richter's syndrome. The blood and bone marrow smear review, together with fine-needle aspiration cytology of the masses, showed diffuse large cells of non-Hodgkin lymphoma consistent with the Richter's syndrome stage of CLL. There was significant improvement in response to the first 4 cycles of CHOP chemotherapy (consisting of cyclophosphamide, doxorubicin, vincristine and prednisolone) instituted, but then there were features of relapse. **Conclusion:** The case report serves to increase awareness and improve the index of suspicion about the terminal phase of CLL and low-grade lymphoma. It equally emphasizes the great need to strengthen further the laboratory diagnosis of haematological malignancies in developing countries.

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Introduction

Richter's syndrome (diffuse large-cell lymphoma) is a complication and disease transformation of chronic lymphocytic leukaemia (CLL) where clinical features, laboratory findings and treatment clearly differ from that of CLL [1]. Unlike CLL, it is a very aggressive disease with progressively increasing peripheral lymphadenopathy and extranodal involvement in which median survival has been established to be only 5 months [1, 2]. Lactate dehydrogenase is often elevated and there is usually monoclonal gammopathy. Immunoglobulin G gene rearrangement and light-chain isotype analysis support a common origin for CLL and large-cell lymphoma [1, 3]. Although the diagnosis here was based on clinical and cytological examination, a definitive diagnosis often requires cytochemistry, immunophenotyping and cytogenetic analysis. Large-cell lymphoma remains a serious complication of CLL, but advancement in the management of CLL has brought a better outlook of the complication [1, 3, 4].

Case Report

A 52-year-old male was referred by his company's medical centre in November 2006 with complaints of recurrent fever for 20 months, neck swelling for 5 months and progressive abdominal swelling for 3 months. The painless abdominal swelling started on the left side and progressively increased to the size of a football. The patient's illness actually started in early 2004, but he remained stable until March 2005 when he started experiencing

weight loss and night sweats. He presented to Quwalalada Specialist Hospital, Abuja, where a diagnosis of CLL was made based on complete blood count and bone marrow aspiration review. He was transfused with 2 units of packed red cells and then commenced on chlorambucil, 5 mg daily, which he complied with for just 6 months and subsequently discontinued. In September 2006, the patient developed painless, progressively increasing neck swelling, which later involved the right side. He also developed anaemia, necessitating the infusion of additional 3 units of packed red cells, for a total of 7 units. It was at this point that he was referred to the University College Hospital, Ibadan.

Examination at presentation revealed a middle-aged man who was pale, ill-looking, afebrile and anicteric with generalized lymphadenopathy. The cervical lymphadenopathy was massive (7 × 6 cm), bilateral and non-tender, giving the appearance of a bull neck. There were bilateral epitrochlear lymph nodes (4 × 6 cm), bilateral inguinal and axillary lymph nodes and massive bilateral pitting oedema. The abdomen was grossly distended, with about 5 craggy abdominal masses 2–4 cm in diameter. There was a 10-cm firm, non-tender hepatomegaly and an 8-cm firm, non-tender splenomegaly with an overlying ovoid mass that was not attached to the abdominal wall. There were moderate ascites. Respiratory and cardiovascular findings were essentially normal.

The laboratory investigations revealed anaemia (packed cell volume 26%), extreme leukocytosis (WBC of 802,000/dl) and moderate thrombocytopenia (platelet count of 50,000/mm³). ESR was 0.3 mm/1st h. Blood smear showed that 90% of the white cells were large lymphoid cells with abundant, deeply basophilic cytoplasm. The nuclei were large with lacey chromatin. The biochemical findings were within reference ranges, except for a uric acid level of 7.5 mg/dl. Abdominal ultrasound scanning confirmed hepatosplenomegaly, multiple intra-abdominal lymphadenopathy and bilateral grade II renal parenchyma disease with back pressure renal changes. Bone marrow aspiration showed hypercellular marrow with heavy infiltration of abnormally large lymphoid cells having abundant basophilic cytoplasm. Their nuclei were large with open chromatin with inconspicuous nucleoli, indicating immunoblastic transformation in a CLL patient. A few smudge cells were also present.

The patient was put on a 21-day-cycle CHOP chemotherapy. There was 90% regression in the size of the masses. After 2 cycles, transfusion requirement decreased substantially, and the white cell count reduced from 802,000 to 60,000/mm³, but still with 90% lymphocytosis. The patient, however, failed to adhere strictly to the 21-day cycle and hence, at the 5th cycle, which was initiated in March 2007, the masses were noticed to be recurring and by the 6th cycle, administered in April 2007, the size of the masses were 70% of those at presentation. This progressive disease was attributable to the poor prognostic nature of the disease. The patient was referred to the National Hospital of Abuja on request.

Discussion

Richter's syndrome is a disease transformation of CLL which affects about 3–5% of CLL patients [3], although the American Society of Haematology recently

reported a higher incidence of 8%. Prolymphocytic leukaemia is a more frequent disease transformation which has been documented in 10% of CLL patients [1]. Other rare transformations include multiple myeloma and acute leukaemia, which usually occur in less than 1% of CLL patients [1]. The literature search did not reveal any earlier report of CLL progressing to Richter's syndrome in Nigeria.

This case is a typical immunoblastic transformation in CLL, which is very rare, especially in Nigeria. There was a prolonged chronic phase during which the patient failed to comply with therapy and migrated from one hospital to another. This was followed by an aggressive phase during which the patient became very ill, was dependent on transfusion and had eruption of fast-growing lymph nodes and abdominal masses.

The emergence of Richter's syndrome in a patient with CLL has largely been attributed to severe immunodeficiency compounding the disease, including viral infection, especially EBV trigger, trisomy 12 or chromosome 11 abnormalities and multiple genetic defects like mutation of the p53 tumour suppressor genes, p16INK4A and p21, and loss of p27 expression. Deletion of Rb, increased copy of C-MYC and decreased expression of the A-MYB gene have also been described [5]. These abnormalities cause the CLL cells to proliferate and, by facilitating the acquisition of new genetic abnormalities, to transform into Richter's syndrome cells.

The very low report rate of Richter's syndrome in this environment might be attributed to a low index of suspicion. Another possibility is that probably our CLL patients do not live long enough for blastic transformations to occur. What we commonly see, by casual observation, is prolymphocytic transformation in CLL. Transformations to multiple myeloma or acute leukaemia, which are other possibilities, are yet to be reported.

Richter's syndrome is a very difficult disease to treat and the prognosis is said to be very poor. The median overall survival duration is estimated to be 9.1 months [3]. Therapeutic strategies include intensive chemotherapy developed for high-grade non-Hodgkin lymphoma or acute lymphocytic leukaemia, monoclonal antibodies and stem cell transplantation. This index case responded appreciably well to CHOP chemotherapy before showing signs of drug resistance. The response rate to these therapeutic strategies is said to range from 5 to 43% [2]. The facilities for monoclonal antibody therapy and stem cell transplantation are not yet available in our setting.

There is a great need to improve facilities and manpower for the diagnosis and treatment of haemato-oncology patients. Access to immunohistochemical diagnosis and cytogenetic analysis, the use of new generation drugs like fludarabine, alemtuzumab (Compath), rituximab for the treatment of lymphoproliferative disorders still remain beyond the reach of an average Nigerian patient. Health policy makers in Nigeria should, therefore, pay attention not only to manpower development, but also to setting up modern regional or supraregional diagnostic services.

Conclusion

Although a cure is not achievable for CLL or low-grade lymphoma except by stem cell transplantation, ensuring good quality of life through good control with lympholytic drugs, transfusion support, and prevention and control of infection always alleviate suffering and contribute to manage the illness. Health care professionals must be alert for possible transformations because Richter's syndrome and other forms of the condition require aggressive management.

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