The Emergence of Hodgkin's Disease in a Patient with Long-standing Chronic Lymphocytic Leukemia

Case Report and Review of the Literature

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B-cell chronic lymphocytic leukemia (CLL) is the most common form of leukemia in Western countries, typically afflicting persons over 50 years of age. With the exception for the possible curative potential of allogeneic bone marrow transplantation, CLL is invariably a fatal disorder. In about 10% of CLL patients the terminal event is transformation into diffuse large cell lymphoma, the so-called Richter's syndrome (1). Furthermore, another 10% of CLL patients terminally show a morphological transformation of blood lymphocytes into prolymphocytes (2), and in extremely rare cases progression into acute lymphoblastic leukemia (3) or multiple myeloma (4). Since relatively little recognition has been given to Hodgkin's disease (HD) supervening in CLL, we report a case of HD emerging in a patient with longstanding CLL and review the literature regarding this rare phenomenon.

Case report. In 1976, a 54-year-old asymptomatic white male was referred to our department for evaluation of leukocytosis, 44×10^9/l, with 96% lymphocytes on differential count. Haemoglobin and platelet counts were normal. Physical examination revealed slightly enlarged lymph nodes in both axillae as well as in the groins. The liver and spleen were normal as was the chest x-ray. Bone marrow aspiration showed predominance of diffusely infiltrating lymphocytes and lymph node biopsy confirmed a diagnosis of CLL. The patient was staged as Binet A, Rai I and was observed without treatment until 1981 when his disease progressed with increasing white blood cell count (WBC), palpable lymph nodes on the neck and a marked growth of his spleen. He was given continuous chlorambucil 2–4 mg daily for one year resulting in a partial response (PR) using recommended response criteria (5). Except for three months chlorambucil treatment in 1984 due to rising WBC, the patient was off therapy and asymptomatic until 1988 when again he exhibited tumour progression, this time with anaemia (haemoglobin 10.0 g/dl). Eight courses of cyclophosphamide, vincristine and steroids (COP) was administered over a period of 8 months, and again the patient attained PR. In the following years he had very slow regrowth of palpable lymph nodes and spleen but since he was asymptomatic, treatment was not instigated. Profound hypogammaglobulinemia resulted in 6 pneumonias between 1990 and 1992. Pulmonary work-up, including bronchoscopy, showed no signs of bronchial obstruction or bronchiectasis. The patient was started on subcutaneous gammaglobulin 50 mg/kg body weight per week (6), which led to an increase of the serum IgG to normal levels and radically decreased the number of infectious complications. In the latter part of 1993 the patient experienced a growth of submandibular lymph nodes on the right side causing local symptoms and was treated with local irradiation. From January 1994, the patient's clinical course was essentially uneventful until November 1995, when he presented with repeated periods of high fever (39–40°C), chills, malaise and highly elevated C-reactive protein (200–400 mg/l). The patient had recurrent episodes, approximately every 2 weeks for three months, was hospitalized on several occasions and seemingly responded clinically to broad spectrum antibiotics each time. However, a thorough investigation failed to identify an infective cause of fever. Repeated routine cultures plus pcr-based analysis of blood samples for fungi and cytomegalovirus were negative. Chest x-ray, CT scans of sinuses, the thoracic cavity and abdomen, as well as echocardiography showed no signs of invasive infection, but progression of lymph nodes in the abdomen and increased spleen size was noted. Evaluation regarding the possibility of a solid tumour in the gastrointestinal tract or kidneys was negative. Since progression was observed on CT scan, fine-needle aspirations of enlarged nodes in the axillae and on the neck were performed to rule out Richter transformation. Cytological analysis still showed CLL in the axillae, but material from the largest node on the left side of the neck suggested possible HD. Lymph node biopsy demonstrated large, pleomorphic cells with clearly visible nucleoli, and Reed-Sternberg (RS) cells were readily demonstrated. Immunohistochemistry showed a distinct phenotype of CD 45-negative but CD15-positive RS cells (7), confirming the diagnosis of HD, which was classified as the nodular sclerosing subtype. The patient was started on MOPP/ABVD treatment, and after almost two rounds of therapy has attained a clinical partial remission.

Discussion. Many types of malignancies may occur after chemotherapy for HD. The most common are acute non-lymphocytic leukemia (ANLL), myelodysplastic syndromes, non-Hodgkin's lymphoma (NHL) and solid tumours (8). After ANLL, NHL is the next common secondary malignancy, with a cumulative 10-year risk of 4 to 5%. The incidence of NHL may also be increased in untreated HD patients (9). In CLL, population-based

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studies have demonstrated an increased risk of other cancers, most notably skin cancer, the cause of which was ascribed to an immunological deficiency and/or chlorambucil treatment (10). The development of HD in patients with CLL is a quantitatively rare event. In 1981, Choi & Keller (11) reported two cases and reviewed 35 cases reported in the literature between 1928 and 1979. However, these older cases occured at a time when confirmation of the HD diagnosis with immunohistochemistry was not possible, and it is well recognized that RS-like cells may be observed in CLL, especially in the terminal phase. These cells have been shown to be activated B-cells lacking CD15 but expressing CD45 (12). Our patient exhibited a typical phenotype of his RS cells and a clinical picture suggestive of HD, and in the recent literature there are some 50 patients described with HD occurring in patients with CLL (13–20). The mean interval between the initial diagnosis of CLL and the emergence of HD has varied between 31–60 months. Our patient differs from most published cases since he developed HD 20 years after his initial CLL diagnosis, and there is only one case in the literature that resembles our patient in this regard; that patient developing HD 27 years after the initial CLL diagnosis (17). Survival when reported has mostly been poor with a mean survival of 3,5 months after HD diagnosis in the largest published series (15). However, two patients have been reported alive 47 and 96 months respectively after diagnosis of HD (13).

The occurrence of two relatively rare disorders in the same patient can be a pure coincidence, and such cases describing the coexistance of CLL and polycythemia vera have been reported (21). It has also been suggested that HD developing after CLL should be a rare coincidence (17). However, a survey of more than 9 000 CLL patients reported to the National Cancer Institute demonstrated that 13 cases of HD were diagnosed compared with 1.69 cases expected, giving an observed/expected ratio of 7.69 which was actually the highest ratio for any malignancy observed in CLL patients (15). It is therefore unlikely that the emergence of HD in CLL is a chance occurrence. The nature of the association between HD and CLL has, however, not been resolved. *bcl-2* expression has been demonstrated in HD cells in occasional patients with HD arising in patients with follicular lymphoma (22), and two patients with HD after CLL were found to express the B-cell marker L-26 in their RS cells, indicating that it is theoretically possible that HD can develop from the malignant CLL clone. However, RS-cells in HD patients without a history of previous CLL in 15–20% of cases express B-cell antigens (23). Furthermore, although most cases of prolymphocytoid progression of CLL usually derive from the CLL clone, different malignant clones have been observed in the Richter syndrome, and this is also true for most cases of multiple myeloma occurring in CLL (24). One patient with HD after initial CLL has, in the same manner, been shown to have a dissimilar light chain expression in his CLL and HD cells respectively, indicating that the disorders were derived from separate clones (18). Since CLL patients are at increased risk for several different malignancies (10,15) it is perhaps more likely that a longstanding immunodeficiency due to CLL and/or treatment with cytostatic drugs account for the majority of HD cases in CLL, and chlorambucil and COP might have contributed to the development of HD in our patient. Finally, due to the presence of Epstein-Barr virus (EBV) RNA in RS-cells in some patients with HD after CLL, it has been suggested that EBV has an important role for the development of HD (20), but in other patients no EBV RNA could be detected (19).

In conclusion, we present a case of HD emerging in a patient with CLL. Although obviously quantitatively very rare, it is suggested that this possibility is worth considering when a CLL patient develops signs or symptoms suggestive of progression/transformation of CLL.

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