Hodgkin's lymphoma as a rare variant of Richter's transformation in chronic lymphocytic leukemia: A case report and review of the literature

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Abstract. Richter's transformation induces an aggressive clinical course in chronic lymphocytic leukemia (CLL). In the majority of cases, Richter's transformation manifests itself as a high-grade B-cell non-Hodgkin's lymphoma (B-NHL). However, other histological types, such as classical Hodgkin lymphoma (cHL), lymphoblastic lymphoma, hairy cell leukemia and high-grade T-cell NHL have been described previously. The present study reports a rare case of CLL with transformation into classical Hodgkin's lymphoma (cHL). The common clonal origin of CLL and cHL was documented by immunoglobulin gene rearrangement analysis performed using multiplex polymerase chain reaction. Following a review of the literature, treatment of secondary Hodgkin's lymphoma is discussed, and prognosis is often poor.

Introduction

Richter's transformation represents an aggressive evolution of chronic lymphocytic leukemia (CLL) (1). High-grade B-cell non-Hodgkin lymphoma (B-NHL) is the most common histological type of Richter's transformation (2). However, other histological types, such as classical Hodgkin lymphoma (cHL) (2-4), lymphoblastic lymphoma (5), hairy cell leukemia (6) and high-grade T-cell NHL (7,8) have been reported previously. B-CLL and cHL can be clonally related or independent lymphomas (9,10).

Different therapy modalities are reviewed in the present study regarding the optimal treatment strategy for Hodgkin transformation. However, despite the different chemotherapeutic regiments, the prognosis remains poor compared to *de novo* Hodgkin's lymphoma (4) and new therapeutic approaches shoud be considered in the future.

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Case report

A 70-year-old male presented with right thoracic pain. A computer tomography (CT) scan showed thoracic and retroperitoneal lymphadenopathy with a maximal diameter of 21 mm, and a pleural effusion at the right side. Routine blood investigations showed normal erythrocyte, platelet and leukocyte counts.

The cytology of the pleural effusion revealed an atypical B-cell population consistent with B-CLL (Fig. 1). Bone marrow aspiration confirmed the diagnosis of CLL, stage Binet B. Fluorescence *in situ* hybridisation (FISH) analyses of bone marrow excluded trisomy 12, and deletions of 11q22.3, 13q14 and 17p13. FISH experiments were performed using commercially available probes from Abbott (Abbott Park, IL, USA), according to the manufacturer's protocol. A watch-and-wait approach was applied. During the following months the patient suffered from repeated infections due to hypogammaglobulinemia with immunoglobulin G (IgG) <3 g/l, and therefore, immunoglobulin substitution and antibiotic therapy was repeatedly necessary.

Two months later the patient complained of fever, cough, right thoracic pain and fatigue. A repeated CT scan of the thorax showed a pleural effusion again. In order to exclude pleural empyema, video-assisted thoracoscopic surgery with pleurectomy was performed. Histological analysis revealed a marked pleural fibrosis with scattered cellular lymphoid nodules. The latter contained a variable mixture of small B- and T-cell lymphocytes, histiocytes, fibroblasts, eosinophils and scattered atypical blasts corresponding to Hodgkin cells and Reed-Sternberg (HRS) cells. The B-cell lymphocytes were cluster of differentiation (CD) 20-positive, but did not co-express CD5 or CD23, as assessed using monoclonal antibodies recognizing these antigens in paraffin-embedded tissue. Therefore, the small aggregates of the B-cells did not fulfil the diagnostic criteria for a B-CLL infiltration. HRS-blasts proved

Table I. Most common described treatment options of Hodgkin's transformation of chronic lymphocytic leukemia (4,11).

Treatment	Specific drugs and therapy
ABVD	Doxorubicin, bleomycin, vinblastine and dacarbazine
CVPP ± involved field radiation	Cyclophosphamide, vinblastine, procarbazine and prednisone ± involved field radiation
MOPP	Mecholrethamine, oncovin, procarbazine and prednisone
CHOP ± R	Cyclophosphamide, doxorubicin, vincristine and prednisone ± rituximab
FCR	Fludarabine, cyclophosphamide and rituximab
Other	Mitoxantrone, vincristine, vinblastine and prednisone; rituximab; or cidofovir

to be CD20-negative, but showed expression of CD30, CD15 and PAX5. Additionally, *in situ* hybridization for Ebstein-Barr virus (EBV) was positive. Accordingly, diagnosis of nodular sclerosis-type classical Hodgkin's lymphoma was rendered. The disease was staged as IV due to the pleural involvement.

Comparative molecular analyses of the IgH of selected tissue compartments of the pleural biopsy and of peripheral blood B-lymphocytes were performed using multiplex polymerase chain reaction (PCR) with BIOMED-2 primer sets, as previously described (11). The resulting PCR amplicons showed identical sizes indicating the same IgH heavy chain rearrangement in both lymphoma manifestations, and thus a common clonal origin of CLL and cHL.

Chemotherapy with 25 mg/m^2 doxorubicin, 10 mg/m^2 bleomycine, 6 mg/m^2 vinblastine and 375 mg/m^2 dacarbazine on days 1 and 15 was introduced, for a total of 8 cycles. A complete remission was achieved.

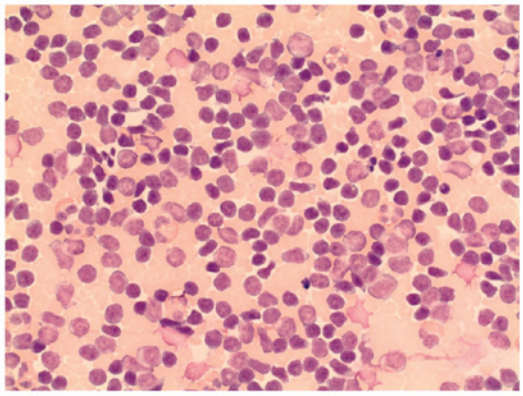

Figure 1. Cytology of the pleural effusion revealing an atypical B-cell population, consistent with B-chronic lymphocytic leukemia.

Discussion

Approximately 2-8% of all patients diagnosed with CLL transform into more aggressive lymphoma known as Richter's syndrome (1). The most common is the transformation of CLL into a high-grade B-NHL (2). Transformation to HL is thought to occur in ~0.4% of all CLL patients (3,4). Other histological types of Richter's transformation have also been described, including lymphoblastic lymphoma (5), hairy cell leukemia (6) and high-grade T-cell NHL (7,8).

A published small series suggested that tumor cells in B-NHL and cHL can be clonally related to B-CLL clone or arise as an independent, secondary lymphoma (9,10). Additionally, it has been postulated that immunosuppressive therapy in CLL, particularly fludarabin, may increase the risk of Richter's transformation to cHL (12,13).

EBV infection is only infrequently detected in CLL by conventional diagnostic approaches. However, it has been shown that EBV persistence in the lymphocytes of patients with CLL may lead to the more aggressive disease and Richter's transformation into cHL (14,15). Several studies showed that EBV small non-coding RNA (EBERs) expressed in latently infected cells have a critical role in B-cell transformation and induction of resistance to apoptosis, which may lead to CLL progression (16).

According to the largest series of published Hodgkin transformation in CLL, in 3 out of 4 analysed patients (75%), EBV was detected (4). In the patient reported in the present study, Hodgkin cells were also EBV-positive, as documented by EBER *in situ* hybridisation. However, the role of antiviral therapy in the treatment of Hodgkin transformation in CLL remains to be elucidated.

Bone marrow cytogenetics revealed a normal karyotype in 42% of the cases in one study (4), wheres abnormalities, including -Y, 11q-, del (13), t(9;15), trisomy 12, -11 and -17, were identified in <40% of the cases (4). FISH analyses of the bone marrow in the present patient were negative for trisomy 12, deletion 11q22.3, deletion 13q14 or deletion 17p13.

cHL transformation in CLL has a poor outcome compared to the *de novo* Chl (4). The administration of different therapy modalities to the patients with HL as Richter's transformation has been described previously (Table I). However, the median overall survival, according to the largest series of published Hodgkin transformation in CLL, was only 8 months (4).

More effective treatment is required for patients who develop Hodgkin transformation of CLL. The role of high-dose chemotherapy with autologous stem cell transplantation in these patients is not well defined. However, this more aggressive approach may not be feasible in elderly groups of patients.

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