Subcutaneous Masses as an Unusual Manifestation of Relapse in a Case of Atypical Chronic Lymphocytic Leukemia with Prolymphocytoid Transformation and Complex Karyotype: A Diagnostic Dilemma and Treatment Challenge

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Patient: Male, 71-year-old
Final Diagnosis: Chronic lymphocytic leukemia • small lymphocytic lymphoma
Symptoms: Subcutaneous indurations • subcutaneous mass
Medication: —
Clinical Procedure: Skin biopsy
Specialty: Hematology

Objective: Unusual clinical course

Background: Most patients with chronic lymphocytic leukemia (CLL) are asymptomatic at diagnosis, but 10% present with B symptoms. Most patients have palpable lymphadenopathy, while 20–50% of the patients have hepatosplenomegaly. Cutaneous infiltrations in patients with CLL can be localized or generalized in the form of erythematous papules, plaques, nodules and, ulceration, which is uncommon.

Case Report: We present the case of a 71-year-old man diagnosed with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with atypical immunophenotype and increased prolymphocytes (CLL/PLL), which was treated initially after white blood counts (WBC) doubling with Bendamustine and Rituximab for 6 cycles, and achieved complete remission. The patient relapsed after 6 months of completion of treatment, with multiple large subcutaneous masses, proved to be infiltration with the same atypical CLL/SLL on tissue biopsy, with pathologic features indicating disease progression. The lack of similar reported cases, and the aggressiveness of the tumor clinically and histopathologically, resulted in the decision to treat with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (R-CHOP) as a case of aggressive lymphoma, with complete remission clinically and radiologically.

Conclusions: We present a rare case of subcutaneous extramedullary masses of atypical CLL/SLL. The high proliferation index (Ki-67) and the increase of large cells are suggestive of aggressive progression of the disease; however, no frank features of Richter’s transformation were noted. Based on this and because of the unusual aggressive-looking skin masses, the panel decided to treat the patient with R-CHOP. The impact of this presentation on the prognosis of the disease is not clear. To date, our patient has responded well to treatment with R-CHOP, with complete remission of the subcutaneous masses and on PET scan, but further follow-up is needed.

MeSH Keywords: Leukemia, Lymphocytic, Chronic, B-Cell • Lymphoma, Non-Hodgkin • Subcutaneous Tissue
Background

Chronic lymphocytic leukemia (CLL) is the most common form of indolent lymphoma diagnosed in the Western world [1]. It is characterized by the clonal proliferation and accumulation of neoplastic, mature-looking B lymphocytes in the blood, bone marrow, and the lymphatic system; these cells are immunologically impaired [2]. Most patients are asymptomatic at diagnosis, 10% present with B symptoms (fever, sweating, and weight loss), and most patients have palpable lymphadenopathy, while 20–50% of patients have hepatosplenomegaly [3]. Cutaneous infiltrations in patients with CLL can be localized or generalized in the form of erythematous papules, plaques, nodules, and ulceration, which is uncommon [4].

Here, we present the case of a 71-year-old man with diagnosed as having chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), with atypical immunophenotype and increased prolymphocytes (40%) (CLL/PLL). Compared to classic CLL, this case had an atypical immunophenotype (bright CD20, bright light chain expression, expression of CD79 and FMC7). The patient was treated initially after white blood counts (WBC) doubling with Bendamustine and Rituximab for 6 cycles, and achieved complete remission. Unfortunately, his disease relapsed after 6 months of completion of treatment, with multiple large subcutaneous masses, proved to be infiltration with CLL/PLL. Compared to classic CLL, this case presented with increased prolymphocytes (40%) (CLL/PLL). After making the diagnosis of atypical CLL with increased prolymphocytes and atypical immunophenotype (bright CD20, bright light chain expression, expression of CD79 and FMC7) initial Binet stage A. Treatment was initiated after less than 6 months of observation when the patient had a doubling of total leukocytic count of $220 \times 10^9/l$ (4–10×$10^9/l$) and marked absolute lymphocytosis of $126.8 \times 10^9/l$ (1–3×$10^9/l$). Flow cytometry on peripheral blood was repeated and showed a higher percentage of monotypic B cells with a phenotype similar to that at presentation. A bone marrow examination performed at this presentation (Figure 2), in which the bone marrow aspirate showed a marked increase in marrow lymphocytes composed of a mixture of small, mature-looking lymphocytes (56%) mixed with many prolymphocytes (larger cells of less condensed nuclear chromatin and few nucleoli) (Figure 2A, 2B) with some smudge cells and some mitotic figures (black arrow) (Figure 2C). The bone marrow biopsy was markedly hypercellular (~95%) (Figure 3) and diffusely infiltrated with sheets of lymphoid cells, including some larger cells with less condensed nuclear chromatin and prominent nucleoli. Immunohistochemistry showed the lymphoid infiltrate was composed of B cells positive for CD20 (diffuse intense), PAX-5, CD5, BCL-2, and CD23 (majority) and negative for CD10, BCL-6, Cyclin D1, SOX11, CD30, P53, and EBV. The percentage of involvement by lymphoid infiltrate was roughly estimated at 90%, with markedly suppressed erythropoiesis, granulopoiesis, and preserved megakaryopoiesis. Flow cytometry on bone marrow aspirate showed a monotypic B cell population ~91% and expressing CD19, CD20 (moderate), CD23, FMC7, CD79b (majority), BCL2, IgD, IgM, and aberrant CD5 with Lambda light chain restriction (dim). There was partial expression of CD43 and CD200 (dim). CD38 was expressed on a minor population of the B cells (approximately 6%). Cytogenetics testing revealed an abnormal karyotype: 46,XY(t(2;7)(p12;q21),t(2;20)(q11.2;p11.2),t(6;8)(p21;q13)[18]/46,XY [12].

These findings are consistent with CD5-positive mature B cell neoplasm with features favoring atypical chronic lymphocytic leukemia with increased prolymphocytes (CLL/PLL). After making the diagnosis of atypical CLL with increased prolymphocytes and Binet stage C, treatment was initiated with Bendamustine (first dose 90 mg/m$^2$, both for 6 cycles, after which he achieved complete remission.

Six months later, he started to develop multiple subcutaneous lumps on the upper limbs, abdomen, and back, which were painful, with red overlying skin induration. He denied

Case Report

A 71-year-old man with background of hypertension and atrial fibrillation on anticoagulation (Dabigatran), presented initially with marked leukocytosis of $77 \times 10^9/l$ (4–10×$10^9/l$), marked lymphocytosis, with absolute lymphocyte count $65.6 \times 10^9/l$ (1–3×$10^9/l$), mild anemia $12.6$ gm/dl (13.0–17.0 gm/dl), and normal platelets count $162 \times 10^9/l$ (150–400×$10^9/l$). A peripheral blood smear showed marked lymphocytosis consisting of small mature-looking lymphocytes mixed with many prolymphocytes (~40%), some prolymphocytoid cells (with features intermediate between lymphocytes and prolymphocytes), and few smudge cells. Flow cytometry performed on peripheral blood (Figure 1) showed a large monotypic B cell population comprising 80% and expressing CD19, CD5, CD20 (bright), CD23, FMC7, CD79b, BCL-2, IgD (bright), and IgM with Lambda light chain restriction (bright). There was partial expression of CD43 (heterogenous). This population is negative for CD10, CD103, CD200, IgG, and IgA, with no significant expression of CD38, CD11c, or CD25. FISH for 11q22.4 ATM/CEP10, IGH/CCND1 t(11;14) (q13;q32), CEP12/CEP1012p11.1-q11.1, TP53/CEP17 (17p13.1/17p11.1-q11.1) were normal. Therefore, the patient was diagnosed with CDS-positive mature B cell neoplasm in favor of CLL with increased prolymphocytes and atypical immunophenotype (bright CD20, bright light chain expression, expression of CD79 and FMC7) initial Binet stage A. Treatment was initiated after less than 6 months of observation when the patient had a doubling of total leukocytic count of $220 \times 10^9/l$ (4–10×$10^9/l$) and marked absolute lymphocytosis of $126.8 \times 10^9/l$ (1–3×$10^9/l$). Flow cytometry on peripheral blood was repeated and showed a higher percentage of monotypic B cells with a phenotype similar to that at presentation. A bone marrow examination performed at this presentation (Figure 2), in which the bone marrow aspirate showed a marked increase in marrow lymphocytes composed of a mixture of small, mature-looking lymphocytes (56%) mixed with many prolymphocytes (larger cells of less condensed nuclear chromatin and few nucleoli) (Figure 2A, 2B) with some smudge cells and some mitotic figures (black arrow) (Figure 2C). The bone marrow biopsy was markedly hypercellular (~95%) (Figure 3) and diffusely infiltrated with sheets of lymphoid cells, including some larger cells with less condensed nuclear chromatin and prominent nucleoli. Immunohistochemistry showed the lymphoid infiltrate was composed of B cells positive for CD20 (diffuse intense), PAX-5, CD5, BCL-2, and CD23 (majority) and negative for CD10, BCL-6, Cyclin D1, SOX11, CD30, P53, and EBV. The percentage of involvement by lymphoid infiltrate was roughly estimated at 90%, with markedly suppressed erythropoiesis, granulopoiesis, and preserved megakaryopoiesis. Flow cytometry on bone marrow aspirate showed a monotypic B cell population ~91% and expressing CD19, CD20 (moderate), CD23, FMC7, CD79b (majority), BCL2, IgD, IgM, and aberrant CD5 with Lambda light chain restriction (dim). There was partial expression of CD43 and CD200 (dim). CD38 was expressed on a minor population of the B cells (approximately 6%). Cytogenetics testing revealed an abnormal karyotype: 46,XY(t(2;7)(p12;q21),t(2;20)(q11.2;p11.2),t(6;8)(p21;q13)[18]/46,XY [12].

These findings are consistent with CD5-positive mature B cell neoplasm with features favoring atypical chronic lymphocytic leukemia with increased prolymphocytes (CLL/PLL). After making the diagnosis of atypical CLL with increased prolymphocytes and Binet stage C, treatment was initiated with Bendamustine (first dose 90 mg/m$^2$, both for 6 cycles, after which he achieved complete remission.
any fever, drenching night sweats, or weight loss (no B symptoms). On examination he looked well, with multiple subcutaneous lumps with overlying red skin induration (Figure 4) on both upper limbs, back, and abdomen; the lower limbs were spared. Multiple small cervical, axillary, and inguinal lymph nodes were palpated, but there was no hepatosplenomegaly.

At this presentation, his lab values showed normal CBC results: WBC of 4.9×10^3/l (4–10×10^3/l), absolute lymphocytes count 1.1×10^3/l (1–3×10^3/l), absolute neutrophils count 3.1×10^3/l (2–7×10^3/l), hemoglobin 13.5 gm/dl (13.0–17.0 gm/dl), platelets count 152×10^9/l (150–400×10^9/l), and normal lactate dehydrogenase 163 u/l (135–225 u/l). A positron emission tomography (PET) scan showed intense hypermetabolism in
multiple subcutaneous lumps. Lymph nodes were involved in the right lower neck, right axilla, and right inguinal stations (Figure 5). Three different skin biopsies were taken and showed similar findings (Figure 6). Histopathologic examination of soft-tissue masses (elbow and shoulder) revealed infiltration of the adipose tissue by sheets of small lymphoid cells, with intervening areas of lymphocytes showing monocytoid features mimicking pseudo-germinal centers. Scattered larger cells and Hodgkin-like cells were seen. No mitosis, apoptosis, or necrosis were appreciated. No abnormal eosinophilia, plasmacytosis, or granulomas were seen in the background. By immunohistochemical stains (Figure 6), most all the lymphoid cells were B cells that were positive for CD20, CD79a, and PAX5, and co-expressing CD5. Ki-67 was significantly increased (70% positive). ZAP-70 was positive in 10% of cells. CD23 showed variable positivity between different cores, ranging from negative to weakly positive. The abnormal lymphoid cells were negative for CD10 and cyclin D1. The large Hodgkin-like cells were positive for PAX5, but were negative for CD15, CD30, and Epstein Barr Virus (EBV). CD3 was positive in the adjacent T cells.

These findings were consistent with the previous diagnosis of B cell atypical small lymphocytic lymphoma with significant increased proliferation index and Reed-Sternberg-like cells. The high proliferation index Ki-67 and the increase of large

Figure 3. Bone marrow biopsy. Bone marrow biopsy (H&E) is markedly hypercellular (~95%) (10×) (A), diffusely infiltrated with sheets of lymphoid cells, including some larger cells with less condensed nuclear chromatin and prominent nucleoli (B). Immunohistochemistry showed the lymphoid infiltrate was composed of B cells positive for CD20, CD5, BCL-2, and CD23 (variable intensities) and negative for CD10, BCL-6, and Cyclin D1.
cells were suggestive of aggressive progression of the disease. However, no frank features of Richter’s transformation were noted. The soft-tissue lesions were submitted for flow cytometry analysis; tissue suspension cytospin preparation showed many atypical lymphoid cells of medium size with irregular nuclear contours and less clumped nuclear chromatin. Few large Reed-Sternberg-like cells and mononuclear cells were seen (arrows) (Figure 7A). Flow cytometry analysis on 2 soft-tissue lesions (left elbow and right shoulder) (Figure 7B) both showed a large monotypic B cell population showing moderately high light side scatter and expressing CD19, CD5, CD20, CD79b, CD23, BCL-2, IgD, and IgM, with Lambda light chain restriction (bright). There was partial expression of FMC7, CD25, and CD11c (in the minority of cells). This population was negative for CD10, CD38, and CD103, with no significant expression of CD200 or CD43. Immunophenotypic findings were like the original flow cytometric findings, with no significant changes. FISH analysis of 200 nuclei from paraffin-embedded tissue was performed for each of the following probe sets (Vysis): MYC (8q24) dual color, break-apart; dual color, dual fusion for IGH (14q32) and BCL2 (18q21); and dual color, break-apart for BCL6 (3q27). The signal patterns for the IGH-BCL2 and BCL6 probe sets were consistent with absence of IGH-BCL2 rearrangement, absence of BCL6 rearrangement, and absence of MYC rearrangement. However, an abnormal pattern indicating presence of additional copies (3–7) of MYC was observed in 87% of nuclei. This abnormal pattern may be due to additional copies of chromosome 8, or unbalanced structural rearrangement resulting in duplication of the intact MYC gene. Interestingly, bone marrow at the time of these skin manifestations was negative for the disease.

Figure 4. Subcutaneous lumps at time of relapse. Multiple subcutaneous lumps with overlying red skin induration, from left to right: right shoulder, left arm, right abdominal wall.

Figure 5. Positron emission tomography–computed tomography (PET/CT) at time of relapse. Maximum-intensity projection (left), computerized tomography (CT) (middle) and fused (right) fluorodeoxyglucose (FDG)-PET/CT images. At relapse, multiple subcutaneous soft-tissue masses (red arrowheads) were found widely scattered, showing intense FDG-uptake as well as FDG-avid right axillary and supraclavicular lymph nodes.
He was started on treatment for high-grade lymphoma because of the lack of similar reported cases and the aggressiveness of the tumor clinically and histopathologically, initially with debulking regimen with cyclophosphamide 750 mg/m², vincristine 1.4 mg/m², and prednisolone 40 mg/m² for 5 days (COP), followed by systemic chemotherapy Rituimab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², and prednisolone 45 mg/m² for 5 days (R-CHOP) for 6 cycles, and he had dramatic improvement in the subcutaneous masses clinically and on PET CT (Figures 8, 9).

**Discussion**

Most patients with CLL are diagnosed based on routine blood count showing absolute lymphocytosis, with no symptoms, while others present with painless swelling of lymph nodes, mostly in the cervical region. However, CLL skin infiltration occurs in 4–20% of CLL patients [5]. The exact classification of the case at presentation was quite challenging as the patient had a CD5-positive mature B cell neoplasm, with increased prolymphocytes and atypical immunophenotype (bright CD20, bright light chain expression, and expression of CD79 and FMC7). After exclusion of mantle cell lymphoma, the...
Figure 7. Subcutaneous tissue suspension cytospin and flow cytometry. Tissue suspension cytospin preparation (A) shows many atypical lymphoid cells of medium size with irregular nuclear contours and less clumped nuclear chromatin. Few large Reed-Sternberg like cells and mononuclear cells are seen (black arrows). Flow cytometry analysis on 2 soft-tissue lesions (B) (LT elbow and RT shoulder), both showing a large monotypic B cell population expressing CD19, CD5, CD20, and CD79b with Lambda light chain restriction. There is partial expression of CD23 and FMC7, with no significant expression of CD200.

Patient was diagnosed with CLL with atypical immunophenotype and increased prolymphocytes. A retrospective review by Cerroni et al. in 1996 of 42 patients with cutaneous infiltrates of CLL indicated that the cutaneous infiltrates did not affect the disease prognosis [4]. One characteristic feature of CLL skin infiltration is cauliflower lesions over both earlobes, especially as the initial presentation as described in several case reports [6–9]. Richter syndrome (RS) is the development of secondary aggressive lymphoma in the setting of CLL/SLL, which most frequently CLL transforms into diffuse large B cell lymphoma (DLBCL) and rarely into Hodgkin lymphoma, which is the so-called Hodgkin variant of Richter's syndrome. RS is characterized by an aggressive clinical course and poor prognosis [10], and is rarely seen in the skin, with <20 cases reported in the literature [11]. As an aggressive lymphoma, CHOP (and more recently R-CHOP) has been the initial treatment for CLL patients who develop RS [12].

Our patient had no frank features of Richter's transformation noted in skin biopsies, but the high proliferation index (Ki-67) and the increase of large cells are suggestive of aggressive progression of the disease, in addition to the atypical
immunophenotype, morphology, and the complex karyotype detected on earlier presentation, as well as the unusual aggressive-looking skin masses, so that the panel decided to treat the patient with R-CHOP.

Our case is unique in that the patient had subcutaneous extramedullary masses of atypical CLL/SLL rather than cutaneous leukemic infiltrate or RS. To the best of our knowledge, no other cases with the same presentation have been reported. The impact of this presentation on the prognosis of the disease is not clear, but our patient responded well to treatment with R-CHOP, with complete remission of the subcutaneous masses and on PET scans as shown above. Further follow-up is needed clinically and possibly with PET scan.

Conclusions

We present a rare case of subcutaneous extramedullary masses of atypical CLL/SLL. The high proliferation index (Ki-67) and the increase of large cells were suggestive of aggressive progression of the disease, but no frank features of Richter’s transformation were noted. Based on this and because of the unusual aggressive-looking skin masses, the panel decided to treat the patient with R-CHOP. The impact of this presentation on the prognosis of the disease is not clear. To date, our patient has responded well to treatment with R-CHOP, with complete remission in the subcutaneous masses and on PET scan, but further follow-up is needed.

Statement

The case report was composed at the National Center for Cancer Care and Research, Hamad Medical Corporation, Doha, Qatar.
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