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TEACHING CASE

Floral leukemic cells transformed from marginal zone lymphoma

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Abstract

There are three clinicopathological entities of marginal zone lymphoma (MZL), including extranodal or mucosa-associated lymphoid tissue (MALT) lymphoma and MZL of nodal (NMZL) or splenic (SMZL) type. Of these, leukemic presentation, usually as small or villous lymphocytes, is more common in SMZL, while leukemic change in NMZL is rare, and the morphology has not been characterized. We present a stage 4 MZL involving lymph node, spleen, and bone marrow with two relapses after chemotherapy. The leukemic cells at the second relapse revealed irregular nuclear contours with multilobated nuclei (so-called flower cells or floral cells) mimicking the neoplastic cells in adult T-cell leukemia/lymphoma (ATLL). The absence of leukemic change and splenic hilar lymphadenopathy at initial presentation, expression of IgD by tumor cells, and cytogenetic changes of +7 suggested that this tumor might be a NMZL. Although the cytomorphologic features of floral leukemic cells might suggest ATLL, thorough clinical and laboratory workup helped to reach a correct diagnosis. Our findings broaden the cytological spectra of leukemic cells in MZL and illustrate the importance of immunophenotyping.

Keywords: Leukemic transformation; Marginal zone lymphoma; Nodal marginal zone lymphoma; Splenic marginal zone lymphoma; Taiwan

Introduction

The WHO classification identified three different entities of marginal zone lymphomas (MZL): extranodal MZL or mucosa-associated lymphoid tissue (MALT) lymphoma and MZL of nodal (NMZL) or splenic (SMZL) origin [3]. SMZL is an indolent lymphoma involving the spleen, bone marrow, and peripheral blood at the initial manifestation. Splenic hilar lymph nodes are frequently involved in contrast to peripheral lymph nodes, which are rarely involved by SMZL. Lymphoma cells in the peripheral blood might exhibit villous outlines or villous appearance, which explains the earlier term of this entity (“splenic lymphoma with villous lymphocytes”). NMZL is a primary nodal B-cell lymphoma morphologically resembling lymph nodes involved by MALT lymphoma or SMZL, but without evidence of extranodal or splenic disease. NMZL with peripheral blood involvement is rare, and to our knowledge, less than ten cases have been reported [6,4,1,7]. Furthermore, the cytomorphologic features of

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the leukemia cells have not been illustrated. Leukemic cells with multilobated nuclei (so-called flower or floral cells) in HTLV-endemic areas such as southwestern Japan are highly suggestive of HTLV-associated adult T-cell leukemia/lymphoma (ATLL) [2]. Rare cases of ATLL have also been described in Taiwan. We report on an unusual case of MZL of probable nodal origin with leukemic change, the neoplastic cells exhibiting irregular nuclear contours and multilobated nuclei resembling floral cells in ATLL.

Case report

A 69-year-old male was admitted due to aggravated shortness of breath and tarry stool for a few days in April 2006. His complete blood count revealed a white blood count of $61.7 \times 10^3/\mu L$ with 77.8% lymphocytes in which 28% were atypical forms, hemoglobin of 7.4 g/dL, and a platelet count of $30 \times 10^3/\mu L$. The atypical lymphocytes exhibited irregular nuclear contours and polylobated nuclei reminiscent of "floral cells" (Fig. 1A), similar to the leukemic cells as seen in HTLV-associated ATLL. Flow cytometry of these leukemic cells showed a B-cell phenotype ($CD19^+$ $CD20^+$ $CD5^+$ $CD10^-$ $CD23^-$ $CD43^+$) with monotypic kappa light chain expression. The bone marrow trephine revealed interstitial infiltration by medium to large-sized atypical lymphocytes expressing CD20, bcl-2, and IgM with high proliferation fraction but not CD3, CD5, CD27, CD43, bcl-6, or IgD (Fig. 1B). Conventional cytogenetic study with G-banding technique using marrow aspiration specimens revealed 49, XY, +inv3(q21q26), +7, t(8;18)(q22;q21), add(19)t(9;19)(q13;p13), marker [cp20]. Serologic study for anti-HTLV was not performed.

Tracing back his medical history, we found that this patient had bilateral cervical and axillary lymphadenopathy 4 years earlier, in October 2001. Biopsy of a cervical lymph node showed nodal architecture effaced by infiltration of medium-sized lymphocytes with focal monocytoid appearance and small aggregates of large cells with vesicular nuclei and prominent nucleoli. Immunohistochemistry showed that these atypical lymphocytes shared the same immunophenotype as the lymphoma cells in the bone marrow. The proliferation fraction was increased in the areas of large cell aggregates (Fig. 1C). Abdominal computer tomography (CT) scan revealed lymphadenopathy over para-aortic, para-iliac and bilateral inguinal regions, and splenomegaly in a diffuse pattern without hilar lymphadenopathy. Bone marrow involvement was confirmed by marrow aspiration, while peripheral blood was not involved. MZL with high-grade transformation at stage IV was diagnosed at that time. However, a nodal or splenic origin could not be determined, as the lymphoma was disseminated, and both lymph nodes and spleen were involved. The disease regressed (disappearance of lymphadenopathy and splenomegaly) after six courses of epirubicin, cyclophosphamide, vinblastine, and prednisone (CEOP) chemotherapy but relapsed 3.5 years later. The first relapse presented with cervical and inguinal lymphadenopathy without abdominal lymphadenopathy, and the spleen was normal in size as revealed by serial abdominal echography. The second remission was achieved by chemotherapy and radiotherapy. The current leukemic presentation was the second relapse, and he died of respiratory failure within 3 days, 55 months after initial diagnosis. Autopsy was not performed.

Discussion

The morphology of leukemic cells in SMZL includes villous lymphocytes, small lymphocytes, plasmacytoid cells, centrocytoid cells, and cells with monocytoid cytoplasm [5], while that in NMZL has not been characterized. The phenotype of NMZL and SMZL is similar except that tumor cells of SMZL are usually $CD43^-$ and IgD^+ in contrast to $CD43^{-/+}$ and $IgD^{-/+}$ in NMZL [5]. There are no characteristic cytogenetic and/or molecular findings in both entities [5]. Cytogenetic alterations in SMZL include +3, +5, +9q, +12q, +18, +20q, t(10;14), t(6;14), and t(2;7). On the other hand, only a few cytogenetic alterations have been reported in NMZL, including trisomy 3, +7 and del 6q21–25 [5]. In our patient, it is impossible to determine nodal vs. splenic origin, as the initial presentation was a disseminated disease involving lymph node, spleen, and bone marrow without peripheral blood involvement. However, the absence of peripheral blood involvement and splenic hilar lymphadenopathy at initial presentation, expression of IgD by tumor cells, and cytogenetic changes including +7 seem to suggest a nodal rather than a splenic origin of the primary tumor.

Leukemic cells with multilobated nuclei (floral cells) are characteristic of ATLL, which is prevalent in southwestern Japan and occasionally seen in Taiwan. In our daily practice, we have encountered floral leukemic cells in various lymphoproliferative disorders, even in a 16-year-old girl with precursor B-lymphoblastic leukemia (S.-S.C. unpublished data 2006). Our case represents leukemic transformation of MZL and is unique in the polylobated/irregular nuclear contours mimicking floral cells in ATLL. The cytomorphologic features of leukemic cells in this case are suggestive of ATLL. However, thorough clinical and laboratory workup is mandatory to reach a correct diagnosis.