Leukemic Presentation of ALK-negative Anaplastic Large Cell Lymphoma in a Patient with Myelodysplastic Syndrome

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Abstract

A 50-year-old woman with a history of aplastic anemia developed cervical lymphadenopathy and atypical lymphocytosis. Atypical cells of lymph nodes were positive for CD3 and CD30 but negative for anaplastic lymphoma kinase (ALK). Bone marrow examination showed trilineage myelodysplasia. She was diagnosed with ALK-negative anaplastic large cell lymphoma (ALCL) with leukemic transformation and myelodysplastic syndrome (MDS) which presumably developed from aplastic anemia. The lymphoma was resistant to intensive chemotherapies, ultimately leading to death. Leukemic presentation of ALK-negative ALCL as an initial manifestation is extremely rare, and the progression of the disease may be influenced by MDS through alteration of immune functions.

Key words: anaplastic large cell lymphoma (ALCL), ALK-negative, leukemic manifestation, myelodysplastic syndrome

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Introduction

Anaplastic large cell lymphoma (ALCL) was first described in 1985 as a neoplasm that characteristically involves lymph nodes and comprises highly pleomorphic lymphoid cells with a predominantly sinusoidal growth pattern (1). Currently, it is defined as a T-cell lymphoma characterized by large lymphoid cells with abundant cytoplasm and pleomorphic nuclei (often horseshoe-shaped) (2). The lymphoma cells express CD30 antigens on the cell membrane and in the Golgi region, with most of them having a unique, balanced chromosomal translocation [t(2;5)(p23; q35)] (3, 4). ALCL is subdivided into 2 groups according to anaplastic large cell lymphoma kinase (ALK) expression (2, 5). ALK-positive ALCL is a well-defined entity based on histological, immunophenotypic, and molecular characteristics. In contrast, ALK-negative ALCL is a heterogeneous disease entity (6-8). Clinical presentations of ALK-negative ALCL vary considerably and include nodal and extranodal involvement of bone, bone marrow, soft tissue, skin, and lungs (6, 7, 9). The incidence of bone marrow involvement in ALCL patients is approximately 10-30% as assessed by immunohistochemistry (7, 10), but ALCL cases with extensive bone marrow and peripheral blood involvement and manifesting a leukemic phase are extremely rare, and most of these reported cases were ALK-positive ALCL in children (11). The International Peripheral T-Cell Lymphoma Project reported that only 3% of ALK-negative ALCL cases had circulating lymphoma cells in the peripheral blood (7).

The development of myelodysplastic syndrome (MDS) secondary to chemotherapy or radiotherapy is a common phenomenon, but the coexistence of de novo MDS and non-Hodgkin’s lymphoma (NHL) prior to chemo-radiotherapy is an extremely unusual finding (12, 13). Here, we report a case of ALK-negative ALCL with leukemic transformation as an initial manifestation in a patient with long-standing...
Case Report

In December 1997, a 40-year-old Japanese woman developed pancytopenia and required red blood cell transfusions. Bone marrow aspiration and biopsy revealed that her bone marrow was hypocellular without dysplasia. Chromosomal abnormalities were not found except for inv(1)(p13q21) as a variant chromosome. She was diagnosed with non-severe aplastic anemia and treatment was initiated with a daily dose of 30 mg prednisolone. Although she became transfusion independent with this treatment, she developed steroid-induced diabetes mellitus and recurrent infections. Therefore, prednisolone was substituted with a daily dose of 20 mg methenolone. Although the patient responded well to this treatment, mild pancytopenia persisted with white blood cell (WBC) counts around 3,000/μL with 20% granulocytes, hemoglobin levels of 7-8 g/dL, and platelet counts of 50,000-80,000/μL. No abnormal cells were found in the peripheral blood.

In November 2007, at the age of 50, the patient developed slight left cervical lymphadenopathy and leukocytosis with atypical lymphocytes. This was followed by bilateral cervical and rapidly progressive submandibular lymphadenopathy, and the patient was admitted to our hospital. She had persistent fever without body weight loss or night sweats. Physical examination at admission revealed a tender inflamed tumor that extended 5 cm into the left submandibular fossa with cervical lymphadenopathy. No other superficial lymphadenopathy was observed. There were no abnormal skin lesions and her liver and spleen were not palpable. Mediastinal or abdominal lymphadenopathy was not found by CT scan.

The laboratory findings were as follows: WBC count, 41.6×10⁹/L with 64% atypical lymphocytes; hemoglobin, 10.4 g/dL; platelet count, 7.2×10¹²/L, lactate dehydrogenase, 368 IU/L; C-reactive protein (CRP), 16.83 mg/dL; and soluble interleukin 2 receptor (sIL-2R), 727 IU/mL. Serological tests for human immunodeficiency virus and human T-cell lymphotropic virus type I were negative. The Epstein-Barr virus early antigen titer was slightly elevated. Flow cytometry revealed atypical lymphocytes in the peripheral blood that were positive for CD2 (99.6%), CD3 (98.0%), CD4 (98.8%), CD5 (96.6%), CD7 (54.1%), and CD30 (88.3%), and negative for CD8, CD16, CD20 and CD56. Bone marrow examination revealed hypercellular marrow with 40.2% atypical lymphocytes (Fig. 1a), and features of myeloid dysplasia, such as a pseudo-Pelger-Huet nuclear anomaly, were observed (Fig. 1b, c). Chromosomal analyses of the bone marrow specimen using G-banding staining were as follows: 46XX,inv(1)(p13q21),del(20)(q11.2q13.3) [16/20]; 46XX,inv(1)(p13q21),inv(6)(p25q11) [3/20]; 46XX,inv(1)(p13q21) [1/20]. Bone marrow biopsy revealed hypercellular marrow with mild dysplasia of erythroid series cells and megakaryocytes in addition to scattered invasion of large abnormal CD3- and CD30-positive cells and proliferation of Kp-1-positive histiocytoid-like cells. A cervical lymph node biopsy revealed diminished nodal structures (Fig. 2a) and diffuse proliferation of atypical lymphoid cells with round or irregular nuclei, distinct nucleoli, and abundant clear cytoplasm. Some mitotic features were seen (Fig. 2b). Immunohistochemical analysis revealed that these cells were CD3- and CD30-positive cells and proliferation of Kp-1-positive histiocytoid-like cells. A cervical lymph node biopsy revealed diminished nodal structures (Fig. 2a) and diffuse proliferation of atypical lymphoid cells with round or irregular nuclei, distinct nucleoli, and abundant clear cytoplasm. Some mitotic features were seen (Fig. 2b). Immunohistochemical analysis revealed that these cells were CD3- and CD30-positive cells and proliferation of Kp-1-positive histiocytoid-like cells.
negative ALCL with leukemic manifestation (clinical stage IVB) and MDS (refractory cytopenia with multilineage dysplasia) were made.

After the administration of methylprednisolone pulse therapy, CHOP chemotherapy [doxorubicin (ADM) 50 mg/m², cyclophosphamide (CY) 750 mg/m², vincristine (VCR) 2 mg, and prednisolone 100 mg] was administered, but the patient showed no response. Subsequently, hyper-CVAD therapy (CY: 300 mg/m², days 1-3; ADM: 50 mg/m², day 1; VCR: 2 mg, days 4 and 11; dexamethasone: 40 mg, days 1-4 and 11-14) and high-dose MA therapy (methotrexate: 1,000 mg/m² by continuous infusion, day 1; cytarabine: 2,000 mg/m² intravenously twice, days 2 and 3) were initiated. The submandibular tumor and cervical lymphadenopathy temporarily disappeared with these therapies, but atypical lymphocytes remained in the peripheral blood and the sIL-2R value increased to 3,400 IU/mL. The patient died of progressive disease with increased lymphoma cells in the peripheral blood and bilateral massive pleural effusions 7 months after the diagnosis of the diseases.

Discussion

In the present case, pathological examination of the cervical lymph node specimen revealed diffuse proliferation of lymphoma cells with round or irregular nuclei and distinct nucleoli, with some nuclei displaying a horseshoe or kidney shape. These cells were strongly positive for CD30 in the cytoplasm and on the surface. CD3 was also positive in this case, although ALCLs are frequently CD3 negative (14, 15). Immunohistochemistry and FISH did not detect ALK. The pathological diagnosis was ALK-negative ALCL.

Lu et al has reported 4 cases of ALK-negative ALCL with leukemic manifestation, and suggested that leukemic manifestation occurs in later stages because of nodal and extranodal involvement of various sites, including the peripheral blood, bone marrow, spleen, liver, and central nervous system (11). There are some reports of ALK-positive ALCL with leukemic manifestation. Its clinical features include significant respiratory distress, diffuse lung infiltrates or pleural effusions, and hepatosplenomegaly. Although ALK positivity is generally associated with a favorable outcome, leukemic ALK-positive ALCL has a highly aggressive clinical course and a poor outcome (16-18). We were able to closely follow the clinical course of the present patient as she regularly visited our hospital for the treatment of pancytopenia; we observed that the development and progression of the lymphoma was remarkably rapid in the leukemic phase. Although ALK-positive ALCL is a different entity from ALK-negative ALCL, it is interesting that our case had a highly
aggressive clinical course similar to ALK-positive ALCL. We suspected this unique clinical course was influenced by her underlying MDS.

We presume that the aplastic anemia developed into MDS concomitant with the development of ALK-negative ALCL, because there was trilineage dysplasia and an additional chromosomal abnormality del(20q) in the bone marrow cells, which had not been detected at the time of the initial presentation in 1997. The differential diagnosis of AA and hypoplastic MDS is often difficult, therefore we could not completely deny the possibility that the patient had hypoplastic MDS from the initial presentation; however, it might be considered that the patient developed an alteration of immune functions due to a dysplastic transformation of the bone marrow. We suspected that this immunological alteration influenced the patient’s unique clinical course of ALK-negative ALCL. Some reports described the coexistence of de novo MDS and NHL or NHL developing after MDS (12, 13, 19). Huang et al proposed 3 hypotheses that may explain this phenomenon (12). The first hypothesis was that the same neoplastic process occurs in both disorders; i.e., they have a common origin. This could explain their case in which they proved that a 20q deletion, which is a common molecular biological abnormality, existed in the myeloid cell lineage in the bone marrow and lymphoma cells in the lymph nodes. In the present case, the 20q deletion was found in the bone marrow, but chromosomal analysis of the lymph nodes was not performed. Therefore, we could not conclude that the lymphoma and MDS had a common origin. The second hypothesis was that MDS predisposes the development of lymphoid neoplasms. MDS is associated with abnormal immunological function, including abnormal lymphocytic numbers and function, and it permits neoplastic cell growth. In our case, EBER1 was negative in the lymph nodes, but it may be possible that the immunosuppressive state due to MDS was associated with lymphoma development and it significantly influenced the unique manifestation and rapid progression. The third hypothesis was that the coexistence of MDS and NHL may be associated with upregulation of certain cytokines such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF). Shimamoto et al described a case of ALK-negative ALCL exhibiting trilineage dysplasia in the bone marrow with an associated increase in the levels of VEGF and IL-6. When the patient achieved complete remission after chemotherapy, the myelodysplastic features disappeared and cytokine levels returned to within normal range (19). In the present case, CRP levels rose remarkably and the histiocytic-like cells proliferated in the bone marrow at the time of lymphoma development. These phenomena suggest that there could have been a high level of inflammation; however, we did not investigate these cytokine levels or re-evaluate dysplasia in the bone marrow after chemotherapy for the ALK-negative ALCL.

In summary, we described a case of ALK-negative ALCL with leukemic transformation as an initial manifestation, which is extremely rare, in a patient with MDS. The atypical development and progression of the disease may have been influenced by the existence of underlying MDS; our experience could provide us a clue to understand the pathophysiology of aggressive transformation in patients with hematological malignancies.

The authors state that they have no Conflict of Interest (COI).

References


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