Advanced Lymphocyte-rich Classical Hodgkin Lymphoma Complicated with Fatal Hemophagocytic Syndrome

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Abstract

Lymphocyte-rich classical Hodgkin lymphoma (LRCHL) is a rare subtype of Hodgkin lymphoma with a favorable prognosis, and an aggressive clinical course of LRCHL is uncommon. A 55-year-old man suffering from swelling in the left neck was diagnosed with LRCHL with extranodal lesions in the lung and bone marrow. Initially, he received standard ABVD chemotherapy; however, disease progression, accompanied by hemophagocytic syndrome (HPS), occurred during the second course of ABVD. He received two subsequent courses of intensive chemotherapy containing high-dose steroids, cyclophosphamide, and etoposide. Nevertheless, this therapy was only temporarily effective, and he died of due to an aggressive disease progression accompanied by uncontrollable HPS and severe coagulopathy.

Key words: lymphocyte-rich classical Hodgkin lymphoma, hemophagocytic syndrome, pulmonary Hodgkin lymphoma

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Introduction

Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis, is a potentially fatal hyper-inflammatory condition caused by a highly stimulated immune reaction (1, 2). HPS is clinically characterized by a high fever, pancytopenia, liver dysfunction, and hypercytokinemia; patients with HPS often present with a poor general condition and their prognosis is poor. In adults, HPS is largely considered to be a secondary disorder and is associated with malignant lymphoma, viral infection [especially Epstein-Barr virus (EBV)], and autoimmune disease. Lymphoma-associated HPS is the most common type, especially in the histology of non-Hodgkin lymphoma (1).

It is uncommon for HPS to occur in cases of Hodgkin lymphoma, although there have been several case reports and reviews regarding Hodgkin lymphoma-associated HPS (HL-HPS), and the following features have been documented. HL-HPS is mostly associated with a lymphocyte-depletion histology subtype (3) and EBV reactivation (4).

We herein report a case of lymphocyte-rich classical Hodgkin lymphoma (LRCHL) associated with severe and fatal HPS, which emerged under chemotherapy and was uncontrollable despite intensive chemotherapy. An aggressive clinical course, multiple extranodal lesions, and complication of HPS are all considered to be uncommon in LRCHL.

Case Report

A 55-year-old man had lymph node swelling in the left neck since June 2014, which had increased over a period of a few months. In October, the local doctor surgically resected the lymph nodes, and he was referred to us in mid-November. At presentation, he was generally well without a fever, weight loss, or night sweats. Positron emission tomography revealed fluorodeoxyglucose uptake in the systemic lymph nodes, the marrow of multiple bones, and pulmonary nodules (Fig. 1). A complete blood count (CBC) revealed no abnormalities. The erythrocyte sedimentation rate and serum soluble interleukin receptor (sIL-2R) level were slightly elevated, 16 mm/h and 1,662 U/mL, respectively.

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There were no particular abnormalities, including lactic dehydrogenase (LDH). A pathological evaluation of the previously resected lymph nodes (Fig. 2) revealed large Hodgkin and Reed-Sternberg (HRS) cells on a nodular and diffuse background of the small lymphocytes. Immunohistochemically, the HRS cells were positive for CD30, CD20, PAX5 and Reed-Sternberg (HRS) cells on a nodular and diffuse background of the small lymphocytes. In situ hybridization for EBV-encoded RNA (EBER) was positive in the HRS cells (g).
(weakly), and OCT2 (weakly); and negative for CD45, CD3, CD5, CD10, CD15, CD79a, and BOB1. In situ hybridization for EBV-encoded RNA (EBER) was positive. The Ki-67 labeling index was high (approximately 80%). The above findings established a pathological diagnosis of LRCHL. A bone marrow biopsy revealed an infiltration of Reed-Sternberg cells, which were CD30+ CD20+ CD15-, coincident with lymphoma cells of the lymph nodes (Fig. 3). From the beginning of December, the patient suffered from a high fever, and computed tomography (CT) revealed rapid enlargement of the left cervical lymph nodes (Fig. 4a, b) and multiple pulmonary nodular lesions (Fig. 4c). We considered this a rapid progression of lymphoma, and he was admitted immediately. Upon admission, he was febrile but his general condition was stable. There were no apparent focal signs of infection. Biochemical analyses revealed an elevation of LDH (967 IU/L) with mild transaminase elevation (AST 72 IU/L and ALT 45 IU/L). The CBC revealed no abnormal findings.

The clinical course is shown in Fig. 5. The ABVD regimen (doxorubicin 25 mg/m², bleomycin 10 mg/m², vinblastine 6 mg/m², and dacarbazine 375 mg/m² on days 1 and 15 in a 28-day cycle) was promptly started. Within a few days, his fever declined, the pulmonary lesions disappeared, and the cervical lymph nodes reduced in size. However, starting on day 12 of the second cycle, he had a high fever.
and experienced severe liver dysfunction. At this point, the bone marrow revealed marked increases in mature and activated macrophages with hemophagocytosis; however, lymphoma infiltration was not detected (Fig. 6). A biochemical evaluation revealed marked elevation of the liver enzymes (AST 514 IU/L, ALT 313 IU/L, ALP 851 IU/L, and LDH 2,175 IU/L) and hyperferritinemia (34,860 ng/mL). The CBC revealed thrombocytopenia with mild anemia (WBC 6,540/μL with 95% neutrophils and 2% lymphocytes, hemoglobin 10.3 g/dL, and platelets 87,000/μL). The serum immunoglobulin levels were not decreased (IgG 1,192 mg/dL, IgA 210 mg/dL, and IgM 50 mg/dL). CT revealed reaugmentation of the cervical lymph nodes. We assumed that an abrupt progression of lymphoma or EBV reactivation could have caused hypercytokinemia resulting in HPS and initiated an ESHAP regimen (etoposide 40 mg/m² on days 1-4, cisplatin 25 mg/m² on days 1-5, methylprednisolone 500 mg on days 1-5, and cytarabine 2,000 mg/m² on day 5). EBV DNA in the peripheral blood was counted at the level of 2.5×10⁵ copies/10⁶ cells. Soon after the initiation of chemotherapy, the patient became afebrile and his liver dysfunction ameliorated. However, from day 20 of ESHAP, his high fever resumed with an abrupt elevation of the liver enzymes and ferritin level. A bone marrow examination revealed residual macrophages with hemophagocytosis. CT indicated that cervical lymph nodes were mildly reduced in size, with-
out apparent changes in the other lesions. We considered that ESHAP was not sufficient for disease control and initiated a BEACOPP regimen (cyclophosphamide 600 mg/m² on day 1, etoposide 100 mg/m² on days 1-3, doxorubicin 25 mg/m² on day 1, prednisolone 40 mg/m² on days 1-14, procarbazine 100 mg/m² on days 1-7, bleomycin 10 mg/m² on day 8, and vincristine 2 mg on day 8). Within a few days, he became afebrile again and his liver enzymes gradually declined, although the high fever resumed with an abrupt elevation of the liver enzymes and coagulatory disturbance from day 19 of BEACOPP. The CBC revealed hyperleukocytosis (41,120/μL with 97% neutrophils) and recovery of the platelet count (74,000/μL). EBV DNA in the peripheral blood was not elevated (4.7×10^6 copies/10^9 cells, on day 16 of BEACOPP). We started dexamethasone administration (20 mg/day) for the suppression of hypercytokinemia and administered brentuximab vedotin (BV, 1.8 mg/kg) on day 20 of BEACOPP. We started dexamethasone administration (20 mg/day) for the suppression of hypercytokinemia and administered brentuximab vedotin (BV, 1.8 mg/kg) on day 21 of BEACOPP. However, the progression of liver dysfunction and coagulatory disturbance were quite severe and uncontrollable. Despite active supportive treatment, including fresh frozen plasma administration, the patient died 3 days after the administration of BV due to a potential intracerebral hemorrhage because of severe coagulatory dysfunction.

**Discussion**

LRCHL is a relatively rare subtype of classical Hodgkin lymphoma and accounts for approximately 5% of all cases of Hodgkin lymphoma (5). It was reported that LRCHL patients generally present with early stage disease typically involving peripheral lymph nodes and show a good prognosis with standard multidrug chemotherapy (6, 7). According to a study of 100 LRCHL patients, Shimabukuro-Vornhagen et al. reported that patients with LRCHL are on average older than those with classical Hodgkin lymphoma, generally present with early stage disease without B symptoms, and the treatment outcome for LRCHL is excellent (7). They also reported that organ involvement was relatively rare, and lung and bone marrow lesions were detected in only 4% and 2% of all LRCHL cases, respectively. In contrast, the present case showed quite different clinical features, including advanced stage at presentation with extranodal lesions (bone marrow and lung) and primary refractoriness to standard chemotherapy, and was thus considered to be an atypical case of LRCHL.

It is uncommon for Hodgkin lymphoma to be associated with HPS. However, several case reports and series concerning HL-HPS have recently been reported (3, 4, 8, 9). Menard et al. retrospectively analyzed 34 patients with HL-HPS and reported characteristics of male predominance, immunodeficiency-like histological features (lymphocyte depletion, 45%; mixed cellularity Hodgkin lymphoma subtype, 40%), and a strong association with EBV (4). To the best of our knowledge, this is the first case report of HL-HPS which occurred in the case of LRCHL. In the present case, the patient had no particular background suggesting immunodeficiency, and the histological subtype was LRCHL. In contrast, EBV reactivation could be at least partially associated with the complication of HPS according to the histological identification of EBV by in situ hybridization of EBV-encoded RNA in the lymph nodes at diagnosis and the transient elevation of the peripheral blood EBV DNA titer.

We assumed that hyperactive cytokines, which are associated with rapid expansion of lymphoma, could have caused such robust emergence and exacerbation of HPS. The simultaneous occurrence of HPS and enlargement of cervical lesions strongly supports the speculation that regrowth of lymphoma cells could cause HPS. It might have been simply caused by viral reactivation or infection; however, this is unlikely because lymphocidic/lymphotoxic agents, such as etoposide, cyclophosphamide, and steroids, which would be expected to be effective for HPS (10), were included in the chemotherapy regimens.

The disease progression of Hodgkin lymphoma toward the lung is rare, and reported cases of pulmonary Hodgkin lymphoma are in histological subtypes of nodular sclerosis and mixed cellularity (11). Honda et al. reported a case of LRCHL with pulmonary infiltration which was characterized by an early response of pulmonary lesions to ABVD therapy (12); multiple parenchymal nodules in both lungs, similar with the present case, were observed. In this case, ABVD and subsequent chemotherapy were also considered to be effective for control of the pulmonary lesions. Residual nodal lesions causing a cytokine storm were quite refractory to chemotherapy, suggesting that there may have been biological differences between the pulmonary lesions and nodal lesions in the present case.

There are some limitations associated with this study. Because sequential histological examinations of the lymph node lesions were not performed, we cannot deny the possibility of histological transformation to a more aggressive subtype. Although there have been no reports regarding cases of LRCHL which experienced histological transformation or complication with other subtypes of lymphoma, it is important to reconfirm the histological findings in case of an unexpectedly aggressive clinical course.

In summary, we herein reported a case of advanced LRCHL which was initially accompanied by unusual extranodal lesions and led to fatal HPS during the course of chemotherapy. To the best of our knowledge, this is the first case report of LRCHL complicated by HL-HPS.

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

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