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Conference Case

A difficult case of angioimmunoblastic T-cell lymphoma with Epstein-Barr virus-negative large mononuclear atypical cells

Keywords: Angioimmunoblastic T-cell lymphoma, Classic Hodgkin lymphoma, Composite lymphoma, HRS-like cell, HRS cell

CASE REPORT

A 74-year-old man with no history of a major medical condition presented with left neck lymphadenopathy that slowly progressed over approximately 2 months. He reported no fever, night sweats, or weight loss. A physical examination revealed generalized lymph node swelling, including the bilateral neck, axillary, and inguinal lymph nodes. On laboratory examination, the complete blood count suggested mild thrombocytopenia at 14.1 $\times 10^4/\mu L$. The results of a chemistry panel were normal, except for a lactate dehydrogenase level of 294 U/L, soluble interleukin-2 receptor level of 2140 U/mL, and hypergammaglobulinemia (IgG, IgA, and IgM levels were 2568, 236, and 547 mg/dL, respectively). Staging positron emission tomography/computed tomography (PET/CT) revealed hypermetabolic lymph nodes in the bilateral cervical, bilateral supraclavicular, paraaortic, and bilateral iliac regions. Moreover, hypermetabolic foci were detected in the mediastinum and spleen (Figure 1). Excisional biopsy of the left neck lymph node demonstrated that the lymph node architecture was affected by small to medium-sized lymphoid cells with a small number of interspersed large mono and binuclear atypical cells. Prominent vascularity and a variety of inflammatory cells were present in the background. On immunohistochemical analysis, large atypical cells were positive for CD30 and PAX5 (weak), and negative for CD15, CD20, and ALK. These results were consistent with the phenotype of Hodgkin and Reed/Sternberg (HRS) cells. The small to medium-sized lymphoid cells exhibited a T follicular helper cell phenotype, and were positive for CD3, CD4, CD10, and PD-1. Both large mononuclear cells and lymphoid cells were negative on EBV-encoded small RNA1 *in situ* hybridization (EBER1-ISH). The histopathological findings are shown in Figure 2. Rearrangements of the immunoglobulin heavy chain (IGH), T-cell receptor γ (TRG), and T-cell receptor β (TRB) were detected using DNA obtained from whole sections of paraffin-embedded specimens by polymerase chain reaction analysis using the BIOMED-2 protocol at SRL, Inc. (Tokyo, Japan).[1] Although the diagnosis of AITL was made mainly based on the histopathological findings, it was difficult to differentiate HRS-like cells from true HRS cells. Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy was initiated. After the completion of six cycles of CHOP, restaging PET/CT demonstrated a complete metabolic response.

AITL is a subtype of the second most common peripheral T-cell lymphoma, followed by peripheral T-cell lymphoma (PTCL), not otherwise specified.[2] Due to the immunological dysfunctions associated with AITL, EBV-positive B lymphocytes can often expand. In rare cases, these reactive EBV-positive B lymphocytes are morphologically and immunophenotypically indistinguishable from true HRS cells. Therefore, they are termed HRS-like cells. HRS-like cells are often associated with EBV reactivation; however, EBV-negative HRS-like cells can exist.[3] On the other hand, in rare instances, two distinct subtypes of malignant lymphomas develop simultaneously or serially in the same patient. Such lymphomas are referred to as composite lymphomas (CLs). CLs account for 1-4% of all malignant lymphomas.[4] To date, eight cases of CL comprising classic Hodgkin lymphoma (HL) and PTCL have been reported. In three cases, HRS cells harbored EBV infection.[5-7] On the other hand, five cases of CL constituting PTCL and HL with EBV negative-HRS cells have been reported.[8] In general, IGH rearrangements are found in approximately 20% of AITL cases. However, B-cell clonality is likely in AITL cases with expanded EBV-infected B lymphocytes.[9]

In summary, when determining the diagnosis, it is challenging to distinguish HRS-like cells from true HRS cells. Furthermore, in the present case, EBV-negative large mononuclear cells and the detection of clonal IGH gene rearrangements without evidence of EBV reactivation made the diagnosis more difficult. We would like to ask experts about how to diagnose the present case.

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CONFLICT OF INTEREST

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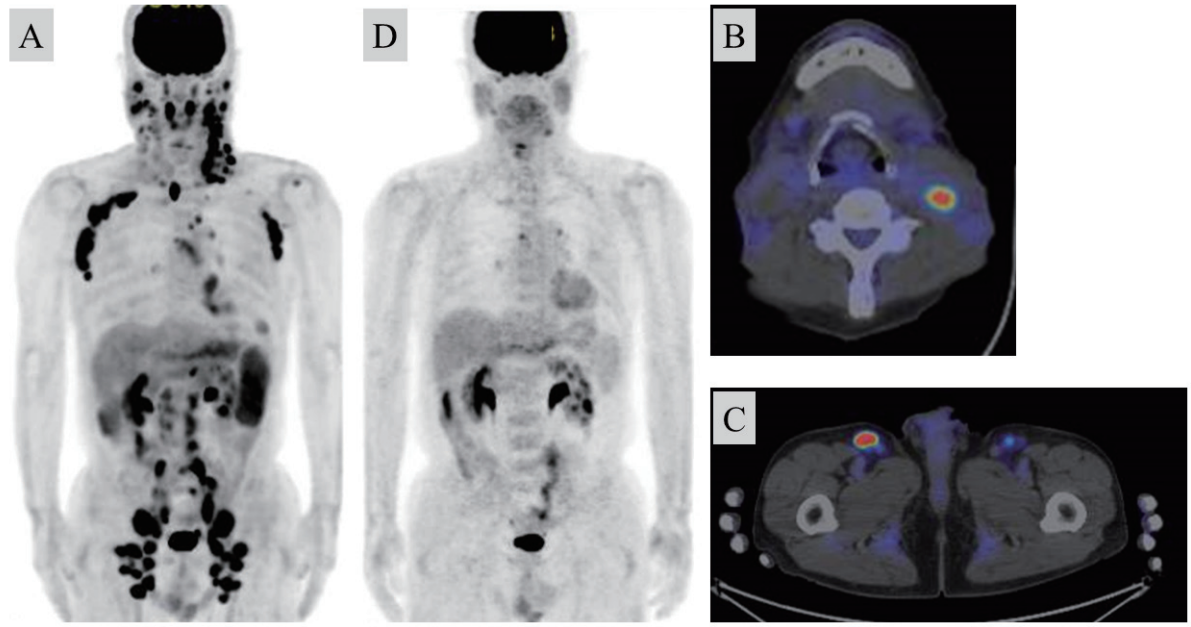

Fig. 1. ***A***, Baseline positron emission tomography/computed tomography (PET/CT) revealed hypermetabolic lymph nodes in the bilateral cervical, bilateral supraclavicular, para-aortic, and bilateral iliac regions. Hypermetabolic foci were also detected in the mediastinum and spleen. ***B***, Left cervical lymph node. ***C***, Right inguinal lymph node. ***D***, Post-chemotherapy PET/CT demonstrated complete metabolic response.

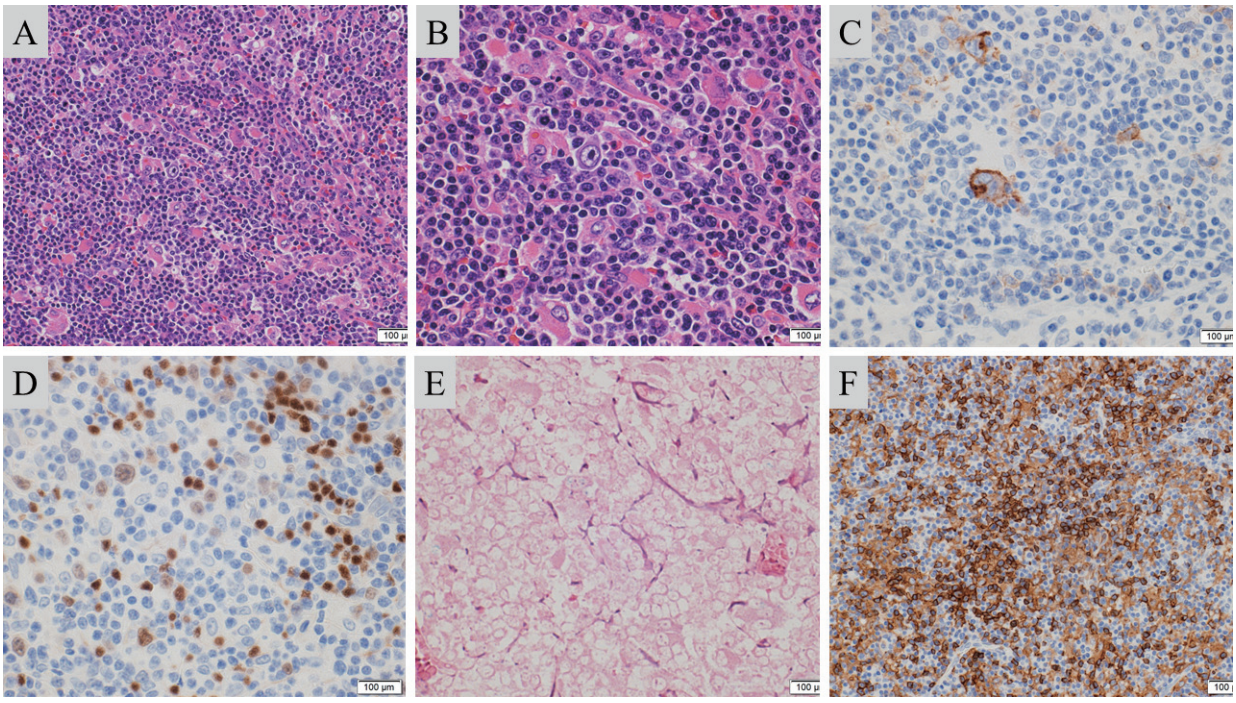

Fig. 2. ***A*** and ***B***, Lymph node biopsy revealed scattered large mononuclear lymphoid cells with infiltrating small to medium lymphocytes. Prominent vascularity and a variety of inflammatory cells, such as eosinophils, were also observed. (hematoxylin-eosin, original magnification ×200, ×400) ***C*** and ***D***, Hodgkin/Reed-Sternberg (HRS) cells were positive for CD30 and weakly positive for PAX-5 compared with normal B-lymphocytes in the background. (original magnification ×400) ***E***, HRS cells and lymphocytes in the background were negative on Epstein-Barr virus-encoded RNA1 *in situ hybridization*. (original magnification ×400) ***F***, Neoplastic T-cells were dominantly positive for CD4. (original magnification ×400)

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