T-Cell/Histiocyte-Rich Large B-Cell Lymphoma: A Challenging Diagnosis

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ABSTRACT
Epstein-Barr virus (EBV) is a double-stranded virus that shows tropism for B-cell lymphocytes. EBV-infected patients usually present with tonsillitis/pharyngitis, cervical lymphadenopathy and fever, but an atypical presentation can mimic lymphoproliferative disease. We present the case of a 77-year-old woman with asthenia, fever, oral ulcers and peripheral lymphadenopathy. After extensive evaluation, including anatomopathological and immunocytochemical examination of excisional lymph node biopsy samples, it was still not clear whether the patient had EBV infection or diffuse large B-cell lymphoma.

In this case report, the authors describe how it can be difficult to differentiate between two different, although related, entities, making diagnosis of lymphoma highly challenging.

LEARNING POINTS
- Lymph node biopsy findings may result in lymphoma being misdiagnosed as acute Epstein-Barr virus infection.
- Immunophenotypic analysis can occasionally be insufficient to establish the clonal nature of the disease.
- Timely diagnosis of lymphoma is necessary so that immunochemotherapy can be initiated and clinical improvement achieved.

KEYWORDS
Diffuse large B-cell lymphoma, Epstein-Barr virus infection, herpes simplex infection

CASE DESCRIPTION
A 77-year-old woman presented for the third time at the emergency department with a 3-month history of progressive asthenia and multiple cervical lymphadenopathy, associated with 3 weeks of recurrent fever with a maximum temperature of 38.7°C (no pattern, no nocturnal sweats and no weight loss) and two crusted lesions, one in the left nostril and the other in the left nasogenian sulcus.

At initial evaluation, the patient presented with pale mucous membranes, left hemifacial oedema, a circular crusted lesion 2 cm in diameter in the left nasogenian sulcus, a left nostril filled with crust, multiple ulcers on the oropharynx including the tonsils, and numerous, movable and pliable posterior cervical lymph nodes approximately 1–2 cm in diameter (Fig. 1). Because of these features, the patient was admitted to the internal medicine ward for diagnostic work-up.

Since the initial clinical features were not specific for a particular pathology, an extensive study was performed. Blood tests showed bicytopenia, with haemoglobin of 8.8 g/dl and 99×10^9/l platelets. The patient had normal renal and hepatic function, minimal elevation of lactate dehydrogenase (281 U/l), elevated β2-microglobulin (10,100 ng/ml), and C-reactive protein of 1.92 mg/dl. To exclude infectious diseases, serology for HIV, cytomegalovirus (CMV), EBV, herpes simplex type 1 (HSV-1), HSV-2, Coxiella burnetii, Borrelia burgdorferi and Bartonella henselae was carried out. Results showed that the patient was IgM and IgG positive for CMV (4.44/4.71 UA/ml) and EBV (1.8/104.40 RU/ml), IgM positive and IgG negative for HSV-2 (2.80/0.00 RU/ml) and IgM negative and IgG positive for HSV-1 (0.60/184 RU/ml). Interferon-gamma release assays were negative.
CT of the neck/ chest/ abdomen/ pelvis showed numerous enlarged lymph nodes and a 178 mm axial plane splenomegaly, suggesting lymphoproliferative disease. To rule out haematological malignancy, a peripheral blood smear (PBS), bone marrow evaluation and excisional lymph node biopsy were carried out. PBS analysis showed rouleaux formation and 18% lymphoplasmacytic cells. Immunophenotypic analysis of bone marrow aspirate revealed 20% B-cells, 18% of which were plasmablasts with strong CD38 expression (negative for CD20 and CD138). Similarly, immunophenotypic analysis of excisional lymph node biopsy samples showed 47% B-cells, 60% of which were plasmablasts with strong CD38 expression. Pathology and immunocytochemistry of excisional lymph node biopsy samples suggested T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL), a variant of diffuse large B-cell lymphoma (DLBCL), although EBV infection could not be ruled out.

Given the presence of facial and oropharyngeal lesions, the patient was also evaluated by the dermatology team. A skin biopsy ruled out paraneoplastic pemphigus but revealed herpetic infection.

Despite this extensive evaluation, it was still not clear whether the patient had EBV infection or lymphoma. In order to clarify the diagnosis, in-situ hybridization for EBV in lymph node tissue samples as well as a molecular study for immunoglobulin gene rearrangement, were performed. Both tests were compatible with the presence of a clonal B-cell population, providing the diagnosis of T-cell/histiocyte-rich DLBCL. Ann-Arbor IV-B, R-IPI 3, CNS-IPI 3, intermediate risk.

The patient was treated with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), as well as anti-infective prophylaxis with trimethoprim-sulfamethoxazole 160–800 mg bid three times a week, acyclovir 400 mg bid and myeloid growth factor support.

The patient demonstrated early clinical improvement and extensive CT examination after seven cycles of chemotherapy showed remission of abdominopelvic lymphadenopathy, and a reduction in spleen size from 178 mm to 138.7 mm. Bone marrow evaluation was negative for THRLBCL. While on treatment, the patient experienced self-limited toxicoderma secondary to myeloid growth factor as well as retinal and systemic CMV infection.

**DISCUSSION**

As described above, the patient presented with various unspecific complaints, compatible with a broad range of diagnoses. The progressive and prolonged complaints made an infectious cause less likely. However, patients with DLBCL often present B symptoms (unexplained fever, weight loss and night sweats) and a rapidly growing tumour mass in single or multiple nodal or extranodal sites.[1]

In this case, the patient presented with a 3-month progressive history of asthenia, fever and cervical lymphadenopathy. Lymph node biopsy was deemed necessary to establish the correct diagnosis, but biopsy findings of extensive proliferation of immunoblasts with marked cytological atypia[2] raised doubts as to whether the patient had THRLBCL or acute EBV infection. Therefore, immunophenotypic analysis was carried out. However, flow cytometry was not able to determine the clonal nature of the disease. In fact, in situ hybridization in nodal tissue samples as well as a molecular study (immunoglobulin gene rearrangement) were needed for a diagnosis of THRLBCL. In this patient, the timely diagnosis of lymphoma was critical for the initiation of immunochemotherapy and subsequent clinical/analytical improvement.
The aetiology of most cases of EBV infection is unknown and its persistence in B-cells may be a contributing factor for the development of DLBCL\(^3\). It is generally thought that with age (in this case the patient was 77 years old) the number B- and T-cell subsets decreases, resulting in more circulating cells with EBV-specific receptors\(^4\), and a higher incidence of lymphomas, with EBV infection promoting the development of subsequent oncogenic events. The exuberant HSV skin infection in our patient at onset was considered a consequence of immunosuppression.

In summary, we report a case where there was a challenging differential diagnosis between DLBCL and acute EBV infection, two related entities with different courses and generally different prognoses. This case highlights the importance of differentiating florid lymphoid proliferation from acute EBV infection and from malignant lymphoma so that an incorrect diagnosis can be avoided and appropriate treatment initiated for a better outcome.

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