Angioimmunoblastic T-Cell Lymphoma Partially Obscured by an Epstein-Barr Virus–Negative Clonal Plasma Cell Proliferation

Case Report

A 60-year-old female presented with progressive and rapid onset of malaise, fatigue, and weakness. On admission to the hospital, she was found to have Coombs-positive anemia (hemoglobin 4.7 g/dL), thrombocytopenia (platelets 1 K/ μ L), lymphadenopathy, and rapidly growing bilateral breast masses. She did not respond to transfusions,

intravenous immunoglobulin (IVIG), or steroids. Since the breast masses exhibited rapid growth, an aggressive lymphoma was a strong clinical concern. However, these masses were not biopsied due to the patient's thrombocytopenia. A bone marrow biopsy revealed panmyelosis (90% cellularity) with 5% to 10% polyclonal plasma cells, and frequent plasmacytoid lymphocytes were seen on the peripheral smear. Serum protein electrophoresis (SPEP) was negative for an M-spike, and free light chain assays were normal. Serum immunoglobulins G (IgG), IgM, and IgA were all elevated. Other laboratory studies included lactate dehydrogenase (LDH) of 462 U/L, positive anti-nuclear antibody, negative HIV testing and normal serum IL-6

Fig 1.

levels. Epstein-Barr virus (EBV) quantitative polymerase chain reaction was 4,945 copies/mL with EBV viral capsid antigen IgM within the reference range. A right cervical lymph node was biopsied. All studies were performed in accordance with approval of the institutional review board.

The lymph node contained focal clusters of medium-sized atypical lymphocytes with abundant clear cytoplasm positioned around high endothelial venules. However, most of the node was replaced by sheets of plasma cells. The plasma cells were cytologically atypical, exhibiting frequent mitotic figures, and surrounded the clusters of clear cells (Fig 1A). Numerous apoptotic bodies and tingible-body macrophages were present. Immunohistochemical stains demonstrated that the atypical clear cells were positive for CD3 (Fig 1B) and CD5, partially positive for CD10 (Fig 1C) and strongly positive for PD-1 (Fig 1D). CD23 staining revealed that some of these cells were associated with expanded follicular dendritic cell meshworks. The plasmacytic cells expressed CD138 (Fig 1E), CD38, MUM1, CD45 and weak kappa light chain (Figs 1F, kappa on right, lambda on left). They had a high proliferation rate as seen with Ki67. They were negative for CD56, cyclin D1, CD10, CD30, and immunoglobulin heavy chains (IgG, IgA, IgM, IgD). Only rare scattered cells were positive for EBV by in situ hybridization (EBER). Mature B-cells, as seen with CD20 and PAX-5, were relatively few.

Formalin-fixed paraffin-embedded sections were submitted for polymerase chain reaction studies. T-cell receptor gamma testing identified two significant peaks, consistent with a clonal T-cell population (Fig 2A). In addition, one and two significant peaks were detected in *immunoglobulin heavy chain gene* frameworks 2 and 3, respectively (Fig 2B-2C). No significant peaks were found in *immunoglobulin kappa light chain gene* tubes A and B (data not shown).

A staging computed tomography scan disclosed extensive lymphadenopathy in the chest, abdomen, and pelvis as well as mild splenomegaly. Further evaluation of the breast masses was not performed. The patient has received two cycles of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin thus far and is reported to be tolerating the therapy well. This case emphasizes the importance of awareness that a proliferation of B cells or plasma cells may overshadow the neoplastic T-cells in angioimmunoblastic T-cell lymphoma (AITL). Careful examination of the pathology should be performed as well as correlation with all clinical and laboratory data. Misdiagnosis as a plasma cell neoplasm in this case would have resulted in a dramatically different treatment strategy.

Discussion

AITL, one of the more common subtypes of peripheral T-cell lymphoma (PTCL), is typically associated with a minor population of EBV-positive B cells. This proliferation will occasionally progress to develop an EBV-positive B-cell lymphoma, either synchronous with or subsequent to the diagnosis of AITL.¹⁻⁴ However, B-cell expansion occurs independently of EBV, and immunoglobulin gene rearrangements may be detected in up to 41% of cases, without correlation to the number of EBV-positive cells at.^{2,5-7} The B-cell expansion observed in AITL is thought to be related to the function of the neoplastic cells as T-follicular helper (TFH) cells,^{8,9} and proliferations of clonal EBV-negative B-cells or plasma cells have been identified infrequently.^{4,10-12}

Balague et al¹⁰ described striking plasma cell differentiation in the majority of EBV-negative B-cell proliferations associated with PTCL, as opposed to the more usual large cell morphology of EBV-positive B-cell proliferations. Eight of their patients had clonal or monotypic

Fig 2.

plasma cells associated with PTCL, of which two had AITL. At the time of last follow-up, two of the eight patients were alive without disease, three were alive with disease (including one AITL patient), and one died of disease. Few clinical studies have examined the prognostic significance of B-cell expansion in AITL, but existing data have shown no correlation between IgH gene rearrangements or EBV-associated proliferation and clinical outcome in AITL.^{3,12,13} One early series¹⁴ even described longer survival in patients with immunoglobulin gene rearrangements, although low overall survival rates did not allow for examination of statistical significance.

AITL is also often associated with polyclonal plasmacytosis and polyclonal hypergammaglobulinemia. Some of these features may be explained by the properties of the neoplastic T-cells as TFH cells.^{8,9,15} Rarely, as demonstrated by this case, the B-cell or plasma cell expansion can be so great, as to partially overshadow or obscure the underlying T-cell neoplasm. Awareness of this eventuality is important to avoid misdiagnosis and inappropriate therapy.

The differential diagnosis in this case includes a plasma cell neoplasm unrelated to the patient's AITL. Features arguing against plasma cell myeloma include polyclonal plasma cells in this patient's bone marrow, normal SPEP/free light chain assays, and immunophenotypic characteristics of the plasmacytic cells such as retained CD45 expression. CD45 was not examined in the series reported by Balague et al,¹⁰ so it is unknown if this will be a consistent feature in these cases. Kappa light chain restriction with absence of heavy chain expression and demonstration of a clonal immunoglobulin gene rearrangement could motivate one to render a diagnosis of extraosseous plasmacytoma. However, the overall characteristics are consistent with this proliferation being associated with the patient's AITL.

A role for rituximab therapy also has been suggested as an addition to the chemotherapeutic regimen due to the B-cell proliferations associated with AITL. However, results of a single phase II trial involving 25 patients with varying numbers of B cells indicate that no clear benefit was identified when rituximab was added to conventional cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy.¹⁶ Larger trials or those targeting only patients with significant B-cell populations may be needed to further clarify this hypothesis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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