Case Report

Epstein-Barr Virus–Induced CD30-Positive Diffuse Large B-Cell Lymphoma in a Patient With Mixed-Phenotypic Leukemia Treated With Clofarabine

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Clinical Practice Points

- Epstein-Barr virus (EBV)–positive lymphoproliferative disorders have been reported in several clinical settings associated with immunosuppression, such as primary immune deficiency, human immunodeficiency virus infection, bone marrow or solid organ transplantation, methotrexate or tumor necrosis factor therapy, and aging. We did not identify any reported cases that described EBV^+ lymphoproliferative disorders after purine analog therapy for acute myeloid leukemia or mixed-phenotype leukemia.
- Patients with acute myeloid leukemia and with persistent or progressive lymphadenopathy should undergo fine needle aspiration to rule out extramedullary leukemia (granulocytic sarcoma) or concurrent lymphoma.
- Identifying the ideal regimen for patients with mixed-phenotype leukemia requires large clinical trials. However, our patient with mixed-phenotype leukemia achieved complete remission with clofarabine, idarubicin, cytarabine, and Solu-Medrol therapy.
- Although antivirals (acyclovir, ganciclovir, and valacyclovir) have been proposed for prevention and treatment of a EBV-driven lymphoproliferative disorder, the infected latent B cells often do not express thymidylate kinase, which is the target for these antivirals, which is clearly seen in our patient because prophylactic valacyclovir was clearly ineffective in preventing the occurrence of EBV-driven lymphoma.

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Introduction

Lymphoproliferative disorders (LPD) have been reported in several clinical settings associated with immunosuppression, such as primary immune deficiency, human immunodeficiency virus infection, bone marrow or solid organ transplantation, methotrexate or tumor necrosis factor-therapy, and aging.[1,2] A significant number of these cases are associated with Epstein-Barr virus (EBV). Although EBV^+ LPDs have been documented in patients with low-grade lymphomas treated with purine analogues, including cladribine[3,4] or fludarabine,[5,6] we could not identify any reports of EBV^+ LPD after purine analogue (including clofarabine) therapy for acute myeloid leukemia (AML) or mixed-phenotype acute leukemia (MPAL). Because clofarabine is being used with increasing frequency in AML therapy,[7,8] such phenomenon may be noted with increasing frequency in the future. In our patient, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) therapy[9,10] effectively treated the EBV^+ LPD, and this may help guide treatment in future occurrences of a similar nature.

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Case Report

A 50-year-old white man presented to the MD Anderson Cancer Center's leukemia clinic with a 30-day history of pancytopenia and fatigue. A significant medical history included hypertension and coronary arthrosclerosis. Results of a physical examination revealed fever and splenomegaly. A complete blood cell count showed a white cell

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count of 1 × 10^9/L (reference range, 4-11 × 10^9/L), hemoglobin level of 72 g/L (reference range, 140-180 g/L), platelet count of 31 × 10^9/L (reference range, 140-440 × 10^9/L), and absolute neutrophil count of 0.06 × 10^9/L (reference range, 1.7-7.3 × 10^9/L). Bone marrow biopsy revealed cellular marrow with 65% blasts. Flow cytometry immunophenotype analysis of bone marrow aspirate material detected a distinct population of immature cells with mixed myeloid–T-lymphocyte phenotype. The neoplastic cells were positive for CD7 (partial), CD34, CD117, HLA-DR (partial), myeloperoxidase (small subset), CD13, CD64, CD33 (partial), CD71, CD123 (partial), TdT, CD10, CD38, and CD33 (partial), and for cytoplasmic CD3. The neoplastic cells were negative for CD1a, CD2, surface CD3, CD4, CD5, CD8, CD14, CD19, CD41, TCR alpha/beta, and TCR gamma/delta. The immunophenotype of the blasts fulfilled diagnostic criteria for MPAL, T/myeloid as defined by the European Group for the Immunologic Characterization of Leukemias[11] and by the 2008 World Health Organization classification.[12] Conventional cytogenetic studies revealed a complex karyotype, including -3, add (5) (q35), -7, -11, -15, -16, -18, and -20 chromosomal aberrations. The patient was seen by the stem cell transplant service at initial diagnosis of biphenotypic leukemia with complex karyotype and was thought to be a good candidate for consolidation with allogeneic stem cell transplantation. He received induction therapy with clofarabine (15 mg/m^2 for 3 days), cytarabine (0.75 g/m^2 for 3 days), idarubicin (8 mg/m^2 for 3 days), and methylprednisolone (40 mg intravenous for 3 days). Day-21 bone marrow aspirate showed complete morphologic and cytogenetic remission.

After chemotherapy, the patient became pancytopenic. Twenty-eight days after completion of induction therapy, he presented to the emergency department with a sore throat and progressive swelling in the neck. Computerized tomography (CT) of the neck showed necrotic lymphadenopathy in bilateral submandibular regions and enhancement of the palatine tonsils. A throat swab and blood cultures grew vancomycin-resistant enterococci. The initial antibiotics included meropenem and linezolid. Subsequently, fine needle aspiration of a submandibular lymph node revealed inflammatory infiltrate with no neoplastic cells and no microbial growth on cultures.

The patient went on to receive 2 cycles of consolidation therapy at 4-weekly intervals per protocol with clofarabine, cytarabine, and idarubicin. Four weeks after completion of the second consolidation cycle, he presented with worsening neck swelling. A repeated CT of the neck showed resolving submandibular lymphadenitis. A CT of the chest showed multiple lung nodules. Biopsy of a lung nodule showed diffuse infiltration by neoplastic cells with perivascular infiltration and necrosis. The neoplastic cells were large, with irregular shaped nuclei and inconspicuous nucleoli (Figure 1C). They were positive for CD20 (Figure 1D), CD30 (Figure 1E), and PAX-5, and were negative for CD3, CD33, CD34, and TdT. In situ hybridization studies for EBV small encoded RNA (EBER) demonstrated that the neoplastic cells were strongly positive for EBER (Figure 1F). Peripheral blood EBV quantitative polymerase chain reaction (PCR) identified a viral load of 16,626 EBV copies/mL of plasma (normally undetectable). These results led to a diagnosis of EBV^+ diffuse large B-cell lymphoma (DLBCL). We retrospectively performed EBER on an initial bone marrow specimen to see if EBV was present at the time of initial diagnosis and may have caused the MPAL. EBER was negative on the initial bone marrow. We were unable to perform fluorescence in situ hybridization for c-myc or BCL2/IGH because extensive necrosis in the tissue sample precluded fluorescence in situ hybridization analysis.

Whole-body positron emission tomography–CT showed increased fluorine-18 fluorodeoxyglucose uptake in bilateral pulmonary nodules, bilateral cervical lymph nodes, stomach, spleen, and liver (Figure 1A). Bone marrow biopsy showed 0% abnormal blasts and no morphologic evidence of DLBCL or morphologic evidence of MPAL. The patient was staged as $IV_{E, S}$ DLBCL (Cotswold modification of the Ann Arbor staging system). He continued to be follow-up with the stem cell transplant service, and a 10/10 sibling donor was identified. Unfortunately, he developed the DLBCL before proceeding to allogeneic transplant for the biphenotypic leukemia.

After discussion with lymphoma specialists, the R-CHOP regimen was initiated. After 1 course, he had significant shrinkage of palpable lymph nodes and significantly diminished fluorine-18 fluorodeoxyglucose uptake on the positron emission tomography (Figure 1A, B). A repeated EBV serology performed 1 week later showed undetectable EBV levels in serum. He received a total of 2 cycles of R-CHOP therapy for the DLBCL. The stem cell transplant service continued to follow up the patient with the hope to proceed to allogeneic transplantation as a potential therapy for both the biphenotypic leukemia and DLBCL. Unfortunately, before he could proceed to allogeneic stem cell transplantation, the patient developed a progressive fungal pneumonia with sepsis and expired in the intensive care unit.

Discussion

We report a case of EBV^+ DLBCL in a patient treated with clofarabine for MPAL. EBV^+ LPD has been reported in several clinical settings associated with primary or acquired immunosuppression.[1,2,11,12] Although cases of EBV^+ LPD have been documented in patients with low-grade lymphomas and hairy cell leukemia treated with fludarabine and cladribine,[3-6] we did not find any reported cases of EBV^+ LPD in patients with MPAL or AML treated with purine analogues.

Our patient initially presented with MPAL, which accounts for fewer than 4% of all acute leukemias.[13,14] Results of several studies have suggested that patients with MPAL have a worse clinical outcome than AML and/or acute lymphoblastic leukemia (ALL).[15,16] There is no consensus as to whether induction therapy should be with lymphoid drugs, myeloid drugs, or combinations.[17] A retrospective study reported that induction with combined AML and ALL drugs led to a high rate of early death in patients with adult and pediatric MPAL, although most of these patients had t(9,22), which, on its own, portends a poor prognosis.[16] In pediatric MPAL, induction with ALL-type therapy or combined therapy with agents that are active against lymphoid and myeloid leukemias has shown to yield higher complete remission rates than AML-type induction therapy.[18,19] It is unknown whether similar strategies are applicable to adults.

The mechanisms by which EBV stimulates lymphoid proliferation and malignant transformation are poorly understood. EBV binds to receptors on B cells and pharyngeal surface molecule