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Diffuse Large B-cell Lymphoma in Patient after Treatment of Angioimmunoblastic T-cell Lymphoma

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ABSTRACT

Relatively few cases of Epstein-Barr (EBV)-positive B-cell lymphomas arising in patients with angioimmunoblastic T-cell lymphoma (AITL) have been reported. We report a case of AITL in which diffuse large B-cell lymphoma arose 13 months after the initial diagnosis of AITL. In a 36-year-old female patient, evaluated for moderate leukocytosis, peripheral and abdominal lymphadenopathy AITL was diagnosed in March 2008, based on results of fine-needle aspiration cytology (FNAC) of the enlarged cervical and supraclavicular lymph nodes. The diagnosis was also confirmed by immunophenotyping and histopathology of the cervical lymph nodes. The patient initially received FED chemotherapy (fludarabine, cyclophosphamide, dexamethasone) followed by elective autologous hematopoietic stem cell transplantation. In April 2009 the patient was hospitalized because of fever, pancytopenia, hyperbilirubinemia and peripheral lymphadenopathy. The FNAC of the enlarged cervical lymph nodes was performed again, but this time the smears were composed of polymorphous population of lymphocytes with the predominance of large cells, CD20+ on immunocytochemical stains. The immunophenotyping confirmed a predominance of monoclonal mature B-cells. Patient had high number of EBV DNA copies in plasma and serologic testing revealed increased titers of EBV VCA IgG and EBV EBNA IgG. CHOP-R chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) was then administered, resulting in good partial response of the disease. Reduced intensity allogeneic stem cell transplantation performed thereafter, resulted in complete remission of the disease. AITL is a rare lymphoproliferative disorder in which the neoplastic T-cells represent the minority of the lymph node cell population and almost all cases harbor EBV-infected B-cells. Various authors postulated that immunodeficiency in AITL patients together with immunosuppressive effects of cytotoxic drugs, may be responsible for EBV-induced proliferation of latently or newly EBV-infected B-cells with eventual clonal selection and progression to aggressive B-cell lymphoma.

Key words: angioimmunoblastic T-cell lymphoma, Epstein-Barr virus, diffuse large B-cell lymphoma

Introduction

We report a case of angioimmunoblastic T-cell lymphoma (AITL) in which diffuse large B-cell lymphoma (DLBCL) arose 13 months after the initial diagnosis of AITL.

Angioimmunoblastic T-cell lymphoma is a systemic lymphoproliferative disorder that produces constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, skin rash and immunological disturbances with the overall median survival less than 3 years¹⁻⁵. AITL pa-

tients tend to be severely immunodeficient and have a propensity for opportunistic infections¹⁻⁵ prior to and during therapy⁶. Histologically, the involved lymph nodes demonstrate partial to complete effacement of the normal architecture with atretic or absent germinal centers, prominent neovascularization and polymorphous infiltration by plasma cells and immunoblasts⁷. Early disease is often associated with intact and sometimes hyperplastic germinal centers⁸. While peripheral sinuses are typi-

cally open and even dilated, the abnormal infiltrate often extends beyond the capsule⁸. Another prominent feature is extensive arborization of post capillary venules which lie in an expanded meshwork of follicular dendritic cells⁸. Large basophilic B immunoblast and polyclonal plasma cells are observed in the parafollicular areas in 25–80% of patients and these B-cells often harbour Epstein-Barr virus (EBV)^{8,9}.

The neoplastic T-cells represent a minority of the lymph node cell population¹⁰. Almost all cases harbor an EBV-infected B-cell population¹⁰ detected by polymerase chain reaction (PCR) or fluorescent in situ hybridization (FISH) analysis⁶. EBV driven B-lymphoid proliferation may occur, analogous to immunodeficiency states such as primary immune disorders, human immunodeficiency virus (HIV) infection and postallogenic organ transplantation¹¹. Relatively few cases of EBV-positive B-cell lymphomas arising in patients with AITL have been reported^{12–14}.

Case Report

A 36-year-old female patient was evaluated in March and April 2008 for mild leukocytosis ($10.88 \times 10^9/L$), left inguinal and cervical lymphadenopathy and edematous left leg. In her medical history, she had infectious mononucleosis 5-years ago. An enzyme immunoassay (EIA)

test for HIV infection was done and it was negative. After an ultrasound examination showed enlarged left paraaortal, mesenteric and left iliac lymph nodes, lymphoproliferative disease was suspected. Fine-needle aspiration cytology (FNAC) of the enlarged inguinal and cervical lymph nodes was performed. The yielded material was placed and smeared on the slides, air-dried and May-Grünwald-Giemsa (MGG) stained. Immunocytochemical stains were done too. The cytology smears were composed of a polymorphous population of the small lymphocytes (partially CD20+, and partially CD3+) with many transformed lymphatic cells, immunoblasts and plasmablasts (Figures 1 and 2), which were CD3+. The cytological diagnosis was non-Hodgkin's lymphoma (NHL) – AITL. An immunophenotyping confirmed abnormal phenotype of the mature T-cells: CD2+, CD5+, CD7+, CD4+, HLA D/DR+, CD38-/+ and CD3-, CD8-. A computed tomography (CT) study showed enlarged abdominal lymph nodes in paraaortal and paracaval region with the largest diameter of the single lymph node 35 mm; in the left iliac region conglomerates of enlarged lymph nodes 50x35 mm in size were found; in the left pelvic region the conglomerates of enlarged nodes were 88x35 mm in size and in the left inguinal region the largest lymph node was 25 mm in diameter. Liver and spleen were of normal size. Biopsy of an enlarged left cervical lymph node was performed. Microscopically, the lymph node architecture was effaced and a polymorphic infiltrate composed of

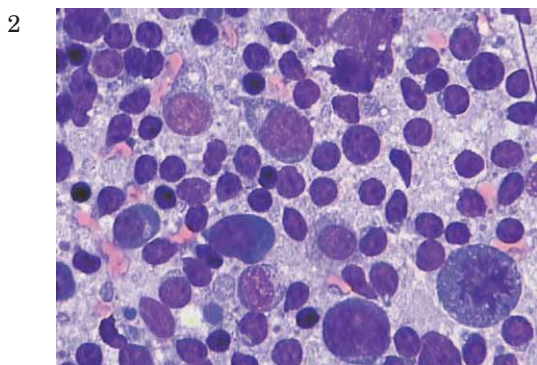
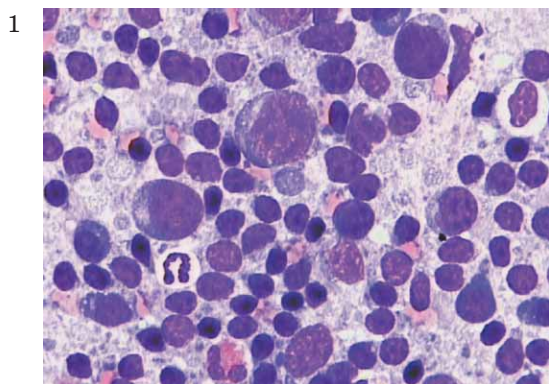


Fig. 1, 2. Polymorphous population of the small lymphocytes with transformed lymphatic cells, immunoblasts and plasmablasts at the first diagnosis (May-Grünwald-Giemsa, x100).

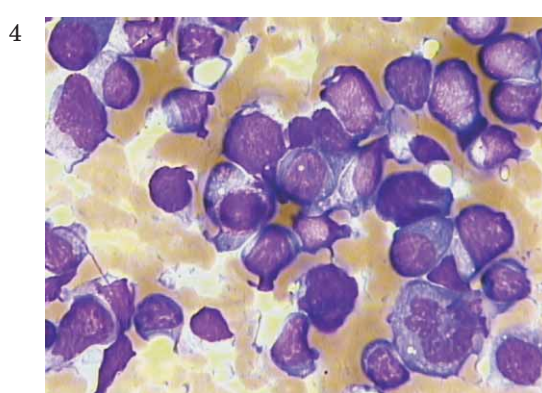
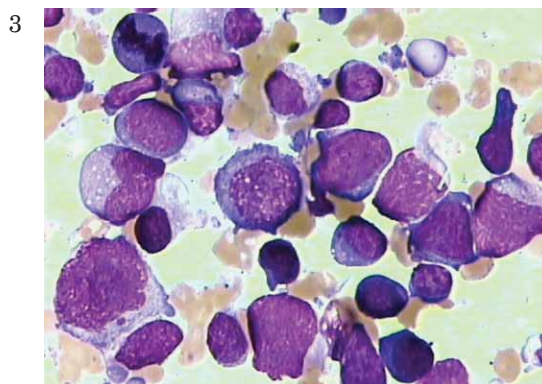


Fig. 3, 4. Smears predominately composed of large cells at relapse (May-Grünwald-Giemsa, x100).

small to medium-sized lymphoid cells with a clear cytoplasm and expansion of immunoblasts and plasma cells was found. On immunohistochemical stains, the infiltrating lymphoid cells were CD2+, CD7+, CD3+ and CD4+ T-cells. There was marked proliferation of arborizing high endothelial venules (HEV). The diagnosis of angioimmunoblastic T-cell lymphoma was revealed. Bone marrow biopsy showed no bone marrow involvement. The patient was treated with FED chemotherapy (fludarabine, cyclophosphamide, dexamethasone) followed by elective autologous hematopoietic stem cell transplantation in November 2008. In April 2009 the patient was hospitalized because of fever, pancytopenia, hyperbilirubinemia (27 $\mu\text{mol/L}$) and peripheral lymphadenopathy. A relapse of non-Hodgkin's lymphoma was suspected. A thoracic CT study showed enlarged lymph nodes in the upper mediastinum and in the left axillary region. An abdominal ultrasound examination showed enlarged lymph nodes in the paraaortal and mesenteric regions, 30 mm in the largest diameter and enlarged spleen 150×50 mm in size. The FNAC of the enlarged cervical and supraclavicular lymph nodes was performed again. This time, the smears were composed of a polymorphous population of small, medium-sized and large lymphocytes (Figures 3 and 4), predominately CD20+ (Figures 5 and 6) and the minority of CD3+ cells. Large lymphocytes were CD3 negative on immunocytochemical stains (Figure 8). The minor part of the large cells was weakly CD30+ (Figure

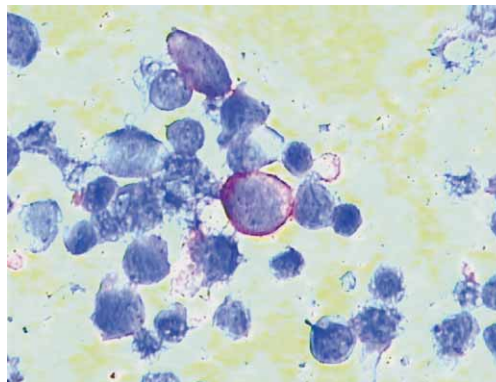


Fig. 7. Large lymphoid cells weakly CD30 positive on immunocytochemical stains at relapse.

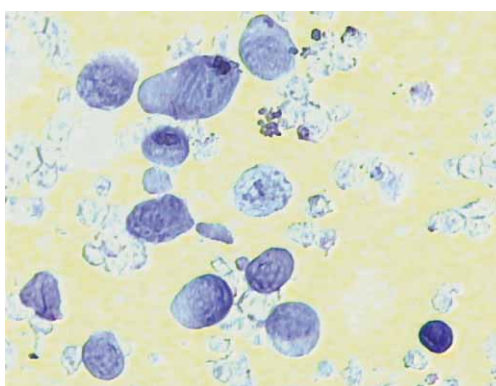


Fig. 8. Large lymphoid cells CD3 negative on immunocytochemical stains at relapse.

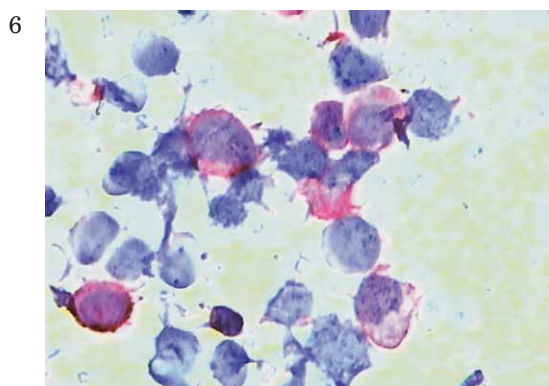
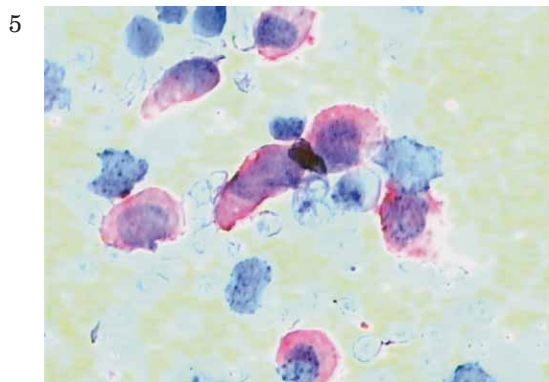


Fig. 5, 6. Large cells lymphoid CD20 positive on immunocytochemical stains at relapse.

7) The cytological diagnosis was NHL-DLBCL. Immunophenotyping confirmed a predomination of mature B-cells: CD45+, CD19+, CD79b+, CD20+, HLA D/DR+ with monoclonal expression of the lambda light chain of immunoglobulins, with middle intensity of expression. A mild infiltration of the bone marrow in bone marrow aspirate smears was confirmed. Autoimmune hemolytic anemia and immunothrombocytopenia were detected. Lactat dehydrogenase level was increased (967 U/L). Patient had high number of EBV DNA copies in plasma (1,610,000 copies/mL) and serologic testing revealed increased titers of EBV VCA IgG of 96 AU/mL and 55 AU/mL for EBNA IgG. A cycle of CHOP-R chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab) was administered. The clinical course following chemotherapy was complicated with pancytopenia, fever, mucositis and herpetic changes on the skin, need for transfusional support and antimicrobial therapy but the treatment resulted in regression of peripheral and abdominal lymphadenopathy. Therefore, she received additional 3 cycles of CHOP-R therapy and a very good partial response was achieved. Reduced intensity conditioning allogeneic stem cell transplantation was performed thereafter, in August 2009, and it resulted in complete remission of the disease.

Discussion

Angioimmunoblastic T-cell lymphoma (AITL) is a rare and aggressive neoplasm clinically characterised by sudden onset of constitutional symptoms, lymphadenopathy, hepatosplenomegaly, frequent autoimmune phenomena, particularly hemolytic anemia and thrombocytopenia and polyclonal hypergammaglobulinemia¹⁰. In our case, the patient presented with mild leukocytosis and peripheral lymphadenopathy. AITL is one of the most common specific subtypes of peripheral T-cell lymphomas, accounting for approximately 15–20% of cases, or 1–2% of all non-Hodgkin lymphomas¹¹. AITL occurs in the middle-aged and elderly, with an equal incidence in males and females¹¹. The median survival of AITL patients has been estimated to be between 11 and 30 months¹¹. More than 75% of AITL patients present with generalized lymphadenopathy¹⁵. Extranodal involvement is common and typically manifests as hepatosplenomegaly, bone marrow involvement and pleural and pericardial effusions. A skin rash is frequently present¹⁶. The presence of immunologic derangements is a hallmark of AITL, often presenting as polyclonal hypergammaglobulinemia, Coombs positive autoimmune hemolytic anemia, cold agglutinins, as well as a number of other immunologic derangements including polyarthritis and thyroid disease¹⁷. Despite the presence of this immune hyperactivity, AITL patients often exhibit immunodeficiency and a propensity for opportunistic infections⁵ prior to and during therapy⁶. In most cases, the neoplastic T-cells account for a small fraction of the infiltrate, varying from 5 to 30%⁶, express pan T-cell antigens such as CD3, CD2, CD5, in vast majority of the cases CD4 and characteristically CD10^{2,11,18}. Molecular studies of the T-cell receptor (TCR) have demonstrated that the vast majority (90%) have biased TCR rearrangements, with more than 75% of cases showing monoclonal pattern and 14% an oligoclonal one¹⁹. It is unclear whether these cases lack lymphocytic infiltrates, or whether they represent false negative results because of limited sensitivity of the Southern blot and PCR techniques applied¹⁰. Molecular

studies also showed the presence of biased immunoglobulin (Ig) H rearrangements in AITL, with 30–35% showing clonal patterns²⁰. These rearranged IgH loci frequently occur in EBV-infected B-cells that exhibit ongoing somatic hypermutation, suggesting a germinal center B-cell derivation²¹. Furthermore, these unique B-cell clones not only survive, but they proliferate and expand alongside the clonal T-cell proliferation despite the frequent acquisition of crippling Ig mutations rendering them Ig-receptor deficient²¹. EBV-positive B-cells are nearly always present. They range in cell size and expansion of B immunoblasts may be prominent, usually present in the paracortex. The EBV-positive B immunoblastic proliferation may progress, either composite with AITL, or at relapse to EBV-positive DLBCL as in other immunodeficiency states, such as HIV infection and post allogeneic organ transplantation¹¹. However, relatively few cases of EBV-positive B-cell lymphomas arising in patients with AITL have been reported. B-cell lymphomas developed between 8 months and 10 years after the initial diagnosis of AITL^{5,12–14}. In the presented case the patient developed DLBCL 13 months after the initial diagnosis of AITL. Various authors postulated that immunodeficiency in AITL patients together with the immunosuppressive effects of cytotoxic drugs, may be responsible for EBV-induced proliferation of latently or newly EBV-infected B-cells with eventual clonal selection and progression to aggressive B-cell lymphoma^{12–14}. In this case, cytotoxic drugs together with immunodeficient status of the patient have probably severely aggravated the already present immunodeficiency. According to some authors, plasma EBV viral load correlates with histological progression of AITL²². PCR of EBV DNA confirmed the infection with high viral load in the presented case and progression of AITL to DLBCL was confirmed after the FNAC of the peripheral lymph node and immunophenotyping were done. Therefore, we suggest EBV viral load monitoring together with performance of repeated FNAC of enlarged lymph nodes for patients affected by AITL in the course of the disease for an early detection of the possible progression to secondary lymphomas.

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DIFUZNI B VELIKOSTANIČNI LIMFOM KOD PACIJENTICE NAKON TERAPIJE ANGIOIMUNOBLASTIČNOG T LIMFOMA

S A Ž E T A K

Relativno malo slučajeva Epstein-Barr virus (EBV) pozitivnih B staničnih limfoma nastalih kod pacijenata s angioimunoblastičnim T limfomom (AITL) je objavljeno. Opisujemo slučaj AITL-a kod kojeg je difuzni B velikostanični limfom nastao 13 mjeseci nakon prvotne dijagnoze AITL-a. Kod 36-godišnje pacijentice s umjerenom leukocitozom, periferanom i abdominalnom limfadenopatijom u ožujku 2008. godine dijagnosticiran je AITL nakon citološke punkcije povećanih cervikalnih i supraklavikularnih limfnih čvorova. Dijagnoza je potvrđena imunofenotipizacijom i biopsijom cervikalnih limfnih čvorova. Pacijentica je liječena kemoterapijom po shemi FED (fludarabin, ciklofosfamid, deksametazon) te joj je učinjena elektivna transplantacija autolognih krvotvornih matičnih stanica. U travnju 2009. godine pacijentica je hospitalizirana zbog vrućice, pancitopenije, hiperbilirubinemije i periferne limfadenopatije. Citološka punkcija povećanih cervikalnih limfnih čvorova je ponovo urađena, ali ovaj put u razmazima je nađena polimorfna populacija limfocita s predominacijom velikih stanica, imunocitokemijski CD20+. Imunofenotipizacija je potvrdila predominaciju monoklonalnih zrelih B stanica. Razina EBV DNA u plazmi bila je vrlo visoka, a serološkim je testiranjem dokazan povišen titar EBV VCA IgG i EBV EBNA IgG. Pacijentica je liječena imunokemoterapijom CHOP-R (ciklofosfamid, doksorubicin, vinkristin, prednizon i rituksimab) na koju je postignut vrlo dobar odgovor, a transplantacijom alogeničnih krvotvornih matičnih stanica nakon kondicioniranja smanjenog intenziteta postignuta je kompletna remisija. AITL je rijedak limfoproliferativni poremećaj kod kojeg neoplastične T stanice čine manjinu populacije limfnog čvora i u skoro svim slučajevima postoje EBV-om inficirane B stanice. Različiti autori pretpostavljaju da imunodeficijencija kod pacijenata s AITL-om zajedno s imunosupresivnim učinkom citotoksičnih lijekova bi mogla biti odgovorna za EBV-om induciranu proliferaciju latentno ili novoinficiranih B stanica uz eventualnu klonalnu selekciju i progresiju u agresivni B-stanični limfom.