

## Two cases of angioimmunoblastic T-cell lymphoma with concomitant positive serology for acute Epstein-Barr virus infection

Davide Facchinelli,<sup>1</sup> Angela Polino,<sup>1</sup>  
 Francesco Dima,<sup>2</sup> Alice Parisi,<sup>3</sup>  
 Achille Ambrosetti,<sup>1</sup> Dino Veneri<sup>1</sup>

<sup>1</sup>Section of Hematology, Department of Medicine; <sup>2</sup>Laboratory of Clinical Biochemistry, Department of Life and Reproduction Sciences, <sup>3</sup>Department of Pathology and Diagnostics, University of Verona and Azienda Ospedaliera Universitaria Integrata Verona, Italy

### Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is a rare type of peripheral T-cell lymphoma. Epstein-Barr virus (EBV) is known to be associated with pathogenesis and histological progression of AITL and the onset of the disease often mimics an infectious process. Here we describe two cases of patients with serology for acute EBV infection at the onset of AITL.

### Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare type of peripheral T-cell lymphoma (PTCL) which accounts for 1-2% of non Hodgkin lymphomas and has an incidence of 0.05 new patient cases per 100,000 people in the USA, without sex predilection. The median age of onset is 64 years and is associated with a very poor prognosis.<sup>1,2</sup> Clinically the disease presents with systemic symptoms, prominent lymphadenopathy, hepatosplenomegaly, skin involvement, polyclonal hypergammaglobulinemia and autoimmune hemolytic anemia.<sup>3,4</sup> Lymph node histology shows an effaced architecture, infiltration by T neoplastic cells (CD2+/CD3+/CD4+/CD10+/CXCL13/PD1+), proliferation of high endothelial venules and expanded follicular dendritic cells (FDCs), in particular the expansion of this type of cell is explained by the recent identification of follicular helper T cell (TFH) as the origin cell of the tumor.<sup>5</sup> Epstein-Barr virus (EBV) and Human Herpes Virus 6 (HHV6) are known to be associated with pathogenesis and histological progression of AITL and the onset of the disease often mimics an infectious

process.<sup>6</sup> Here we describe two concomitant cases of patients with serology for acute EBV infection at the onset of AITL.

### Case Report #1

In March 2016, a 34 years-old male complaining fatigue and night sweats persisting since one month together with enlargement of a median submandibular lymph node was examined by his primary care physician. After an acute mononucleosis infection was excluded by monospot test, the patient was referred to our observation due to the worsening of clinical conditions.

Enlarged lymph nodes in all the surface anatomy stations and splenomegaly were detectable by physical examination. Initial laboratory tests showed mild anemia (Hb 10.7 g/dL), severe thrombocytopenia (22,000/mmc), normal blood count (8800/mmc) and differential, hyperuricemia (8.5 mg/dL), increased lactate dehydrogenase (1138 U/L, normal range 240-480 U/L) and polyclonal hypergammaglobulinemia. Suspecting a lymphoproliferative disease, excisional biopsy of an enlarged right inguinal lymph node was performed. Histological examination showed the presence of a diffuse infiltrate of T-cells (CD3+) positive for CD4/PD1 and partially positive for bcl6/CD10; a prominent vascular proliferation, follicular dendritic cells expansion were also described and clonal rearrangements in T-cell receptor genes were detected. According to this finding, a diagnosis of AITL was performed. The presence of rare non-clonal B cells positive for EBV encoded small RNA (EBER) was also reported (Figure 1B).

Bone marrow lymphoid infiltration was detected on trephine biopsy and FDG-PET/CT showed extensive involvement of spleen and lymph nodes over and under the diaphragm (Figure 2). A stage IVB disease was assessed and the patient resulted at high risk disease according to the new prognostic index for AITL (PIAI index 3) with a prospecting 5-year overall survival probability lower than 20%.<sup>1</sup>

Unexpectedly, microbiologic serological screening revealed a positive antibody panel for ongoing EBV infection due to the detection of IgM antibodies to viral capsid antigen (VCA), jointly to IgG antibodies to VCA and EBV nuclear antigen (EBNA). The EBV viral load in peripheral blood was of 27,077 copies/mL. These findings, in addition to the intense FDG-PET/CT tonsillar glucose uptake, lead to consider a concomitant acute EBV infection.<sup>7,8</sup> Interestingly the patient was a regular blood

Correspondence: Dino Veneri, Section of Hematology, Department of Medicine, Policlinico GB Rossi, University of Verona-AOUI, P.le L. Scuro, 10, Verona, Italy.  
 Tel: +39.045.8124420 - Fax: +39.045.8027488.  
 E-mail: dino.veneri@univr.it

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donor; he was screened for EBV infection few months before the diagnosis and his antibody framework was compatible with previous infection. The peripheral blood smear showed a panel of morphologically different cells, some compatible with lymphoid blast cells at immunophenotypic analysis, (CD3-/CD4+/ CD10+/CD5+/cyCD3+) and others with Turk cells (Figure 1A). A monospot test and an immunophenotypic analysis from peripheral blood for infectious mononucleosis were repeated, both with negative results.

The patient was hospitalized and treated with a course of chemotherapy regimen containing prednisone, etoposide, vincristine, cyclophosphamide and anthracyclines (DA-EPOCH) (without the immunotherapy (Rituximab) because there were no clonal B cell associated with EBV).<sup>10</sup>

He was discharged home with excellent response in adenopathy and in EBV viral load (754 copies/mL) but within 5 days a new enlargement of the tumor masses, recurrence of leukemic cells in peripheral blood (8%) and an increase in EBV viral load (2829 copies/mL) were detected. As a consequence, we decided to treat the patient with a more intensive chemotherapy regimen containing cyclophosphamide with high-doses of arabinosylcytosine and methotrexate (HyperCHiDAM).<sup>11</sup>

After two cycles of chemotherapy the patient obtained a radiological complete remission of the disease, negativity of the

viral load; the serology for EBV was compatible with a previous infection (VCA-IgG+, EBNA-IgG+, VCA-IgM-). Actually, 4 months after the end of the treatment the patient still maintain a complete remission of disease and an allogenic stem cell transplant is planned.

## Case Report #2

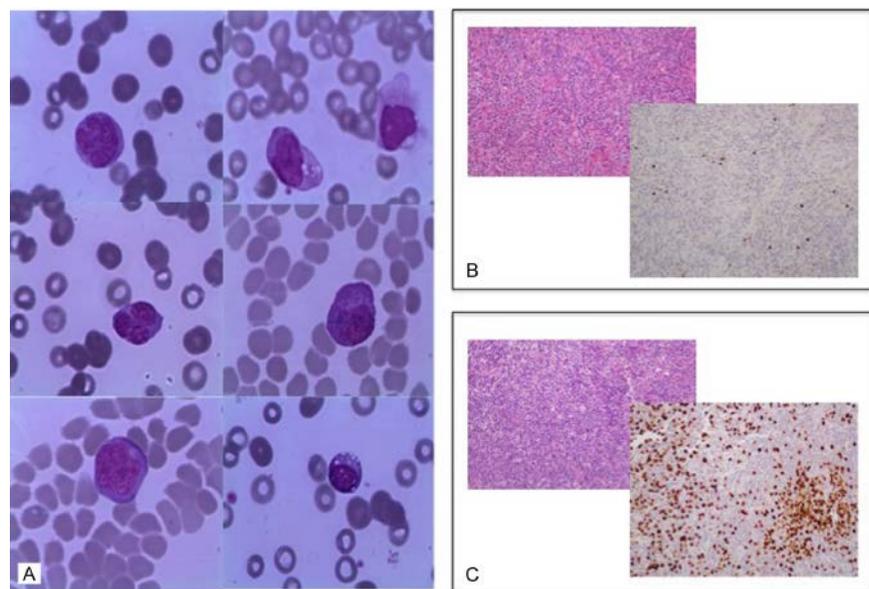
Approximately two weeks later, a 61 years-old man was referred to our department from a community hospital with a suspected diagnosis of lymphoproliferative disease. A few days before he went to the emergency room for fatigue and exertional dyspnea; on physical examination he had enlarged lymph nodes in all the surface anatomy stations and splenomegaly. Initial laboratory tests revealed anemia (Hb 11 g/L), thrombocytopenia (38,000/mm<sup>3</sup>) and increased white blood cells count (27,230/mm<sup>3</sup>), increased lactate dehydrogenase (731 U/L). The immunoelectrophoresis revealed the presence of a small monoclonal IgG lambda component in absence of hypergammaglobulinemia. During the hospitalization he developed a worsening dyspnea associated with rapid onset of a massive pleural effusion. A thoracentesis was performed and the immunophenotypic assay of the cells of pleural fluid sample was compatible with a T-cell lymphoproliferative disease (CD4+, CD10+, CD5+, CyCD3+). Peripheral blood examination was characterized by the presence of 15% of immature lymphoid cells. An axillary lymph node biopsy and a bone marrow biopsy were quickly performed. Unfortunately, his clinical condition worsened rapidly and the expired for an critical cardiac complication. A few days after the patient death, the lymph node histology revealed complete effacement of nodal architecture, a diffuse infiltrate of CD4+, PD1+ and CD10+ T-cells associated with a monoclonal B-cell population CD20+, MUM1+, CD30+/- and EBV encoded small RNA +(EBER) (Figure 1C); again the diagnosis was angioimmunoblastic T-cell lymphoma, confirmed by bone marrow localization on trephine biopsy. Unexpectedly the standard serology tests revealed that EBV testing was positive for IgG antibodies to viral capsid antigen (VCA-IgG), EBV nuclear antigen (EBNA-IgG) and IgM antibodies to viral capsid antigen (VCA-IgM); it was too late for dosing EBV-DNA in the blood-stream.

## Discussion and Conclusions

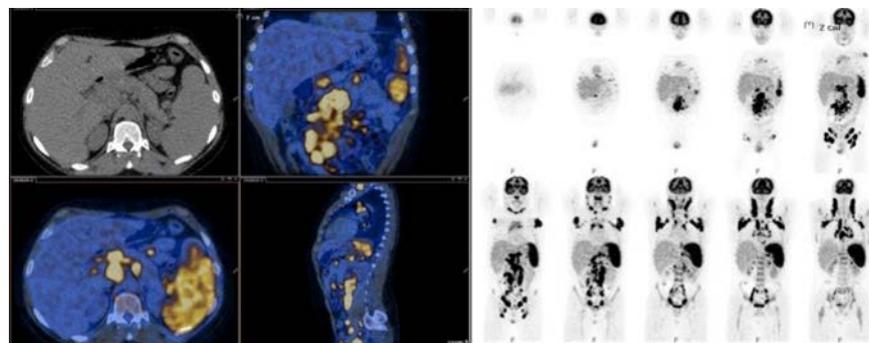
A relationship between AITL and viral infections, particularly EBV infection, is suggested and the infection might contribute to disease progression both from the histological and clinical point of view.<sup>6</sup> A paper of Delfau-Larue described a strong relationship between the presence of circulating AITL tumor cells and higher levels of peripheral EBV DNA at initial presentation of disease. In addition, a high viremia at onset would be associated with a poor response to therapy.<sup>12</sup> The cases described confirm all of these relations. In fact the change of clinical course towards greater aggressiveness coincided with the detection IgM anti VCA. Only one other case with an

acute serological profile for EBV infection coexisting with angioimmunoblastic T-cell lymphoma is reported in medical literature by Beer.<sup>9</sup> The case described is very similar to our first and in both patients a polyclonal hypergammaglobulinemia was detected. It may not be excluded that in this panel of antibodies some recognized EBV with a random cross reactivity. Also in the second case we described IgM anti VCA that were assessed in spite the patient did not present hypergammaglobulinemia; unfortunately we don't have neither a data regarding viremia nor a serology preceding disease onset.

In our opinion, the important thing is the temporary positive reaction of anti VCA-IgM antibody in spite of the past



**Figure 1.** A) Peripheral blood smear of the first patient. It shows a panel of morphologically different cells, some compatible with lymphoid blast cells and others with Turk cells. B) Lymph node histology and EBER reaction of the first patient. Note the presence of rare non-clonal B cells positive for EBV encoded small RNA (EBER). C) Lymph node histology and EBER reaction of the first patient. In this case there is a monoclonal B-cell population CD20+, MUM1+, CD30+/- and EBV encoded small RNA+ (EBER).



**Figure 2.** First patient's FDG-PET/TC: disseminated disease with localization to the Waldeyer's ring.

infection of EBV. This finding suggests the following two mechanisms: a part of hypergammaglobulinemia or reactivation of the virus.

The relationship between EBV and AITL is debated; some authors argue that the presence of EBV reflects a profound immunodeficiency due to AITL while others argue that the EBV drives the development or a rapid progression of the tumor.<sup>6</sup> Also in our patients an EBV reactivation, or maybe a *de novo* infection for the second one, may have triggered a rapid progression of disease. On the other hand, there are various evidences that in patients with AITL continuous antigenic stimulation by EBV may promote firstly the proliferation of polyclonal B-lymphocytes in the neoplastic microenvironment and successively the appearance of genetic lesions driving the development of a B-cell lymphoma. The diagnosis of associated B-cell lymphoma may be simultaneous to the diagnosis of AITL: in this case the diagnosis is directly the one of composite lymphoma. Otherwise, the onset of B-cell lymphoma may occur later.<sup>13-15</sup>

The cases we described stand as a contribution in favor of EBV possible role in the development or increased aggressiveness of AITL. Monitoring of EBV serology to AITL diagnosis and during treatment would be considered to add more data to development research.

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