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Is triple-positive serology for Epstein-Barr virus (VCA-IgG, VCA-IgM, EBNA-IgG) a specific feature of angioimmunoblastic T-cell lymphoma?

Davide Facchinelli[1], Alice Parisi[2], Mauro Krampera[1] and Dino Veneri[1]

Abstract

Purpose: We assessed the frequency of triple-positive serology (viral capsid antigen [VCA]–immunoglobulin G [IgG], VCA–immunoglobulin M, Epstein-Barr nuclear antigen–IgG) for Epstein-Barr virus (EBV) in a small number of patients with angioimmunoblastic T-cell lymphoma (AITL) at disease onset.

Methods: Nine patients with newly diagnosed AITL were retrospectively enrolled in the present study. For all of them, EBV serology data were available.

Results: Of 9 patients, 7 (77.7%) had a triple-positive serology (VCA-IgG, VCA-IgM, EBNA-IgG) for EBV. These patients were characterized by bone marrow involvement, high incidence of thrombocytopenia, and poor prognosis according to Revised International Prognostic Index and Prognostic Index for Angioimmunoblastic T-cell Lymphoma scores.

Conclusion: Assessment of both viremia and serology for EBV could be useful in patients with clinical and laboratory data suggesting lymphoma diagnosis; furthermore, although our data need to be validated in a larger cohort of patients, triple positivity for EBV serology might help to direct the diagnosis toward AITL.

Keywords

Angioimmunoblastic T-cell lymphoma, Epstein-Barr virus, serology for acute infection

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Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare type of peripheral T-cell lymphoma accounting for 1%–2% of non-Hodgkin lymphomas. AITL is characterized by the incidence of 0.05 new cases/100,000 people in the United States, without sex difference, median age at onset 64 years, and very poor prognosis.[1,2] Patients with AITL often present with systemic symptoms, prominent lymphadenopathy, hepatosplenomegaly, skin involvement, polyclonal hypergammaglobulinemia, and autoimmune hemolytic anemia.[3,4] Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV6) are associated with the pathogenesis and histologic progression of AITL and the onset of the disease often mimics an infectious dosorder.[5] However, it is unknown whether EBV-positive B cells are involved in AITL lymphomagenesis or develop as the result of the underlying immunodeficiency.[5] The prognostic roles of EBV DNA in plasma have been explored in many EBV-associated lymphomas and also in AITL, while few studies have analyzed the serologic pattern.[6,7] In EBV serology, 3 parameters are evaluated: viral capsid antigen (VCA)–immunoglobulin G (IgG), VCA–immunoglobulin M (IgM), and Epstein-Barr nuclear antigen (EBNA)–IgG.[8]

[1]Section of Hematology, Department of Medicine, University of Verona and Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy
[2]Department of Pathology and Diagnostics, University of Verona and Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy

Corresponding author:
Davide Facchinelli, Section of Hematology, Department of Medicine, Policlinico GB Rossi, University of Verona-AOUI, P.le L. Scuro, 10, Verona, 37134, Italy.
Email: davide.facchi@hotmail.it

In the literature, only 3 AITL cases with positive serology for anti-EBV IgM at disease onset are described.[9,10] In this study, we analyze EBV serology retrospectively in a series of patients with AITL at disease onset.

Methods

This single-center study was conducted according to the 1964 Helsinki declaration and its later amendments. All patients with AITL observed from January 2010 to December 2018, were evaluated, as long as EBV serology (VCA-IgG, VCA-IgM, and EBNA-IgG) and clinical features were available.

Results

Fourteen consecutive patients with AITL diagnosis were observed over 9 years. Data regarding EBV serology were available for only 9 of them, so the other 5 were excluded. Clinical data for patients with triple-positive serology for EBV are listed in Table 1. The median age was 64 years (range 34–81 years) and 71.4% of patients were older than 60. There was a male predominance (6 men and 1 woman). All patients presented advanced stage disease and 71.4% had high levels of serum lactate dehydrogenase (LDH). B symptoms and Eastern Cooperative Oncology Group (ECOG) performance status >1 were present in 71.4% and 42.8% of patients, respectively. Bone marrow involvement was found in 85.6% and splenomegaly in 71.4% of patients. Four patients (57.1%) had autoimmune hemolytic anemia with positive Coombs test. The majority of patients had a poor prognosis according to the Revised International Prognostic Index (R-IPI) (71.4%) and Prognostic Index for Angioimmunoblastic T-cell Lymphoma (PIAI) (85.6%).

Table 2 describes the serologic pattern and viremia for EBV. Seven patients (77.7%) had serology positive for VCA-IgG, VCA-IgM, and EBNA-IgG, in agreement with a late primary infection or a viral reactivation.[8] Detectable viremia was shown in 4 of these patients and not performed in the others. The remaining 2 patients had a serologic panel compatible with a past infection (VCA-IgG-positive, VCA-IgM-negative, and EBNA-IgG-positive) without detectable viral DNA in peripheral blood. In one of these patients, histologic analysis of the lymph node was negative for EBV-encoded small RNA, while in the other patient, immunohistochemistry for EBV was not performed.

Table 1. Clinical features of patients with angioimmunoblastic T-cell lymphoma with triple-positive serology for Epstein-Barr virus.

Characteristic	No. (%) or mean (range)
Age, y	64 (34–81)
Male sex	6 (85.6)
B symptoms	5 (71.4)
Eastern Cooperative Oncology Group ⩾2	3 (42.8)
Stage III–IV	7 (100)
LDH > ULN	5 (71.4)
Hemoglobin <10 g/dL	1 (14.2)
Platelets $<150 \times 10^9$/L	4 (57.1)
Bone marrow involvement	6 (85.6)
Splenomegaly	5 (71.4)
Blasts in peripheral blood	4 (57.1)
Positive Coombs test	4 (57.1)
R-IPI >2	5 (71.4)
PIAI >1	6 (85.6)

LDH: lactate dehydrogenase; PIAI: Prognostic Index for Angioimmunoblastic T-cell Lymphoma; R-IPI: Revised International Prognostic Index; ULN: upper limit of normal.

Table 2. Cytomegalovirus/Epstein-Barr virus (EBV) viremia and serology.

Patient	Age, y	Sex	EBV viral load, copies/mL	VCA IgG	VCA IgM	EBNA IgG
1	34	M	27,000	+	+	+
2	61	M	ND	+	+	+
3	67	M	14,700	+	+	+
4	81	M	250	+	+	+
5	66	F	307,000	+	+	+
6	78	M	ND	+	+	+
7	58	M	ND	+	+	+
8	77	F	–	+	–	+
9	80	F	–	+	–	+

EBNA: EB nuclear antigen; IgG: immunoglobulin G; IgM: immunoglobulin M; VCA: viral capsid antigen.

Discussion

A close relationship has been suggested between AITL and viral infections, particularly by EBV, related to histologic and clinical disease progression.[5] High levels of serum EBV DNA at diagnosis is associated with the presence of circulating AITL tumor cells as well as a poor response to therapy.[6,11] Few data are available regarding the anti-EBV serology status and clinical outcome.[9,10] Here, although in a small cohort of patients, we show that a triple-positive anti-EBV serology is very frequent (77.7%) at the diagnosis of AITL. This finding does not allow us to differentiate a late primary infection from a viral reactivation; serology prior to the development of lymphoma is not available.

The relationship between EBV infection and AITL is debated. Some authors argue that EBV presence reflects a profound immunodeficiency due to AITL, while others hypothesize that it is EBV that drives the development or rapid progression of the tumor.[5] There is evidence that in patients with AITL the persistent immune stimulation by EBV antigen may promote both the proliferation of

polyclonal B-cells in the neoplastic microenvironment and the appearance of genetic lesions driving the development of B-cell lymphoma.[11] Recently, Liu et al.[12] showed that patients with complicated infectious mononucleosis display a significant increase of circulating cells with the immunophenotypic pattern of AITL cells.

Patients with AITL and triple-positive serology currently display bone marrow involvement, high incidence of thrombocytopenia, and poor prognosis according to R-IPI and PIAI score.

Our data derive from a small cohort of patients and therefore need to be confirmed in a larger study. To this aim, we recommend collecting information about both EBV viremia and serologic status in patients with AITL, as triple positivity for EBV serology might help direct the diagnosis towards AITL.

Declaration of conflicting interests

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ORCID iD

Davide Facchinelli https://orcid.org/0000-0002-7581-5824

References

1. Federico M, Rudiger T, Bellei M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. *J Clin Oncol* 2013; 31: 240–246.
2. Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD and Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. *Blood* 2006; 107: 265–276.
3. de Leval L, Gisselbrecht C and Gaulard P. Advances in the understanding and management of angioimmunoblastic T-cell lymphoma. *Br J Haematol* 2010; 148: 673–689.
4. Dogan A, Attygalle AD and Kyriakou C. Angioimmunoblastic T-cell lymphoma. *Br J Haematol* 2003; 121: 681–691.
5. Zhou Y, Attygalle AD, Chuang S-S, et al. Angioimmunoblastic T-cell lymphoma: histological progression associates with EBV and HHV6B viral load. *Br J Haematol* 2007; 138: 44–53.
6. Liang J-H, Lu L, Zhu H-Y, et al. The prognostic role of circulating Epstein-Barr virus DNA copy number in angioimmunoblastic T-cell lymphoma treated with dose-adjusted EPOCH. *Cancer Res Treat* 2019; 51: 150–157.
7. Chen Y, Zheng X, Chen B, et al. The clinical significance of Epstein-Barr virus DNA in peripheral blood mononuclear cells in patients with non-Hodgkin lymphoma. *Leuk Lymphoma* 2017; 58: 2349–2355.
8. De Paschale M and Clerici P. Serological diagnosis of Epstein-Barr virus infection: problems and solutions. *World J Virol* 2012; 1: 31–43.
9. Facchinelli D, Polino A, Dima F, Parisi A, Ambrosetti A and Veneri D. Two cases of angioimmunoblastic T-cell lymphoma with concomitant positive serology for acute Epstein-Barr virus infection. *Hematol Rep* 2017; 9: 7088.
10. Beer T and Dorion P. Angioimmunoblastic T-cell lymphoma presenting with an acute serologic Epstein-Barr virus profile. *Hematol Rep* 2015; 7.
11. Delfau-Larue M-H, de Leval L, Joly B, et al. Targeting intratumoral B cells with rituximab in addition to CHOP in angioimmunoblastic T-cell lymphoma: a clinicobiological study of the GELA. *Haematologica* 2012; 97: 1594–1602.
12. Liu J, Zhou Y, Yu Q, et al. Higher frequency of CD4+CXCR5+ICOS+PD1+ T follicular helper cells in patients with infectious mononucleosis. *Medicine* 2015; 94: e2061.