Angioimmunoblastic T-cell lymphoma Masquerading as Infectious Mononucleosis - a case report

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ABSTRACT

A 71-year-old patient presented with low-grade fever, sore throat, tonsils swelling with exudates, a pruritic rash and splenomegaly. Autoimmune hemolytic anemia (AIHA) was demonstrated, together with an acute Epstein-Barr virus serological profile, and evidence of acute cytomegalovirus infection. A monoclonal IgG lambda peak was found by immuno-fixation. The AIHA responded fully to Prednisone 60mg/day and a short course of methyl-prednisolone, but the severe anemia relapsed and by the third admission to the Internal Medicine Ward, lymphadenopathy had developed, and an inguinal lymph node biopsy was performed. The lymph node largest diameter was 3.5 cm. On histology, sinuses were patent, a vague nodularity without germinal centers was evident, composed mainly of small regular B cells, while small to medium-sized T lymphocytes were predominant in the interfollicular areas. Large B-cells, mostly CD30+ immunoblasts, were scattered and EBER +++ was found mainly in and around the nodules. No evidence of necrosis was noted. We hereby discuss the differential diagnosis between infectious mononucleosis in the elderly, angioimmunoblastic T-cell lymphoma and follicular peripheral T-cell lymphoma a propos our patient.

Key Words: angioimmunoblastic T-cell lymphoma; acute EBV serology; peripheral T-cell lymphoma - follicular; EBV reactivation

INTRODUCTION

Epstein-Barr virus (EBV)-associated malignancies include mainly B-cell lymphomas, a variable proportion of Hodgkin lymphomas and, in contrast, every case of nasopharyngeal carcinoma [9]. Recently a few T-and natural killer cell lymphomas, relatively infrequent, at least in the Western world, have also been related to EBV. In these cases, as in the previously mentioned conditions, the role of this virus in the carcinogenesis, if any, has not been determined precisely.

One of the latter T-cell lymphomas has raised the hematologists' and hematopathologists' attention, but also that of the internists: the angioimmunoblastic T-cell lymphoma (AITL). The special interest elicited herein, has been due to the clinical features of this disease which strongly evoke those of an infection: fever, rash, fatigue, night sweats, anemia, thrombocytopenia, raised transaminases and polyclonal hyperγglobulinemia in serum immunoelectrophoresis. And indeed, a form of this disease entity was regarded as reactive: it was designated (angio) immunoblastic lymphadenopathy, though generally showing a high rate of transformation to AITL [3]. More recently, it has been admitted, including by the vast majority of lymphologists that, even the most benign-looking case of this entity, was in fact a (malignant) T-cell lymphoma [7].

Although originally thought to be caused by drugs, mainly antibiotics, or by infectious conditions, probably subsequent to an abnormal immune response, the etiology of AITL remains obscure. While suggested to play a role in lympho-magenesis, EBV is found in this condition almost exclusively in transformed B cells in up to 96% of the cases. In this location, EBV infection reflects the immuno-deficiency inherent to this lymphoma, rather than the pathogenesis of AITL. However, an isolated study has proposed a role for EBV in inducing the T-cell proliferation of this neoplasm.

In this report, a patient is depicted who presented with an unusual primary EBV infection, as demonstrated by serological findings including positive EBV VCA IgM (62.50 U/ml); EBV VCA IgG (120.00 U/ml); EBV IgG EBNA (146.00 U/ml); an EBV viral count of 812733, at the time of the lymph node biopsy. Evidence of an acute CMV infection was also found, the overall picture sustaining a possible EBV and CMV reactivation, as described in some cases of AITL [13]. The differential diagnosis between AITL and infectious mononucleosis, as well as with follicular peripheral T-cell lymphoma is described [12].

REPORT OF A CASE

A 71-year-old Caucasian patient was admitted to the Internal Medicine Ward because of AIHA (HB - 4.8 g/dL, LDH - 560 U/L, total bilirubin - 2.0 mg/dL with indirect bilirubin 1.7 mg/dL). He had visited the ER a week previously because of sub-febrile temperature, sore throat, anorexia, weakness, widespread itching and an urticaria-like eruption, puffiness over the face, and enlarged tonsils with exudates. Augmentin had been administered with no improvement. Five years prior to admission, the patient had undergone a left hemicolectomy for colon carcinoma. The patient was also treated for essential hypertension and dyslipidemia.

Upon admission, splenomegaly (15 cm in length), was detected; on CT-scan suspicion for splenic lacerations was raised, with minimal perisplenic fluid. At this point, no lymphadenopathy nor clear evidence of a lymphoproliferative disorder were noted. Serology for CMV and EBV IgM was positive. No other viral infection was detected.

A bone marrow biopsy was unremarkable, except for polyclonal plasmacytosis and a moderate small T-cell

lymphocytosis. A PCR for TCRg disclosed a single reproducible clonal peak, with a polyclonal background. Concern was raised for a possible T-cell lympho-proliferative disorder. The patient was administered Prednisone 1mg/kg, which the subsequent resolution of the AIHA. He was then released from the hospital.

Four months later, he was re-admitted to the Internal Medicine Ward, due to severely symptomatic anemia, but no evidence of active hemolysis (LDH, total bilirubin and haptoglobin were all in the normal range).

A second bone marrow biopsy showed marked erythropoietic hypoplasia, at the limit of red cell aplasia. CD20+ B lymphocytes were loosely aggregated. CD3+++/CD5++ T lymphocytes were predominantly small. A PCR for TCRg disclosed weakly clonal T cells and a repeat biopsy with a flow analysis requested.

A repeated serology for CMV and EBV was positive for IgM. A new CT-scan did not differ from the first. In spite of the absence of AIHA, the patient received a similar course of Prednisone as previously for the anemia. A brisk clinical and laboratory improvement was observed, following which the patient was released.

Towards the end of the course of steroids, the patient was re-admitted with severe anemia again, in the absence of active hemolysis. Generalized lymph-adenopathy was now evident, as were signs of the superior vena caval syndrome. The above findings were confirmed by CT-scan. Moreover, bilateral deep vein thrombosis was diagnosed by Duplex examination. By immunofixation, a mono-clonal IgG -lambda peak was disclosed. A PCR for EBV revealed a viral load of 812733 U/L.

An inguinal lymph node was then excised. The node was 3.5 cm in diameter and was discreet. On histology, the lymph node was only partially effaced, sinuses persisted as well as a vague nodularity, in the absence of germinal centers (Figure 1 and 2). No evidence of necrosis was found. Numerous blood vessels, some branching, were more consistent with capillaries. The predominant interfollicular space consisted of small to medium-sized T-cells, showing no pan-T cell restriction. In these areas, as well as in the B-cell predominant regions, large B-cells, CD30+ immunoblasts were dispersed. Polyclonal plasma cells were numerous. CD21 and CD23 were negative for follicular dendritic cells. CD4+++; PD1+++ (moderate intensity); Bcl-6 + (weak); ICOS+ (very weak); CXCL13(-), highlighted a limited content of T follicular helper cells. An EBER in situ hybridization analysis was strongly positive (figure 3).

PCR for TCRg showed weak clonality of T cells, while PCR for TCRb revealed a clear monoclonality of T cells. PCR for IGH showed monoclonality of B cells. Retrospectively, we have compared the PCR amplification of TCR gamma gene rearrangement of the two bone marrow biopsies obtained and of the lymph node biopsy. This comparison confirms the origin of the tumor of the three samples in the same T-cell clone.

The clinical, histopathological and molecular picture was more in favor of a lymphoid malignancy and supported pre-dominantly AITL. However, in the presence of a limited component of T follicular helper cells and a near total absence of follicular dendritic cells, and of high endothelial venules, the picture might be consistent, at best with that of a very unusual variants of AITL. One may consider also a variant peripheral T-cell lymphoma, especially the follicular peri-pheral T-cell lymphoma which has been viewed as related to AITL. Although infrequently biopsied, infectious mono-nucleosis in the elderly might simulate a lymphoma, especially in the presence of an acute EBV serologic profile, as seen in this patient.

The hematologist retained the diagnosis of AITL with B-cell monocle-nality (but no clear evidence of a diffuse

large B-cell lymphoma), as proposed by the hematopathologist, as it was consistent with the clinical picture. Following the first course of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), which was uneventful, an interim PET-CT showed complete resolution of the lymphadenopathy and splenomegaly. The patient has now completed the third course of CHOP and he presently feels well, with a normal CBC, except for a mild anemia. The marked edema that had involved previously his upper and lower extremities has resolved.

DISCUSSION

Infectious mononucleosis was suspected at one point in this patient, based on bilateral tonsillar enlargement, exudates and splenomegaly with suspected lacerations. Moreover, an acute serological EBV profile, notably, with a positive EBV VCA IgM (62.50 U/ml) and a viral load of 812733 U/L were in favor of this diagnosis, which in the elderly may be misdiagnosed as a lymphoma. However, a similar, though more discreet EBV profile had been shown 4 months previously, during the first admission of the patient. The serological findings might alternatively be interpreted as an EBV reactivation and the high titers of CMV, including IgM, could support this view [1, 6, 11].

The finding of a monoclonal IgG-lambda peak by immunofixation, performed at a later stage of the clinical course, may sustain the diagnosis of a malignant tumor. However, only the occurrence of the superior vena caval syndrome, the lymph node histopathology, together with the demonstration of a T-cell monoclonality by TCRb and of B-cell monoclonality by IGH by PCR supported the diagnosis. Of note, it has rarely been stated that false positive gene rearrangements may be found in the presence of high EBV titers. At times, the diagnosis of malignancy may seem equivocal, the demonstration of monoclonality being uncertain, as the molecular study sensitivity and specificity are not absolute [8]. In such complex cases, help may obtain from performing two complementary studies, like PCR for TCR gamma as well as for TCR beta, which may increase significantly the specificity of the results. Moreover, when several biopsies from the same patient are available, a comparison of the molecular studies from the various biopsies may disclose the presence for an identical clone, as shown in our patient.

The exact nature of the malignancy was subject to a debate. The presence of a clinical picture suggestive of an infectious disease lent support, as mentioned above, to AITL. However, we had difficulties in relating the lymph node histopathology to a specific variant of AITL. A similar case has been reported recently and the authors faced comparable difficulties, when confronted by their patient's data [2]. We have previously described the impact of prior corticosteroid administration on the diagnostic process in lymphomas [5]. We believe that the diagnosis of AITL was especially arduous in this patient, due to previous treatment with high doses of Prednisone.

Our final pathological diagnosis was AITL, with a clonal large B-cell proliferation, but in the absence of a diffuse large B-cell lymphoma [1, 4, 10]. IGH rearrangement showing B cell monoclonality together with TCR rearrangement detecting monoclonal T cells is reported in 10-20% of cases of AITL [4].

On the other hand, the paucity of follicular dendritic cells, of follicular T helper cells and of high endothelial venules, may also be accounted for by the differential diagnosis of follicular peripheral T-cell lymphoma (formerly, follicular T-cell lymphoma). But some consider this disease entity as a further variant of AITL.

CONCLUSION

The report of an elderly patient with AITL and an acute serological EBV

profile is presented, with a rare positive serology for EBV-IgM. The case underlines the diagnostic difficulties in such a composite disease and it is not excluded that additional cases might have escaped the scrutiny of their physicians. One may suggest that an infectious mononucleosis like disease might have represented in our patient a lengthy prodromal episode, preceding the development of a full blown AITL.

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Conflict of interest:

The authors declare they have no conflict of interest.

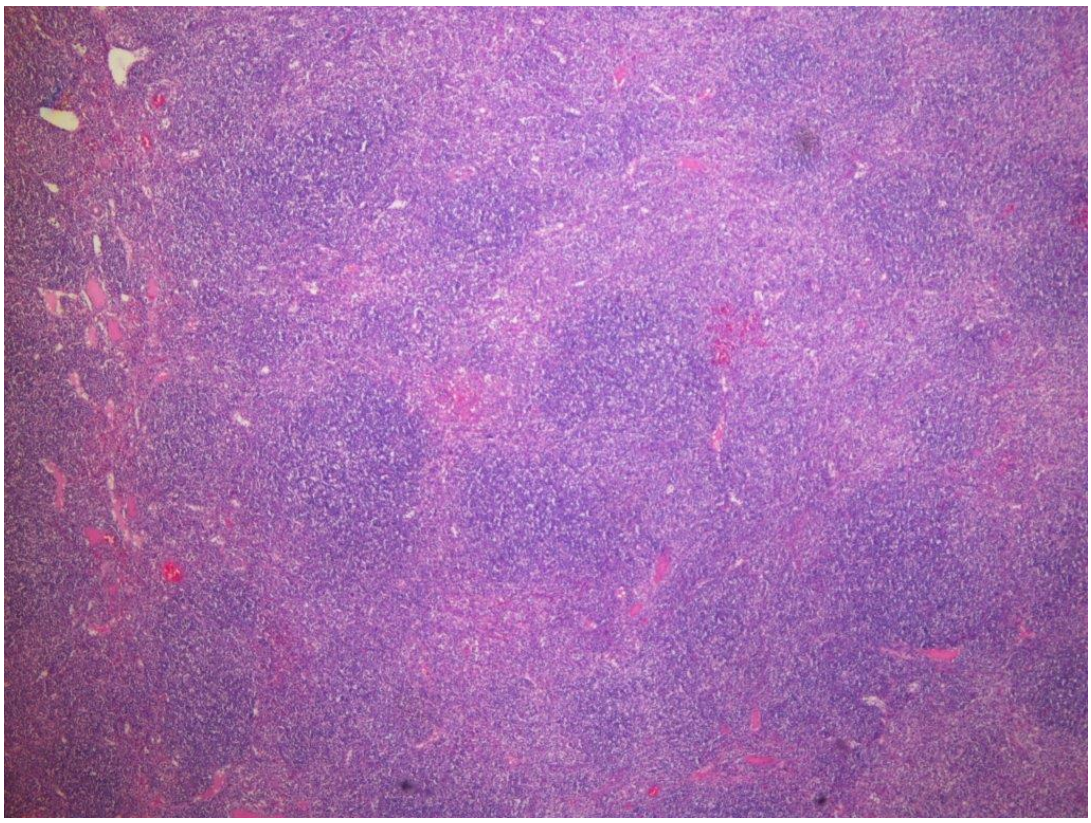

Figure 1. Low-power view of the lymph node section. Note a vague nodularity (H&E x 135).

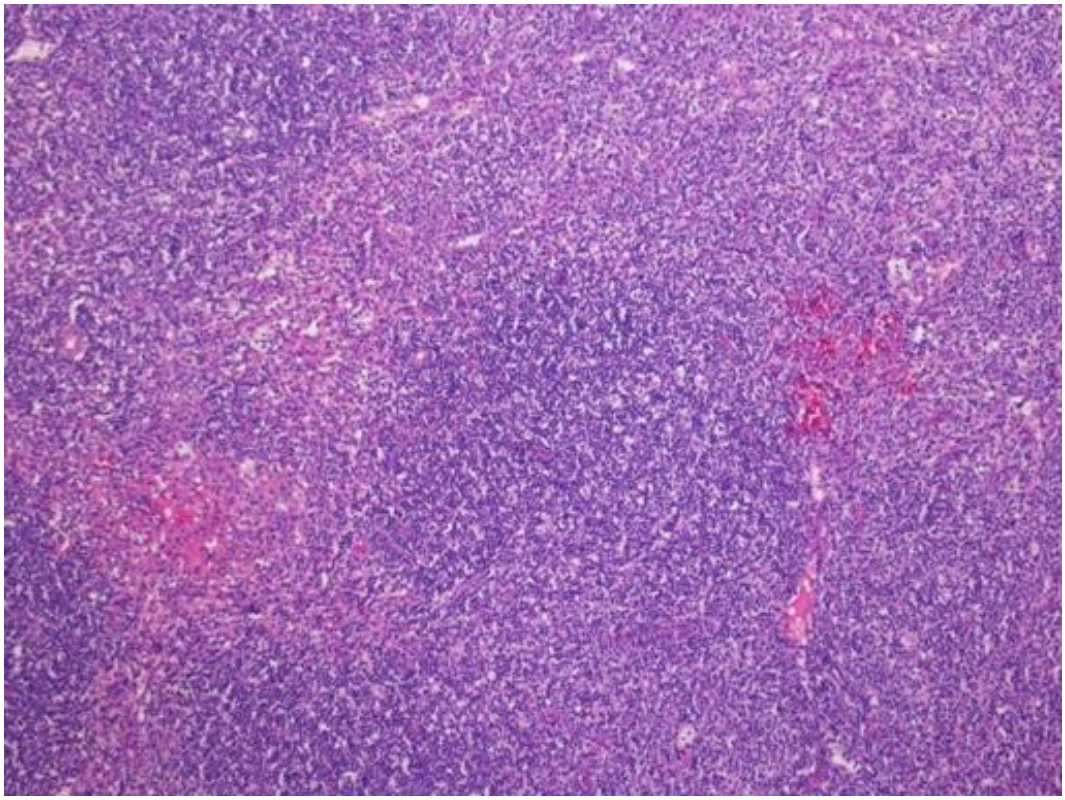

Figure 2. Closer view of one of the nodules. It is composed predominantly of small, almost regular lymphoid cells (H&E x 340).

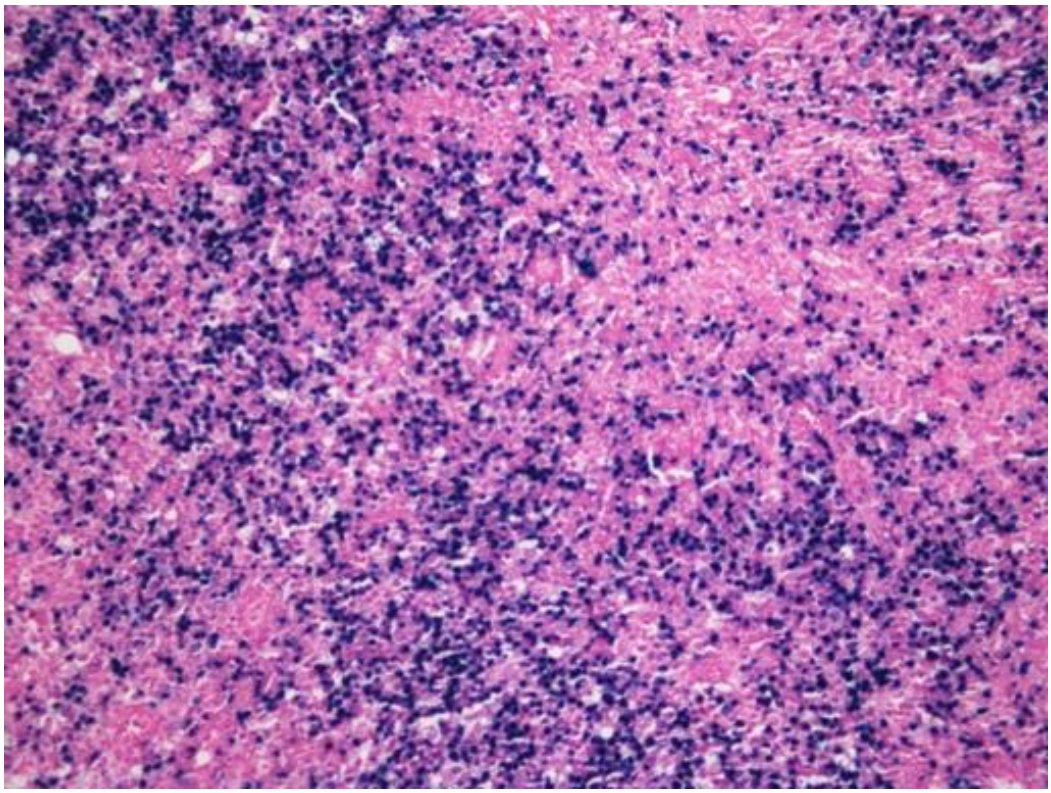

Figure 3. A majority of the lymphoid cell in the lymph node are positive for EBER small RNAs and stain blue (*in situ* hybridization x 340).

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