Clinical case

Epstein–Barr virus related hemophagocytic syndrome in a T-cell rich B-cell lymphoma

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Summary

We report the case of a 30-year-old woman who presented with an EBV related hemophagocytic syndrome. After a few months she developed a T-cell rich B-cell non-Hodgkin's lymphoma with liver involvement. Serological data demonstrated a reactivation of the EBV infection. Tumor progression with liver involvement occurred during treatment with conventional chemotherapy. Tumor reduction and disappearance of all masses was seen after starting high-dose sequential chemotherapy, followed by an autologous peripheral blood progenitor transplantation. LMP-1 could be amplified in the tumor material by PCR technology, but no LMP-1 expression could be found in the few malignant B-cells with Reed–Sternberg morphology. Sequence analysis of the carboxy terminal of the LMP-1 region revealed the naturally occurring 30 bp deletion variant of the LMP-1 with multiple point mutations within the NF kb region. Since LMP-1 was not expressed in the malignant tumor cells, no evidence could be found, that EBV participated in the tumorigenesis of this case.

Key words: chemotherapy, Epstein–Barr virus, LMP-1, peripheral blood stem cells, T-cell rich B-cell non-Hodgkin's lymphoma (TCRBCL)

Introduction

The term T-cell rich B-cell non-Hodgkin's lymphoma (TCRBCL) has been introduced in 1988 by Ramsay et al. [1]. This entity is characterized by a predominance of reactive T-cells and a minor population of malignant B-cells. Accordingly to the R.E.A.L. classification the TCRBCL should be considered as a diffuse large B-cell lymphoma [2].

TCRBCL seems to be a rare entity of NHL comprising only 1% of all NHL seen in a single Institution [3], but there is only limited information regarding the initial clinical presentation and the response to therapy. Although long lasting complete remission can be obtained in patients, who receive chemotherapy for high-grade lymphomas [4, 5], patients with liver involvement have an extremely poor prognosis [6].

Epstein–Barr virus (EBV) genomes and the EBV encoded latent membrane protein 1 (LMP-1), including its naturally occurring 30 bp deletion variant, are frequently found within the blasts of different non-Hodgkin's lymphomas [7, 8]. They may play some role in EBV related lymphomagenesis, because LMP-1 has been identified as a multifunctional oncoprotein [9].

There is little data in TCRBCL concerning the EBV genome in the clonal and malignant B-cell population [10–12].

We describe an unusual presentation of a TCRBCL with an EBV – associated hemophagocytic syndrome of the spleen. Although serological data showed a reactivation of EBV infection and the 30 bp variant of the LMP oncoprotein could be identified, no correlation between the virus and the malignant B-cell clone was found.

Case report

A 30-year-old woman presented in March 1994 after a normal pregnancy, at her local hospital, complying of generalized pruritus, night sweats, fever and weight loss of more than five kg in one month. Physical examination showed only splenomegaly; no peripheral lymphadenopathy was found. A computer tomogram (CT) of the chest was normal and showed no mediastinal adenopathy, CT of the abdomen revealed an enlarged spleen (17 cm longitudinal diameter) and a few enlarged retroperitoneal lymph nodes. Laboratory findings included a moderate pancytopenia (WBC 2500/μl, neutrophils 71%, Hgb 10,8 g/dl and platelets: 88.000/μl). Her erythrocyte sedimentation rate was slightly elevated (37/1 hour) and lactate hydrogenase was two times the normal value (424 U/l). Her erythrocyte sedimentation rate was slightly elevated (37/1 hour) and lactate hydrogenase was two times the normal value (424 U/l). A moderate hypogammaglobulinemia of IgG type was found (408 mg/dl). IgA was 44 mg/dl and the IgM level was within the normal range. The serological pattern of EBV antibodies at different timepoints was consistent with a chronic EBV infection (VCA: IgG pos, IgM neg. EBNA 1:40). Detection of a high titer (1:128) against early antigen (EA) suggested a recent reactivation. Bilateral bone marrow biopsy was negative for lymphoma infiltration.
Diagnostic splenectomy was carried out; the histological findings revealed a prominent hemophagocytosis of the spleen and diagnosis of EBV associated hemophagocytic syndrome was established. The retroperitoneal lymph nodes were necrotic and therefore non-diagnostic. During the following month, an enlarged lymph node was detected and excised in the left axilla. Lymphocyte predominant Hodgkin’s disease was diagnosed. Chemotherapy with MOPP–ABV was initiated, but massive tumor progression developed during therapy. B symptoms increased during the therapy free intervals. Enlarged lymph nodes in both axillae and the mediastinum were found after completing the second cycle of the MOPP–ABV regimen; multiple nodular liver masses were found by ultrasound and CT (Figure 1a). Liver histology revealed infiltrates of small lymphocytes; immunophenotypically a few B cells, within a background of small T-lymphocytes were found.

After transfer to our institution, the interpretation of the histology of the axillary lymph node was revised to T-cell rich B-cell non-Hodgkin’s lymphoma. As shown in Figure 2a, only few cells, including large and bi/or multinucleated cells were strongly positive for CD79a expression. Mib-1, a proliferation marker was also found in the large and multinucleated cells (Figure 2b) The few B-immunoblasts were negative for LMP-1 expression, even though LMP-1 could be amplified in the tumor derived DNA. Sequence analysis of the LMP-1 revealed the 30 bp deletion of the LMP-1 (168285-168256) with several replacement mutations within the carboxy terminal region of the LMP-1 oncogene.
The clinical presentation of this TCRBCL was unusual; the B symptoms, the moderate pancytopenia, the serological findings of a reactivated EBV infection and the histological finding of massive hemophagocytosis in the spleen were consistent with the diagnosis of an EBV related hemophagocytic syndrome [13]. On the other hand, hemophagocytic syndromes are frequently associated with malignant lymphomas, often of the T-cell type, including the EBV associated peripheral T-cell lymphoma [10-12]. In two of these cases LMP-1 expression within the malignant cells [11, 12] was found. Furthermore it has been shown, that LMP-1 expression, including its naturally occuring deletion variant promote the formation of multinuclear cells [9].

The immunoblasts in our case show a typically multinucleated morphology (Figure 2a), but no LMP-1 expression in the malignant and proliferating cells was detected. The serological picture of the reactivated EBV infection at diagnosis, the complete disappearance after successful therapy and the negativity of the malignant immunoblasts for LMP-1 suggest, that EBV could not be the causative agent of lymphomagenesis in this case.

Reactivated EBV infection was more probably related to the immunodeficiency, often found in hemophagocytic syndromes. The abundant T-cell reaction and the paucity of malignant B cells in this disorder may be due to IL4 expression [14]. Alternatively, T-cell assembly to the GIanni procedure [19]. After the administration of 7 g/m² cyclophosphamide, 7.5 x 10⁶ CD34+ cells/kg were collected. After the high-dose methotrexate (8 g/m²) and vincristine 2 mg, her B symptoms disappeared and the enlarged lymph nodes reduced in size and there was a complete disappearance of the liver lesions. (Figure 1b). Reactivation of herpes simplex virus infection occurred twice during the first two cycles of high-dose sequential therapy. To reduce the complications of the immunodeficiency (the patient was hypogammaglobulinemic) and to abbreviate the duration of the aplasia following high dose VP16 (2 g/m²) administration, 2 x 10⁶ CD34+ cells/kg were reinfused. The patient was then conditioned with melphalan (140 mg/m²) and mitoxantrone (12 mg/m²) and transplanted with an unpurged PBSC product, containing 5.5 x 10⁶ CD34+ cells. The engraftment of neutrophils and platelets was rapid and stable. Restaging after the completing the therapy showed complete disappearance of all previously described lesions (Figure 1). The patient is now out of therapy for more than 24 months with no evidence of disease. Three different analyses of EBV serology after peripheral blood progenitor cell transplantation have been carried out and showed a normal pattern (VCA: IgG: pos IgM: neg; EA: < 1:16; Table 1). The values of immunglobulins returned to values within the normal range.

Discussion

The clinical presentation of this TCRBCL was unusual; some TCRBCL contain Reed-Sternberg-like cells [4]. A correct diagnosis is crucial, because the administration of inadequate initial therapy decreases the possibility of long-term survival. Treatment for Hodgkin disease (MOPP-ABV) was not successful in this case and tumor progression with liver involvement was observed during administration of the chemotherapy. TCRBCL with liver involvement has a very poor prognosis with a median overall survival, normally not exceeding three months [6]. We therefore decided to start sequential high-dose chemotherapy; peripheral blood stem cells were immediately collected after cyclophosphamide administration, because no tumor infiltration was found in the bone marrow. Because in patients with a disease or drug induced immunodeficiency and especially in patients with a hemophagocytic syndrome, a fatal outcome is possible [18], we have transplanted our patient even after the high-dose VP-16 therapy, in order to reduce the aplasia associated complications. Subjective signs of tumor regression such as disappearance of B symptoms, as well as objective tumor regression was documented during the high-dose sequential therapy.

The link between the LMP-1 oncoprotein and malignant lymphomas is well documented [7-9, 17] and mutational hot spots within the carboxy terminal region of the LMP-1 oncogene of the EBV are frequently found in different lymphoproliferative disorders [17]. Only few data are available about the EBV genome in the malignant B-cells of TCRBCL [10-12]. In two of these cases an LMP-1 expression within the malignant cells [11, 12] was found. Furthermore it has been shown, that LMP-1 expression, including its naturally occuring deletion variant promote the formation of multinuclear cells [9].

The immunoblasts in our case show a typically multinucleated morphology (Figure 2a), but no LMP-1 expression in the malignant and proliferating cells was detected. The serological picture of the reactivated EBV infection at diagnosis, the complete disappearance after successful therapy and the negativity of the malignant immunoblasts for LMP-1 suggest, that EBV could not be the causative agent of lymphomagenesis in this case. Reactivated EBV infection was more probably related to the immunodeficiency, often found in hemophagocytic syndromes. The abundant T-cell reaction and the paucity of malignant B cells in this disorder may be due to IL4 expression [14]. Alternatively, T-cell assembly could be EBV related, because LMP-1 30 bp variant expression might favor a cytokine mediated process, since LMP-1 interacts with TNF receptor associated proteins (TRAFs) and induces CD40 signaling [9].

References

2. Harris NL, Jaffe ES, Stein H et al. A revised European–American
   Classification of lymphoid neoplasms: A proposal from the Inter-
3. Baddoura FK, Chan WC, Masih AS et al. T-cell rich B-cell
   lymphoma. A clinicopathologic study of eight cases. Am J Clin
   Pathol 1995; 103: 65-75.

Tabl e 1. Serological data of reactivated EBV infection.

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
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Received 24 February 1998; accepted 10 March 1998

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