Pathology – Research and Practice 213 (2017) 277–280

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Case Studies

Coexistence of age-related EBV-associated follicular hyperplasia and large B-cell EBV+ lymphoma of the elderly. Two distinct features of the same T-cell dysfunction related to senescence?

Jean-Baptiste Gibier[a,*], Brigitte Bouchindhomme[a], Romain Dubois[a], Benedicte Hivert[b], Nathalie Grardel[c], Marie-Christine Copin[a]

[a] Univ. Lille, Institute of Pathology, Centre de Biologie Pathologie, CHU Lille, F-59000 Lille, France
[b] Univ. Lille. Department of Hematologic Oncology and Blood Disorders, Hôpital Claude Huriez, CHU Lille, F-59000 Lille, France
[c] Univ. Lille. Institute of Hematology, Centre de Biologie Pathologie, CHU Lille, F-59000 Lille, France

ARTICLE INFO

Article history:
Received 16 August 2016

Keywords:
Diffuse large B-cell lymphoma
Epstein Barr virus
Reactive hyperplasia
Elderly

ABSTRACT

Age-related EBV-associated lymphoproliferative disorders form a new clinicopathological group. Until recently, this group was associated with diffuse large B-cell lymphoma (DLBCL), characterised by an aggressive clinical presentation and a poor prognosis. Recent findings in Western Caucasian patients, however, suggest that this entity covers a wide spectrum of diseases, ranging from reactive follicular hyperplasia (HR) to DLBCL. We report the case of an 85-year-old Caucasian man showing lymphadenopathy and numerous hypodense lesions of the liver. Examination of a lymph node revealed follicular hyperplasia with EBV expression confined to germinal centres. The patient was treated with Rituximab and subsequently, the lesions of the liver were explored. They showed extensive necrosis and a polymorphic large B-cell population with strong EBV expression. This is the first report to describe age-related EBV-associated follicular hyperplasia at one site coexisting with DLBCL at another. This case warrants undertaking further investigations each time a diagnosis of age-related EBV-HR is associated with extranodal lesions.

1. Introduction

EBV-positive lymphoproliferative disorders of the elderly (AR-EBVLPD) are rare conditions occurring in patients over fifty with no known immunodeficiency or prior lymphoma [1]. Some studies suggest that this category should include entities ranging from reactive follicular hyperplasia (HR) to diffuse large B-cell lymphoma (DLBCL) [2,3]. Usually the outcome of EBV-positive age-related follicular hyperplasia (AR-EBVHR) is favourable [2], but here we report, for the first time, the coexistence of AR-EBVHR in an inguinal lymph node and EBV-positive DLBCL in the liver. This illustrates that the AR-EBVLPD disease group spans a complex spectrum not yet fully understood, and that further investigations are required to deal with them more effectively.

2. Case report

2.1. Clinical summary

An 85-year-old Caucasian man with a history of chronic bronchitis, type-2 diabetes, multiple vascular events, and treated melanoma reported quick tiredness and a 3-kg weight loss over a one-week period. Upon physical examination, the patient presented with hepatosplenomegaly and multiple swollen inguinal lymph nodes. Laboratory findings were as follows: bicytopenia (haemoglobin 8.7 g/dL, platelet cells 11,000/mm^3), lymphocytopenia with a normal CD4/CD8 ratio, hypoproteinaemia and hypogammaglobulinaemia observed by electrophoresis, no sign of haemolysis, increased LDH (510 UI/L, twice the upper limit) and an inflammatory syndrome. Liver function tests revealed cholestatis (1.5 times the upper limit of the normal range of the laboratory) but no elevated transaminases. Serological tests for hepatitis A, B, and C, cytomegalovirus, and human immunodeficiency virus (HIV)

Abbreviations: AR, age related; cHL, classical Hodgkin lymphoma; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein Barr virus; HR, reactive follicular hyperplasia; HIV, human immunodeficiency virus; LPD, lymphoproliferative disorders; PCR, polymerase chain reaction; TEP, positron emission tomography.

* Corresponding author at: Institute of Pathology, Centre de Biologie Pathologie, CHU de Lille, CS 70001, 59037 Lille Cedex, France.
E-mail address: jeanbaptiste.gibier@chru-lille.fr (J.-B. Gibier).

http://dx.doi.org/10.1016/j.prp.2016.12.012
0344-0338/

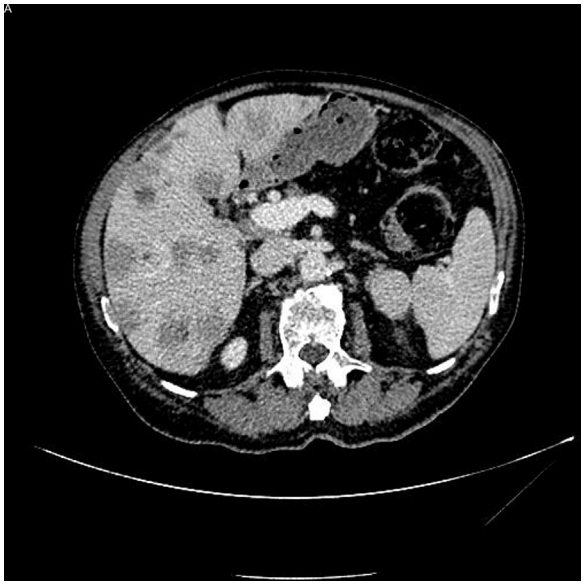

Fig. 1. Computed tomography scan of the abdomen, showing multiple hypodense nodules in the liver.

were negative. The patient's serum tested positive for anti-EBV IgG and negative for anti-EBV IgM. EBV-PCR applied to his blood gave positive results (3260 copies/ml). A computed tomography (CT) scan of the abdomen confirmed hepato- and splenomegaly, extensive lymphadenopathy (coelio-mesenteric, lombo-aortic, axillary, and cervical) and showed multiple hypodense lesions in the liver (Fig. 1).

As deep thrombocytopenia made a liver biopsy impossible, a multidisciplinary team decided to perform an excision biopsy of the patient's inguinal adenopathy. The lymph node exhibited a preserved architecture with various follicular changes. Interestingly, staining for EBER was intense and confined to germinal centres. We proposed the diagnosis of AR-EBVHR. The patient was subsequently given four cycles of Rituximab at 375 mg/m^2. During this eight-month treatment, the platelet count increased and the patient underwent a good clinical evolution marked only by an episode of dermo-epidermitis, which was managed with local care and antibiotics. A TEP scan showed a decrease in size of most of the lymphadenopathies, except in the coelio-mesenteric area. The liver lesions failed to improve during treatment.

A liver biopsy was performed after stabilisation of the platelet count, 9 months after excision of the adenopathy. The observed histology was consistent with the diagnosis of EBV-associated DLBCL of the elderly (AR-EBVDLBCL). The patient benefited from R-miniCHOP treatment (Rituximab-adriamycine, cyclophosphamide, vincristine, and prednisone), as reflected by a major size reduction observed at each location on a control CT scan. Unfortunately, the therapy had to be interrupted after 3 cycles because of side effects (pulmonary infection). The patient received 90Y-ibritumomab tiuxetan (90Y-IT, Zevalin®) as consolidation therapy. He is currently in a stable clinical condition, and treatment response will be assessed on the basis of further CT scans.

2.2. Pathological findings

2.2.1. Inguinal lymph node

Upon examination at low magnification, the normal lymph node architecture appeared preserved, with a diffuse expansion of the paracortical region (Fig. 2). The lymphoid follicles showed a heterogeneous morphology and ill-defined borders, with a combination of hyperplastic and atrophic features. At higher magnification, some germinal centres displayed penetration by hyalinised vessels. The interfollicular space was filled with small lymphocytes, some immunoblasts, and rare plasma cells.

Immunohistochemical analysis revealed a pattern consistent with HR. CD20 staining revealed B-cells within follicles (Fig. 2). Like haematoxylin-eosin staining (HES), CD20 staining highlighted an increase in paracortical immunoblasts, positive for CD30 but negative for CD15. The germinal centres were CD30 and Bcl2 negative but highly CD10 and Bcl-6 positive (Fig. 2). MUM1 staining was moderate within the germinal centres (Fig. 2). CD3- and CD5-positive T-cells were found mostly in the paracortical region, only a few being observed inside germinal centres. In the interfollicular area, the T-cells were predominantly CD4 positive. CD23 staining revealed a regular arrangement of the follicular dendritic meshwork within most of the hyperplastic follicles. CD138 staining demonstrated the presence of plasma cells and immunohistochemical detection showed a normal ratio of kappa to lambda light chains. No HHV8 staining was observed.

In situ hybridisation revealed numerous EBER-positive large cells within some of the germinal centres, and a few such cells scattered through the paracortex (Fig. 2). TCR gamma rearrangements were compatible with the presence of an oligoclonal T-cell population and no clonal immunoglobulin rearrangements were found.

2.2.2. Liver biopsies

Two liver samples were collected under ultrasound guidance. Upon microscopic examination, one biopsy showed a normal hepatic parenchyma infiltrated by a cluster of small lymphocytes. The other showed extensive necrosis surrounded by a population of polymorphic large cells without any residual hepatocyte (Fig. 3). Tumour cells showed various shapes and sizes but none was Sternberg- or Hodgkin-like (Fig. 3). They reacted with antibodies against CD20 (Fig. 3), CD79a, and PAX5, and their proliferation index was high (80% Ki67-positive neoplastic cells). MUM1 staining revealed diffuse nuclear positivity (80% of the neoplastic cells). Focal expression of Bcl6 was observed (30% of the neoplastic cells). A few large cells appeared weakly CD30 positive. The neoplastic cells appeared CD15 and CD10 negative. Staining for T-cell markers confirmed the existence of a population rich in reactive CD3+ CD5+ T-lymphocytes at the periphery of the large B-cells. No HHV8 staining was observed. The majority of neoplastic B-cells were EBER positive, supporting the diagnosis of AR-EBVDLBCL (Fig. 3). Molecular studies showed evidence of a clonal IGH FR3 rearrangement without associated TCR rearrangements.

3. Discussion

In 2008, a new provisional entity was included in the World Health Organization classification: AR-EBVDLBCL. This entity was first described in Japanese patients as a B-cell neoplasm occurring mostly in patients over 50 without any known immunodeficiency or prior lymphoma [1]. It is commonly associated with frequent extranodal sites [4], an aggressive clinical presentation, and a poor diagnosis [5]. Morphologically, AR-EBVDLBCL is a polymorphic lesion showing a mixed proliferation of immunoblasts and medium lymphoid cells with various proportions of Hodgkin- and Reed-Sternberg-like cells associated with reactive cells [6]. The DLBCL observed in the liver biopsies of our case showed characteristic features of EBV-DLBCL as previously described [4,5], with tumour cells of various shapes and sizes, a post-germinal centre phenotype, and necrosis of the surrounding tissue. Differential diagnosis between AR-EBVDLBCL and EBV-positive classic Hodgkin's lymphoma (cHL) can be challenging [8], and some cases of evolution from EBV-HR to cHL have been reported [6]. In the present case, however,