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Case report

Epstein barr virus hemophagocytic lymphohistiocytosis related to rituximab use and immunopathogenetic insights

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ABSTRACT

Anti-CD20-based chemo-immunotherapeutic regimens have been suggested to assist in the management of Epstein-Barr virus (EBV)-induced hemophagocytic lymphohistiocytosis (HLH) and EBV-associated post-transplant lymphoproliferative disorders (EBV-PTLD), by reducing EBV viral load and EBV-induced inflammation.

Herein we report a fatal EBV-related HLH in the context of Hodgkin lymphoma (HL)-like Richter's transformation of B chronic lymphocytic leukemia (B-CLL), two months after rituximab treatment. The complex balance between EBV driven T-cell stimulation and immunosuppressive therapy in the context of multiple immune deficits is discussed.

1. Introduction

Rituximab-based chemo-immunotherapeutic regimens have been used for EBV-induced hemophagocytic lymphohistiocytosis (HLH) [1]. Furthermore, anti-CD20 therapy has emerged as an efficient agent in improving the outcome of EBV-associated post-transplant lymphoproliferative disorders (EBV-PTLD) [2–4]. By rapidly depleting circulating EBV-carrying B-lymphocytes, rituximab reduces EBV viral load and associated inflammation, and may be considered as a possible therapeutic option for a variety of other EBV–associated clinical manifestations [5].

We herein report the case of a 66 year-old male with EBV reactivation, manifesting as HLH in the context of Hodgkin lymphoma (HL)-like Richter's transformation of B chronic lymphocytic leukemia (B-CLL), while receiving rituximab. In addition, we discuss the complex balance between EBV driven T- cell stimulation and immunosuppressive therapy in a patient with multiple immune deficits.

2. Ethical statement

Ethics committee approval is not included as it is commonly accepted that case reports do not require such approval. Because our work did not use patients' data that would allow identifying them, informed consent is not necessary.

3. Case report

A 66 year-old man presented to the Hematology Unit of our hospital with 1 month history of fever up to 39.5 °C, malaise, and 6 kg weight loss. He had previously been admitted to another hospital and treated with broad spectrum antibiotics with no response. Current medical history included B chronic lymphocytic leukemia ((B-CLL) Stage II by Rai staging system) diagnosed in 2002, for which he had received multiple therapeutic schemes since 2007. Cytogenetics was positive for 13q14 deletion on

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Table 1
Results of laboratory investigations at presentation.

COMPLETE BLOOD COUNT		SEROLOGY	
WBC	1.4 K/μl	Leishmania IgG/IgM	Negative
Neutrophils	0.8 K/μl	Brucella IgG/IgM/IgA	Negative
Lymphocytes	0.5 K/μl	Quantiferon TB	Negative
Monocytes	0.09 K/μl	HBsAg	664 IU/ml
Eosinophils	0 K/μl	HBeAg	1238 IU/ml
Baseophils	0 K/μl	Anti – HBs	Positive
Haematocrit	24%	Anti – HBc IgM	Negative
Haemoglobin	8.1 g/dl	Anti – HBc	Negative
MCV	88.7 fl	Anti – HBe	Negative
MCH	29.5 g/dl	CMV plasma viral load	Negative
Platelets	61 K/μl	EBV plasma viral load	Positive (< 1000 IU/ml)
BIOCHEMISTRY		EBV EBNA IgG	Positive
Glucose	82 mg/dl	EBV VCA IgG	Positive
Creatinine	1.6 mg/dl	EBV VCA IgM	Negative
Sodium	133 mmol/l	CULTURES	
Potassium	4.6 mmol/l	Blood cultures	Sterile
Calcium	8.5 mg/dl	Blood cultures – mycobacteria	Sterile
LDH	230 U/l	Bone marrow culture	Sterile
ALT	51 U/l	Bone marrow aspirate – acid fast bacilli staining	Negative
AST	23 U/l	Gastric aspirate – acid fast bacilli staining	Negative
γGT	204 U/l	Leishmania staining	Negative
ALP	305 U/l	Fungi staining	Negative
Bilirubin	1.02 mg/dl	Urine cultures	Sterile
Triglycerides	321 mg/dl	Sputum cultures	Sterile
CRP	199 mg/dl	Sputum cultures – mycobacteria	Sterile
ESR	120 mm/hr		
Ferritin	5541 ng/ml		
COAGULATION			
INR	1.32 s		
PT	15.3 s		
aPTT	34 s		
Fibrinogen	793 mg/dl		

both chromosomes 13. Past regimens included chlorambucil, rituximab-cyclophosphamide, vincristine and prednisone, (R-COP), ofatumumab and bendamustine. He was currently under treatment with rituximab and methylprednisolone (80 mg/day tapered to 16 mg/day within one month period, and continued thereafter as maintenance dose) for the last 6 months, due to autoimmune hemolytic anemia (AHA), which led to HBV reactivation and HBsAg positivity, followed immediately by initiation of entecavir. He had received 4 weekly rituximab administrations of 375 mg/m^2, the last one given 2 months prior to the initiation of his symptoms.

On examination he was febrile (39 °C), hemodynamically stable, with tachycardia. There was hepatosplenomegaly and painless axillary lymphadenopathy. On admission complete blood count revealed profound pancytopenia and biochemistry results were notable for elevated ALP/γ-GT and hyperferritinemia (results of laboratory investigations are depicted in Table 1).

In order to rule out Richter's transformation, bone marrow biopsy and whole body CT scan were immediately performed. CT scan revealed hepatosplenomegaly and generalized abdominal and thoracic lymphadenopathy, without significant changes from his last imaging follow-up. His bone marrow aspirate revealed hypocellular bone marrow and hemophagocytosis (Fig. 1). Bone marrow biopsy was infiltrated (in approximately 20% of the sample) by small lymphocytes, whose immunophenotype (CD20, CD5 and CD23 positive) was consistent with the initial diagnosis of B-CLL. Moreover, a multitude of non–caseating granulomas were seen (Fig. 1A–B). They were diffusely permeated by large, Reed-Sternberg-like, CD15, CD30 and LMP-1 protein positive cells; the presence of EBV was further confirmed by in situ hybridization using EBV encoded small RNAs (EBER). The density of the aforementioned cells was lower within granulomas compared to the rest of the marrow (Fig. 2C–H). Simultaneous EBER in situ hybridization with anti-CD20 immunostaining disclosed a few double positive cells (Fig. 3). Further imaging using 18-FDG–PET scanning, revealed multiple lymph nodes with minimally increased FDG uptake at the right cervical, left submandibular, right supraclavicular, bilateral axillary and various infradiaphragmatic lymph nodes which were compatible with low 18-FDG uptake of indolent lymphoma (SUVmax up to 4.5). PET/CT images also revealed metabolic activity in various mediastinal lymph nodes with intense FDG uptake (SUVmax = 11.0) and multifocal 18-FDG uptake in the bone marrow (score 5), suggesting the diagnosis of B-CLL transforming into classical HL. Special stains showed no fungi, leishmaniae or acid-fast bacilli. Aspirate cultures were sterile; PCR was negative for mycobacteria. In accordance with the diagnostic criteria for hemophagocytic syndrome, a diagnosis of EBV-induced HLH was rendered. In addition, our patient developed a second, distinct EBV-associated lymphoproliferative disorder, the HL-variant of Richter's syndrome.

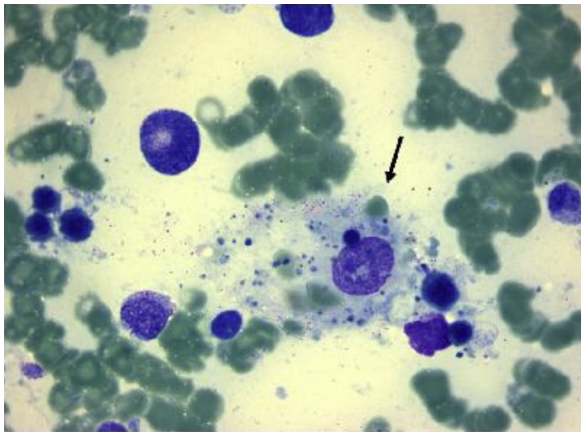

Fig. 1. Bone marrow aspirate: pancytopenia; activated macrophage showing hemophagocytosis (arrow). May-Gruenwald-Giemsa stain ×100.

Given the fact that he was already treated with rituximab for AHA, we decided to choose a therapeutic scheme which included IVIG and corticosteroid administration. Following the first infusion, the patient's clinical status and laboratory tests gradually improved. Fever subsided, whereas complete blood count, ferritin level and inflammatory markers improved (Table 1, Fig. 4). However soon after the second infusion he began to deteriorate again, his clinical status and laboratory tests consistent with relapse of his underlying hemophagocytosis. A rituximab-based therapeutic scheme, along with Doxorubicn, Bleomycin, Vinblastine and Dacarbazine (R-ABVD) was initiated; nevertheless, the patient died 2 days later. No autopsy permission was granted.

4. Discussion

The case of a 66 year-old man with EBV reactivation, presenting with HLH, HL-like Richter's transformation of B-CLL and bone marrow granulomas is presented. Although not often reported in the literature, EBV infection may manifest as bone marrow granulomas