

The role of rituximab in a case of EBV-related lymphoproliferative disease presenting with haemophagocytosis

Dear Editor,

With interest we read the case report by Wijsman, *et al.*¹ In addition to their patients, we describe a 21-year-old woman with a systemic inflammatory response syndrome (SIRS) and pancytopenia after a primary Epstein-Barr virus (EBV) infection. Three weeks earlier she had been admitted elsewhere with fever, anorexia, cervical lymphadenopathy, jaundice, rash and myalgias. Her medical history consisted of ulcerative colitis (UC), for which she received treatment with azathioprine (150 mg daily). EBV IgM and monospot were positive and EBV load determined by PCR was markedly elevated, consistent with the diagnosis of a primary EBV infection. Laboratory investigation now revealed pancytopenia, haemoglobin level 5.5 mmol/l, leucocyte count $0.9 \times 10^9/l$, thrombocyte count $58 \times 10^9/l$, elevated CRP level 194 mg/l, bilirubin 309 $\mu\text{mol/l}$, elevated ALAT 91 U/l and ASAT 180 U/l, elevated LDH 1279 U/l, hyperferritinaemia $>15,000 \mu\text{g/l}$, and a normal level of triglycerides. A CT scan confirmed the slightly enlarged lymph nodes in neck and both axillae, and showed only slight hepatosplenomegaly. Quantitative PCR for EBV was positive with a viral load of 200,000 c/ml. At first a diagnosis of EBV-related lymphoproliferative disease (LPD) was considered, but bone marrow biopsy showed an increased number of macrophages with phagocytosed red blood cells (= haemophagocytosis) and no signs of a LPD. Therefore, and because she met the clinical and laboratory criteria for secondary haemophagocytic (HLH),² a primary EBV infection complicated by HLH was diagnosed.

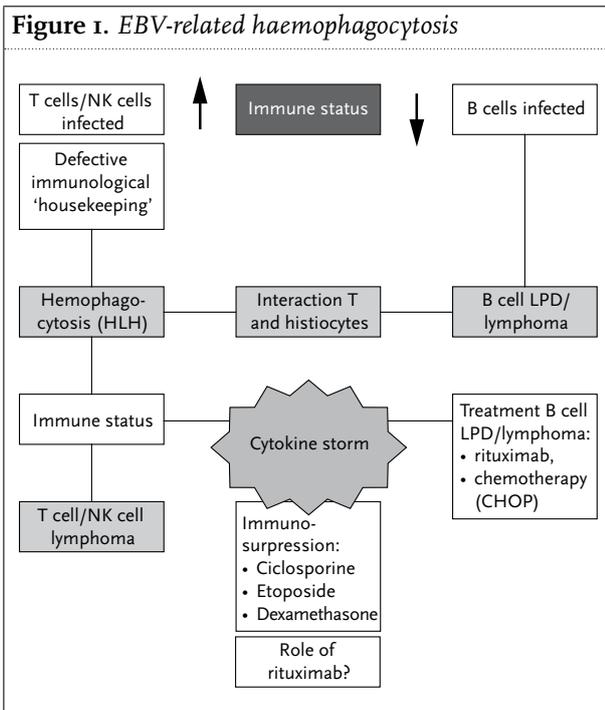
She needed haemodynamic and respiratory support, and was treated in the ICU according to the treatment protocol of the second international HLH study with cyclosporine and dexamethasone (but without etoposide and methotrexate).² She improved with resolution of the pancytopenia, although the EBV viral load did not decrease. Also, subset analysis of the patient's lymphocyte population showed that the cytotoxic T cells and NK cells were not infected with EBV, as has been reported in case of EBV-related HLH.^{3,4} This urged us to re-evaluate the possibility of an underlying EBV-related LPD. Meanwhile, she developed a bacterial peritonitis caused by perforation of the large intestine, and a partial resection of the

colon was performed. Pathological examination revealed monomorphous EBV-related B-LPD, histologically a diffuse large B cell lymphoma. A repeated CT scan now showed multiple circumscribed lesions in the lungs, liver, spleen, kidneys and pancreas.

We concluded that she was suffering from an EBV-related LPD following a primary EBV infection whilst on azathioprine. Cyclosporine was immediately discontinued and the patient was treated with rituximab and CHOP chemotherapy (cyclophosphamide, adriamycin, vincristine and prednisone), after which she improved. After eight courses of R-CHOP she is now in a complete remission with a good clinical condition and with EBV viral transcript that is no longer detectable.

Our case demonstrates that clinical pictures overlap and that differentiation is essential for immediate appropriate treatment. Although our patient was suffering from an EBV-related B-LPD, resulting from a primary EBV infection during immunosuppressive therapy because of UC, on admission her clinical picture was dominated by SIRS, ARDS and haemophagocytosis, consistent with secondary HLH. The haemophagocytosis on presentation was probably caused by the cytokine storm or indirect functional impairment of T cells/histiocytes resulting from the rapid B cell proliferation in combination with immunosuppressive UC therapy.

Haemophagocytosis due to EBV-related B-LPD and EBV-related HLH are two different but overlapping pathophysiological entities. In fact, the most important difference is the primary cell type infected by EBV. In HLH mainly cytotoxic T cells and NK cells, both essential for immune regulation, are infected.⁴ In EBV-related B-LPD B lymphocytes are infected and ultimately transformed to lymphoma. This process can be accompanied or facilitated by functional impairment of histiocytes/T cells and cytokine release with subsequent haemophagocytosis. In patients, detecting the infected cell type could therefore be useful for differentiating these two entities. In our patient, the cytotoxic T cells and NK cells were not infected with EBV, therefore the clinical picture could not be classified



as 'classic' secondary HLH. This knowledge, if known earlier in the course of her illness, could have prevented the occurrence of the rapidly progressive EBV-related LPD. The differences between EBV-related HLH and LPD have important consequences for the initiation of appropriate treatment.⁵ The common feature of EBV-related LPD and HLH is the so-called 'cytokine storm', caused by a deregulated immune response. Although immunosuppressive therapy is necessary to prevent SIRS and even death, not all patients benefit from immunosuppression alone, especially those with mainly infected B cells. Our patient was treated with rituximab to prevent the originally polymorphic EBV-related LPD from evolving monomorphic lymphoma during immunosuppressive therapy. Rituximab, by destroying infected B cells, decreases the EBV-induced hyperactive immune response by decreasing the load of the causative pathogen EBV as well as the chance of malignant transformation of these B cells.⁶ On the other hand, secondary HLH, a problem of T cell and NK cell dysfunction, can safely be treated with immunosuppression

alone, as it is rarely complicated by lymphoma. Since it involves predominantly T cells and NK cells not expressing CD20, addition of rituximab seems of little benefit.

Concluding, EBV-related LPD and HLH are life-threatening disorders. In case of EBV-related haemophagocytosis an underlying malignant lymphoproliferative process should be considered and excluded, especially with EBV infection/reactivation in the immune-compromised host. EBV viral load should be carefully monitored during treatment and if possible the infected cell type determined. Early treatment with rituximab results both in the reduction of the viral load and the elimination of transformed B cells, reducing the risk of LPD. The role of rituximab in 'classic' EBV-related HLH is however not defined. Therefore treatment with rituximab should be considered in EBV-related haemophagocytosis, especially when fast differentiation between LPD and HLH is not possible.

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