Long-time remission of epstein-barr virus associated hemophagocytic lymphohistiocytosis by interferon-α treatment

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To the Editor: A 59-year-old Chinese woman was admitted for fatigue and fever for 1 month. She was diagnosed with chronic active Epstein-Barr virus (CAEBV) infection 3 years ago due to intermittent fever and documented Epstein-Barr virus positive serology. On physical examination, her spleen, liver, and superficial lymph nodes were not palpable. There was no sign of pulmonary infection. Initial laboratory tests were as follows: white blood cell count 0.92×10^9/L, hemoglobin 66 g/L, platelet count 15×10^9/L. Serum biochemistry: alanine aminotransferase 44 U/L, aspartate transaminoferase 142 U/L, albumin 26.7 g/L, triglyceride 3.02 mmol/L, and lactate dehydrogenase 1166 U/L. Coagulation indexes were as follows: prothrombin time 14.3 s, activated prothromboplastin time 65.9 s, thrombin time 32.2 s, D-dimer 18.35 mg/L, and fibrinogen 0.81 g/L. Serum ferritin level was significantly elevated to as high as 8500 ng/mL and serum soluble interleukin-2 receptor (sIL-2R) was 13,200 U/mL. On admission, her serum EBV-DNA load was 1.99×10^3 copies/mL. Computed tomography did not find any enlarged lymph nodes and the spleen and liver had a normal size. The bone marrow morphology and pathology revealed no sign of lymphoma but slight hemophagocytosis. Flow cytometry of the bone marrow aspirate found no clonal lymphoproliferation. Thus the patient was diagnosed EBV-associated hemophagocytic lymphohistiocytosis (HLH) due to fever, pancytopenia, elevated triglyceride, liver dysfunction, coagulopathy, and obviously elevated serum ferritin and sIL-2R. We initiated HLH-2004 protocol to control her HLH immediately upon diagnosis. In addition to dexamethasone, etoposide, and cyclosporin A, subcutaneous recombinant human interferon (IFN)-α2b of 300 million units was given every other day. Her temperature returned to normal soon and her laboratory indexes improved rapidly within 2 weeks. Her complete blood count, serum biochemistry, and coagulation test were fully normalized in 4 weeks, even though her serum EBV-DNA load remained at a low level of 1.02×10^2 copies/mL. We tapered off the chemotherapy gradually and her etoposide, dexamethasone, and cyclosporin A were fully stopped six weeks later. IFN-α2b was continuously given as the only maintenance therapy and it was gradually reduced to once weekly 6 months later. This patient was followed for 3 years. She remained complete remission, even if her serum EBV-DNA could always be detected between 10 and 100 copies/mL.

Currently most knowledge of HLH is derived from pediatric experience, in which mortality of it remains high, ranging from 20% to 88% in several large cohort studies. Compared to pediatric-onset CAEBV infection, adult-onset CAEBV infection had a poorer prognosis. In a recent cohort study, the overall survival is only 13% after 50 months from diagnosis. The prognosis of EBV associated HLH was even poorer. In the long term of follow up, almost all patients died of disease relapse or progression.[1] Although HLH-2004 protocol could improve its outcome, maintenance therapy is still controversial.[2] IFN-γ acts through the up-regulation of suppressors of cytokine signaling molecules, which impairs signaling of several cytokine receptors. Previous researches into the basic pathoetiology of systemic inflammatory disorders have led to the introduction of next-generation biologic treatments including kinase inhibitors and targeted interleukin-18 or IFN-γ blockade into systemic juvenile idiopathic arthritis and macrophage activation syndrome.[3] In comparing two cytokine reporter mouse strains, IFN-γ was identified as a mediator of systemic auto-inflammatory disease. Chronically elevated levels of IFN-γ resulted in progressive multi-organ inflammation.[4] So recently anti-IFN-γ monoclonal antibody (emapalumab) was approved for HLH by the US Food and Drug Administration.[2] On the other hand, IFN-α is known to suppress viral DNA replication by affecting its basal promoter activation process, it is rarely used in CAEBV patients. More recently IFN-α was shown to be an effective anti-viral agent in a patient with CAEBV and concomitant interstitial pneumonitis.[5] In the present case, IFN-α2b seems to be effective in maintenance therapy for CAEBV

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and EBV-associated HLH. To the best of our knowledge, this was a rare documented use of IFN-α for CAEBV and concomitant HLH with sustained remission.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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