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Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis presenting with acute sensorineural hearing loss: a case report and review of the literature

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SUMMARY

Epstein-Barr virus-associated haemophagocytic lymphohistiocytosis (EBV-HLH) is a life-threatening catastrophic and rarely seen complication of EBV infection especially in adults. While typical presentation of EBV infection is easily diagnosed as mononucleosis syndrome in teenagers and adults, some atypical clinical presentations may be challenged. We did not encounter any patient presenting with sudden sensorineural hearing loss associated with EBV infection in our English medical literature research (1966-2016). In this study, we report an adult patient who was complicated with EBV-HLH under high dose steroid therapy after diagnosis as sensorineural hearing loss. Our aim is to emphasise the atypical presentation of EBV infection and to discuss steroid therapy complication in sensorineural hearing loss that had been simply defined as idiopathic.

Keywords: Epstein Barr virus, hearing loss; haemophagocytic lymphohistiocytosis, steroid.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening clinical condition caused by excessive immune responses that result in tissue destruction [1]. Cytopenia, elevated liver enzymes, high serum ferritin levels, hypertriglyceridemia, and hypofibrinogenemia are seen as laboratory abnormalities in HLH patients. Clinical features of HLH include fever, hepatosplenomegaly, lymphadenopathy, neurological symptoms (convulsions, cranial nerves involvement), and skin manifestations [2]. While the primary form of HLH occurs due to an underlying genetic disorder in early childhood, the secondary form is associated with diverse conditions ranging from hematological malignancies to autoimmune diseases and viral infections [3]. Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) is a catastrophic and rarely seen complication of EBV infection [4]. The common EBV infection is generally diagnosed as a mononucleosis syndrome in teenage and adults, so atypical presentations may pose a clinical diag-

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nostic challenge [5]. As to whether concomitant or a previous viral infection such as herpesviruses, parainfluenza virus, and influenza may play a role in SSNHL remains controversial [6]. In a clinical trial that evaluated 48 SSNHL patients plasma samples, acute EBV infection seropositivity was detected in 3 (6,25%) patients [7]. However, to the best of our knowledge, there has not been any report on EBV infection associated with sudden sensorineural hearing loss (SSNHL) in the medical literature. In this study, we described an adult patient who developed EBV-HLH as a complication while under high dose steroid therapy and diagnosed with SSNHL afterward. We aim to emphasize on the atypical presentation of EBV infection and discuss its association with an idiopathic etiology of SSNHL.

CASE REPORT

A 43-year-old male was admitted to the emergency department with complaints of high fever, weakness, blurry vision and diplopia, decreased hearing, ear fullness, and tinnitus in both ears. He had experienced sudden hearing loss in his both ears a month before hospitalization, but no etiologic factor associated with the hearing loss had been identified. Hearing loss did not resolve despite the use of daily 1mg/kg steroid and hyperbaric oxygen for 20 days after which it occurred in the right ear as well. He also reported a long lasting fever resistant to conventional antibiotic therapies for two weeks before hospitalization.

Physical examination findings were significant for fever and splenomegaly but no signs of enlarged lymph nodes. Laboratory examination showed pancytopenia (hemoglobin: 10.1 g/dl, white blood cells: 1,5 cells/L, lymphocytes: 0,79 cells/L, platelets: $122x10^3$), ferritin: 25.500 ng/ml (normal range 30-400 ng/ml), creatinine: 2,28, AST: 117 U/L, ALT: 61,8 U/L, LDH: 751 U/L, total bilirubin: 1,72 mg/dL, direct bilirubin: 1,41 mg/dL, and a number of atypical cells with lymphomonocytoid appearance on peripheral blood smear. C-reative protein (CRP), and procalsitonin (PCT) were in normal range. Hepatitis markers, EBV VCA IgM, CMV IgM, anti-HIV antigen/antibody, antinuclear antibody tests were negative.

The patient was consulted with an otolaryngology specialist due to hearing loss complaint. On physical examination, bilateral tympanic membranes and ear canals were normal, Rinne test was positive for both ears, and the Weber test showed no lateralization. Pure tone audiometry (PTA) revealed bilateral sensorineural hearing loss (SNHL) starting at 4 kHz and reaching 70 dB at 8 kHz.

The patient had blurry vision and diplopia, but cranial computerized tomography findings were non-contributory. Cerebrospinal fluid analysis after lumbar puncture showed lymphocytosis and hemophagocytosis. Bone marrow aspiration and biopsy showed proliferation of either immature or mature histiocytic cells with prominent hemophagocytosis. Liver biopsy results were consistent with features of hemophagocytosis. There were diffuse bone infiltrations on Positron emission tomography-CT (PET-CT) imaging. Bone biopsy revealed histiocytic proliferation.

The patient was started on an HLH-2004 protocol with active transfusion support. The initial response to therapy was satisfactory. However, he experienced septic shock, and peripheral blood cultures grew *Klebsiella pneumoniae* after ten days. During the same time, he developed herpetic lesions in the genital area. Treatment with antibiotics chosen according to the antimicrobial susceptibility was initiated. On repeated blood analysis EBV VCA IgM, CMV IgM HSV-1 IgM, and HSV-2 IgM were negative, but EBV VCA IGG, EBV-EBNA and EBV-EA antibody were detected as positive. EBV-DNA PCR was positive (6.498.762 copies/mL).

Since EBV DNA was detected as positive, rituximab was given once weekly, and intravenous immunoglobulin was added to continued therapy. Following a brief period of improvement in his clinical condition, the patient had rectal bleeding. Both endoscopic and colonoscopic evaluations did not show any bleeding sources. His liver function deteriorated while his recorded total bilirubin levels increased to 25 mg/dl. A second bone marrow biopsy was performed, and its results showed EBV-positive T-cell lymphoproliferative disease of childhood with hemophagocytic lymphohistiocytosis. From these results, the patients was diagnosed with Epstein-Barr Virus-Associated Hemophagocytic Syndrom-induced sudden SNHL. The patient expired within three months of hospitalization.

Other similar and contrasting cases in the literature
EBV VCA- IgM negativity does not rule out acute EBV infection. Elazar et al. reported six EBV-HLH patients confirmed by EBV DNA PCR, but four of the six were seronegative as seen in our patient [8]. Steroid therapy for EBV mononucleosis syndrome is controversial [9]. A patient who presented with odynophagia and altered voice while under physiological-dose steroid therapy for congenital adrenal hyperplasia developed hypoglossal nerve palsy when the therapeutic steroid dosage was increased. Subsequently, the patient was diagnosed with EBV mononucleosis syndrome [5]. Brandfonbrener et al. compared lymphocyte subtypes in steroid treated EBV mononucleosis patients with an untreated group [10]. They found that lymphocyte subtypes were similar within the non-infected control group of the steroid treatment arm. T lymphocytes play a major role in EBV infection. Meanwhile, EBV latent membrane protein activation of T lymphocyte or EBV-infected T lymphocytes clonal proliferation may cause EBV-HLH [11]. EBV-HLH was reported after sulphasalazine associated hypersensitivity syndrome that led to EBV reactivation in a patient [12]. In an another case, EBV-HLH developed in a patient treated with high-dose steroid therapy for Polyarteritis Nodosa [13].
In contrast, Gardiner et al. reported a patient with EBV mononucleosis preceded with EBV-HLH who was successfully treated with a high dose of steroid therapy [14].

DISCUSSION

All herpesviridae family members can reproducibly create a latent infection and reactivate spontaneously in immunocompetent patients or under immunosupression. HSV reactivations as presented with orolabial and/or genital lesions or VZV reactivation in elderly people which is commonly called as shingles are frequently seen in immunocompetent patients. However, EBV associated reactivation (from latent to lytic infection) is related with oncogenesis such as Burkitt lymphoma, Hodgkin disease, nasopharyngeal carcinoma, gastric cancer, NK/T cell lymphoma, and AIDS- or transplantation-associated lymphomas [15]. Additionally, we know that primary hemophagocytic lymphohistiocytosis triggered by EBV infection in early childhood are well-known clinical manifestations due to decreased natural killer activity or perforine gene mutations [16]. Unresolved EBV infection can lead to catastrophic hemophagocytosis in adult patients [17]. We could not seek our patient's genetical analysis to detect mutational patterns. We did not find any EBV related malignancy or intense immunosupression in our patient that is why we regarded our case as an EBV infection not a reactivation.
EBV commonly causes mononucleosis syndrome in adults and may affect any organ system that has been associated with different disease manifestations [15]. Particularly, the neurological manifestation of EBV infections is not well described in the medical literature. Neurologic involvements can include Guillain-Barré syndrome, facial nerve palsy, meningoencephalitis, aseptic meningitis, transverse myelitis, peripheral neuritis, and optic neuritis [15]. These clinical conditions are called idiopathic generally after the main causes are excluded. The significant clinical benefit of antiviral and steroid therapy has lacked for EBV-induced mononucleosis or its atypical forms [9]. EBV is a well-defined initiating cause of hemophagocytic lymphohistiocytosis (HLH) in childhood and adult patients [4]. On the other hand, steroids may play a role in the treatment of secondary HLH. However, it may trigger an infection related to HLH. Similar to the case described above, the timing of therapy, dosage, and susceptibility of the host are unknown issues for the steroid therapy paradox in HLH.
In conclusion, in similar cases, EBV may present with an atypical presentation or specifically a neurological presentation. Moreover, it should be kept in mind that SSNHL is a rare complication of EBV-related neuropathic involvement.

Conflict of interest
There is no conflict of interest

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