Axonal Polyneuropathy as an Unusual Manifestation of Acute Epstein-Barr Virus Infection in an Adult

Keren Kremer MD[1], Michal Dekel MD[2], Avi Gadoth MD[3], Giris Jacob MD DSc[1] and Jacob N. Ablin MD[1]

Departments of [1]Internal Medicine F and [2]Infectious Diseases, Internal Medicine Division, and [3]Department of Neurology, Tel Aviv Sourasky Medical Center, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Epstein-Barr virus (EBV) is a widely disseminated herpes virus spread by intimate contact between susceptible persons and asymptomatic EBV shedders. Primary infection, although often asymptomatic, results in lifelong infection, kept in check by the host immune system. In some cases, primary infection can result in infectious mononucleosis (IM) [1]. EBV has been associated with a wide range of acute neurologic diseases in children [2]. In adults it has been implicated in the etiology of several neurologic conditions, including meningitis, encephalitis, optic neuritis, and more. We describe here an adult patient who developed symptomatic primary EBV infection with unusual neurologic manifestations.

PATIENT DESCRIPTION

A 60 year old woman was hospitalized following 4 days of diffuse abdominal pain. The patient suffered an episode of sore throat, fever and night sweats 2 weeks prior to admission and had been empirically treated with amoxicillin/clavulanate. Physical examination revealed bilateral tonsillar exudate and a weakly positive Murphy sign. The rest of the examination was normal. Laboratory tests demonstrated lymphocytosis 4.9 10^3/µl (normal range 1.2–3.0), elevated lactate dehydrogenase levels 844 U/L (208–378), mildly elevated levels of serum aspartate transaminase 103 U/L (7–40), alanine transaminase 184 U/L (5–35), gamma glutamyl transferase 221 U/L (6–28), alkaline phosphatase 219 U/L (25–100) and C-reactive protein 44.3 mg/L (0.00–5.00). Urinalysis revealed elevated protein levels of 200 mg/dl (0.0–15.0), without leucocytes or nitrites. Abdominal computed tomography (CT) demonstrated signs of mild transverse colitis and an enlarged gallbladder containing a stone.

Abdominal symptoms gradually resolved over 3–4 days, while new symptoms evolved, including bilateral foot and palm paresthesia, pain in the lower limbs, and gait disturbance. Walking became increasingly difficult and unstable as lower limb numbness increased. Neurologic examination revealed normal eye movements, symmetric face and preserved facial sensation. Motor strength was 5/5 in all four extremities but patellar and Achilles tendon reflex were absent. General dysesthesia was noted. Cerebellar function was preserved, but hesitated gait was reported and the patient found it difficult to walk on tiptoes and heels. Viral serologies revealed highly positive IgM antibodies against EBV. Serum polymerase chain reaction (PCR) for EBV was positive. Epstein-Barr nuclear antigen (EBNA) IgG was negative. Serology for cytomegalovirus, human immunodeficiency virus, and hepatitis B and C were negative. Cerebrospinal fluid (CSF) analysis revealed pleocytosis with a cell count of 22 leukocytes (90% lymphocytes) and 12 red blood cells. Protein level was 215 mg/dl (12–60) and glucose 69 mg/dl (serum glucose 101 mg/dl). The CSF culture and cytology were negative. CSF PCR for EBV was not detected. Electromyography/nerve conduction velocity (EMG/NCV) studies demonstrated low amplitude sensory nerve action potential and low compound motor action potential with normal myographic activity, results interpreted as representing axonal polyneuropathy.

The patient was consequently diagnosed as having primary EBV infection with neurologic expression and was treated with valcyclovir for 14 days, with pregabalin for pain. Gradual amelioration of neurologic symptoms was observed, although she continued to complain of numbness and paresthesia 3 weeks after the appearance of symptoms.

COMMENT

Infectious mononucleosis (IM) is the most common clinical manifestation of EBV infection. IM often begins with malaise, followed several days later by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. Atypical lymphocytosis is a frequent finding [1]. EBV primary infection in adults is rare, and elderly patients have significantly less frequent occurrences of pharyngitis, lymphadenopathy and splenomegaly compared with young adults [3]. EBV can affect virtually any organ system and has been associated with such diverse disease manifestations as pneumonitis, myocarditis, pancreatitis, parotitis and pericarditis [1]. Neurologic complications of IM, although well recognized, are rare. Their incidence has been

reported to be between 0.37% and 7.3%. Previously reported neurologic syndromes include meningitis, encephalitis, Guillain-Barre syndrome (GBS), optic neuritis, cranial nerve palsies, transverse myelitis and cerebellar ataxia. EBV-related psychosis has also been reported, such as "Alice in Wonderland" syndrome (metamorphopsia) [2].

Peripheral neuropathy may be associated with EBV infection. Several mechanisms have been postulated. EBV can directly invade the peripheral nervous system, usually resulting in focal or multifocal neuritis rather than polyneuropathy [4], or it may cause an immune mediated neuropathy such as GBS and (possibly) chronic demyelinating neuropathy [5]. EBV infection has been reported to precede GBS so frequently that the association appears authentic. Since most adults become infected with EBV, IgG antibodies to this virus are ubiquitous. Strict criteria for serologic diagnosis of primary infection, as compared to reactivation, have therefore been developed [5]. While GBS is considered to be the result of infection-induced autoimmunity (and is treated accordingly), it is difficult to determine with certainty whether the unusual neuropathy observed in the current case represents another variation of autoimmune neuropathy or rather a direct viral "neuronitis." This distinction carries obvious implications regarding the management of such patients, i.e., choosing between immune suppressive and antiviral treatment (and possibly both).

The use of corticosteroids in the treatment of EBV-induced IM is controversial. Corticosteroids are generally given to patients with impending airway obstruction, profound thrombocytopenia or hemolytic anemia. Some practitioners also give glucocorticoids or immunoglobulins (IVIG) to ameliorate severe constitutional symptoms, but this practice is controversial. The use of B cell-depleting treatment such as rituximab has been reserved for life-threatening fulminant IM in patients suffering from X-linked lymphoproliferative disease, a congenital immunodeficiency characterized by an abnormal immune response to primary EBV infection. The use of acyclovir has shown a reduction of EBV in the oral compartment, but clinical efficacy was not demonstrated. There are few data in the literature regarding the use of valacyclovir in acute IM, but some reports suggested symptomatic improvement [1]. Primary EBV infections rarely require more than supportive therapy. While GBS is considered a serious life-threatening condition requiring intensive care, the indications for specific antiviral treatment in rare cases of milder neurologic involvement of EBV infection are less clear. In the current case, in which axonal polyneuropathy developed rapidly during the course of acute EBV infection in an adult, we chose to administer antiviral treatment despite the lack of any known underlying immune suppression.

EBV infection has been extensively studied in terms of its possible pathogenic role in the development of autoimmune disorders as well as lymphoproliferative disorders and other malignancies. In view of the unusual and severe presentation of the case described, increased vigilance and long-term follow-up may be indicated to rule out such developments.

Atypical neurologic manifestations of EBV should be considered in the differential diagnosis of patients presenting with the combination of a compatible febrile disorder and suggestive neurologic symptoms. Although EBV does not constitute a life-threatening disorder, antiviral treatment may be considered in this unusual systemic manifestation of acute EBV infection.

Correspondence
Dr. J.N. Ablin
Dept. of Infectious Diseases, Tel Aviv Sourasky Medical Center, Tel Aviv 69234, Israel
Phone: (972-3) 697-3668
Fax: (972-3) 697-4987
email: Jacobab@tlvmc.gov.il

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