CASE REPORT

A Novel Case of Chronic EBV Infection Mimicking Polymyositis with Hemophagocytic Syndrome

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SUMMARY

Background: The combination of EBV associated myositis and hemophagocytic syndrome is very rare and is lacking sufficient clinical study. The authors describe a novel case of myositis and hemophagocytic syndrome in a 17-year-old boy with chronic EBV infection.

Methods: Hematological and immunological blood investigation, bone marrow aspirate, labial and muscle pathological test and immunohistochemistry staining of Epstein-Barr virus-encoded small RNA (EBER) were performed.

Results: The patient was started on prednisolone and methotrexate for treatment of the myositis and his symptoms decrease for 2 months and rapidly progressed with worsening cytopenia, liver function tests, and coagulation profile. The patient was treated empirically with intravenous antibiotics and human immunoglobulin G. He developed fulminant hemophagocytic syndrome and passed away due to multiorgan failure 14 months after the onset of the disease.

Conclusions: Performing a limited IHC with EBER will be helpful to diagnose EBV infection involving muscle. EBV infection as a prognostic factor of myositis needs further studies.


KEY WORDS

Epstein-Barr virus, polymyositis, hemophagocytic syndrome

CASE REPORT

A previously healthy Chinese 17-year-old boy first presented in May 2018 with unregularly symmetrical muscle twitches and stiffness of the upper or lower limbs which disappeared a few minutes to half an hour later without medication. He had acne-form eruptions and edema of the face with migraine headache, oral ulcers, and transient low-grade fever. In January 2019, he complained of right forearm swelling. He was otherwise feeling well with no systemic symptoms. His family history was normal.

Laboratory investigations at this point revealed a bicytopenia with total white cell count 2.62 x 10^9/L (NEUT% 66.4%), Red Blood Cell count 3.36 x 10^12/L, Platelet 217 x 10^9/L, abnormal liver function tests AST...
372 U/L, ALT 138 U/L, ALB 36.4 g/L, a raised lactate dehydrogenase (LDH) 1,160 U/L, and raised muscle enzymes (creatine kinase 14,889 U/L and myoglobin 1,359.0 U/L). C-reactive protein was not raised and blood culture performed showed no bacterial growth. A $^{[18F]}$ fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) scan performed and did not reveal any significant lymphadenopathy or organomegaly. However, there were diffuse multiple FDG-avid muscle lesions scattered in the neck, chest, waist, buttock, and limbs. SUVmax was 2.6 (right lateral thigh muscle, Figure 1A). Muscle density of lower extremities was decreased, and a small amount of liquid density shadow was seen around the posterior leg muscle. Small nodules were seen on bilateral skin of his face and the larger one was about 5 x 2 mm (SUVmax 2.0). Further investigations of EBV antibody panel revealed elevated serum immunoglobulin titers of CA-IgG (> 200), EA-IgG (139), EBNA-1-IgG (53). Further investigations revealed negative results for Jo-1 antibody, hepatitis B surface antigen, hepatitis B core IgM antibody, hepatitis C virus antibody, and hepatitis A IgM antibody. A biopsy of the left leg muscle and the labial gland was subsequently performed and revealed a multifocal, chronic inflammatory infiltration of small lymphocytes and neutrophils. The atrophic muscle fibers contain slightly basophilic cytoplasm and is consistent with a diagnosis of myositis (Figure 1B). Bone marrow (BM) examination done at this point did not reveal any morphologic evidence of lymphoma, and 16 items of myositis related serum antibody were negative. Plenty of plasma cells and lymphocytes infiltration aggregate in the interstitium (> 50 foci in one field) of the labial gland and salivary gland (Figure 1D).

He was started on prednisolone and methotrexate for treatment of the myositis and his symptoms decrease for 2 months. Beginning July 2nd, 2019, his symptoms rapidly progressed with worsening of new onset of fever and jaundice for more than 1 month with T<sub>max</sub> 39°C. At this point, EBV DNA level from the peripheral blood was significantly increased at 5.67 x 10<sup>4</sup> copies viral DNA/mL plasma. The leg muscle and labial gland biopsy was reviewed. The added immunohistochemistry staining revealed co-expressed Epstein-Barr virus-encoded small RNA (EBER) (Figure 1C, E). Taken together, findings are consistent with EBV infection. We diagnosed his disease as chronic active EBV infection from clinical findings and the antibody titer particular to EBV, EBER in the tissue and viral DNA in the blood. The patient’s clinical condition deteriorated with worsening cytopenias, liver function tests, and coagulation profile. Patient was treated empirically with intravenous Meropenem, Caspofungin Acetate, and human immunoglobulin G. A repeated BM examination showed significant hemophagocytic activity. He got fever every day during the last days. B ultrasound revealed splenomegaly (15.3 cm x 5.7 cm) and hepatomegaly change. Blood test revealed ANC 0.77 x 10<sup>9</sup>/L (<1.0 x 10<sup>9</sup>/L), HB 86 g/L (<90 g/L), PLT 91 x 10<sup>9</sup>/L (<100 x 10<sup>9</sup>/L), triglyc-eride 3.55 mmol/L (≥ 3.0 mmol/L), fibrinogen 0.6 g/L (<1.5 g/L), serum ferritin 3,112.4 mg/L (≥ 500 mg/L), LDH 930 U/L, muscle enzymes (creatine kinase 480 U/L and myoglobin (321.2 U/L), direct bilirubin 171 μmol/L, total bilirubin 202 μmol/L. Hemophagocytic syndrome related gene tests were negative. He developed fulminant hemophagocytic syndrome, rapidly deteriorated and passed away due to multiorgan failure on July 21st, 2019.

**DISCUSSION**

Infection with Epstein-Barr virus (EBV) is common and induces a broad spectrum of illness. Approximately 90 to 95 percent of adults are EBV seropositive worldwide; however, in a large public university in the United States, the seroprevalence of EBV antibodies among entering freshman declined from 64 percent in 2006 to 52 percent in 2012 [1]. The popularity of myositis or hemophagocytic syndrome is very rare and unknown until now. Not to say the combination of EBV associated myositis and hemophagocytic syndrome.

In this case, however, despite a clinical picture of myositis, the cause of the muscle involvement was due to infiltration by EBV positive lymphocytes. EBV infection characteristically involve infectious mononucleosis. There have been about 5 cases of B cell [2-7] lymphoma and 8 cases of T cell [8,9] lymphoma reported before which were both associated with EBV and myositis as well as some gastric cancer, thyroid cancer, and nasopharyngeal carcinoma [10-12]. Also, there are a few cases associated with muscle pathological evidence of myositis with chronic EBV infection [13,14]. Almost all these patients died because of infection, DIC or multiorgan failure. What is striking in this case is that our patient had extensive and generalized muscle involvement and also hemophagocytic syndrome. Our patient also had an extremely fulminant clinical course and he died just 8 months after initial presentation of the forearm swelling. This case also highlights several clinicopathologic diagnostic challenges. Clinically, this unusual case of EBV infection mimicked polymyositis and is firstly presented with initial muscle involvement and developed into hemophagocytic syndrome. The unusual clinical course of this patient offers different, although to a great extent speculative, explanations regarding the pathogenesis and interplay between EBV, myositis, and hemophagocytic syndrome. Early diagnosis is important as EBV infection with predominant muscle involvement is associated with a fulminant clinical course. Histologically, the diagnosis on the muscle biopsy was challenging for several reasons. Firstly, the lymphoid infiltrate comprised mainly small lymphocytes without significant atypia. Secondly, this patient had no immune-disorder history. Thirdly, there were no autoantibodies including anti-Jo-1 antibodies, or extramuscular symptoms suggestive of polymyositis or dermatomyositis. Hence, performing a limited IHC without EBER, will
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Figure 1. (A) PET/CT scan showed multiple intensely FDG-avid muscle lesions scattered throughout the body, including muscles of the neck, chest, waist, buttock and limb regions, SUVmax was 2.6 (right lateral thigh muscle). (B) Left leg muscle lesions. Lesions revealed a multifocal, chronic inflammatory infiltration of small lymphocytes and neutrophils. The atrophic muscle fibers contain slightly basophilic cytoplasm and was consistent with a diagnosis of myositis (hematoxylin and eosin, 200*magnification). (C) EBER (200*magnification) positive cells scattered between the muscle fibers. (D) Labial and salivary gland lesions revealed plenty of plasma cells and lymphocytes infiltration aggregate in the interstitium (> 50 foci in one field, hematoxylin and eosin, 200*magnification). (E) EBER (200*magnification) positive cells scattered in the interstitium of the labial and salivary gland.

not be helpful to diagnose EBV infection involving muscle. Although a variety of therapeutic modalities have been applied, prolonged severe EBV infection is unlikely to be successfully treated. It is not known what could be the exact cause of myositis in these patients. In 1986 Walker and Jeffrey searched the protein chain sequence mimicry of EBV and muscle proteins and put forward a hypothesis that may be the mechanism of the autoimmunity that invoke the virus associated myositis [15]. It may be a direct virus-induced toxicity or, on the other hand, mediated by a possible myotoxic effect of the antibodies elaborated as a consequence of the EBV infection. We hope future research will throw some light on this issue.

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The author reports no conflicts of interest in this work.

References:


