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EPSTEIN-BARR VIRUS INDUCED MYOSITIS IN A PATIENT WITH MITOCHONDRIAL DIABETES

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ABSTRACT

Epstein-Barr virus (EBV) is a rare but well-known trigger for acute myositis. Diagnosis is primarily based on the clinical presentation and an accounting laboratory profile. Patients with mitochondrial dysfunction are potentially at a higher risk of myopathic exacerbations upon exposure to acute insults. This is due to the high energy requirements of myofibers and their reliance on sufficient mitochondrial performance. Hence, any mitochondrial insult can compromise the function of myofibers. This has implications on the management of people with pre-existing mitochondrial dysfunction, with scope for preventative measures and a lower threshold for diagnosis of myopathies. Usually, management is limited to conservative measures. Medications which predispose to muscle injury need to be withheld during the acute episode and their long-term need reviewed based on a risk-benefit analysis. Here, we present a case of acute EBV-induced myositis on a background of maternally inherited diabetes and deafness and chronic statin intake.

KEYWORDS

Mitochondrial diabetes, maternally inherited diabetes and deafness, MIDD, Epstein-Barr virus, myositis, statins

LEARNING POINTS

- Myositis can be an infrequent complication of Epstein-Barr virus infection.
- The presence of mitochondrial dysfunction could potentially increase the risk of myositis. In patients with mitochondrial diabetes a prolonged course of acute myositis symptoms can be expected.
- Statins should be discontinued during an acute myositis episode in patients with mitochondrial diabetes but can potentially be re-initiated (with preference to hydrophilic ones) after episode resolution at the lowest possible dose.

INTRODUCTION

Myositis refers to a heterogenous group of diseases resulting in inflammation of myofibers. It can have a primary aetiology (idiopathic inflammatory myopathy) or can occur secondary to external triggers. Such triggers might involve exposure to toxins, drugs, infections, connective tissue disorders, inflammatory myopathies, thyroid pathologies and malignancies[1]. Alternatively, myositis can be categorised

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into acute, i.e. occurring suddenly and resolving within a few days, and chronic, referring to inflammation that persists over a period of several weeks to months.

There exists a wide spectrum of presentations, ranging from mild myalgia to life-threatening rhabdomyolysis. Diagnosis tends to be heavily clinically based, in conjunction with an indicative laboratory work-up. In line with this, creatinine phosphokinase (CPK) is considered a common biomarker for muscle pathology, since it is an enzyme primarily found in muscle tissue. CPK is released into the bloodstream during periods of muscle injury when the sarcoplasmic reticulum membrane within myocytes becomes permeable, leaking intracellular enzymes.

Infections are one of the most well-known causes of secondary myopathies, with the most common infections presenting with myositis being viral. Viruses involved include Epstein-Barr virus (EBV), influenza, enteroviruses, herpes simplex virus (HSV), cytomegalovirus (CMV) and coronavirus disease (COVID-19) among others. The pathogenesis of infection-induced acute myositis is not yet clear but may likely involve either an autoimmune antigenic response (molecular mimicry) or a direct pathogenic invasion.

EBV belongs to the herpesvirus family and is a double-stranded deoxyribonucleic acid (DNA) virus which infects B lymphocyte cells, by utilising the envelope glycoproteins to attach and enter host cells. It is estimated that EBV infection has a prevalence of more than 90% in the adult population worldwide[2]. However, in most immunocompetent individuals, presentation tends to be subclinical or result in transient acute illness. Acute myositis following EBV infection has only been documented as a rare complication.

We describe EBV-induced myositis in a patient with a background of maternally inherited diabetes and deafness (MIDD) who was on long-term statin treatment. To our knowledge, this is the first reported case of a patient with mitochondrial diabetes presenting with acute myositis.

CASE DESCRIPTION

The patient was a 33-year-old Caucasian male previously reported in connection with his MIDD[3]. He had been formally diagnosed with MIDD at the age of 31 following a presentation of atypical diabetes with a low body mass index (BMI), negative autoantibody screen and detectable C-peptide levels. Following diagnosis, he had been established on a basal-bolus insulin regime which normalised his glycaemic control. His other medications included telmisartan 40 mg daily, co-enzyme Q10 and atorvastatin 10 mg daily.

The patient presented to the outpatient clinic complaining of pyrexia, fatigue and generalized myalgias that had begun almost 24 hours previously. Detailed history did not reveal any possible precipitants and there had been no recent changes in his medications or lifestyle. His past medical history included microalbuminuria, trigeminal neuralgia, hyperlipidaemia and brachial plexus palsy. He had never reported any such previous episodes in the past.

Laboratory work-up revealed acute transaminitis with mild lymphocytosis and monocytosis as well as thrombocytopenia. His inflammatory markers were elevated, and CPK was also significantly elevated at 908 units/l *(Table 1)*. In line with the evidence of acute transaminitis and raised CPK, an extensive infection panel was performed for common precipitants of acute muscle and liver injury which revealed a positive result for Epstein Barr IgM antibodies. Hepatitis, human immunodeficiency virus and cytomegalovirus panels were all negative. In line with the clinical presentation of generalised acute myalgia and fever, along with evidence of acutely raised CPK, serum transaminases and EBV IgM positivity, the differential diagnosis included acute inflammatory myopathy secondary to EBV infection, mitochondrial myopathy secondary to MIDD with an infectious acute trigger, statin-induced myopathy and idiopathic inflammatory myopathy. A differential of systemic pathology in its early stages was also considered.

Due to the age of onset of myopathy, congenital causes were lower down on the differential list. Endocrine mediated myopathies were also deemed less likely since the patient's thyroid function and diabetic control were optimised. Moreover, there was no suggestion of adrenal dysfunction. His electrolytes were also within normal range, making

Investigation	Baseline	Acute episode	2 weeks later	8 months later	1 year later	2 years later	Normal ranges
Creatinine phosphokinase (units/l)	88	908	66	78	82	72	21-215
Platelets (×10^3/l)	202.000	90.000	Not tested	Not tested	234.000	244.000	150.000-400.000
White blood cell count (×10^3/l)	7.38	6.1	Not tested	Not tested	9.2	9	4-10
Neutrophils (%)	59	34	-	-	50	57	40-75
Lymphocytes (%)	34	49	-	-	41	35	20-45
Alanine transaminase (units/l)	12.8	151	10	23	26.9	18.3	< 34
Aspartate aminotransferase (units/l)	9.03	151	10	17	26.9	16.0	< 31
Erythrocyte sedimentation rate (mm/hour)	10	32	Not tested	Not tested	Not tested	13	< 20

Table 1. Relevant laboratory panel before, during and after myositis episode.

electrolyte-induced myopathy less likely. Because of the known association between EBV infection and myositis and due to the evidence of acute EBV infection with raised IgM, antibodies which rise only during the acute phase of infection, it was considered that there was no need for further invasive investigations including muscle biopsy and a diagnosis of EBV-induced myositis was made. However, due to the underlying mitochondrial pathology, the possibility remains that mitochondrial myopathy might have exacerbated the presentation. In addition to this, statin-induced myopathy is a well-known complication of statin therapy with an estimated prevalence of 27.8% of patients receiving statins[4]. Hence, both the patient's underlying mitochondrial pathology and statin therapy might have contributed to the acute presentation, triggered by EBV infection.

Following diagnosis of EBV-induced myositis, symptomatic management was pursued. This involved regular analgesia with paracetamol and ibuprofen along with advice for adequate oral hydration. Moreover, statin therapy was discontinued with no other changes in medications. A repeat CPK test 2 weeks later showed normalization (66 units/l) *(Table 1)*. However, despite the fact that the fever had subsided, the patient reported that the intense muscle aches persisted for about 1 month after the initial presentation necessitating analgesic treatment. Following symptom resolution, atorvastatin was switched to rosuvastatin 10 mg daily. Ezetimibe 10 mg daily was also added in an attempt to use the minimal statin dose possible. During long-term follow-up no more myositis symptoms or CPK elevations *(Table 1)* were reported.

DISCUSSION

To our knowledge, this is the first case of EBV-induced myositis in a patient with MIDD reported in literature. Although myopathy has been reported as one of the possible complications of MIDD, albeit rare, in these cases it tends to present chronically and there have not been any specific reports of EBV-induced pathology with a background of MIDD. Nonetheless, patients with metabolic myopathies may experience triggering of their myopathic phenotypes by states of metabolic stress, one of which being infection. It is likely that this presentation is of multifactorial origin with both EBV infection, statin therapy and mitochondrial dysfunction contributing[3]. The fact that both statin therapy and his mitochondrial diagnosis had been established long before this incidence, makes it more likely that the EBV infection was the main trigger for this myositis episode. Although the pathogenesis of viral myositis is yet unclear, in many cases, muscle biopsies have revealed muscle fibre injury of different degrees on a histopathologic level.

Statins are 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors and act by reducing hepatic cholesterol synthesis and promoting serum cholesterol clearance. However, common side effects of statin therapy include myopathy. This has a multifactorial pathogenesis with mitochondrial dysfunction due to co-enzyme Q10 reduction, oxidative stress and impairment of metabolic pathways being implicated. Lipophilic statins (atorvastatin, simvastatin, fluvastatin, cerivastatin, lovastatin) seem to have a greater side effect profile compared to hydrophilic ones (rosuvastatin, pravastatin) due to higher and non-selective penetrance into muscle fibres via passive diffusion compared to carrier-mediated, selective uptake for hydrophilic ones[5]. Their excretion via the cytochrome P450 system (mainly CYP3A4) also renders them at a risk of drug-induced interactions[5].

Current consensus regarding the management of acute viral myositis recommends conservative management as first line with adequate rest, hydration and symptomatic management with analgesia and antipyretics.

Although our patient exhibited a prolonged symptomatic state, spontaneous recovery is the most common outcome thus there is no need for aggressive therapy. However, if there is no recovery in the expected time frame, further investigations are needed for any underlying pathology or autoimmune causes of myopathy with tailored treatment according to the cause.

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