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Epstein-Barr Viral Infection in a Young Healthy Female with Complicated Klebsiella Pyelonephritis: Co-infection, Causing Severe Rhabdomyolysis without Renal Injury

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Abstract

Background: Rhabdomyolysis can be caused by several factors including bacterial and viral infections. In rare cases, Epstein Barr Virus (EBV) infection can cause rhabdomyolysis. to date, there have been only 6 case reports of EBV-linked rhabdomyolysis, all of which have been associated with significant elevations in CK levels. Aggressive hydration is at the forefront of medical therapy to prevent complications, including acute renal failure.

Case Summary: Here, we present a case of a 19-year-old female with no significant medical history who presented with a complicated Klebsiella-UTI and was found to have severe rhabdomyolysis and positive EBV titer. Renal impairment did not occur despite the klebsiella-induced renal insult and the severe rhabdomyolysis caused by EBV co-infection.

Conclusion: Co-infection of EBV with other bacterial infections, as in this case with Klebsiella Pneumonia, may occur, which may obscure the diagnosis and create challenges for management of rhabdomyolysis if occurs. Clinicians should clinically suspect EBV co-infection in appropriate clinical scenarios.

Keywords: Rhabdomyolysis; Epstein-Barr virus; Creatinine
kinase; Acute kidney injury

Introduction

Rhabdomyolysis is a skeletal muscle injury that can be caused by numerous factors including viral and bacterial infections. Pathogens can cause rhabdomyolysis *via* various mechanisms including direct viral or bacterial invasion of skeletal muscle, and toxin generation in conjunction with drug therapies in the critically ill patients. Epstein-Barr Virus (EBV) can be associated with broad pathological manifestations in humans and can be rarely associated with rhabdomyolysis. The detection of such association is clinically important given that rhabdomyolysis adds to the already elevated risk of renal failure in EBV infection. Whether renal injury risk can be increased by a co-infection of EBV in a patient pre-disposed by a complicated Urinary Tract Infection (UTI) is not known. In this report, we present another example of rarity of EBV-induced rhabdomyolysis in a young healthy female patient who had a Klebsilla-UTI and EBV co-infection.

Case Presentation

A 19-year-old female with history of recurrent Urinary Tract Infections (UTI) not associated with renal defects presented with a 3-day history of subjective fever, generalized myalgias along with worsening fatigue. She had no sick contacts and denied any recent travel. She denied taking any medications. She admits drinking wine frequently. Family history is significant for diabetes mellitus in the mother. She denies history of autoimmune conditions. Physical examination was unremarkable except for fever and costovertebral tenderness, and she was started on antibiotic treatment for pyelonephritis. Chest X-ray showed no consolidation or evidence of an effusions. Her laboratory tests **(Table 1)** revealed hemoglobin of
13.3 g/dL, white blood cell count of 20.6 (7% lymphocytes, no atypical cells). Platelet count was 188.000 serum creatinine was 0.8 mg/dL, and serum high sensitivity troponin was less than 12 ng/L. Follow-up laboratory workup revealed hemoglobin of 12 g/dL, and white count improving to 7.000, while creatinine remained stable at 0.7 mg/dL. Urine culture grew klebsiella and was started on ceftriaxone and later broadened to piperacillin/tazobactam based on anti-microbial biogram and bacterial antibiotic sensitivities. Echocardiogram revealed preserved ejection fraction (68%) and no evidence of pericardial effusion. The patient continued to show significant muscle aches out of proportion to her infectious status and her hospital course was further complicated by rhabdomyolysis, which was refractory to fluid management, as evident by initial CK level of 9636 U/L which continued to trend up with a maximum level of 450,250 U/L **(Figure 1)**. She was transferred to the Intensive Care Unit (ICU) for further management and was continued on aggressive IV fluids treatment. In the ICU, aldolase level was 1190 U/L.

Workup for etiologies of severe rhabdomyolysis were done and the patient was found to have a positive IgG for EBV and EBV nuclear antigen with levels of 315 U/ml, while other causes of rhabdomyolysis were negative including TSH, urine toxicology, Anti-Nuclear Antibodies (ANA), hepatitis A IgM, Hepatitis C antibody, herpes simplex viral load by PCR, anti-mitochondrial antibody, and smooth muscle antibody. After 4 days of aggressive hydration CK levels eventually improved without worsening in renal functions. Overall, the patient had clinical improvement with subsiding of fever, recovery of myalgia, and normalization of laboratory parameters and was discharged from ICU to the floors and later was discharged home. The patient continues to be feeling well to this day. A written informed consent for presentation and publication of the case details was obtained from the patient.

	Laboratory values					
Laboratory test	**Initial**	**Day 1**	**Day 2**	**ICU day1**	**ICU follow-up***	**Pre-discharge**
Hemoglobin (g/dL)	13.3	12.5	12.6	13.4	12.3	14.8
White cell count (cells/microliter)	20.6	11.6	11.5	12.5	9.2	7.1
Lymphocytes (cells/microliter)	1.4	1.7	2.1	2.3	2.8	2.5
Platelets (cells/microliter)	188	160	163	230	280	337
Creatinine (mg/dL)	0.8	0.7	0.6	0.6	0.6	0.7
AST (U/L)	586	789	-	852	1330	167
ALT (U/L)	124	180	-	200	330	300
High sensitivity troponin (ng/L)	<12	<12	-	<12	-	-
Aldolase (normal range: ≤ 8.1 U/L)	1190	-	-	-	-	-
ANA	Negative	-	-	-	-	-
Hepatitis B core total antibody	Positive	-	-	-	-	-
Hepatitis A IgM	Negative	-	-	-	-	-
HCV antibody	Negative	-	-	-	-	-
HSV by PCR	Negative	-	-	-	-	-
Anti-mitochondrial Ab	Negative	-	-	-	-	-
Smooth muscle Ab	Negative	-	-	-	-	-
Immunoglobulin A (Normal range: 47 mg/dL-310 mg/dL)	56	-	-	-	-	-

AFP (normal range: ≤ 6.1 ng/mL)	<1.8	-	-	-	-	-
Alpha-1antitrypsin (normal range: 83 mg/ dL-199 mg/dL)	142	-	-	-	-	-
Epstein Barr nuclear antigen (normal range: <18 U/mL)	315	-	-	-	-	-

Table 1: Laboratory measurements throughout admission.

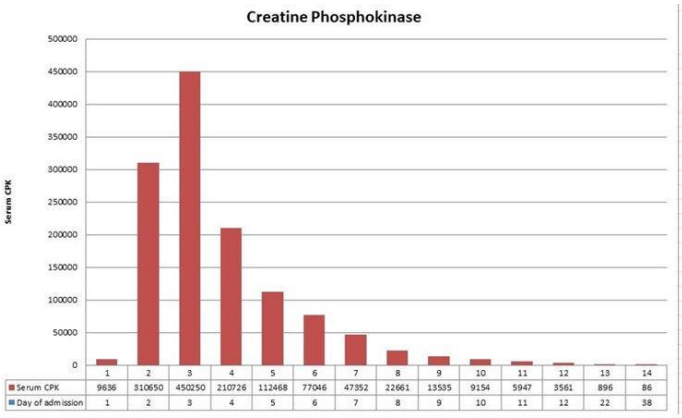

Figure 1: Serial follow-up of Creatinine Kinase (CK) levels during admission. CK levels were significantly higher and continued to increase despite appropriate hydration until day 3 when they started to decrease. CK levels normalized on the 13th day of hospitalization.

Discussion

The case presented here involved severe persistent rhabdomyolysis caused by co-infection of chronic EBV infection in a young female with complicated klebsiella UTI that did not cause any renal damage. Co-infection between EBV and Klebsiella has been previously reported **[1]**. Importantly, the suspicion of rhabdomyolysis in this patient was challenging given the non-specific nature of the constitutional symptoms which seemed to be reasonable given the obvious source of infection. The severe continuous myalgia without any history of trauma or significant muscle injury that was not responding to antibiotics or pain medications warranted CK measurements. CK level was markedly elevated despite aggressive fluid management. Importantly, the temporal course of the CK rise was paralleled with clinical and laboratory signs suggestive of the improvement of UTI, making klebsiella infection an improbable cause for rhabdomyolysis. A muscle biopsy or electro-myelogram was not done given the fact that she denied any muscle weakness or significant tenderness. Despite that the patient admitted drinking wine the day before admission, her presentation and workup were unusual for acute alcoholic myopathy due to lack muscle tenderness or swelling, absence of acute renal failure, liver injury, or any other organ involvement. The transaminitis noted during hospitalization **(Figure 2)** was proportional to CK elevation together with lack of bilirubin elevation, and predominantly ALT elevation denoted muscle rather than hepatic origin of transaminitis **[2,3]**. EBV-associated myocarditis has also been described in the literature **[4,5]**. However, given the fact the troponin was not elevated in our patient, and that there was echocardiographic changes suggestive of myocardial insult, myocarditis could be safely ruled out. Ultimately, workup of other rare causes of severe elevation of CK confirmed that the patient had a co-infection of EBV.

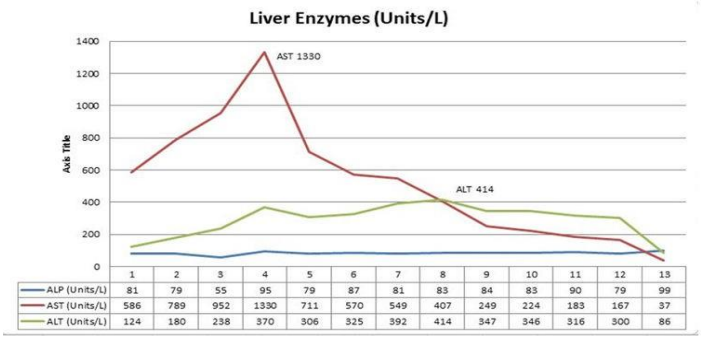

Figure 2: Serial follow-up of liver function tests during admission. Liver function tests were serially monitored and were observed to elevate and decrease in a fashion that mirrored that of the CK levels as can be seen in Figure 1.

A literature review revealed 6 cases of EBV-associated rhabdomyolysis reported to date (Table 2) 6-11 . Most of the reported cases had infectious mononucleosis, and myoglobinuria, however, similar to our patient, they had diffuse myalgia and significantly elevated CK levels, often to hundreds of thousands of units/L. Ultimately, it is uncommon to have a significant elevation of CK to such high levels without renal injury **[12]**.

Though renal injury may occur in EBV infection from dehydration, acute tubular necrosis, or interstitial nephritis, rhabdomyolysis causing renal injury is uncommon. AKI was reported in only two of the previously reported six patients, however, the rest of the patients had normal renal functions similar to our case. In our patient, a degree of AKI was suspected

given the very high level of CK and the predisposed renal insult by infection. However, our patient continued to not suffer any due to the young age, lack of concurrent use of medications AKI throughout the hospitalization. AKI was possibly avoided or drugs, and adequate oral hydration **[13]**.

Authors	Year	Age/sex	Maximum CK (IU/L)	Serum creatinine (mg/dL)	Serum aldolase	LDH (U/L)	AST (U/L)	ALT (U/L)
Osamah et al.	1995	18 year male	115,000	0.6	310	1920	-	856
McCabe et al.	1988	23 year male	482,000	Normal	1560	1560	3650	782
Friedman et al.	1986	6 year female	86,400	2.9	-	454	1764	372
Attanasi et al.	2018	1.5 year male	6723	3.6	-	2988	898	2135
Roychowdhury et al.	2007	18 year male	179,200	Normal	636	-	Normal	Normal
Current case	2021	19 year female	310650	0.8	1190	-	1330	370

Table 2: Comparison between previously reported cases and current case.

Regardless of the etiology of rhabdomyolysis, the mortality rate is 8% **[14]**, and timely management should always be priority to prevent of complications with aggressive fluid resuscitation, avoidance or removal of the offending agents **[15]**.

Conclusion

Epstein Barr Virus (EBV) is a common infection of teenagers and adolescents and can be rarely associated with life-threatening rhabdomyolysis with extreme elevations of CK. Co-infection of EBV with other bacterial infections, as in this case with Klebsiella Pneumonia, may occur, which may obscure the diagnosis and create challenges for management of rhabdomyolysis if occurs. Clinicians should clinically suspect EBV co-infection in appropriate clinical scenarios as recognizing the infection and aggressive hydration is key to clinical recovery.

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