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COMPLICATED INFECTIOUS MONONUCLEOSIS IN B-THALASSEMIA PATIENT, A RARE CASE

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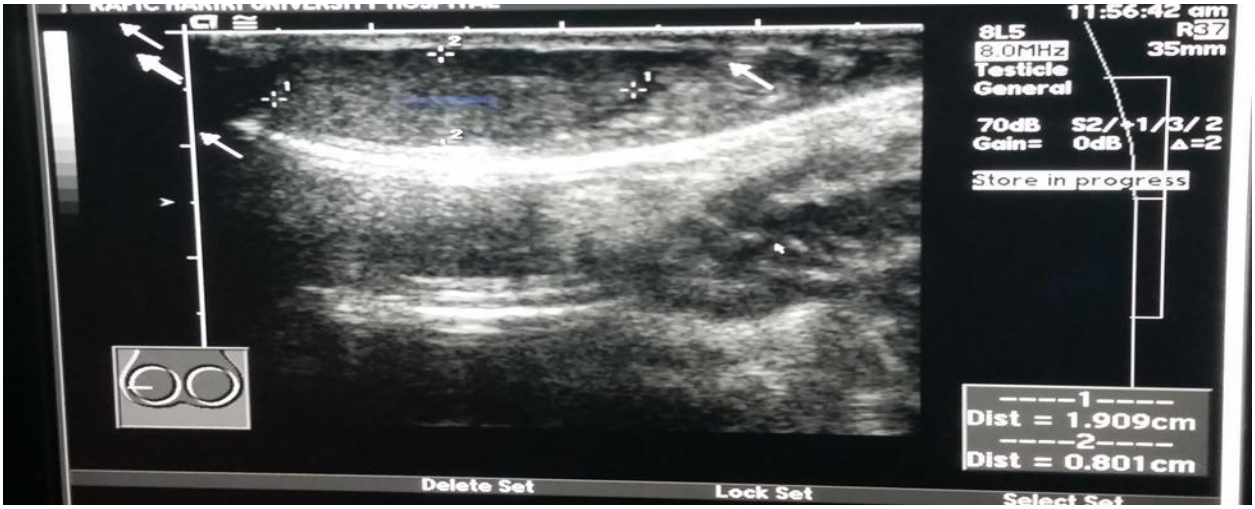
ABSTRACT
The Epstein–Barr virus (EBV is one of the most common viruses in humans. It is best known as the cause of infectious mononucleosis (Glandular Fever). Infectious mononucleosis, generally results in mild, self-limited illness characterized by fever, sore throat, and lymphadenopathy. Occasionally, EBV infection has more severe sequelae; Lymphoproliferative lesions, Hepatitis, Encephalitis, and Hemolytic Anemia have been reported. Although kidney involvement is relatively common, acute renal failure associated with EBV infection is rare. Acute Tubular Necrosis (ATN) is a kidney disorder involving damage to the tubule cells of the kidneys. This reported case is a twelve year old boy known to have β-Thalassemia major post splenectomy, on packed red blood cell transfusion, developed many complications and his kidney biopsy done and showed acute tubular injury treated with Steroid.

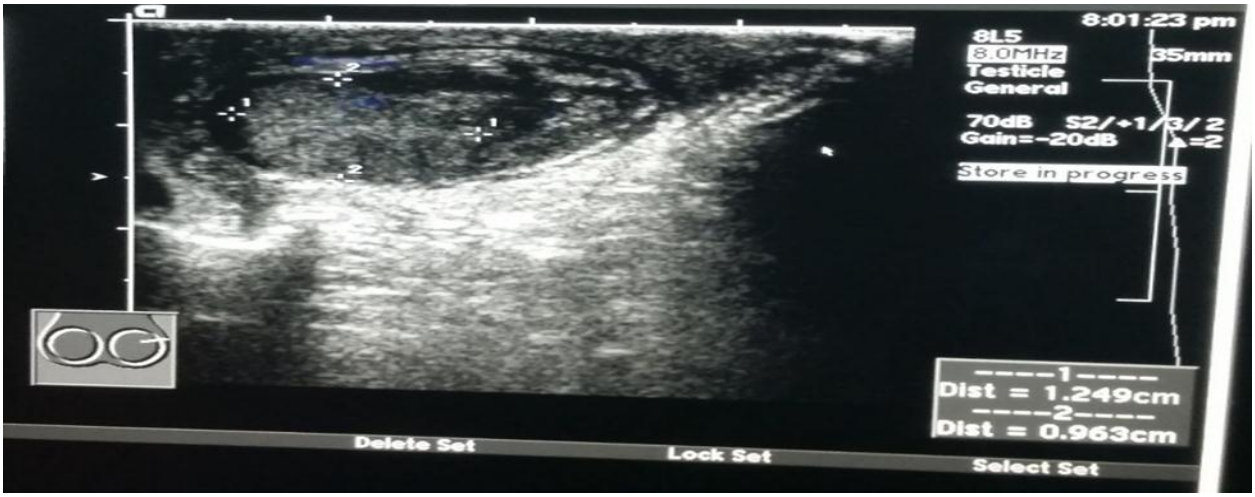
KEYWORDS: Epstein Barr Virus (EBV), Human Herpes Virus (HHV), Acute Tubular Necrosis (ATN).

INTRODUCTION
The Epstein–Barr Virus (EBV), also called human Herpes Virus 4 (HHV-4), is one of eight known viruses in the herpes family and is one of the most common viruses in humans. It is best known as the cause of infectious mononucleosis (Glandular Fever).[1] Infectious mononucleosis, generally results in mild, self-limited illness characterized by fever, sore throat and lymphadenopathy.[1] Occasionally, EBV infection has more severe squeals; Lymphoproliferative lesions, Hepatitis, Encephalitis, and Hemolytic Anemia have been reported[2,3] Although kidney involvement is relatively common, acute renal failure associated with EBV infection is rare.[3] Acute Tubular Necrosis (ATN) is a kidney disorder involving damage to the tubule cells of the kidneys. This case report presents a twelve year old boy with β-Thalassemia who developed infectious mononucleosis disease complicated by renal abnormalities.

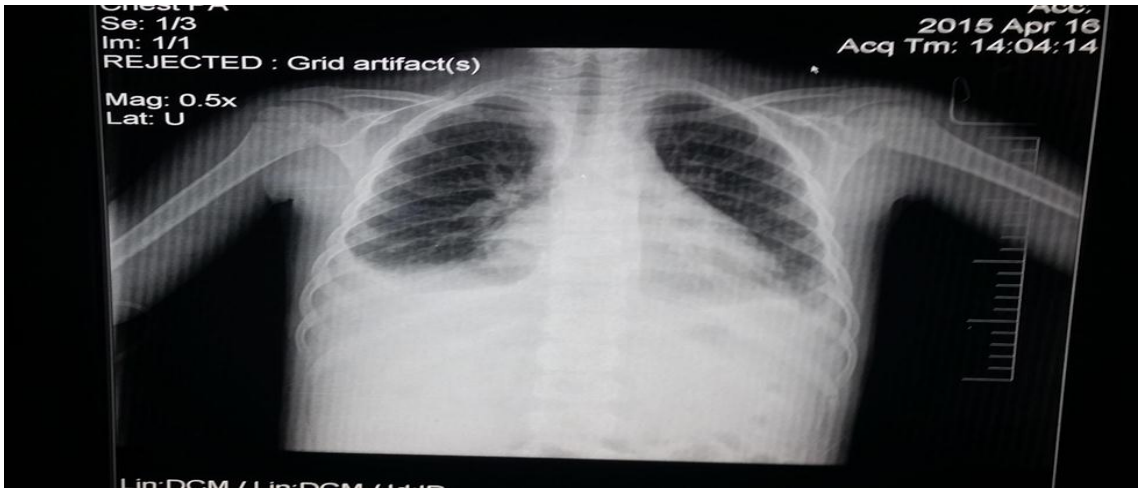
CASE REPORT
A 12-year-old boy known to have β-Thalassemia major post splenectomy, on monthly packed red blood cell transfusion presented for one day history of three episodes of not projectile non bilious vomiting, not tolerating per os intake and not improving on antiemetic drugs. He also had watery diarrhea, several episodes, not mucoid, non-bloody. No abdominal pain, no fever, no dysuria, no urinary symptoms, no respiratory symptoms, no other complaints. So the patient was admitted for IV hydration. To notice that the patient was presented two days prior to admission to the emergency room for history of ten days of right ankle pain, erythema, mild edema not improving on pain killer, but without any evidence of joint tenderness or any limitation in movement, no history of trauma, no other finding. Laboratory studies done at that time upon arrival to ER and showed: WBC 22000 109/L, Hemoglobin 6.2 g/L, ESR 40 mm/hr, Albumin 4, 4 g/dl, diagnosed as having Cellulitis and discharged on Amoxicillin-Clavulinic acid for 10 days course. At this presentation, his vital signs were normal; he was pale, lethargic, with normal limit examination except for hepatomegaly four cm below costal margin and mild suprapubic pain with soft non tender abdomen. Laboratory studies taken upon admission showed increase in WBC 36,000 109/L with left shift, Neutrophils 86%, Hb 6.8 g/L, Platelet 975 109/L, LDH 164 IU/L, CRP 12.6 mg/L, ESR 110 mm/hr, BUN, Creatinine and Electrolytes were normal. Urine analysis taken showed PH 5, Specific Gravity 1.025, numerous WBC, numerous RBC, protein 3+, Hb 3+, granular cast and Bacteria 1 +. Next day of admission the patient developed fever, with diffuse sharp abdominal pain mainly suprapubic, associated with right scrotal edema and erythema with tenderness on palpation, also had mild dysuria but no evidence of urethral discharge

and no other complaints. Urgent U/S Doppler testicles done to rule out testicular torsion and was normal.

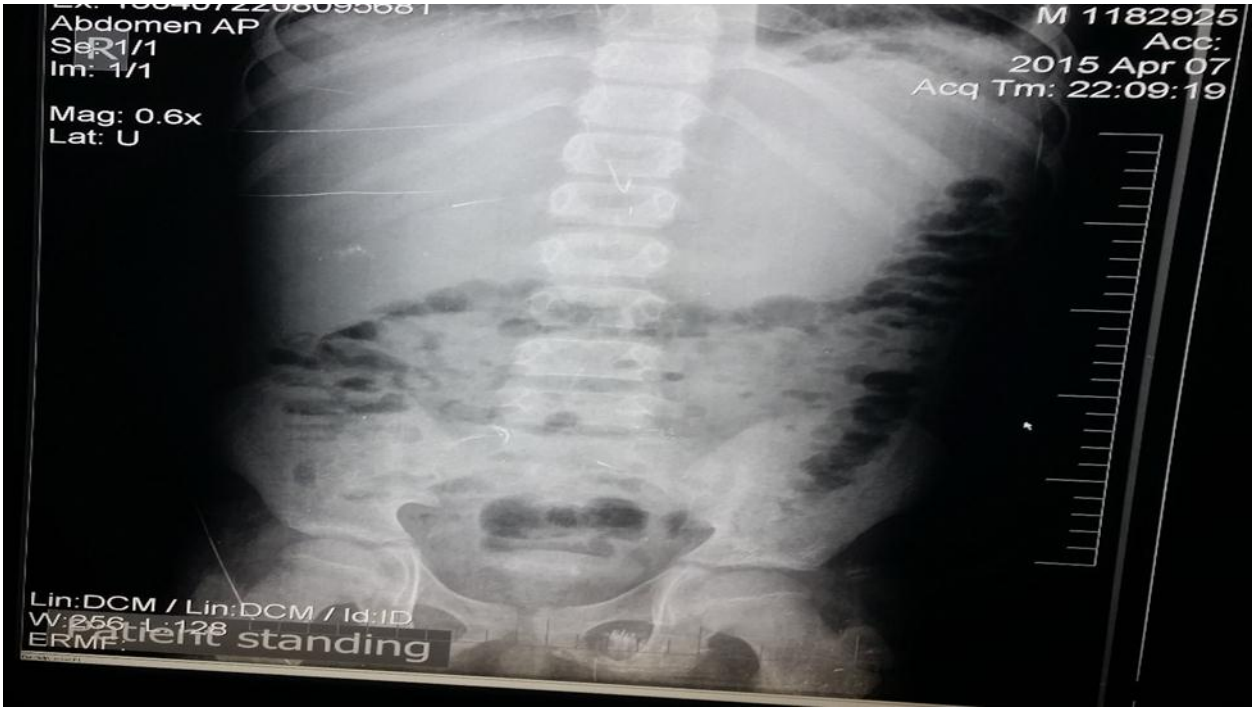


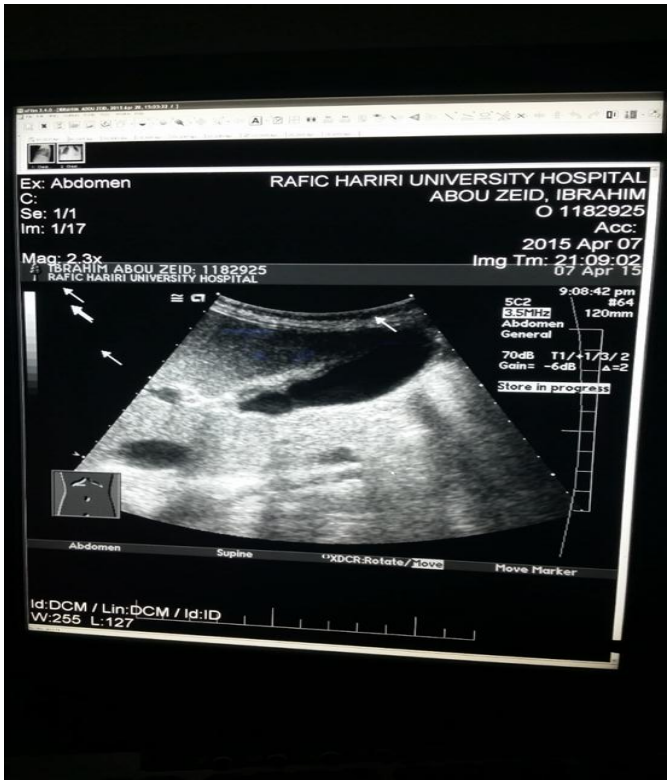


Pediatric Infectious specialist was consulted and the patient diagnosed as having Epididymo- Orchitis so he was started on Amoxicillin-Clavulinic and Cefotaxime, also developed nonspecific macular and some vesicular lesions on his bilateral lower limbs. On Third day of hospitalization the patient continued to have severe abdominal pain with high grade fever. Laboratory studies repeated WBC 30,000 109/L, Neutrophils 79%, Hb 8.8 g/L, ESR 135 mm/hr, CRP 90 mg/L, Albumin 2,5 g/dl, Total Serum Protein 6 g/dl, Amylase 21 U/L, Lipase 9 U/L, Alkaline phosphatase 88 U/L, SGPT 66 U/L and CXR showed bilateral pleural effusion.



KUB and U/S abdomen and pelvis done to reveal normal findings.





CT abdomen and pelvis done on fourth day of hospitalization was normal except for evidence of mild ascites. Pediatric infectious consultant suggested shifting antibiotics to Vancomycin and Meronem, but unfortunately despite of broad spectrum antibiotics the patient continued to have high grade fever, continuous day and night, not spacing, with severe abdominal pain not relieved by pain killer or antispasmodic. All Cultures taken during hospital stay including Urine culture, Blood culture three times two days in-between and Throat swab culture revealed no growth. The Leukocytosis, Thrombocytosis, sterile pyuria, hematuria, high ESR and CRP, mild ascites, raised the suspicion of Henoch-Shonlein Purpura (HSP), atypical Kawasaki, or Systemic Inflammatory diseases in the differential diagnosis list. Uveitis was ruled out after ophthalmologist fundoscopic

examination. Doppler Echo-Cardiograph done on Day four of hospitalization and was normal except for a trace mitral regurgitation with no evidence of coronary arteries abnormality. For HSP the lower limbs rash had fades and was not a typical non blanching purpura, stool occult blood taken was negative, but it remains in the differential. Indeed, on the fifth day of hospitalization, the patient started to have high blood pressure (Systolic 130/ Diastolic 80 mmHg), while off pain, with bilateral lower limbs pitting edema (2+), with mild dyspnea on exertion, no cough, no rhinorrhea, no decrease in urine output, no other complaints. Repeat Urine analysis showed PH 5, specific gravity 1.025, numerous WBC and RBC, Protein 3+, Granular Cast +. So ordered with the help of the pediatric nephrologist Urine spot Protein / Creatinine which revealed 5.2 > 2 nephrotic range proteinuria, with Albumin 2, 5 g/dl and Lipid panel requested but was not done due to financial issue. Diagnosed as having Nephrotic range proteinuria with Glomerulonephritis, so he was transferred under pediatric nephrologist care. Further workup requested: for lupus (ANA, Anti Ds DNA), C3, C4, Ig Q, Ig A, viral serology for EBV, CMV, Hepatitis B, Hepatitis C, HIV, parvovirus, ASO titer and TST done. During that time spot Urine for Creatinine / Protein was followed every other day and showed persistence of proteinuria, also the blood pressure remained relatively high. Fever, abdominal pain, pleural effusion, and abdominal ascites persisted also. Systemic diseases especially Vasculitis was high on the list of the differential diagnosis. So Kidney biopsy performed on day fifteen of hospitalization. Steroid for suspicion of Vasculitis was started after biopsy as 2 mg /kg/day on day sixteen of hospitalization while pending biopsy and requested blood tests. Investigations result showed ANA negative <1/10, ANCA negative <1/10, Anti Ds DNA negative, HbsAg negative 0.18 mIU/, HIV negative 0.13 mIU/L, HCV Abs negative 0.1 mIU/L, Anti EBV Ig M positive 1.5, Ig G 1.67 also positive, TST read after two days and was negative. Kidney biopsy showed evidence of acute tubular injury. So the patient found to have Acute Tubular Necrosis (ATN) with positive recent EBV infection. The patient markedly improved and became afebrile, no more pain, no edema, no dyspnea, no urinary or other symptoms. He was discharged on Steroid for four weeks.

DISCUSSION

The Epstein–Barr virus (EBV), also called Human Herpes Virus 4 (HHV-4), it is one of eight known viruses in the herpes family and is one of the most common viruses in humans.

It is best known as the cause of infectious mononucleosis (glandular fever).[1] Infectious mononucleosis, generally results in mild, self-limited illness characterized by fever, sore throat and lymphadenopathy.[1] Occasionally, EBV infection has more severe squeals; Lymphoproliferative lesions, Hepatitis, Encephalitis and Hemolytic Anemia have been reported.[2,3] Although kidney involvement is relatively common, Acute Renal Injury associated with EBV infection is rare.[3] Acute Tubular Necrosis (ATN) is a kidney disorder involving damage to the tubule cells of the kidneys. It is often caused by a lack of blood flow and oxygen to the kidney tissues (ischemia of the kidneys). It may also occur if the kidney cells are damaged by a poison or harmful substance. The internal structures of the kidney, particularly the tissues of the kidney tubule, become damaged or destroyed. ATN is one of the most common structural changes that can lead to acute renal injury.[4] Renal involvement with EBV infection occurs in ~16% of the cases that come to medical attention.[5] The spectrum of renal involvement with EBV is broad. Mild Nephropathy may result in only microscopic hematuria or asymptomatic proteinuria. Rhabdomyolysis resulting in Acute Renal Failure has been described in association with EBV infection.[6,7] Renal involvement in systemic EBV infections typically manifests as Acute Tubular Necrosis or tubule-interstitial nephritis. Rarely, EBV infection causes Nephrotic Syndrome due to minimal change disease. A study done among 165 previously healthy children hospitalized with serologically proven primary EBV infection, 8 had Acute Renal Failure, of whom 5 (group A) did not have Virus-Associated Hemophagocytic Syndrome (VAHS), while 3 (group B) did have VAHS. Two patients in group A had renal biopsies showing Acute Tubulo-Interstitial Nephritis and the clinical and laboratory findings in the other 3 group A patients were consistent with Acute Tubulo-Interstitial Nephritis.[8] Another case report of a previously healthy toddler developed severe Acute Renal Failure with nephromegaly and peripheral atypical lymphocytosis. Profound interstitial nephritis with acute tubular necrosis was diagnosed by renal biopsy and both the clinical picture and serological evaluation suggested Epstein-Barr virus (EBV) as the etiological agent.[9] In a literature review, thirty four cases were reviewed by Ramelli et al. in 1990.[10] Also Mayer et al. recently reviewed 27 cases.[11] Of these cases, 5 were associated with Rhabdomyolysis and Myoglobinuria. Hyperuricemia was a factor in one and there were single cases of either minimal change Nephrotic Syndrome or Hemolytic Uremic Syndrome. There were 18 instances in which renal dysfunction appeared to be due to EBV infection itself; of these cases, 10 involved Interstitial Nephritis. Since then, additional cases have been reported. In 1996, Nephrotic Syndrome was reported in a 19 month old infant with acute EBV infection. Proteinuria resolved after resolution of the viral infection. A renal biopsy was not done.[12] Two cases of EBV-associated Renal Failure were reported in 2000 and 2002 associated with Interstitial Nephritis and one of these also had minimal change disease.[13, 14] Therapy for Acute Interstitial Nephritis is mainly supportive, but pharmacological treatment with Immunosuppressive drugs may be appropriate, particularly in cases associated with Autoimmune Disease or Glomerulonephritis.[15] Controlled, prospective clinical trials of Steroid therapy for EBV-associated Tubulo-interstitial Nephritis are lacking, but several small studies

supporting its use were recently summarized in a review by Michel and Kelly.

Several patients with Interstitial Nephritis had diuresis or a fall in the Creatinine level within 72 hours of initiation of Steroid therapy, whereas a few untreated patients recovered more slowly or not at all. Treating underlying infection can be important in the treatment of Acute Interstitial Nephritis, and there are anecdotal reports of Acyclovir treatment, alone or in conjunction with Steroids, for Acute Renal Failure[16,17] and Lymphoproliferative disorder[18] associated with EBV infection. However, Acyclovir has only limited efficacy in the treatment of acute EBV infection and can itself be nephrotoxic.[19,20]

CONCLUSION

Acute Renal Injury is a rare but serious complication of EBV infection. Interstitial Nephritis and Acute Tubular Necrosis are the most common lesion associated with primary EBV infection and it appears to be mediated by cytotoxic/suppressor T lymphocytes. Afflicted patients may benefit from early aggressive intervention with corticosteroid therapy.

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