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NEWEST "CO-MEMBERS" OF THE 1000S CLUB: A CASE OF SEVERE TRANSAMINITIS SECONDARY TO EPSTEIN-BARR AND DENGUE VIRUS CO-INFECTION IN A RETURNING TRAVELER

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ABSTRACT

Background: Timely identification of the etiology of transaminitis is critical in informing subsequent management as strategies can vary from supportive care to urgent transplant assessment. This is especially important in returning travelers as there may be multiple causes of injury that need to be addressed.

Case report: We present a case of severe transaminitis secondary to non-hepatitis viral co-infections. A 28-year-old south Asian male returning traveler presented with an acute liver injury (aspartate aminotransferase/alanine aminotransaminase levels of ≥4000 IU/l) and marked jaundice. A thorough and expanded work-up of acute hepatitis was negative aside from positive mononucleosis spot testing and positive dengue fever serologies. This atypical presentation of mononucleosis and dengue fever was managed conservatively, and the patient was discharged with outpatient follow-up after an eight-day admission.

Conclusions: Usually, non-hepatitis viruses typically do not present with severe transaminitis or hyperbilirubinemia. These viruses, such as infectious mononucleosis and dengue fever, may work synergistically to cause an elevated inflammatory response, resulting in severe transaminitis in returning travelers. In the absence of a classic clinical presentation, clinicians should be aware of co-infections in returning travelers and test for them based on a thorough history and physical examination.

KEYWORDS

Epstein-Barr virus, severe transaminitis, acute liver injury, dengue fever

LEARNING POINTS

- The differential diagnosis for severe transaminitis is narrow and commonly includes viral hepatitis (A-E), drug-induced liver injury, vascular and autoimmune causes; however other causes exist, and greater clinical awareness is needed.
- This case study demonstrates that even in the absence of a classic clinical presentation; in returning travelers, clinicians should have a low index of suspicion to order appropriate screening serologies based on a thorough history and physical examination as they can be sensitive diagnostic tools in detecting the etiology of severe transaminitis.

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- In rare cases, non-hepatitis virus may act synergistically to cause severe transaminitis and should be considered in returning travelers when viral hepatitis serologies are negative.

INTRODUCTION

The differential diagnosis for severe hepatocellular transaminitis, defined as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 1000 IU/l is narrow, typically includes drug-induced liver injury, viral hepatitis, and vascular etiologies (shock liver or Budd-Chiari syndrome). Less common etiologies include acute biliary obstruction, autoimmune hepatitis, and Wilson's disease[1]. Non-hepatitis viruses such as Epstein-Barr virus (EBV), or endemic viruses such as dengue fever, may result in modest liver enzyme elevations, but typically do not present with severe transaminitis[1-3]. The interaction of these specific viruses as they relate to hepatic damage is understudied. In this case study, we report an otherwise healthy 28-year-old male returning from India presenting with severe transaminitis and hyperbilirubinemia, secondary to infectious mononucleosis and dengue fever co-infection.

CASE REPORT

A 28-year-old South-Asian male with no significant past medical or surgical history returning two weeks after travel from Gujarat, India presented to the emergency department with symptoms of malaise, fever, and marked jaundice for one week. Prior to his trip, he was not taking any regular medications aside from a daily multivitamin. He had no history of smoking, or intravenous drug use, and had one standard alcoholic drink per week. He received a general medical check-up in India and was told that he had normal liver enzymes at that time. He did not visit any farms, funerals or slaughterhouses. Furthermore, he denied any exposure to animal bites, freshwater, body-fluid exchanges, or new sexual contacts and remained in urban areas throughout his stay. He consumed street foods during his vacation and endorsed having several mosquito bites. One week after returning to Canada, the patient began experiencing malaise, myalgias, fevers, and decreased oral intake. His review of systems was otherwise negative. He later developed scleral icterus and worsening constitutional symptoms, prompting presentation to hospital. On presentation, he was vitally stable, afebrile with no mental status abnormalities. On first assessment, the patient appeared to be in some discomfort with marked scleral icterus and right upper quadrant non-peritonitic tenderness. He did not present with any stigmata of liver disease including hepatosplenomegaly or ascites. His cardiorespiratory exam was unremarkable, and no focal neurologic deficits were noted. He did not present with any lymphadenopathy, tonsillar exudates, uvular deviation or rashes. The patient's initial laboratory work was significant for transaminitis and hyperbilirubinemia as well as lymphocyte-predominant leukocytosis. A two-pronged work-up was initiated; one for severe transaminitis, and one for fever in a returning traveler. Pertinent results on admission are highlighted in *Table 1*. He was eventually found to have positive IgM serologies for dengue fever as well as positive monospot and anti-viral capsid antigen (VCM) IgM positive serologies. Other etiologies, including infectious sources leading to transaminitis were ruled out on the basis of serological testing or pre-test probability based on history and physical examination. The gastroenterology service was consulted regarding this patient's acute liver injury and to perform a potential transplant assessment. Given the lack of encephalopathy and international normalized ratio (INR) elevation, his transaminitis was managed conservatively. His EBV infection was managed conservatively with fluids, antiemetics, and appropriate analgesia. With regard to his dengue positive serologies, aside from myalgias, he did not meet the definition of high-risk classical dengue fever as per the World Health Organization (WHO) and therefore did not require any specialized treatments, including intensive care level management. The patient also presented with a hemolytic anemia, as demonstrated in *Table 1*. A blood smear revealed reactive lymphocytes with no other abnormalities, including platelets. A Coombs test was IgG negative but positive for C3d. Hemoglobinopathy work-up was negative. The patient presented with a hemoglobin of $131x10^6$ µl, reaching a nadir of $91x10^6$ µl on day five of admission. A further in-patient work-up or management of the anemia was deferred at the request of the patient. Following eight days of improvement, he was discharged with both outpatient internal medicine and gastroenterology referrals.

DISCUSSION

The most common presentations of severe transaminitis are drug-induced liver injury, viral hepatitis, vascular, and autoimmune causes. Both EBV and dengue fever have been known to cause severe transaminitis, although the incidence is quite low, especially in EBV. Presentations such as dengue fever with warning signs or severe dengue are known to cause massive elevations in hepatocellular markers[2]. Aside from abnormal liver enzyme levels, the presentation of this patient was not consistent with WHO definitions of severe dengue fever. Therefore, if both viral infections do not seem to independently cause severe transaminitis, it follows that there may be a synergy between these two viral processes that results in acute liver injury. More specifically, while there have been previous case reports noting massive liver enzyme elevations with concomitant comorbidities, such as hereditary hemochromatosis, there are no such documented occurrences of co-infection of EBV and dengue fever[4]. Infectious mononucleosis, whose

Investigation	Result
Complete blood count	- Hemoglobin 131x10^6 µl - White blood cell count 12.1x10^3 µl with lymphocyte predominance at 4.8x10^3 µl, - Platelet count 224 x10^3 µl
Basic metabolic panel	- No electrolyte abnormalities noted - No abnormalities to kidney function
Septic/fever of returning traveler work-up	- Nasopharyngeal swab: Negative - Blood cultures x2: Negative - Urinalysis and culture: Negative - Chest and abdominal X-ray: No acute findings - Malaria screen: Negative x3 - Zika virus*: Negative - Chiknungya virus*: Negative - Dengue virus*: Positive
Liver function tests	- AST: 4395 IU/l - ALT: 4151 IU/l - Total bilirubin: 393 µmol/l - Conjugated bilirubin: 324 µmol/l - Unconjugated bilirubin: 61 µmol/l - ALP: 121 IU/l - GGT: 126 IU/l - Lipase: 159 µmol/l
Transaminitis workup	- Hepatitis A: Negative - Hepatitis B: sAg -, cAb -, sAb – - Hepatitis C: Negative - Hepatitis D: Canceled - Hepatitis E: Negative - HIV*: Negative - CMV IgG: Negative - Ceruloplasmin: Negative - Alpha-1-antitrypsin: Negative - Quantitative immunoglobulins: Negative - Hereditary hemochromatosis: Negative - Autoimmune hepatitis negative (antinuclear antibody, rheumatoid factor, anti-mitochondrial antibody, anti-smooth muscle antibody, anti-parietal, anti-liver kidney microsome type 1 negative) - Monospot nucleosis test: Positive with subsequent positive anti-VCA IgM and negative EBNA IgG
Miscellaneous markers of liver function	- Glucose 5.5 - INR 1.7
Metabolic screen	- HBA1C 4.5%, - HDL 0.42 mmol/l, - LDL 1.49 mmol/l - Triglycerides 3.91 mmol/l
Iron studies	- Ferritin 29,200 µg/l
Hemolytic screen	- LDH 4517 U/l - Haptoglobin absent - Reticulocyte count 7.5% - Smear reactive lymphocytes - DAT IgG negative (C3d positive) - Hemoglobinopathy negative
Imaging	- Doppler US liver + spleen: Targeted scan. - The spleen demonstrates normal reflectivity. The spleen measures up to 11.9 cm. It is not enlarged. The splenic vein is patent at the hilum. - CT scan abdomen/pelvis with contrast: Severe fatty liver. - No identifiable biliary tree dilatation, no pancreatic masses. Few prominent porta hepatis lymph nodes are likely reactive. The hepatic veins and portal vein are widely patent. There is no evidence of portal vein thrombus nor Budd-Chiari syndrome
Drug screen	- Urine drug screen negative - Acetaminophen, salicylate levels within normal limits
Cardiac work-up	- Troponin negative - ECG normal sinus rhythm

* The laboratory test was sent to the public health laboratory, and it took up to a week to receive the result
Abbreviation: AST, aspartate amino transferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; CMV, cytomegalovirus; VCA, viral capsid antigen; EBNA, Epstein-Barr nuclear antigen; INR, international normalized ratio; HBA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDH, lactate dehydrogenase; US, ultrasound; CT, computed tomography; ECG, electrocardiogram.

Table 1. Summary of investigations on presentation.

etiologic agent is most commonly EBV in immunocompetent patients, describes a viral syndrome of fever, sore throat, cervical lymphadenopathy and general malaise[5]. Diagnosis of infectious mononucleosis is typically made through the monospot test, but EBV infection was confirmed in this case report with the presence of IgM positivity of VCA, EBV generally has an incubation period of 4-6 weeks and is spread through nasopharyngeal secretions. Hepatic involvement is rare, and management involves conservative measures. Typically, EBV causes mild elevations of liver enzymes, usually around 2-3 times the upper limit of normal. Other complications such as hemolytic anemia or cholestatic derangements are atypical[5]; a 13-year retrospective study conducted by Vine et al. showed that only one patient with EBV infection presented with severe transaminitis, and no patients had AST or ALT elevations above 1500 IU/l[6]. The exact pathogenesis of hepatocellular damage is likely related to CD8+ T cell accumulation in hepatocytes. Subsequent cytokine activation results in the usual modest liver function abnormalities[7]. The patient also presented with hemolytic anemia, which is a rare complication of EBV[3], and an even rarer complication of dengue fever. The patient had extremely elevated ferritin and lactate dehydrogenase, absent haptoglobin, elevated reticulocyte count, and had an indirect bilirubin elevation in addition to his cholestatic bilirubin elevation. The true etiology of the anemia is difficult to elucidate given the acute liver injury, but Coomb's test was negative for IgG and positive for complement component C3d. As such, it was thought that the hemolysis was likely related to his EBV infection, as his presentation was similar, albeit less severe, to a presentation of concomitant EBV and hereditary hemochromatosis Forsberg et. al. described in a 2020 case report[4]. Fortunately, the patient did not require any intensive management such as transfusions or steroids and declined further work-up.

Dengue fever has a wide array of presentations, ranging from asymptomatic fevers and arthralgias to more severe forms of hemorrhagic fever, severe plasma leakage, and circulatory shock. It is a member of the *Flavivirdae* viral family and is spread primarily via mosquito bites[8]. Liver involvement is not uncommon; in one retrospective study conducted in Kathmandu (Nepal) it was found that 42.5% of total patients presenting with dengue fever had concurrent transaminitis. In these cases, however, other lab markers were associated with elevated liver enzymes, such as thrombocytopenia in roughly 80% of patients[8]. The degree of liver enzyme elevation may also vary; a review of an intensive care unit at a tertiary care center in Karnataka, India found 8.8% of individuals admitted with dengue fever had grade 4 transaminitis (more than 20 times the upper limit of normal)[2]. In this study, however, patients presented with systemic symptoms that would classify them as having severe dengue fever, as per WHO definitions. In contrast, our patient did not present with any other features consistent with severe dengue fever, such as severe bleeding, plasma leakage, other organ dysfunction or involvement, or altered level of consciousness. This patient also did not present with warning signs of severe dengue fever, which would include abdominal pain, persistent vomiting, clinical fluid accumulation (pleural effusion, ascites), mucosal bleeding, hepatomegaly greater than two centimeters, or increasing hematocrit with concurrent thrombocytopenia. This patient, presenting with no other systemic symptoms aside from malaise, is not a typical manifestation of dengue fever that would occur with AST or ALT elevations above 1000 IU/l. For example, in a study by Swarmy et al. the mean hepatocellular enzyme elevation of severe dengue was half of this patient's presentation and other classic markers of severe dengue fever were absent, including thrombocytopenia. Interestingly, the highest enzyme levels of that study (AST 4942 IU/l and ALT 1306 IU/l) presented with refractory shock causing death and hemorrhagic complications respectively[9]. This patient presentation is of particular interest because elevated transaminase levels are generally associated with disease severity[2]. This indicates that while dengue fever alone can cause severe transaminitis, a presentation of AST/ALT >4000 IU/l without any other systemic signs are exceedingly rare and should warrant further examination, especially in the context of a second viral infection, as few studies have examined the relationship between dengue fever co-infections liver enzyme abnormalities[10].

While not fully understood, the pathophysiology of hepatocellular toxicity is likely cytokine-related, such as IL-17 and IL-22[11]. Given this pathophysiology, there may therefore be an element of synergy between dengue fever and EBV that has yet to be elucidated, possibly through cytokine activation. A case report of dengue fever and EBV co-infection resulting in cerebellitis may lend some credibility to the idea that co-infection of these viruses can result in atypical presentations[10].

CONCLUSION

This comorbid presentation of EBV and dengue-induced severe transaminitis represents the nuances of diagnosing acute liver injuries, especially when the work-up of classic causes of severe transaminitis is negative. EBV should always remain on the differential of severe transaminitis, even in the absence of typical mononucleosis symptoms. Furthermore, in returning travelers with elevated liver enzymes, appropriate infectious testing should be performed with an understanding that viruses outside of hepatitis A and E may contribute to these presentations. This is especially important in acute liver injuries where management, such as transplant or antidotes, is dependent on disease etiology. Lastly, this study is evidence that co-infections of endemic and non-endemic viruses that may act synergistically to cause more severe hepatocellular injury. We hope this case helps clinicians further explore the interactions between non-hepatidies viruses and liver toxicity.

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