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A Case of Infectious Mononucleosis Induced Jaundice Complicated by Possible Drug Induced Liver Injury (DILI)

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Abstract

In this case, a young female presented with non-specific features such as fever, sore throat, headache and fatigue. She went on to develop epigastric pain, darkening of urine and jaundice, with no resolution of prior symptoms. Physical and Laboratory tests confirmed the primary diagnosis of infectious mononucleosis, however, prior history of treatment with multiple drugs led to a diagnosis of DILI as a complication. Appropriate treatment with I.V. antibiotics, hepatoprotective agents, steroids as well as discontinuation of all potential hepatotoxic agents showed significant improvement in patients' symptoms and overall condition.

Keywords

Infectious Mononucleosis, Jaundice, Drug Induced Liver Injury, Lymphadenopathy

1. Introduction

Infectious mononucleosis is caused by Epstein Barr Virus (EBV) and presents with the classic triad of fever, tonsillitis, and lymphadenopathy. Additional findings include tonsillar exudates, palatal petechiae, hepatosplenomegaly, and hepatitis. Elevations in liver transaminases are commonly seen, but are usually transient and rarely progress to fulminant hepatitis. Most infections are self-limiting with good prognosis. However, there is a <5% risk of developing significant cholestasis and jaundice, which are rare complications [1].

Previous case reports published on infectious mononucleosis leading to hepa-

titis exhibit symptoms such as fever, malaise, abdominal pain often associated with nausea, vomiting and constipation. Patients appeared to be icteric and labs show elevated liver transaminases. A confirmatory diagnosis of IM-induced hepatitis can be made on the basis of a positive monospot (heterophile antibody) test, hypertransaminasemia, high titers of antibodies against EBV (Anti-VCA IgM, Anti-VCA IgG, Anti-EBNA-1 IgG). However, we should keep in mind that a negative monospot test does not rule out IM and hence requires further serological testing. A liver biopsy done to further confirm the diagnosis often shows EBV latent membrane protein [3] [4].

The liver is the main point of metabolism of most drugs, making it susceptible to drug-induced injury. DILI can mimic all forms of acute and chronic liver diseases, which poses a significant challenge [5]. Symptoms of drug-induced liver injury include jaundice, weakness, abdominal pain, dark stools or urine, nausea, and pruritis. It can also present as acute or chronic liver failure, which further complicates the diagnosis [6]. Although liver parameters are sensitive in detecting DILI, they cannot be used to predict the patient's subsequent clinical course. DILI is also a leading cause of drug withdrawals, restrictions and project terminations [7].

Various case reports published on DILI show the same pattern of symptoms viz. fever, nausea, fatigue and jaundice which follow the introduction of a new drug. Increase in liver transaminases and bilirubin levels, along with a liver biopsy (revealing portal and lobular chronic inflammation with mild cholestasis) often confirms the diagnosis of DILI after all other possible etiologies of liver injury have been ruled out. Furthermore, resolution of symptoms after cessation of the offending drug/agent supports the diagnosis. [8] [9] [10]. It is also noted that some case reports also suggest the use of steroids in the treatment of DILI [11].

In this article, we present an original case of infectious mononucleosis induced jaundice complicated by possible superimposed drug induced liver injury encountered in our hospital.

2. Case Presentation

A 29-year-old female presented to the outpatient department with complaints of continuous fever for 1 week associated with sore throat, headache and fatigue. Prior to this visit, she consulted another physician for her complaints. Investigations such as CBC, CRP, COVID PCR, Influenza, and chest X-ray were done then, which were within normal limits. She received inj. Ceftriaxone 1g, inj. vitamin B complex (Medivitan) and I.V. Paracetamol, and discharged on amoxicillin-clavulanic acid (Amoxiclav) and anticongestant (Fludrex).

However, she felt that her symptoms did not improve and now developed epigastric pain and noticed darkening of her urine. Repeat laboratory tests revealed a C-Reactive protein of 59 (normal: <5) and deranged Liver Function Tests (Bilirubin-4.1 mg/dL, SGOT-250 U/L, SGPT-250 U/L). She was then referred to our

hospital for further management.

Her past medical history is significant for PCOD and insulin resistance, controlled on Glucophage and GLP-1 receptor antagonist. She also disclosed that she had recently completed a 1-week course of doxycycline 100mg for PCOD-related acne. Her drug history was insignificant for any other short- or long-term drug use. No other known comorbidities such as diabetes mellitus, hypertension, dyslipidemia, asthma, or liver/biliary diseases were present. There was no past surgical history and family history was insignificant for any comorbidities or liver diseases.

On general physical examination, she was conscious, alert, and oriented, however she appeared febrile and pale. Inspection of the sclera revealed mild icterus. Capillary refill time was normal (<2 seconds) and no asterixis present. There were enlarged and painful cervical lymph nodes. No stigmata of chronic liver disease were found. The abdominal exam on inspection showed normal abdominal contour and symmetry. No masses, skin changes, dilated veins, change in hair distribution, or surgical scars were noted. No hepatosplenomegaly, hepatic or splenic bruit noted. No peripheral edema was observed.

Laboratory investigations were ordered (Table 1) which revealed mildly low hemoglobin, low hematocrit, high CRP, mild neutropenia, low eosinophils, and marked lymphocytosis. LFTs showed deranged liver function (high total, direct and indirect bilirubin, high liver transaminases, high ALP and GGT) (Table 2). LFTs were also repeated on day 2 and day 5. A blood culture came out negative. A renal function panel revealed low urea, creatinine and albumin levels. Urine microscopic examination and urine culture were negative. Serum amylase and lipase levels were within normal range. A hepatitis panel was done covering

Table 1. Laboratory investigations sought in this patient.

Parameter	Results	Reference
Hemoglobin	11.8 g/dL	12 - 15 g/dL
Hematocrit	34.1%	36% - 46%
WBC	10.24×10^3/uL	4 - 10×10^3/uL
Platelet	304×10^3/uL	150 - 410×10^3/uL
Neutrophils	38.1%	40% - 80%
Lymphocytes	57.1%	20% - 40%
Monocytes	3.6%	2% - 10%
Eosinophils	0.1%	1% - 6%
Basophils	1%	0 - 1%
CRP	43.7 mg/L	<5 mg/L
Total Protein	6.6 g/dL	6.4 - 8.3 g/dL
Globulin	3.13 g/dL	2.3 - 3.5 g/dL
A/G ratio	1.0	1.0

Table 2. LFT values. Note the change in liver parameters over the course of treatment in the hospital.

Parameter	Reference range	Day 0	Day 2	Day 5
Total bilirubin	0.1 - 1.2 mg/dL	5.01	6.54	5.36
Direct bilirubin	<0.3 mg/dL	3.33	6.21	5.06
Indirect bilirubin	0.1 - 1.0 mg/dL	1.68	0.33	0.30
SGOT (AST)	<35 U/L	178	220	285
SGPT (ALT)	<33 U/L	199	165	187
ALP	35 - 104 U/L	398	548	559
GGT	<42 U/L	144	-	-

HAV, HBV, HCV, HEV, which were all negative. Antibody serology screen which included Liver Kidney Microsomal (LKM) antibody, anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), serum immunoglobulin IgG, anti-soluble liver antigen, were all negative. However, a monospot test yielded a positive result.

On abdominal ultrasound, hepatosplenomegaly was detected along with slightly elevated echogenicity of the liver and mild pericholecystic edema. The head and body of the pancreas appeared mildly bulky, however there was no evident peripancreatic fluid accumulation. A neck ultrasound was then pursued which revealed several bilaterally enlarged cervical lymph nodes (level 1A, 1B, 2, 3 and 5), with the largest one measuring 13.6 × 5.4 mm in size on the right side and 23 × 10.8 mm in size on the left (**Figure 1**). These lymph nodes showed increased vascularity, according to a Doppler examination (**Figure 2**). Positive monospot test along with lymphocytosis and enlarged cervical lymph nodes led to the diagnosis of infectious mononucleosis. MRCP done to rule out any hepatobiliary disorders revealed hepatosplenomegaly with edema of the gallbladder wall; however, no cholelithiasis or choledocholithiasis was noted (**Figure 3**). A liver biopsy was advised to confirm the underlying disease, however our patient refused.

The patient was admitted and broad-spectrum IV antibiotics were started initially in view of the potential causes of FUO and since the diagnosis of IM and DILI had not been established. These antibiotics and all other medications were stopped once IM was diagnosed and DILI suspected. Ursodeoxycholic acid (Ursofalk) and N-acetylcysteine were started for liver protection. This patient was also started on steroids on day 5 as she remained persistently symptomatic with worsening liver parameters, which eventually led to complete resolution of her symptoms. She was kept under observation in the hospital for one week and her LFTs were closely monitored (**Table 2**). Follow up of the patient at 4 days after discharge showed declining liver parameters and follow up after 2 weeks showed complete recovery with normalization of liver function (**Table 3**) (**Figure 4** and

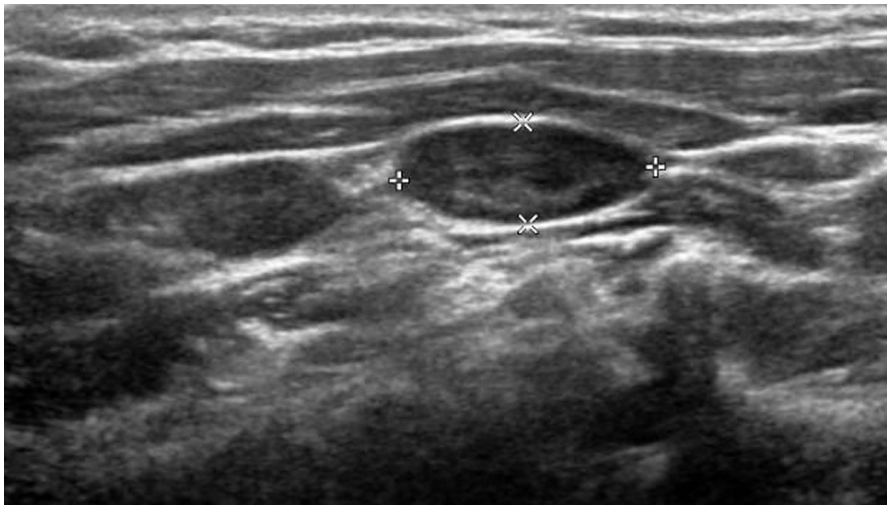

Figure 1. Lymphadenopathy seen on USG of the cervical lymph nodes.

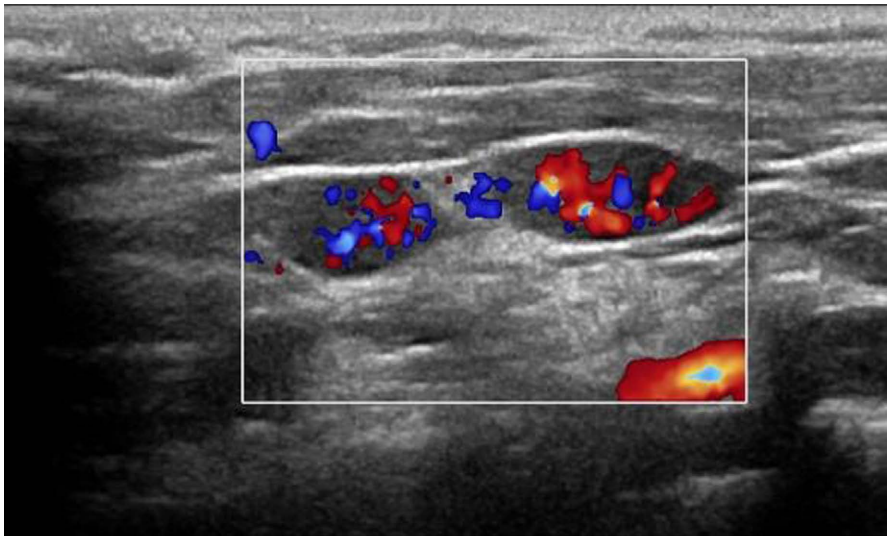

Figure 2. Doppler scan of cervical lymph nodes showing increased vascularity.

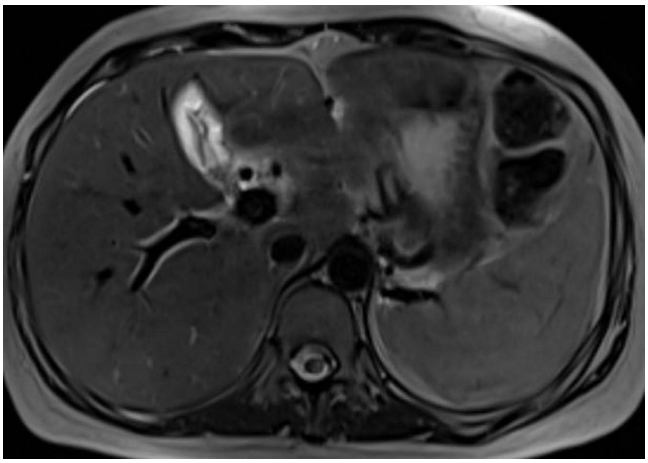

Figure 3. MRI of the abdomen revealing hepatomegaly with edema of gall bladder wall.

Figure 5). The patient had an excellent prognosis with no derangement of liver function on any subsequent follow ups.

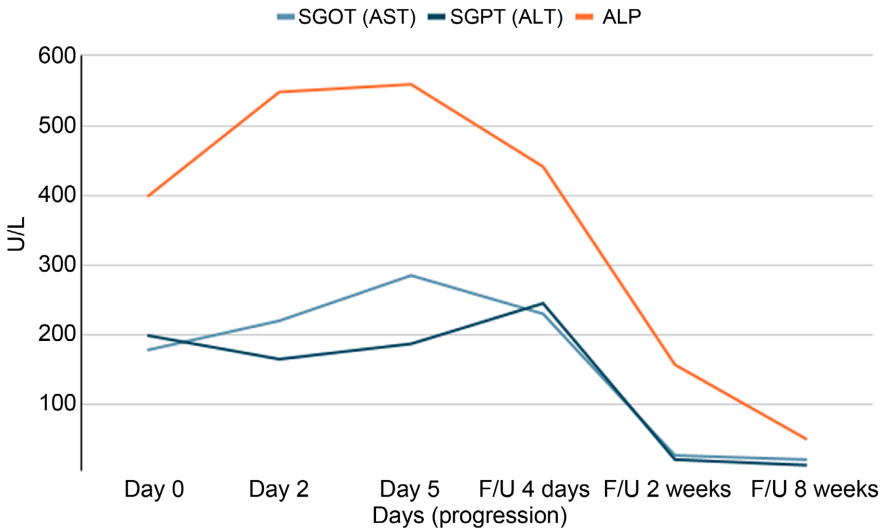

Figure 4. Progression of SGOT, SGPT and ALP over the course of 8 weeks.

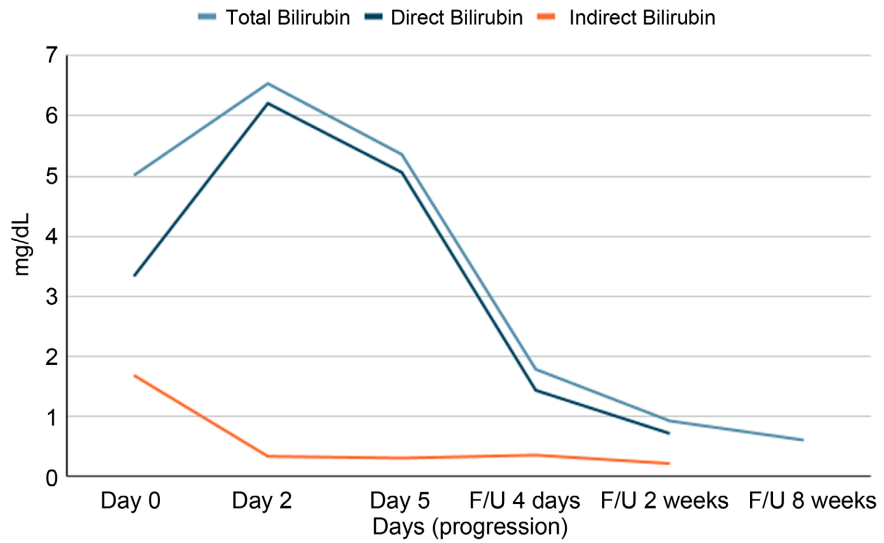

Figure 5. Progression of total, direct and indirect bilirubin over the course of 8 weeks.

Table 3. LFT values on subsequent follow up visits.

Parameter	Reference range	F/U 4 days	F/U 2 weeks	F/U 8 weeks
Total bilirubin	0.1 - 1.2 mg/dL	1.78	0.92	0.6
Direct bilirubin	<0.3 mg/dL	1.43	0.71	-
Indirect bilirubin	0.1 - 1.0 mg/dL	0.35	0.21	-
SGOT (AST)	<35 U/L	230	27	21
SGPT (ALT)	<33 U/L	245	21	13
ALP	35 - 104 U/L	441	157	50

3. Discussion

Infectious mononucleosis may present with the following symptoms: fever, sore throat, headache, body ache, swollen lymph nodes in neck and armpit with enlarged liver and spleen. About 75% of patients who have EBV infection show an increase in aminotransferases, which suggests liver tissue damage. However, cholestatic hepatitis and jaundice are rare complications (<5%) [1]. In our patient, infectious mononucleosis was diagnosed based on clinical suspicion and laboratory testing revealing lymphocytosis and a positive heterophile antibody test (mono spot test). Normally no specific treatment is required and most immunocompetent patients make uneventful recovery. Rest, hydration and pharmacological therapy including nonsteroidal anti-inflammatory medications, acetaminophen, and throat lozenges or anesthetic sprays are usually used. Steroids may be required in some patients for significant complications like impending upper airway obstruction, massive splenomegaly or myocarditis [2]. Interestingly, steroids also help in treating severe drug induced liver injury, which cannot be ruled out in this patient [11] [12]. Liver biopsy may help in determining the underlying etiology of jaundice/hepatitis [3] [4] [8] [9] [10]. It also helps in ruling out other possible causes of acute/sub-acute liver injury. We do not have this information since patient refused liver biopsy due to its invasive nature.

Liver is the main point of metabolism of most drugs, making it susceptible to drug-induced injury. DILI can mimic all forms of acute and chronic liver diseases, which poses a significant challenge, as seen in this case. Acetaminophen and amoxicillin/clavulanic acid have been common causes of DILI in developed countries. However, many other commonly used drugs are now being reported as well. In some cases, time period between initiation of therapy and onset of DILI can provide clues to the pathogenesis. For example, early onset DILI can clue in to direct toxicity by the drug or its metabolites, as in the case of acetaminophen overdose. The mainstay treatment of DILI is early identification and removal of the offending agent as well as appropriate supportive treatment. Significant insult to the liver function can lead to the immediate need for liver transplantation or even death [5] [6]. The role of steroids is limited and they are usually reserved for immune-mediated DILI [2] [12]. DILI is the most common cause of acute liver failure in the United States. Incidence of this disease is not well established as it is usually under reported, however, recent studies have shown that the numbers may be approximately 20 in 100,000 [6]. Medications consumed by our patient (acetaminophen, amoxicillin/clavulanic acid, doxycycline, ibuprofen) may have contributed to subsequent DILI.

Acetaminophen: A small portion of acetaminophen is metabolized by the liver enzyme CYP 2E1 into a hepatotoxic metabolite known as *N*-acetyl-para-benzo-quinone imine (NAPQI) which binds to a number of cellular proteins, especially mitochondrial proteins leading to ineffective mitochondrial function. Other mechanisms of hepatotoxicity include the formation of toxic free radicals

in the mitochondria, which leads to damage of the mitochondrial DNA and termination of ATP production. All of this eventually leads to hepatocellular necrosis [13].

Doxycycline: It causes a mixed pattern of liver injury; from hepatocellular to cholestatic and arises 7 - 14 days after starting the drug. The exact mechanism of liver injury is unknown but owing to the fact that it has a short latency period and reoccurs with re-exposure, an immuno-allergic etiology is likely [14].

Amoxicillin-clavulanic acid: Hepatotoxicity from amoxicillin and clavulanate is most likely immuno-allergic in nature. Re-exposure to amoxicillin alone has not been linked to recurrence but re-exposure to the combination is generally followed by a rapid onset of severe hepatic injury, suggesting that the liver injury appears to be caused by the clavulanate rather than the amoxicillin [15].

Ibuprofen: Although the exact mechanism of ibuprofen-induced liver damage is unknown, it may be multi-factorial. The quick onset points to a toxic metabolite, yet the hypersensitive symptoms that come along with liver damage suggest an immuno-allergic response [16].

4. Conclusion

This case highlights the importance of thorough history taking, especially when a patient presents with such vague symptoms. A high index of suspicion is crucial in such cases and all differentials should be explored and ruled out. Even though this case seemed fairly straightforward in the beginning, several factors complicated the symptoms which prompted a thorough evaluation. DILI is a common occurrence; however, it is usually a diagnosis of exclusion and other possible causes of liver injury must be explored.

Ethical Approval

Informed consent and written informed consent for publication of the case details with any accompanying images were taken from the patient involved in this case.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations and Acronyms

IM—Infectious mononucleosis, Anti-VCA—Anti-Viral Capsid Antigen antibody, Anti-EBNA-1—Anti-EBV Nuclear Antigen antibody, DILI—Drug induced liver injury, CBC—Complete Blood Count, CRP—C Reactive protein, LFT—Liver Function Tests, MRCP—Magnetic Resonance Cholangiopancreatography, SGOT—Serum Glutamic Oxaloacetic Transaminase, SGPT—Serum Glutamic Pyruvic Transaminase, ALP—Alkaline Phosphatase, GGT—Gamma-glutamyl transferase, PCOD—Polycystic Ovarian Disease, F/U—Follow up, HAV—Hepatitis A virus, HBV—Hepatitis B virus, HCV—Hepatitis C virus, HEV—Hepatitis E virus.