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Short Report

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A case of amoxicillin/clavulanate induced prolonged cholestatic liver injury: Case report

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Abstract

Drug induced liver injury is an acute or chronic response to a variety of medications, herbal supplements and natural compounds. The pattern of injury could be hepatocellular, cholestatic, or mixed depending on the ratios of alanine aminotransferase and alkaline phosphatase upper limit elevations (R value). Cholestatic injury is characterized by an R value of <2. One of the antibiotic causes of cholestatic injury is amoxicillin/clavulanate. Symptoms are non-specific which makes laboratory evaluation or imaging important to exclude potential underlying liver problems. Prolonged symptoms can happen in cholestatic than hepatocellular injury. Discontinuation of the offending drug is the treatment in addition to supportive care. Avoidance of re-challenge is also important.

Keywords: Cholestasis; Drug induced liver injury; Genetic susceptibility.

Abbreviations: ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; ANA: Anti-Nuclear Antibody; Anti-LKM: Anti-Liver-Kidney Microsomal Antibody; ASMA: Anti-Smooth Muscle Antibody; AST: Aspartate Transferase; DILI: Drug-Induced Liver Injury.

Introduction

Drug-Induced Liver Injury (DILI) is common and nearly all classes of medications can cause liver disease. Most cases of DILI are benign, and improve after drug withdrawal. It is important to recognize and remove the offending agent as quickly as possible to prevent the progression to chronic liver disease and/or acute liver failure. There are no definite risk factors for DILI, but pre-existing liver disease and genetic susceptibility may predispose certain individuals [1]. Drug induced cholestatic liver disease is a subtype of liver injury that is characterized by predominant elevations of alkaline phosphatase and bilirubin secondary to the administration of a hepatotoxic agent [2]. Cholestatic DILI can manifest clinically in a range of presentations, including asymptomatic ALP elevation, mild non-specific symptoms (fatigue, fever, anorexia, weakness, vomiting, chills, right upper quadrant pain, pruritus, skin rash, etc.) to severe protracted jaundice, ascites, coagulopathy, and encephalopathy [3]. The use of the offending drug must be stopped as soon as DILI is suspected [4].

Case discussion

This is a 37yr old female patient from Addis Ababa, Ethiopia who presented with yellowish discoloration of the eyes of 4 months duration after she took “Augumentin” for the treatment of Pneumonia at a local health center. She also had pruritus, loss of appetite, urine color change (dark urine) and weight loss. There was no family history of liver disease and no known chronic medical illness. Physical examination was remarkable

for deeply icteric sclera. Laboratory work up initially showed normal CBC, coagulation profile, and RFT. Liver enzymes determination were ALT-549, AST-329, and ALP-1788. R value was <2. Serum total bilirubin was 5.5 mg/dL with the direct fraction being 4.4 mg/dL. Albumin=3.1 gm/dL. RBS-130 mg/dL. Hepatitis panels were negative. HIV test was negative. Autoantibody titers (ANA, ASMA, anti-LKM, and AMA) were negative. Serum IG G level was normal. Urine HCG test was negative. Doppler ultrasound of hepatic and portal veins were normal. The background liver was normal with no evidence of biliary dilatation, cirrhosis, and ascites. Gall bladder was normal on ultrasound evaluation. Abdominal CT scan was done as the hospital was not having MRCP and it turned out to be normal. With the above data the patient was serially evaluated with liver enzymes and bilirubin. Finally after 7 months of the initial drug intake the liver enzymes, bilirubin, and clinical symptoms all resolved. The patient was further advised not to take augumentin in the future. Prednisolone was given initially. Later it was tapered to be discontinued after 1 month as autoimmune marker results turned out to be negative. Liver enzymes and bilirubin finally normalized after 3 months of follow up (Table 1).

Table 1: Trend of liver enzymes and bilirubin during follow up.

Liver enzymes and Bilirubin (normal range)	At diagnosis	After 1 month	After 3 months
AST (5-40IU/L)	321	116	28
ALT (0-45IU/L)	549	171	27
ALP (30-120IU/L)	1788	562	106
BIL-T (0.1-1.2 mg/Dl)	5.5	2.3	0.6
BIL-D (<0.3 mg/Dl)	4.4	0.67	0.13

Discussion

Amoxicillin/clavulanate is a synthetic penicillin that is currently commonly used, especially for the treatment of respiratory and cutaneous infections. In general, it is a well-tolerated oral antibiotic. However, amoxicillin/clavulanate can cause adverse effects, mainly cutaneous, gastrointestinal, hepatic and hematologic, in some cases [5]. Cholestatic DILI is defined as an elevation of alkaline phosphatase greater than twice the normal level and/or an alanine aminotransferase/alkaline phosphatase ratio less than 2 [6]. The clinical presentation of cholestatic DILI is variable, ranging from asymptomatic elevation in ALP to symptoms of jaundice, pruritus, and fever. Unfortunately, there are no serologic markers that can reliably diagnose DILI, and therefore a thorough history is necessary regarding use of prescription and over-the-counter medications as well as vitamin and herbal supplements, along with the timing of when these products were used [7]. Some drugs can lead to chronic cholestasis with prolonged jaundice and features resembling Primary Biliary Cirrhosis (PBC), such as xanthomas, pruritus, and melanoderma. In contrast with PBC, these drug-induced forms are generally considered benign, because in most instances they eventually resolve [8]. Diagnosis is made further difficult as DILI follows diagnosis by exclusion [9]. The first and most important therapeutic measure when DILI is suspected is the immediate withdrawal of all possible causative agents and avoidance of rechallenge [10]. Spontaneous recovery is seen in most patients with DILI; nonetheless, close clinical and biochemical monitoring is vital [11].

Conclusion

Cholestatic DILI diagnosis and management can be a challenge as there are many differential diagnosis. Recognition then removal of the offending drug is the vital step in the management. Follow up of biochemical parameters is important.

Declarations

Data sharing: Supporting data for the current case report are available from the corresponding author on reasonable request.

Informed consent and ethical approval: Prior to data collection, written informed consent was acquired from the patient after the studies had been well explained. The case report was approved by the Research Ethics Review Committee of the hospital.

Disclosure: The authors report no conflicts of interest in this work.

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