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Case Report
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Rare Doxycycline Antibiotic Therapy Induced Cholelithiasis: A Case Report

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Abstract

Patient information: A 61-year-old female patient presented with a complaint of heartburn, bloating and belching for the past month. Upon examination, no abnormalities were noted, and the patient did not have any pre-existing chronic diseases or metabolic abnormalities. During the assessment of the patient's medical history, it was revealed that she had been taking doxycycline 100 mg twice daily for the management of skin pruritus for the past two months.

Clinical findings: The patient's cardiovascular and respiratory systems showed no abnormalities, and the abdomen was soft and non-tender. A chest X-ray performed a month prior showed basolateral fibrosis without severe lung parenchymal damage with low voltage sinus rhythm and atrial fibrillation in ECG (Electrocardiogram). Ultrasonography of the abdomen revealed the presence of two calculi in the gall bladder, indicative of cholelithiasis. Other organs, including the liver, spleen, pancreas, urinary bladder, and kidneys, appeared normal in shape, size, and echotexture. Pathological findings showed total protein levels of 6.38 g/dL, an AST: ALT ratio of 1.02, a platelet count of 112 thou/µL, a lymphocyte percentage of 43.30%, and an absolute basophil count of 0.01 thou/µL.

Follow-up and Outcomes: Considering the patient's clinical history, investigations, and findings, the diagnosis of doxycycline-induced cholelithiasis was made. The patient underwent surgical management, specifically laparoscopic cholecystectomy, which was performed two days after admission and one month after the onset of symptoms. This case report does not provide specific information regarding the postoperative or long-term outcomes of the patient.

Keywords: Liver toxicity; Overdose; Side-effect; Adverse event

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Highlights & Learning Points

- Doxycycline can potentially cause liver injury, and clinicians should be aware of this rare phenomenon during doxycycline therapy.
- The case suggests a possible association between doxycycline use and the development of cholelithiasis or gallstones, although the exact mechanism is unknown.
- Obtaining a thorough medication history is crucial to identify potential drug-related adverse events, including those caused by doxycycline.
- Surgical management, such as laparoscopic cholecystectomy, may be required for symptomatic gallstones associated with doxycycline-induced cholestasis, emphasizing the need for individualized treatment approaches based on the patient's condition.

Introduction

Drug-Induced Liver Injury (DILI) is a significant burden on the healthcare system. In addition, the identification of DILI and can be difficult because it is often diagnosed, the clinical presentation may vary where, there are few data available on risk factors [1]. The liver is the central organ responsible for the selective absorption, metabolism and excretion of drugs, xenobiotics and environmental toxins. This essential function makes the liver vulnerable to drug toxicity and is the primary reason why drugs fail during drug development [2].

Doxycycline-induced liver injury is a rare phenomenon whose clinical course and pathogenesis are unknown. The onset of lesions can be acute to subacute, in forms ranging from hepatocellular or

cholestatic to mixed, and usually lasts up to several weeks [3]. Drug-induced cholestasis may be acute or chronic liver damage. In most cases of cholestatic DILI, it goes away quickly when you stop taking the medicine [1].

Drug-induced cholestasis can be triggered by three types of triggers, namely (1) changes in transporters, such as inhibition of function, reduced expression and abnormal subcellular localization, (2) changes in hepatocytes, including impaired cytoskeleton tight junctions and decreased membrane fluidity, and (3) Altered, dilated, or constricted bile duct dynamics. These stimuli lead to the accumulation of cells and the subsequent activation of two cell responses, the decay response and the adaptive response [4].

Importance of this case report: This case report may contribute to the clinical decision-making regarding the long-term use of the antibiotic doxycycline. Monitoring of liver function can prevent morbidity in patients on doxycycline therapy. All clinicians, clinical pharmacists and pharmacologists must address the outcomes of long-term doxycycline therapy to the patient and their attendees. Also counselled about early signs and symptoms of associated outcomes.

Case Presentation

A 61-year-old female with heartburn, bloating and belching for 1 month, on clinical examination it does not, shows any abnormalities. The patient is conscious and oriented while examining the Cardiovascular System (CVS) both S1 and S2 are present with no cardiac murmur or regurgitation. Upon chest auscultation, basolateral airy entry with no other anomalies is presented. Where abdomen is soft and non-tendered with well-stable vitals (heart rate 72 beats/min; respiratory rate 16/min; blood pressure 120/80 mmHg; and oxygen saturation 99% in room air). The patient does not have any chronic disease or metabolic abnormalities (including hypertension, diabetes mellitus, and cardiovascular disease). During the collection of the patient's past medication history, the patient's attender reveals that she is taking a tablet of doxycycline 100 mg in twice daily doses for 2 months for the management of skin pruritus.

Investigation

As a course of the investigation, an Electrocardiogram (ECG) was taken to evaluate cardiac involvement where it found low voltage sinus rhythm and atrial fibrillation with limb leads I and III <5 mm, pericardial leads <10 mm and slow ventricular response shown in (Figure 1).

A chest X-ray done 1 month back showed basolateral fibrosis with no severe lung parenchymal damage shown in (Figure 2).

Ultrasonography (USG) whole abdomen was done on the same day of admission showing two calculi of size ~ 8 mm to 10 mm in the lumen of the gall bladder suggestive of cholelithiasis. Uterus appears post-menopausal with atrophic changes; endometrial echo is seen in the midline and measures 2.9 mm in thickness. The liver, spleen, pancreas, urinary bladder, and right and left kidneys are seen as normal in shape, size and in echotexture as shown in (Figure 3).

Pathological findings show 6.38 g/dL total protein, 1.02 AST: ALT ratio, 112 thou/µL platelet count, 43.30% lymphocytes, 0.01 thou/µL absolute basophil count and other findings are shown in (Table 1). Hence patient develops heartburn and bloating after 1 month of doxycycline therapy and all the above investigations are suggestive of doxycycline-induced cholelithiasis since there is no exact known mechanism of the developed event.

Differential diagnosis

Doxycycline-induced cholelithiasis should be considered a potential cause of cholelithiasis in patients recently exposed to this antibiotic. However, it is crucial to differentiate it from other conditions with similar clinical presentations. A thorough evaluation, including history, physical examination, laboratory tests, and imaging studies, can help establish an accurate diagnosis and guide appropriate management decisions [2].

Native cholelithiasis: Gallstones formed independently of doxycycline use, often associated with risk factors such as obesity, female gender, pregnancy, rapid weight loss, or a family history of

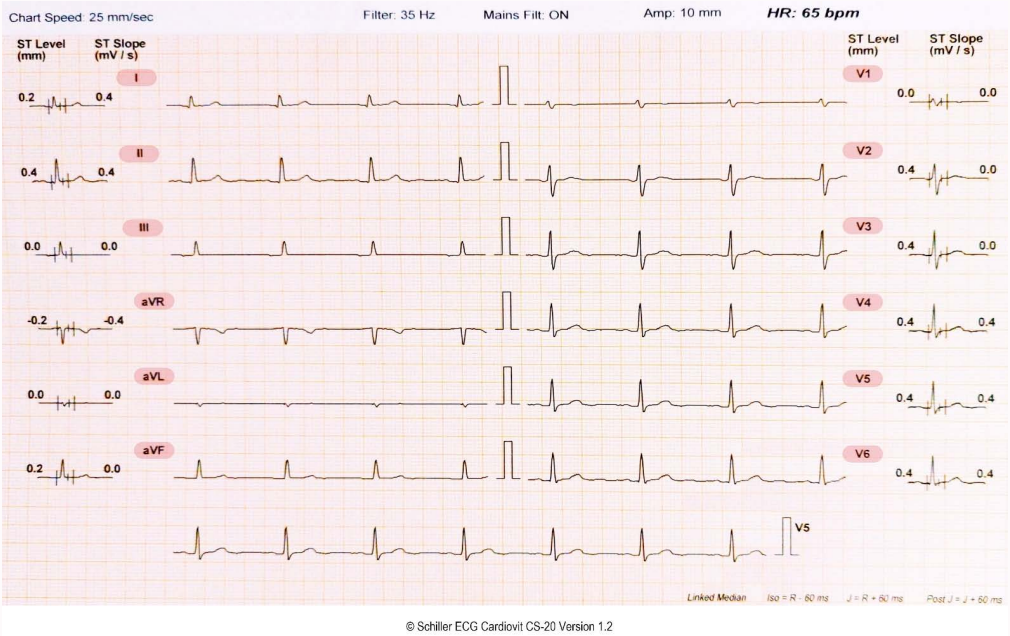

Figure 1: ECG showing low voltage sinus rhythm with limb leads I and III <5 mm, pericardial leads <10 mm and atrial fibrillation with slow ventricular response.

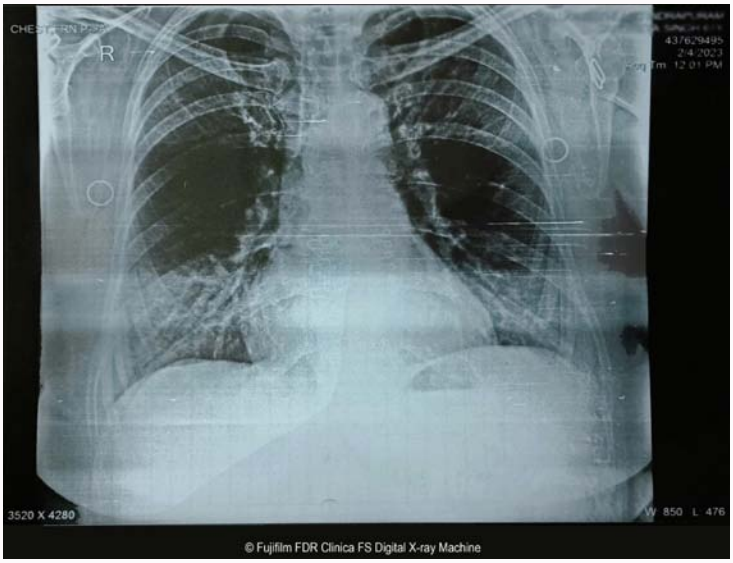

Figure 2: Chest X-ray showing B/L mild fibrosis with mild to moderate thorax enlargement, most probably cardiomegaly and no lung parenchymal damage.

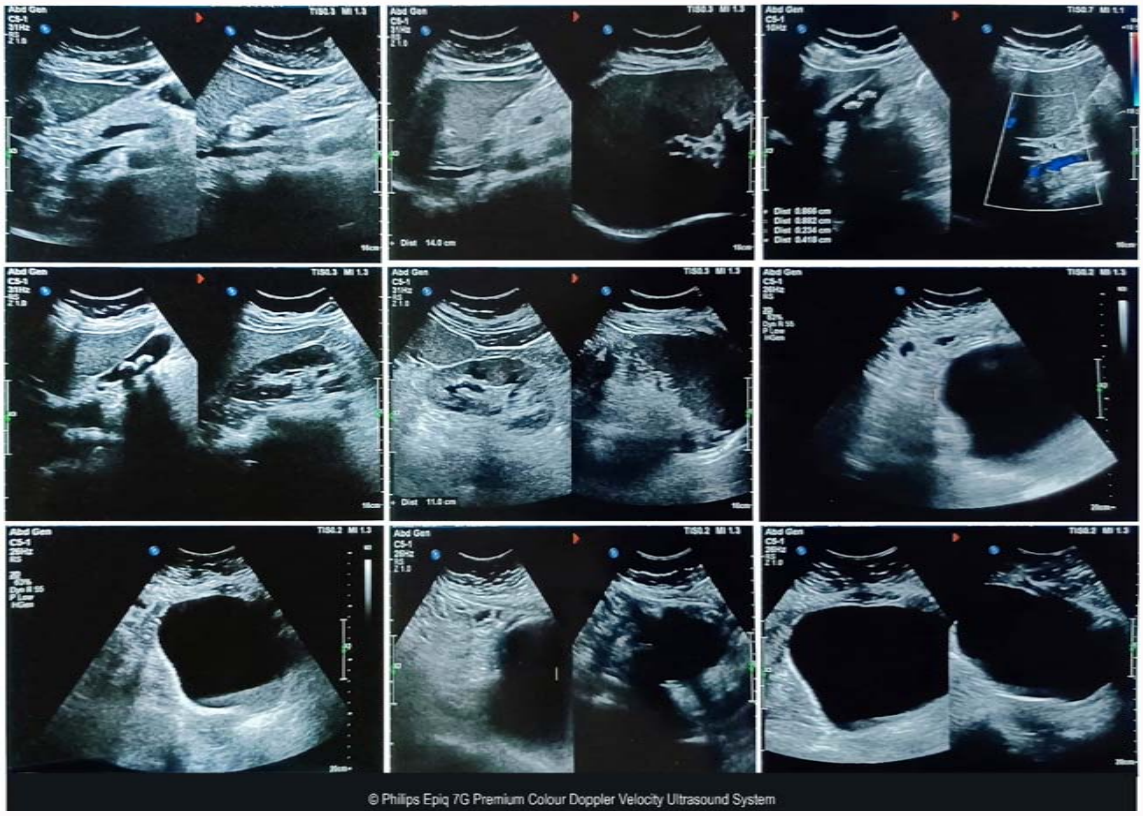

Figure 3: A gall bladder is distended with no wall thickening (2.3 mm), and two calculi of size 8 mm to 10 mm are seen in the lumen – suggestive of cholelithiasis. Spleen size (11.0 cm) and Liver size (14.0 cm) shape and echotexture are normal. The uterus is post-menopausal and shows atrophic change, endometrial echo is seen in the midline and measures 2.9 mm in thickness.

gallstones.

Acute cholecystitis: Inflammation of the gallbladder typically caused by gallstone impaction in the cystic duct, leading to right upper quadrant pain, fever, and leukocytosis.

Choledocholithiasis: Gallstones that migrate from the gallbladder into the common bile duct, resulting in obstructive jaundice, biliary colic, and potential complications such as cholangitis or pancreatitis.

Biliary dyskinesia: Functional disorder characterized by impaired gallbladder contraction and/or sphincter of Oddi dysfunction, leading to similar symptoms as cholelithiasis but without the presence of gallstones.

Hepatitis: Inflammatory conditions affecting the liver, including

Table 1: Pathological findings upon admission.

Investigation	Result
1. Complete Hemogram	
Haemoglobin	12.5 g/dL
Red Blood Cell (RBC) Count	4.19 mil/µL
White Blood Cell (WBC) Count	6.10 thou/µL
Platelet Count	**112 thou/µL**
Haematocrit	37.20%
Mean Corpuscular Volume (MCV)	88.9 fL
Mean Corpuscular Haemoglobin (MCH)	29.8 pg
Mean Corpuscular Haemoglobin Concentrated (MCHC)	33.5 g/dL
Red Cell Distribution Width	13.90%
Neutrophils	49%
Lymphocytes	**43.30%**
Monocytes	9%
Eosinophils	3%
Basophils	0%
Absolute Neutrophil Count	2.99 thou/µL
Absolute Lymphocyte Count	2.38 thou/µL
Absolute Monocyte Count	0.55 thou/µL
Absolute Eosinophil Count	0.18 thou/µL
Absolute Basophil Count	**0.01 thou/µL**
2. Digestive Enzyme	
Serum Amylase	99 U/L
Serum Lipase	41 U/L
3. Liver Function Test	
AST/SGOT	26 U/L
ALT/SGPT	25.5 U/L
AST:ALT Ratio	**1.02**
GGTP	12 U/L
Alkaline Phosphate (ALP)	81 U/L
Total Bilirubin	0.64 mg/dL
Bilirubin, Direct	0.12 mg/dL
Bilirubin, Indirect	0.52 mg/dL
Total Protein	**6.38 g/dL**
Albumin	4.11 g/dL
A:G Ratio	1.81
4. Coagulation Profile	
Activated Partial Thrombin Time (APTT)	27.90 sec
Prothrombin Time (PT)	11.20 sec
Prothrombin Ratio (PR)	1.06 sec
International Normalization Ratio (INR)	0.99 sec
5. HIV and Hepatitis Screening	
Serum HIV 1&2 Antibodies Screening Test	Negative
Hepatitis B Surface Antigen (HBsAg)	Non-Reactive
Hepatitis C Antibody (Anti-HCV)	Non-Reactive

viral hepatitis (e.g., hepatitis A, B, or C), autoimmune hepatitis, drug-induced hepatitis, or alcoholic hepatitis, which may present with right upper quadrant pain and abnormal liver function tests.

Peptic Ulcer Disease (PUD): Gastric or duodenal ulcers can cause epigastric pain that may radiate to the right upper quadrant, mimicking cholelithiasis.

Gastroesophageal Reflux Disease (GERD): Chronic acid reflux can cause substernal or epigastric pain that may be mistaken for biliary colic.

Pancreatitis: Inflammation of the pancreas characterized by severe epigastric pain that may radiate to the back, often associated with elevated serum amylase and lipase levels.

Prognosis

Doxycycline-induced cholelithiasis refers to the formation of gallstones as a potential side effect of taking doxycycline, a commonly prescribed antibiotic [1]. The prognosis for this condition depends on various factors such as the severity of the gallstones and the overall health of the individual. In most cases, once doxycycline is discontinued, the gallstones may resolve on their own without causing significant complications [3]. However, if the gallstones are large or cause blockage in the bile ducts, medical intervention such as surgical removal of the gallbladder may be necessary. Patients need to discuss their symptoms and treatment options with a healthcare professional for an accurate prognosis and appropriate management [5].

Intervention

After the final decision was made a doxycycline-induced cholelithiasis drug was immediately stopped and the patient underwent surgical intervention in the form of laparoscopic cholecystectomy, which was conducted after two days of hospitalization and approximately 1 month to the onset of symptoms. After surgery, the patient was kept on intravenous fluids and multivitamins, injection of cefuroxime sodium 1.5 gm twice daily, pantoprazole 40 mg once daily, and ondansetron 4 mg once daily. Patients were discharged on oral antibiotic tablet cefuroxime axetil 500 mg twice daily for the next 5 days and suggested follow-up after 10 days of discharge.

Follow-up

Based on a comprehensive evaluation of the patient's clinical history, diagnostic investigations, and pertinent findings, the conclusive diagnosis of doxycycline-induced cholelithiasis was established. Subsequently, the patient underwent surgical intervention in the form of laparoscopic cholecystectomy, which was conducted within two days following admission and approximately one month after the manifestation of symptoms. It is noteworthy to mention that this particular case report lacks explicit details regarding the patient's postoperative progression or long-term prognosis.

Discussion

Doxycycline-induced liver injury is a rare condition with unknown pathogenesis and incomplete clinical course. The type of injury can be cholestatic, with potentially serious obstructive consequences [3]. Although minocycline is well documented, no cases link doxycycline to the rare but serious side effects of drug-induced autoimmune hepatitis. Ali Fakhreddin et al. reported a case of doxycycline-induced autoimmune hepatitis secondary to chronic systemic tetracycline use for acne [5].

DILI usually occurs within 1 to 2 weeks of exposure to doxycycline and resolves after weeks after discontinuation. Early recognition and quick charge removal medications are the basis of initial treatment [1,5]. This clinical course, in addition to positive serological markers

and a suggestive liver biopsy, strongly supports Drug-Induced AIH secondary to doxycycline (DI-AIH), over idiopathic AIH or DILI [5].

Sanskriti Varma et al. 2021; presented a case of cholestatic liver injury secondary to doxycycline use in a middle-aged woman. In patients with a history of doxycycline exposure and subsequent liver injury, adverse drug reactions due to doxycycline should continue to be identified and the adverse drug should be withdrawn promptly with close monitoring of the clinical situation [3].

Conclusion

In conclusion, this case report highlights the importance of recognizing and monitoring Drug-Induced Liver Injury (DILI) associated with the long-term use of doxycycline. DILI is a significant burden on the healthcare system, and its identification can be challenging due to varying clinical presentations and limited data on risk factors. Doxycycline-induced liver injury is a rare phenomenon with an unknown clinical course and pathogenesis. The onset of lesions can range from acute to subacute, presenting as hepatocellular or cholestatic, or mixed forms, and typically lasting for several weeks. In cases of cholestatic DILI, the liver damage often resolves quickly upon discontinuation of the medication. Drug-induced cholestasis, a type of DILI, can be triggered by various factors affecting transporters, hepatocytes, and bile duct dynamics. These triggers lead to cell accumulation and the activation of decay and adaptive responses in the liver.

The significance of this case report lies in its contribution to clinical decision-making regarding the long-term use of doxycycline. Monitoring liver function in patients receiving doxycycline therapy is crucial to prevent morbidity associated with DILI. Clinicians, clinical pharmacists, and pharmacologists should educate patients and their caregivers about the potential outcomes and counsel them on recognizing early signs and symptoms of associated liver injury. By raising awareness of the potential risks and promoting proactive monitoring, this case report aims to improve patient safety and facilitate informed decision-making when considering long-term doxycycline therapy.

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