Archives of Surgery and Clinical Case Reports
Ali Butt M, et al. Arch Surg Clin Case Rep 7: 220.
www.doi.org/10.29011/2689-0526.100220
www.gavinpublishers.com

Case Report

Unveiling the Uncommon: Co-occurrence of Drug-Induced Liver Injury and Erythema Multiforme Following Cefazolin Administration

Muhammad Ali Butt[1*], Sameen Aamer[1], Usman Tariq[2], Rachel Toney[2]

[1]Department of Internal Medicine, Allegheny General Hospital, Pittsburgh, PA, USA

[2]Department of Gastroenterology and Hepatology, Allegheny General Hospital, Pittsburgh, PA, USA

[*]**Corresponding author:** Muhammad Ali Butt, Department of Internal Medicine, Allegheny General Hospital, Pittsburgh, PA, USA.

Citation: Ali Butt M, Aamer S, Tariq U, Toney R (2024) Unveiling the Uncommon: Co-occurrence of Drug-Induced Liver Injury and Erythema Multiforme Following Cefazolin Administration. Arch Surg Clin Case Rep 7: 220. DOI:10.29011/2689-0526.100220

Received: 08 February 2024; **Accepted:** 17 February 2024; **Published:** 21 February 2024

Abstract

Adverse drug reactions have a wide variety of manifestations including allergic reactions, anaphylaxis, skin rashes, liver or kidney injury, and gastrointestinal disturbances. Erythema multiforme (EM) and Drug induced Liver injury (DILI) represent significant outcomes of adverse drug reactions. We present a unique case of a 21-year-old female who experienced co-occurrence of EM and DILI following antibiotic administration, an observation which has not been reported before. This case highlights the potential for patients to develop multiorgan involvement in adverse drug reactions. Recognition of such adverse effects is crucial for timely diagnosis, management, and the prevention of unnecessary testing, invasive procedures, and associated complications.

Keywords: Erythema Multiforme; Drug Induced Liver Injury; Cefazolin Induced Drug Reaction; Adverse Drug Reactions.

Introduction

Adverse drug reactions have a wide variety of manifestations including allergic reactions, anaphylaxis, skin rashes, liver or kidney injury, and gastrointestinal disturbances. [1]. Drug reactions leading to skin disorders is a common phenomenon and can have a wide range of manifestations including erythema multiforme (EM), anaphylactic stomatitis, oral lesions, lichenoid changes, pemphigoid like drug reactions and Steven Johnson Syndrome [2]. Similarly, liver damage caused by both prescription and over-the-counter medications is becoming a growing public health problem, with Drug Induced Liver Injury (DILI) being the single most frequent rationale for the Food and Drug Administration's regulatory actions against specific drugs and supplements [3]. EM and DILI are two important manifestations of adverse drug reactions. We present a unique case of co-occurrence of EM and DILI.

Case Presentation

A 21-year-old female presented to our hospital with a worsening pruritic rash. The patient initially presented to an outside hospital with nausea, vomiting, and fever for 1 week. Her blood work was remarkable for elevated liver function tests (LFTs). A right upper quadrant ultrasound was performed which revealed mild gallbladder wall thickening and cholelithiasis. The patient subsequently underwent laparoscopic cholecystectomy on the same day. On postoperative day 1 she was discharged home in stable condition.

However, five days later the patient presented to our hospital with a rash. The patient reported that the rash initially appeared on the face and subsequently spread caudally to involve the neck, chest, abdomen, and bilateral upper and lower extremities. It was

pruritic and painful in nature and was associated with dry eyes. The patient's review of systems was otherwise unremarkable with pertinent negatives including nausea, vomiting, abdominal pain, fever, and chills. The patient also denied any sick contacts, recent travel history, or use of any over-the-counter medications, herbal supplements, new vitamins, or wild mushrooms. The patient had been in a heterosexual monogamous relationship and did not have any history of tattoos or intravenous drug use. Her past medical history was significant for anxiety and depression. Past surgical history included a cesarean section and a recent cholecystectomy. The patient did not have any personal or family history of liver, pancreas, or gallbladder disease. She did not take any medications at home. She did receive a preoperative antibiotic (Cefazolin) at the outside hospital.

On presentation, the patient was afebrile and had stable vital signs. Physical examination showed a diffuse macular erythematous skin rash involving her face, chest, torso, and bilateral upper and lower extremities (Figure 1). No palpable lymphadenopathy or oral mucosal involvement was appreciated. Cardiopulmonary and abdominal examination was unremarkable. No edema was noted in the lower extremities.

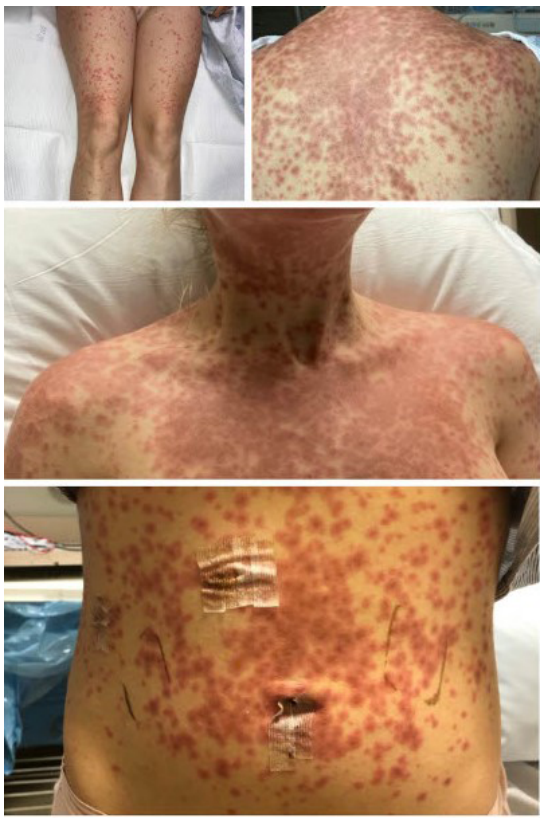

Figure 1: Diffuse Macular Erythematous Rash with Target Lesions.

On admission, the initial laboratory workup showed a complete blood count and basic metabolic panel within normal limits. Her LFTs were elevated AST 573 U/L, ALT 910 U/L, Total bilirubin 6.0 mg/dL, Alkaline Phosphatase 280 U/L and INR 1.2. A right upper quadrant ultrasound was performed which was notable for prior cholecystectomy, with no hepatobiliary pathology. A computed tomography (CT) scan of the abdomen was also done which showed no acute intraabdominal process. Therefore, a series of laboratory tests were performed to rule out infectious, autoimmune, and toxic etiologies. The results of these labs are summarized below in Tables 1 and 2. (Table 1).

Hepatitis A	Hep A IgM-Negative
	Hep A IgG-Positive
Hepatitis B	Hep B sAg-Negative
	Hep B cAb (total and IgM)-Negative
	Hep B sAb-Negative
Hepatitis C	Hep C Ab- Negative
CMV, EBC	Negative
HSV 1, 2	Negative
Parvovirus B19	Negative
Mycoplasma Pneumoniae	IgM-Negative IgG-Negative

Table 1: Infectious Work-up.

The patient was started on symptomatic treatment for rash with topical triamcinolone ointment and per-oral cetirizine. A skin biopsy was performed which showed basal vacuolar interface dermatitis with negative direct immunofluorescence, the totality of findings consistent with changes of erythema multiforme. Patient's LFTs continued to rise, increasing up to AST 928 U/L, ALT 1823 U/L, T.bilirubin 6.6 mg/dL, Alk Phos 537 U/L, INR 1.2 (Table 3). Subsequently, a liver biopsy was performed and the patient was started on N-Acetyl Cysteine (NAC). Unfortunately, the patient developed an urticarial reaction to NAC so it was discontinued. The liver biopsy showed liver parenchyma with canalicular cholestasis and spotty foci of hepatocellular dropout. In the setting of no specific features of autoimmune hepatitis on liver biopsy, and laboratory work-up negative for infectious and autoimmune etiologies, drug-induced liver injury was thought to be the most likely diagnosis. A retrospective review was done which revealed that the only new medication that the patient recently received was preoperative Cefazolin. Patient was thus diagnosed with drug-induced EM and liver injury. Over the course of the patient's hospitalization, her rash improved and LFTs started trending down after peaking (Table 2). Given the improvement in clinical status, the patient was ultimately discharged home with plans for outpatient follow-up. 3 weeks later outpatient Blood work done

showed normalization of liver function tests (Table 3). The patient also reported a resolution of rash on telephone follow-up.

Antinuclear Antibody	Negative
Anti-mitochondrial Antibody	Negative
Anti-Smooth muscle Antibody	Negative
Alpha-1 Antitrypsin Levels	Normal
Ceruloplasmin Levels	Normal
Ig G Levels	Normal
Ig M Levels	Normal
Liver Kidney Microsome Type 1 Antibody	Normal

Table 2: Autoimmune and Immunological Workup.

	Day 0	Day 2	Day 4	Day 6	Day 21
Aspartate Aminotransferase (U/L)	573	754	928	557	37
Alanine Aminotransferase (U/L)	910	1473	1823	1459	59
Alkaline Phosphatase (U/L)	280	512	537	552	125
Total Bilirubin (mg/dl)	4.1	6.5	6.6	6.7	1.2
International Normalized Ratio	1.2	1.2	1.2	1.3	1.1

Table 3: Liver Function Tests – Trend.

Discussion

Adverse drug reaction (ADR) can be described as an inadvertent reaction that occurs in response to medication administration [1]. ADRs can be classified as Type A- augmented reactions which are dose-dependent vs Type B-bizarre reactions which are idiosyncratic. Adverse drug reactions can have multiple manifestations like allergic reactions, anaphylaxis, skin rashes, liver injury, kidney injury, and gastrointestinal disturbances [1].

EM is an acute, self-limiting skin condition that mostly affects women between 20-40 years of age [4]. The prevalence of the disease is less than 1% [4]. It is characterized by mild prodromal symptoms such as malaise and sore throat, followed by a skin rash. [5, 6]. It can be caused by infections (herpes simplex virus 70%), heavy metals, herbal agents, and poison ivy [2, 7]. Multiple medications have also been linked with EM including nonsteroidal anti-inflammatory drugs and antibiotics [2, 7]. Cephalosporins are the most commonly associated medications [4]. The clear etiology of the disease is unknown but it has been hypothesized that genetic predisposition to HLA genes and hypersensitivity reactions to antigens, result in the activation of CD8+ T lymphocytes and apoptosis of keratinocytes, causing cell necrosis [2, 8]. The disease is diagnosed clinically on the basis of the history and physical exam. However, a skin biopsy can be performed to confirm the diagnosis [7]. The treatment for EM is directed at the removal of the causative agent and symptomatic management with steroids and antihistamines [6,7].

DILI is another manifestation of ADR. Multiple etiologies of the disease have been hypothesized, including mitochondrial toxicity, intrinsic liver injury, immune-mediated damage, and variations in drug pharmacokinetics [9]. It can manifest over a wide spectrum of diseases starting from mild disease with abnormalities in the liver function tests only, to severe disease ranging from fibrosis to acute liver failure [10]. DILI can be caused by a myriad of drug classes including oral hypoglycemic agents, statins, acetaminophen, antiretrovirals, antibiotics, and dietary supplements [11]. Antibiotics are the most common class of medications responsible for DILI, constituting 45.4% of the total cases [12]. Hepatotoxicity caused by antibiotics is usually idiosyncratic [10]. Most commonly involved antibiotics include amoxicillin-clavulanate, cephalosporin, isoniazid, and nitrofurantoin [11]. Cefazolin has been found to be the sixth most common medication associated with DILI according to Drug-induced Liver Injury Network (DILIN)- an ongoing prospective study in the US [13].

Laboratory workup for DILI includes complete blood count, complete metabolic panel (CMP), viral and autoimmune workup, toxicology screen, and right quadrant ultrasound [14]. More importantly, DILI is a clinical diagnosis [10]. Liver biopsies are not indicated but can be performed to look for the type and severity of injury [11]. Management for DILI consists of withdrawal of the causative agent, avoiding rechallenge with the medication, and symptomatic treatment. It is a self-limiting disease that resolves after drug cessation, however, in some patients, it progresses to acute liver failure or cirrhosis [11].

Due to uncertainties regarding the precise diagnosis in patients presenting with liver injury, patients end up undergoing extensive testing such as CT scans, MRIs, and invasive procedures including ERCPs and Liver biopsies which are often not required and can result in complications [13].

This case is unique as our patient developed erythema multiforme and Drug-induced liver injury simultaneously after cefazolin administration. To the best of our knowledge, co-occurrence of EM and DILI has not been reported previously. This shows that patients can develop adverse drug reactions involving multiple organ systems concurrently. Knowing this in the right clinical setting can help prevent unnecessary work-up and invasive procedures given the self-limiting nature of EM and DILI.

Conclusion

In conclusion, it is important to recognize the adverse effects of antibiotics such as EM and DILI, which are often missed as they are uncommon when compared to side effects such as gastrointestinal symptoms and allergic skin reactions. Timely diagnosis, thorough causation assessment, and management are crucial to avoid unnecessary work-up, invasive procedures, and complications. This case is also important as it is the first case that reports co-occurrence of EM and Liver injury as an adverse drug reaction.

Learning Points

1. Erythema Multiforme and Drug-Induced Liver Injury are important manifestations of adverse drug reactions, and although rare, they can occur concurrently.
2. Adverse Drug Reactions can result in the involvement of multiple organs simultaneously.
3. Timely recognition can help prevent unnecessary testing and invasive procedure.

Conflicts of Interest: The authors have no conflict of interest to declare.

Consent: Informed Consent was obtained from the patient for publication of this case.

References

1. Coleman JJ, Pontefract SK (2016) Adverse drug reactions. Clin Med (Lond) 16(5):481-485.
2. Shah SN, Chauhan GR, Manjunatha BS, Dagrus K (2014) Drug induced erythema multiforme: two case series with review of literature. Journal of Clinical and Diagnostic Research JCDR 8(9): ZH01-4.
3. Bell LN, Chalasani N (2009) Epidemiology of idiosyncratic drug-induced liver injury. Semin Liver Dis 29(4):337-47.
4. Yavuz IH, Yavuz GÖ, Biligili SG, Bayram I, Savas H (2018) Erythema Multiforme; Sixty Six Case Series with Review of Literature. Eastern Journal of Medicine 23: 308-312.
5. Kamala R, Usha RR, Sonia S, Gigi R, Neha G (2018) Drug induced erythema multiforme: Reporting 2 cases. Journal of Indian Academy of Oral Medicine and Radiology 30(3): 306-309.
6. Karthik R, Ravikumar PT, Fenn SM, Durgadevi P, Mohithan S, et al. (2021) Drug induced bullous form of erythema multiforme in a 75-year-old male: A case report. J Clin Images Med Case Rep 2(3): 1205.
7. Hafsi W, Badri T (2023) Erythema Multiforme. 2023 Mar 16. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
8. Fitzpatrick SG, Cohen DM, Clark AN (2019) Ulcerated Lesions of the Oral Mucosa: Clinical and Histologic Review. Head and Neck Pathol 13: 91-102.
9. Low EXS, Zheng Q, Chan E, Lim SG (2020) Drug induced liver injury: East versus West - a systematic review and meta-analysis. Clin Mol Hepatol 26(2):142-154.
10. Guarino M, Perna B, Pastorelli A, Bertolazzi P, Caio G, et al. (2022) A case of ceftriaxone-induced liver injury and literature review. Infez Med 30(2): 293297.
11. Yang K, Moga T, Nallapeta N S, Duve R, Miranda CJ, et al. (2022) Severe Cholestatic Drug-Induced Liver Injury With Cephalosporin Use. Cureus 14(12): e32262.
12. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, et al. (2015) United States Drug Induced Liver Injury Network. Features and Outcomes of 899 Patients with Drug-Induced Liver Injury: The DILIN Prospective Study. Gastroenterology 148(7): 1340-52.e7.
13. Alqahtani SA, Kleiner DE, Ghabril M, Gu J, Hoofnagle JH, et al. (2015) Identification and Characterization of Cefazolin-Induced Liver Injury, Clinical Gastroenterology and Hepatology 13(7): 1328-1336.e2.
14. Tajiri K, Shimizu Y (2008) Practical guidelines for diagnosis and early management of drug-induced liver injury. World J Gastroenterol 14(44): 6774-85.