Idiosyncratic Drug-Induced Liver Injury Due to Ciprofloxacin: A Report of Two Cases and Review of the Literature

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Conflict of interest: None declared

Case series
Patient: Male, 35 • Male, 82
Final Diagnosis: Idiosyncratic DILI due to Ciprofloxacin
Symptoms: Abdominal discomfort • fever • jaundice • nausea
Medication: Ciprofloxacin
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Challenging differential diagnosis
Background: Drug-induced liver injury (DILI) can present clinically as a spectrum that includes asymptomatic elevation of transaminases, acute or chronic hepatitis, and acute liver failure. Idiosyncratic DILI is more likely to affect individuals with comorbidities, and to have a wide range of clinical presentations. Although antibiotics are associated with DILI, the fluoroquinolone, ciprofloxacin, is a rarely reported cause. Two cases of idiosyncratic DILI following ciprofloxacin treatment are described, including a review of the literature.
Case Report: Case 1: A 35-year-old man was treated with ciprofloxacin for periorbital cellulitis. On the second day of ciprofloxacin treatment, he developed abdominal pain, nausea, vomiting and increased serum levels of liver transaminases, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). Further investigations excluded infectious hepatitis, autoimmune disease, or structural liver disease. Exclusion of other causes of DILI and cessation of ciprofloxacin resulted in clinical improvement and normalization of liver function tests (LFTs). Case 2: An 82-year-old man was treated with ciprofloxacin for osteomyelitis. On the tenth day of ciprofloxacin treatment, he developed jaundice and abnormal LFTs, including increased AST, ALT, alkaline phosphatase (ALP), and total bilirubin. Further investigations excluded infectious hepatitis, autoimmune disease, or structural liver disease. Exclusion of other causes of DILI and cessation of ciprofloxacin resulted in clinical improvement and normalization of LFTs.
Conclusions: Idiosyncratic DILI due to ciprofloxacin treatment is rare. These two cases have shown that timely diagnosis and discontinuation of ciprofloxacin can prevent the progression of DILI, reduce liver damage, and reduce mortality rates from DILI.

MeSH Keywords: Ciprofloxacin • Drug-Induced Liver Injury • Liver Failure, Acute

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Background

Drug-induced liver injury (DILI) presents as a spectrum of disease that can range from asymptomatic elevation of transaminases, acute or chronic hepatitis, to acute liver failure [1]. DILI has been reported to be the most common cause of acute liver failure in Europe and the United States (US) [2,3]. The diagnosis of DILI can be challenging due to the wide range of potential causative drugs, the varied clinical presentation, and the lack of specific diagnostic tests [4]. DILI can be divided into two types: intrinsic DILI, or type A, which is predictable and drug dose-dependent; and the less common idiosyncratic DILI, or type B, which is non-predictable, and drug dose-independent [5]. Idiosyncratic (type B) DILI is more likely to affect susceptible individuals, who may have comorbidities, has a wider range of clinical presentations, and has yet to be reproduced in animal studies [4].

Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic that exerts its bactericidal effect by targeting two essential enzymes, gyrase, and topoisomerase [6]. Ciprofloxacin inhibits bacterial DNA gyrase and stabilizes the DNA-topoisomerase-drug complex, which leads to bactericidal and bacteriostatic effects, respectively [6]. Also, treatment with ciprofloxacin increases the release of reactive oxygen radicals, which contributes to its overall bactericidal effect (6). Ciprofloxacin is widely used due to its broad antimicrobial spectrum of activity, good bioavailability, low cost, and ease of administration [7]. The active form of ciprofloxacin is excreted in the saliva, bronchial secretions, lymph, bile, the prostate, and urine, which make it a good antibiotic choice for a wide range of bacterial infections [8]. Ciprofloxacin is usually well-tolerated, and it has a low incidence of adverse side effects [5]. The most severe side effects of fluoroquinolone antibiotics, in general, include tendon rupture, hemolytic uremic syndrome, interstitial nephritis, and prolongation of the cardiac Q-T interval [5,8].

The idiosyncratic form of DILI associated with ciprofloxacin treatment has previously been considered to be rare, but increasing numbers of reports have been published recently [9]. The first case of DILI associated with ciprofloxacin was described in 1992 [10]. Since then, 25 cases have been reported in the English literature [10–31], including the two cases described in this report.

Case Report

Case 1

A 35-year old man, who was living in a homeless shelter, had a history of intravenous (IV) heroin use and chronic untreated hepatitis C virus (HCV) infection. He was admitted to hospital with periorbital swelling, redness, pain, and a pruritic maculopapular rash. He denied smoking or drinking alcohol, he was heterosexual and denied any history of sexually-transmitted infections. He was not taking any prescription or over-the-counter medications.

On hospital admission, his vital signs were stable, except for a temperature of 39.3°C. On physical examination, he was not in distress, his heart rate was regular, and there were no cardiac murmurs. His chest, his lungs were clear bilaterally. His abdomen was soft and non-tender, with normal bowel sounds. Examination of his skin showed a diffuse maculopapular rash, with prominent areas of scaling and hypertrophy on the flexor surfaces, suggestive of prolonged scratching. Because the rash was suggestive of scabies, skin scraping were examined, which confirmed the diagnosis of scabies. The skin around his left eye was red, swollen, and without discharge. Due to severe periorbital edema, his left eye was closed most of the time, but his vision in the left eye was normal, and there was no pain during eye movement.

His liver function tests (LFTs) were within the normal range for our laboratory, as follows: aspartate aminotransferase (AST), 0–41 U/L; alanine aminotransferase (ALT), 0–45 U/L; alkaline phosphatase (ALP), 30–115 U/L; total bilirubin, 0.2–1.2 mg/dl. Serology for hepatitis A virus (HAV) and hepatitis B virus (HBV) were negative. The hepatitis C virus (HCV) viral load was 37,857 IU/ml. Cytomegalovirus (CMV) and Epstein–Barr virus (EBV) serology were positive for IgG and negative for IgM, indicating previous infection. Human immunodeficiency virus (HIV) p24 antigen and a fourth-generation combination immunoassay for HIV were negative. Serology for syphilis and leptospirosis were negative as well. Blood cultures showed no growth. Laboratory investigations for autoimmune hepatitis included serum antinuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-mitochondrial antibodies (AMA), which were all were negative. Ceruloplasmin, alpha-1 antitrypsin, and ferritin levels were all within the normal range. The plasma cortisol level was borderline low, and the adrenocorticotropin (ACTH) stimulation test was normal. Thyroid-stimulating hormone (TSH) and free thyroxine (T4) were within the normal range. Liver ultrasound (US), including Doppler US, were performed to evaluate the liver parenchyma, biliary tract, and to exclude Budd-Chiari syndrome and portal vein thrombosis. Abdominal computed tomography (CT) showed no focal liver abnormality and excluded the presence of liver abscess and biliary tract dilatation.

Because the patient was diagnosed with periorbital cellulitis, he was treated with intravenous (IV) clindamycin (600 mg every 8 hours), and with IV ciprofloxacin (400 mg every 12 hours), which reduced the orbital redness and swelling. However, on the second day following antibiotic treatment, he developed nausea,
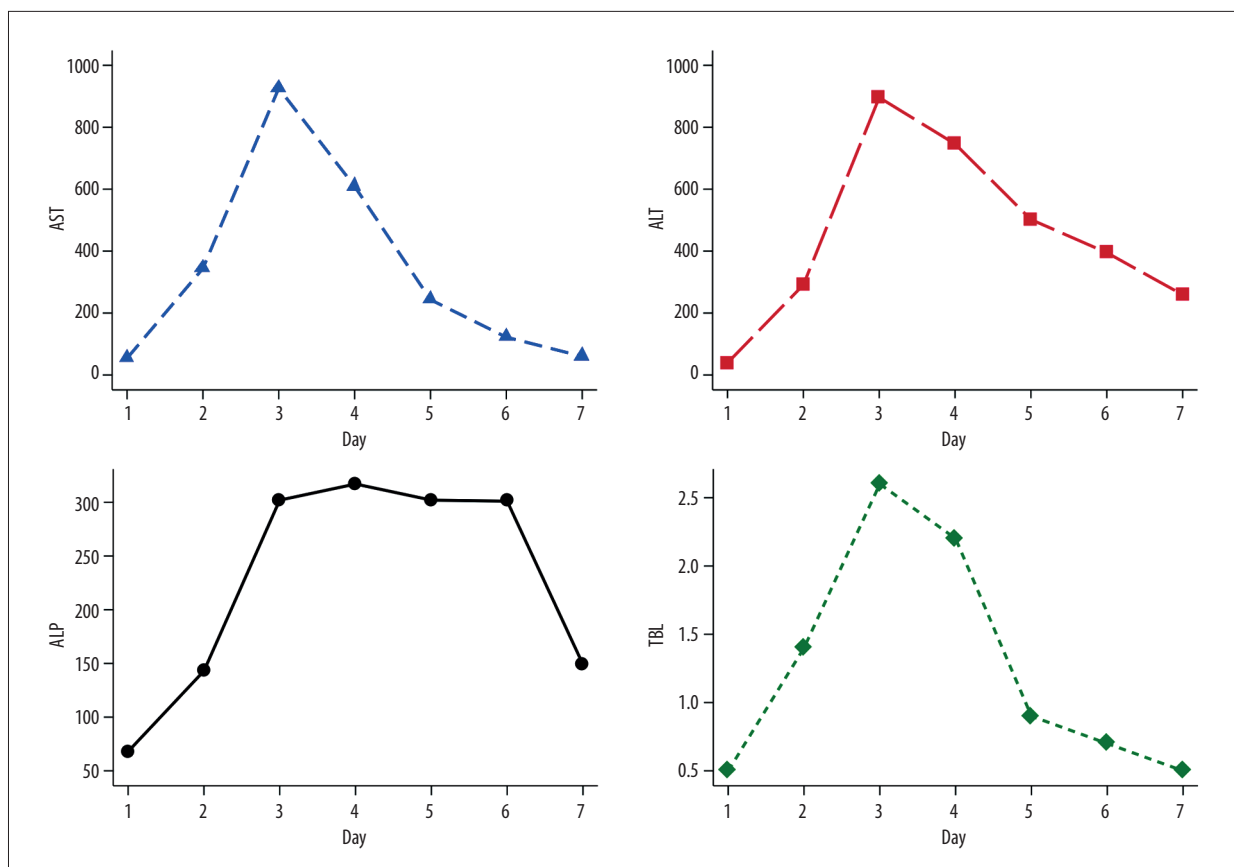
Figure 1. Case 1. A graph showing the increase in selected liver function tests (LFTs) in the days following the start of ciprofloxacin therapy. AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; TBL – total bilirubin. Normal values for LFTs in our institution: AST – 0–41 U/L; ALT – 0–45 U/L; ALP – 30–115 U/L; TBL – 0.2–1.2 mg/dl.

right upper quadrant (RUQ) abdominal pain, and fatigue, and his LFTs began to increase, reaching a peak on the third hospital day, as shown in Figure 1. Treatment with ciprofloxacin was stopped on the fourth day of treatment due to a presumptive diagnosis of idiosyncratic drug-induced liver injury (DILI).

In this patient, a diagnosis of idiosyncratic DILI associated with ciprofloxacin therapy was made by excluding other potential causes of acute liver injury, including infection, autoimmune disease, biliary tract obstruction, and structural liver diseases. The diagnosis of idiosyncratic DILI was also supported by the patient's clinical improvement, as well as the normalization of liver enzymes, within four days following cessation of ciprofloxacin therapy. The Roussel Uclaf Causality Assessment Method (RUCAM), a method of patient assessment used to quantify the strength of the association between liver injury and the drug that might be the cause of the injury, showed that this patient had a scale that was categorized as 'highly probable.'

Case 2

An 82-year-old man with a history of hypertension, type 2 diabetes mellitus, and who had undergone a right tympanomastoidectomy two months previously, was admitted to hospital with a severe headache and right ear pain that began two days prior to admission. The patient was a non-smoker, and he did not drink alcohol or use any illicit drugs. His regular medication included amlodipine and metformin.

On admission to hospital, he was found to be febrile with a temperature of 39.2°C, and a leukocytosis of 19×10^{12} per liter, but with otherwise stable vital signs. Physical examination showed tenderness on palpation of the tragus of the right ear and mastoid. Examination of the ear showed a mass in the right external auditory canal that obstructed the view of the right tympanic membrane. Pure-tone air and bone conduction testing showed a moderate to severe mixed hearing loss in the right ear. There were no stigmata of chronic liver disease, and there was no abdominal pain or tenderness.
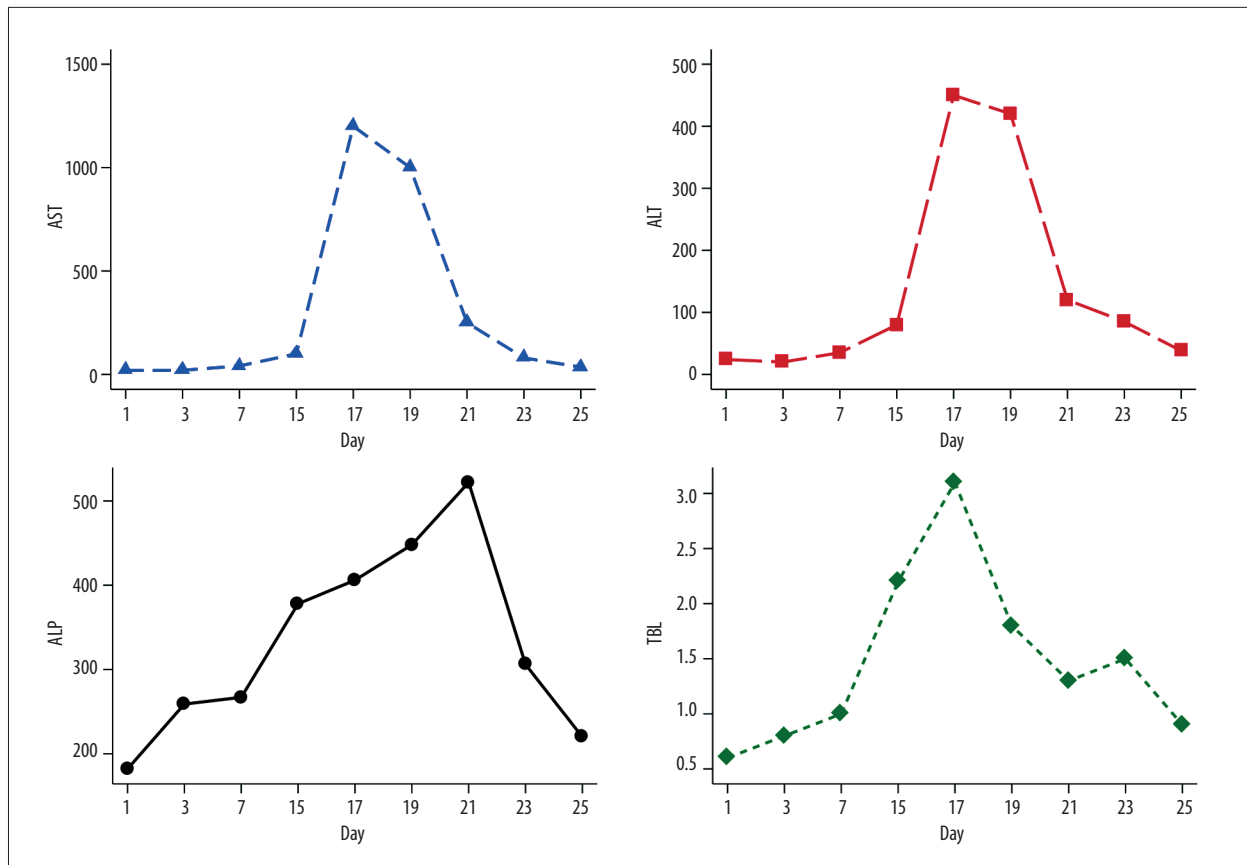
Figure 2. Case 2. A graph showing the increase in selected liver function tests (LFTs) in the days following the start of ciprofloxacin therapy. AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; TBL – total bilirubin. Normal values for LFTS in our institution: AST – 0–41 U/L; ALT – 0–45 U/L; ALP – 30–115 U/L; TBL – 0.2–1.2 mg/dl.

Viral serology, including for HAV, HBV, HCV, HIV, EBV, and CMV, were all negative for acute infection. An autoimmune disease diagnostic workup, including ANA, ASMA, and AMA was also negative. Liver imaging, including abdominal ultrasound and abdominal CT scan, did not demonstrate any biliary obstruction, vascular obstruction, or abscess. A head CT scan showed abscess formation in the right posterior nasopharynx, anterior to the clivus. Brainstem magnetic resonance imaging (MRI) showed the presence of an abscess measuring 21×11×10 mm in size, with osteomyelitis of the clivus. Drainage of the abscess was performed, and culture of the aspirate grew *Pseudomonas aeruginosa*. He was initially treated with imipenem (500 mg every 6 hours) for two weeks, which was then changed to ciprofloxacin (400 mg IV every 12 hours). His LFTs were initially normal on hospital admission. On the seventh day of ciprofloxacin treatment, his LFT levels increased (Figure 2). As a result, ciprofloxacin was discontinued.

However, at this time, the patient developed aspiration pneumonia. Treatment with piperacillin with tazobactam was started, and continued for the next seven days, resulting in clinical improvement. The patient was discharged to a nursing home without any sequelae from his episode of idiosyncratic DILI. The RUCAM, used to quantify the strength of the association between liver injury and the drug that might be the cause of the injury, showed that this patient had a scale that was categorized as 'highly probable' for ciprofloxacin and 'probable' for imipenem.

Discussion

Drug-induced liver injury (DILI) can be divided into intrinsic DILI, which is drug dose-dependent, and the less common idiosyncratic DILI, which is drug dose-independent, more likely to affect susceptible individuals, who may have comorbidities, and has a wider range of clinical presentations [4,5]. Antibiotics and antiepileptic medications are recognized to be associated with DILI in more than 60% of cases [32]. While amoxicillin is the most common cause of DILI in Europe, anti-tuberculosis drugs are the most common cause of DILI in India [1,56]. Acute severe liver injury due to treatment with fluoroquinolones is rare, and it is estimated to occur in less than 10 patients per million [7].

A case-controlled study from Canada showed that the risk of liver injury was most commonly associated with moxifloxacin and levofloxacin from this antibiotic group, while ciprofloxacin appeared to be the safest in clinical practice [33]. The same study found that two-thirds of patients had begun their medication within two weeks of hospital admission for idiosyncratic DILI, consistent with earlier reports of the rapid onset and a short latency period between exposure to fluoroquinolones and the development of DILI [9,23]. These findings were also shown by Case 1 and Case 2 in this report, with both patients having a short latency period, and both patients developed liver injury on the second and the seventh day following initiation of ciprofloxacin therapy. Orman et al. reported that the median latency period or the time between commencing ciprofloxacin treatment to the development of elevated liver function tests (LFTs) was 2.5 days [9]. In Case 1 and Case 2 in this report, the latency period for the onset of ciprofloxacin-associated idiosyncratic DILI occurred at two days and seven days respectively; in the literature review of previously published cases, the median latency period for the development of ciprofloxacin-associated idiosyncratic DILI was eight days.

The liver is the most commonly affected visceral organ in drug reactions, with a drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), also known as drug-induced hypersensitivity syndrome (DIHS), which can present clinically in a similar way to idiosyncratic DILI. It has previously been reported that the short latency periods in cases of quinolone-induced idiosyncratic DILI could distinguish between DILI and hepatitis as part of the DRESS syndrome, which usually has a long latency period [34].

The mechanism of liver injury in idiosyncratic DILI can be divided into two categories, immunological, and metabolic [35–37]. Between 25–30% of all cases of idiosyncratic DILI are secondary to immune or allergic drug reactions [35]. The exact mechanism of idiosyncratic DILI remains unknown, mainly because the condition is difficult to reproduce and study in animal models. However, some theories of the mechanism of idiosyncratic DILI have recently included 'the inflammatory stress hypothesis,' which involves bacterial lipopolysaccharide, released during the inflammation or infection together with antibiotic metabolites, which serves as a trigger for idiosyncratic DILI [38,39]. This hypothesis is plausible since antibiotics prescribed for bacterial infection cause the majority of cases of idiosyncratic DILI.

Another theory of the mechanism of idiosyncratic DILI includes the 'danger hypothesis,' which emphasizes a co-stimulatory trigger as an essential step in the pathogenesis of idiosyncratic DILI, which could be a drug metabolite. However, a co-stimulus (usually a cytokine released by damaged or stressed cells) is necessary to initiate the cascade of events leading to cell damage and death. This co-stimulus (cytokine) usually activates an antigen-presenting cell, which in turn leads to the recruitment of helper and cytotoxic T-cells, resulting in antibody-mediated cytotoxicity [40,41]. This immune 'danger theory' could explain the observations that patients with pre-existing liver disease, including alcoholic cirrhosis or chronic viral hepatitis, are more prone to develop idiosyncratic DILI [40].

Based on the available clinicopathologic data, it appears that ciprofloxacin can cause idiosyncratic DILI as a dose-independent idiosyncratic toxic reaction, which is supported by the relatively short delay between the initiation of ciprofloxacin and the development of liver injury in the majority of the reported cases [33]. Also, both the acute onset of idiosyncratic DILI and the lack of correlation between the dose of ciprofloxacin and the onset of DILI and its severity support idiosyncratic nature of the injury. Unlike ciprofloxacin, some medications, such as nitrofurantoin and minocycline, tend to cause DILI after a long latency period [4]. Others drugs tend to have a signature pattern of DILI response, such as dapsone and sulfonamide, which are associated with granulomatous hepatitis. Tamoxifen is associated with steatohepatitis, while methyldopa, minocycline, and nitrofurantoin are most commonly associated with the development of autoimmune hepatitis [40].

It remains unclear what patient-specific risk factors are associated with the development of DILI. While pre-existing liver disease can predispose patients to idiosyncratic DILI, this finding comes from observational studies only and is not supported by controlled clinical studies [33]. However, the presence of pre-existing liver disease might place these patients at risk for a more complicated clinical course and might increase mortality [42,43]. The data regarding specific demographic and clinical associations, including female gender, the presence of diabetes mellitus, human immunodeficiency virus (HIV) infection, and chronic use of alcohol, as potential risk factors for the development of idiosyncratic DILI are inconsistent between different studies [43]. In our review of the literature of previously published cases of idiosyncratic DILI following ciprofloxacin treatment, the predominant gender was male, and the presence of HIV infection, as well as alcohol use, were not found in any of the 25 cases (Table 1). In this report, Case 1 and Case 2 were male patients. Case 1 had untreated hepatitis C infection, which might have been a risk factor, although there have been no studies to support the significance of this association. Case 2 had no previously reported risk factors for the development of idiosyncratic DILI following ciprofloxacin treatment.

The spectrum of the clinical presentation of patients with DILI is broad, but most frequently DILI presents as a viral-like hepatitis syndrome with fatigue, nausea, and right upper quadrant (RUQ) abdominal pain associated with an elevation in liver

Table 1. Summary of published case reports of idiosyncratic drug-induced liver injury (DILI) due to ciprofloxacin.

Case	Reference	Age	Sex	Dose/formu-lation/regimen	Latency/time to injury (days)	Outcome	Type of injury	ALT (U/L)	AST (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	INR	Liver biopsy/histology	Steroids
1	Grassmick et al. (1992) [10]	66	M	500 mg PO BID	2	Death	Hepato-cellular	2608	2625	269	15.4	7.5	Autopsy: extensive centrilobular necrosis; lymphoplasmacytic infiltrate	No
2	Levinson and Kumar (1993) [11]	46	F	N/A	several days	LFT normalized	Cholestatic	519	305	1459	10.6	N/A	N/A	No
3	Fuchs et al. (1994) [12]	92	M	200 mg IV BID	2	Death	Hepato-cellular	Elevated	Elevated	N/A	N/A	N/A	N/A	No
4	Sherman and Beizer (1994) [13]	84	F	500 mg PO BID	7	LFT normalized	Cholestatic	226	126	1411	8.2	WNL	N/A	No
5	Villeneuve et al. (1995) [14]	44	F	500 mg PO BID	15	LFT normalized	Hepato-cellular	745	750	284	16.5	N/A	Severe hepatitis with centrilobular bridging necrosis and collapse	No
6	Alcalde et al. (1995) [15]	27	M	750 mg PO BID	10	LFT normalized	Hepato-cellular	248	493	N/A	4.3	N/A	N/A	No
7	Aggarwal and Gurka (1995) [16]	36	M	750 mg PO BID	5	LFT normalized	Cholestatic	61	33	792	3	N/A	N/A	No
8	Hautekeete et al. (1995) [17]	50	M	250 mg PO BID	5	LFT normalized	Cholestatic	202	111	314	8.2	WNL	Centolobular cholestasis, minimal infiltration by lymphocytes and single eosinophiles	No
9	Labowitz and Silverman (1997) [18]	47	M	500 mg PO BID	2	LFT normalized	Cholestatic	308	109	163	10	1.6	Intracellular and intacanallicular cholestatis, scattered necrotic hepatocytes and foci of inflammatory cells	No
10	Contreras et al. (2001) [19]	32	M	500 mg PO BID	2	LFT normalized	Hepato-cellular	2144	1782	N/A	N/A	1.33	Submassive periportal and centrilobular necrosis	Yes
11	Bataille et al. (2002) [20]	63	F	500 mg PO daily	200	LFT normalized	Cholestatic with ductopenia	740	660	662	13.9	N/A	Fibrosing cholestatic hepatitis; chronic inflammation (lymphocytes and neutrophils); duct paucity, cholangiolitis	No
12	Zaidi (2003) [21]	80	M	500 mg PO BID	12	LFT normalized	Mixed	972	577	358	1.9	1.2	N/A	No
13	Goetz et al. (2003) [22]	79	F	500 mg PO BID	2	LFT normalized	Hepato-cellular	4878	16564	6111	1.61	1.77	N/A	No
14	Zimpfer et al. (2004) [23]	22	M	250 mg PO BID	14	LFT normalized	Hepato-cellular	890	907	180	16.9	1.4	Extensive hepatocellular necrosis; mixed inflammatory infiltration containing abundant eosinophils	Yes
15	Thakur et al. (2007) [24]	26	M	500 mg PO BID	5	LFT normalized	Hepato-cellular	1700	1055	N/A	43	N/A	Bile stasis with pericholangiolar lymphocytic inflamatory infiltration; focal parenchymal necrosis	Yes

Table 1 continued. Summary of published case reports of idiosyncratic drug-induced liver injury (DILI) due to ciprofloxacin.

Case	Reference	Age	Sex	Dose/formulation/regimen	Latency/time to injury (days)	Outcome	Type of injury	ALT (U/L)	AST (U/L)	ALP (U/L)	Total bilirubin (mg/dL)	INR	Liver biopsy/histology	Steroids
16	DIchiara et al. (2008) [25]	65	M	500 mg PO BID	6	LFT normalized	Cholestatic	157	319	711	25.3	6.6	Canalicular and intrahepatic cholestasis; acute cholangitis with lymphocytes and neutrophils	No
17	Bhagirath (2008) [26]	39	F	500 mg PO BID	60	LFT normalized	Cholestatic	2009	1406	160	17.8	1.59	Eosinophilic infiltration of portal tracts and adjacent lobules. Mid and peri-central zones necrosis	Yes
18	Cholongitas et al. (2009) [27]	66	M	400 mg IV BID	3	LFT normalized	Cholestatic	582	520	1234	N/A	1.25	N/A	No
19	Alan et al. (2011) [28]	56	M	500 mg PO BID	2	LFT normalized	Hepato-cellular	500	230	152	3.2	4.75	N/A	No
20	Alan et al. (2011) [28]	62	M	500 mg PO BID	5	LFT normalized	Hepato-cellular	320	190	132	2.3	2.8	Diffuse eosinophil infiltrations and sporadic hepatocellular necrosis	No
21	Moreno et al. (2015) [29]	56	F	N/A	4	LFT normalized	Cholestatic	506	271	455	9.5	0.9	N/A	No
22	Unger and Al-Jashaami (2016) [30]	74	F	N/A	4	death	Cholestatic	870	1263	496	8.9	1.2	Chronic active hepatitis with cholestasis and portal/periportal fibrosis	No
23	Qutrio et al. (2017) [31]	29	F	500 mg PO daily	7	LFT normalized	Hepato-cellular	766	354	159	1.5	N/A	N/A	No
24	Radovanovic et al. (Our case 1)	35	M	400 mg IV BID	2	LFT normalized	Hepato-cellular	896	926	317	2.6	1.36	N/A	No
25	Radovanovic et al. (Our case 2)	82	M	500 mg PO TID	7	LFT normalized	Cholestatic	453	1141	1647	3.1	1.43	N/A	No

M – male; F – female; LFT – liver function test; ALT – alanine aminotransferase; AST – aspartate aminotransferase; ALP – alkaline phosphatase; INR – International Normalized Ratio; N/A – non applicable; WNL – within normal limit.

function tests (LFTs), which was the presentation described in Case 1 in this report. However, some patients remain mainly asymptomatic, which was the presentation described in Case 2 in this report. The most severe symptoms include the development of encephalopathy, jaundice, and coagulopathy, which indicate the onset of acute liver failure [32]. There are no pathognomonic signs or symptoms that would indicate a drug-induced etiology of liver injury or imply a specific drug [44]. However, unlike other types of drug-related reactions, idiosyncratic DILI is not associated with eosinophilia [45]. Minor elevation in aspartate aminotransferase (AST), and alanine aminotransferase (ALT), from pre-existing conditions such as cirrhosis or non-alcoholic fatty liver disease (NAFLD), should not be classified as DILI, and mildly increased levels in transaminases, resulting from adaptive mechanisms, for example during statin therapy, should also not be classified as DILI [45].

The most recent guidelines for the diagnosis and management of idiosyncratic DILI have been published by the American College of Gastroenterology (ACG) [4]. The guidelines support that the diagnosis of idiosyncratic DILI requires a high index of suspicion, cautious exclusion of other causes of liver disease, such as infection, autoimmune disease, liver ischemia, biliary obstruction, and malignancy [4]. The ACG guidelines also recommend a careful review of the patient's medication history, and awareness of the hepatotoxicity profile of the administered drugs and herbal products. The diagnosis of idiosyncratic DILI is challenging since there are no pathognomonic clinical features or laboratory tests specific for this diagnosis. However, some characteristic features of idiosyncratic DILI include an appropriate latency period between drug ingestion and liver injury, as well as characteristic patterns of abnormal LFTs.

The R-ratio is often used to distinguish between the different patterns of liver injury in patients with DILI. The R-ratio can be calculated as follows:

ALT value/ALT upper limit of normal versus the ALP value/ALP upper limit of normal.

An R-ratio >5 is consistent with a hepatocellular pattern of injury; an R-ratio <2 represents cholestatic pattern of injury; and an R-ration 2–5 represents a mixed pattern of injury [1,4]. Depending on the pattern of liver injury, as indicated by the R-ratio, the differential diagnosis, and further clinical investigations can be identified, leading to an improved differential diagnosis or definitive diagnosis. For example, patients who are found to have cholestatic damage should be evaluated for biliary obstruction, unlike patients with a hepatocellular pattern of injury, who are more likely to have viral or ischemic hepatitis.

The Roussel Uclaf Causality Assessment Method (RUCAM) is an objective method of patient assessment used to quantify the strength of the association between liver injury and the drug that might be the cause of the injury [46]. Because RUCAM uses a scale or scoring system, the categories that help to distinguish between hepatic drug toxicity and liver injury due to other causes include the following: definite or highly probable (score >8); probable (score, 6–8); possible (score, 3–5); unlikely (score, 1–2), and excluded (score ≤0) [47, 48].

The presence of hyperbilirubinemia of more than 2 mg/dL (Hy's law) is indicative of a worse clinical outcome, as the presence of jaundice is associated with severe disease, with patient mortality of up to 50% in those who have bilirubin >2 mg/dL and an ALT/AST ratio that is three times the upper limit of normal [40].

To support the presentation of two case reports, Case 1 and Case 2, a literature review of previously published cases of DILI associated with ciprofloxacin was undertaken, using Medline/PubMed for publications in the English language. The following search terms were used, both individually and in combination: 'ciprofloxacin,' 'liver injury,' 'hepatotoxicity,' 'liver failure,' 'drug-induced liver injury,' 'DILI,' 'hepatocellular,' and 'cholestasis.' The literature search initially identified 184 publications, which following exclusion of duplicate case reports, review articles, cases reported in a language other than English, and cases that were not clearly associated with ciprofloxacin, 23 previously published cases of ciprofloxacin-associated DILI were identified, with the first case reported in 1992 (Table 1) [10–31]. Currently, including the two cases described in this report, 25 cases of ciprofloxacin-associated DILI have been documented in the literature 16 (64%) in men and 9 (36%) in women, with the age at diagnosis ranging from between 22–92 years (mean 54±4 years) [10–31]. None of the patients in these previously published reports had documented underlying liver disease, cirrhosis, or chronic alcohol use [10–31]. The most common indication for prescribing ciprofloxacin was urinary tract infection (44%), followed by osteomyelitis, colitis, and cellulitis (each 16%), with isolated cases of endometritis and bronchitis (each 4%) [10-31]. The most common antibiotic formulation was oral (Table 1), except for three cases, where IV antibiotics were used. Total daily doses of ciprofloxacin ranged from 500–1500 mg, although in four cases, the dose was not reported. The time between initiation of ciprofloxacin and acute hepatic injury ranged from 2–200 days (mean, 14±8 days). The longest latency period was reported in one case of delayed fibrosing cholestatic hepatitis with bile duct damage, likely to have been related to ciprofloxacin, which occurred after six months of treatment with ciprofloxacin [20]. If this single case of a six-month latency period is excluded, the time between initiation of ciprofloxacin and acute hepatic injury ranged from between 2–60 days (mean, 8±2 days). The most common clinical presentations found in the review of the literature of previous cases of idiosyncratic DILI associated with ciprofloxacin treatment were jaundice, pruritus, nausea, vomiting, and abdominal pain or discomfort [10–31]. Similarly, in the present report, Case 1 had non-specific complaints of RUQ pain, nausea, and fatigue. However, Case 2 was mainly asymptomatic but had highly elevated levels of LFTs.

In the literature review of previously reported cases of idiosyncratic DILI associated with ciprofloxacin treatment, in all reported cases but one (96%), acute or chronic infection with hepatitis A, B, and C virus was excluded [10–31]. In 14 cases (56%), patients were tested for acute EBV and CMV; in 11 cases (44%), patients were tested for herpes simplex virus (HSV); and in 6 cases (24%), patients were tested for HIV, and all results were negative [10–31]. In 80% of the reported cases, autoimmune hepatitis was excluded [10-31]. The most common imaging modality used to investigate abnormal liver function was abdominal ultrasound (US) in 84% of cases, followed by abdominal computed tomography (CT) scans in 24%, while magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) were performed in 12% of cases [10–31]. Given its widespread availability, affordability, and the lack of radiation exposure, it is not surprising that US was most widely used imaging modality in previously published studies of cases of idiosyncratic DILI associated with ciprofloxacin treatment [10–31].

In this report, an extensive evaluation of acute liver injury was undertaken for Case 1 and Case 2, to rule out the most common infections, inflammatory, autoimmune, and structural causes for the abnormal LFTs. The close association between the onset of acute liver injury and abnormal LFTs with the onset of treatment with ciprofloxacin in both cases

supported the diagnosis of ciprofloxacin-induced idiosyncratic DILI. Liver biopsy is not considered to be mandatory in the clinical workup of suspected cases of DILI, and in the Drug-Induced Liver Injury Network (DILIN) registry, less than 50% of patients had a liver biopsy [50]. In the cases identified from the current literature review, liver biopsy was performed in 11% of cases (Table 1) [10–31]. Liver biopsy should be considered if a diagnosis of autoimmune hepatitis is suspected and especially if long-term immunosuppressive therapy is being considered [4]. Since the two cases reported, Case 1 and Case 2, improved shortly following cessation of ciprofloxacin treatment, liver biopsy was not done since the risk associated with liver biopsy was considered to outweigh the potential benefit.

In the literature review of reported cases of idiosyncratic DILI due to ciprofloxacin, a pure hepatocellular pattern was present in 12 cases (48%); a cholestatic pattern of injury was reported in 12 cases (48%); a mixed pattern of liver injury was present in one case (4%) [10–31]. In this report, Case 1 was the younger patient and had the hepatocellular pattern of injury, while Case 2 had a cholestatic pattern of injury. Although the cholestatic pattern of injury has the lowest mortality, it is associated with the highest risk of a protracted clinical course that can lead to the development of chronicity [40]. Reported mortality figures from the Spanish registry are 2% for the mixed pattern, 5% for the cholestatic pattern, and 7% for the hepatocellular pattern [49]. In contrast, the DILIN network from the US found higher mortality rates in patients with a cholestatic pattern of injury when compared with the hepatocellular pattern (14.3% *vs.* 7.5%, respectively) [50]. While bilirubin is not incorporated into the R-value, it remains a cornerstone of Hy's law, with both Case 1 and Case 2 in this report having met the criteria for severe acute liver injury, having a bilirubin >2 mg/dL and an ALT more than three times the upper limit of normal (ULN) (Hy's law). However, with timely diagnosis, and timely withdrawal of ciprofloxacin, combined with supportive clinical measures, both of our patients recovered uneventfully.

The Model for End-Stage Liver Disease (MELD) is a scoring system used to assess the severity of chronic liver disease, and the international normalized ratio (INR) is a marker of acute liver failure that reflects the associated coagulopathy (INR >1.5). However, in the literature review, neither MELD nor INR was reported in almost one-third of published cases (32%), which highlights the importance of developing standardized investigations for cases of idiosyncratic DILI [10–31]. A rising INR is a predictor of a poor clinical outcome and is a component of the definition of acute liver failure (along with encephalopathy), and it should be routinely measured in all cases of idiosyncratic DILI. Early recognition of acute liver injury and timely transfer to tertiary transplant centers might reduce patient mortality associated with this most severe type of DILI.

The cornerstone of treatment of idiosyncratic DILI is the withdrawal of the causative medication and the provision of supportive care. Currently, in the cases published in the literature, all patients rapidly improved after cessation of ciprofloxacin, except in three cases where ciprofloxacin-intake resulted in fulminant hepatitis and death (12%) [10–31]. In four cases (16%), steroids were used with ciprofloxacin cessation and supportive management [10–31]. The role of steroids in DILI is controversial, but may be considered in cases with features of hypersensitivity and acute liver failure [4]. Also, in 2009, N-acetylcysteine (NAC) was evaluated in a randomized placebo-controlled trial for the treatment of DILI [51]. In this trial, the overall survival was not affected, but transplant-free survival was significantly increased in the NAC-treated group when compared with the placebo-treated group (52% *vs.* 30%) [51]. Some of the findings from previously published cases of ciprofloxacin-associated idiosyncratic DILI are similar to Case 1 and Case 2 presented in this report, with both patients improving on stopping ciprofloxacin and without clinical sequelae.

Conclusions

Idiosyncratic drug-induced liver injury (DILI) due to ciprofloxacin treatment is rare but has a varied clinical presentation that can include asymptomatic elevation in transaminases, jaundice, and cholestasis to acute liver failure resulting in death. Antimicrobials are the drugs that most commonly cause idiosyncratic DILI, but although ciprofloxacin is widely used, it is rarely associated with liver toxicity, including idiosyncratic DILI. In this report, two cases of ciprofloxacin-associated idiosyncratic DILI have shown that timely diagnosis and discontinuation of ciprofloxacin can prevent the progression of DILI, reduce liver damage, and reduce patient mortality.

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