Ceftazidime induced liver injury

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SUMMARY

A 65-year-old woman with type II diabetes mellitus complicated by non-healing ulcers with recurrent osteomyelitis was admitted for progression of cellulitis after treatment failure with an outpatient course of amoxicillin-clavulanate. She was found to have persistent osteomyelitis and started on ceftazidime for a culture documented *Pseudomonas aeruginosa* infection. After two parenteral doses, she had a rapid rise in liver function tests (LFTs) in a hepatocellular pattern. Due to rapid identification, all medications with potential hepatotoxicity, including ceftazidime, were discontinued and the LFTs promptly returned to baseline over 3 days. Of note, the patient did not experience any symptoms of liver injury. Other causes of acute liver injury were effectively ruled out, but the case was confounded by usage of other potential hepatotoxic medications. Still, the most likely culprit was ceftazidime, a rare cause of drug induced liver injury with very few reports in the literature.

BACKGROUND

Cephalosporins are a rare but known cause of drug induced liver injury (DILI), usually causing mild elevations in liver function tests (LFTs) 1–4 weeks after initiation in a cholestatic pattern without progressing to more severe liver injury.[1–4] Ceftriaxone and cefazolin, in particular, are known to cause cholestatic jaundice, but there are reports of hepatocellular or mixed-type injuries with cephalosporins as well.[1 4] Based on LiverTox,[1] a resource created by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to provide information on liver toxicity of various medications, cephalosporins are assigned as category B—meaning the drugs are known or highly likely to cause idiosyncratic liver injury. Still, reports of ceftazidime associated DILI are extremely uncommon with only one case report identified as of 2016 by the NIDDK and ceftazidime by itself is assigned category D—meaning there are single case reports and it is only possible that the drug can be a rare hepatotoxin.[3] This case report adds another instance of probable ceftazidime caused DILI, a likely under-reported phenomenon, to the literature.

CASE PRESENTATION

A 65-year-old woman with medical history remarkable for schizophrenia on chlorpromazine, hyperlipidaemia on atorvastatin and type II diabetes mellitus complicated by Charcot foot and non-healing ulcers with recurrent osteomyelitis was admitted to the hospital with worsening right lower extremity swelling, erythema and clear drainage around a non-healing ulcer that had not resolved after a 10-day outpatient course of amoxicillin-clavulanate. On admission her atorvastatin 40 mg was switched to rosuvastatin 20 mg per hospital formulary and she was started on intravenous vancomycin. All other home medications were continued. Admission labs are shown in table 1.

An MRI of her right foot demonstrated progression of osteomyelitis involving the cuboid and the base of the fourth metatarsal. Consequently, she had a resection with clear margins of her right distal cuboid and fourth metatarsal with insertion of vancomycin and tobramycin beads with flap closure. Deep wound cultures grew *Corynebacterium striatum* (resistant to everything besides vancomycin) and pan-susceptible *Pseudomonas aeruginosa* on day 9 of admission. She was started on ceftazidime and received two doses before routine labs demonstrated hepatocellular liver injury from a previously normal baseline (LFTs last measured 1 year prior to admission) (table 1). Notable labs were alkaline phosphatase 491 U/L, alanine aminotransferase (ALT) 891 U/L, aspartate aminotransferase (AST) 679 U/L and gamma-glutamyl transferase 996 U/L. Bilirubin, total protein, albumin, International normalized ratio (INR) and Partial thromboplastin time (PTT) were within normal limits. She remained asymptomatic and denied any nausea, vomiting, pruritus or abdominal pain and physical examination was unremarkable: she was not jaundiced or confused and did not have any stigmata of chronic liver disease. The patient does not have a history of significant alcohol use and does not use acetaminophen or other over the counter medications or supplements. Of note, the patient has been on atorvastatin 40 mg for more than 9 years and a low dose of 50 mg daily of chlorpromazine for at least 4 years without incident. She had not previously been exposed to rosuvastatin. She had at least four instances of prior treatment with amoxicillin-clavulanate with normal documented LFTs 1–2 months after usage. She did receive a short 3-day course of ceftazidime 5 years prior to this admission but no LFTs were documented for 1–2 months after usage.

INVESTIGATIONS

A workup was started for causes of acute liver injury while potentially hepatotoxic medications including ceftazidime, chlorpromazine and rosuvastatin were held. The patient had a normal INR and PTT (table 1) reducing concern for liver synthetic dysfunction. R-factor was 6.5 suggesting a hepatocellular pattern of injury[5] so antibody testing was obtained to rule out acute viral hepatitis (hepatitis A, B and C) and autoimmune hepatitis (Antinuclear antibodies and antismooth muscle antibody). All labs were negative and ceruloplasmin, ferritin

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Table 1 Selected lab values during admission

Time	Baseline (1 year prior to admission)	Day of admission	Day 10 of admission (after 1 day of ceftazidime)	Day 11 of admission (after ceftazidime discontinued for 1 day)	Day 16 of admission (discharge date)	One month after discharge
BMP						
Na (mmol/L)	140	139	139	141	141	140
K (mmol/L)	3.6	3.8	3.2	3.4	3.8	3.5
Cl (mmol/L)	100	100	103	102	104	104
CO_2 (mmol/L)	27	27	26	27	27	27
BUN (mg/dL)	12	7	9	7	10	10
Creatine (mg/dL)	0.50	0.50	0.50	0.50	0.60	0.84
Glucose (mg/dL)	291	229	182	216	168	–
Ca (mg/dL)	9.2	9.4	8.8	9.1	9.1	9.0
LFTs						
ALT (U/L)	13	–	891	489	131	16
AST (U/L)	12	–	679	343	30	14
ALP (U/L)	120	–	491	376	196	123
Total bilirubin (mg/dL)	0.2	–	0.4	0.4	0.5	0.4
Direct bilirubin (mg/dL)	<0.2	–	<0.2	–	–	
GGT (U/L)	–	–	996	–	–	
Total protein (g/dL)				6.9	6.5	6.7
Albumin (g/dL)				3.6	3.7	4.2
Coagulation panel						
PT (s)		–	10.6			
INR		–	1.02			
PTT (s)		–	25.1			
CBC*						
WCC (x10^9/L)	7.1	5.9	5.1	5.5	5.6	4.5
HCT (%)	32.1	34.1	33.6	34.4	33.5	36.5
Hgb (g/L)	93	105	105	105	102	115
Plt (x10^9/L)	260	266	203	257	257	271
Miscellaneous						
CK (U/L)	–		42			
CRP, high sensitivity (mg/L)	–	27.3			3.9	
Ferritin (ng/mL)	–		74			
Ceruloplasmin (mg/dL)	–		27 (18–51 normal)			
ANA			<1:80			
Antismooth muscle (F-actin) IgG (U/mL)	–		9 (<20 normal)			

*Normal differential and mean corpuscular volume.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, Antinuclear Antibodies; AST, aspartate aminotransferase; BMP, Basic Metabolic Panel; CBC, complete blood count; CK, creatine kinase; CRP, C reactive protein; GGT, gamma-glutamyl transferase; HCT, haematocrit ; Hgb, haemoglobin; INR, International Normalized Ratio; LFT, liver function test; Plt, platelet; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; WCC, white cell count.

and creatine kinase were within normal limits. Patient was HIV negative as well. Abdominal ultrasound with doppler was limited by body habitus but demonstrated hepatomegaly with hepatic steatosis likely reflecting non-alcoholic fatty liver disease. The gall bladder was not visualised but the common bile duct was not dilated (3 mm). There was no evidence of thrombus or any other acute intrabdominal abnormality. Given that the patient's ALT and AST significantly decreased in the afternoon (ALT 734 U/L, AST 343 U/L) after discontinuing all potential hepatotoxic medications further workup was not pursued due to likely DILI and LFTs were followed daily to monitor.

DIFFERENTIAL DIAGNOSIS

The differential for acute hepatocellular injury is broad including viral hepatitis, autoimmune hepatitis, DILI, genetic diseases (haemochromatosis and Wilson's disease) and/or shock liver. However, given the sudden rise of LFTs 10 days into the hospital stay without any incidence of hypotension, negative antibody panels, the rapid decline with normalisation in almost 5 days after discounting hepatotoxic medications, and the lack of other symptoms, DILI is highly probable.

The patient's course is somewhat obfuscated by the fact that LFTs were not obtained during the hospitalisation until the day after ceftazidime was started and the last known baseline was 1 year prior. Thus, it cannot be stated with certainty that the patient had normal LFTs before starting ceftazidime. Based on available evidence there were four medications in the patient's history that could have caused DILI: amoxicillin-clavulanate, atorvastatin/rosuvastatin, chlorpromazine and/or ceftazidime.[1] Although amoxicillin-clavulanate is a common cause of DILI, even weeks after discontinuation (as in this patient who received last dose 14 days prior to measurement of LFTs) this patient had received amoxicillin-clavulanate four times in the past with normal LFTs measured during and 1–2 months after usage.

Similarly, the patient was on atorvastatin 40 mg for at least 9 years without adverse reactions and the low dose of 50 mg daily of chlorpromazine for at least 4 years without incident. Notably the patient was switched to rosuvastatin 20 mg for the hospitalisation (which the patient had not previously received) but this medication is less commonly associated with DILI compared with atorvastatin, creatine kinase was within normal limits, and it would be unusual for there to be such a rapid decline in LFTs despite only missing one dose of the medication after a 9 day course. Thus, ceftazidime appeared to be the most likely cause of the DILI.

TREATMENT

All potentially hepatotoxic agents were discontinued including ceftazidime, chlorpromazine and rosuvastatin. The patient only received one dose of acetaminophen during admission but that was discontinued as well. Due to the patient's anxiety, concern over psychiatric symptoms and rapidly falling LFTs, chlorpromazine was restarted 1 day prior to discharge and LFTs continued to fall (table 1). The patient was discharged on a course of piperacillin-tazobactam and vancomycin for osteomyelitis with a plan to restart atorvastatin as an outpatient. Ceftazidime was added to her allergy list in the electronic health record to avoid future exposures.

OUTCOME AND FOLLOW-UP

The patients LFTs continued to fall and normalised on recheck 1 week after discharge and remained within normal limits at 1 month follow-up (table 1). The patient did not experience any symptoms associated with liver injury and has returned to her usual state of health. Outpatient labs 3 months after discharge demonstrated transaminases within the normal limits.

DISCUSSION

This case report suggests that ceftazidime can indeed cause DILI with a rapid and severe rise in LFTs in a hepatocellular pattern (R-factor >5)[5] after even two doses. Though baseline LFTs were not obtained in this patient during the hospitalisation immediately prior to ceftazidime initiation, the rapid fall after discontinuation of the medication is highly suggestive that ceftazidime was the culprit. The patient may have been previously sensitised to ceftazidime when it was used 5 years earlier (without LFT measurement). Moreover, based on the updated Roussel Uclaf Causality Assessment Method, a commonly used score to rapidly and quantitatively assess causality in suspected cases of DILI, ceftazidime was assigned a score of 8 despite confounding medications which places it in the 'probable' category as the cause.[6]

This case also speaks to the importance of routine LFT testing in hospitalised patients because it is a relatively low cost and low risk test that can help catch such cases early. This importance is underscored by the evidence of severe hepatocellular injury in the absence of any patient symptoms or physical examination findings. It is possible that many cases of DILI are not reported because of lack of proper surveillance.

Learning points

- Ceftazidime, and cephalosporins as a class, can cause liver injury even after 1–2 doses.
- Cephalosporin associated drug induced liver injury (DILI) usually causes mild liver function test (LFT) elevations in a cholestatic pattern, however, it can also present as severe hepatocellular or mixed pattern injury.
- Routinely measuring LFTs in the hospital is a low risk and low cost intervention that can catch cases of DILI, a not uncommon side effect of many medications used in hospitalised patients.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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