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A case of ceftriaxone-induced liver injury and literature review

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SUMMARY

Background: Liver injury evoked by drugs spans various clinical manifestations ranging from mild biochemical abnormalities to acute liver failure. Ceftriaxone is a third-generation cephalosporin often used in clinical practice for its long half-life, high tissue penetration rate, wide spectrum and good safety profile. Ceftriaxone, as other cephalosporins have little hepatotoxicity; however, few cases of toxic hepatitis induced by this antibiotic have been reported.
Case Presentation: We describe a case of acute, drug-induced liver injury ('hepatitis') in a 77 years-old female patient treated with ceftriaxone for pneumonia. After 48 hours from antibiotic administration, clinical condition worsened with a clinical and laboratory profile compatible with an acute non cholestatic liver injury. Ceftriaxone administration was immediately stopped and the patient was treated with hydro-electrolyte replacement, high-flow oxygen, vitamin K infusion, steroids and proton-pump inhibitors with a progressive clinical improvement.
Conclusions: Even if rare, a ceftriaxone-induced hepatotoxicity (confirmed by RUCAM score), should be considered when all other possible causes have been excluded.

Keywords: ceftriaxone, drug-induced, emergency medicine, hepatitis, hypertransaminasemia.

INTRODUCTION

Drug-induced hepatitis includes a wide spectrum of clinical diseases ranging from mild biochemical abnormalities to acute liver failure. In particular, hepatotoxicity associated with antibiotics (the class of drugs most commonly related to idiosyncratic, *i.e.* unpredictable, drug-induced liver injury) is frequently asymptomatic and generally characterized by mild hepatic injury that is often unrecognized. The diagnosis is essentially clinical, as no diagnostic tests and/or biomarkers are available, and requires the exclusion of other causes responsible for abnormal liver tests [1-4]. The Naranjo's algorithm is a valuable tool used by physicians to determine the likelihood of a drug being responsible for an adverse reaction [5]. Furthermore, the Roussel Uclaf Causality Assessment Method (RUCAM) is a score system assessing clinical, biochemical, serologic and radiologic features of liver damage indicating the likelihood that a specific treatment causes hepatic injury [6, 7].
To our knowledge, only four cases of ceftriaxone-induced hepatitis can be detected in the literature, thus leading to consider this drug as a safe therapeutic option in terms of liver function tests [8-11]. Herein, we report a case of ceftriaxone-induced hepatitis and reviewed the literature in order to provide emergency physicians with an update, which may help recognizing and managing ceftriaxone-evoked liver injury, a potentially life-threatening clinical condition.

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CASE PRESENTATION

A 77-year-old female was admitted to the Emergency Department of St. Anna University Hospital, Ferrara, Italy, for increasing dyspnoea and palpitations begun since about 3 days. Her clinical history disclosed multiple comorbidities, such as hypertension, previous ischemic heart disease, mitral valve substitution and paroxysmal atrial fibrillation in preventive anti-coagulant therapy with warfarin as the patient suffered from mild-to-moderate chronic kidney disease. The patient was recently diagnosed to have a colic and right pulmonary mass of 4 cm of uncertain nature. The vital parameters were within the normal range except for tachycardia with 150 bpm. The physical examination disclosed thoracic bilateral crackles without any other significant findings. Her ECG showed a wide-complex irregular tachy-arrhythmias compatible with atrial fibrillation with high ventricular response leading to left bundle branch block. A chest X-ray showed a middle lobe pneumonia with ipsilateral pleural effusion (in addition to the known mass). The patient was treated by increasing home diuretic regimen (furosemide 40 mg t.i.d.), adding beta-blockers (metoprolol 5 mg t.i.d.) and starting empiric antibiotic therapy with ceftriaxone (2 g daily) because of pulmonary infection proved microbiologically negative (already performed during a previous hospitalization). A trans-thoracic echocardiography was performed showing bi-atrial dilatation with normal systolic function. After 48 hours of treatment her clinical conditions worsened with hypotension, oxygen desaturation and contraction of diuresis. Lab tests showed a slight worsening of renal function, a moderate increase of gamma-glutamyl transferase (157 U/l, n.v.: <38) and a severe increase of aspartate aminotransferase (11961 U/L, n.v.: <35), alanine aminotransferase (6111 U/L, n.v.: <35) and INR (24.92, n.v.: 0.8-1.2) with normal bilirubin and alkaline phosphatase levels (all these tests were in the normal range on admission at the Emergency Department). The clinical and laboratory profile were compatible with an acute non cholestatic liver injury. Common causes of infective, metabolic or endocrine liver damage were excluded. Ultrasonography showed minimal enlarged liver size with an apparently preserved parenchyma and normal, non lythiasis gallbladder. No clinical bleeding manifestations occurred despite the high INR values. In the hypothesis of a drug-induced liver injury, ceftriaxone administration was immediately stopped. Hydro-electrolyte replacement (30 mL/kg), high-flow oxygen treatment and vitamin K infusion (phytomenedion 10 mg b.i.d.) were rapidly administered. Pulse methylprednisolone treatment was begun at 60 mg t.i.d. for the first 3 days then tapered down to 40 mg b.i.d. for other 4 days until discontinuation. The possible gastrolesive action of high-dose steroids and a possible stress gastritis were prevented with omeprazole e.v. 80 mg / day. The patient had a progressive reduction of the abnormal liver function tests (more than 50%) and clinical improvement occurred in about 72 hours (Table 1). Finally, after about two weeks from admission, the patient could be discharged in stable condition.

DISCUSSION

In the western countries, drugs are one of the most common cause of acute liver damage hence 'drug-induced liver injury' (DILI). Nonetheless, the diagnosis of DILI (in the absence of specific diagnostic tests) requires an accurate differential diagnosis aimed to exclude other causes of abnormal liver tests. The drugs that have been most frequently associated with liver damage include non-steroidal anti-inflammatory agents and antibiotics. Among the latter compounds, cephalosporins are thought to exhibit a better safety

Table 1 - Trend of liver damage tests during hospitalization.

	Day 0	*Day 1*	*Day 3*	*Day 5*	*Day 7*	*Day 10*
ALT	34	68	6111	2899	622	177
AST	N.A.	65	11961	4737	67	70
γGT	N.A.	30	157	80	80	60
INR	2.31	2.98	24.92	2.01	1.45	1.39

Note: N.A. = not available.

Table 2 - The Naranjo's algorithm (NA) showed the correlation between adverse reactions and drug administration. In our case NA gave a scaffold of 6 leading to a probable correlation between the clinical situation and ceftriaxone administration.

	Question	*Yes*	*No*	*Not known*	*Score*
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event appear after the suspect drug was administered?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or specific antagonist was administered?	+1	0	0	+1
4	Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
5	Are there alternative causes that could solely have caused the reaction?	-1	+2	0	+2
6	Did the reaction re-appear when a placebo was given?	-1	+1	0	+1
7	Was the drug detected in any body fluid in toxic concentration?	+1	0	0	0
8	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	0
				TOTAL	*6*

Note: Yellow boxes denote the reported case.
The interpretation of the final score is as follows: 0 or less indicate that the drug is "unlikely" as a cause; 1 to 4 that it is "possible"; 5 to 8 "probable"; and greater than 8, "sure".

profile than amoxicillin/clavulanate and isoniazid because of a virtually absent hepatotoxicity [1-4]. However, ceftriaxone has been associated with development of biliary sludge, biliary colic and even cholestatic hepatitis when given in high doses [12, 13]. Furthermore, only a previous retrospective cohort study proposed a possible correlation between the dosage of ceftriaxone and the onset of liver damage [14]. Since in the reported case ceftriaxone was administrated in low-dose (*i.e.*, 2 g/die), an idiosyncratic etiology should be considered.

In our case, the main causes responsible for acute hepatitis, including viral agents, autoimmune disease, cholelithiasis, storage and endocrine diseases, were all excluded by specific tests. In consideration of the suspected adverse drug reaction, the Naranjo algorithm showed a scaffold of 6, which corresponded to a "probable" correlation between the drug administration and the clinical picture presented by the patient (Table 2) [5]. The RUCAM score, more specific for DILI, showed a scaffold of 7 points (Table 3). This tool confirmed the Naranjo assessment providing consistency to a "probable" correlation between cephalosporin and hepatic injury [6, 7]. A direct correlation with ceftriaxone could be verified by several approaches:

1) liver biopsy;
2) measurement of drug levels in the serum;
3) withdrawal/re-challenge of the drug leading to elevated transaminase levels, thus supporting the diagnosis of ceftriaxone-induced DILI (although in these studies the RUCAM score was not applied) [8-11].

In our case, all of these possibilities were excluded either for technical (the laboratory was unable

Table 3 - The Roussel Uclaf Causality Assessment Method (RUCAM) score in our patient showed a total of 7 points making "probable" the correlation between ceftriaxone and liver injury (R ratio >5).

	Calculation of the RUCAM Score	*Points*
1	Time to onset	+2
2	Course	+3
3	Risk Factors (Alcohol abuse/Age ≥55 years)	+1
4	Concomitant Drug(s)	+0
5	Search for Non-Drug Causes	+0
6	Previous Information on Hepatotoxicity of the Drug	+1
7	Response to Readministration	+0
	Total	*7*

The interpretation of the final score is as follows: 0 or less indicate that the drug is "excluded" as a cause; 1 to 2 that it is "unlikely"; 3 to 5 "possible"; 6 to 8 "probable"; and greater than 8, "highly probable".

Table 4 - Comparison between the laboratory tests of previous cases of drug induced liver injury (DILI) and the herein presented patient.

	ALT (U/l)	*AST (U/l)*	*gGT (U/l)*	*ALP (U/l)*	*INR*
Bell MJ et al. [6]	8098	21575	N.A.	N.A.	2,23
Longo F et al. [7]	385	525	795	720	N.A.
Nadelman RB et al. [8]	N.A.	N.A.	N.A.	N.A.	N.A.
Peker E et al. [9]	871	819	285	143	N.A.
Present case	6111	11961	157	80	24,92

Note: N.A. = not available.

to detect serum ceftriaxone levels) or ethical reasons: specifically, the patient denied consensus to undergo a liver biopsy; whereas, the withdrawal/re-challenge of ceftriaxone was impossible because of the patient's clinical condition. Thus, we had to rely upon an exclusion diagnosis reinforced by the positive RUCAM score as the most probable one.

Among the reported cases the time between the start of antibiotic therapy and the onset of hepatitis varied from 2 to 4 days and the clinical conditions progressively improved (with a reduction in liver damage tests) from 2 to 7 days after discontinuation of ceftriaxone in all reported patients (see Table 4 for comparison of lab tests between previous cases and the present one at the onset of liver injury) [8-11]. In previous evidence and likewise in our patient, the therapeutic approach was based on vital function emergency support, hydro-electrolytic replacement, high-dose steroids and prevention of bleeding with vitamin K (along with proton pump inhibitors). After discontinuation of antibiotic therapy, no fatal outcome has been described.

In conclusion, in cases of DILI, the clinical picture may result from idiosyncratic (unpredictable) or, less likely, non-idiosyncratic (predictable) toxic effects evoked by different compounds [12, 13]. Cephalosporins including ceftriaxone are known to have little hepatotoxicity [15, 16]. However, as in our patient, a related hepatotoxicity ceftriaxone-induced, as measured by RUCAM score, should be considered in any case characterized by elevated liver enzymes, when all other possible causes have been excluded.

Ethics approval and consent to participate

As a literature review, not actively involving patients, ethics committee approval was not deemed necessary.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this Case report. A copy of the written consent is available for review by the Editor of this journal.

Competing interests

None declared.

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Contributors

Matteo Guarino, Benedetta Perna, Alessandra Pastorelli and Paolo Bertolazzi design and conceptualisation and wrote the first draft of the manuscript. Alessandra Pastorelli, Paolo Bertolazzi and Giacomo Caio reviewed the literature. Matteo Guarino, Martina Maritati, Roberto De Giorgio and Carlo Contini participated in the clinical assessment of the patient and critically reviewed the paper. All authors have read and approved the manuscript.

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