Clinics and Research in Hepatology and Gastroenterology (2019) 43, e82—e85

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

LETTER TO THE EDITOR

## Fatal cholestatic hepatitis after a single dose of celecoxib

**KEYWORDS**
Celecoxib;
Drug-induced liver injury;
Cholestatic hepatitis;
Vanishing bile duct syndrome

*Dear Editor,*

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclo-oxygenase-2 (COX-2) [1]. It is mainly used in rheumatology, in particular to treat chronic pain. Celecoxib belongs to the class of NSAID that has the best gastrointestinal safety profile (few ulcers or gastritis) [2].

In the literature, celecoxib is known for its very low potential for hepatic toxicity, even after long exposure (more than two years) at therapeutic doses. For instance, in a study by Maddrey et al., the overall incidence of hepatic adverse events in arthritic patients receiving celecoxib was similar to that of placebo [3].

A 74 year-old woman was admitted for acute jaundice. She had no significant history except lumbar osteoarthritis. On the 6th of April 2017, she took 200 mg of celecoxib for back pain. She felt nauseous and asthenic 4—5 hours later and experienced abdominal pain. A skin rash, not pruritic, in both armpits and inguinal regions appeared on 08/04 and then quickly disappeared. She had never taken celecoxib in her life and was not taking any other treatment. She did not take any food supplements or medicinal plants. No allergy in particular to sulfonamides was reported. A blood test performed a few weeks earlier did not find any abnormal liver function.

She was hospitalized on the 10th of April 2017. Clinical examination found sensitivity in the right hypochondrium, acute jaundice and fever (38.5 °C). There was no hepatomegaly, no adenomegaly and no evidence of hepatocellular insufficiency. The skin rash had disappeared.

Blood tests confirmed jaundice with hyperbilirubinemia [total: 360 μmol/L (N: < 21 μmol/L), conjugated: 330 μmol/L] and major cholestasis: gamma glutamyltransferase 435 U/L (N: 5—36 U/L) and alkaline phosphatase 1295 U/L (N: 35—105 U/L). We noted hepatic cytolysis with high levels of aspartate amino-transaminase 243 U/L (N: 10—35 U/L) and alanine amino-transaminase 189 U/L (N: 10—35 U/L). The prothrombin time (PT) and the international normalized ratio (INR) were normal. Albumin was 20.7 g/L. C-reactive protein was high: 178 mg/L (N: < 5 mg/L) and there was no leukocytosis. Hepatitis A, B, C, E serology was negative, a serum immunoglobulin analysis was normal, no specific antibodies were found. Parvovirus B19 and CMV serology indicated old infections. Abdominal computerized tomography-scan (CT-scan) and cholangio-Magnetic Resonance Imaging (MRI) showed distension of the gallbladder with infiltration around the gallbladder and parietal enhancement. There was slight dilation of the principal biliary duct (8 mm) but the intra-hepatic bile ducts were normal. Endoscopic retrograde cholangiopancreatography (ERCP) showed vacuity of the biliary duct.

Progression was marked by an increase in jaundice (Fig. 1). The bilirubinemia was 528 μmol/L (conjugated: 484 μmol/L) and alkaline phosphatase was 3600 U/L at day 7. Albumin was 24.9 g/L and remained stable after. Severe pruritus emerged at day 7. A hepatic biopsy was performed at day 7 that revealed suppurative cholangitis, periductal fibrosis and atrophy of some biliary ducts. There was no eosinophils, plasmocytes or fibrous septa (Fig. 2).

Ursodesoxycholic acid was introduced (10 mg/kg/d) at day 7, which transiently improved the cholestasis but not the jaundice or the pruritus. Hydroxyzine and rifampicin did not reduce the pruritus.

Because of the lack of improvement, ERCP, abdominal CT-scan and a liver MRI with cholangio-MRI were performed again, but showed similar results to the previous examinations. To exclude lymphoma, an osteo-medullary biopsy was performed but was normal. A positron emission tomography scan was also normal. A second hepatic biopsy was obtained at day 30. The major change was total ductopenia with no other specific lesion (Fig. 3). Due to the vanishing bile duct syndrome associated with severe pruritus, she received several sessions of plasmapheresis, with only partial and

https://doi.org/10.1016/j.clinre.2018.10.007

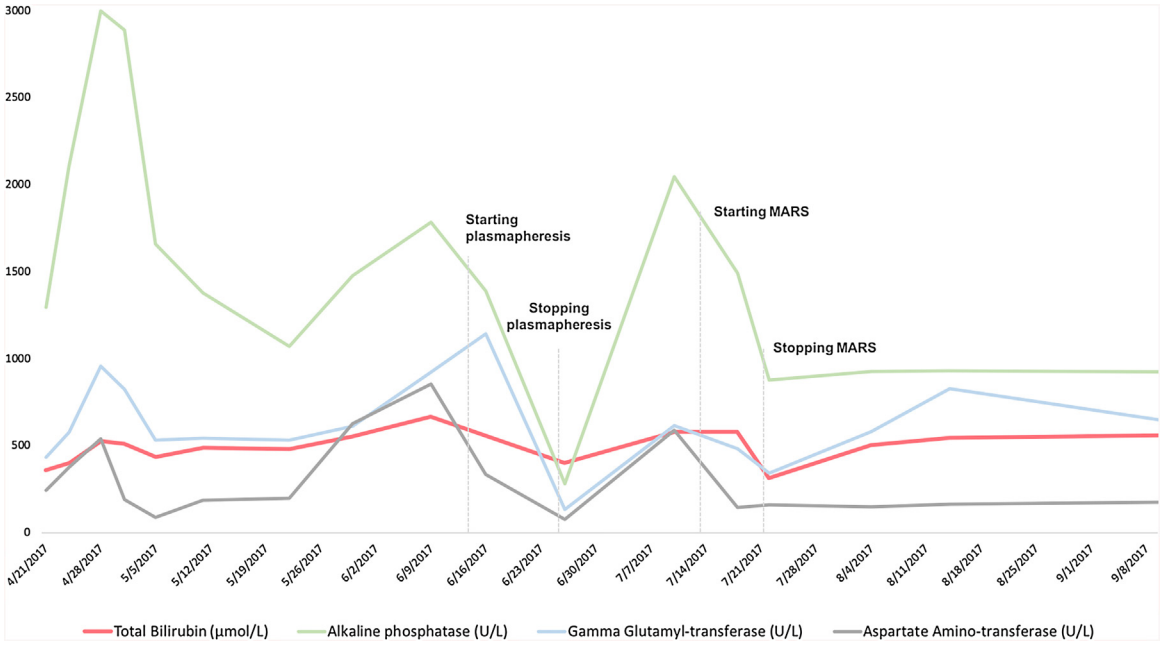


**Figure 1** Results of blood tests over time.

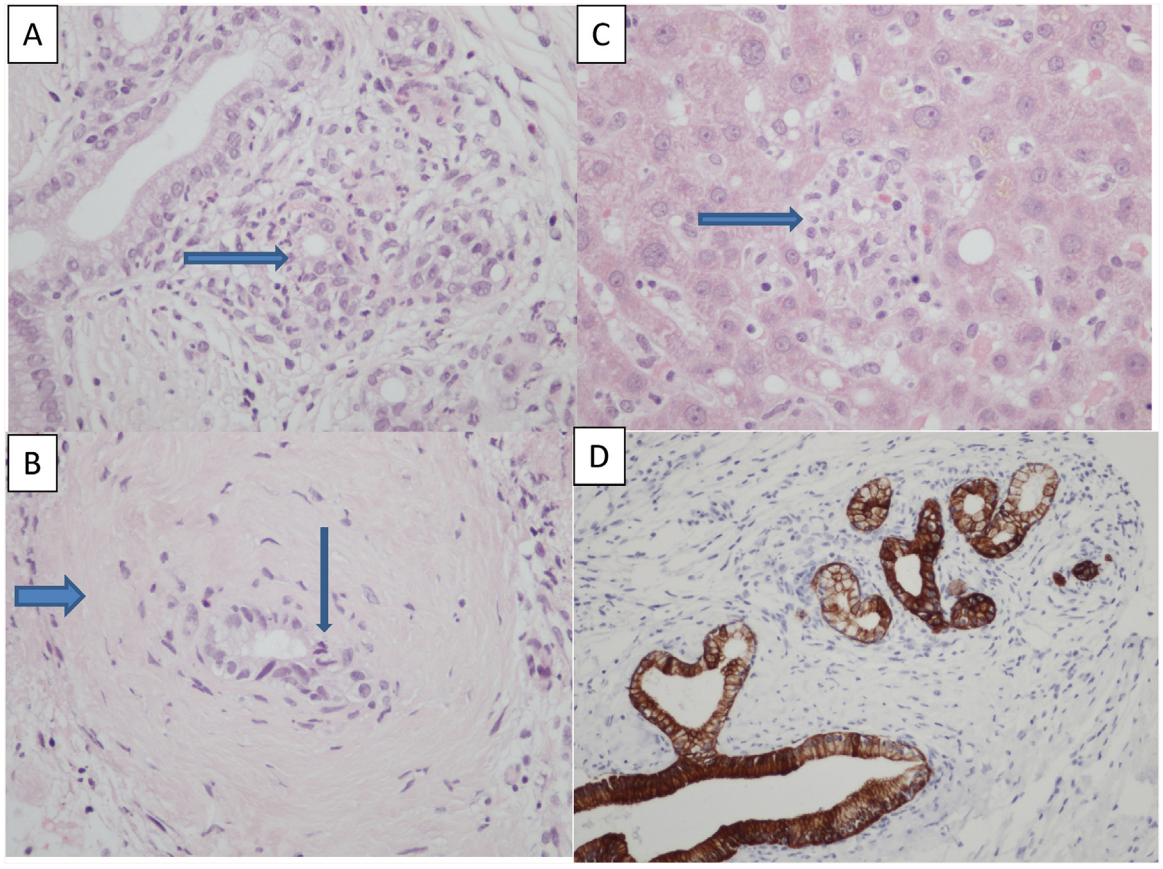


**Figure 2** Pathology of the first liver biopsy Panel A HE (x400): cholangitis with neutrophilic polynuclears (arrow); Panel B HE (x400): periductal fibrosis (thick arrow), neutrophilic exocytosis (thin arrow); Panel C HE (x400): epithelioïd granuloma without caseous necrosis (arrow). Panel D immunostaining anti-CK7 (x200): revealed biliary ducts.

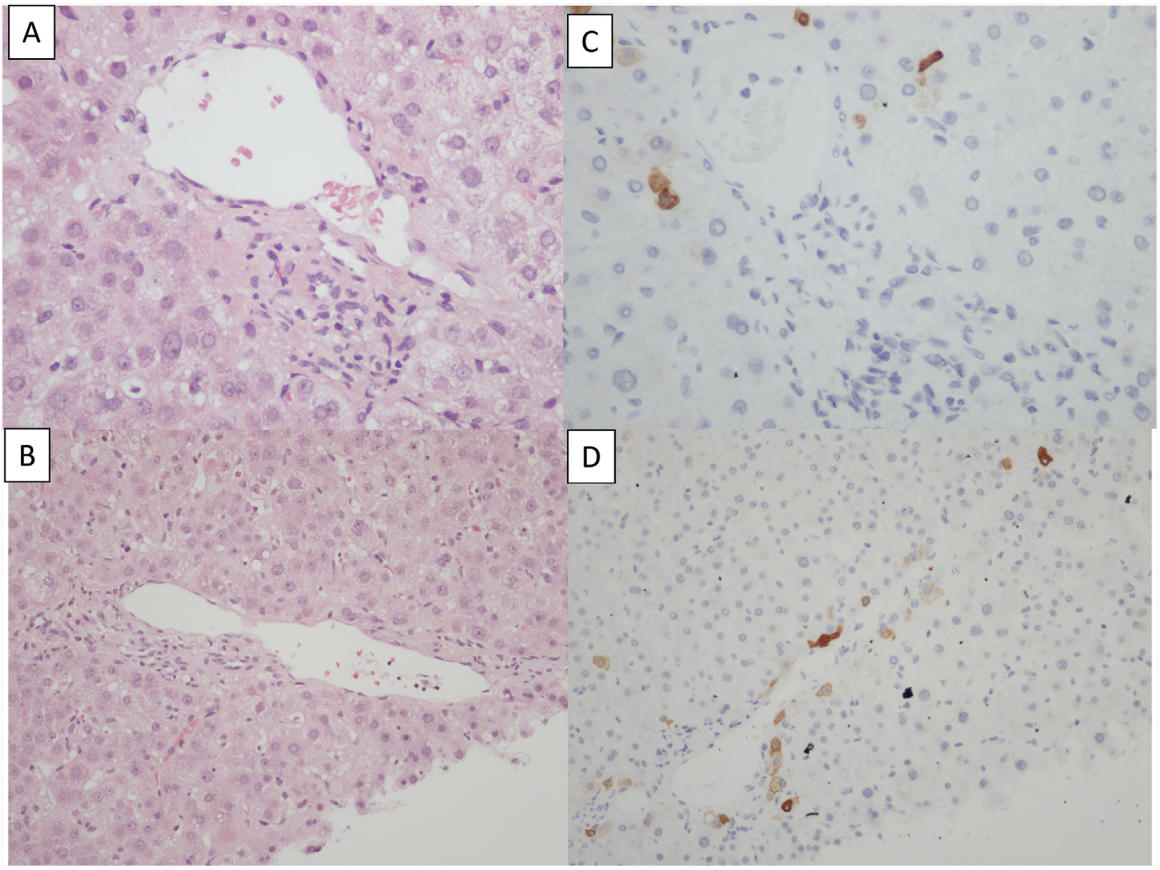


**Figure 3** Pathology of the second liver biopsy Panel A and B HE (x400): total ductopenia, Panel C (x400) and D (x300): Immunostaining anti-CK7 showing total ductopenia.

transient clinical-biological improvement. Three sessions of Molecular Adsorbants Recirculation System (MARS) did not improve the pruritus and hyperbilirubinemia (Fig. 1). Anorexia started at the beginning of symptoms and increased with the severity of jaundice. This resulted in a major loss in weight and malnutrition during hospitalization, which led to the introduction of enteral nutrition with a nasogastric tube. Her general state improved slightly after 4 months of hospitalization, despite hyper-bilirubinemia over 500 μmol/L, and allowed transfer to a convalescent home on the 14th of August 2017.

She was hospitalized again on the 30th of September 2017 for degradation of her general state of health associated with febrile aplasia from an undetermined cause, in addition to a systemic inflammatory response syndrome. Blood tests revealed leucopenia (0.6 G/L), thrombopenia (113000/mm$^3$) and anemia (haemoglobin 9.5 g/dL). There was no hepatocellular failure (Factor V: 150%). Bacteriological and viral analyses, including blood and urinary cultures, did not show evidence of an active infection. A myelogram was discussed but not carried out because of the decision to cease administration of active therapies and to limit treatment to the best supportive care, as decided jointly by the medical team and the family. She died on the 10th of October 2017 of multivisceral failure.

A recent analysis of published case reports found 18 cases of hepatotoxicity induced by celecoxib. The type of the liver injury is non-specific, often mixed (44%) and sometimes hepatocellular (30%) or cholestatic (22%). Liver biopsies found cholestasis in 83% of cases. The median (range) duration of treatment was 13 (1—730) days and latency between ingestion and symptoms was 15 (2—730) days. No deaths were reported, but two patients needed a liver transplant [4]. To date, only one case of hepatotoxicity after taking only one pill of celocoxib (200 mg) has been described. Symptoms appeared 16 days later. The biopsy showed moderate cholestasis with portal inflammation and evolution was spontaneously favorable [5]. El Hajj et al. reported a case of cholestatic hepatotoxicity with major ductopenia after 3 days of treatment with celecoxib. A liver transplant was performed and the explant histology revealed, like in our patient, a vanishing bile duct syndrome [6].

A skin rash and initial fever may suggest a hypersensitivity reaction with immunization and can also explain the outcome despite the discontinuation of the causative agent. Nevertheless, the general practitioner and the family indicated that no celecoxib or other coxib had been taken.

The selective COX-2 inhibitor celecoxib has a sulfonamide-like structure. Celecoxib is contraindicated for use in patients who have demonstrated allergic reactions to sulphonamides although the information is inconsistent in the literature [7]. In our case, we did not find that any sulphonamide had been taken in the past.

A specific human leukocyte antigen (HLA) haplotypes can explain drug-induced cholestasis. It is well known in drug-induced liver injury with amoxicillin/clavulanate [8]. More recently, Singer et al. found a strong association between lumiracoxib and DILI in HLA DRB1*15:01 haplotypes [9]. Although it was possible that our patient had a genetic predisposition, we did not characterize her HLA haplotypes.

This report shows that a single dose of celecoxib can trigger severe cholestatic hepatitis, which can progress to a vanishing bile duct syndrome with consequential death. The striking point of this case report is the severity of the disease in response to a single dose of celecoxib.

Despite the low prevalence of celecoxib-induced liver injury, this drug should be used with cautious.

## Role of the funding source

None.

## Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgments

The authors thank Dr M C Brahimi-Horn for editing assistance.

## References

[1] Antoniou K, Malamas M, Drosos AA. Clinical pharmacology of celecoxib, a COX-2 selective inhibitor. Expert Opin Pharmacother 2007;8:1719—32.
[2] Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci USA 1999;96:7563—8.
[3] Maddrey WC, Maurath CJ, Verburg KM, Geis GS. The hepatic safety and tolerability of the novel cyclooxygenase-2 inhibitor celecoxib. Am J Ther 2000;7:153—8.
[4] Mukthinuthalapati PK, Fontana RJ, Vuppalanchi R, Chalasani N, Ghabril M. Celecoxib-induced liver injury: analysis of published case reports and cases reported to the food and drug administration. J Clin Gastroenterol 2018;52:114—22.
[5] Schmeltzer PA, Kosinski AS, Kleiner DE, Hoofnagle JH, Stolz A, Fontana RJ, et al. Liver injury from nonsteroidal anti-inflammatory drugs in the United States. Liver Int Off J Int Assoc Study Liver 2016;36:603—9.
[6] El Hajj II, Malik SM, Alwakeel HR, Shaikh OS, Sasatomi E, Kandil HM. Celecoxib-induced cholestatic liver failure requiring orthotopic liver transplantation. World J Gastroenterol 2009;15:3937—9.
[7] Knowels S, Sahapiro L, Shear NH. Should celecoxib be contraindicated in patients who are allergic to sulfonamides? Drug Saf 2001;24:239—47.
[8] Hautekeete ML, Horsmans Y, Van Waeyenberge C, Demanet C, Henrion J, Verbist L, et al. HLA association of amoxicillin-clavulanate-induced hepatitis. Gastroenterology 1999;117(5):1181—6.
[9] Singer JB, Lewitzky S, Leroy E, Yang F, Zhao X, Klickstein L, Wright TM, Meyer J. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. Paulding CA Nat Genet 2010;42(8):711—4.

E. Larrey[a,*]
S. Patouraux[b,c,d]
A. Spreux[e]
C.M. Canivet[a,c,d]
T. Piche[a,d]
A. Tran[a,c,d]
R. Anty[a,c,d]

[a] *CHU de Nice, Digestive Center, Nice, France*
[b] *CHU de Nice, Biological Center, Pasteur Hospital, Nice, France*
[c] *INSERM, U1065, C3M, Team 8 ''Hepatic complications in obesity and alcoholism'' Nice, France*
[d] *Université Côte d'Azur, Nice, France*
[e] *CHU of Nice, Pharmacovigilance Center, Nice, France*

* Corresponding author.
*E-mail address:* larrey.e@chu-nice.fr (E. Larrey)

Available online 16 November 2018