

**Case Report**

Increasing Jaundice Secondary to an Acute Toxic Hepatitis Induced by Levofloxacin in a 20-year-old Man with a Fibrolamellar Hepatocarcinoma

Robert Diaz Beveridge^{1*}, Gema Bruixola¹, Javier Caballero¹, Enrique Jimenez², Martin Prieto³, Encarnacion Reche¹, and Jorge Aparicio¹

¹ Medical Oncology Department, University Hospital La Fe, Valencia, Spain

² Pathology Department, University Hospital La Fe, Valencia, Spain

³ Gastroenterology and Hepatology Department, University Hospital La Fe, Valencia, Spain

Abstract

Introduction: Levofloxacin-induced liver injury is rare and usually mild and transient. Presentations in the form of acute fulminant hepatitis are extremely uncommon.

Presentation of the case: We report the case of a 20-year old man with a fibrolamellar hepatocellular carcinoma (fHCC), with affected retroperitoneal lymph nodes but no hepatic disease involvement. After receiving levofloxacin for the treatment of a community-acquired pneumonia, he developed hyperbilirubinemia and abnormal liver function tests in the context of an acute cholestatic toxic hepatitis. In spite of optimal supportive treatment, that included admission in the Intensive Unit Care and extracorporeal albumin dialysis detoxification, the patient developed a rapidly progressive liver failure and died a month after the beginning of the process. The necropsy findings confirmed extensive drug-induced hepatic necrosis. No liver involvement by the fHCC was found in the autopsy.

Conclusion: Rarer intercurrent conditions, such as drug-induced hepatotoxicity, should be taken into account in cancer patients with deranged liver function tests, even in those patients with advanced disease.

Keywords: fibrolamellar hepatocarcinoma; toxic hepatitis; levofloxacin; drug-induced liver injury (DILI); hepatotoxicity

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***Correspondence to:** Robert Diaz Beveridge, Medical Oncology Department, University Hospital La Fe, Valencia, Spain; **Email:** diaz_rob@gva.es

Introduction

Fluoroquinolone-induced hepatotoxicity is uncommon; its manifestations are usually mild and transient, in the form of mildly elevated transaminases and with few associated symptoms [1]. Levofloxacin is a new-generation fluoroquinolone with an excellent safety profile and a convenient once-daily dosage that has led to its widespread use in the treatment of respiratory, skin and genitourinary tract infections [1]. Regarding its hepatic toxicity, elevation of liver enzymes has been described as relatively common (rate $\geq 1/100$ to $< 1/10\%$). Severe forms of acute liver injury, however, including those cases with fatal acute liver failure, are much less common, with only twelve cases reported in the literature [2-12].

Case Report

Our patient was a 18-year man who was diagnosed in May 2007 of a mass in the right hepatic lobe. There was no personal history of interest. His family history was unremarkable. There was no previous history of alcohol, tobacco or other drugs abuse. Blood liver-function test and viral serologies were normal. Alpha- fetoprotein levels were within normal levels. There was no extra-hepatic spread in the staging computed tomography (CT).

A right hepatectomy, cholecystectomy, right adrenalectomy and retroperitoneal lymphadenectomy were performed. A large 12-cm solid tumour with calcified and necrotic areas in a non-cirrhotic liver was identified. Large and polygonal tumour cells arranged in cords and separated by sheet-like fibrous bands arranged in a lamellar distribution were seen in the microscopic analysis. Margins were clear and there was no lymph node involvement. All these findings were compatible with a fibrolamellar hepatocellular carcinoma (fHCC).

The patient began routine follow-ups. Fifteen months after the surgery, in October 2008, a routine CT-scan showed two small solid nodules in the left lung, both 1.5 cm of diameter, and a large 11-cm heterogeneous retroperitoneal mass that infiltrated the duodenum and the inferior cava vein. Enlarged retrocrural lymph nodes in the right side were also seen. No new liver masses or dilation of the intrahepatic bile ducts were found (Fig.1). An ultrasonography-guided biopsy of the retroperitoneal mass was compatible with metastases of the fHCC.

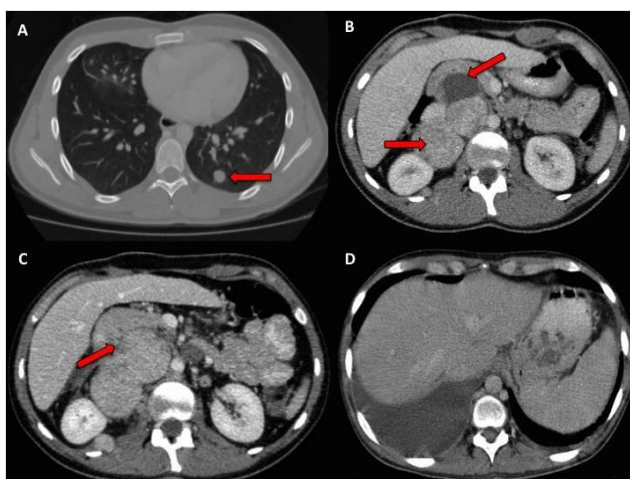


Fig. 1 Thoracic and abdominal computed tomography (CT) scan images. Panel (A) and (B) axial images from November 2008. They show a relapse with 2 solid nodules in left lung and a heterogeneous retroperitoneal mass. Panel (C) axial image from April 2009. It shows a partial response with a reduction in size of the retroperitoneal

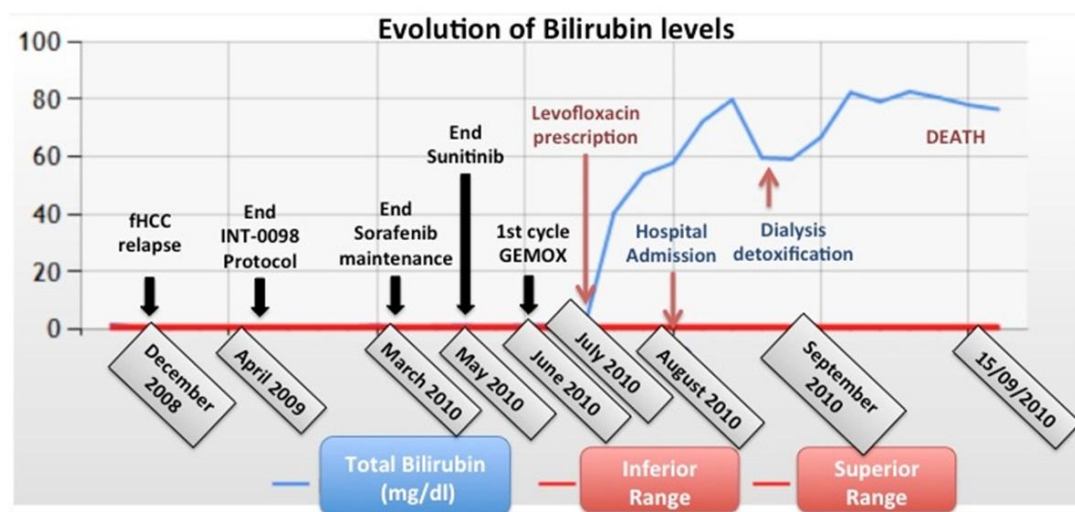
mass. Panel (D) axial image from August 2010. Levofloxacin-induced liver injury, liver without focal lesions

In December 2008, first-line palliative chemotherapy was started with the combination of cisplatin at doses of 90 mg/m² on day 1 and doxorubicin 20 mg/m²/day administered by a 96-hour intravenous continuous infusion, every 21 days, with granulocyte colony-stimulating factor support, according to the INT-0098 protocol [13]. He received six cycles in total until April 2009 with no relevant toxicity ending on April 2009. The evaluation CT scan showed a partial response according to RECIST criteria, with a significant decrease in size of the retroperitoneal mass that measured 4.5 cm in diameter (Fig. 1).

Afterwards, maintenance treatment with sorafenib at a standard dose of 400mg twice a day was prescribed. The main side-effects experienced were grade 2 fatigue and hand-foot syndrome. The successive CT scans showed stable disease.

Unfortunately, an increase in the retroperitoneal mass was noted in March 2010, ten months after the beginning of sorafenib. Sunitinib was begun at a dosage of 37.5 mg daily. However on May 2010, after two months of treatment, the patient developed an intestinal subocclusion. The diagnostic CT showed an enlargement of the retroperitoneal mass that was causing an extrinsic duodenal compression; these findings were compatible with a new progression of the disease. A palliative gastrojejunostomy was required in order to resolve the intestinal obstruction.

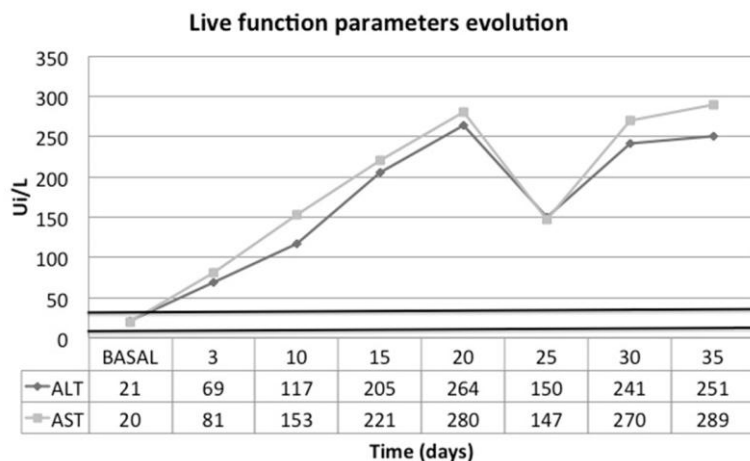
Taking into consideration that the patient had presented a progressive disease after two lines of tyrosine-kinase inhibitors, but maintained a good performance status, it was decided to begin a new palliative chemotherapy combination with gemcitabine and oxaliplatin on June 2010. However, before the second cycle of chemotherapy, the patient referred subacute dyspnea and low-grade fever. An X-ray showed a small left lower lobe pneumonia. His general status was acceptable, no hypoxemia was noted, there was no neutropenia and the liver and kidney function tests were normal. The total bilirubin level was 1.8 mg/dl. With the diagnosis of a community-acquired pneumonia, empiric levofloxacin was prescribed at an oral dosage of 500 mg twice daily on the first day followed by 500 mg once a day for a total treatment course of 10 days.



Graph 1 Correlation between bilirubin levels and history of the disease

The patient referred a quick symptomatic improvement with no need of antipyretics. However, three days into the treatment course, the patient referred the appearance of dark urine and a yellow tinge of the

skin. At that moment, the bilirubin level was 5 g/dl. He was admitted as an inpatient for further studies. Blood tests showed an elevated deshydrogenase lactate (LDH) level but the Coombs test was negative; thus the possibility of a haemolytic anemia was rejected. Imaging evaluation with a liver ultrasonography, an abdominal CT scan and a magnetic resonance cholangiopancreatography ruled out both liver progression of disease as well as any type of bile duct dilation (Fig. 1). Serologies for hepatitis viruses (A, B, C, D, E, CMV and VEB) and autoimmune hepatitis antibodies (ANA, SMA and anti-LKM1) were both negative. The clinical picture did not favour any type of biliary infection or sepsis as the patient's general status was acceptable, he was not septic and there was no fever. However, the total bilirubin levels continued to increase (Graphs 1 and 2).



Graph 2 Evolution of liver function parameters after onset of the levofloxacin. Abbreviations: ALT, alanine aminotransferase. AST, aspartate aminotransferase

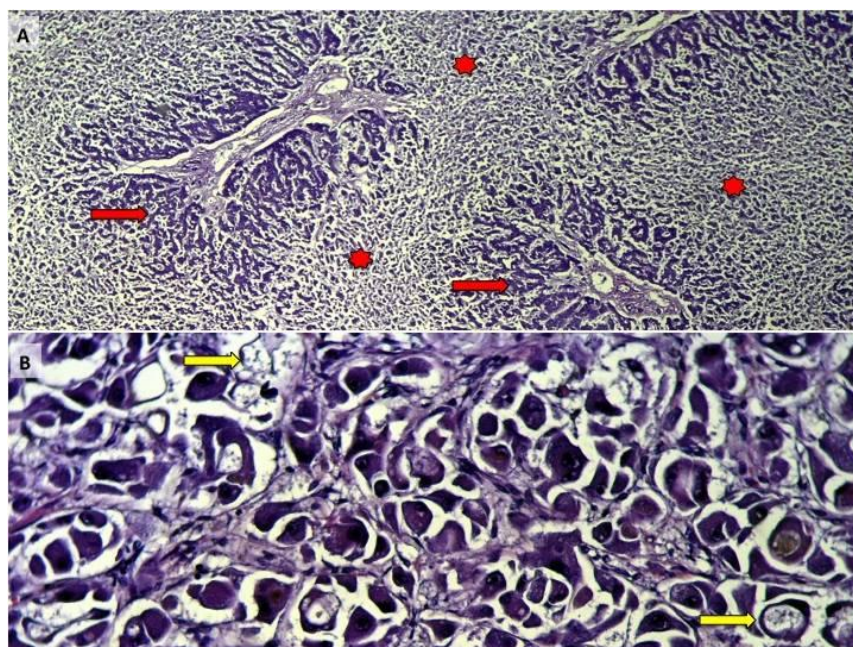


Fig. 2 Pathological images from the autopsy. Panel (A) (hematoxilin-eosin, magnification x40) Loss of normal architecture of the liver due to centrolobulillar necrosis. Panel (B) (hematoxilin-eosin, magnification x400) Cellular necrosis and cholestasis.

A liver biopsy was performed; it revealed cytoplasmic cholestasis and microvesicular steatosis, with

small fatty intracellular drops. These findings were indicative of a toxic-induced liver injury. The patient again referred not taking any other drugs apart from the levofloxacin. He had not taken any toxic substances. The last systemic therapy for his fHCC was more than 30 days before the development of the hepatocellular injury. New imaging tests ruled out both obstructive pathology and tumour liver progression as the main causes of the liver failure. It was decided that the hepatotoxicity due to the antibiotic therapy was most probably responsible for the process.

Empirical prednisone at a dose of 1 mg/kg/24 hours was begun with little improvement in the increasing bilirubin levels. Supportive treatment with fluid therapy, omeprazol, lactulose and vitamin K was begun. Once the bilirubin had reached the level of 87.8 mg/dl, he was transferred to the Intensive Care Unit; there, the patient received extracorporeal albumin dialysis as a detoxification procedure in order to manage the increasing bilirubin levels.

He experienced an initial improvement with the detoxification procedure, with a slight decrease in bilirubin levels (60 mg/dl). However, a few days later the patient suffered widespread gastrointestinal bleeding associated with a severe respiratory distress syndrome that determined an irreversible clinical deterioration. The patient died, a month after jaundice first developed, on September 2010.

An autopsy was performed. It established an extensive drug-induced hepatic necrosis and widespread digestive bleeding as the final cause of death (Fig. 2). There was malignant disease in the lungs and in the retroperitoneum. Of note, there were no hepatocellular carcinoma deposits in the liver.

Discussion

Fibrolamellar hepatocellular carcinoma (fHCC) was described for the first time in 1956. This entity represent an uncommon primary liver malignant tumor, with an incidence that ranges from 0.6% to 6.6 % [14] of all liver neoplasms, almost 100-fold less frequent than hepatocellular carcinoma (HCC).

Compared to hepatocellular carcinoma, fHCC typically appears in young patients with no previous liver disease in the form of large liver tumours with frequent lymph node involvement. The presence of calcifications is typical, as was our case. Alpha- fetoprotein levels are usually within normal levels. Prognosis tends to be better with fHCC compared to HCC, probably related to a higher chemosensitivity, to the younger age and to the absence of cirrhosis in these patients.

Surgery is the initial approach in most cases, while liver transplantation remains an experimental strategy. Resectability is considered the main prognostic factor [14]; unfortunately almost 75% of patients will present an unresectable relapse over the course of their illness and, at the moment, there is a lack of reliable prognostic markers [14].

Advanced fHCC is an orphan disease and there is little evidence to choose the best treatment, as there are only two clinical trials published and both were performed in a mixed population (fHCC and HCC) [13,14]. In our case, we decided to use the INT-0098 protocol of cisplatin and doxorubicin that has shown efficacy and safety in the 1st line treatment in children and adolescents with HCC [13], as was our case. Unfortunately, in further lines of treatment there are no specific data in fHCC. There is a trend to extrapolate the experience with the more frequent HCC, such as the use of sorafenib (approved in the 1st line setting of advanced HCC in patients with preserved liver function) and other molecularly targeted therapies such as sunitinib or erlotinib or chemotherapy regimens such as gemcitabine-oxaliplatin. After an exhaustive review of the literature, we found that our treatment regimens were similar to those reported in previously published papers: a case series treated with sorafenib, a phase 1 trial with sunitinib published only in abstract form, and a report of clinical case treated with gemcitabine-oxaliplatin [15].

Regarding the levofloxacin-induced drug injury, to our knowledge, this is the first case described in an oncologic patient that is supported both by a biopsy and autopsy confirmation.

First, we need to define “liver injury”, term which refers to an increase in ALT or total bilirubin (TB) of over 2 times (x) the upper limit of normal (ULN), or a combined increase in AST, ALP, and TB provided one of them is over 2xULN [16]. Likewise, in 1978 there was an agreement to define “drug-induced liver injury” (DILI) as elevations in the liver enzymes, AST and ALT of more than 3xULN or alkaline phosphatase (ALP) more than 1.5xULN in combination with an elevated bilirubin (> 3x the ULN) as a sign of serious liver injury any time after a new drug is started [17-18]. There is a wide spectrum of severity, although a mortality rate of 10% has been reported in cases of drug-induced liver injury (DILI) associated with clinical jaundice, as was seen in our patient [11]. The pattern of injury can be classified as either hepatocellular, cholestatic or mixed, according to the ratio (R) of ALT/ALP [1]. Hepatocellular pattern, with a $R > 5$, is the most frequent seen with fluoroquinolones (51.7%) [1]; however, our case, with a $R < 2$ is included in the cholestatic pattern (which represents up to 28.6% of cases related to fluoroquinolones). Finally, the mixed pattern is characterized by $R > 2$ and < 5 is the pattern less frequently seen when fluoroquinolones are involved (20%) [1].

In spite of being a well-characterized entity, DILI is often a diagnosis of exclusion. Hence, we should first consider well-known risk factors associated with DILI, which comprehend genetic susceptibility (P450 polymorphisms), individual characteristics (older than 55 years, female gender, obesity and malnutrition), lifestyle (concomitant abuse of alcohol or drugs), history of past drugs reactions and pregnancy. Our patient did not present any of these factors, but he had had a right hepatectomy and been heavily pretreated with different systemic treatments which should be taken into consideration.

A biopsy is often necessary to correlate pathological histological and laboratory findings, especially in those cases where more frequent causes of liver dysfunction have been ruled out. In many cases, however, the findings are not specific although they can help rule out other conditions and aid in the management of these patients

In cases of suspected DILI, there is an established role for scales of causality assessment; in our patient, the Naranjo Adverse Drug Reaction Probability Scale score for this association was “probable” (score 7) and the Roussel Uclaf Causality Assessment Method Scale score was also “probable” (score 8). However, both have been criticized due to their variability and poor specificity [19]. Recently a new standard scale, the CIOMS scale, has been published that tries to overcome these limitations [19]. With this new consensus scale, the score for the association of the cholestatic injury with the use of levofloxacin was “probable” as well (score 6).

Unfortunately, the management of severe DILI has experienced few advances; the removal of the causal agent and the optimizing of supportive care are the mainstays of therapy. The use of steroids or antioxidant therapies have been tried, with inconsistent results. In our case, we performed an aggressive multimodal strategy that combined prednisone, maximal supportive care in an intensive care setting and extracorporeal albumin dialysis as a detoxification procedure, and we achieved a transient improvement in the liver function parameters of our patient. Unfortunately the benefit was short-lived and the patient died of widespread gastrointestinal bleeding in the setting of an acute liver failure.

In conclusion, it is noteworthy to emphasize the case of our patient who died secondary to a toxic hepatitis rather than from the advanced malignancy. This fact highlights the need to take into account not only any progressive malignant disease but also other intercurrent rarer factors, such as DILI [2-12], in patients with advanced cancer that can influence the course of the disease.

Conflicts of interest

All the authors have indicated that they have no conflicts of interest regarding the content of this article.

Consent

The patient unfortunately died on September 2010 and no consent is available.

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