DRESS syndrome secondary to ibuprofen as a cause of hyperacute liver failure

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ABSTRACT

Acute liver failure has a high mortality and its most frequent cause in Spain is viral infection. In this article, we present a case of fulminant liver failure. The failure is secondary to an idiosyncratic reaction to ibuprofen, an entity included in the DRESS syndrome. This syndrome plays a key role in the differential diagnosis of acute liver failure, since its unfortunate course often requires liver transplantation as the only useful therapeutic weapon. This case illustrates the need for an efficient coordination between hospitals as a key factor for improving the prognosis.

Key words: DRESS syndrome. Ibuprofen. Acute liver failure.

INTRODUCTION

Acute liver failure is defined as a severe hepatocellular dysfunction, triggering coagulopathy and hepatic encephalopathy, in a patient without pre-existing liver disease (1). It is classified into hyperacute, acute and subacute attending to temporal criteria. Because of its high mortality it is a process that should be considered in a patient with clinical or laboratory signs of impaired liver function. It is vitally important to closely monitor the patient and his hepatocellular function from the beginning, trying to find out the etiology of the liver failure in order to anticipate a possible clinical deterioration. The idiosyncratic hepatic adverse events continue to be today, despite the undoubted progress in this area occurred in recent years, a real diagnostic challenge. They represent the group of poorest prognosis, being capital to discard them with proper clinical history and the adequate tests (2,3). DRESS syndrome (Drug Rash with Eosinophilia and Systemic Symptoms) is a drug hypersensitivity reaction that causes rash, fever, generalized lymphadenopathy and visceral injury, including interstitial nephritis, interstitial pneumonia and fulminating hepatic failure.

CASE REPORT

22-year-old male who had a history of Kawasaki disease at age 14 discharged for rheumatology. Born in Madrid. He had no known drug reactions or cardiovascular risk factors. There was no history of drug and alcohol consumption.

He had no family history of acute or chronic liver disease within two ascending generations. He had been inconsistently living with someone who had been recently diagnosed with acute Q fever. There was no history of autoimmune diseases in the family. The patient consulted dentist eight days before going to the emergency room for dental extraction taking three capsules of 575 mg metamizol during the day as analgesic treatment. He remained asymptomatic and 5 days later had an episode of mild headache, myalgias, arthralgias and dysthermia feeling. Therefore, he was treated with ibuprofen reaching a total take 1200 mg and 1 tablet of acetaminophen 500 mg with initial improvement.

Within hours, the patient developed fever of 38º C. It was valued by the primary care physician. The episode was diagnosed of flu syndrome and Algidol© (paracetamol 650 mg, codeine 10 mg, and 500 mg ascorbic acid) was prescribed. Several hours later, he developed an itchy rash on
the chest region. Therefore, the medication was removed again and prescribed ibuprofen. At this time, he went to the emergency room. There was no history of herbal products’ intake, neither fungi or mushrooms or spoiled food. He had not travelled outside Spain in the recent past. The patient denied any sexual relationship other than his regular partner, nor realization of tattoos, piercings or any other risky behaviours.

On arrival to the emergency room, the patient was hemodynamically stable, with a soft abdomen, painful to palpation in the right hypochondrium coinciding with hepatomegaly without ascites semiology. On examination of the skin, macular rash pruritic highlighted with predominance of trunk and upper limbs, being confluent and yielding slightly when pressure was applied, respecting palms and soles. The rest of the examination was normal, including a thorough neurological examination. The analytical evolution can be observed in table I. Chest radiography showed no pathological changes. Paul Bunnell test was negative.

An abdominal ultrasound was made, revealing plenty of free peritoneal fluid and hepatomegaly without signs of thrombosis in portal and hepatic circulation. In the peripheral blood smear, abundant number of activated lymphocytes in blood were observed. Despite intensive fluid therapy and administration of vitamin K, the patient developed negatively, without improvement of liver function tests, extreme coagulopathy maintenance and development of hypotension refractory to volume.

He was admitted in the intensive care unit, being transferred later to a hospital with liver transplant unit and liver support system. Within hours, the patient developed clinical hepatic encephalopathy, bilateral pleural effusion with respiratory failure, severe metabolic acidosis and worsening skin symptoms.

In the analytical evolution, called attention the progressive eosinophilia, with an amount at 48 hours of 4,270 eosinophils per microliter (18.7 %).

Due to his clinical status, it was necessary to initiate external liver support by MARS (Molecular Adsorbents Recirculation System). The patient was placed on the transplant protocol 0. At 24 hours, the patient underwent cadaver donor liver transplantation (58-year-old, subarachnoid hemorrhage).

There were no problems in the postoperative period, and he could be extubated without complications three days later. There was progressive improvement of cytolysis and cholestasis enzymes with normalization of coagulation, with persistent mild thrombocytopenia. He was discharged several days later without further complications. Serology extracted twice tested negative for HAV, HBV, HCV, EBV, HSV, syphilis, HIV, CMV, and parvovirus B19. Determination of paracetamol in blood on admission was in a low range of toxicity and decreased to normal levels within a few hours after treatment with N-acetylcysteine.

Considering histopathology, findings of the explant are summarized in submassive confluent necrosis with inflammatory polymorphous reaction, hypereosinophilia and phlebitis, all suggestive of adverse reactions due to hypersensitivity.

**DISCUSSION**

DRESS syndrome is a dermatosis secondary to an adverse drug reaction with poor prognosis characterized by fever, rash, lymphadenopathy, and visceral blood disorders that can include acute liver failure. It has been described in connection with aromatic anticonvulsants, some antiviral drugs (abacavir, nevirapine, zalcitabine), antibiotics...
(tetracycline and sulfonamides) or some salts like strontium ranelate (4-6).

The main cause of acute liver failure in the western world is dose dependent toxicity caused by paracetamol, constituting 39% of their cases in U.K. and the U.S. (7,8). In Spain the first cause is viral infection, with 37% of cases, predominantly HBV. Second one is drug toxicity (19.5%) (9). Autoimmune hepatitis comes third, with other causes such as ischemic, infiltrative, or Wilson’s disease.

In this case the determination of paracetamol showed slight toxic levels that, as explained, responded to the administration of antidote within hours of hospitalization. This did not have clinical correlation in the subsequent course of the patient. Another reason for discarding the acetaminophen’s etiology was the lack of the typical analytical evolution of acute liver failure caused by this molecule, being characteristic a further increase of bilirubin and especially ALT. Moreover, serology of all hepatotropic viruses were negative in both hospitals.
Idiosyncratic drug reactions are caused by an unpredictable and immunoallergic event in contrast to direct toxicity that occurs with other drugs like acetaminophen. It occurs in a frequency of 1/10,000-1,000,000 patients/year/exposure. There are many drugs described to be potentially harmful in this way, being the most relevant isoniazid (16 %), propylthiouracil (9 %), phenytoin (7 %) and NSAIDs (5 %), including ibuprofen (10). Ruled out in principle the viral etiology and acetaminophen, the most common causes, differential diagnosis was expanded to other potential etiologies. Integrating the findings of eosinophilia, rash pruritic, odynophagia and general deterioration, became clear that our patient fulfilled diagnostic criteria for DRESS syndrome, and suspicion was confirmed by the explant pathology as previously described.

In the context of the onset of the episode, apart from acetaminophen, codeine and metamizole were ingested. In the case of metamizol, the administration was more than 96 hours before the start of the clinic and there are no similar reactions described in the literature, so it seems coherent to discard it as the etiological factor. Codeine itself coincides temporally with ibuprofen, but it was discarded because there was no history of liver toxicity in the literature despite being a ubiquitously used drug. So the only drug candidate to be the cause of DRESS would be ibuprofen, NSAID with multiple dermal and liver reactions described (11).

The pathogenesis of DRESS syndrome is not precisely known, but it is believed that metabolic, immunological and inflammatory factors, both constitutional and acquired, are involved. Some risk factors such as vitamin D deficiency and skin phototype have been described, as it is more common in black people. Vitamin D has an anti-inflammatory and antiproliferative effect, so that its deficit has been proposed to increase the Th1 response and IL-18, apparently implicated in the pathogenesis of the syndrome. Although several hypotheses have been proposed in the literature, it seems to be clear that this disease is due to excessive production of toxic metabolites in the drug detoxification pathway caused by genetic or environmental injuries.

In some cases, it has been found an association between DRESS syndrome and infection reactivation of human herpesvirus 6, but it has not been possible to demonstrate the pathogenic mechanism enabling the action of the virus (12). Slow acetylators and patients with hypersensitivity to hydroxylamine metabolites have a greater predisposition to DRESS syndrome induced by sulfonamides (13). Furthermore, there are immunological phenomena that appear critical in the pathogenesis, namely the expansion of cytotoxic T cells (CD8 +) specific for the drug, which destroy the hepatocytes by direct contact, engaging cytokines like GranzimaB and expression of FasL (14).

As for the present case, both the clinical and pathology are similar to the cases provided in the literature, although the cytotoxic response is not as obvious as in other studies and identifies CD4 response in equal proportion.

In conclusion, acute liver failure has a low prevalence (is responsible for 3.5 deaths per million), but because of its high mortality it must be present in our differential diagnosis of various symptoms of apparent banal progress. It is hence convenient to apply for clotting times and other patterns of liver function under suspicion of acute liver damage.

Within the poor prognosis that presents acute liver failure, some etiologies are noted for their particular course, such as those caused by idiosyncratic drug reactions that occur with even further negative developments.

An example of such reactions is the DRESS syndrome, an often unfortunate process that has to be known in order to avoid confusion with other common processes such as acute mononucleosis or viral rash, as they share certain symptoms in early stages: Odynophagia, fever, rash or cytolytic altered pattern of transaminases.

When confirming the diagnosis of acute liver failure, the patient should be taken to a hospital with transplant unit at shortest possible time. Such transfer must be done even if there are still no transplant criteria, because the transfer in advanced stages presents major risks for the patient for several reasons (extreme coagulopathy, cerebral edema or hepatic encephalopathy) and because the scores more used for transplantation in acute liver failure, such as the King’s College Hospital of London (15), have sensitivities only around 50 % when the etiology is different to acetaminophen toxicity.

REFERENCES


