CASE REPORT

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Unexplained severe liver failure under Mycophenolate Mofetil treatment

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ABSTRACT

Mycophenolate mofetil is a potent immunosuppressive agent used in renal transplantation and in the treatment of some immunological disorders.

Although hepatotoxicity has been rarely reported in the literature, there are a few series describing the hepatic side effects of mycophenolate mofetil. The authors present a case of an unexplained fulminant acute hepatitis in a patient with lupus nephritis under recent treatment with mycophenolate mofetil.

Key-Words:
Hepatitis; lupus nephritis; mycophenolate mofetil.

INTRODUCTION

Mycophenolate mofetil (MMF) is a potent immunosuppressive agent initially used in renal transplantation, but positive experience in the field of solid organ transplantation has made the drug attractive for the treatment of several autoimmune diseases. MMF targets the *de novo* purine biosynthesis pathway by noncompetitive inhibition of inosine monophosphate dehydrogenase, acting against the proliferation of T and B lymphocytes[1]. It is generally well tolerated and the most prominent adverse effects are nausea, vomiting, diarrhoea and haematological side effects[2].

Although hepatotoxicity has been rarely reported in the literature, there are some cases describing hepatic side effects of MMF[2,3] that may be life threatening[4]. The authors present a case of fulminant acute hepatitis in a patient with lupus nephritis under recent treatment with mycophenolate mofetil.

CASE REPORT

The patient was a 64-year-old Caucasian male with hypertension, obesity (BMI=31 kg/m^2), hypercholesterolaemia and WHO class V lupus nephritis diagnosed in 1995, who presented with nephrotic syndrome and normal renal function. To reduce the risk of relapse, he was initially treated with six monthly cyclophosphamide pulses and corticosteroids, with no response. Thereafter, cyclosporine was tried but with poor compliance. Proteinuria was reduced to 1 g/day, with mantained serologic activity. In July 1999 the nephrotic syndrome relapsed after stopping immunosuppression at the patient's own initiative. Cyclosporine was restarted and prednisolone dose increased, achieving complete remission. The patient maintained an irregular treatment with cyclosporine because of noncompliance.

In July 2001, pulmonary tuberculosis was diagnosed and the patient completed six months of treatment with isoniazid, ryfampicin, ethambutol and

pirazinamide. He was considered cured and prophylaxis with isoniazid was maintained.

In March 2007 after acute ischaemia of the right foot, he started warfarin. Antiphospholipid antibodies were negative at that time.

In July 2007, the patient suffered a new relapse of the nephrotic syndrome (proteinuria 16 g/day), under cyclosporine. He presented with acute renal failure (creatinine 3.4 mg/dl), active urinary sediment, hypocomplementaemia and elevated antinuclear (ANAs) and anti-dsDNA antibodies. The kidney biopsy was compatible with diffuse prolipherative glomerulonephritis with moderate signs of chronicity. Given the efficacy of MMF and to avoid a high cumulative dose of cyclophosphamide, treatment with MMF was started (1000 mg twice daily). Renal function stabilised and proteinuria reduced to 4.4 g/day.

He was admitted to our hospital one month later, obnubilated and oliguric. Patient's vital signs were stable. He presented jaundiced skin and sclerotics and was dehydrated. He also complained of a moderate pain in the right upper abdominal quadrant without signs of peritoneal irritation. Asterixis was absent.

Kidney function was deteriorated (creatinine 6.8 mg/dl, urea 191 mg/dl) and he presented abnormal liver function tests: alanine aminotransferase 532 IU/L (normal 14-41 IU/L), aspartate aminotransferase 147 IU/L (normal 10-42 IU/L), lactate dehydrogenase 1778 IU/L (normal 266-500 IU/L), alkaline phosphatase 171 IU/L (normal 30-126 IU/L), γ-glutamyl transpeptidase 172 IU/L (normal 8-50 IU/L), total bilirubin 6.4 mg/dl (normal 0.4-1 mg/dl) with direct bilirubin 4.5 mg/dl. Liver function tests were in the normal range in all previous laboratory tests, performed every 3 months. Prothrombin time was prolonged (120 sec) and normocytic normochromic anaemia was present, without leukopaenia or thrombocytopaenia. He had no previous history of liver or biliary disease, alcohol abuse, drug addiction, blood transfusion or foreign travel. There was no history of recent ingestion of medicinal herbs or mushrooms. He was not receiving nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics.

The abdominal ultrasound showed medium volume ascites and moderate hepatomegaly, with a normal Doppler of the hepatic vessels. There was no evidence of intra- or extrahepatic dilatation or other abnormality of the biliary ducts in computed tomography (CT) or colangio-magnetic ressonance.

The patient progressed with neurologic, hepatic and renal deterioration in the 24 hours following admission. Hyperbilirubinaemia reached more than 20 mg/dl and haemodialysis was performed for five days. Isoniazid, MMF and warfarin were suspended because of their possible hepatotoxic effects. The oral prednisolone dose was increased to 60 mg/day and empiric antibiotherapy with meropenem was started, without clinical improvement.

The serology for possible viral hepatitis (including Hepatitis A, B, C, D, E, cytomegalovirus and Epstein-Barr virus), *leptospira* and *leishamnia* were negative. All cultures, including fungi, were negative. ANAs remained positive and anti-dsDNA antibodies were stable (64 IU/ml). Antimithocondrial, anti-LKM and antismooth muscle antibodies were negative. Sarcoidosis and haemochromatosis were excluded.

Transjugular hepatic biopsy at the 20th day was compatible with acute cholestatic hepatitis, with dilated portal spaces, marked signs of cholestasis and ductal hyperplasia. There were also areas of hepatocellular necrosis and inflammatory infiltrate with lymphocytes and neutrophils (Fig. 1).

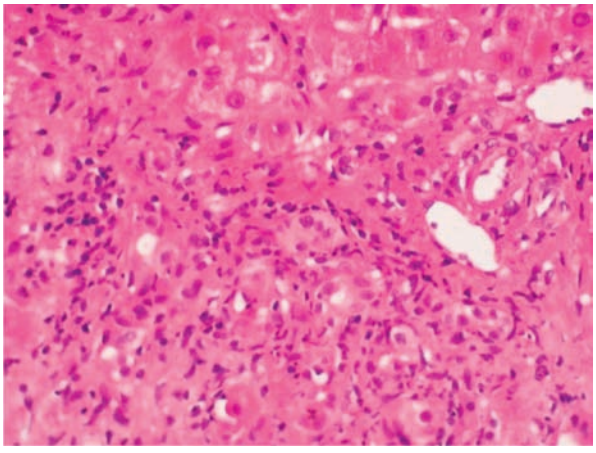

Figure 1

H&E. Dilated portal spaces and ductal hyperplasia, with inflammatory infiltrates.

The patient progressed to hepatic failure and died at the 26th day.

DISCUSSION

The authors report a case of severe hepatic failure in a patient with systemic erythematosus lupus under long-term isoniazid treatment and recently started on MMF.

Hepatitis may be a serious adverse reaction associated with MMF treatment with a frequency between 3 and 20% [5]. Sollinger *et al.*[3] documented elevated liver enzymes in several (n=5) patients receiving MMF. Balal *et al.*[2] documented that 11 of 79 patients taking MMF had a progressive increase in liver enzymes after renal transplantation and restarting the drug caused recurrence in six patients. The median time of increase in liver enzymes was 28 days (4-70) and the median time to normalisation after a reduction of 50% or withdrawal of the drug was 16 days (4-210).

In our patient, toxic hepatitis could be related to MMF based on temporal relationship, negative serology for acute viral infection and lower probability of hepatotoxic effect of the other drugs. Obviously, in the absence of rechallenge, proof was not possible. Although PCR (polymerase chain reaction) studies for Hepatitis B and C were not performed, the histological findings were not the most usual in viral hepatitis.

The possibility of an autoimmune hepatitis part of systemic lupus could not be ruled out. It is, however, less likely, considering the disease evolution, stability of the immunological markers and absence of suggestive haematological abnormalities.

Another hypothesis that could not be completely excluded was acute hepatitis associated with isoniazid, although some features of this case make it less likely. Since its introduction in 1952, isoniazid has been widely used as first-line treatment for both latent and active tuberculosis. Its most important side effect is liver toxicity[6]. Liver function test abnormalities occur in 10-20% of cases and symptomatic hepatitis develops in 1-2% of patients[7]. Although the drug can cause an idiosyncratic reaction[8,9], with the possibility of hepatic damage at any stage of the treatment, most cases are diagnosed in the first three months of treatment[9]. The average duration of therapy before clinical manifestations was 12.4 weeks (1-25) in a series of 14 patients over a five-year period[8]. In our case, the time between treatment initiation and acute hepatitis was 71 months, later than in other large series[8,9] and the marked hyperbilirrubinaemia is not a common feature in isoniazid hepatotoxicity[9,10].

The histological pattern was also not typical of isoniazid toxicity. Usually it is indistinguishable from that of viral hepatitis, with hepatocellular necrosis and a predominantly mononuclear inflammatory response, but with numerous eosinophils in some cases[8]. Cholestatic reaction is also not common[8] and was evident in our patient's biopsy.

These facts raise the possibility of MMF toxicity, something that should be seriously considered, although not completely proven. MMF-induced liver injury affects a minority of patients but implies frequent liver test monitoring, especially when associated with other possible hepatotoxic drugs. Measurement of mycophenolic acid levels may help to prevent or reduce the risk of toxicity, although this is not routinely done. MMF hepatotoxicity must be kept in mind in the presence of elevated liver enzymes and dose reduction or withdraw may be necessary to avoid serious complications.

Conflict of interest statement. None declared.

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