Methylprednisolone-Induced Liver Injury: A Diagnostic Challenge

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Drug-induced liver injury is an important and frequent drug adverse reaction in clinical practice. The manifestations are highly variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. The diagnosis should focus on thorough review of medications and dietary supplements. The typical pattern of elevated liver enzymes of the possible causative drug can be helpful; however, other causes of acute liver injury must be excluded. Many drugs can cause DILI, but antibiotics remain the most common prescribed drug, causing DILI mainly in the United States and Europe [1].

Steroids are considered safe drugs and are not believed to cause DILI, and are even used in the treatment of severe hepatitis [2]. Pulse intravenous therapy with high dose steroids is used in many autoimmune diseases and is better tolerated, with reduced risk of cushingoid features. We report the rare case of a patient with Graves' ophthalmopathy who was treated with pulse therapy of intravenous methylprednisolone and developed hepatotoxicity during the treatment.

PATIENT DESCRIPTION

A 52 year old man presented to the emergency room with weakness, arthralgia and jaundice. His past medical history was remarkable for hyperlipidemia on atorvastatin and ciprofibrate for many years, and Graves' disease following treatment with radioactive iodine and left hemithyroidectomy thereafter. He is currently hypothyroid on levothyroxin treatment. Four months before admission he developed ophthalmopathy and started treatment with intravenous methylprednisolone 500 mg/week for 4 weeks followed by 250 mg/week once a week. After a month of treatment he started to feel weakness and arthralgia, and his liver enzymes were elevated. All his medications were stopped for 2 weeks, with amelioration of his symptoms and improvement in liver enzyme levels. He restarted the treatment with a lower dose of intravenous methylprednisolone, 250 mg/week, for 2 weeks and again weakness and arthralgia reappeared with raised liver enzymes. At that point, it was decided to refer him to the emergency room for further evaluation.

On physical examination he was afebrile, jaundiced on skin and sclerae, with normal vital signs. The abdomen was soft with light sensitivity on the right upper quadrant, without signs of peritoneal irritation; the liver and spleen could not be palpated. Complete blood count showed hemoglobin 12.4 g/dl, hematocrit 37.9%, leukocytes 11,700/µl and platelets 135,000/µl. Prothrombin time (international normalized ratio) was 1.43 and prothrombin time 20.4 seconds. The biochemistry panel was normal except for total bilirubin 3.4 mg/dl, direct bilirubin 2.4 mg/dl, alanine aminotransferase 465 U/L, aspartate aminotransferase 283 U/L, gamma-glutamyl transferase 185 U/L, and alkaline phosphatase 80 U/L. Serum albumin was 4.25 g/dl and total protein 7.47 g/dl. Viral hepatitis serology showed anti-hepatitis A IgG positive, anti-hepatitis A IgM negative, anti-HBsAgAb positive, hepatitis B sur.Ag negative, anti-hepatitis B core IgM negative, and anti-hepatitis C Ab negative. Atypical viral serology (Epstein-Barr virus and cytomegalovirus) revealed anti-EBV IgM negative, anti-EBV IgG positive, anti-EB nuclear antigen IgG antibody positive, anti-CMV IgM negative, and anti-CMV IgG positive. Serum immunoglobulins, antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver kidney microsomal antibodies were normal. Serum ceruloplasmin and copper urinary levels were at normal levels as was alpha-fetoprotein.

Abdominal ultrasonography showed no signs of dilated intra- or extrahepatic bile ducts or any other parenchymal abnormalities. Methylprednisolone, atorvastatin and ciprofibrate were discontinued and the patient's clinical condition rapidly improved. The patient's liver enzymes were followed at an outpatient clinic, with slow but gradual improvement and normalization after approximately 7 months. Atorvastatin and ciprofibrate treatment was resumed without complications.

COMMENT

DILI is a very common (13%) and potentially serious and fatal cause of acute liver failure in both children and adults. It is also the single most common adverse drug reaction leading to a halt in the development

DILI = drug-induced liver injury

EBV = Epstein-Barr virus
EB = Epstein-Barr
CMV = cytomegalovirus

Summary of reported cases of methylprednisolone-induced liver toxicity

Author [ref]	Age Gender	Symptoms	ALT/AST (U/L) ALP/GGT (U/L)	Diagnosis	Naranjo score	Biopsy	Outcome
Topal et al. [2]	47 F	Weakness, nausea, anorexia, pruritus, jaundice	2478/1600 138/242	CNS vasculitis	6	Not done	Recovery after 45 days
Rivero et al. [3]	57 F	Asymptomatic	1223/543 113/71	MS	9	Acute hepatitis with bridging necrosis	Recovery after 3 months
Hofstee et al. [4]	46 F	Asymptomatic	1095/755 140/56	MS	9	Not done	Recovery after 4 months
Present case	52 M	Weakness, arthralgia, jaundice	465/283 80/185	Graves' ophthalmopathy	9	Not done	Recovery after 7 months

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, GGT = gamma-glutamyl transferase, CNS = central nervous system, MS = multiple sclerosis

Naranjo score: Definite ≥ 9, Probable 5–8, Possible 1–4, Doubtful ≤ 0

of new medications by pharmaceutical companies, failure of new drugs to obtain regulatory approval, and withdrawal or restriction of existing drugs from the market. Although DILI is thought to account for a small proportion of all idiosyncratic adverse drug reactions, and there is a relatively low incidence of DILI with many approved drugs (i.e., only 1 per 10,000 to 100,000 treated patients), up to 10% of patients with drug-induced jaundice will die. Population-based studies that accurately estimate the incidence and full spectrum of DILI are limited. Using data from a prospective population-based French study with an annual estimated incidence of 13.9 ± 2.4 DILI cases per 100,000 inhabitants, it has been extrapolated that nearly 44,000 individuals in the United States will suffer from DILI each year [1].

Hepatotoxins are often classified as predictable if they follow the dose-response curve, or unpredictable. The latter causes idiosyncratic hepatotoxic reactions subject to individual susceptibility. Clinical onset usually occurs within 2–6 weeks after therapy is started but may occur on the day the drug is first administered or not until 6 months later. Steroid-related hepatotoxicity is thought to be an idiosyncratic reaction to steroids and their metabolites or it could be due to the compounds used as preservatives [3]. Steroid-related liver injury has been observed in only a limited number of previous case reports, all of them related to intravenous pulse therapy [Table]. It is worth noting that most cases were observed in middle-aged women, probably due to the wide use of pulse therapy in autoimmune diseases that are more prevalent in this population group. Only three of the previous seven cases were deemed definitely related to steroids; all of them recovered spontaneously. Histological findings were allergic hepatitis, steatohepatitis and bridging necrosis, considered a bad prognostic finding in other settings. Lethal cases, specially presenting with steatohepatitis and liver necrosis, were reported but in these cases the Naranjo score [5] pointed to steroids as a probable but not definite cause.

Our patient had no prior liver disease known before admission to hospital, and other causes of acute hepatitis were ruled out. Although liver toxicity developed during concurrent use of atorvastatin and ciprofibrate, the chance that one of these drugs was the cause of his liver toxicity is low since rechallenge with only intravenous methylprednisolone at a lower dose led to the reappearance of symptoms with elevated liver enzymes. Again this was followed by improvement and normalization; moreover, these drugs were resumed after normalization of liver enzymes without complications at follow-up.

The present case, with an associated autoimmune disease, raised the suspicion of autoimmune hepatitis, but it was not corroborated by serology tests. Moreover, spontaneous recovery argues against this diagnosis. Steroids are regarded as first-line treatment for this entity, rendering the possibility of autoimmune hepatitis extremely remote. Although we did not perform a formal rechallenge test we considered the re-exposure of the patient to methylprednisolone by the team treating the Grave's ophthalmopathy to be nearly equivalent to a rechallenge test. After applying the objective causality assessment of Naranjo scale in our case, we reached a score of 9 points, linking hepatotoxicity to methylprednisolone, although liver biopsy was deemed unnecessary.

In conclusion, clinical case reports of hepatotoxicity related to methylprednisolone are uncommon despite the drug's extended medical use. However, these drugs may result in extremely dangerous hepatotoxicity. A timely recognition of this complication and early drug withdrawal may obviate unnecessary interventions and prevent the perpetuation of liver injury.

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