CASE REPORT

Methylprednisolone-induced acute liver injury in a patient treated for multiple sclerosis relapse

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Accepted 14 February 2018

SUMMARY

Drug-induced liver injury is the fourth most common cause of liver disease in industrialised countries. Methylprednisolone is often considered to be a treatment with a low hepatotoxicity. We report a case of methylprednisolone-induced liver injury in a 35-year-old woman. She was admitted to our department for acute liver injury 2 months after a treatment with high dose of methylprednisolone (1 g/day) for a multiple sclerosis relapse. No other cause of liver injury could be found (screening for hepatotropic viruses, autoimmune antibodies, ceruloplasmin, abdominal ultrasonography and liver biopsy). Liver function tests spontaneously improved and returned to normal range within 6 weeks. We also performed a brief review of the literature and identified 12 other cases of methylprednisolone-induced liver injury in patients treated for multiple sclerosis relapse. An immune rebound phenomenon could be responsible for rare but true hepatotoxicity of high-dose methylprednisolone therapy.

BACKGROUND

Drug-induced liver injury (DILI) is the fourth most common cause of liver disease after alcoholic liver disease, non-alcoholic fatty liver disease and viral hepatitis in industrialised countries.¹ Patients with DILI have high rates of morbidity and mortality: 53% of patients require hospitalisation, 2% require liver transplantation and the mortality rate is estimated to be 5%.² The diagnosis is made after excluding other causes of liver disease and therefore DILI is often underestimated.³ Some drugs such as acetaminophen, non-steroidal anti-inflammatory drugs and azathioprine are known to be frequently involved in acute liver injury.⁴

Methylprednisolone is one of the most efficient drugs for acute exacerbation of multiple sclerosis (MS).⁵ We often consider steroids to have a low hepatotoxicity, if any. Hence, steroids are also the first-line treatment for autoimmune hepatitis. In MS, steroids may be used at a very high dose as a pulse therapy. We report a case of methylprednisolone-induced liver injury confirmed by liver biopsy. We also discuss the potential mechanisms involved according to our observation and a review of the literature.

CASE PRESENTATION

A 35-year-old woman with a 13-year history of relapsing–remitting MS was admitted to our department in March 2017 for acute liver injury

incidentally identified on routine blood tests. Her medical history did not reveal any pre-existing liver disease. The family medical history was unremarkable. There was no history of illicit drug and alcohol abuse, no sexual promiscuity and there was no mention of foreign travel. Two months earlier, she was treated with a 5-day course of high-dose (1 g/day) intravenous methylprednisolone due to MS relapse. She did not take any other drugs in the last period.

On admission to our department, clinical examination revealed normal liver and spleen size, no signs of chronic liver disease and no jaundice. The rest of the physical examination was unremarkable.

INVESTIGATIONS

Laboratory studies at diagnosis showed the following results: alanine aminotransferase (ALT) 1512 IU/L (upper limit of normal (ULN)=35 IU/L), aspartate aminotransferase (AST) 778 IU/L (ULN=35 IU/L), gamma-glutamyl transferase (GGT) 109 IU/L (ULN=36 IU/L) and alkaline phosphatase 86 IU/L (ULN=98 IU/L). Serum total bilirubin level at diagnosis was 49 µmol/L (ULN=17 µmol/L), and direct bilirubin was 21 µmol/L (ULN=6 µmol/L). Prothrombin time at diagnosis was 68% (ULN=70%). Her complete blood count was unremarkable. Renal function, serum electrolytes, serum lipids, glycated haemoglobin and serum thyroid-stimulating hormone were within the normal range. The exhaustive screening for hepatotropic viruses was negative: serological tests for hepatitis viruses (A, B, C and E), cytomegalovirus, Epstein-Bar virus, HIV, herpes simplex virus 1 and 2; viral load of human herpes virus 6 and 8. The serum protein electrophoresis was normal except for a slightly elevated total immunoglobulin level (14.7 g/L; normal range=8–13.5 g/L). The serum immunoelectrophoresis showed normal IgM (1.09 g/L; normal range=0.74–2.09 g/L) and IgA (1.13 g/L; normal range=0.84–2.69 g/L) levels, and a slightly elevated IgG (15.4 g/L; normal range=6.81–12.66 g/L) level. Anti-smooth muscle, anti-mitochondrial, anti-liver kidney microsomal 1 and anti-soluble liver antigen antibodies were negative. Anti-nuclear antibodies were found in low titres (1:80). Ceruloplasmin level was within the normal range. Abdominal ultrasonography was normal.

A liver biopsy was performed at diagnosis and showed lesions of acute hepatitis. Confluent necrosis (estimated area of necrosis: 30%), more severe near the terminal hepatic venule with condensation of

To cite: Bresteau C, Prevot S, Perlemuter G, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223670

Figure 1 Liver biopsy showing acute hepatitis: confluent necrosis (estimated area of necrosis: 30%), more severe close to terminal hepatic venule with condensation of the reticulin framework in the centrilobular zones; mild portal tract inflammation (containing lymphocytes and eosinophils but non-plasma cells) throughout the biopsy without damage of the bile ducts; no visible cholestasis. PicroSirius Hemalun x5 – H&E Saffron x10.

the reticulin framework in the centrilobular area was associated with mild portal tract inflammation (containing lymphocytes and eosinophils but non-plasma cells) throughout the biopsy without damage of the bile ducts (figure 1). There was no visible cholestasis on liver biopsy.

DIFFERENTIAL DIAGNOSIS

Lacking a valid diagnosis marker, DILI is a diagnosis of exclusion, and all other causes of liver injury should be considered for differential diagnosis. In our patient, differential diagnosis included acute viral hepatitis, autoimmune hepatitis, overlap syndrome of autoimmune hepatitis, gall stone migration, ischaemic liver injury, acute Budd-Chiari syndrome and Wilson's disease. We therefore performed an exhaustive investigation panel. The exclusion of seronegative autoimmune hepatitis is particularly difficult in our case, as the patient already has an autoimmune background (MS). Nevertheless, liver function test (LFT) spontaneously normalised and were still within the normal range at 6-month follow-up. Furthermore, liver biopsy showed no sign of chronic hepatitis arguing for a DILI phenomenon rather than a true seronegative autoimmune hepatitis.

OUTCOME AND FOLLOW-UP

The patient was initially hospitalised for investigations and surveillance. LFTs spontaneously improved compared with those at diagnosis and returned to normal range within 6 weeks of follow-up. A routine blood test performed at 6-month follow-up showed normal LFT.

DISCUSSION

In the present observation, we report a case of DILI induced by high-dose steroid therapy. The causal relationship between high-dose methylprednisolone pulse therapy and DILI was assessed using the Roussel Uclaf Causality Assessment Method (RUCAM) Scale.⁶ This imputability scale includes several criteria such as temporal relationship between drug intake and development of liver injury, evolution of LFT following

drug withdrawal, previous case reports of DILI, concomitant medication, exclusion of all potential causes of liver damage, alcohol consumption, age and drug rechallenge.³ In our patient, the RUCAM score was 8 on a scale ranging from –8 to +14, corresponding to causality estimated as 'probable'. Of note, in the absence of rechallenge, the highest possible score is +11 instead of +14. The patient had not taken any other medicines and LFT spontaneously normalised within 3 months after the last high-dose steroid therapy use.

Few cases of liver damage related to high-dose methylprednisolone are reported in the literature. We identified 12 other case reports of methylprednisolone-induced liver injury in patients treated with high-dose intravenous methylprednisolone for MS relapse (table 1).^{7–18} All patients were women with a median age of 35 years (ranged: 11–57 years). Seven patients were hospitalised for non-specific symptoms such as fatigue, jaundice, abdominal pain and nausea. Other patients were diagnosed with routine blood tests and benefited from preclinical diagnosis of liver injury. We calculated, when possible, the R ratio ($R = \text{ALT/ULN} \div \text{AP/ULN}$). R ratio is used to define the type of DILI: hepatocellular DILI (R ratio >5), cholestatic DILI (R ratio <2) or mixt DILI (R ratio between 2 and 5). In all the eight cases when the R ratio was calculable, methylprednisolone-induced liver injury was of hepatocellular type. Of note, the RUCAM score was calculated in only one of the 12 previously published cases. Therefore, relatedness of methylprednisolone to the liver injury may be questioned in these reports (table 1).

The mechanism of methylprednisolone-induced liver injury is unclear due to the small number of reported cases. Use of steroids may cause three forms of hepatic injury: steatosis/steatohepatitis, hepatitis B virus reactivation and DILI.¹⁹ For patients treated with high-dose methylprednisolone pulse therapy, intrinsic hepatotoxicity of methylprednisolone is unlikely. Liver biopsy was performed in 9 of the 13 reported cases (including our patient). Histological examinations showed confluent necrosis ($n=6/9$) and inflammatory infiltrates with lymphocytic cells ($n=9/9$). These lesions could also be seen in autoimmune hepatitis. Furthermore, anti-smooth muscle antibodies were detected in three cases, but LFT improved and returned to normal values after methylprednisolone discontinuation. We therefore hypothesise that in methylprednisolone-induced liver injury, a transient immune rebound phenomenon may have occurred after withdrawal of high-dose corticotherapy. Furthermore, the half-life of intravenous methylprednisolone is estimated to be 210 min. In all case reports except one, the time from the last exposure to methylprednisolone and the occurrence of liver injury was 2 weeks or more. Thus, in all these cases, liver injury occurred after complete elimination of methylprednisolone. The spontaneous improvement of LFT and the pharmacokinetics data are also in favour of a transient immune rebound. This phenomenon has been suggested by some authors in patients treated with high-dose methylprednisolone for Graves' ophthalmopathy.²⁰ Graves' ophthalmopathy and MS are both autoimmune diseases that share similar autoimmune mechanisms and occur in a context of dysimmunity.

Our case report is an illustration of rare but true hepatotoxicity of high-dose methylprednisolone therapy. Methylprednisolone discontinuation allowed normalisation of LFT within several weeks in this case report. This type of DILI, probably related to a transient immune rebound, should be known by physicians to avoid misdiagnosis and to follow-up patients treated with high-dose methylprednisolone pulse therapy.

Table 1 Published cases of high-dose intravenous methylprednisolone-induced liver injury in patients with multiple sclerosis.

Case	Age (years)	Sex	Dose and duration of treatment	Latency (days)	Symptoms	AST (IU/L)	ALT (IU/L)	R	RUCAM	Antibodies	Liver biopsy features	Treatment	Outcome	Reference
1	46	Female	1 g daily, 3 days	42	No	755	1095	NS	NS	No	NS	No	Normalisation in 4 months	Hofstee <i>et al</i> ⁷
2	48	Female	NS	42	Jaundice, nausea	1500	1600	NS	NS	No	Infiltration with lymphocytes, eosinophils, occasional plasma cells, ballooning, councilman-type bodies	No	Normalisation	Das <i>et al</i> ⁸
3	57	Female	1 g daily, 3 days	3	No	543	1223	32.6	NS	No	Lytic necrosis and ceroid-laden macrophage hyperplasia	No	Normalisation in 3 months	Rivero Fernandez <i>et al</i> ⁹
4	43	Female	1 g daily, 6 days	37	Abdominal pain, nausea	1102	1067	42.9	NS	ANA (1:80), anti-smooth muscle antibody	Bridging perivenular necrosis with infiltration of inflammatory cells including eosinophils	Prednisolone+UDCA	Normalisation in 3 months	Takahashi <i>et al</i> ¹⁰
5	42	Female	5 g, NS	21	No	485	1082	NS	NS	No	Active hepatitis with portal lymphocytic infiltration and fibrosis	No	Not normalised	Reuß <i>et al</i> ¹¹
6	30	Female	1 g, NS	21	Jaundice, nausea	1731	2899	NS	NS	ANA (1:160)	bridging necrosis, lymphocytic inflammatory infiltrate with a few plasma cells and rare eosinophils	No	Normalisation in 7 months	Carrier <i>et al</i> ¹²
7	11	Female	1 g daily, 3 days	40	Fatigue	278	428	10.6	NS	ANA (1:80)	NS	Glycyrrhizin	Normalisation in 2 weeks	Furutama <i>et al</i> ¹³
8	48	Female	1 g daily, 3 days	19	Abdominal pain, nausea	2384	3028	40.8	NS	No	NS	No	Normalisation	D'Agnolo and Drenth ¹⁴
9	35	Female	1 g daily, 5 days	30	Jaundice	1104	2000	56.8	NS	No	Incomplete septal cirrhosis, portal tracts contained a moderately dense mixed inflammatory infiltrate, bridging and confluent necrosis, ballooning, apoptotic bodies, hepatic rosettes	No	Normalisation in 1 month	Grilli <i>et al</i> ¹⁵
10	23	Female	1 g daily, 3 days	21	Jaundice, abdominal pain	1515	2011	34.7	9	Anti-smooth muscle antibody	Hepatocyte dropout in the central areas, accompanied by congestion and chronic inflammation, the portal tracts were enlarged due to chronic inflammation, composing of lymphocytes, eosinophils and a few plasma cells	No	Normalisation in 3 months	Davidov <i>et al</i> ¹⁶
11	24	Female	0.5 g daily, 6 days	28	Jaundice	900	1740	34.6	NS	Anti-smooth muscle antibody (>1:320)	NS	No	Normalisation in 3 weeks	Gutkowski <i>et al</i> ¹⁷

Continued

Table 1 Continued

Case	Age (years)	Sex	Dose and duration of treatment (days)	Latency (days)	Symptoms	AST (IU/L)	ALT (IU/L)	R	RUCAM	Antibodies	Liver biopsy features	Treatment	Outcome	Reference
12	27	Female	1 g daily, 3 days	25	No	2235	1704	50	NS	No	Severe necroinflammatory lesions, architecture preserved, without any sign suggestive of chronic liver disease, portal tracts were slightly expanded; moderate inflammatory infiltrate made of lymphocytes	NAC	Normalisation in 154 weeks	Dumortier <i>et al</i> ¹⁸
13	35	Female	1 g daily, 5 days	60	No	778	1512	49.1	7	ANA (1:80)	Confluent necrosis, more severe near the terminal hepatic venule, portal tracts inflammation without damage of the bile ducts	No	Normalisation in 6 weeks	Our case

ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; NAC, N-acetyl cysteine; NS, not specified; R, R ratio; RUCAM, Roussel Uclaf Causality Assessment Method; UDCA, ursodeoxycholic acid.

Early recognition of liver injury and drug withdrawal could prevent hepatic failure. A better knowledge of the mechanism is necessary to identify risk factors and prevent methylprednisolone-related DILI.

Learning points

- High-dose methylprednisolone therapy can induce liver injury.
- Methylprednisolone discontinuation is necessary for normalisation of liver function tests.
- Methylprednisolone-induced liver injury could be related to a transient immune rebound.
- Early recognition of liver injury in patients treated with methylprednisolone for multiple sclerosis relapse could prevent hepatic failure.

Contributors CB: acquisition of data, manuscript writing, approval of final version. SP: analysis and interpretation of liver biopsy, approval of final version. GP: analysis and interpretation of data, approval of final version. CV: conception of the manuscript, analysis and interpretation of data, approval of final version.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests Clement Breteau: none declared. Sophie Prevot: none declared. Gabriel Perlemuter: reimbursement for conferences from Abbvie, Gilead, Janssen and Servier; speaking and consulting fees from Biocodex, Gilead, Pileje and Servier; royalties from Elsevier/Masson, John Libbey and Solar. Cosmin Voican: reimbursement for conferences from Gilead, Biocodex, Aptalis Pharma, Abbvie and Janssen; speaking fees from Gilead.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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