Methylprednisolone induced liver injury in a patient with multiple sclerosis

To the Editor,

Patients with multiple sclerosis (MS), are commonly treated with high doses of corticosteroids during the periods of acute exacerbation [1]. We report a case of methylprednisolone (MP) idiosyncratic drug induced liver injury (DILI).

A 28-year old female patient was admitted for acute exacerbation of MS manifested as severe weakness and disbalance. Work up on admission revealed normal complete blood cell count (CBC) as well as normal electrolytes, liver and renal chemistry. After completion of pulse regimen of intravenous MP (total dose 3 gr over the three days), the clinical symptoms improved, and the patient was discharged. One month later, she was readmitted for similar symptoms and treated with the same therapy of intravenous steroids which led to yet another clinical remission. However, routine tests following completion of therapy showed serum level of aspartate aminotransferase (AST) of 73 IU/L, alanine aminotransferase (ALT) of 459 IU/L, while the values of alkaline phosphatase, gamma-glutamyl transferase, serum bilirubin, international normalized ratio, and CBC were within the normal range. On the day of the admission, the patient was asymptomatic and her physical examination was unremarkable. She was a nonsmoker, did not drink alcohol or use illicit drugs. There was no family history of inherited liver disorders. She denied taking any new prescription medication or herbal and over the counter supplements. Abdominal ultrasonography revealed normal-sized spleen and no signs of parenchymal liver abnormalities. Serological tests for hepatitis B virus, hepatitis C virus, cytomegalovirus, Epstein Barr virus, Human immunodeficiency virus and immunological panel blood tests (ANA, AMA, ASMA, APA, anti-LKM) were negative. Laboratory check for Wilson's disease was negative. We performed a liver biopsy which was consistent with portal and lobular hepatitis (Fig. 1). She recovered following discontinuation of MP.

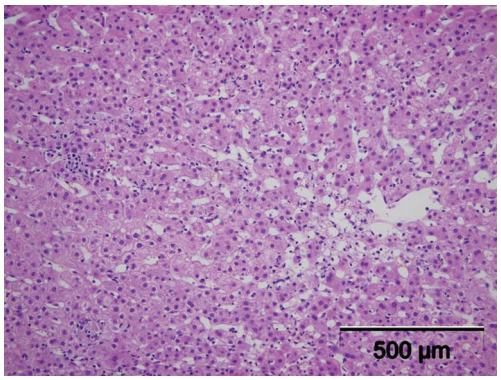

Fig. 1. Liver biopsy specimen showed numerous areas of necrosis in lobules, especially around the central vein and mild lymphocytic infiltrate in the portal tract (H&E stain).

Drug induced liver injury is defined as a liver injury or disease due to medications, herbs, or other toxic substances [2] with the highest incidence reported in a population-based study conducted in Iceland describing 19.1 cases per 100,000 [3]. Underreporting of drug reactions is common, so it is reasonable to assume that the actual incidence of DILI may be much higher. The diagnosis of DILI is made by the exclusion of any other possible cause of liver disease (infectious, inflammatory, autoimmune and structural causes) [4]. Since the clinical manifestations of DILI are variable, a high degree of suspicion and a detailed evaluation of other differential diagnosis is crucial for accurate diagnosis. Nonspecific biomarkers of liver injury are elevated levels of serum aminotransferases, alkaline phosphatase and total bilirubin. Liver biopsy is not mandatory or routinely performed in order to diagnose DILI. It is, however, valuable in excluding other differential diagnosis e.g. autoimmune hepatitis or Wilson's disease. Liver biopsy is particularly helpful in differentiating autoimmune hepatitis from DILI which often might have a similar presentation and clinical course. So far, there is a lack of standard treatment for DILI. The first step in the management of DILI is the prompt cessation of the suspected hepatotoxic drug [5].

The present case demonstrated a rarely reported adverse event of methylprednisolone, one of the most used drugs in medicine. Clinicians who treat patients with deranged liver function test should be familiar with this side effect.

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Liver transplantation for hepatocellular carcinoma after down staging with sorafenib: a monocentric case-matched series

To the Editor,

For more than twenty years, access to liver transplantation (LT) has been limited by the Milan Criteria for patients with hepatocellular carcinoma (HCC). By treating both underlying liver disease and HCC, LT offers the best survival and recurrence-free survival rates.

Since January 2013, the French Biomedicine Agency has integrated a new predictive score, the AFP model, for the allocation of grafts in HCC patients. This model was shown to significantly improve the prediction of HCC recurrence after LT compared to Milan criteria [1]. For HCC patients outside AFP score, locoregional therapies have been proposed in order to obtain a radiological and biological tumour response which allows transplantation. This down staging strategy is a way to expand access to LT with survival and recurrence outcomes comparable to patients transplanted as first line therapy [2].

We would like to draw attention to the interest of sorafenib as an additional tool in the down staging strategy. Initially used for palliative purposes in HCC patients, these indications have been widened in recent years. It is now established that in spite of antiangiogenic property, sorafenib does not increase complications after liver resection or transplantation.

We report here, the first comparative case matched series using this down staging strategy in HCC patients between 2008 and 2014 (Table I). In order to overcome confounding factors, we matched 7 patients transplanted after down staging with sorafenib for HCC with 14 patients transplanted as first line therapy, based on clinical characteristics (i.e., gender and the age at the time of LT), underlying liver disease (i.e., viral C cirrhosis, non-alcoholic steatohepatitis related cirrhosis, and alcoholic cirrhosis), and AFP model. A minimum observation period of 3 months after down staging was required before LT. As expected, postoperative complications were comparable between the two groups (p = 0.67) and no deaths occurred within 90 days after LT. Even if down staging with Sorafenib provided comparable 5-year overall survival (57% vs 93% p=0.07) and recurrence free survival (57% vs 85% p=0.09) to LT as first line therapy (Fig. 1), the patients down staged with sorafenib had a recurrence rate three times higher than other patients.These results should therefore be interpreted with caution. Moreover, an increased risk of recurrence after down staging and LT has already been identified in the meta analysis of Parikh et al. [3] and more recently by Ravaioli et al. [4]. Nevertheless, in our series, the sorafenib group had a 5-year survival >50% which is much better than the results of palliative treatment.

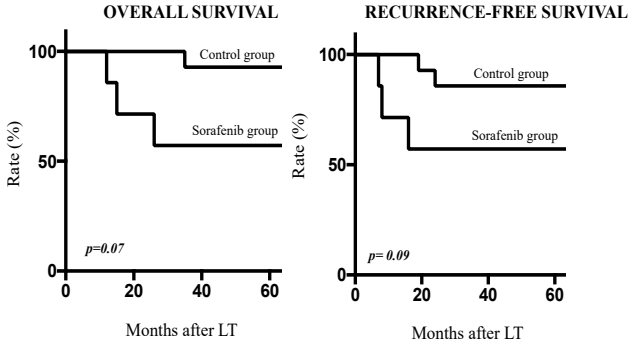

Fig. 1. Overall and Recurrence-free Survival

This work leads to a reflection regarding the eligibility criteria for transplantation after down staging. Indeed, the applicability of this score in patients in a down staging strategy has not been evaluated. Although an observation period after down staging is a way of selecting the right transplant candidates and assessing tumour behaviour, it seems obvious that other risk factors of recurrence should be taken into account before transplantation (as the serum AFP level > 100 ng/mL [1] or the use of new biomarkers - AFP-L3%, GPC3, h-TERT mRNA[5]).

Table I. Sorafenib group characteristics

Patients							
Gender, Age at LT years	M, 55	M, 63	F, 46	M, 64	M, 61	M, 51	M, 55
Liver disease	HCV	HCV	HCV	NASH	HCV	NASH	HCV
Characteristics before downstaging							
Active nodules	1	2	4	4	2	4	2
Largest tumour diameter (mm)	53	40	43	60	38	22	46
LT exclusion criteria	Yes[a]	No	No	No	Yes[a]	No	Yes[b]
AFP level (ng/mL)	3400	300	2	5000	65	126	13
AFP model (points)	4	3	3	6	1	4	1
Milan Criteria	Out	Out	Out	Out	Out	Out	Out
Duration of sorafenib therapy* (months)	7	4	8	21	8	6	13
LRT	TACE	RFA	TACE	TACE/TARE	TACE/RFA	TACE/RFA	-
Characteristics after downstaging							
Active nodules	2	2	3	1	2	2	0
Largest tumour diameter (mm)	21	30	33	25	23	16	-
AFP level (ng/mL)	6	290	3	5	222	63	3
AFP model (points)	0	2	1	0	2	0	0
Milan Criteria	In	In	Out	In	In	In	In
LT exclusion criteria	No	No	No	No	No	No	No
Long-term results after LT							
Death	No	Yes	No	Yes	Yes	No	No
Overall survival (months)	31	12	77	15	26	39	30
Recurrence	No	Yes	No	Yes	Yes	No	No
Recurrence-free survival (months)	31	7	77	8	16	39	30

LT: liver transplantation, LRT: loco-regional therapy HCV: hepatitis C virus, NASH: non-alcoholic steatohepatitis, AFP: α-fetoprotein, TACE: transarterial chemo-embolization, TARE: transarterial radio-embolisation, RFA: radiofrequency ablation. *Duration of sorafenib in months from introduction to LT, [a] portal vein thrombosis; [b] coeliac lymph node invasion

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