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Drug-Induced Liver Injury by Methylprednisolone in Patients with Multiple Sclerosis: A Case Series and Literature Review

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Abstract

Background and Aim: High dose methylprednisolone (MP) pulse therapy is often used and thought to be safe for short term use. It is commonly used to treat hepatotoxicity, such as drug-induced liver injury (DILI). Only recently has it become increasingly recognized as an etiology of liver injury. In this series, three cases of MP-induced liver injury in patients with multiple sclerosis (MS) were reported and characterized, combined with literature review.

Case Series: Three patients with MS were treated with high dose intravenous (IV) MP. One patient had re-exposure to MP pulse dose that resulted in typical recurrent liver injury. Liver injury was biochemically mainly hepatocellular, and histologically varied from mild to severe, occurring 5 days to 8 weeks after MP administration.

Conclusion: Our cases demonstrate that MP pulse therapy can cause significant liver injury in patients with MS. We recommend that liver enzymes be closely monitored after pulse dose IV MP administration.

Keywords: Drug induced liver injury (DILI); Methylprednisolone (MP); Multiple sclerosis (MS)

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system, characterized by relapsing and remitting demyelinating lesions separated in time and space. High-dose steroids and glatiramer acetate (GA) are commonly used medications for treating MS. Steroids are usually used as a treatment for severe inflammatory and autoimmune disorders, including MS. Steroids are also implemented as the treatment for some forms of hepatitis including autoimmune hepatitis (AIH), which can also be associated with drug induced liver injury. As such, steroids are not often thought to be directly hepatotoxic. Despite this, more recent literature reviews have revealed at least 50 case reports of acute liver injury in the setting of pulse corticosteroid therapy [1-4].

Case reports of hepatotoxicity following pulse dose MP therapy usually occur between 3 days to 6 weeks but may occur up to 6 months after discontinuation of the drug [5-7].

However, these reports were limited by concurrent use of other medications. For instance, GA is not thought to be significantly hepatotoxic, but mild transaminase elevations can be observed. These elevations are usually transient and resolve within 1 to 3 months of drug cessation. Interestingly, many of these GA hepatotoxicity case reports concurrently received high dose steroids as a part of their treatment course, making it very difficult to conclude which was the true offending drug [8]. Intravenous immune globulin (IVIg) is known to cause transient liver enzyme elevations, but generally considered to be safe. Some older reports on cases with more severe hepatotoxicity might be secondary to lack of screening for viral hepatitis in IVIg pooled donors, then transmitted to immunocompromised patients [9]. More recent reports on this are mild and thought to be secondary to the maltose-containing stabilizing agents in IVIg [10].

In this case series, we reviewed three instances of drug induced liver injury in patients with MS who underwent MP plus another treatment at our institution. All three cases had pre-event baseline liver function tests (LFTs), dynamic LFT monitoring while on MS treatment, and liver biopsy histology. Although two patients received both GA and MP, one case received repeat MP therapy after stopping GA, resulting in recurrent liver injury. The other case was treated with IVIg and MP.

Case Series

Case 1:

A 54-year-old Asian female was referred to hepatology clinic for elevated liver enzymes. She had history of MS for thirteen years, followed by neurology, as well as history of breast cancer, status post mastectomy and bilateral oophorectomy, obstructive sleep apnea, and type 2 diabetes mellitus. As her MS was not adequately controlled, she was switched from teriflunomide (Aubagio®) 15mg PO daily to GA (Copaxone®) 40mg/ml injection three times per week starting on 9/25/2021. She was also scheduled for high dose IV steroid (MP 1g) treatment monthly for a 6-month course, starting 10/5/2021.

Her baseline LFTs were completely normal on 8/3/2021 before the above-mentioned medications were started. In the period after starting GA during an unrelated encounter for a COVID vaccination reaction, she had blood tests on 11/9/2021 with only mild transaminase elevation, alanine aminotransferase (ALT) 78IU/L and aspartate aminotransferase (AST) 38IU/L, as shown in (Figure 1A). However, her next routine labs on 12/1/2021 (29 days after her last MP infusion) showed significantly elevated liver enzymes to ALT 1147 and AST 470IU/L, with normal alkaline phosphatase (ALP) and total bilirubin (TBil). She received her next scheduled intravenous MP 1g on 12/2/2021 and the next day labs showed mild improvement of ALT to 846 and AST to 219IU/L. Follow-up labs on 12/14/2021 (12 days after MP dosing) peaked at ALT 2233, AST 1105, ALP 160IU/L, TBil 0.7mg/dL. During this time course, her only new medications were GA and MP. GA had been continued from 9/25/2021 through 12/15/2021 at the same dose. The rest of her medication list had been stable for many years, and included atorvastatin, denosumab (last dose in 12/2021), metformin, glipizide, cinnamon, turmeric, fish oil, cranberry supplement, vitamin D, and calcium. She denied any other over the counter medications or supplements. She also denied history of tobacco, alcohol, intravenous drug use, blood transfusions, high risk sexual activity, and tattoos.

Her hepatology work-up at an outside facility at this time included negative hepatitis A virus antibody (anti-HAV) immunoglobulin M (IgM), hepatitis B core antibody (anti-HBc) IgM, hepatitis B surface antigen (HBsAg), hepatitis E antibody (anti-HEV) IgM and immunoglobulin G (IgG), antinuclear antibodies (ANA), actin antibody IgG, liver kidney microsome-1 (LKM-1) antibody, herpes simplex virus (HSV) 1 and 2 IgM, cytomegalovirus (CMV) DNA, Epstein-Barr virus (EBV) IgM, heterophile antibody, alpha-1 antitrypsin (A1AT) genotype, total IgG, copper, ferritin, ceruloplasmin. Due to severity of liver enzyme elevation, a diagnostic liver biopsy was performed on 12/21/2021 with results shown in (Figures 1B through 1E). The liver biopsy pathology reported possible DILI versus AIH-like inflammation.

With cessation of all her medications, her LFTs improved to ALT 258, AST 82, alkaline phosphatase 110IU/L, and TBil 0.6 mg/dL on 1/17/2022 (46 days after the most recent MP dose). Her GA was still held given concern for DILI, but MP was restarted (re-exposure event), given intravenously on 1/17/2022 and 2/14/2022. Stably elevated liver function enzymes were noted 2/7/2022, but another marked increase was seen 2/21/2022 with ALT 1009, AST 542IU/L, and normal ALP and TBil. Given worsening of liver numbers after MP redosing, there was concern that immunosuppression was causing flare of liver injury. Given her Asian background, hepatitis B serologies were re-obtained, which resulted as negative.

Her liver biopsy from 12/21/2021 was further reviewed and shown in (Figures 1B through 1E). There was an acute panlobular hepatitis pattern, characterized by zone 3 mixed inflammatory infiltration throughout the cores with frequent acidophil bodies, single hepatocytes drop-out, and ceroid-laden macrophages (highlighted by PASD staining) clusters primarily in zone 3 (Figures 1B and 1C). Trichrome stain revealed light blue staining around the inflammation, but there was no significant fibrosis (Figure 1D). Focal bridging necrosis between the portal tract and central vein is also seen (Figure 1E). No bile duct injury, ductular proliferation, significant interface activity, or steatosis was identified. It was concluded that these changes were favored to be related to an adverse drug/toxin reaction, if other possible etiologies are ruled out clinically, such as viral infection. Given the liver biopsy results, repeated episode of acute hepatitis with re-challenge of MP, and the patient's clinical course, all the data suggested that our patient was having steroid induced liver injury.

As shown in (Figure 1A), the patient was followed closely after her last MP dosing on 2/14/2022, with a peak of liver enzymes on 3/4/2022, and subsequent normalization of all liver enzymes by April 2022 without any further MP re-exposure.

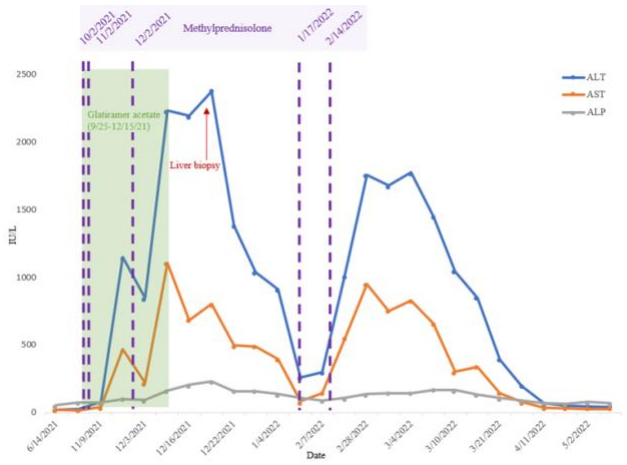
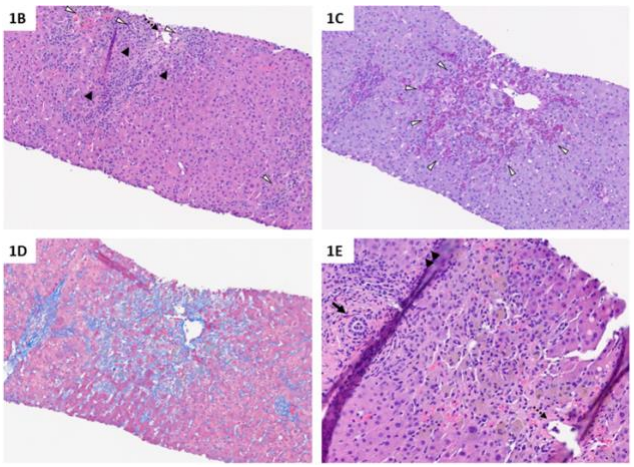


Figure 1A: Time Course of Liver Enzyme Trend, MP Dosing, and Liver Biopsy for Case 1.

Patient had normal baseline LFTs, elevation of liver enzymes with each pulse dose of MP therapy, and followed by normalization of liver enzymes after cessation of MP. MP pulses are marked with a purple dotted line. Duration on GA therapy three times a week is blocked in green. Timing of liver biopsy is marked by a red arrow. (Legend in top right corner of the graph. ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase); X axis= time course by date; Y axis = liver enzyme elevation in IU/L.



Figures 1B through 1E: Hepatic Histological Findings of Case 1.

(1B): Liver biopsy from case 1 shows an acute panlobular hepatitis pattern, characterized by mixed inflammatory infiltration with frequent acidophil bodies (black arrowheads), single hepatocytes drop out, and clusters of ceroid laden macrophages (white arrowheads) primarily in zone 3 areas around the central veins (dotted arrow). [H&E, 100x magnification]; **(1C):** The ceroid laden macrophages are highlighted by PASD staining (white arrowheads). [PASD, 100x magnification]; **(1D):** Trichrome stain reveals light blue staining in the area of inflammation. Still, there is no significant fibrosis. [Trichrome, 100x magnification]; **(1E):** Focal bridging necrosis between a portal tract (arrow) and central vein (dotted arrow) is also seen. [H&E, 200x magnification].

Case 2:

A 51-year-old female newly diagnosed with MS (3/2021) was found to have abnormal liver tests prior to being evaluated for MS therapy. Patient reported she had a history of intermittently elevated liver enzymes since her 20s. She was evaluated by an outside gastroenterologist prior to starting MS treatment, and her baseline labs showed ALT 74, AST 40, ALP 82IU/L, and TBil 0.3mg/dL. Work-up showed fatty liver on imaging and a positive ANA. The differential for her elevated liver enzyme fluctuations included fatty liver versus a relapsing, remitting AIH in the setting of an elevated ANA and diagnosis of MS.

Liver biopsy at this time showed multiple small aggregates of brown-pigmented ceroid laden macrophages within the hepatic lobule predominantly around central veins in the zone 3 area, suggestive of resolving acute liver injury. The clusters of ceroid-laden macrophages were easily seen on the Hematoxylin and Eosin (H&E) slides (Figure 2B) and highlighted by PAS with Diastase (PASD) stain (Figure 2C). No significant lobular necroinflammatory activity, portal inflammation, steatosis, or abnormal fibrosis were identified in the specimen. Features suggestive of autoimmune hepatitis such as lymphoplasmacytic inflammation, interface activity, or rosette formation were not identified. At this time, patient was only taking atorvastatin (a chronic medication for 5 years) and omeprazole. Atorvastatin was discontinued in the setting of possible DILI.

She was started on teriflunomide on 5/6/2021. Her labs on 6/9/21 showed slight elevation of her liver enzymes: ALT 186, AST 92, ALP 114IU/L, TBil 0.3mg/dL. The teriflunomide was discontinued on 6/10/21, and pt had almost normalization of her liver enzymes. Meanwhile off all MS medication, she experienced worsening of her MS symptoms. She was started on GA together with 3 days of MP 1g daily for 3 days (9/21-9/23/21) as an induction treatment. After that, the patient experienced progressive worsening of her liver enzymes, peaking around 12/16/2021 with ALT 414, AST 184, ALP 132IU/L, TBil 0.6mg/dL, as shown in (Figure 2A).

A subsequent liver biopsy was performed on 1/21/2022 after another dose of MP demonstrated similar histomorphology; multiple clusters of ceroid-laden macrophages were found in the hepatic lobule, primarily around the central vein (zone 3) but also at the portal area (Figures 2D through 2G). The aggregates appeared somewhat more abundant than previous, accompanied by a mild lymphocytic predominant portal and lobular inflammation, and scattered acidophil bodies suggestive of ongoing and past injury to the hepatocytes (Figure 2F and 2G). There was no significant interface activity reminiscent of autoimmune hepatitis. There was no bile duct injury, ductular proliferation, significant steatosis, or fibrosis, confirmed by trichrome stain (figure not shown).

Given the concern for DILI, there was initially concern that the liver injury was secondary to GA. However, her neurologist continued to treat through with GA because her MS symptoms were significantly improved on this therapy. Without any further doses of MP and with continuation of GA, her liver enzymes all normalized by 3/15/2022 as seen in (Figure 2A).

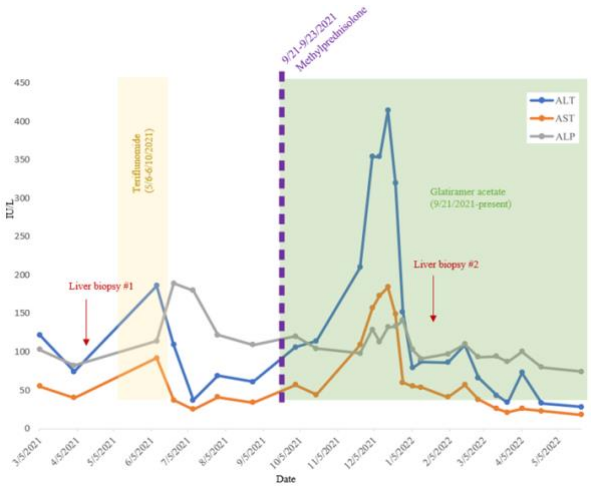
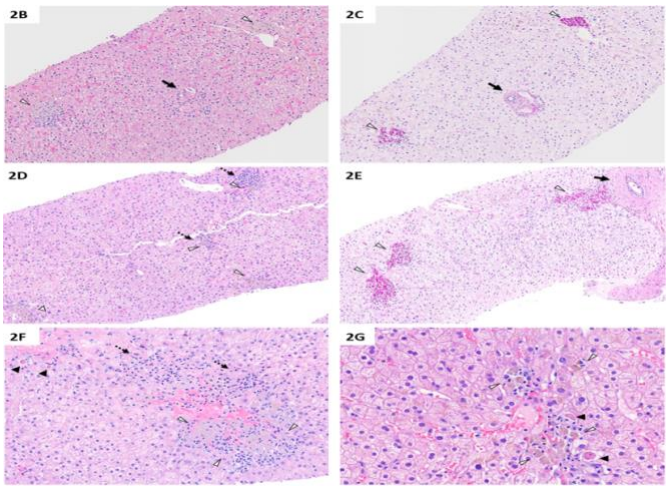


Figure 2A: Time Course of Liver Enzyme Trend, MP Dosing, and Liver Biopsy for Case 2.

Patient has elevation of liver enzymes after MP pulse, with normalization of liver enzymes after in the setting of continuing GA. MP pulses are marked with a purple dotted line. Duration on GA therapy three times a week is blocked in green. Duration of teriflunomide therapy is blocked in yellow. Timing of liver biopsies are marked by a red arrow. (Legend in top right corner of the graph. ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase); X axis= time course by date, Y axis= liver enzyme elevation in IU/L.



Figures 2B through 2G: Hepatic Histological Findings for Case 2.

(2B): Initial liver biopsy. H&E staining of the liver cores shows multiple small aggregates of brown-pigmented ceroid laden macrophages (white arrowheads) within the hepatic lobule predominantly around central veins in zone 3 area. Portal areas (arrow) are devoid of inflammation and ceroid-laden macrophages. No significant lobular necroinflammatory activity, portal inflammation, steatosis, or abnormal fibrosis is identified. Features suggestive of autoimmune hepatitis such as lymphoplasmacytic inflammation, interface activity, or rosette formation are also not identified. [H&E, 100x magnification]; **(2C):** Initial liver biopsy. PASD staining highlights the ceroid laden macrophages (white arrowheads) and connective tissue around the portal tracts (arrow). [PASD, 100x magnification]; **(2D and 2E):** Second liver biopsy. The liver biopsy demonstrates more abundant clusters of ceroid laden macrophages (white arrowheads) found in the hepatic lobule as well as near the portal area (arrows), accompanied by mild lymphocytic predominant portal and lobular inflammations (dotted arrows). There was no significant interface activity, bile duct injury, steatosis, or fibrosis. [D: H&E, 100x magnification; E: PASD, 100x magnification]; **(2F and 2G):** Second liver biopsy. Scattered acidophil bodies (black arrowheads) are also noted. [F: H&E, 200x magnification; G: H&E, 400x magnification].

Case 3:

A 23-year-old male with recently diagnosed MS presented to the hospital for worsening weakness. His previous care was at an outside facility, for which records were limited. He was treated with three days of MP from 4/7-4/9/2022 for MS symptoms and was discharged to acute rehab. However, he had progression of his weakness with blurry vision, and presented to our facility on 4/13/22. At this time, he had normal liver enzymes as shown in (Figure 3A) He was then treated with IVIg from 4/14-4/16/22 and MP 1.5g twice daily IV from 4/16-4/19/22. The only other medications he received in this period included MRI gadolinium contrast on 4/14/22.

He started having mildly elevated transaminases on 4/18/22 with ALT 96, AST 72IU/L and normal ALP and TBil, with peak in liver enzymes on 4/24/22 (ALT 565, AST 182, ALP 104IU/L, TBil 0.4mg/dL). Work-up showed fatty liver on imaging, positive anti-HBc total and negative HBsAg, hepatitis B surface antibody (anti-HBs), and HBV DNA. It was unclear if patient had exposure to HBV in the past, or a transient anti-HBc positivity due to recent IVIg therapy. Liver biopsy was done on 4/22/22. The main finding of the liver biopsy was easily identifiable acidophil bodies throughout the cores (Figure 3B). Patchy minimal to mild lymphocytic predominant lobular inflammation was also noted, without conspicuous ceroid-laden macrophages. No significant portal inflammation, interface activity or fibrosis was seen. Presence of acidophil bodies without ceroid-laden macrophages indicates that the pathology in this liver biopsy was in the acute or subacute phase (not chronic), as ceroid-laden macrophages are the Kupffer cells that reside in the sinusoidal spaces and are responsible for phagocytizing dead hepatocytes. This was most consistent with DILI and thought to be most likely due to the high dose MP he received. As shown in (Figure 3A), his LFTs down trended to almost normal by 4/29/2022.

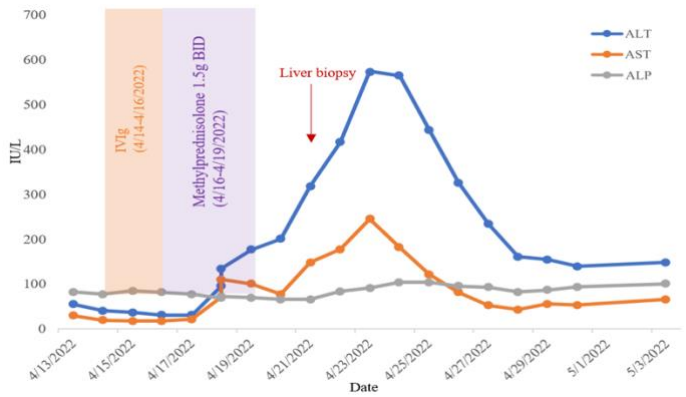


Figure 3A: Time Course of Liver Enzyme Trend, MP Dosing, and Liver Biopsy for Case 3.

Patient has elevation of liver enzymes after MP with normalization over time. Duration of MP therapy with 1.5g twice daily is blocked in purple. Duration on IVIg therapy daily is blocked in orange. Timing of liver biopsy is marked by a red arrow. (Legend in top right corner of the graph. ALT= alanine aminotransferase; AST= aspartate aminotransferase; ALP= alkaline phosphatase); X axis= time course by date; Y axis= liver enzyme elevation in IU/L.

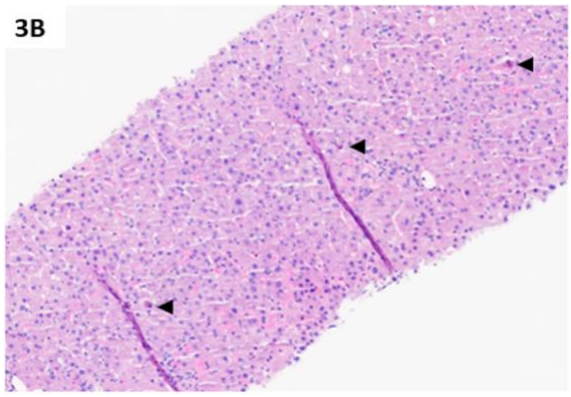


Figure 3B: Hepatic Histological Finding of Case 3.

The liver biopsy shows easily identifiable acidophil bodies (black arrowheads) scattered throughout the cores. Patchy mild lymphocytic predominant lobular inflammation is also noted. No significant portal inflammation, interface activity, or fibrosis is seen. [H&E, 100x magnification].

Discussion and Literature Review

MP is not often thought to be a cause of DILI, as it can be used for treating DILI. In recent years, there have been increasing case reports indicating that MP may cause DILI. However, many of these previous case reports of MP-induced DILI were inconclusive as they either included only one case (often with variable underlying primary disease), limited laboratory data, limited observation of clinical course, lack of histological support, or had more complicated history [4,6,7]. Some cases had other concurrent medications that could complicate whether MP was the causative agent. Pulse MP is commonly used for induction of autoimmune treatment courses, for example, when starting GA or IVIg. This made delineation of the offensive drug very difficult and often overlooked MP in some case reports [11,12]. Some other case reports lacked histological support. For those with available histological data, the reports had mixed histological findings of autoimmune hepatitis which were categorized in a broader group of MP-induced "hepatotoxicity."

Our case series has strengths in these regards. We have three patients with a primary diagnosis of MS. All three cases have liver biopsy samples and temporal evidence of MP as the causative agent of DILI in multiple clinical scenarios. This includes MP re-exposure in Case 1, where the patient had repeat liver injury with steroid re-administration in the absence of GA. In Case 2, the patient had resolution of their liver injury while continuing through with GA treatment, the other medication in question as a cause of the DILI. Case 3 had high dose twice a day pulse MP therapy with resultant liver injury. This case series has high quality close follow-up with detailed time course prior to steroid administration, during liver injury from MP, through full recovery of liver enzymes.

In our case series, it is most plausible that high dose IV steroids like MP were involved in the DILI these patients have experienced. The first two cases were initially contested as to whether GA was the culprit. However, as described previously, Case 1 had repeat liver injury with pulse dose MP therapy in the absence of GA, and Case 2 had lack of repeat liver injury with continuation of GA therapy. For Case 3, it was possible that IVIg contributed to liver enzyme elevations. We were unable to obtain outside lab work to show evidence of liver lab elevations after the initial administration of MP, but that information would give more support that MP was the root cause of his liver injury. All three of our cases as well as support from previous case reports as referenced, have enriched our understanding that pulse dose MP can be a cause of DILI in patients with MS.

The liver injury observed in our case series was largely of a hepatocellular pattern, with only mild alkaline phosphatase elevation and very minimal bilirubin elevation. Liver injury was noted as early as 5 days and as late as 8 weeks, though in Case 2 it was difficult to pinpoint the exact time of liver injury onset given she had waxing and waning liver enzyme elevations prior to starting any new medications.

Much of the literature revolving around steroid-induced liver toxicity is done in patients with MS or other autoimmune disorders. The extensive literature review by Zoubek et al [4]. showed 50 case reports of MP-induced liver injury. Interestingly, 29 of 50 cases were in patients with MS, and 13 of the 50 cases were Graves' ophthalmopathy patients. The rest of the diseases treated were autoimmune in nature, including autoimmune thyroid diseases, interstitial lung, disease, demyelinating encephalopathy, central nervous system vasculitis, retrobulbar optic neuritis, post-liver transplant rejection, and Hashimoto's thyroiditis. Most likely this is selection bias because this population of patients often requires steroids as part of their treatment course.

There is some question as to whether the pathophysiology of autoimmune conditions makes these patients more susceptible to DILI from immunosuppressive agents like high-dose steroids. Steroids have been implicated in inducing AIH through an immunoallergic mechanism due to immune rebound phenomenon [13]. Supported by the conclusions from prospectively collected MP-DILI cohort by Allgeier et al [14], our case series, as mentioned previously, did not have any pathologic features of AIH on liver biopsy, which argues against this theory and supports MP as an etiology of DILI. The Allgeier prospective case series is the only new case report or series that has been published since the detailed literature review by Zoubek et al [4].

Though our patients all had improvement of liver enzymes after discontinuation of MP, there are case reports of MP-induced liver failure that have resulted in death [4,6,14]. Given increasing reports that pulse dose steroid treatment can result in liver injury, it is paramount that more awareness is needed regarding the fact that MP pulse therapy can cause DILI. Liver enzyme elevation can be seen within 2 weeks of treatment but seems to resolve after cessation of therapy, as evidenced in our case series and previous literature review. Based on previous case reports and our present case series, it is recommended that close liver enzyme monitoring should be routinely done, especially in MS patients, after high-dose pulse steroids.

Conclusion

Patients with autoimmune disorders, especially those with MS can experience MP-induced DILI. This should be closely monitored when MP is used either independently or concurrently with another immune suppressing agent. LFT elevations (predominantly in a hepatocellular pattern) can be seen within 1 to 8 weeks from MP administration. LFTs will usually improve with early diagnosis and timely discontinuation of MP.

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