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Letter to Editor

Rituximab induced transaminitis in pemphigus foliaceus

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Sir,

Rituximab is a chimeric murine-human monoclonal antibody directed against the CD20 antigen present on the surface of B cells.[1] Rituximab causes the death of B cells by multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and effects directly induced by antibody binding to CD20 antigen.[2] It has been approved by the Food and Drug Administration (FDA) in 1997 for the treatment of CD20+ B-cell neoplasms and later in rheumatoid arthritis and antineutrophil cytoplasmic antibodies-associated vasculitis and has been used off-label in systemic lupus erythematosus, chronic immune thrombocytopenic purpura, and autoimmune bullous diseases.[1] The use of rituximab in pemphigus vulgaris was first reported in 2002 and has been found to be highly effective in pemphigus, particularly in resistant cases.[3] Furthermore, recent studies suggest its usefulness as first-line treatment in moderate-to-severe types of pemphigus. Rituximab allows a major corticosteroid (CS) sparing effect, a rapid tapering of CS doses, and in turn improves treatment tolerance.[3] The US FDA in 2018 has approved its use in moderate-to-severe pemphigus vulgaris in adults.[4] Rituximab is a relatively safe drug. Reactions to its infusion include hypotension, fever, chills, rigors, urticaria, bronchospasm, angioedema, nausea, fatigue, headache, pruritus, dyspnea, rhinitis, vomiting, and flushing usually occurring at the beginning of the initial infusion within 30 min–2 h.[5] Other possible adverse reactions are infections, tumor lysis syndrome, mucocutaneous reaction, progressive multifocal leukoencephalopathy, hepatitis B reactivation with fulminant hepatitis, cardiac arrhythmias, renal toxicity, and bowel obstruction and perforation.[5] Although rituximab has been documented to produce reactivation of viral infections, particularly viral hepatitis, there are only isolated reports of direct drug-induced hepatocellular pattern of liver injury[5,6] and none in pemphigus.

A 66-year-old female with a history of coronary artery disease (CAD), hypothyroidism, and diabetes mellitus (DM) presented with moderate to severe pemphigus foliaceous. She was on treatment with clopidogrel, thyroxine, and insulin. The patient was initially started on systemic steroids (intravenous dexamethasone 8 mg) with a plan to start on rituximab after clearing secondary infection in view of severe disease, previous CAD, and uncontrolled DM. Rituximab was given after 3 weeks of hospital admission by which time steroids were tapered to dexamethasone 4 mg along with 10 mg of prednisolone and there were no new lesions, and the older lesions showed partial healing. Before initiating rituximab, her hemogram, liver function tests (LFT), renal function tests, and chest X-ray were normal, and viral markers and Mantoux test were negative. Electrocardiogram did not show any fresh changes, and echocardiogram showed a mild diastolic dysfunction. Rituximab was started as per lymphoma protocol. Infusion of 500 mg in 250 ml normal saline was started at 25 ml/h for first 30 min with an increase in the rate at 25 ml/h every 30 min until 150 ml/h with regular monitoring of vitals, after pre-medicating with 100 mg hydrocortisone, 25 mg pheniramine maleate, and 500 mg acetaminophen. Infusion and post-infusion period was clinically uneventful. 1 week after, before the second infusion, the blood

Table 1: RUCALM score calculation for drug induced liver injury*.

Parameter	Score assigned to our patient
Time to onset	1
Course	3
Risk factors	1
Concomitant drugs	0
Non-drug causes	1
Previous information on the hepatotoxicity of drug	1
Re-challenge	0
Total score**	7

*Initial step in the RUCAM assessment is to define whether the hepatic injury is "hepatocellular," "mixed," or "cholestatic," defined by calculation of the "R ratio." R = (SGPT value ÷ SGPT ULN) ÷ (ALP value ÷ ALP ULN). R ratio below 2 indicates cholestatic, 2-5 mixed and >5 hepatocellular pattern of liver injury. Since the SGPT was around eight times the ULN and the ALP was normal in our patient, the pattern was hepatocellular.
**Interpretation of the final score: 0 or less indicates that the drug is "excluded" as a cause; 1–2 that it is "unlikely," 3–5 "possible," 6–8 "probable," and >8 "highly probable." RUCAM: Roussel Uclaf Causality Assessment Method, ALP: Alkaline phosphatase, SGPT: Serum glutamic pyruvic transaminase, ULN: Upper limit of normal

parameters were repeated. Her transaminases were found to be elevated with serum glutamic-oxaloacetic transaminase of 106U/L (approximately 2.5 times upper limit of normal [ULN]) and serum glutamic pyruvic transaminase of 310U/L (around 8 times ULN), with normal bilirubin levels, alkaline phosphatase, and prothrombin time. Hepatitis A, B, and C serologies including hepatitis B core antigen were repeatedly negative. Ultrasonogram of the abdomen did not reveal any pathology. The patient was on no other hepatotoxic medication. Further rituximab infusions were withheld as the liver function test was suggestive of a hepatocellular pattern of liver injury, possibly drug-induced. 1 week later, the LFT values were repeated and were found to be within normal range. Interestingly, the patient's lesions improved well on further follow-up and her systemic steroid dose could be reduced (to prednisolone 20 mg over 3 months).

Considering the negative serology, the fact that the patient was not on any other hepatotoxic drugs, the prompt reversal of LFT on stopping rituximab, and a score of 7 on Roussel Uclaf Causality Assessment Method [Table 1], diagnosis of probable case of direct drug-induced hepatocellular pattern of liver toxicity was made.[7,8] Rituximab-induced reversible direct hepatic injury has been reported in two previous cases – a case of immune thrombocytopenic purpura[6] (where LFT derangement occurred after 3rd weekly infusion of rituximab) and a case of chronic lymphocytic leukemia[5] (derangement after 2 cycles of rituximab/flucytosine/cyclophosphamide) – both cases recovering after 1 week of stopping rituximab. LFT derangement as part of systemic inflammatory response due to cytokine release in the treatment of B cell neoplasms with high tumor burden has been reported.[9] Transaminitis, associated with rituximab treatment in pemphigus, has not been reported previously. Despite receiving only single dose of rituximab, which is inadequate as per standard recommendation, we were able to attain disease control and maintain the patient in remission on low dose of steroid. This suggests the need to assess the efficacy of low dose rituximab as an adjuvant in management of pemphigus. Although this has been reported previously in case series, larger studies and long-term follow-up are essential to form a conclusive evidence.[10]

As rituximab is being increasingly used successfully and with relative safety in newer conditions, more side effects are being discovered. Drug-induced hepatocellular pattern of liver toxicity is a possible side effect which is rarely reported. This case highlights the importance of being on the lookout for such rare adverse effects.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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