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CASE REPORT

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Denosumab-induced autoimmune hepatitis: Case report

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Abstract

This report described a patient not known to have a hepatic disease, found to have a drug-induced autoimmune hepatitis from denosumab. This is an unreported side effect, and here, we presented the possible predisposing factors and suggested monitoring parameters.

KEYWORDS

autoimmune hepatitis, denosumab, drug-induced hepatitis, hepatitis

1 | INTRODUCTION

Autoimmune hepatitis (AIH) is a liver disease that can affect anyone regardless of age, gender, or ethnicity. It is considered rare and is characterized by self-sustaining inflammation. The hallmarks of AIH include hypergammaglobulinemia, the presence of autoantibodies, and interface hepatitis upon histological examination. Although the exact etiology of AIH is unknown, AIH can be triggered by environmental factors.[1] Furthermore, AIH may be induced by drugs like Infliximab, minocycline, nitrofurantoin, etc.[2] The immunopathogenesis of AIH is based on autoreactive CD4 and CD8 T cells, which are linked to the body's impaired immunoregulatory mechanisms that result in the loss of self-tolerance to antigens on hepatocytes, which causes autoreactive T cells to destroy hepatic parenchyma.[3,4] The clinical presentation of AIH can range from entirely asymptomatic to experiencing general symptoms (such as malaise, fatigue, anorexia, arthralgias and weight loss).[5,6]

To diagnose AIH, a liver biopsy and compatible histology findings are necessary. In addition, it is crucial to evaluate specific clinical and laboratory findings, including elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), as well as serum IgG, and the presence of specific autoantibodies such as antinuclear antibodies, SMA, and anti-LKM1[3,7] Hepatotoxicity induced by drugs can either be a predictable, dose-related reaction, or it usually results from direct toxicity of the drug or its metabolite. It can also be an unpredictable, idiosyncratic reaction that is not dose-related and is primarily host-dependent, with intermediate (1–8 weeks) or long latency periods (up to 12 months).[8–10]

Several causality assessment tools can be used. Among these tools, RUCAM (Roussel Uclaf Causality Assessment Method) is utilized to evaluate causality in instances of suspected drug-induced liver injury (DILI). It is mainly used to distinguish DILI from AIH[11,12] Another helpful tool is Naranjo, which assesses the causality of drug-induced adverse events.[13] Even though this adverse effect is rare, it is noteworthy. In this case, we aim to describe the occurrence of AIH due to denosumab and identify factors that may contribute to this incidence.

2 | CASE REPORT

2.1 | Case history and examination

A 70-year-old female with a history of hypertension, hypothyroidism, and dyslipidemia was admitted to the hospital

with a chief complaint of yellowish skin discoloration, abdominal pain, and dizziness. The patient complained of weight loss and a change in urine color, and she was jaundiced. She is on amlodipine 5 mg for hypertension, levothyroxine 75 mcg for hypothyroidism, atorvastatin 40 mg for dyslipidemia, and 3 months ago started denosumab 60 mg for osteoporosis.

2.2 | Methods

Upon the admission investigations, laboratory findings showed high liver function tests (total bilirubin: 171 μmol/L, Albumin: 26 g/L, ALP: 123 μ/L, ALT: 510 μ/L), high immunoglobulin counts (IgG: 20.40, IgA: 6.19) and positive antinuclear antibodies (ANA) titer of 1:320. The history of COVID-19 vaccinations is unknown; she didn't have a history of COVID-19 infection. Also, there was no family history of any liver diseases. Liver diagnostic tests and biopsy were done to investigate the causes of liver toxicity. A liver biopsy showed liver cirrhosis, inflammation, bile duct injury, and histological findings characterized the injury as AIH. The patient was managed with IV fluid and prednisolone 40 mg.

2.3 | Conclusion and result

Upon follow-ups, the patient's liver function tests improved, and prednisolone was tapered to 10 mg daily. Azathioprine 50 mg orally was started for the patient to prevent further flares and decompensations. On a recent visit, her liver function tests were normal, and she is on prednisolone 5 mg and azathioprine 50 mg orally as a maintenance therapy for AIH. In conclusion, in this reported case, we suggested an AIH induced by denosumab after excluding all other possible causes and thoroughly screening the patient upon admission by interviewing and taking medical and medication history from the patient and the family. We suggest monitoring for the signs and symptoms of liver diseases and liver function tests periodically for patients on denosumab to prevent complications. Also, further investigations are required to assess the causality association and to evaluate the correlation between patients' characteristics and denosumab-induced AIH.

3 | DISCUSSION

Two post-marketing case reports were found in the literature on DILI linked to denosumab.[14,15] Malnick et al. reported a case of a 72-year-old female who was started on denosumab 60 mg only 1 month before her admission. The study used Naranjo scaling to obtain the causality of denosumab, which resulted in a score of 6 (Probable drug-induced adverse reaction).[16,14] It came to our attention that this patient's case was similar to our reported case in terms of age, gender, denosumab dose, the timing of initiation, and nearly the timing of the elevated liver enzymes. A notable difference between the two cases is the slow tapering of the steroids in the former case, which led to the patient's deterioration. In contrast, in our reported case, steroids were continuously given to the patient. Another report by Ostrovsky et al. described a case of a 43-year-old female who was started on denosumab 60 mg 3 years before her admission. A Naranjo scale of 6 was calculated, indicating a drug-induced adverse reaction, and a RUCAM scale of 4, meaning it is a possible drug-induced adverse reaction.[15] It was noted that this patient's case was similar to our reported case regarding gender, liver biopsy results, liver function tests, and the denosumab dose. In contrast, the case differs in terms of age, the timing of the liver toxicity with the timing of initiation and duration of denosumab treatment and negative antibodies (ANA). A summary of these reports is provided in Table 1.

TABLE 1 Summary of case reports in the literature.[14,15]

Study	Age/gender	Chief complain	Time onset	Laboratory results	Diagnose	Recovery
2017, Malnick	72 years old, female	unremarkable	One month after starting denosumab	Transaminases were five times the ULN and reached 50 times the ULN. GGT: 755 U/L. ANA not investigated	DILI	Recovered
2021, Ostrovsky	43 years old, female	Tired and poor appetite	Three years after starting denosumab	Transaminase ten times the ULN, and the GGT was 67 U/L. ANA negative	DILI	Recovered

Abbreviations: ANA, antinuclear antibody; DILI, drug-induced liver injury; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.

AUTHOR CONTRIBUTIONS

Bushra Albuqami: Validation; writing – original draft. **Wadha Alotaibi:** Validation; writing – original draft. **Rawan M. Al Ghamdi:** Writing – review and editing. **Mohammed Alaskar:** Resources; supervision. **Jawaher J. Alotaibi:** Investigation; resources. **Hadi kuriry:** Investigation; validation. **Nasser Almasri:** Supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

INSTITUTIONAL REVIEW BOARD STATEMENT

Informed consent was obtained from the patient.

CONSENT

Written informed consent to publish this paper has been obtained from the patient. The patient was informed that their data would be used for research and publication, and their identity would be protected. The patient was assured that she has the right to have the option to withdraw their consent at any time before publication without any consequences.

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