CASE REPORT

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Immune-Related Hepatotoxicity After Atezolizumab and Isoniazid

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ABSTRACT

Immune checkpoint inhibitor therapy has transformed the prognosis of multiple solid-organ malignancies; however, such advances are not without significant adverse events known as immune-related adverse events. A novel pattern of autoimmune-like hepatitis following exposure to certain medications, including statins, isoniazid, nitrofurantoin, anti-tumor necrosis factor-alpha therapy and minocycline, has recently been recognized. We present the case of a 66-year-old male patient with extensive-stage small-cell lung carcinoma who developed acute liver injury while receiving concomitant atezolizumab therapy and isoniazid prophylaxis for latent tuberculosis. The patient subsequently developed grade 4 hepatotoxicity, which improved after discontinuation of isoniazid therapy and initiation of corticosteroid treatment. The aim of this report is to contribute to the literature by presenting a rare case of grade 4 immune-related hepatotoxicity under atezolizumab therapy in a patient receiving isoniazid prophylaxis for latent tuberculosis.

Keywords: Atezolizumab, small-cell lung carcinoma, immune-related hepatotoxicity

INTRODUCTION

Immune checkpoint inhibitor (ICI) therapy is a groundbreaking advancement in the field of oncology, with widespread use in the treatment of multiple solid-organ malignancies, including lung cancer, providing significant survival benefits (1). Nonetheless, immune-related adverse events (irAEs) with multisystem involvement remain a major concern. ICI-related hepatotoxicity affects 1% to 17% of patients receiving ICI monotherapy, ranging from asymptomatic elevations in aminotransferase levels to liver failure (2). Although the majority of these adverse effects are subclinical, serious complications, such as severe hepatitis, may progress rapidly if not recognized and managed promptly. This case report describes atezolizumab as the suspected causative agent, with possible additive effects of isoniazid, and outlines the clinical course and diagnostic evaluation that led to this conclusion.

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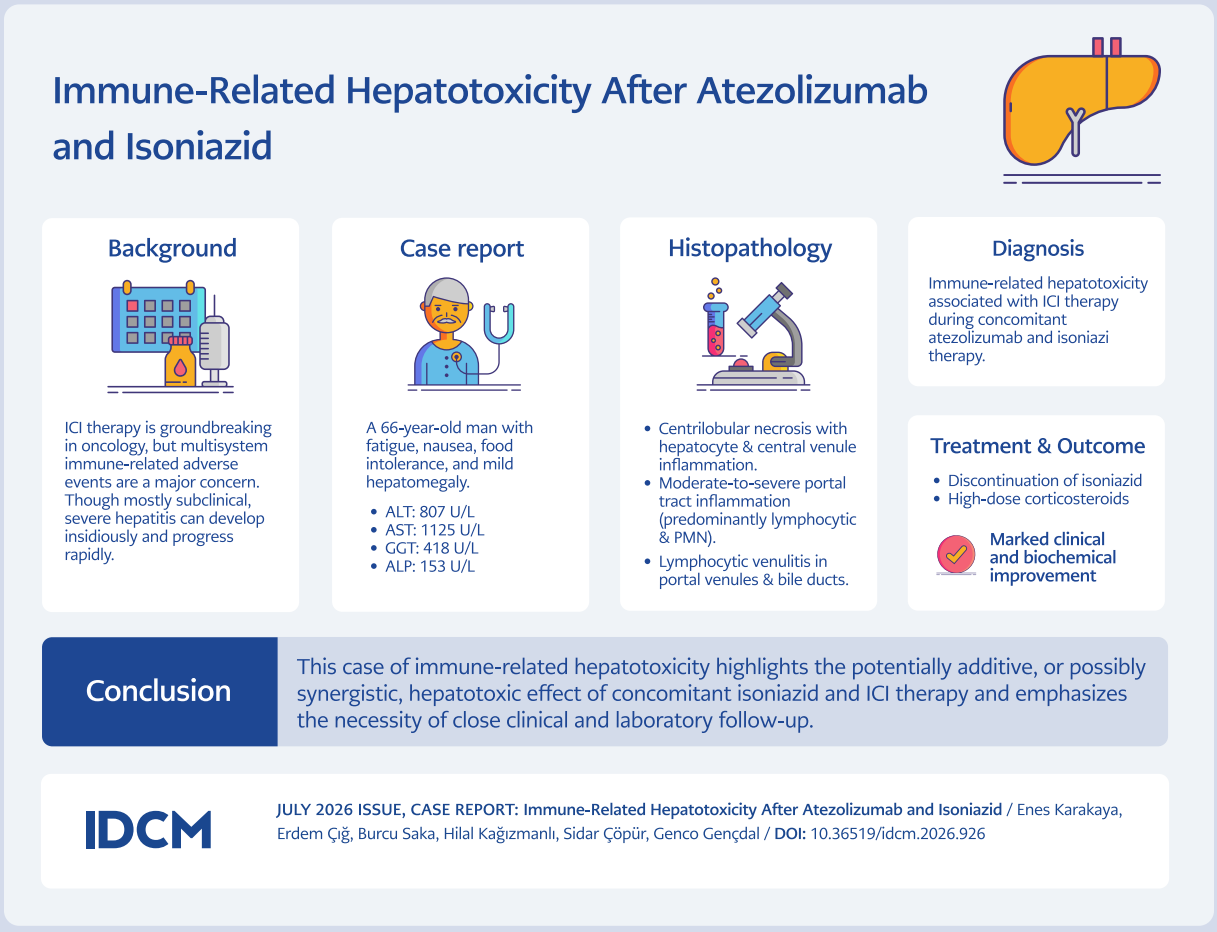

Graphical Abstract

CASE

A 66-year-old male patient with extensive-stage small-cell lung carcinoma, chronic obstructive pulmonary disease, essential hypertension, type 2 diabetes mellitus, and coronary artery disease presented with weakness, fatigue, food intolerance, and nausea. The patient had completed the fourth cycle of atezolizumab maintenance therapy three weeks earlier, following an initial four-cycle regimen of carboplatin, etoposide, and atezolizumab. During the ICI maintenance phase, the patient tested positive for a QuantiFERON-TB (Qiagen, Hilden, Germany) assay after cavitary lesions were identified on thoracic computed tomography (CT). Bronchoalveolar lavage was negative for *Mycobacterium tuberculosis* DNA by polymerase chain reaction (PCR) and for acid-fast bacilli (AFB) on microscopy. Isoniazid prophylaxis was initiated approximately 6.5 weeks before the onset of liver enzyme elevation. On physical examination, the Glasgow Coma Scale (GCS) score was 15. There was mild palpable hepatomegaly (2–3 cm below the costal margin), but the remaining findings were unremarkable. Vital signs were blood pressure 90/50 mmHg and heart rate 80 beats/min.

Initial laboratory investigations revealed grade 4 hepatotoxicity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), with elevated alanine aminotransferase (ALT, 807 U/L), aspartate aminotransferase (AST, 1125 U/L), alkaline phosphatase (ALP, 153 U/L) and gamma-glutamyl transferase (GGT, 418 U/L) levels, while total bilirubin and albumin levels remained within the normal range. The R factor was calculated as 15.8, indicating a hepatocellular injury pattern. Complete blood count and other biochemical markers were normal. The patient's additional medical history included a 100-pack-year smoking history without alcohol use. The

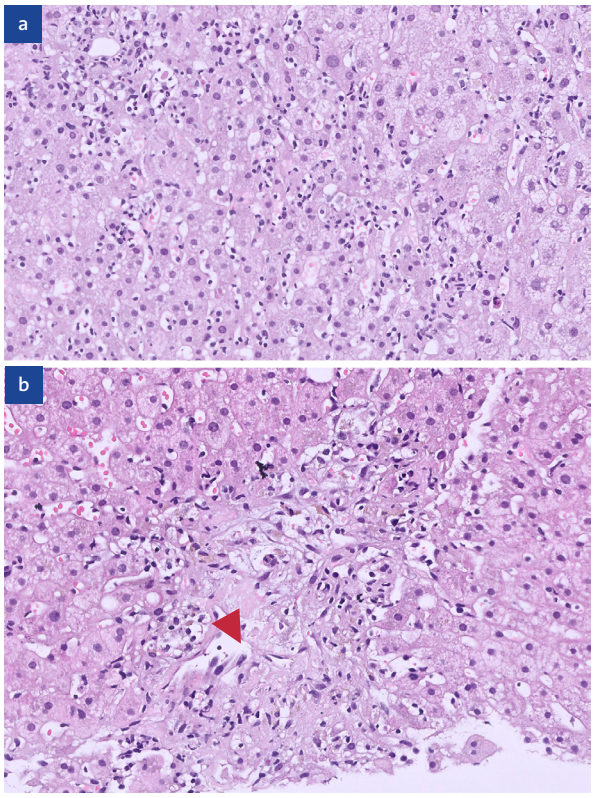

Figure 1. (a) The hepatic parenchyma showed multifocal and confluent necrosis, most prominent in the centrilobular zones (>5 per low-power field [LPF]). (b) Centrilobular hepatocyte dropout was accompanied by inflammatory infiltrates involving both hepatocytes and central venules (arrowhead, central vein lumen).

patient was admitted with the primary differential diagnosis of immune-related hepatotoxicity and isoniazid-induced hepatotoxicity.

Viral serologic tests for hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus, human immunodeficiency virus types 1 and 2, and cytomegalovirus, as well as autoimmune hepatitis markers, including antinuclear, anti-smooth muscle, and anti-liver-kidney microsomal antibodies, were negative. Hepatobiliary ultrasonography revealed hepatomegaly (liver span, 18.5 cm), grade 1 hepatic steatosis, and increased echogenicity extending from periportal areas to the gallbladder lining. Isoniazid therapy was discontinued because of its potential hepatotoxicity. A percutaneous ultrasound-guided liver biopsy was performed. ICI-related hepatotoxicity was considered the leading diagnosis, and methylprednisolone 80 mg/day was started.

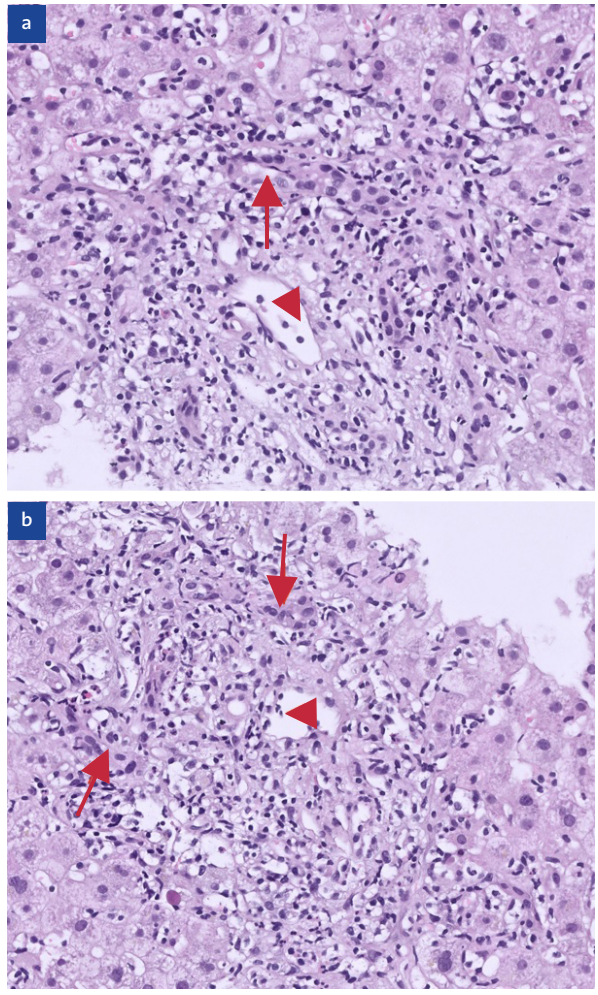

Figure 2. All portal tracts showed moderate-to-severe inflammation, composed mainly of lymphocytes with admixed plasma cells and occasional polymorphonuclear leukocytes. Marked interface activity was noted. Portal venules (arrowhead) displayed endothelial injury and lymphocytic venulitis, while bile ducts (arrow) showed degenerative changes and lymphocytic ductulitis. (a and b, representative portal tracts)

Histopathologic examination of the liver biopsy revealed severe acute hepatitis with centrizonal necrosis (Figure 1) accompanied by lymphocytic ductulitis and venulitis (Figure 2). No fibrosis was identified. Morphologically, the findings were interpreted as indicating an immune-mediated hepatocellular injury. In the context of atezolizumab therapy, this pattern was considered consistent with ICI-related hepatic injury. Although isoniazid is a known hepatotoxic agent, the coexistence of ductulitis and acute rejection–like venulitis was

considered more characteristic of atezolizumab-associated injury than of isoniazid-induced hepatotoxicity. ALT and AST levels began to decrease, accompanied by parallel declines in total and direct bilirubin levels (Figure 3). ALP and GGT levels had an independent course with respect to corticosteroid therapy. Considering the downward trend in liver enzyme levels and the absence of clinical suspicion for additional etiologies, the patient was discharged on corticosteroid (methylprednisolone 80 mg/day) therapy. Following discharge, mycobacterial culture yielded a nontuberculous mycobacterium after eight weeks. Written informed consent was obtained from the patient for publication of this case report.

DISCUSSION

We hereby present a rare case of histopathologically confirmed grade 4 immune-related hepatotoxicity in a patient with a solid-organ malignancy receiving treatment for latent tuberculosis with isoniazid.

Immune-related hepatotoxicity is estimated to affect approximately 10% of patients receiving single-agent ICI therapy, whereas clinically significant toxicity occurs in less than 2% of patients (3). Although substantial advances have been made in the field of cancer immunology, improving our understanding of immune-related adverse events, the complex interplay between host and environmental factors has yet to be fully elucidated. As the liver is constantly exposed to foreign antigens via the portal circulation, robust immune tolerance mechanisms that discriminate between self and non-self antigens, together with appropriate regulation of immune responses, are of utmost importance in preventing excessive immune activation. Low expression of major histocompatibility complex class I and co-stimulatory molecules, along with reduced production of pro-inflammatory cytokines, appear to be crucial components of this immunotolerant state (4). Disruption of self-tolerance mechanisms in an organ continuously exposed to foreign antigens is the central mechanism leading to immune-related hepatotoxicity. However, establishing the diagnosis is challenging and requires the exclusion of alternative causes, a comprehensive biochemical and serologic

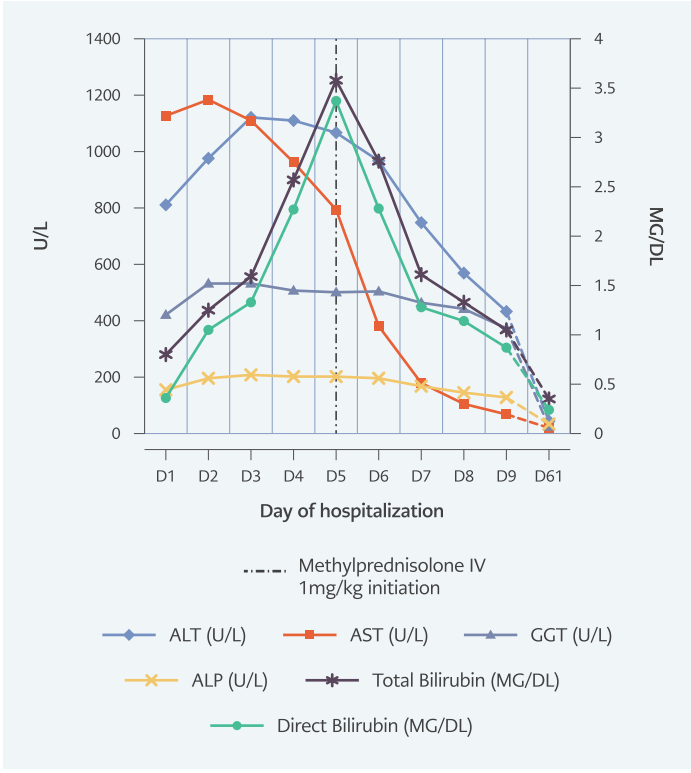

Figure 3. Trends in liver biochemical test results during follow-up under methylprednisolone therapy.

evaluation, including autoantibody testing, and, in many cases, histopathologic examination. Our patient presented with a hepatocellular pattern of injury with serologic evidence of autoimmunity and with histopathologic examination findings consistent with immune-related hepatotoxicity.

Isoniazid, a fundamental component of both active and latent tuberculosis treatment worldwide, has been linked to liver injury in up to 20% of patients, although most cases are asymptomatic, with mild elevations in transaminase levels that are reversible after drug discontinuation (5). Recently, drug-induced autoimmune-like hepatitis (DI-ALH) has gained clinical significance, as most patients require long-term immunosuppressive treatment despite sharing considerable similarities with drug-induced liver injury in their clinical and biochemical presentation (6). Isoniazid-induced liver injury has long been linked to metabolic idiosyncrasy caused by metabolites such as acetylhydrazine; however, this concept has evolved with growing evidence suggesting an immune-mediated

response to isoniazid metabolites (7). Nevertheless, isoniazid-related DI-ALH has been described only in isolated case reports (8,9). Most DI-ALH cases occur within three months of therapy initiation, with a hepatocellular pattern of injury predominating (6). The literature contains few reports of isoniazid-induced autoimmune hepatitis supported by biopsy findings of hepatitis. In contrast, the pattern of severe acute hepatitis with centrizonal necrosis (Figure 1) accompanied by lymphocytic ductulitis and venulitis observed in our patient has been reported more frequently in association with atezolizumab therapy (10,11). The clinical and histopathologic findings in our patient were consistent with immune-related hepatotoxicity; although difficult to prove, the possible contribution of isoniazid to potentiating this immune-mediated injury should not be overlooked.

Close monitoring of liver function tests should be performed in oncology patients receiving latent tuberculosis prophylaxis who may be at increased risk of hepatotoxicity. Infectious diseases and gastroenterology specialists should be involved in the multidisciplinary evaluation of hepatotoxicity, particularly when the clinical or histopathologic pattern is atypical for the suspected offending agent. Additionally, the Roussel Uclaf Causality Assessment Method (RUCAM) for drug-induced liver injury was not utilized because of its limitations in the evaluation of ICI-related hepatotoxicity, potentially leading to misclassification of causality despite characteristic biopsy findings (12). Our patient developed grade 4 immune-related hepatotoxicity while receiving concomitant ICI therapy and isoniazid for latent tuberculosis. Such an additive, or possibly synergistic, effect should be considered in patients receiving simultaneous isoniazid and ICI therapy, who warrant close clinical and laboratory monitoring.

CONCLUSION

The present case depicts a rare but severe presentation of immune-related hepatotoxicity associated with ICI therapy in the setting of concomitant isoniazid therapy for latent tuberculosis. Clinicians should be aware of this potential additive or synergistic hepatotoxic effect in patients receiving concomitant isoniazid and ICI therapy and should ensure close clinical and laboratory follow-up through multidisciplinary collaboration to facilitate early recognition and management of hepatotoxicity.

Ethical Approval: Not applicable.

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

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AI Statement: The authors declared that no artificial intelligence (AI) or AI-assisted technologies were used in the preparation, writing, or analysis of this manuscript.

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