ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Tacrolimus for the Management of Delayed Onset and Treatment-Refractory Immune-Related Hepatitis

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ABSTRACT

Immune checkpoint inhibitors, such as pembrolizumab, are effective in the management of metastatic malignancies, such as melanoma, and are associated with a spectrum of immune-related organ toxicities, including immune-related hepatitis (ir-hepatitis). The clinical presentation of ir-hepatitis varies in onset and severity, and management involves immunosuppression with corticosteroids and mycophenolate mofetil as first and second-line agents. Several agents have been proposed as third-line options for treatment-refractory disease. We report the successful use of tacrolimus for delayed onset and treatment-refractory ir-hepatitis secondary to pembrolizumab.

KEYWORDS: immune checkpoint inhibitor; pembrolizumab; immune-related adverse events; hepatitis; tacrolimus

INTRODUCTION

Immune checkpoint inhibitors (ICIs) target key regulators of the immune system in metastatic malignancies, such as melanoma, and are associated with a spectrum of immune-related organ toxicities, including immune-related hepatitis (ir-hepatitis). Pembrolizumab is a monoclonal antibody against programmed cell death 1 (PD1) receptor and is one of several ICIs associated with ir-hepatitis. Guidelines exist for the management of ir-hepatitis; however, the treatment of refractory ir-hepatitis is not well-established. We describe the case of a patient with treatment-refractory ir-hepatitis, which responded to tacrolimus.

CASE REPORT

A 73-year-old man presented with 3 days of lethargy and anorexia. His medical history included melanoma with pulmonary metastases and melanoma-associated retinopathy. The patient had received 7 cycles of pembrolizumab, which was ceased 9 weeks before presentation, because of the development of new visual symptoms despite regression of metastatic disease. This was attributed to immune-related retinopathy (ir-retinopathy) and was managed with prednisolone 75 mg daily, which had been tapered to 25 mg daily by the time of presentation, and trimethoprim-sulfamethoxazole 800-160 mg 3 times a week for Pneumocystis jirovecii prophylaxis. There were no other recent medication changes. Physical examination demonstrated a jaundiced, elderly man who was alert and did not have asterixis. The abdomen was benign with no tenderness or palpable masses.

Investigations demonstrated an alkaline phosphatase of 354U/L, gamma-glutamyl transferase of 839U/L, alanine transaminase of 1341U/L, and serum bilirubin of 60 μmol/L on admission (Figure 1). There was no liver synthetic dysfunction, and viral hepatitis serology was negative. Anti-nuclear antibody (ANA) was positive with titer >1,280; however, other markers of autoimmune hepatitis (AIH) were negative. A diagnosis of ir-hepatitis was made after imaging, which excluded biliary tract obstruction, metastatic liver disease, and portal vein thrombosis.

In accordance with guidelines for the management of grade 4 ir-hepatitis,[1–3] intravenous methylprednisolone was commenced at 2 mg/kg, with prompt addition of mycophenolate mofetil (MMF) 1 g twice daily on day 3 because of worsening liver function tests (LFTs). Liver biopsy was consistent with ir-hepatitis (Figure 2). Owing to persistently rising serum bilirubin peaking at 252 μmol/L

ACG Case Rep J 2023;10:e01007. doi:10.14309/crj.0000000000001007. Published online: April 19, 2023

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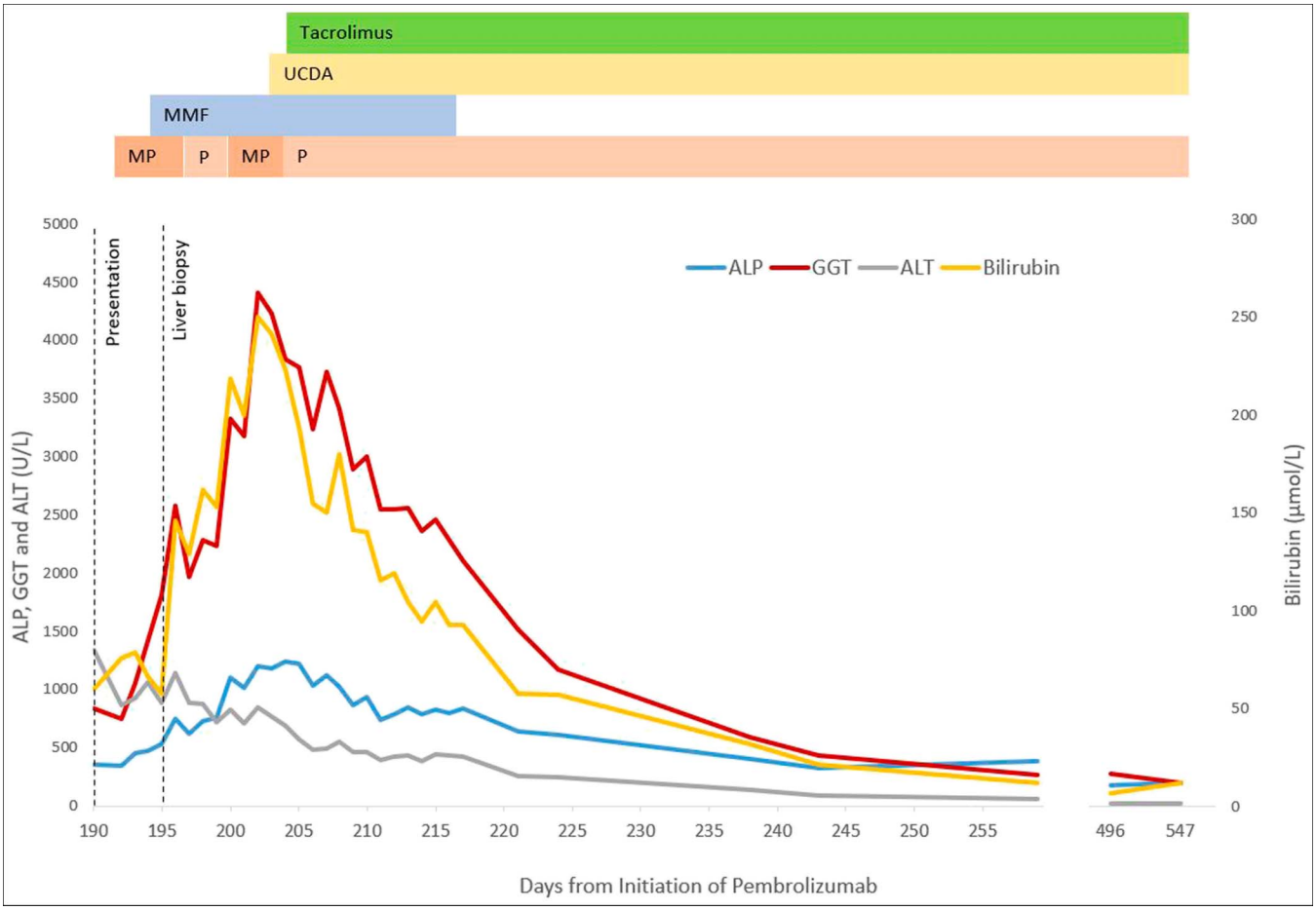

Figure 1. Trend of liver function tests with corresponding medications used, from presentation to the current period. MMF, mycophenolate mofetil; MP, methylprednisolone; P, prednisolone; UDCA, ursodeoxycholic acid.

and gamma-glutamyl transferas peaking at 4403 U/L on day 13, oral tacrolimus was commenced at 3 mg twice daily. Ursodeoxycholic acid was also added for symptomatic relief of pruritus. Slow corticosteroid tapering was commenced, and MMF was ceased when the target tacrolimus trough level of 5–8 ng/mL was achieved. There was a sustained improvement in LFTs despite this. Complete cessation of prednisolone and near-resolution of LFTs occurred approximately 12 months

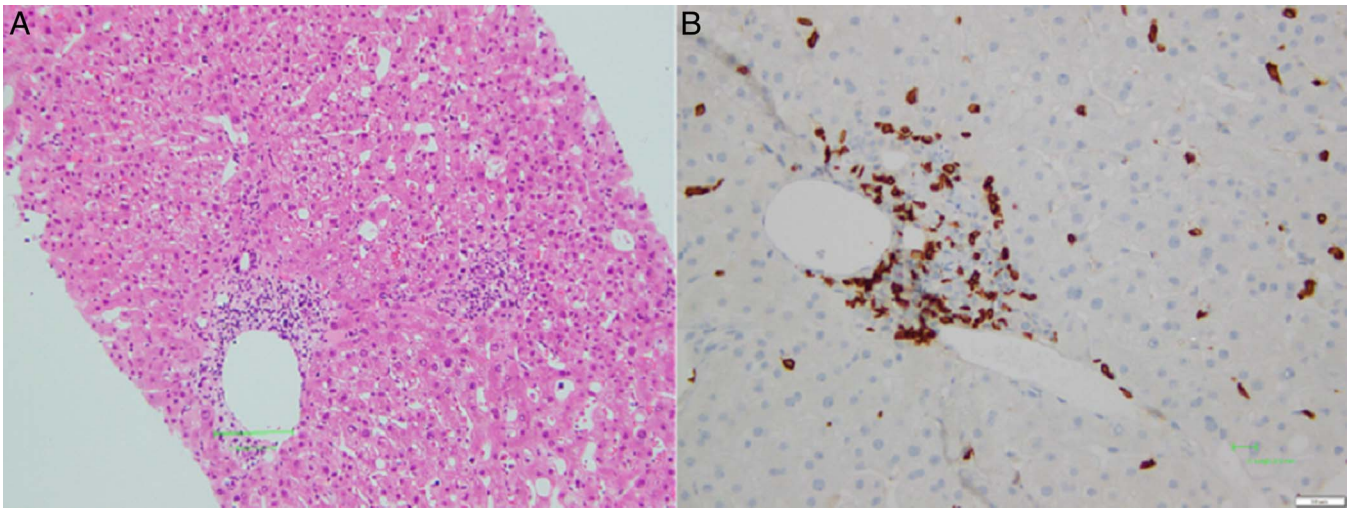

Figure 2. Histological features under hematoxylin and eosin staining including lobular and portal inflammation with lymphocytic infiltrate, bile pigment within centrilobular hepatocytes and sinusoids, and mild steatosis (A). Immunohistochemistry for CD8 T cells (B).

from presentation, and further ICI therapy was deemed inappropriate because of the severity of ir-hepatitis. Restaging computed tomography scans 11 months from cessation of pembrolizumab demonstrated a persistent partial response of known pulmonary metastases despite the ongoing use of tacrolimus and prior cessation of immunotherapy.

DISCUSSION

This case highlights the temporal variability of ir-hepatitis and the use of tacrolimus as a third-line therapeutic. The onset of ir-hepatitis usually occurs at 4–12 weeks, although wider ranges have been reported.[1] In our case, there was delayed onset with presentation occurring 27 weeks after initiation of pembrolizumab. ir-Hepatitis may also occur after cessation of ICIs, with onset after 9 weeks from the last dose in our case and at 7 and 8 months in other cases involving pembrolizumab and nivolumab, respectively.[4,5] In a review study, delayed onset of immune-related adverse events after discontinuation of ICIs occurred more frequently in patients who had shorter courses of immunotherapy and who experienced previous immune-related adverse events while on therapy.[6]

ir-Hepatitis is a diagnosis of exclusion, and consideration of differential diagnoses is vital. Liver metastases have been the predominant cause of liver injury in patients receiving ICIs, given the use of ICIs for advanced malignancy.[7] In addition, the dysregulation of T lymphocytes by ICIs may unveil underlying AIH, which differs by female predominance, more frequent autoantibody positivity, and higher ANA titers compared with ir-hepatitis.[8,9] In our case, the ANA titer of >1,280 raised the possibility of AIH, although other serological markers were negative and ANA may be raised in paraneoplastic syndromes, such as melanoma-associated retinopathy.[10,11] Imaging is useful in excluding other causes of elevated LFTs, such as malignancy and biliary tract obstruction. However, characteristic findings of severe ir-hepatitis on computed tomography, including mild hepatomegaly, periportal edema, and periportal lymphadenopathy, are nonspecific.[12]

Given the heterogeneity of disease and the nonspecific nature of imaging findings in ir-hepatitis, liver biopsy should be considered to exclude differential diagnoses. Characteristic histological findings of anti-PD1 hepatitis include lobular inflammation with infiltrating lymphocytes and milder portal tract inflammation while additional findings may include bile duct injury, cholestasis, steatosis, and hepatocyte ballooning.[9,13] In anti-CTLA4 hepatitis, there may be a specific pattern of granulomatous hepatitis with necrosis.[9] The immunophenotype of lymphocytes in ir-hepatitis is clinically significant because the predominance of CD8+ T lymphocytes helps distinguish it from AIH and drug-induced liver injury.[14]

Management of ir-hepatitis is largely based on guidelines formed from expert opinion. Corticosteroids are the mainstay of treatment, and MMF may be used as a second-line agent.[2,3] The management of treatment refractory ir-hepatitis is less established, and case reports have shown the potential of anti-thymocyte globulin,[15] tacrolimus,[16–18] tocilizumab,[19] and plasmapheresis[20] as third-line options. Currently, tacrolimus is the favored agent and is suggested in the European Society for Medical Oncology guidelines.[2] This may be because of familiarity from use in organ transplantation and AIH and measurability of serum levels.

Tacrolimus binds to FK-binding protein and forms a complex that inhibits calcineurin, subsequently blocking T-cell proliferation and immune overactivity. There is a paucity of literature to dictate the ideal serum trough level for ir-hepatitis, with targets from 3 to 10 ng/mL quoted in 3 case reports using tacrolimus for ir-hepatitis.[16–18] However, there is in vitro evidence demonstrating that tacrolimus may inhibit antitumor T-cell activity provided by ICIs, with one study suggesting a circulating level of <5 ng/mL be maintained to avoid this.[21] We targeted a serum trough level of 5–8 ng/mL, which was effective in managing the ir-hepatitis and maintaining partial remission of metastatic disease. Further research is required to explore the optimal target level.

In conclusion, delayed onset of ir-hepatitis can occur weeks after cessation of ICI and the diagnosis should be considered in patients with ICI exposure. Our case supports the use of tacrolimus for refractory ir-hepatitis but highlights gaps in the literature including the optimal target drug level and the impact on metastatic disease progression.

DISCLOSURES

Author contributions: V. Ea: review of the literature, substantial contributions to the conception and design of the work, and drafting and revising the work. NLY Ngu: substantial contributions to the conception and design of the work and drafting and revising the work. HW Kua: analysis and interpretation of data for the work and revising the work critically for important intellectual content. G. Mishra: substantial contributions to the conception of the work and revising the work critically for important intellectual content. V. Ea is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received October 1, 2022; Accepted February 6, 2023

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