EDITORIAL

Immune Checkpoint Inhibitor-Related Autoimmune Pancreatitis—Risk Factors and Outcomes

Immune-related adverse events (irAEs) are a critical part of immune checkpoint inhibitor (ICI) therapy management. Its occurrence, severity, organ-specificity, and impact on the outcome depend on multiple factors, including the primary tumor and ICI agent (programmed cell death protein 1 vs programmed death ligand 1 vs cytotoxic T-lymphocyte associated protein 4 vs their combination).[1] The management of severe irAEs (≥ grade 3/4) has come a long way, from steroids or infliximab to intravenous immunoglobulins, mycophenolate, and tocilizumab.[2] Thomas et al.[3] presented a retrospective study exploring the presentation patterns, management, and outcomes of patients with autoimmune pancreatitis (AIP) secondary to ICI (irAE-AIP), including pancreas volume (PV) loss and diabetes mellitus (DM). The latter separates this from other studies on this topic.[4–7]

The incidence of irAE-AIP is rare (<5%) and is classified as AIP type-3, differentiating it from immunoglobulin-related (Ig-related, type-1) and pancreas-specific (type-2).[8] This group studied changes in the PV associated with irAE-AIP and reported an increase in PV at diagnosis (compared to pre-ICI) and a drop in the following 1 year.[8] They focused on the clinically pertinent aspects of irAE-AIP patients, such as profiling (based on lipase elevation, symptoms, and imaging), management (holding ICI, narcotic, and/or steroid use), and changes in PV post-irAE.

Patients with elevated lipase (≥3 × upper limit of normal) up to 2 years after initiating ICI were diagnosed as irAE-AIP and were included in this study (N = 229). Genitourinary tumors and melanoma were this study's major primary tumor types (2010–2020). It may not reflect the current ICI use, with approvals for other cancers, including upper gastrointestinal, liver, and biliary tract cancer, in the last 3–4 years. About 38% (N = 86) had pain at irAE-AIP diagnosis, and half of them (55%) also had nausea, vomiting, or both. The pain was typical (radiating to the back) in 21% (18/86), while it was generalized (abdominal) in 45%. A quarter (25%) of the patients did not have concerning changes in the computerized tomography (CT) when diagnosed with irAE-AIP. The lipase levels normalized in most irAE-AIP patients (62%) while persistently elevated in 18%, irrespective of the management offered. About 7% (17/229) had new onset in DM within 2 years post-irAE.

We have not established patient-specific or primary tumor-specific or agent-specific risk factors or biomarkers that could predict irAE-AIP's occurrence as we did for some irAEs.[1] This study gave valuable insights into some risk factors. The history of pancreatitis was negligible in the study population. Documented history of DM, alcohol, and smoking was noted in 14%, 45%, and 51%, respectively. The asymptomatic group had higher rates of DM (29% vs 16%) and alcohol (46% vs 42%), while the symptomatic had higher smoking rates (56% vs 48%). We need larger studies to establish the causal relationship, but close monitoring with serial lipase testing for at least the first 3–4 months (based on median doses [3–4 doses] and interval for AIP in this study) can help in identifying asymptomatic cases as CTs are not reliable. New-onset DM was reported in 7% (17/22) during the follow-up period.

We did not have the typical grading (G2-4) of subjects (based on symptoms and CT findings) used in clinical practice to comment on the management. The approach to AIP in this study varied from holding ICI (61%, 139/229) with (19%) or without (42%) steroid use. The ICI was continued without steroids in a fraction (26%) of the study population. This allowed a comparison of the approaches effective in management. Most of the patients (57%) could not restart ICI in this study. PV changes are the highlight of this study. The findings were similar to their previous study (rise at the time of irAE-AIP and drop over one year).[9] About 54% of patients with CTs available prior to ICI and up to one year had ≥ 20% loss. A higher percentage (74%) of patients with pancreatitis-related changes on CT had more volume loss than those with normal CT (47%). Interestingly, steroids recommended for symptomatic irAE-AIP did not help with pain (alleviating the severity or reducing the duration), preventing recurrences, or restarting ICI in that study population. On the contrary, it made the PV loss significantly worse (no steroids vs steroids, 42% vs 75%, $P = .02$), suggesting a need to re-evaluate the management in larger trials.

An individualized model to identify irAEs early and a better understanding of their management would allow clinicians to continue life-saving cancer treatment. The work of Thomas et al. sheds light on multiple aspects of irAE-AIP, especially its lasting consequences on PV, underdiagnosis (secondary to asymptomatic presentation and poor CT sensitivity), and response to steroids.

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References

1. Chennamadhavuni A, Abushahin L, Jin N, et al. Risk factors and biomarkers for immune-related adverse events: a practical guide to identifying high-risk patients and rechallenging immune checkpoint inhibitors. Front Immunol 2022;13:779691.
2. Immune-related adverse events of immune checkpoint inhibitors. Ann Intern Med 2024;177(2): ITC17–ITC32.
3. Thomas AS, Abreo M, Sayed SA, et al. Immune checkpoint inhibitor-induced pancreatic injury: clinical and radiological profile and response to steroids. Gastro Hep Adv 2024;3(3):361–367.
4. Liu Y, Zhang H, Zhou L, et al. Immunotherapy-associated pancreatic adverse events: current understanding of their mechanism, diagnosis, and management. Front Oncol 2021;11:627612.
5. Kramer S, van Hee K, Blokzijl H, et al. Immune checkpoint inhibitor-related pancreatitis: a case series, review of the literature and an expert opinion. J Immunother 2023;46(7):271–275.
6. Hana C, Rehman T, Park K, et al. Pancreatic adverse events in patients treated with immune checkpoint inhibitors. JGH Open 2023;7(3):204–207.
7. Jiang C, Tang W, Yang X, et al. Immune checkpoint inhibitor-related pancreatitis: what is known and what is not. Open Med 2023;18(1).
8. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40(3):352–358.
9. Thomas AS, Abreo M, Sayed SA, et al. Autoimmune pancreatitis secondary to immune checkpoint inhibitor therapy (type 3 AIP): insights into a new disease from serial pancreatic imaging. Gastroenterology 2023; 164(1):154–155.

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