

[EDITORIAL]

Two Types of Immune Checkpoint Inhibitor-related Pancreatitis

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Although the use of immune checkpoint inhibitors (ICIs) as therapeutics against malignancies has been increasing, adverse events induced by ICIs have also been reported. According to the National Comprehensive Cancer Network (NCCN) guidelines (1), elevated amylase levels are a common phenomenon that occurs during the usage of ICIs. A total of 53% of the patients with type 1 diabetes caused by immune-related adverse effects (irAEs) showed elevated amylase levels (1).

In this issue of the journal, Yazaki et al. reported a case of acute pancreatitis and colitis during treatment with the ICI, nivolumab, for a patient with renal cell carcinoma and multiple metastasis (2). Stopping the administration of nivolumab did not improve the pancreatitis or colitis, but corticosteroid therapy dramatically improved the condition, suggesting that ICI therapy may cause an autoimmune disorder of the pancreas and colon.

Immune checkpoints, including PD-1 and CTLA-4, lead to the inhibition of antigen-presenting cells (APCs) and T-cell activation (Figure A, B). Thus, ICIs, such as PD-1 inhibitors (nivolumab) and CTLA-4 inhibitors (ipilimumab), can promote the reactivation of APCs and T cells (Figure C). At the initial phase of the immune response, antigens are presented to T-cells by APCs, resulting in the activation of the T cells. The inflammatory cytokines/chemokines from the activated T cells then attack the target cells and synergistically activate APCs again. An excessive immune response to antigens is a major cause of autoimmune diseases. For instance, Toll-like receptor 9 (TLR9) and its antigens are regulators of disease pathogenesis in systemic lupus erythematosus. Therefore, when ICIs inhibit PD-1 or CTLA-4, over-activation of APCs and T cells against their antigens can occur, resulting in immune responses such as autoimmune diseases.

In Yazaki et al.'s report, one reason why the ICI induced pancreatitis and colitis may have been due to an excessive immune response to their antigens. Organs, such as lungs, skin and intestines, are constantly exposed to foreign antigens (e.g. bacteria or viruses). ICIs can induce an excessive response to foreign antigens in these organs, thus resulting in parenchymal damage with infiltration of CD14-positive cells (3). The foreign antigens involved in the pathogenesis of acute pancreatitis have been recently identified (4), and the innate immune system may play a key role in the pathophysiology. In fact, the C minor allele of the CD14 gene, which increases circulating soluble CD14 levels, is associated with acute pancreatitis (5). Likewise, the CD14 gene C-260T polymorphism was considered a promising candidate marker in susceptibility to ulcerative colitis, especially among Asians (6). Since the CD14 antigen is known to be strongly expressed on APCs, such as monocytes and macrophages, the reactivation of APCs by ICIs may induce pancreatitis and colitis as an excessive immune response.

According to recent case reports regarding pancreatic disruption due to ICIs, there are two phenotypes: acute pancreatitis, as in the present case reported by Yazaki et al. (2), and autoimmune pancreatitis (AIP)-like cases (7). The differences in these two phenotypes of ICI-related pancreatitis might aid in our understanding the mechanism underlying the development of AIP. Interestingly, type 2 AIP is known to have a risk of inducing the development of both pancreatitis and colitis. It is therefore necessary to investigate the homology of ICI-related pancreatitis to AIP and ICI-related colitis to ulcerative colitis or Crohn's disease.

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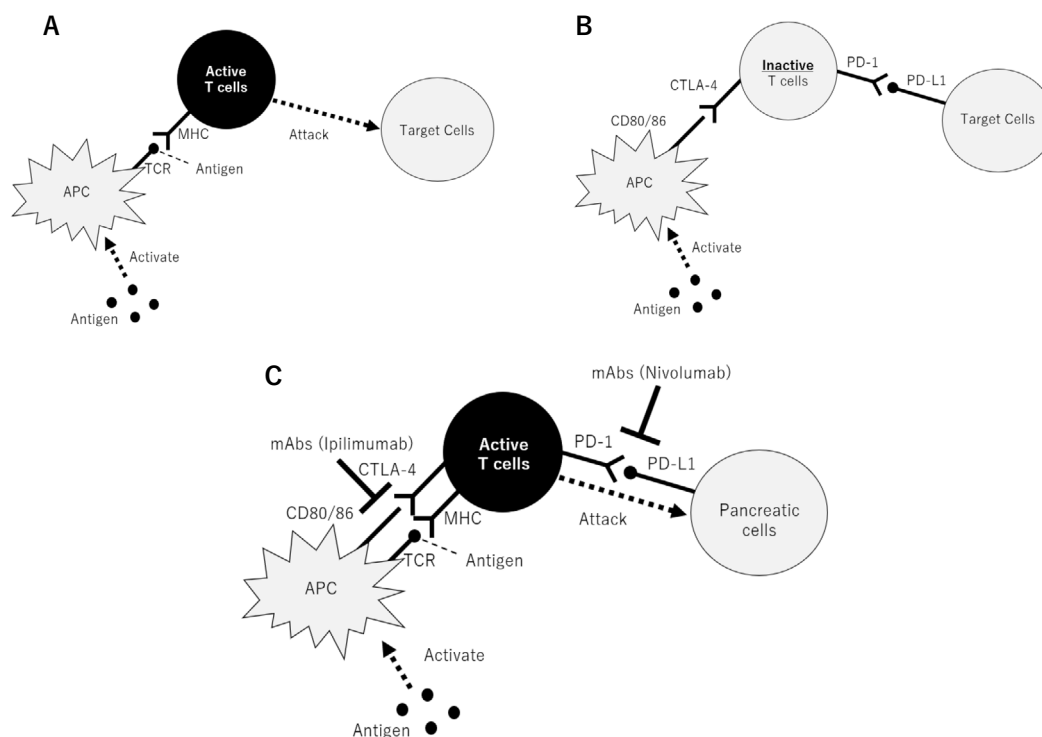


Figure. Possible mechanism underlying ICI-induced pancreatitis. **A:** T cell activation. Antigen-presenting cells (APCs) present to T cells through the interaction of the major histocompatibility complex (MHC) and T cell receptor (TCR), resulting in T cell activation and their attack on target cells. **B:** T cell inactivation by immune checkpoints. The interaction between CD80/86 on APC and CTLA-4 on T cell or PD-1 on T cell and PD-L1 on target cells can mediate T cell inactivation. **C:** Immune checkpoint inhibitors (ICIs), such as mAbs targeting CTLA-4 (ipilimumab) and PD-1 (nivolumab), can re-activate T cells, which may attack pancreatic cells, as in auto-immune diseases.

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