

Case Report

Nivolumab-Induced Exocrine Pancreatic Insufficiency

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Keywords

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Abstract

Immunotherapy is increasingly gaining applicability for several malignancies. While the survival of several malignancies has dramatically improved, immune-related adverse events (irAEs) can occur and can cause severe damage to patients. Side effects such as colitis are well known nowadays; however, with increased use of immunotherapy, less common side effects should also be addressed. In this article, 2 patients that received nivolumab developed exocrine dysfunction of the pancreas. Endocrine dysfunction has been well known, but exocrine dysfunction is less often described. It is important to be aware of this side effect because it is possibly underdiagnosed. Symptoms often mimic symptoms of malignancy, chemotherapy side effects, or immune-related colitis. Although the exact mechanism is yet to be elaborated, dormant CD8+ T cells are likely to be involved. No known therapy is yet been proven to be effective. More knowledge and research about irAEs will lead to possible therapies that will be effective. Currently, high-dose prednisone is recommended based on expert opinion.

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Introduction

The use of immunotherapy for the treatment of various malignancies is increasingly gaining applicability. While the 5-year survival rate of patients with metastatic melanoma was only 15% prior to the introduction of immunotherapy, due to immune checkpoint inhibitors

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(ICIs) such as PD-1/PD-L1 and CTLA-4 inhibitors, this has improved to a 5-year survival rate of 52% [1, 2]. Despite their efficacy, important side effects have been described [3, 4].

The most important side effects of ICIs are immune-related adverse events (irAEs). Although the exact pathophysiology has not been fully elaborated, it is likely that multiple factors contribute to developing irAEs [4]. The frequency of irAEs in patients varies between different classes of ICIs. Approximately, 10% of patients receiving PD-1 inhibitors have severe (grade 3 or 4) irAEs. Endocrine pancreatic dysfunction presenting as autoimmune diabetes, often with antibodies against glutamic acid decarboxylase (GADA), however is a rare event [5]. Even less is known about the occurrence of exocrine pancreatic insufficiency after the use of ICIs [3]. The unfamiliarity with this condition can cause delay in the diagnosis especially because the symptoms of pancreatic insufficiency, most often diarrhea and weight loss, can be similar to symptoms caused by the malignancy itself, immune-related colitis, or side effects of other treatments like conventional chemotherapy [6]. Treatment of exocrine pancreatic insufficiency is relatively easy with oral pancreatic enzyme replacement products. In this report, we describe 2 patients who developed exocrine pancreatic insufficiency after administration of nivolumab, a PD-1 inhibitor.

Case Report 1

A 60-year-old woman visited the emergency department in early 2020 because of abdominal pain and diarrhea. The abdominal pain first started about one and a half week before presentation followed by diarrhea a few days later.

Two years earlier, the patient was diagnosed with a melanoma on the right breast with a positive axillary sentinel lymph node (pT2bN1a, stage IIIB). One year later, she had a recurrent axillary metastatic melanoma and was treated with an axillary lymph node dissection and adjuvant nivolumab. Two months before presentation, her sixth dose of nivolumab was administered.

On examination, the patient did not appear severely ill. Her abdomen was tender in the upper quadrant. The remainder of the physical examination was normal. Laboratory tests revealed an elevated lipase of 681 U/L (normal range 15–65 U/L). Her nonfasting glucose level was 6.0 mmol/L (normal range 3.5–7.8 mmol/L). The patient had no history of excessive alcohol consumption, and abdominal ultrasound did not yield cholelithiasis or other abnormalities. A diagnosis of acute pancreatitis was made, but no definitive etiology could be established.

During follow-up, the patient continued to experience abdominal pain for about 6 weeks, and lipase levels remained elevated for 4 weeks. The diarrhea persisted, and the patient started to lose weight. At that time, pancreatic insufficiency was suspected. Additional stool examination revealed excessive fat excretion (49.2 g per 72 h, normal range 2–7 g/day) and undetectable levels of feces elastase. Also, serum lipase dropped below the lower limits (<4 U/L). Abdominal CT however showed no atrophy or calcification of the pancreas. Since all other common causes of chronic pancreatitis were excluded, nivolumab-induced autoimmune pancreatitis with pancreatic insufficiency was the most likely diagnosis. The patient was started on pancreas enzyme supplements after which the diarrhea subsided, and the patient began to gain weight again.

Four months after presentation, the patient started to experience mild polyuria. Workup yielded a fasting glucose of 10.1 mmol/L (normal range <6.1 mmol/L). Endocrine pancreatic insufficiency was suspected. Anti-glutamic acid decarboxylase autoantibody (GADA) turned out to be positive as it is a common finding in nivolumab-induced autoimmune diabetes. Although insulin was recommended to prevent ketoacidosis, the patient insisted on using

monotherapy with metformin. After a brief period of insulin administration, glucose levels remained within acceptable limits on metformin monotherapy.

Case Report 2

A 61-year-old male patient was diagnosed with a pT3aN2a, stage IIIC melanoma on his back in 2011. In March 2019, he presented with apathy and bradyphrenia and was diagnosed with a solitary brain metastasis in the left frontal lobe. A PET-CT ruled out extracerebral metastases. A complete resection of the brain metastasis was performed, and the patient initiated adjuvant nivolumab in July 2019. At follow-up PET-CT in September 2019, a pattern of slightly increased diffuse FDG uptake of the pancreas was observed with no melanoma metastases. In the additional blood analysis, lipase was elevated (229 U/L, normal range 15–65 U/L). The patient was asymptomatic, and he had no abdominal pain in particular. A subclinical immunotherapy-induced pancreatitis was suggested. One week later, he presented with grade 2 diarrhea, and treatment with loperamide was initiated. Stool cultures were performed and ruled out bacterial or viral infection. Nivolumab was withheld.

Diarrhea did not improve, and a colonoscopy was performed and showed a mild colitis. Grade 2 immunotherapy-induced colitis was suggested, and treatment with budesonide was initiated. At follow-up 2 weeks later, diarrhea was improved, but the patient complained of weight loss, polydipsia, and polyuria. Blood analysis showed severe hyperglycemia (34.1 mmol/L), mild ketone level in urine (1+), and normal acid base status (pH 7.41, HCO₃⁻ 21.2 mmol/L, and PaCO₂ 4.6 kPa). The patient was treated with intravenous insulin and fluids. Additional C-peptide was low 68 pmol/L, normal range 400–1,500, and GADA were negative. Immunotherapy-induced new-onset diabetes mellitus was suspected, and treatment with nivolumab was permanently stopped. In the following weeks, diabetes mellitus was well controlled with subcutaneous insulin treatment, but the patient experienced again diarrhea and further weight loss. Exocrine pancreas insufficiency was suggested, and pancreas enzyme supplements were initiated, resulting in a complete resolution of both diarrhea and weight loss. Elastase analysis in the stool was undetectable (<15 mcg/g, normal 200) and confirmed the diagnosis of exocrine pancreas insufficiency.

Discussion

Nivolumab is a PD-1 inhibitor belonging to the ICIs. Some malignancies have evolved immune escape mechanisms by inactivating CD8⁺ T cells. ICIs activate CD8⁺ T cells and are therefore an effective strategy to fight cancer [7]. However, there is a risk of adverse events, especially irAEs. The gastrointestinal tract, endocrine glands, skin, and liver are the organs most commonly involved. It is hard to establish which patients have the greatest risk of developing an irAE. Research to establish which patients are most at risk is a field that has a lot of interest, especially because these adverse events can lead to severe pathology and even death [8].

One irAE is pancreatitis. The reason why this complication occurs is not completely understood. The proposed mechanism of action is diminished self-tolerance. Before starting ICIs, CD8⁺ T cells are already present, but inactivated in the pancreas. It is proposed that in a physiological state, PD-1 B cells prevent autoimmune attacks by these dormant T cells. B cells are thus responsible for the inactivation, by using PD-1 ligands [8]. With the loss of this inhibition with PD-1 inhibitors, the dormant T cells become reactivated and

attack the own pancreatic cells. Research is done whether inactive T cells are present in patients before starting immunotherapy, and if so whether it can predict the likeliness of irAEs [3].

A more common clinical presentation of pancreatic insufficiency due to nivolumab is type 1 diabetes mellitus with a rapidly developing ketoacidosis. In 95% of these cases, a PD-1 inhibitor is involved [9]. Prior to the use of ICIs, this form of diabetes sometimes occurred in patients with Asian ethnicity. Since the introduction of ICIs, this disease has also been described in the Caucasian population although it is likely that a different pathophysiological mechanism is responsible [10]. One of the arguments for this is that there are no genes in Caucasian patients that are related to previously described fulminant diabetes mellitus in Asian ethnicities [11]. Interestingly most patients that develop nivolumab diabetes have antibodies against glutamic acid decarboxylase.

Even though diabetes mellitus is a frequently reported adverse event with nivolumab, in the current medical literature, little is known about exocrine dysfunction of the pancreas. The literature describes 3 case reports [12, 13]. These patients showed diverse clinical presentation. The exact mechanism is not understood but seems to be due to atrophy of the pancreas due to CD8+ T-cell activation. Exact data about pancreas volume are not known. In 1 patient, fulminant diabetes mellitus has also been reported, making it likely that pancreas destruction has been the underlying cause. In the years to come, more awareness and research of this adverse event is necessary, especially because of the increasing number of patients that will start using ICIs.

Conclusion

In this article, we have described 2 patients with pancreatitis after administration of nivolumab resulting in both endocrine and exocrine pancreatic insufficiency. Reactivation of dormant CD8+ T cells by the PD-1 inhibitor causing loss of self-tolerance of pancreas tissue and consequently autodestruction seems to be the most likely mechanism.

ICIs-associated pancreatitis is a rare adverse event, and both asymptomatic and symptomatic pancreatitis has been described. In case of symptomatic pancreatitis, treatment with high-dose prednisone is recommended. Clinicians should be aware that ICI-induced pancreatic injury can result in endocrine and exocrine insufficiencies. Prompt recognition and treatment of these metabolic and nutritional complications is important.

Statement of Ethics

Subjects have given their informed written consent to publish their case. The study is exempt from ethical approval due to the design of the study.

Conflict of Interest Statement

The authors disclose that they do not have any conflicts of interest.

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Author Contributions

All authors, Boudewijn Sweep, Sofie Wilgenhof, and Sander Anten, contributed equally to the manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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