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Nivolumab-induced tumour-like gastritis: a case report and literature review

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Abstract

BACKGROUND

Background: Immune checkpoint inhibitors are one of the modern treatment methods for advanced malignancies. However, this group of medications is also associated with various immune-related adverse events, such as colitis or pneumonitis. Immune checkpoint inhibitor-induced gastritis is a less common adverse event.

CASE SUMMARY

Case summary: We describe a 64-year-old woman presenting with diarrhea, nausea, and discomfort in the upper abdominal region. The patient had a history of metastatic lung cancer, which was treated with nivolumab. During the first endoscopy infiltrating gastric tumour was suspected. Later, based on endoscopic, histological and radiological findings, nivolumab-induced gastritis was diagnosed. The patient was successfully treated with three courses of omeprazole.

CONCLUSION

As a consequence of the increased use of immune checkpoint inhibitors, a growing number of reported immune-related adverse events could be expected. The diagnosis of immune checkpoint inhibitor-induced gastritis should be considered when assessing a patient treated with nivolumab with upper gastrointestinal distress.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are a novel treatment option for various types of cancer, among them non-small cell lung carcinoma [1]. ICIs, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) inhibitors, facilitate cancer cell destruction through either CTLA-4 or PD-1 receptor pathway blockade, thus reversing cancer tolerance of the immune system. However, due to the ICIs mechanism of action, the toxicity of the therapy is also immune-mediated [2,3].

We present a patient who developed ICI-induced gastritis after nivolumab immunotherapy and was successfully treated with proton pump inhibitor (PPI) monotherapy (***Table 1***). We also provide a short review of the literature that is similar to the cases already described by other authors (***Table 2***).

CASE PRESENTATION

Chief complaints

A 64-year-old Caucasian woman experiencing diarrhea, nausea, early satiety and discomfort in the upper abdominal region was referred for a gastroenterologist consultation by her pulmonologist.

History of present illness

The patient was diagnosed with poorly differentiated metastatic non-small cell lung carcinoma (G3) (T2aN1M1a) in 2018. She received chemotherapy with carboplatin, paclitaxel, and bevacizumab. After the initial good response, the oncological disease relapsed in 2019, and treatment with Nivolumab was started. At first, the patient tolerated immunotherapy well, but after the seventh course of Nivolumab, the patient was diagnosed with diabetes possibly caused by immunotherapy-associated beta cell destruction. Diabetes was managed with insulin therapy. In December 2020, after 64 courses of Nivolumab therapy, the patient started experiencing diarrhea, nausea

without vomiting, early satiety and upper abdominal discomfort. In February 2021, after performing an esophagogastroduodenoscopy (EGD) with biopsy, the patient was diagnosed with ICI-induced gastritis. Initial omeprazole treatment was effective and well tolerated, and thus continued. During the following years, several EGDs with biopsies and abdominal CT (CT) scans were performed to evaluate the endoscopic, pathohistological, and radiological response to treatment and the natural course of the disease. The course of the disease and its treatment are presented in ***Table 1***.

History of past illness

The patient denied any other chronic diseases or the concomitant use of other medications. She underwent conization of the cervix and tonsillectomy.

Personal and family history

The patient denied allergy to food or drugs. She developed a rash after the first course of chemotherapy. Her family history was insignificant.

Physical examination

The patient was slightly underweight (BMI 18.22 kg/m^2). No other significant changes were detected.

Laboratory examinations

No remarkable abnormalities were observed in the patient's recent blood laboratory examination results.

Imaging examinations

To evaluate the possible origin of symptoms related to upper gastrointestinal tract dysfunction, an EGD with multiple biopsies was performed.[1] Colonoscopy was not performed due to typical upper gastrointestinal symptoms. Tumour-like endoscopic changes in the stomach were found. The stomach mucosa was covered with whitish

plaques throughout the entire stomach, affecting the course of the gastric folds in the upper curve. However, when the air was insufflated, the folds were almost completely smoothed out. In the prepilliary region, the mucosa was thicker ***(Figure 1)***. Infiltrating stomach neoplasm was suspected, therefore an abdominal CT scan was performed. It revealed stomach changes related to chronic gastritis: the wall of the pyloric part of the stomach was evenly thickened, and edematous, the mucosa clearly differentiated, diffusely more intensively accumulated contrast material, clear masses were not differentiated. The stomach body wall was evenly stretched, not thickened ***(Figure 2)***.

PATHOLOGICAL FINDINGS

Finally, pathohistological examination of biopsies from the first upper gastrointestinal endoscopy denied the suspected gastric tumour. It showed active chronic gastritis with erosions, lymphatic follicles and lymphoepithelial lesions. The possibility of MALT lymphoma was excluded by immunohistochemical analysis. There was no Helicobacter pylori infection reported.

FINAL DIAGNOSIS

After evaluation of EGD, abdominal CT and pathohistological results, the patient was diagnosed with ICI-induced gastritis.

TREATMENT

Due to the mild symptoms of the patient and the satisfactory results reported by other clinicians, the patient was treated with three courses of omeprazole: first – March-April 2021 (60 days, 20 mg per day), second – July-August 2021 (60 days, 20 mg per day), third – October 2021 (30 days, 20 mg per day). The first and second courses were prescribed by the gastroenterologist, and the third course was initiated by the patient herself whenever she felt the recurrence of related symptoms. The patient was also referred to a nutritionist for evaluation of possible malnutrition.

OUTCOME AND FOLLOW-UP

Several follow-up EGDs with multiple gastric mucosa biopsies were performed to evaluate the dynamics of stomach changes due to treatment and the general natural course of the disease.

The second EGD (March 2021) revealed negative endoscopic changes in the stomach – a progression of tumour-like changes ***(Figure 3)***. New endoscopic abnormalities like fragile and prone to bleeding mucosa were observed together with changes described previously. Biopsies showed active chronic gastritis with erosions and intestinal metaplasia, and immunohistochemical analysis rejected cytomegalovirus infection.

The third EGD (July 2021) showed a decrease in diffuse inflammation and infiltration of the stomach wall ***(Figure 4)***. There was no bleeding at contact, erosions, or white plaques. Additionally, a polyp of 0.5 cm diameter was discovered. Biopsies revealed active chronic non-erosive gastritis with pyogenic granuloma and a hyperplastic polyp.

During the fourth EGD (January 2022) gastric mucosal atrophy was observed with some spots of intestinal metaplasia and a 1.0 cm polyp ***(Figure 5)***. The histological report was compatible with a hyperplastic gastric polyp.

Treatment with omeprazole was effective, resulting in symptom relief after several weeks. The patient received three courses of omeprazole and is now in remission with no significant gastrointestinal symptoms or the need for an additional course of PPI. The complete patient's disease and treatment timeline are concluded in ***Table 1***.

DISCUSSION

As the use of ICIs rises, an increasing number of immune-related adverse events (irAEs) are reported [1]. ICIs, namely nivolumab, the PD–1 receptor inhibitor, may cause irAEs in various organ systems, for example, the colon, skin, liver, and thyroid gland. The most common side effects of nivolumab are diarrhoea (incidence rate approx. 10-

13%) that can be associated with ICI-induced colitis [4], skin rash and pruritus (approx. 2%), hypothyroidism (<2%), hepatitis (<2%), pneumonitis (approx. 3%), renal failure (approximately 2% [5]. In contrast, nivolumab-induced gastritis is a less known adverse event.

An electronic search of the literature on nivolumab-induced gastritis was performed. Articles available in the PubMed, Medline, Cochrane, and Web of Science databases were reviewed up to December 1, 2022. The search terms used were "ICI-induced gastritis", "nivolumab-induced gastritis", "nivolumab and gastritis". No time restrictions were used for the publications. A total of 30 articles and abstracts met the initial search criteria. The inclusion criteria were: well-documented full-text articles written in English. We analysed a total of 19 case reports, which are summarised in ***Table 2***.

In patients with nivolumab-induced gastritis, the most often reported symptoms include nausea, pain, diarrhea, loss of appetite, and weight loss [2–8]. Less commonly seen symptoms are hematemesis and dysphagia [9,10]. The onset of symptoms after the initiation of treatment varies considerably between a few weeks and 32 mo. In our case, the patient had diarrhea, nausea, epigastric discomfort, loss of appetite and mild weight loss – symptoms similar to other reported cases of nivolumab-induced gastritis. However, in our case, the symptoms manifested later than in most other cases – after 64 courses of nivolumab or, approximately, after 21 mo.

There are few case reports that provide the radiological findings, but the ones that do show uptake of fluorodeoxyglucose in the stomach wall in positron emission tomography/CT scans [8,10–12,21]. Some of the published cases displayed stomach wall thickening seen in CT scans [5,13,20], like in our case, while others reported no significant findings on this investigation [3,14–16]. Thus, the importance of the CT scan in diagnosing nivolumab-induced gastritis is not yet clear.

EGD and multiple biopsies play one of the most significant roles in the diagnostic process of ICI-induced gastritis. In most instances, EGD findings show erythema [2–

[5,7,8,10,13,16,17,19], friable mucosa [3,5,7,16,19], erosions [2,7,8,17], white fibrin-like exudate on the mucosa [7–10,13–16]. These endoscopic changes were also observed in our patient.

Because of the rarity of ICI-induced gastritis, there are few currently available recommendations on how to treat this irAE. Brahmer et al. [19] advised to treat this form of gastritis with corticosteroids and keep tumour necrosis factor-α blockers reserved for cases resistant to steroids (suggestions based on previous case studies). In most of our reviewed cases, patients received corticosteroids (17 out of 19 cases), most of whom resolved to improve symptoms. However, in our case, the nivolumab-induced gastritis was not managed with steroids. Instead, the patient was successfully treated with three courses of omeprazole monotherapy and remains in remission. PPIs were used alone or in combination with other therapies in 9 of the 19 cases we reviewed. One of the more commonly used PPIs was pantoprazole [4,5,7,8]. In some of the cases that reported improvement in symptoms, PPIs were used in combination with other medications, namely – prednisone, methylprednisolone [4,7,8,10,12] or infliximab [2,8].

Shi *et al* reported that treatment with pantoprazole and ranitidine gave desirable results only after cessation of nivolumab [3]. Similar results were observed in a case report by Martínez-Acitores de la Mata *et al* [16]; remission was achieved after PPI therapy and cessation of nivolumab. Overall, in 9 of the 19 reviewed cases, ICI-induced gastritis was managed in part by discontinuing nivolumab therapy. In our case, nivolumab was not terminated because the patient did not have significant gastroenterological symptoms after treatment and the benefit of tumour suppression outweighed the risk of associated irAE.

In recent years, immune checkpoint inhibitors have become an option for the treatment of various types of cancer, but not much is known about biomarkers that predict adverse immune reactions. To date, none of the suggested biomarkers has demonstrated sufficient precision in predicting or signaling irAEs to be useful in clinical practise and more high-quality studies are needed to establish a balance between the antitumour effects of ICI therapy and the irAEs it causes.

CONCLUSION

ICI-induced gastritis, as a complication of immunotherapy, is much less common among clinicians and, consequently, much less known. As immunotherapy evolves and becomes more widely used, the probability of irAEs, including ICI-induced gastritis, will grow. When assessing a patient on immunotherapy presenting with symptoms of upper gastrointestinal tract distress, this diagnosis should be taken into account to provide a patient with timely intervention. Controlled clinical trials are needed to establish guidelines for the management of ICI-induced gastritis.

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