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NIVOLUMAB-INDUCED CHYLOTHORAX IN A PATIENT WITH ADVANCED GASTRIC ADENOCARCINOMA

Youssef Hayssam Sultan[1]*, Radwan Zeidan[2]*, Mohammed Abdallah[2], Stephanie Joseph Mitri[3], Francois Georges Kamar[4,5]

[1] Resident of Internal Medicine, University of Balamand, Beirut, Lebanon
[2] Pulmonary and critical care fellow, University of Balamand, Beirut, Lebanon
[3] Pulmonary and critical care medicine, Balamand University, Mount Lebanon University Medical Center, Beirut, Lebanon
[4] Haematology and Oncology Division, Department of Medicine, University of Balamand, Beirut, Lebanon
[5] Hematology Oncology Department, Mount Lebanon University Medical Centre. Hazmieh, Lebanon
* Contributed equally

Corresponding author's e-mail: stepanie.joseph.mitri@gmail.com

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ABSTRACT

Chylothorax refers to the presence of chyle in the pleural space leading to respiratory compromise. Chylothorax secondary to gastric adenocarcinoma or immune checkpoint inhibitors, such as nivolumab, is exceedingly rare and has been documented only in isolated case reports. The exact mechanism by which nivolumab may induce chylothorax remains unclear, though immune-mediated increased lymphatic permeability induced by anti-PD-1 has been hypothesised. This report highlights a unique presentation of chylothorax in a patient with gastric adenocarcinoma undergoing nivolumab therapy.

KEYWORDS

Nivolumab, chylothorax, immune adverse event, advanced gastric adenocarcinoma, PD-1 inhibitor

LEARNING POINTS

- Chylothorax can be a rare immune-related adverse event of nivolumab.
- In differentiating between malignant chylothorax in advanced malignancy and immune-related adverse events, chylothorax can be difficult. Negative pleural cytology, lack of thoracic duct obstruction and response to immunotherapy can guide clinicians in attributing the cause, which is essential for making decisions about continuing or discontinuing immunotherapy.

INTRODUCTION/BACKGROUND

Chylothorax refers to the presence of chyle in the pleural space leading to respiratory compromise. It is a rare condition associated with dysfunction or disruption of chyle flow through the thoracic duct. Causes are classified into traumatic and non-traumatic, with malignancy being a leading cause of non-traumatic chylothorax[1]. Most cases of malignant associated chylothoraxes occur in advanced malignancies with lymphomas accounting for around a quarter of chylothoraxes. Chylothorax secondary to gastric

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adenocarcinoma or immune checkpoint inhibitors, such as nivolumab, is exceedingly rare and has been documented only in isolated case reports[2].

Gastric adenocarcinoma is the fourth leading cause of cancer-related deaths worldwide, with the majority of newly discovered cases already in advanced, non-curable stages[3]. Gastric adenocarcinoma has a high propensity of metastatic spread including the lymphatic system, which could explain the development of chylothorax in selected patients[4]. The interplay however, between tumour biology and lymphatic disruption in patients with chylothorax, remains poorly understood.

Nivolumab, an anti-PD-1 immune checkpoint inhibitor, whether given with chemotherapy or other immune modulatory drugs, offers improved survival in gastric cancer patients and remains a viable therapeutic option[5]. Immune-related adverse events are well documented in nivolumab, with gastrointestinal, dermatologic, hepatic, endocrine and pulmonary toxicities predominating[6]. Pleural effusion is rarely reported with chylothorax and only mentioned in case reports. The exact mechanism by which nivolumab may induce chylothorax remains unclear, though immune-mediated increased lymphatic permeability induced by anti-PD-1 has been hypothesised[7]. This case highlights a unique presentation of chylothorax in a patient with gastric adenocarcinoma undergoing nivolumab therapy.

CASE DESCRIPTION

A 62-year-old female patient with no previous significant medical history, no known allergies and a family history positive for breast cancer in a first degree relative, presented to our oncology clinic on 25 June 2024 for chest wall pain of almost two-month duration. The patient reported that her pain was exacerbated by palpation and respiration. The patient also reported an 8 kg weight loss over six weeks. She consulted her physician who ordered a chest computed tomography (CT) scan.

Initial imaging on 8 May 2024 revealed multiple sclerotic lesions involving the left clavicle, sternum, ribs and vertebral bodies from T2 to T12, with a subsequent T12 minimal depression fracture.

A subsequent PET scan on 20 May 2024 demonstrated multiple hypermetabolic foci, including increased fluorodeoxyglucose (FDG) uptake in the left clavicle – maximum standardised uptake value (SUVmax) of 2.4, vertebral bodies (SUVmax 3.2–4.4), sternum (SUVmax 3.6), left iliac bone (SUVmax 3.7) and sacrum (SUVmax 4.4). A bone biopsy performed on 1 June 2024 confirmed metastatic carcinoma with positive staining for cytokeratin and in particular CK7, but markers TTF1, HER2, GATA3, ER, SOX10, CDX2, PAX8, CD56, CD34, CD31, CD99 and NKX2.2 were negative. A colonoscopy on 19 June 2024 was unremarkable, while a gastroscopy revealed a fundic ulcer. Biopsy of the ulcer confirmed a poorly differentiated adenocarcinoma in a background of chronic gastritis. The tumour was negative for CERB2 and PDL1.

Following the diagnosis of gastric adenocarcinoma, the patient was initiated on a chemotherapy regimen consisting of FOLFOX (oxaliplatin, leucovorin and folinic acid), and infusional 5-FU combined with nivolumab. A follow-up fluorodeoxyglucose positron emission tomography (FDG-PET) scan and magnetic resonance imaging (MRI) on 9 October 2024 after three treatment cycles showed complete remission; the patient completed a total of six cycles and remained in complete remission. She was therefore continued on single agent nivolumab as maintenance therapy.

However, after five treatment cycles, the patient presented on 20 December 2024 with worsening dyspnoea, which had become severely symptomatic by the time of admission. She also reported orthopnoea, a dry cough and vague abdominal pain, though she remained afebrile. At the time of this presentation, her medications included prednisone 10 mg daily, which had been initiated for presumed nivolumab-related fever, along with pantoprazole 20 mg daily, vitamin D 20,000 IU weekly, cobalamin 1,000 µg daily, epoetin alfa 40,000 IU subcutaneously weekly, and filgrastim 300 mg orally for five days per week.

A chest X-ray revealed bilateral pleural effusions. A chest CT scan confirmed moderate bilateral pleural effusions, which



Figure 1. A cut of chest CT scan showing mild to moderate right sided pleural effusion and moderate left sided effusion, left lower atelectatic changes noted.

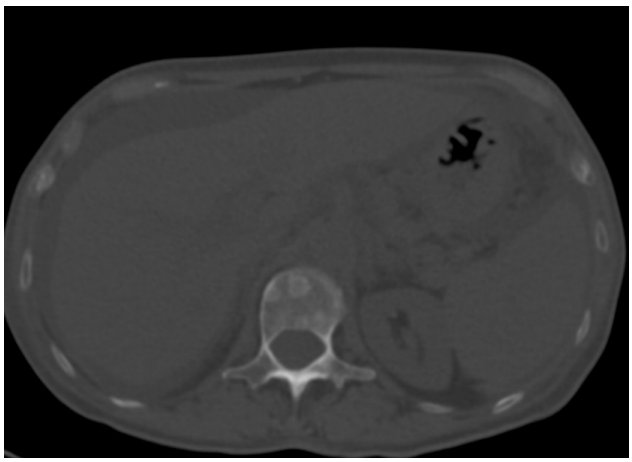


Figure 2. A cut from abdomen pelvic CT scan showing moderate abdominal and pelvic ascites.

were more pronounced on the right side, without significant mediastinal or hilar lymphadenopathy *(Fig. 1)*. The scan also showed diffuse sclerotic and lytic bone lesions (*Fig. 2*). A CT scan of the abdomen and pelvis was notable for moderate ascites *(Fig. 3)*. An echocardiogram was performed and was within normal limits. A diagnostic thoracentesis was subsequently performed, and the pleural fluid analysis was consistent with chylothorax *(Fig. 4)*. Triglycerides in fluid were 260 mg/dl, lipase 33 IU/l, amylase 59 IU/l, PH 8. Cytology was negative for malignant cells, and bacterial cultures were also negative. The patient was also placed on a low-fat diet.

A follow-up CT scan of the chest on 23 December 2024 showed a decrease in bilateral pleural effusions, with stable fissure and subpleural nodules. However, an FDG-PET scan revealed that although previously active sites of disease demonstrated decreased metabolic activity the pleural effusions persisted, and new omental thickening was observed, raising suspicion for peritoneal carcinomatosis. An MRI confirmed these findings, and a CT-guided biopsy of the omentum confirmed adenocarcinoma, consistent with disease progression. Given these findings, the patient was offered second-line chemotherapy with paclitaxel and ramucirumab.

DISCUSSION

This case highlights a rare presentation of chylothorax in a patient with gastric adenocarcinoma on nivolumab with no evidence of thoracic duct obstruction on imaging.

Taking into consideration the lack of thoracic duct obstruction, the occurrence of chylothorax in our patient might be multifactorial and a combination of malignant lymphatic spread, obstruction and dysfunction, and a nivolumab-induced immune adverse event. Gastric adenocarcinoma has a tendency for lymphatic spread, with nearly 15% of early gastric adenocarcinoma cases having lymphatic involvement[8]. Peritoneal carcinomatosis in our case indicates the presence of advanced disease where extensive lymphatic invasion is likely. The absence of malignant cells in pleural tap fluid cytology makes direct invasion of the pleura as a primary driver improbable. Instead, lymphatic congestion and increased permeability may be the leading cause behind chylothorax. In select patients when direct invasion of pleura is highly suspected and cytology results are negative for malignant cells, a pleural biopsy is warranted[9].

Another reasonable explanation is that chylothorax is a result of a nivolumab-induced immune-related adverse event. Nivolumab, a PD-1 inhibitor, is known to cause a wide range of immune-mediated toxicities affecting multiple organ systems, including the pulmonary and lymphatic systems. Increased lymphatic permeability due to an immune-mediated inflammatory response targeting the endothelial lining of lymphatic vessels is the potential mechanism of chylothorax in patients receiving PD-1 inhibitors. This hypothesis is further backed up by several case reports



Figure 3. A cut from abdominal scan, bone view showing diffuse sclerotic and lytic lesions of osseous elements clearly visible in vertebral bones.



Figure 4. Picture showing drained pleural fluid.

of capillary leak syndrome in patients treated with PD-1 inhibitors. In an earlier case report, nivolumab was associated with chylothorax in a patient with melanoma[10]. Other PD-1 inhibitors such as pembrolizumab also demonstrated similar adverse events[11,12].

Differentiating between nivolumab immune-mediated and malignancy-induced chylothorax remains a challenge. In our case, keeping in mind the advanced disease state and lymphatic involvement in similar cases, the absence of mediastinal lymphadenopathy, thoracic duct obstruction and negative pleural cytology argue against direct tumour compression and invasion of pleural carcinomatosis as potential causes for chylothorax. Thus, a nivolumab immune adverse-related event should be considered. According to the 1981 Naranjo Criteria, the chylothorax in this patient scores a 4 and is classified as a possible adverse drug reaction (ADR) related to nivolumab[13] *(Table 1)*.

CONCLUSION

Given the potential of an immune-related aetiology, it is important to consider nivolumab disconsolation or dosage modification in such cases. However, this decision must be weighed against the potential therapeutic benefit of nivolumab specially in patients who have evidence of

Naranjo question	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes	+1
2. Did the adverse event appear after the suspected drug was administered?	Yes	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	+1
4. Did the adverse reaction reappear when the drug was readministered?	Not applicable	0
5. Are there alternative causes that could have caused the reaction?	Yes	-1
6. Did the reaction reappear when a placebo was given?	Not applicable	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	No	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Not applicable	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No	0
10. Was the adverse event confirmed by any objective evidence?	Yes	+1
Total score	**4**	
ADR probability	**Possible**	

Table 1. Demonstrating Naranjo adverse reaction score (≥9 definite ADR, 5–8 probable ADR, 1–4 possible ADR, ≤0 doubtful ADR).

response. Chylothorax coupled with disease progression necessitated discontinuation of nivolumab and transition into second-line chemotherapy.

Other possible solutions can be considered. Corticosteroids use to manage a wide range of immune-mediated reactions may have a role in reducing lymphatic endothelial wall inflammation. However, data to support the usage of steroids in PD-1 inhibitor induced chylothorax is scarce. Other measures in chylothorax management remain relatively similar regardless of the aetiology, such as chylous effusion drainage and low-fat diets.

From a broader clinical perspective, this case highlights the need for increased awareness of potential new immune-related adverse events such as chylothorax in patients on nivolumab. As the use of immune checkpoint expands, clinicians should be vigilant to rare complications that do not fit the classical adverse events profile. With the presence of several case reports tying nivolumab and lymphatic disruption, future research is warranted to further clarify the mechanisms linking nivolumab in specific and other PD-1 inhibitors to lymphatic dysfunction.

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