APJAI
Asian Pacific Journal of
Allergy and Immunology

CASE REPORT

Nivolumab-induced diffuse type 2 rhinosinusitis: A case report

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Abstract

Background: Nivolumab, an immune checkpoint inhibitor is used to treat advanced metastatic malignancies. Data showed that nivolumab can cause exacerbated response of T-Helper 2 cells and lead to airway inflammation.

Objectives: To present the upper airway findings of a 69-year-old woman after treatment with nivolumab.

Methods: Case report

Results: A 69-year old woman with no history of chronic rhinosinusitis developed complaints of nasal congestion, rhinorrhea, sneezing, and anosmia. These symptoms started after one year of treatment with nivolumab. Pale polyps were observed on fiberoptic endoscopy examination. A gradual increase in eosinophil blood counts was noted. On histopathology, heavy infiltrates of eosinophils were seen in the tissue.

Conclusion: Nivolumab is used to treat various advanced metastatic malignancies, with a good safety profile. Nevertheless, physicians must be alert to the possibility of evolving type II inflammation in patients, as appropriate therapy can be provided to improve their quality of life.

Key words: Nivolumab, Immune check point inhibitor, Immune-related adverse event, Chronic rhinosinusitis, Programed cell death-ligand, Nasal polyps

Citation:
Kassem, F., Rosman, Y., Blau, I., Nageris, B., Zakharov, A., Biadsee, A. (2025). Nivolumab-induced diffuse type 2 rhinosinusitis: A case report. *Asian Pac J Allergy Immunol*, 43(1), 93-96. https://doi.org/10.12932/ap-240721-1196

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Introduction

Immune checkpoint inhibitors (ICI) are used as a targeted chemotherapy to reverse immune suppression and promote T cell activation. Nivolumab, an immunoglobulin G4 (IgG4) ICI antibody, is used to treat many cancers, including melanoma, lung, and renal cell carcinomas.[1] Immune-related adverse events are related to immune checkpoint inhibitor therapy. Many immune related adverse events (irAEs) are known and published; rash, pruritus, colitis, hepatitis, pancreatitis and pneumonitis.[2] These irAEs are more prevalent in patients receiving dual ICI therapy. In this case report, we present diffuse, type 2 eosinophilic rhinosinusitis as the sole irAE of nivolumab, in a patient with metastatic, non-small cell lung cancer.

Case report

A 69-year-old woman presented to our department with worsening nasal symptoms, including rhinorrhea, sneezing, nasal congestion and anosmia. She had no previous nasal complaints until one year prior to her admission, when nasal congestion began and gradually worsened. When the nasal symptoms began to severely impact her quality of life, she sought medical help.

Her previous medical history was significant for past smoking, ductal carcinoma in situ (DCIS) of the right breast in 1989 that was treated with surgery and radiation. Mammotomy was performed in 2012 due to recurrent DCIS. In 2011, she was diagnosed with stage I, non-small cell lung carcinoma, and underwent right lower lobe lobectomy. Due to metastasis to the lumbar spine (L1) in 2014, she was treated with radiation and started biological treatment with denosumab (XGEVA). In 2015, she was diagnosed with multiple lesions in both lungs and was treated with a combination chemotherapy protocol of carboplatin, pemetrexed (Alimta), and bevacizumab (AVASTIN). Chemotherapy was discontinued after 3 sessions due to severe weakness. Biological treatment with bevacizumab was continued for 3 years, until lung metastasis worsened and new lesions in the liver were seen on computed tomography (CT). As a result, a regimen of nivolumab (OPDIVO) was started in November 2017 (IV Nivolumab 165 mg*2/month). She has been on this regimen to date, with good clinical and radiological response.

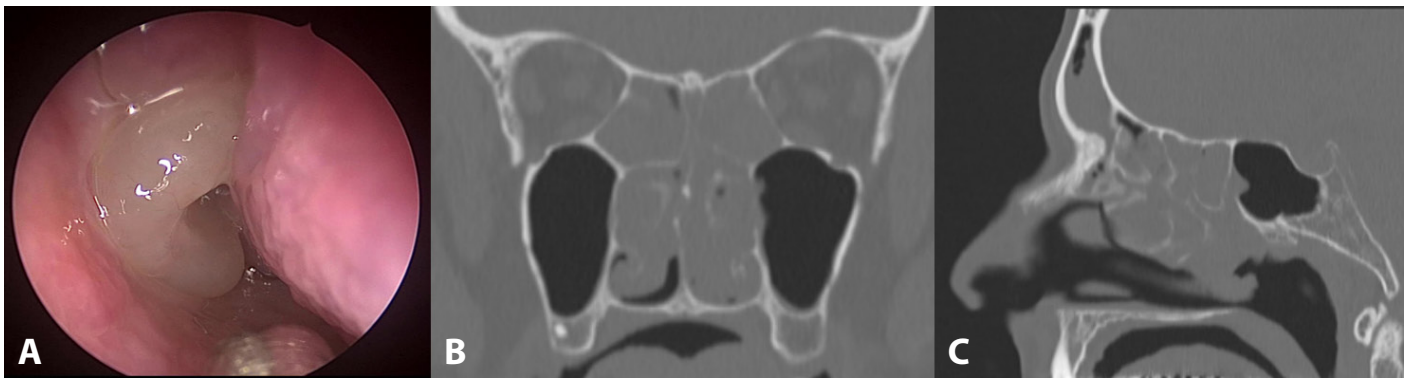

Figure 1.
A. Nasal polyp originating from the left middle meatus with watery discharge, pale edematous middle concha (view with 0° endoscope). B. Coronal computed tomography (thin slices 0.6 mm), C. Sagittal CT. CT Images show mucosal swelling in the anterior, posterior ethmoid cells and right frontal sinus. Lund Mackey score = 12.

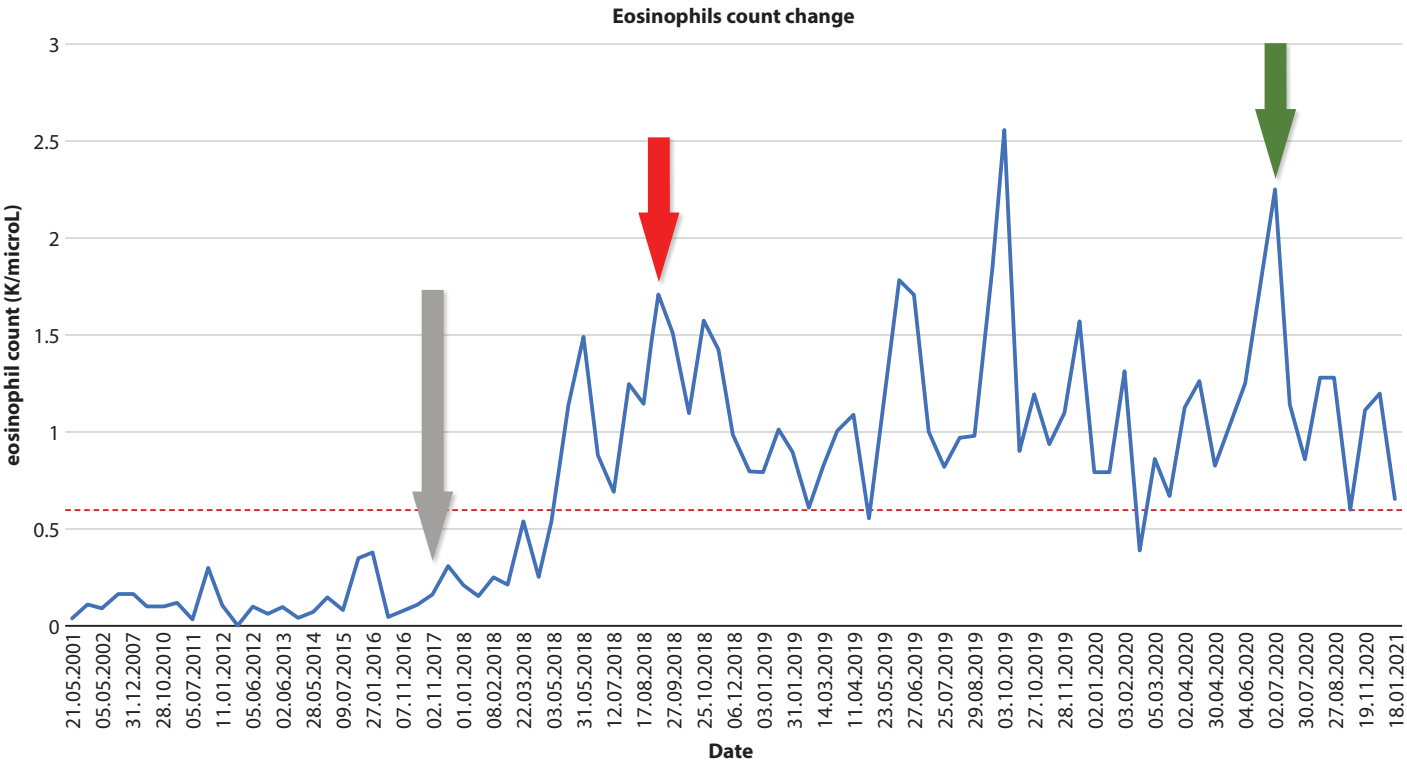

Figure 2. Eosinophil blood counts on a time scale; Y-axis: eosinophil blood count (K\µl), X-axis: time scale. Gray arrow indicates the start of nivolumab treatment (11/2017), red arrow indicates the onset of nasal symptoms, green arrow indicates the time of the first visit to our ENT clinic. Red dashed line is the upper limit of normal eosinophil blood count.

The patient presented to our rhinology clinic at Meir Medical Center in July 2020. Her nasal complaints had started at the end of 2018, about one year after starting Nivolumab. She was experiencing nasal congestion, rhinorrhea, post-nasal drip, facial pain, dysgeusia, anosmia and sneezing. She was treated with corticosteroid inhalers and antihistamines by her family physician, with no improvement. On fiberoptic laryngoscopy examination, pale polyps originating from the middle meatus were evident in both nostrils and the nasal mucosa appeared swollen, pale and congested. Enlargement of the middle concha with clear discharge was also evident (**Figure 1A**).

She scored 32/100 on a validated Hebrew version of the Sino-nasal outcome test (SNOT-22) and underwent CT of the para-nasal sinuses in July 2020. Bilateral mucosal thickening in the ethmoid air cells and in the right frontal sinus were seen, along with thickening and blockage of the osteo-meatal complex and large concha bullosa, bilaterally (**Figures 1B, 1C**).

According to the 2020 revised criteria for Rhinosinusitis and Nasal Polyps, the patient was diagnosed with diffuse bilateral chronic rhinosinusitis (CRS). She was advised to start saline nasal rinses with nasal corticosteroid spray. A short trial of systemic steroids was also suggested. However, she started nasal spray only, because her oncologist did not recommend a trial of oral systemic corticosteroids.

Skin prick tests for airborne allergens were negative. Blood tests were normal except for a gradual increase in the absolute eosinophilic count, peaking at 2.56 K/µl (N < 0.6; **Figure 2**). There were no infiltrates on chest X-ray and lung spirometry was normal, with no evidence of obstructive or restrictive lung disease.

She returned to our clinic after 2 months with worsening nasal symptoms and similar naso-endoscopic findings. Due to uncontrolled, diffuse bilateral CRS, she underwent functional endoscopic sinus surgery and septoplasty. During the surgery, bilateral antrostomy, ethmoidectomy and frontal sinusotomy were performed and large amounts of polypoid tissue and thick discharge were cleaned. Post-operative antibiotic treatment with amoxicillin/clavulanic acid (Augmentin) was administered after sinus cultures returned positive for *Proteus mirabilis* and *Enterobacter aerogenes*; both sensitive to amoxicillin. On pathology evaluation, nasal polyposis with heavy eosinophilic infiltrates in the lamina propria (up to 90/1HPF) were evident bilaterally.

At follow-up check-up one month after surgery, the patient reported major improvement of sino-nasal symptoms with a post-op SNOT-22 score of 7/110. On fiber optic endoscopy, bilateral, swollen mucosa with open sinuses and no discharge were noted.

Discussion

Nivolumab is the first, fully human IgG4 PD-1 (Programed cell death protein 1, also called CD279) ICI antibody. PD-1 receptor can be found on different types of lymphocytes, such as T lymphocytes, including CD4 and CD8, B lymphocytes and natural killer (NK) cells.

PD-1 interacts with 2 ligands: PD-L1 and PD-L2.[1] The interaction between PD-1 and PD-L1/2 downregulates T-cell function and the cellular immune response, and has a crucial role in physiological immune balance. Nonetheless, this axis can negatively regulate the immune response against tumors; thus, promoting tumor escape.[3]

Akbari et al.[4] showed that mice lacking PD-L2 or with blocked PD-L2, displayed increased airway inflammation, exacerbated TH2 response and elevated levels of interleukin-4 (IL-4). This suggests that inhibiting the PD-1-L1/2 axis with ICI, can revive the hypo-sensitive TH2 cells and facilitate Th2 inflammation. Several recent case reports supported this notion and demonstrated eosinophilic lower airway inflammation induced by ICI treatment.[5,6]

A case report by Dein et al,[7] reported 2 cases of rhinosinusitis following treatment with ICI. The first case consisted of recurrent acute rhinosinusitis without nasal polyposis and discharge while the second presented with acute facial pressure without nasal discharge and mucosal thickening in the maxillary sinus on imaging. Both cases were treated with Adalimumab, a monoclonal antibody that inactivates tumor necrosis factor alpha (TNFα). The resolution of rhinosinusitis after the inactivation of TNFα suggests a non-type 2 inflammation associated with neutrophilic inflammation and pro-inflammatory cytokines IL1β, IL-6, IL-8, interferon γ and TNFα.[8] This represents a different rhinosinusitis pathogenesis with a different endotype and phenotype. In summary, Dein et al. presented two case of acute rhinosinusitis that were of less than 12 weeks' duration, lacked clinical symptoms suggesting ongoing type II inflammation symptoms, pathology and histology. To our knowledge, no other evidence of sole eosinophilic upper airway disease due to ICI treatment has been published.

In this case report, we described a 69-year-old patient, who presented with new complaints, of upper airway symptoms and nasal polyposis, persisting for more than a year. On pathology, heavy eosinophilic infiltrates were found. This is compatible with primary diffuse type 2 CRS (eCRS), without lower airway symptoms during treatment with nivolumab.

Conclusion

Nivolumab is used to treat various advanced metastatic malignancies, with a good safety profile. Nevertheless, physicians should be alert to the possibility of evolving type II upper airway inflammation in these patients, as appropriate therapy can be provided to improve their quality of life.

Statement of Ethics

This case report was exempted from requiring ethics approval, by the Meir Medical Center Helsinki Committee.

Conflict of Interest Statement

The author declares that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability

The data that support the findings of this study are not publicly available, since they contain information that could compromise the privacy of research participants, but are available from Dr. Ameen Biadsee (Corresponding author) upon reasonable request.

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