Received: 25 July 2024 | Accepted: 4 September 2024

DOI: 10.1002/rcr2.70022

CASE SERIES

Respirology Case Reports | WILEY

Eosinophilic reactive airways disease after immune checkpoint inhibitor treatment

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Associate Editor: Lauren Troy

Abstract

Immune checkpoint inhibitors (ICI) are increasingly utilized as first-line treatment for many solid tumour malignancies. One downside of ICI therapy is autoimmune-mediated organ inflammation, or immune-related adverse events (irAE). ICI-related pneumonitis, or non-infectious inflammation of the lung, is a well-described irAE. While guidelines surrounding ICI-related pneumonitis are well established, other ICI-related pulmonary toxicities, including reactive airways disease, are rarely described in the literature. Here, we present a series of patients without pre-existing COPD or asthma who developed reactive airways disease with peripheral eosinophilia after ICI therapy and without radiographic evidence of pneumonitis. The patients were treated with typical therapies for reactive airways disease, including– inhaled steroids, bronchodilators, systemic steroids, and in one instance, dupilumab. All experienced symptomatic improvement with these therapies, enabling some of the patients to continue receiving ICI therapy.

KEYWORDS

dupilumab, eosinophilia, immune checkpoint inhibitor, immune-related adverse event, reactive airways disease

INTRODUCTION

Immune checkpoint inhibitors (ICI) have revolutionized cancer care and are increasingly used as first line treatment for a variety of solid tumour malignancies. Recent estimates indicate that more than 43% of patients with cancer are eligible for ICI treatment.[1–4] ICIs are antibodies designed to block interactions (PD-1 and CTLA-4 proteins on T-cells, PDL-1 proteins on tumour cells) that regulate the immune system, allowing T-cells to mount a more effective anticancer response. A consequence of increased immunologic activity following ICI treatment is autoimmune-mediated organ inflammation, termed immune-related adverse events (irAE).[5,6] ICI-related pneumonitis, or non-infectious inflammation of the lung, is a well-described complication of ICI treatment.[7] Depending on the extent of radiographic involvement, the severity of respiratory symptoms, and the degree of respiratory failure and need for oxygen supplementation, society guidelines recommend treating ICI-related pneumonitis with systemic corticosteroids and temporary or permanent discontinuation of ICIs.[8,9] While severity grading and management recommendations for parenchymal inflammation related to ICI therapy are well established, the approach to diagnosis and treatment for new-onset airways disease without parenchymal involvement following ICI is not clear. Furthermore, as the American Society of Clinical Oncology and Society for Immunotherapy of Cancer guidelines[8,9] do not comment on pulmonary-related irAE without parenchymal inflammation, guidance on ICI discontinuation or reintroduction and management of respiratory symptoms in these cases is unknown. To address this, we present the clinical course of a series of patients who developed eosinophilic reactive airways disease without parenchymal lung inflammation following ICI treatment.

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Methods

Data collection

We examined a series of patients who received at least one dose of ICI from 2022 to 2023 at The Ohio State University Wexner Medical Center. The study protocol was approved by the Ohio State Institutional Review Board (IRB number 2023C0198), and a waiver of informed consent was granted due to the retrospective nature of the study.

Attribution of ICI-reactive airways disease

Two hundred and four patients who received at least one dose of ICI from 2022 to 2023 were screened for potential inclusion in this case series. ICD-10 codes (J45.20, J45.21, J45.30, J45.31, J45.40, J45.41, J45.50, J45.901, J45.909, and J98.01) were utilized to identify patients with reactive airways disease that developed after ICI treatment. Patients were considered to have ICI-related eosinophilic reactive airways disease if they met all the following criteria:

1. New respiratory symptoms
2. No acute parenchymal abnormalities or lung inflammation on chest CT
3. No previous diagnosis of chronic obstructive pulmonary disease (COPD) or asthma
4. Peripheral eosinophilia following ICI initiation defined as absolute eosinophil count greater than or equal to 500 cells/μL and lack of pre-ICI eosinophilia
5. Obstruction on pulmonary function testing (PFTs) following ICI treatment
6. Exclusion of alternate diagnosis

We did not exclude asymptomatic patients with obstruction on PFTs before ICI therapy as asymptomatic physiologic obstruction is not considered diagnostic for asthma or COPD.[10,11]

Eosinophil count

Absolute peripheral blood eosinophil count was recorded preceding, during, and following ICI treatment. If there were multiple values, the maximal value was used in each scenario.

Imaging review

The lack of acute parenchymal abnormalities, lung inflammation, and emphysema were determined by the interpreting radiologist at the time of diagnosis and retrospectively confirmed by a member of the study team that was blinded to all other aspects of the patients' clinical history. All chest imaging up to 3 months following development of respiratory symptoms was reviewed.

Pulmonary function test review

Patients who had PFTs completed before ICI initiation and after development of ICI-reactive airways disease were recorded. Obstruction was defined by a ratio of forced expiratory volume in 1 s (FEV1) divided by forced vital capacity (FVC) less than 0.70 or FEV1 divided by slow vital capacity (SVC) of less than 0.70.

RESULTS

Six patients met our diagnostic criteria for eosinophilic reactive airways disease following ICI treatment. The patients ranged from age 28 to 76 (median 67), included 4 males and 2 females, were all former smokers, and had been diagnosed

TABLE 1 Patient demographics.

Patient	Age	Gender	Smoking status[a]	Primary malignancy	Type of ICI	Number of ICI[b] doses received
1	66	Male	Former smoker, quit >6 months before diagnosis	Oesophageal Adenocarcinoma	PD-1	14
2	76	Male	Former smoker, quit >6 months before diagnosis	Head and neck squamous cell carcinoma	PD-1	22
3	28	Female	Former smoker, quit >6 months before diagnosis	Appendiceal carcinoma	PD-1	22
4	67	Female	Former smoker, quit >6 months before diagnosis	Urothelial bladder carcinoma	PD-1	11
5	67	Male	Former smoker, quit >6 months before diagnosis	Lung adenocarcinoma	PD-1	23
6	75	Male	Former smoker, quit >6 months before diagnosis	Lung adenocarcinoma	PD-1	1

[a]Smoking status at time of reactive airways disease diagnosis.
[b]ICI, immune checkpoint inhibitor.

TABLE 2 Clinical course of patients with eosinophilic reactive airways disease following immune checkpoint inhibitor treatment.

Patient	Maximum eosinophil count prior to ICI[a]	Maximum eosinophil count (per uL) during ICI treatment	Maximum eosinophil count after ICI treatment	FEV1/FVC or FEV1/SVC before ICI treatment	FEV1/FVC or FEV1/SVC after ICI treatment	Reactive airways disease treatment	Clinical course
1	300	1190	N/A	N/A	0.69	ICS + LABA[b], systemic corticosteroids	Symptoms improved, no ICI treatment delay
2	130	500	110	0.74	0.66	ICS + LABA, SABA[c]	Symptoms improved, ICI discontinued
3	240	1680	750	N/A	0.65	ICS + LABA, SABA, systemic corticosteroids, dupilumab	Symptoms improved following dupilumab, ICI discontinued
4	140	1240	400	N/A	0.62	ICS + LABA, SABA, montelukast, systemic corticosteroids	Symptoms improved, no ICI treatment delay
5	250	1600	680	0.67	0.62	ICS + LABA, SABA	Symptoms improved, ICI treatment concluded prior to reactive airways disease treatment
6	260	N/A	970	0.69	0.60	ICS + LABA, SABA, systemic corticosteroids	Symptoms improved, ICI treatment concluded prior to reactive airways disease treatment

[a]ICI, immune checkpoint inhibitor.
[b]ICS + LABA, inhaled corticosteroid and long-acting beta agonist.
[c]Short-acting beta agonist.

with various primary solid tumours. All were treated with anti-PD-1 ICIs with a median of 18 doses (range 1–23). Patient characteristics are detailed in Table 1.

Each of the patients developed new peripheral eosinophilia following ICI treatment (median 1215 eosinophils/μL, range 500–1680 eosinophils/μL) with symptoms consistent with reactive airways disease: cough, shortness of breath, and dyspnea on exertion. None had parenchymal abnormalities or emphysema on chest imaging, and each had new or worsening airflow obstruction on PFTs. All patients were treated with inhaled corticosteroids, long-acting beta agonist inhalers, and as-needed short acting beta-agonist inhalers. Four patients received systemic steroids. All but one of the patients reported subjective improvement with these therapies, and two patients were able to continue receiving ICI therapy without any treatment delay. One patient had persistent reactive airways disease despite inhaler treatment, ICI discontinuation, and several courses of systemic steroids. This patient was eventually treated with dupilumab and had a complete resolution of respiratory symptoms. Individual treatment outcomes are outlined in Table 2.

DISCUSSION

Eosinophilic obstructive lung disease can be a significant source of patient morbidity, leading to treatment interruptions and premature and permanent discontinuation of ICI treatment. In a similar case series, Scanvion et al identified 37 patients who developed eosinophilia following ICI treatment, with over half developing symptoms related to elevated eosinophil count.[12] As ICIs are increasingly being incorporated into the multimodal approach to cancer treatment, close monitoring of absolute eosinophil count and recognition of eosinophilic obstructive lung disease as an irAE following ICI treatment is crucial as prompt treatment may prevent premature ICI discontinuation or enable the reintroduction of ICI treatment.

There are several reasons why ICIs can induce eosinophilic reactive airways disease. ICIs can induce eosinophilia, and through a similar pathway may provoke Th2-mediated reactive airways disease.[12] Additionally, PD-1 agonism ameliorates airways hyperreactivity and blocking the PD-1 pathway could lead to increased bronchospasm and increased airways resistance.[13]

In cases of refractory eosinophilic reactive airways disease where ICI discontinuation is necessary and symptoms persist despite optimized inhaler regimens and systemic steroid administration, further therapies may be indicated. Dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha, inhibiting IL-4 and IL-13 signalling, which are crucial cytokines in the Th-2 mediated pathway responsible for eosinophilic asthma. While dupilumab use in eosinophilic and steroid-dependent asthma is well established, use in irAE following ICI is rare. Outside of use for ICI-related bullous pemphigoid,[14] there are no other reports of dupilumab use for irAE. In our patient, dupilumab was added because of persistent symptoms despite maximal

inhaler treatment and multiple courses of systemic steroids. On this therapy, the patient experienced resolution of respiratory symptoms, required no further courses of systemic steroids, and had marked improvement in peripheral eosinophilia, suggesting eosinophilic reactive airways disease following ICI treatment may be a Th-2 mediated process. By the time dupilumab was initiated for this patient, ICI therapy had been discontinued. Further study will be needed to assess whether dupilumab could be used concomitantly with ICI to manage eosinophilic reactive airways disease and allow for continued cancer-directed therapy.

In conclusion, we show six cases of eosinophilic obstructive lung disease following ICI treatment in patients with no prior history of pulmonary co-morbidities. Further study of this potential iRAE, need for ICI discontinuation, and the role of targeted biologic treatment for severe cases is needed.

AUTHOR CONTRIBUTIONS

Parker Cordial: Conceptualization; data curation; writing – original draft. **Ian Bentley**: Methodology; writing – original draft. **Jeffrey Horowitz**: Critical review; writing- final draft. **Kevin Ho**: Conceptualization; data curation; methodology; writing- original draft.

FUNDING INFORMATION

The authors declare no funding was utilized for this research.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

Data will be made available upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the Ohio State Institutional Review Board (IRB number 2023C0198), and a waiver of informed consent was granted due to the retrospective nature of the study.

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How to cite this article: Cordial P, Bentley ID, Horowitz JC, Ho K. Eosinophilic reactive airways disease after immune checkpoint inhibitor treatment. Respirology Case Reports. 2024;12(9):e70022. https://doi.org/10.1002/rcr2.70022