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Case Report

Sarcoidosis and Airway Disease After Immune Checkpoint Inhibitor Therapy: Case Study and Review of the Literature

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ABSTRACT

Pulmonary toxicity from immune checkpoint inhibitor therapy is typically a severe and potentially fatal complication, but these observations are driven by the most common toxicity, pneumonitis. Rarer pulmonary immune related adverse events, like airway disease and sarcoidosis, may have a more benign course. In this case report, we present a patient in whom therapy with the PD-1 inhibitor pembrolizumab resulted in severe eosinophilic asthma and sarcoidosis. This is the first case showing that anti–IL-5 inhibition may be safe in patients who develop eosinophilic asthma after ICI therapy. We further show that sarcoidosis does not necessarily require treatment cessation. This case highlights relevant nuances when clinicians face pulmonary toxicities other than pneumonitis.

Keywords: immune checkpoint inhibitor, sarcoidosis, severe asthma, eosinophilia

INTRODUCTION

Pulmonary immune-related adverse events (irAEs) account for the largest burden of treatment-related mortality among patients undergoing immune checkpoint inhibitor (ICI) therapy.[1] The most commonly described pulmonary irAE is pneumonitis, which is characterized by inflammation of the lung parenchyma[1]; however, other pulmonary irAEs, such as ICI-induced sarcoidosis and bronchiolitis, have been described in the literature[2–11] but are not as well studied. It is important to distinguish these atypical pulmonary irAEs from pneumonitis because they do not necessarily present a need to interrupt or discontinue ICI therapies. Here, we present a case of ICI-induced sarcoidosis and an eosinophilic exacerbation of asthma in a single patient with nasopharyngeal carcinoma who was able to continue ICI therapies despite these irAEs. The patient consented to publication of this case.

CASE DESCRIPTION

A 55-year-old man was referred to the pulmonary medicine department presenting with fatigue, dry cough, slight shortness of breath, and wheezing. More than a decade before the current presentation, he was diagnosed overseas with episodic bronchitis. This was attributed to airborne dust, and he intermittently used inhaled budesonide/formoterol to treat these episodes but had never been diagnosed with asthma. Seven years before presentation, the patient had three surgeries for chronic rhinosinusitis. One year before the current presentation, the patient was seen at our institution after he developed nasopharyngeal carcinoma and underwent five cycles of cisplatin and docetaxel administered every 3 weeks, with a complete response on positron emission tomography (PET)

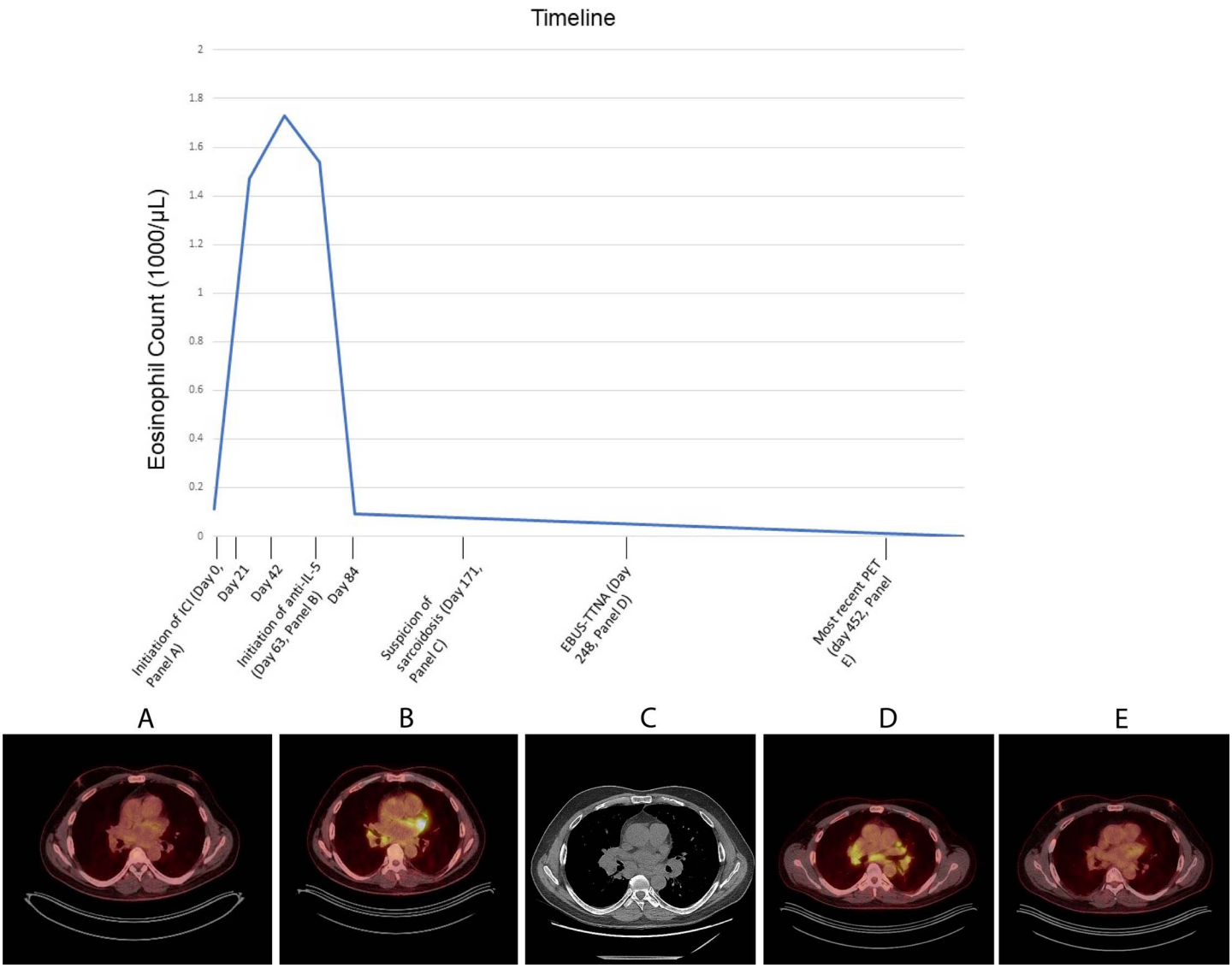

Figure 1. The top panel shows absolute eosinophil counts over time. Day 0 represents the initiation of pembrolizumab; on day 63, anti–IL-5 therapy was started, and subsequently the eosinophil count remained undetectable to day 452. The bottom panels (A–E) show key representative images. (A) PET-CT images of the mediastinum and lung hila before ICI therapy. (B) New FDG avidity on PET-CT in hilar lymph nodes 63 days after ICI initiation. (C) Standard non-contrast CT assessment of new hilar and mediastinal lymphadenopathy seen 171 days after ICI initiation. (D) Increasing FDG avidity on PET-CT assessment of the mediastinum and lung hila 248 days after ICI initiation. (E) Resolution of PET-CT FDG avidity without anti-inflammatory therapy 452 days after ICI initiation. CT: computed tomography; EBUS-TTNA: endobronchial ultrasound with transthoracic lymph node aspiration; FDG: F-fluorodeoxyglucose; ICI: immune checkpoint inhibitor; IL-5: interleukin-5; PET: positron emission tomography.

imaging. However, shortly before the current presentation, he developed metastatic disease in the neck lymph nodes, the iliac bone, and the left C1 transverse process (stage IVB, cT4, cN3, pM1). The patient was then initiated on maintenance monthly pembrolizumab and carboplatin. At the time of start of the ICI therapy, 2% of the patient's white blood cells were eosinophils, and his absolute eosinophil count was 0.11.

Interestingly, by the time of the second infusion, the percentage of eosinophils had risen to 23% of all white blood cells, and his absolute eosinophil count rose to 1.47 (Fig. 1). After three cycles of pembrolizumab, the patient began to complain about increased shortness of breath and cough. This cough was severe, kept him awake at night, and was unrelenting. He was started on budesonide with formoterol without any relief. On presentation to our department, laboratory results showed that 24% of his white blood cells were eosinophils and the absolute eosinophil count was 1.73. PET–computed tomography showed F-fluorodeoxyglucose (FDG)-avid nodes in the left cervical chain (maximum standardized uptake value [SUVmax], 2.6), paratracheal region (SUVmax, 3.5), and bilateral hila (SUVmax, 3.5). Pulmonary function tests revealed an obstructive pattern and air trapping; the forced expira-

tory volume in 1 second was 67% of predicted values, and the residual volume to total lung capacity (RV/TLC) ratio was 144%. At this point, the patient was felt to have a good response to immunotherapy, but his eosinophil percentage remained at 19%, with an absolute count of 1.54, after the fourth infusion (Figure 1). Laboratory results for unusual cases of eosinophilia, including antineutrophil cytoplasmic antibody levels and strongyloides titers, came back negative; however, the immunoglobulin (Ig)E level was elevated at 821 IU/mL.

Given the need for a longer course of pembrolizumab due to his favorable response but ultimately incurable disease, the patient elected to initiate therapy with interleukin (IL)-5 inhibitors.[12] A single dose of benralizumab (30 mg/mL) was administered. Impressively, within 5 days, laboratory results came back showing that the eosinophils had dropped to 1.5%, with an absolute eosinophil count of 0.09 (Fig. 1). In parallel, the patient had a total resolution of his severe bronchitis. The patient continued on both pembrolizumab and benralizumab therapies, and his eosinophil count remained at 0. However, the patient had progressive lymphadenopathy, raising a question as to whether he was developing progression of his cancer. In addition, he was noted to have increasing sclerotic areas in bony metastases of the vertebrae. He also began to report a new cough, although far less severe than the original presentation and not interfering with his quality of life. This occurred in the absence of fever, shortness of breath, chest pain, or wheezing.

To evaluate for progression of metastatic disease, interventional pulmonary performed endobronchial ultrasound with transthoracic lymph node aspiration (EBUS-TTNA) of the mediastinal and hilar lymph nodes. The 4R lymph node measured 10 mm, irregular, hypoechoic, and heterogeneous, and the 7 (subcarinal) node measured 13 mm and was hypoechoic, heterogeneous, but with well-defined margins (Fig. 2). Histopathology for both nodes showed no evidence of cancer, but nonnecrotizing epithelioid granulomas and lymphoid tissue were present. Fungal and bacterial culture grew *Aspergillus fumigatus* and *Paecilomyces*, methicillin-resistant *Staphylococcus aureus*, moderate *Hemophilus parainfluenzae,* and *Hemophilus parahaemolyticus*. Other tests for lower respiratory infection were negative. The patient was treated with doxycycline and levofloxacin for bacterial tracheobronchitis and began a 4-week course of voriconazole. Infectious disease consultants felt that the suspicion for active invasive fungal disease was low, and that the *Paecilomyces* were a contaminant. The patient did not undergo a formal evaluation of immune function, so an underlying immunodeficiency syndrome could not be ruled out.

A week before his 10th infusion, the patient presented an atypical cutaneous eruption in the left elbow. Skin biopsy reported granulomatous dermatitis, predominantly involving superficial and mid-reticular dermis; the differential included a sarcoidlike reaction to pem-

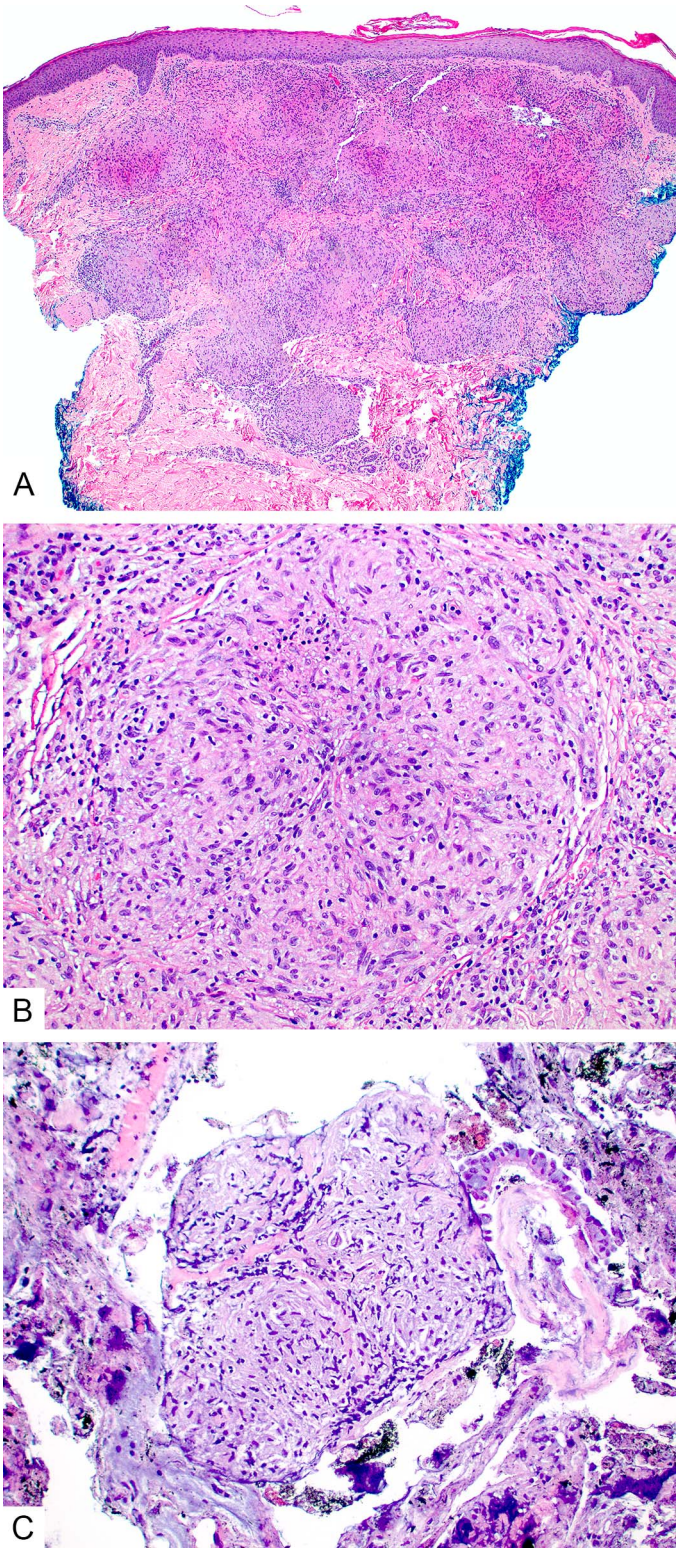

Figure 2. Representative histopathologic images show granulomatous inflammation involving skin and hilar lymph nodes. (A and B) Skin biopsy from left elbow shows clusters of epithelioid granulomata in dermis. Hematoxylin-eosin, original magnification A, ×40; B: ×200. (C) Hilar lymph nodes, transbronchial fine needle aspiration cytology shows granuloma in a background of lymphohistiocytic infiltrate with anthracotic pigment and small fragment of bronchial epithelium (right). Hematoxylin-eosin, original magnification ×200.

brolizumab (Fig. 2A, B). Despite the absence of cancer in the prior EBUS-TTNA evaluation, he continued to have progressive lymphadenopathy and the treating clinicians were concerned that the prior negative result for malignancy was a false negative. A second EBUS-TTNA was performed, and histopathology from the sub carinal (12 mm, level 7), right superior interlobar (7 mm, level 11Rs), and left interlobar (9 mm, level 11L) nodes showed benign-appearing lymphoid tissue, with non-caseating granulomas. The patient continued on pembrolizumab therapy with further treatment with carboplatin given his bony disease, and he continues to do well. His cough eventually resolved without further intervention.

DISCUSSION

Pneumonitis is a common and potentially deadly adverse event of using ICIs.[1,13] Despite the theoretical implications of immune checkpoint blockade on airway inflammation, there has been little scant evidence that ICIs exacerbate airway disease[14] For example, in one study of 73 patients with non–small cell lung cancer treated with ICI therapies, there was no increase in chronic obstructive pulmonary disease (COPD) severity or exacerbations among patients with COPD. COPD was also associated with longer progression-free intervals when compared with those without COPD.[15] However, there have been case reports of both severe bronchiolitis[16–18] and COPD exacerbations[19] in association with ICI treatment. The diagnosis of airway exacerbations is made difficult by the commonality of certain symptoms, like dyspnea and cough, with the primary cancer.

Eosinophilia is common in ICI therapy, and transiently occurs in about a third of patients.[20] Although uncommon, severe or persistent eosinophilia can result in adverse events. A French pharmacovigilance database of approximately 1500 patients treated with ICIs identified 37 cases of severe eosinophilia, of which two developed eosinophilic bronchitis. There have also been cases of eosinophilic asthma exacerbation after ICI therapy[9-11] ICI-induced airway disease can occur without eosinophilia; in one case that was considered to be ICI-induced asthma, a patient had fatal respiratory failure due to noneosinophilic inflammation of the airway, characterized by CD8+ lymphocytic expansion and infiltration[8] Whether this episode is distinct from prior case reports of ICI-induced bronchiolitis is unclear.[16–18]

Although eosinophilia after ICI therapies is recognized, its relevance to tumor response is not. The mechanism of action of ICI is thought to primarily rely on T helper (Th) 1 and Th17 immunity, as opposed to type 2 inflammation, which is characterized by atopic inflammation and eosinophilia. In patients with melanoma, eosinophilia after ICI therapy is associated with better survival[20] Eosinophils release molecules that may have antitumor activity, including tumor necrosis factor-α, granzymes, cationic proteins, and IL-18[21] On the other hand, type 2 responses have been associated with tumor progression in certain cancers like lymphomas and cervical cancer[22] This has been attributed to molecules that may facilitate tumor growth, such as vascular endothelial growth factor-A,[21] or due to the opposition of IL-2 and interferon (IFN)-γ.[22] A third possibility is that eosinophils are just bystanders in the immune response to cancer. This has been described in nasopharyngeal cancer, in which eosinophils do not modify survival[23] Therefore, given the lack of clear evidence that benralizumab would cause cancer progression in combination with his debilitating symptoms, we chose to initiate anti–IL-5 therapy. However, despite the success of anti–IL-5 therapy in this case, certain questions remain unanswered. For example, it is not clear whether drug-drug interactions exist between pembrolizumab and benralizumab. Furthermore, benralizumab withdrawal usually results in a recurrence of eosinophilic airway inflammation,[24] but it is unclear whether airway eosinophilia will recur if both ICI therapy and benralizumab are stopped. Finally, we cannot definitively ascertain whether the anti–IL-5 therapy is impairing the efficacy of pembrolizumab.

Sarcoidosis is a disease that causes nonnecrotizing granulomatous inflammation in the skin and lungs and in other organs[25] ICI-induced sarcoidosis is a rare irAE, with only approximately 100 reported cases in the literature,[26] and although more severe inflammation has been reported, many patients may be asymptomatic. Because of the varied manifestations, sarcoidosis has been referred to as the "great imitator."[27] Although early studies suggested that Th17 cells were the drivers of disease in patients with sarcoidosis,[28] more recent data suggest that sarcoidosis is caused by type 1 polarization of Th17 cells, or Th17.1 cells.[29] Th17.1 cells have similar lineage markers to Th17 cells, but produce IFN-γ. Th 17.1 cells have a high expression of programmed cell death protein (PD) 1 to recruit B cells leading to an adaptive humoral response. However, recent data suggest that T follicular helper cells may have a significant role in the pathogenesis of sarcoidosis, and paradoxically, increased PD-1 expression in these cells is a marker of activity, and not exhaustion[30] How ICI blockade differentially effects these two distinct T-cell subsets to rarely lead to sarcoidlike disease is unclear, but it is likely that the effects are in opposition. Th17 inflammation may be beneficial[31] or deleterious[32] to tumor response depending on cancer type. The presence of Th17.1 cells before ICI therapy has been associated with a high rate of sarcoidosis in patients with melanoma.[33] Furthermore, anti–PD-1 therapy has been shown to result in the clonal expansion of Th17.1 cells[34] Therefore, it is possible that ICI therapy may lead to the preconditions necessary to induce sarcoidlike reactions. It is also possible that the granulomatous inflammation of sarcoidosis (involving the mammalian target of rapamycin pathway in immune cells, Th17 polarization and T regulatory cell dysfunc-

Table 1. Case reports on eosinophilic airway disease after ICIs

Article	ICIs	Type of Eosinophilic Disease	Treatment	Discontinuation and Rechallenge
Wang et al, 2021[2]	Toripalimab	Asthma exacerbation	Ventilatory support, systemic steroids	Discontinued but then rechallenged with no further complications
Hamada et al, 2022[3]	Pembrolizumab	Asthma de novo	Inhaled and systemic steroids, LABA, SABA, LTRA	Unclear how ICI was handled
Sumi et al, 2021[4]	Atezolizumab	Asthma exacerbation	Inhaled and systemic steroids, LABA, SABA, LTRA , anti– IL-5	Discontinued but then rechallenged with no further complications
	Durvalumab	Asthma exacerbation	Inhaled and systemic steroids, LABA, LAMA, LTRA, anti– IL-5	Discontinued but then rechallenged with no further complications
Rembalski and Steinberg[5]	Nivolumab	Asthma exacerbation	Anti–IL-5	Discontinued but then rechallenged with no further complications
Kissoonsingh et al[6]	Pembrolizumab	Asthma de novo	Inhaled and systemic steroids, LABA	Unclear how ICI was handled
Domblides et al[7]	Durvalumab	Bronchiolitis	Systemic steroids, LABA	Discontinued permanently with no further complications
Ogawa et al[8]	Pembrolizumab	Asthma exacerbation	Inhaled and systemic steroids, LABA, SABA, LTRA	Died
Uemura et al[9]	Durvalumab	Asthma de novo	Inhaled steroids, LABA	Discontinued but then rechallenged with no further complications
	Durvalumab	Asthma de novo	Inhaled steroids, LABA	Discontinued but then rechallenged with no further complications
Marcus et al[10]	Pembrolizumab	Asthma exacerbation	Ventilatory support, inhaled and systemic steroids	Discontinued permanently, asthma remains poorly controlled
Maeno et al[11]	Nivolumab	Asthma de novo	Inhaled steroids, LABA	Discontinued but then rechallenged with no further complications

ICI: immune checkpoint inhibitor; IL-5: interleukin-5; LABA: long-acting β agonists; LAMA: long-acting muscarinic antagonist; LTRA: anti-leukotriene inhibitors; SABA: short-acting β agonists.

tion), has benefits for ICI effectiveness. In a series of 18 patients with melanoma receiving either anti–PD-1 or cytotoxic T lymphocyte antigen (CTLA-4) alone or in combination, as well as 67 case report reviews, patients had an objective response rate of more than 65%.[35] This is higher than the 11% to 15% of anti–CTLA-4 alone, the 43% of anti–PD-1 alone, or the 58% of the combination.[36–38]

ICI-induced sarcoidosis does not necessarily pose an imminent danger to patients, unlike pneumonitis. In a series of 32 patients, mostly with melanoma, patients generally had a mild presentation, systemic immunosuppression was rarely required, and some patients resumed ICI therapies.[39] In another series of 28 patients with ICI sarcoidosis, sarcoidosis was more commonly associated with melanoma as a primary cancer and with combined PD-1 and CTLA-4 inhibitions. Parenchymal fibrosis was seen in only one patient, and sarcoidosis was associated with improved survival compared with other irAEs. Sarcoidosis can often mimic disease progression,[40] as in our case, so a histologic diagnosis is imperative because of the radically different prognoses associated with these two disparate conditions. Importantly, unlike pneumonitis, a diagnosis of sarcoidosis may not require ICI cessation or interruption. Prospective data are needed to determine the safety of ICI continuation after a diagnosis of ICI-induced sarcoidosis.

In summary, we present a novel case of a patient who developed two rare non-pneumonitis irAEs after ICI therapy. We show for the first time that anti–IL-5 inhibition may be safe in patients who develop eosinophilic asthma after ICI therapy. Further, we show subsequent ICI-induced sarcoidosis that presented in a similar fashion to cancer progression. Oncologists and pulmonologists should be aware of these atypical pulmonary irAEs, and further prospective studies are necessary to better understand risk factors, prognoses, treatments, and the impact of these irAEs on cancer progression and survival. See Table 1 for related case reports.

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