

Nivolumab-associated Nasal Polyposis and Eosinophilic Asthma Responsive to Benralizumab, An Anti-IL5R Biologic

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Summary: We present a case report of nivolumab-aggravated treatment-resistant chronic rhinosinusitis with nasal polyposis with asthma, suggestive of aspirin-exacerbated respiratory disease, normalized with the IL-5R antagonist benralizumab. For patients experiencing symptomatic complications of immunotherapy-associated eosinophilia, this case suggests anti-IL-5(R) biologics may durably resolve nasal polyposis and asthma symptoms, permitting continuity of checkpoint inhibitor therapy and sparing of systemic corticosteroids. Postulated mechanisms of checkpoint inhibition favoring eosinophilia and polyposis, and the uncertain effect of eosinophil reduction upon malignancy progression, are reviewed.

Key Words: benralizumab, eosinophilia, nivolumab, nasal polyposis, asthma, aspirin exacerbated respiratory disease, checkpoint inhibitor

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BACKGROUND

Immune checkpoint inhibitor therapeutics, most targeting programmed death T-cell co-stimulatory signaling, have improved outcomes for multiple malignancies through disinhibition of antitumor T-cell tolerance or exhaustion. Adverse checkpoint inhibitor side-effects, termed immune-related adverse effects (irAE), are relatively common (74% of treated patients), broad in nature and qualitatively different than those from cytotoxic therapies.¹ As checkpoint inhibitors risk reactivation of latent or exhausted antigen-specific T cells, autoimmune complications such as hypo/hyperthyroidism, pneumonitis, and colitis have been reported.¹

Eosinophilic irAE have been reported. Incident treatment-related isolated eosinophilia with PD-(L)1 inhibitors were observed in 2.8% of treated patients after a median of

3 months, with a median absolute eosinophil count (AEC) of 1000/ μ L (range 600–5600/ μ L).² The etiology often is unclear; ACTH deficiency was the suspected cause in most lung adenocarcinoma patients on anti PD-1 therapy.³ Causal association remains unproven; however, a single case report found a pattern of recurring and remitting eosinophilia linked with nivolumab cycles.⁴

A granulocyte with innate immune function, eosinophils are activated through pattern recognition motifs to release preformed and rapidly synthesized mediators, such as prostaglandins, leukotrienes, reactive oxygen species – inducing peroxidases, connective tissue matrix remodeling enzymes, and multiple cytotoxic cationic proteins. These mediators induce injury to parasitic and helminthic targets beneficial to a host, yet risk collateral injury to host tissues.⁵

Hypereosinophilia is often associated with widely variable end-organ injury and clinical presentations. In large studies of irAE from checkpoint inhibitors, systemic hypereosinophilic complications are rare. In contrast, single case reports have described severe organ-restricted eosinophilic injury and rare systemic disease. Single case reports of symptomatic anti-PD-1 eosinophilia include a diffuse eczematous dermatitis; DRESS syndrome, and atypical cerebritis and obstructive lung disease.^{6–10} Eosinophilic obstructive lung disease without nasal polyposis has been reported in case reports.^{9,10} There have been rare cases of sinusitis induced by checkpoint inhibition: 2 cases of eosinophilic granulomatosis with polyangiitis (EGPA)-like polyp-free sinusitis with colitis and arthritis, responsive to adalimumab.¹¹ Otherwise, there has been only 1 reported case of eosinophilic asthma with chronic rhinosinusitis with nasal polyposis (CRSwNP), controlled with inhaled and nasal steroids.¹²

CASE REPORT

The patient is a 71-year-old male retired contractor and Vietnam War veteran, with a past medical history of osteoarthritis, gout, benign prostatic hypertrophy, hypertension, seizure, shellfish and venom allergies, a 10 pack-year smoking history, allergic rhinitis, and a 25-year history of low-risk and impairment mild persistent asthma. Asthma had been well controlled per EPR3 criteria on montelukast 10 mg daily and budesonide/formoterol 160/4.5 mcg 2 puffs inhaled twice daily. Patient had 1 lifetime course of corticosteroid and no prior hospitalizations for asthma exacerbations. Patient denied prior nonsteroidal anti-inflammatory drug (NSAID) allergy, neither a prior history of pneumonia nor chronic sinusitis.

The patient was initially evaluated for a new onset treatment-resistant cough 3 years prior. A fiberoptic rhinolaryngoscopy performed at an academic otorhinolaryngology clinic was unremarkable, however, was immediately followed by new hemoptysis and acute hoarseness. Another laryngoscopy, performed at the same clinic just 2 weeks after the first, identified a new large benign

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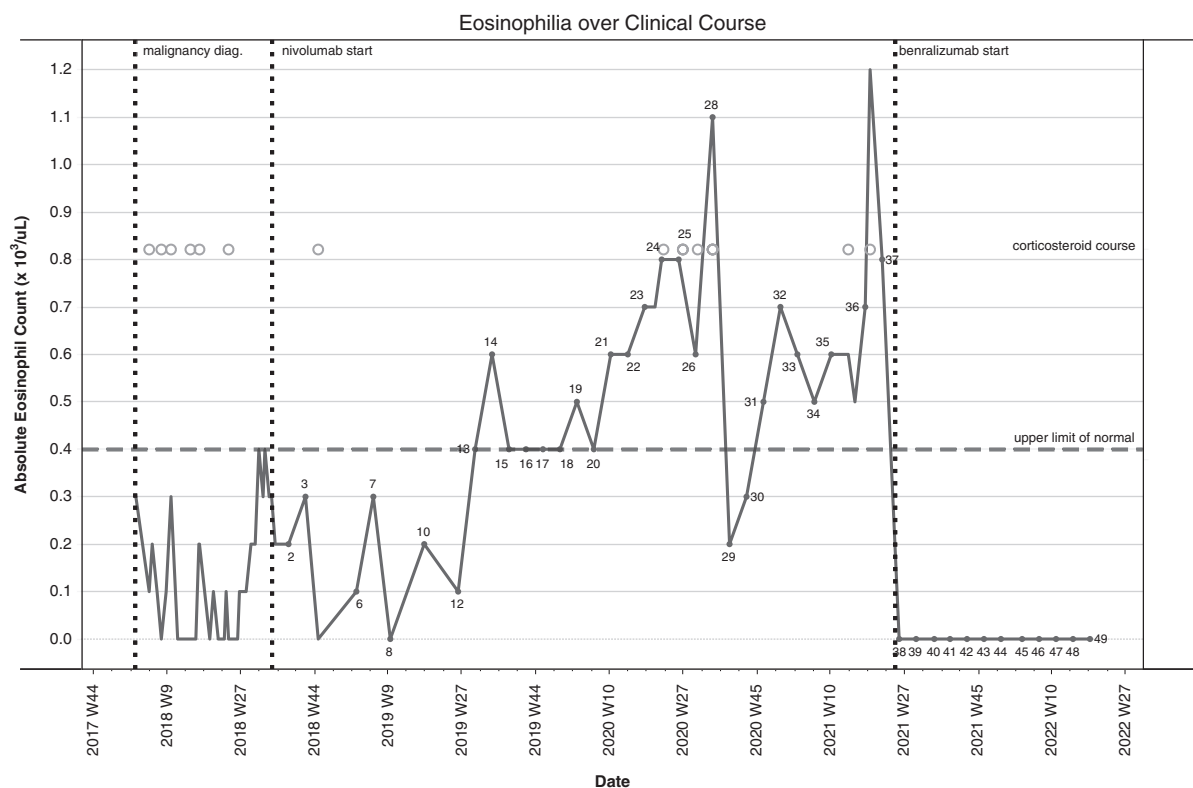


FIGURE 1. Absolute eosinophil count over time (year and week number). Nivolumab treatment cycles numbered. Pertinent clinical events are highlighted including prescribed systemic corticosteroid courses (circles).

appearing polyp in the left posterior nasal cavity and a paralyzed right true vocal cord. Subsequent bronchoscopy, positron emission tomography (PET)/CT and biopsy ultimately identified a metabolically active 5.3 cm dia. matted right paratracheal mass biopsy consistent with lung adenocarcinoma, stage IIIB.

Patient completed a chemoradiation course consisting of 60Gy XRT in 30 fractions targeting the mediastinum, cisplatin 75 mg/m² and pemetrexed 500 mg/m² every 3 weeks for 3 cycles, followed by pemetrexed consolidation every 3 weeks for 4 cycles. Computed tomography (CT) chest found mild focal radiation changes without fibrotic progression.

After consolidation chemotherapy, new abdominal pain led to identification of necrotic mesenteric lymph nodes, suggestive of metastatic disease. Given a TPS of 30, adjuvant nivolumab (anti-PD-1) monotherapy was initiated at 480 mg IV monthly. The abdominal disease resolved radiographically after the first 2 cycles of nivolumab. Subsequent tonic-clonic seizures led to the identification of ring-enhancing brain metastases, the largest 1.7×1.5 cm in diameter. Patient received levacetiriam and dexamethasone, 4 cycles of adjuvant cisplatin/pemetrexed, and underwent 3 stereotactic brain XRT procedures. Patient had near complete resolution of new brain metastases after this treatment.

The patient had no oncologic progression through cycle 20, however, developed new dyspnea, anosmia with concomitant bifrontal sinus pressure and obligate mouth breathing, and peripheral eosinophilia (Fig. 1). For presumed community-acquired pneumonia and acute sinusitis, he was treated with azithromycin then amoxicillin/clavulanate without benefit. CT chest noncontrast demonstrated nonspecific mild bronchial mucus plugging and wall thickening, inconsistent with immunotherapy-associated pneumonitis.

Upon the 24th cycle of nivolumab, acute dyspnea and cough were aggravated for the next 3 days postinfusion prompting outpatient evaluation. Audible wheezing was observed, and patient was treated with a 5-day course of oral prednisone with marked subjective improvement. Patient again noted recurrence days after his

25th cycle of nivolumab, prompting treatment with amoxicillin/clavulanate, prednisone and fluticasone nasal, again with subjective resolution of symptoms. Eight days after cycle 26 of nivolumab, he reported same recurrence prompting treatment with an oral prednisone. Upon the 27th nivolumab cycle, recurrent acute dyspnea with cough prompted an inpatient admission for diagnostic evaluation.

Pertinent findings included an AEC of 1200 cells/μL, normal AM cortisol, IgE 182 IU/mL, and sIgE panel positive to dog and cat dander. Spirometry demonstrated a severe obstructive and restrictive pattern; however, normal lung volumes excluded restriction. CT chest identified no etiologic cause and no oncologic progression. Serial CT and magnetic resonance (MR) brain studies demonstrated progression of existing ethmoidal disease, with frequent coinvolvement of other sinuses and a prominent R posterior nasal cavity polyp (Fig. 2A–E; Supplemental Figure 1a–h, Supplemental Digital Content 1, <http://links.lww.com/JIT/A679>).

Differential diagnosis included checkpoint inhibitor-induced pneumonitis, EGPA, lymphocytic or myeloid hypereosinophilic syndrome, eosinophilic pneumonia, and aspirin-exacerbated respiratory disease (AERD). Pneumonitis was radiographically excluded after a comprehensive tumor board review. A normal IgE level excluded ABPA. EGPA was not suggested with normal anti-neutrophil cytoplasmic antibodies and erythrocyte sedimentation rate/C-reactive protein. Myeloid hypereosinophilic syndrome was not suspected given responsiveness of the eosinophilia to systemic steroids. Patient had no history of NSAID intolerance consistent with AERD.

His asthma action plan was expanded to include adjunctive tiotropium, mometasone inhaled, and guaifenesin, however, without benefit and with persistent peripheral eosinophilia. The allergy service was consulted and initiated benralizumab 30 mg subcutaneous monthly after the 37th cycle. After the second dose, the patient reported rapid resolution of all lower respiratory symptoms, anosmia, and facial pain. Nasal examination after third dose found

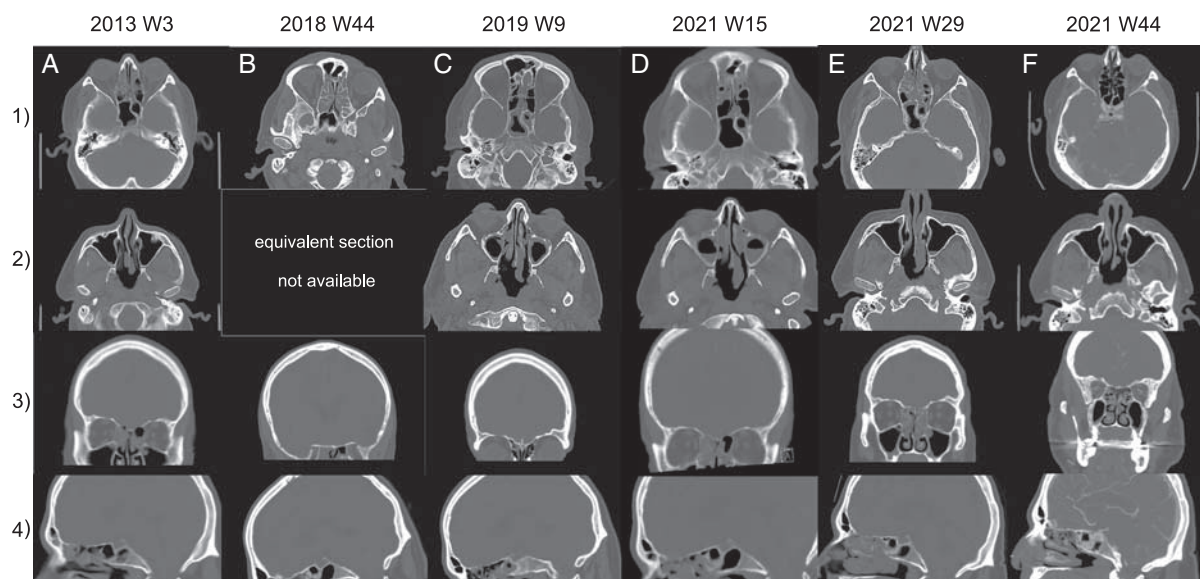


FIGURE 2. Representative serial computed tomography (A) brain studies demonstrating extent of sinonasal polyposis and sinus disease over time (year and week number). A, Five years before malignancy diagnosis (B) before initiation of nivolumab (C–E) during nivolumab therapy, (F) on benralizumab therapy. Rows demonstrate (1) superior axial, (2) inferior axial, (3) coronal, and (4) sagittal planes. Rows (2) and (4) planes highlight the prominent L posterior nasopharyngeal cavity polyp.

no residual polyps or mucopurulence, and improvement of sinonasal disease and the L posterior nasal cavity polyp as noted by CT and MR (Fig. 2F, supplemental Figure 1i, Supplemental Digital Content 1, <http://links.lww.com/JIT/A679>). Per Food and Drug Administration (United States) dosing guidelines, after the third dose benralizumab was provided every 2 months. After a late administration of his fourth dose, mild cough and nasal congestion returned. CT and MR brain found return of sinonasal OMU obstruction, R maxillary opacification and mild regrowth of the L posterior nasal cavity polyp [supplemental Figure 1j, Supplemental Digital Content 1, <http://links.lww.com/JIT/A679>]. The benralizumab frequency was increased to every 30 days, yielding normalization of subjective respiratory and nasal symptoms. To date, the patient has had resolved anosmia, no corticosteroid or antibiotic indications for respiratory symptoms, no asthma exacerbations, no side-effects from benralizumab, and has been able to tolerate 12 subsequent cycles of nivolumab with durable resolution of peripheral eosinophilia (Fig. 1).

Patient's oncologic progression remained minor and limited to the brain, complicated by a seizure and subsequent single event of transient expressive aphasia despite levacitram prophylaxis. Oncologic plan included indefinite continuation of palliative nivolumab.

DISCUSSION

PD-1 pathway signaling is likely relevant in polyp pathophysiology. Human polyps express PD-1^{high} on CD4⁺ lymphocytes, and PD-1 mRNA expression correlates with polyp disease severity.^{13,14} Ligand PD-L1/L2 expression in polyp tissue has been suggested to be lower compared with healthy mucosa.¹⁵ PD-1 blockade of allergen specific CD4⁺ cells enhanced T-helper type 2 lymphocytes (Th2) proliferation and cytokine production.¹⁶ PD-1 agonism was found to suppress airway hyperreactivity and lung inflammation in murine models.¹⁷ PD-1 is a known regulator of Th2-like type-2 innate lymphoid (ILC2) cell metabolism, activation, and proliferation.¹⁷ The recent discovery of extrafollicular PD-1^{high}CXCR5⁺CD4⁺ cells inducing nasal Th2 and antibody production, and low levels of soluble and membrane-bound PD-L1/L2 in polyp tissue have been proposed as therapeutic targets.^{15,18} As such, there is plausibility

anti-PD-1 checkpoint inhibitors induce IL-5, mucosal eosinophilia and promote polyposis.

How eosinophilia affects malignancy remains uncertain, but data have been mixed.¹⁹ In non-small cell lung cancer (NSCLC), elevated peripheral AEC is a significant independent variable associated with better progression-free survival and overall survival.²⁰ One study found elevated AEC whereas on checkpoint inhibitor therapy was strongly associated with improved progression-free survival and overall survival; however, there were no eosinophil-associated irAE reported.²¹ In contrast, there are case reports of hyperprogressive disease with immunotherapy-induced hypereosinophilia.²² As such, the effect of inducing sustained eosinopenia with anti-IL5(R) biologics upon malignancy progression remains unknown. In contrast, tolerance by cancer patients could reasonably be expected, as anti-IL5 (R) biologics generally are very well tolerated and have not demonstrated an increased risk of serious infections. The IL5(R) pathway has few off-target adverse effects given high selectivity for eosinophil and basophil compartments.²³

CONCLUSION

This is the first reported case suggesting benefit of anti-IL5R therapy for checkpoint inhibitor aggravated severe CRSwNP with severe eosinophilic obstructive lung disease. This case also represents another instance supporting anti-eosinophil biologics for checkpoint inhibitor-induced eosinophilic obstructive lung disease,^{9,10} and a potential new therapeutic for checkpoint inhibitor-induced AERD-like phenotypes with nasal polyposis.

Although this patient did not report a history of cyclooxygenase-1 (COX-1) inhibitor intolerance, the phenotype of abrupt onset nasal polyposis and obstructive lung disease is otherwise consistent with AERD. A varied sequence of onset of symptoms in AERD is typical, with COX-1 inhibitor intolerance often the last feature of the triad to develop.²⁴ AERD's pathophysiology is due to

eicosanoid dysregulation through overproduction of inflammatory cysteinyl leukotrienes and PGD₂ and defective inhibitory regulation through PGE₂(R) and COX-2.²⁵ Diagnostic confirmation of AERD without a history of NSAID/aspirin intolerance remains challenging given the absence of a sensitive biomarker to date.²⁶

Although this patient had pre-existing mild persistent asthma and developed asymptomatic polyposis before starting nivolumab, a cyclical pattern of aggravation with nivolumab and improvement with benralizumab suggests a probable association. Anti-IL5R blockade rapidly and durably improved this patient's CRSwNP, obstructive respiratory disease and peripheral eosinophilia without side-effects or acceleration of metastasis, permitting uninterrupted use of nivolumab for disease control.

Given the uncertain role of eosinophils in cancer, provision of anti-IL5(R) therapy in patients with malignancies requires further investigation as to whether induced eosinopenia could significantly affect malignancy progression. A risk/benefit consideration of anti-IL5(R) biologics is recommended if clinically significant eosinophilic complications or treatment with systemic corticosteroids are interfering with oncologic management.

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CONFLICTS OF INTEREST/FINANCIAL DISCLOSURES

All required declarations were listed in the Editorial Manager. ICMJE disclosure forms are available upon request of the Journal. All authors have declared that there are no financial conflicts of interest with regard to this work.

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