Case report

Granulomatous hyperinflammatory state induced by dupilumab treatment for eosinophilic esophagitis

Kanak V. Kennedy, MD,[a,b]* Anna Costello, MD,[b,c]* Melissa A. Lerman, MD, PhD,[b,c] Jon M. Burnham, MD,[b,c] Aoife Corcoran, MD,[b,d] Joseph Piccione, DO,[b,d] Alexandra Grier, MD, PhD,[b,e] Kathleen Sullivan, MD, PhD,[b,e] Terri Whitehorn-Brown, MD,[b,e] Caitlin J. Alexander, MD,[f] Laura S. Finn, MD,[f] Benjamin J. Wilkins, MD, PhD,[f] and Amanda B. Muir, MD[a,b] *Philadelphia, Pa*

We present the first case of a dupilumab-induced hyperinflammatory state in the setting of underlying eosinophilic esophagitis characterized by multisystem granulomatous inflammation. Although clinical trial data and subsequent real-world experience support dupilumab as a highly effective therapy for eosinophilic esophagitis, close monitoring for development of adverse symptoms following initiation remains paramount. (J Allergy Clin Immunol Global 2024;3:100314.)

Key words: *Dupilumab, biologics, eosinophilic esophagitis, granuloma, adverse effect*

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disease characterized by symptoms of esophageal dysfunction and eosinophilic mucosal inflammation.[1] Its pathogenesis is incompletely understood but is associated with T_H2 cell–mediated inflammation, often in response to food antigen exposure. Dupilumab, a humanized mAb targeting the α-subunit of the IL-4 receptor, broadly suppresses T_H2 cell inflammation by inhibiting downstream IL-4 and IL-13 signaling; it recently became the first US Food and Drug Administration–approved therapy for adults and children (aged >1 year) with EoE. Case reports have described eosinophilic granulomatosis with polyangiitis (EGPA), inflammatory arthritis, and enthesitis[2] after introduction of dupilumab, raising the question of its propensity to induce inflammatory processes. We describe a pediatric patient who developed a nonspecific multisystem inflammatory process following initiation of dupilumab for treatment of EoE that receded with withdrawal of the drug.

CASE

A 12-year-old male presented to care with a history of allergic rhinitis, mild intermittent asthma, multiple IgE-mediated food allergies, and EoE. He was diagnosed with EoE at age 10 years in the setting of an esophageal food impaction. Endoscopy at that time showed furrowing, with mucosal eosinophils numbering greater than 125 eosinophils/hpf. The patient's symptoms and inflammation persisted despite dietary elimination (specifically, dairy, egg, and gluten elimination), a high-dose proton pump inhibitor, and topical corticosteroid therapy, prompting initiation of dupilumab (a 300-mg subcutaneous injection weekly based on his weight of 59.9 kg at the time of therapy initiation).

Following dupilumab initiation, the patient reported initial improvement in his symptoms over the subsequent 2 to 3 months, after which he noted recurrence of dysphagia and heartburn. Repeat endoscopy performed 6 months after dupilumab initiation showed diffuse stomach ulcerations, and esophageal biopsy samples had minimal eosinophilic inflammation (≤8 eosinophils/hpf), with new necrotizing and nonnecrotizing granulomas within the superficial lamina propria (Fig 1). Concurrent laboratory evaluation showed an elevated fecal calprotectin level (427 μg/g), elevated inflammatory markers (erythrocyte sedimentation rate, 108 mm per hour; C-reactive protein level, 8.0 mg/dL), microcytic anemia (hemoglobin level, 10.0 g/dL; mean corpuscular volume, 70.6 fL), and peripheral eosinophilia (absolute eosinophil count, 600-840/μL).

On the basis of the constellation of laboratory and histopathologic findings, the differential diagnosis included systemic vasculitides (such as EGPA and granulomatosis with polyangiitis), inflammatory bowel disease, sarcoidosis, immune dysregulation syndromes, and infections. A chest radiograph and computed tomography demonstrated several solid pulmonary nodules with prominent hilar and mediastinal lymph nodes (Fig 2). Computed tomography of the sinuses demonstrated opacification of the bilateral maxillary sinuses and bilateral sphenoid sinus mucosal thickening. A right upper quadrant ultrasound showed hepatosplenomegaly. Slit-lamp examination did not reveal uveitis. Immunologic workup demonstrated elevated levels of IgG, IgA, IgM, and IgE; an advanced naive-to-memory T-cell ratio but otherwise normal lymphocyte subsets (including double-negative T cells); and a normal neutrophil oxidative burst. The patient's levels of lysozyme, angiotensin-converting enzyme, 1,25 dihydroxyvitamin D, and 25-hydroxyvitamin D and his urine calcium-to-creatinine ratio were not suggestive of sarcoidosis. The results of testing for antineutrophil cytoplasmic antibodies,

From [a]the Division of Gastroenterology, Hepatology, and Nutrition, [b]the Department of Pediatrics, [c]the Division of Rheumatology, [d]the Division of Pulmonary and Sleep Medicine, [e]the Division of Allergy and Immunology, and [f]the Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia.

*These authors are co-first authors.

Patient consent for publication: Consent was obtained directly from patient's parent (given that the patient was younger than 18 years).

Received for publication March 5, 2024; revised May 8, 2024; accepted for publication May 16, 2024.

Available online July 26, 2024.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections

2772-8293

https://doi.org/10.1016/j.jacig.2024.100314

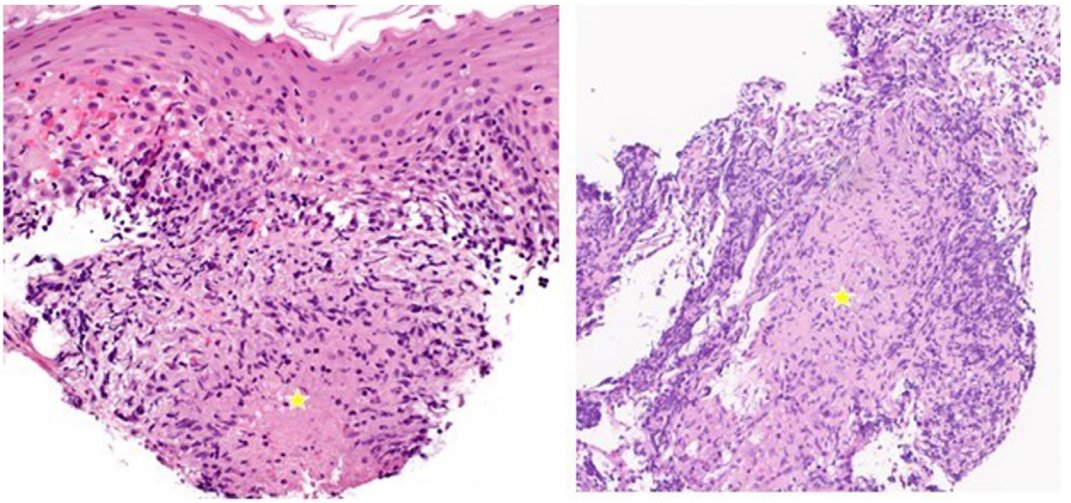

FIG 1. Histopathologic findings in the setting of dupilumab-induced hyperinflammatory response. Necrotizing granuloma (*left* [*yellow star*]) noted on a distal esophageal biopsy sample and nonnecrotizing granuloma (*right* [*yellow star*]) on a hilar lymph node biopsy sample.

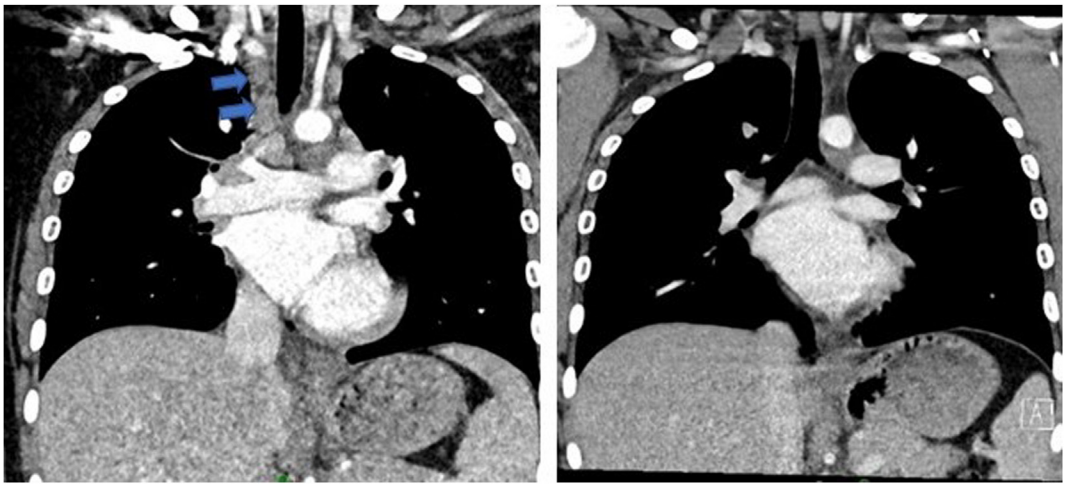

FIG 2. A chest computed tomography image (*left*) demonstrating perihilar lymphadenopathy (*blue arrows*) improved significantly (*right*) after discontinuation of dupilumab therapy.

antimyeloperoxidase, and antiproteinase 3 were negative. The results of a colonoscopy were normal. Flexible bronchoscopy with bronchoalveolar lavage, endobronchial ultrasound-guided transbronchial needle aspiration, and endobronchial ultrasound-guided transbronchial biopsies of the enlarged hilar lymph nodes were performed; the gross findings were notable for nodular tracheobronchitis. Histologic sections of lymph node showed mature lymphoid tissue with focal necrotizing and nonnecrotizing granulomas without demonstrable fungi or acid-fast bacilli (Fig 1). The results of fungal and acid-fast bacilli culture of the lymph node and associated bronchoalveolar lavage fluid were negative.

In summary, the patient is a 12-year-old with a history of atopy, including EoE that is now complicated by granulomatous inflammation of the esophagus and hilar lymph nodes, pulmonary nodules, sinus disease, hepatosplenomegaly, peripheral eosinophilia, anemia, and significant systemic inflammation. His workup results were reassuring against inflammatory bowel disease, sarcoidosis, inborn errors of immunity, and endemic mycoses. His inflammatory process has many features suggestive of small vessel vasculitis (specifically, lung and sinus involvement, peripheral eosinophilia, and significant systemic inflammation). However, the results of his antineutrophil cytoplasmic antibody serology studies were negative, and the examined tissues did not demonstrate vasculitis. Given the temporal association between dupilumab initiation and onset of symptoms, dupilumab was discontinued 8 months after the start of therapy. The patient resumed taking a high-dose proton pump inhibitor and using fluticasone (Flovent [GSK, Brentford, United Kingdom]) as dual therapy for EoE.

The patient's inflammatory markers were monitored for several months after he had stopped taking the dupilumab, and his erythrocyte sedimentation rate and C-reactive protein level normalized. Repeat chest imaging obtained 3 months after dupilumab discontinuation showed decreased size and bulk of the bilateral pulmonary nodules without evidence of new nodules; his hilar and mediastinal lymphadenopathy had resolved (Fig 2). Ultimately, his course was thought to represent a dupilumab-induced

hyperinflammatory state that resolved after medication withdrawal. Repeat endoscopy 3 months after dupilumab discontinuation demonstrated persistent active eosinophilic inflammation (≤55-60 eosinophils/hpf) without granulomas, as well as visual healing of gastric ulceration.

DISCUSSION

To our knowledge, we have described the first pediatric case of a dupilumab-induced hyperinflammatory process in the setting of EoE. Hypereosinophilia has been reported in 4% to 25% of patients treated with dupilumab; it is typically transient and resolves within 6 months of therapy initiation.[3] Published cases describe the occurrence of EGPA after introduction of anti–IL4/IL-13 biologics in patients with severe asthma and/or allergic rhinosinusitis without a history of vasculitis.[4-6] Olaguibel et al examined an electronic pharmacovigilance database, demonstrating 61 cases of EGPA among patients taking dupilumab (0.45%).[7] Other case reports have demonstrated the association of inflammatory arthritis, tenosynovitis, and enthesitis with dupilumab. In many of these cases, withdrawal of the medication resulted in complete resolution of symptoms. Our patient presented with a unique clinical phenotype that mimicked many of the symptoms of EGPA, albeit without classic serologic and histopathologic features. As in prior case reports of patients with EGPA or other inflammatory processes following dupilumab initiation, our patient's symptoms and biochemical manifestations resolved following dupilumab discontinuation.

The pathophysiology underlying inflammatory processes following dupilumab initiation remains unclear, but several mechanisms have been proposed. First, dupilumab antagonizes the IL-4 receptor and therefore attenuates the protective role of the IL-4/IL-13 axis against the IL-23/IL-17 axis,[8] which is a well-known driver of inflammatory arthritis.[9] IL-17 has also been implicated in many other inflammatory diseases, including inflammatory bowel disease.[10] Furthermore, dupilumab inhibits eosinophil infiltration into tissues, as a result of which more activated eosinophils remain in the peripheral blood, with the potential to cause vascular damage.

Dupilumab is US Food and Drug Administration–approved for treatment of atopic dermatitis, asthma, chronic sinusitis with nasal polyposis, prurigo nodularis, and EoE. Although clinical trial data and subsequent real-world experience support dupilumab as a highly effective therapy for EoE, clinical and laboratory monitoring for development of adverse symptoms following initiation remains paramount.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: A. B. Muir receives consulting fees from Bristol-Meyers Squib, Nexstone Immunology, and Regeneron, as well as research funding from Allakos and Morphic. The rest of the authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Muir A, Falk GW. Eosinophilic esophagitis: a review. JAMA 2021;326:1310-8.
2. Jay R, Rodger J, Zirwas M. Review of dupilumab-associated inflammatory arthritis: an approach to clinical analysis and management. JAAD Case Rep 2022;21:14-8.
3. Wechsler ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med 2022;10:11-25.
4. Suzaki I, Tanaka A, Yanai R, Maruyama Y, Kamimura S, Hirano K, et al. Eosinophilic granulomatosis with polyangiitis developed after dupilumab administration in patients with eosinophilic chronic rhinosinusitis and asthma: a case report. BMC Pulm Med 2023;23:130.
5. Fargeas M, Devouassoux G, Gerfaud-Valentin M. Onset of eosinophilic granulomatosis with polyangiitis (EGPA) after anti-Th2 biotherapy initiation in severe asthma patients: report of 3 cases. Respir Med 2023;85:101070.
6. Kai M, Vion PA, Boussouar S, Cacoub P, Saadoun D, Le Joncour A. Eosinophilic granulomatosis polyangiitis (EGPA) complicated with periaortitis, precipitating role of dupilumab? A case report a review of the literature. RMD Open 2023;9:e003300.
7. Olaguibel JM, Sastre J, Rodríguez JM, Del Pozo V. Eosinophilia induced by blocking the IL-4/IL-13 pathway: potential mechanisms and clinical outcomes. J Investig Allergol Clin Immunol 2022;32:165-80.
8. Bridgewood C, Sharif K, Freeston J, Saleem B, Russell T, Watad A, et al. Regulation of entheseal IL-23 expression by IL-4 and IL-13 as an explanation for arthropathy development under dupilumab therapy. Rheumatology 2021;60:2461-6.
9. Tsukazaki H, Kaito T. The role of the IL-23/IL-17 pathway in the pathogenesis of spondyloarthritis. Int J Mol Sci 2020;21:6401.
10. Iwakura Y, Ishigame H. The IL-23/IL-17 axis in inflammation. J Clin Invest 2006;116:1218-22.