



Correspondence

Dupilumab-induced peripheral neuropathy in a patient with severe asthma



The anti-interleukin (IL)-4 receptor, an antibody dupilumab is used in the treatment of severe asthma, atopic dermatitis, and chronic rhinosinusitis with nasal polyps. Common adverse events reportedly include injection site reactions, conjunctivitis, headache, and oral herpes. Dr Lee et al¹ provided the first reported case of very severe chronic inflammatory demyelinating polyradiculoneuropathy that developed 1.5 years after the initiation of dupilumab treatment for atopic dermatitis. Similarly, we have encountered a case of peripheral neuropathy in a patient with severe asthma being treated with dupilumab and wish to share this case with the readers.

A 53-year-old woman with severe allergic asthma refractory to high-dosage inhaled fluticasone propionate, formoterol, tiotropium, oral montelukast, and oral prednisolone at 10 mg/d, omalizumab, and subsequent bronchial thermoplasty was treated with dupilumab. Edema and numbness in the left wrist and ankle appeared 2 hours after the second subcutaneous injection of dupilumab in the abdomen. Although edema gradually improved, numbness developed after each injection of dupilumab, improving within a few days with early injections, but persisting with later ones. A nerve conduction study after complete resolution of edema revealed reduced amplitudes of sensory nerve action potentials for both the median and ulnar nerves at the wrist and elbow, suggesting axonopathies of the left median nerve and ulnar nerve. Differential diagnoses of peripheral neuropathy included eosinophilic granulomatosis with polyangiitis, compression disorder of the neck, and compression of the peripheral nerves by edema. The normal peripheral blood eosinophil count, serum immunoglobulin E and C-reactive protein levels, negative results for myeloperoxidase- and proteinase-3-antineutrophil cytoplasmic antibodies, and a lack of anatomic compression on magnetic resonance imaging at the vertebrae C7 and C8 levels ruled out these diseases, so we diagnosed dupilumab-induced peripheral neuropathy. Dupilumab improved asthma symptoms, but it was discontinued owing to sustained peripheral neuropathy. Numbness resolved 6 months after withdrawal of dupilumab.

The clinical course of our patient clearly suggests a direct association between the development of peripheral neuropathy and administration of dupilumab. The mechanisms underlying dupilumab-induced peripheral neuropathy remain unclear. Antagonism of IL-4 receptor inhibits production of T_H2 cytokines and promotes interferon- γ production in CD4⁺ T cells from patients with atopic dermatitis.² IL-4 suppresses IL-23 and T_H17 responses,³ whereas IL-13 attenuates IL-17A production from human T_H17 cells.⁴ Taken

together, blockade of both IL-4 and IL-13 signalings by dupilumab may inhibit T_H2 inflammation, thereby promoting an immune balance shift toward the predominance of other pathways, such as T_H1 and T_H17. T_H1 and T_H17 cells have been found to mediate acute inflammatory peripheral neuropathy.^{5,6} Although we do not have any biopsy-confirmed evidences of inflammatory neuropathy, we agree with the idea put forward by Dr Lee et al that inhibition of T_H2-mediated inflammation by dupilumab may result in an immune balance shift toward T_H1- or T_H17-mediated inflammation.¹ The previous case and our own differed in severity and the timing of onset of peripheral neuropathy. The findings in these cases suggest that physicians need to be aware of the various types of peripheral neuropathy during treatment with dupilumab.

Mayuka Yamane, MD

Hiroshi Ohnishi, MD, PhD

Kimiko Tsuji, MD, PhD

Kazuki Anabuki, MD, PhD

Akihito Yokoyama, MD, PhD

Department of Respiratory Medicine and Allergology

Kochi Medical School

Kochi University

Kochi, Japan

honi@kochi-u.ac.jp

References

1. Lee AYS, Hannaford A, Vucic S, Berglund LJ. Chronic inflammatory demyelinating polyneuropathy after commencement of dupilumab for atopic dermatitis: coincidence or contributory? *Ann Allergy Asthma Immunol*. 2022;128(1):105–106.
2. Brøgger P, Blom LH, Simonsen S, Thyssen JP, Skov L. Antagonism of the interleukin 4 receptor promotes Th1-signalling among T cells from patients with atopic dermatitis after stimulation. *Scand J Immunol*. 2020;91(1):e12835.
3. Guenova E, Skabytska Y, Hoetzenecker W, Weindl G, Sauer K, Tham M, et al. IL-4 abrogates T(H)17 cell-mediated inflammation by selective silencing of IL-23 in antigen-presenting cells. *Proc Natl Acad Sci U S A*. 2015;112(7):2163–2168.
4. Newcomb DC, Boswell MG, Zhou W, Huckabee MM, Goleniewska K, Sevin CM, et al. Human TH17 cells express a functional IL-13 receptor and IL-13 attenuates IL-17A production. *J Allergy Clin Immunol*. 2011;127(4):1006–1013.e1–e4.
5. Zhu J, Mix E, Link H. Cytokine production and the pathogenesis of experimental autoimmune neuritis and Guillain Barre syndrome. *J Neuroimmunol*. 1998;84(1):40–52.
6. Zhang Z, Zhang ZY, Schluesener HJ. Compound A, a plant origin ligand of glucocorticoid receptors, increase regulatory T cells and M2 macrophages to attenuate experimental autoimmune neuritis with reduced side effects. *J Immunol*. 2009;183(5):3081–3091.

Disclosures: The authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

<https://doi.org/10.1016/j.anai.2022.01.028>

1081-1206/© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.