

Dupilumab as a novel steroid-sparing treatment for hypereosinophilic syndrome



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Key words: eosinophils; pulmonary; skin; therapy; type 2 inflammation.

INTRODUCTION

Dupilumab, a human monoclonal antibody against interleukin (IL) 4 receptor α , inhibits the signaling of IL-4 and IL-13. It is an effective treatment for several conditions characterized by the recruitment of eosinophils to sites of inflammation, such as asthma, atopic dermatitis, chronic spontaneous urticaria, and eosinophilic esophagitis.¹ Recently, dupilumab was reported to be markedly effective and well tolerated in a treatment-recalcitrant patient with hypereosinophilic syndrome (HES).²

HES is characterized by hypereosinophilia and abnormal accumulation of eosinophils in organs and systems, including the skin, lungs, and gastrointestinal tract.³ Clinical manifestations of HES are highly variable, ranging from asymptomatic eosinophilia to severe tissue damage and organ failure. Conventional treatment of HES includes systemic steroids as first-line therapy, which is often linked to side effects, especially when used for a long term.^{4,5} Here, we present a patient with lymphocytic-variant HES who experienced a rapid and marked clinical improvement in response to dupilumab treatment, with remarkable steroid-sparing effects.

Abbreviations used:

HES: hypereosinophilic syndrome
IL: interleukin

CASE REPORT

A 51-year-old nonsmoking woman had received a diagnosis of allergic asthma at the age of 40. She had a history of previous chronic sinusitis and allergic rhinitis. Moreover, she had experienced intermittent abdominal cramping pain and generalized itchy erythematous patches and plaques, predominantly located on the trunk and extremities (Fig 1, A). She had also developed urticaria-like rashes (Fig 1, B) in response to hot baths and certain drugs (eg, clarithromycin and gefarnate). She came to our clinics with symptoms of chronic cough and mild breathing difficulties. Her asthma control test score was 18 out of 25, indicating uncontrolled asthma. Pulmonary auscultation revealed bilateral wheezing, and pulmonary function test showed mild obstructive ventilation dysfunction and increased fractional exhaled nitric oxide values (Fig 2). Thoracic computed tomography showed localized bilateral ground glass

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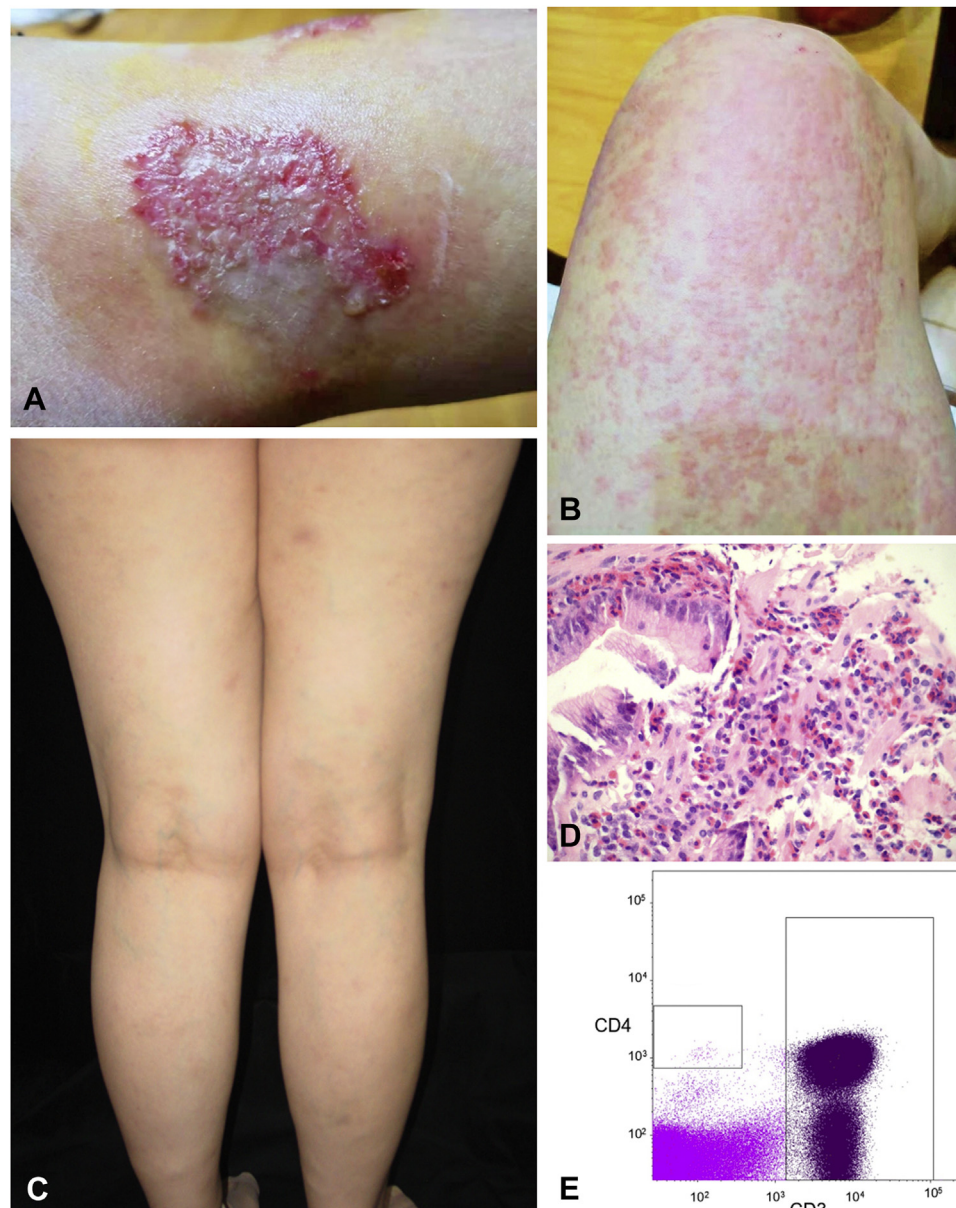


Fig 1. Clinical manifestation and laboratory examination. **A**, Subacute eczematous lesion on the ankle at baseline. **B**, Urticaria-like rashes induced by a hot bath at baseline. **C**, Complete remission of the skin symptoms after dupilumab injection. **D**, Biopsy specimen obtained by gastroscopy showed lymphocytes and eosinophils infiltrating the mucosa lamina propria (hematoxylin-eosin stain; original magnification: $\times 100$). **E**, Flow cytometry confirmed the presence of CD3⁻/CD4⁺ T cells in peripheral blood.

opacities, which may be related to eosinophil infiltration. Sinus computed tomography indicated sinusitis, and a gastric biopsy specimen revealed more lymphocytes and eosinophils infiltrating the mucosa lamina propria (Fig 1, D). Furthermore, she presented with itchy, erythematous patches and plaques on her trunk and extremities. Her pruritus was severe (ie, 8 of 10), as assessed by the use of a

numerical rating scale, and her quality of life was markedly impaired, with a dermatology life quality index score of 25.

With multiple organ systems involvement, we considered differential diagnoses. Screening for perinuclear antineutrophil cytoplasmic antibodies and cytoplasmic antineutrophil cytoplasmic antibodies was negative, which ruled out autoimmune

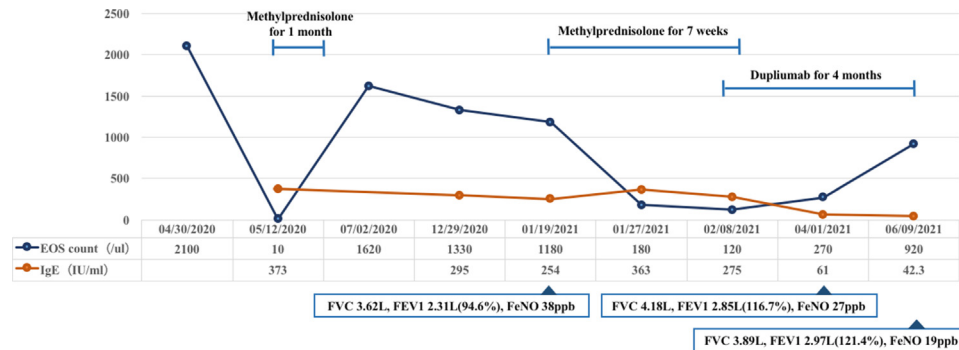


Fig 2. Treatment and clinical course. *EOS*, eosinophils; *IgE*, immunoglobulin E; *FVC*, forced vital capacity; *FEV1*, forced expiratory volume in the first second; *FeNO*, fractional exhaled nitric oxide.

disease and vasculitis. There was no evidence in support of infection from parasites or other pathogens. We considered an underlying malignancy but did not find any solid tumor on physical examination, and serum tumor biomarkers were unremarkable. Imaging of the chest and the abdominal and pelvic cavity failed to reveal any pathology, and the patient had no manifestation of hepatosplenomegaly or lymphadenopathy. Routine blood tests showed normal hemoglobin concentration, platelet count, and white cell differential count, except for eosinophilia, with 2100 eosinophils/ μL . Her total immunoglobulin E concentration was elevated (373 IU/mL). We identified $\text{CD3}^-/\text{CD4}^+$ T cells by flow cytometry (Fig 1, E) and diagnosed lymphocytic-variant HES.

We started to treat our patient with oral methylprednisolone at 40 mg/day. Her clinical symptoms improved rapidly, but she was concerned about the risk of adverse effects and stopped the oral steroid on her own after 4 weeks. Several weeks later, she made an unscheduled visit for acute exacerbation of asthma.

We reinitiated daily use of a moderately-dosed inhaled corticosteroid combined with a long-acting β agonist and leukotriene receptor antagonist. Oral methylprednisolone treatment was initiated, with 40 mg daily at first and a gradual decrease by 4 mg per week, together with subcutaneous dupilumab, initially with 600 mg and subsequently 300 mg every 2 weeks. With her symptoms being well controlled, the dose of her oral corticosteroid was regularly reduced until discontinuation, with a total duration of oral corticosteroid use of 7 weeks. After 4 months of dupilumab treatment, her pruritus score was reduced to 4 of 10 (numerical rating scale), her dermatology life quality index score was reduced to 9, and her asthma control test score increased to 24 with a significant increase in forced expiratory

volume in the first second, indicating well-controlled disease.

After consecutive treatment with dupilumab for 6 months, our patient discontinued her treatment on August 23, 2021. After only 2 months, her rashes and abdominal pain relapsed. She received oral methylprednisolone combined with dupilumab therapy again, which resulted in complete control and consequent tapering of her oral steroid treatment again. At present, this patient is under continued dupilumab treatment and visits our department regularly.

DISCUSSION

Appropriate therapy in HES requires several considerations, including the degree of eosinophilia, associated end-organ dysfunction, and possible adverse effects. Corticosteroids have been the most widely used and effective therapeutic agents in the treatment of HES; however, they come with a high rate of adverse reactions. In a previous multicenter study, most patients with HES received systemic corticosteroids at a moderate or high dose for a long time, between 2 months to 20 years, in 75% of the cases.³

Recently, biologics that target T helper type 2 cell inflammation have been shown to be effective in the treatment of asthma and atopic dermatitis, with observed steroid-sparing benefits.^{6,7} Very recently, a case of successful dupilumab treatment of HES with a rapid and remarkable symptomatic response was reported.⁸ This suggests that type 2 inflammatory cytokines such as IL-4 and IL-13 contribute to the pathogenesis of HES and that targeting these can block eosinophil trafficking to the skin, lung, and other organs.

Of note, our patient showed transient blood eosinophil elevation in response to dupilumab

therapy. However, this was not associated with worsening of clinical symptoms and is in line with findings from clinical trials demonstrating that transient blood eosinophilia occurs in a small subset of both patients with asthma and atopic dermatitis treated with dupilumab, with less than 1% of them showing high-grade eosinophilia.⁹ Overall, the levels of eosinophils during dupilumab treatment need to be further investigated.

Advances in the knowledge of eosinophil immunologic mechanisms have advanced our understanding of HES, through applying molecular-targeted therapy like dupilumab in HES patient. To our knowledge, this is the first report on the use of dupilumab in a Chinese patient with HES. Further studies should be performed to confirm and extend our observations and to explore the mechanisms of action of dupilumab in the treatment of HES.

Conflicts of interest

Dr Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Alnylam, Amgen, Aralez, ArgenX, AstraZeneca, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Dyax, FAES, Genentech, GInnovation, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, Third HarmonicBio, UCB, and Uriach. Drs Du, Chen, Chang, Sun, Yue Zhang, Meng Zhang, Li, Zhao, and Tong have no conflicts of interest to declare.

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