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From Anti-Neutrophil Cytoplasmic Antibody–Negative to Positive: Eosinophilic Granulomatosis with Polyangiitis Under Benralizumab After Steroid Cessation

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ABSTRACT

Background: Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare systemic vasculitis characterized by asthma, eosinophilia, and small- to medium-vessels inflammation.

Case Report: We present the case of a 28-year-old woman with severe eosinophilic asthma, chronic rhinosinusitis with nasal polyposis, and recurrent pruritic skin lesions. She was diagnosed with EGPA based on the presence of asthma, peripheral eosinophilia, histopathologically confirmed vasculitis, and sinus-related involvement. Long-term corticosteroid therapy resulted in adverse effects, necessitating a transition to mepolizumab and subsequently to benralizumab. Although systemic corticosteroids were successfully discontinued under benralizumab therapy, the patient developed pruritic papular-plaque skin lesions in the eighth month of treatment. Laboratory evaluation revealed new-onset perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) positivity despite normal eosinophil counts.

Conclusion: This case highlights the importance of close ANCA monitoring and increased awareness of skin manifestations in patients treated with benralizumab in whom systemic corticosteroids can be discontinued.

Keywords: Benralizumab, corticosteroid therapy, eosinophilic granulomatosis with polyangiitis, skin involvement.

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INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic immunological disorder characterized by tissue damage resulting from hypereosinophilia and necrotizing vasculitis affecting small- to medium-sized blood vessels.[1] The hallmark features distinguishing EGPA from other vasculitides are eosinophilia and asthma. Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) are detected in approximately 30–35% of patients.

Benralizumab, an anti-interleukin-5 receptor (IL-5R) monoclonal antibody, targets type 2 (T2)-driven eosinophilic inflammation. It was initially approved for the treatment of severe eosinophilic asthma and has since gained approval for use in EGPA.[2] In EGPA cases that are not life- or organ-threatening, mepolizumab may be utilized as a maintenance therapy option.

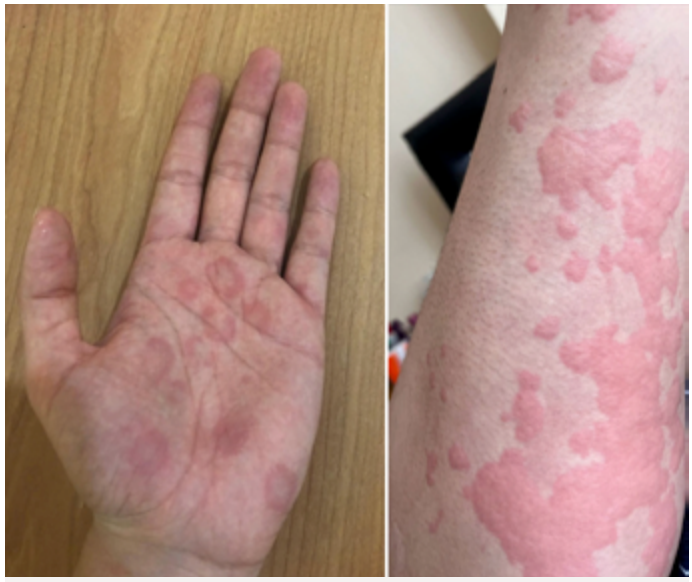

Figure 1. Skin lesions at the time of diagnosis of EGPA.

In this case, due to the development of adverse effects associated with long-term oral corticosteroid use, benralizumab was initiated as maintenance therapy. The patient, who was ANCA-negative at baseline, developed ANCA positivity following corticosteroid discontinuation and initiation of anti-IL-5R therapy. This case highlights the potential importance of monitoring ANCA status in patients with EGPA when transitioning from systemic corticosteroids to anti-IL-5R therapy.

CASE REPORT

A 28-year-old woman was referred to our clinic with a diagnosis of non-atopic severe eosinophilic asthma and chronic rhinosinusitis with nasal polyposis. She had been diagnosed with asthma approximately four years earlier. Despite treatment with high-dose inhaled corticosteroids, long-acting beta-2 agonists (LABAs), and montelukast, her symptoms persisted with minimal clinical improvement. Over the preceding year, she had received systemic corticosteroid therapy on six separate occasions. Although symptom control was achieved during corticosteroid treatment, symptoms recurred following tapering or discontinuation.

The patient also reported recurrent pruritic, erythematous papular lesions on the abdomen; pruritic papules with a pale erythematous center on the palmar surfaces; and erythematous, itchy plaques of varying morphology on the lower extremities. All skin lesions were unresponsive to high-dose antihistamine therapy. A skin biopsy of the lesions was reported as consistent with vasculitis (Fig. 1). Cutaneous involvement in EGPA exhibits a broad clinical spectrum. In this case, the skin lesions were atypical, lacking the classic presentations of palpable purpura or urticaria. Therefore, histopathological confirmation of vasculitis played a crucial role in establishing the diagnosis.

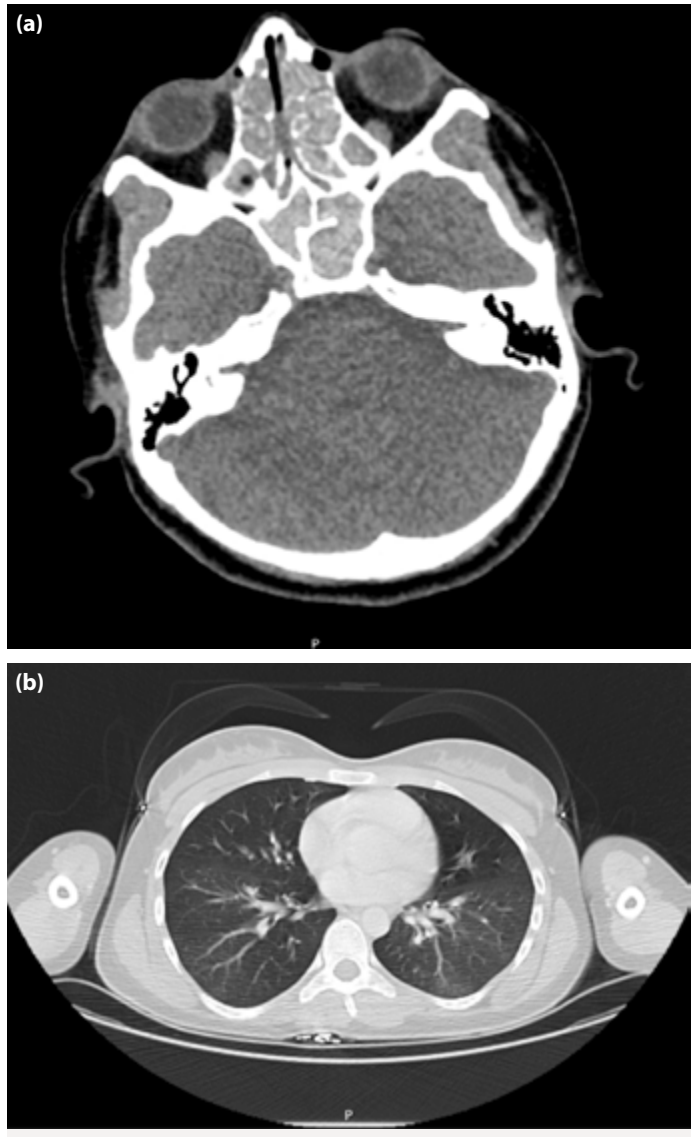

Figure 2. (a) Paranasal sinus CT image of the patient. **(b)** Thoracic CT image of the patient. Şeklinde düzeltilmeli.

On admission, the patient's vital signs were stable. Respiratory examination revealed widespread expiratory wheezing. Nasal endoscopy demonstrated visible bilateral nasal polyps, previously confirmed by otolaryngologic examination and paranasal sinus computed tomography (CT) (Fig. 2a). The patient reported no cardiac symptoms, and physical examination revealed no clinical signs suggestive of cardiac involvement. Electrocardiography and troponin levels were

Table 1. Laboratory findings at the time of diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA)

Test	Result
Erythrocyte sedimentation rate (ESR), mm/s, [normal range: 0-20]	56
C-reactive protein (CRP), mg/dL, [normal range: 0-5]	3.15
Procalcitonin, ng/mL, [normal range: 0-0.5]	<0.02
Hemoglobin, g/dL, [normal range: 12-16]	14.6
Hematocrit, %, [normal range: 37-47]	41
Leukocyte count, 10^9/L, [normal range: 4-10]	10.32
Platelet count, 10^9/L, [normal range: 130-400]	224
Eosinophil count (absolute), /µL, [normal range: 0-200]	1,400
Total serum IgE, IU/mL, [normal range: 0-100]	223
LDH, U/L, [normal range: 135-250]	228
Creatinine, mg/dL, [normal range: 0.50-0.90]	0.66
BUN, mg/dL, [normal range: 6-20]	6.8
Urinalysis	Normal
Autoimmune panel [includes c-ANCA, p-ANCA, anti-dsDNA, ANA panel]	Negative
Parasitological examination (stool, ×3)	Negative

LDH: Lactate dehydrogenase; BUN: Blood urea nitrogen; ANCA: Antineutrophil cytoplasmic antibodies; ANA: Antinuclear antibodies; anti-dsDNA: Anti-double stranded DNA.

normal. As echocardiography was also normal, no further advanced investigations, such as cardiac magnetic resonance imaging (MRI) was performed. No abnormalities were detected on abdominal or other systemic examinations.

Thoracic CT imaging demonstrated peripheral ground-glass opacities (Fig. 2b). Pulmonary function testing revealed a forced vital capacity (FVC) of 5.25 L (104% predicted), a forced expiratory volume in one second (FEV1) of 2.91 L (69% predicted), and an FEV1/FVC ratio of 55%, consistent with an obstructive pattern. Skin prick testing, including testing for Aspergillus species, revealed no sensitizations. Aspergillus-specific immunoglobulin E (IgE) was also negative. Hematology consultation excluded lymphoproliferative malignancy. ANCA testing was performed using indirect immunofluorescence for screening, followed by antigen-specific immunoassays for myeloperoxidase (MPO) and proteinase 3 (PR3); all results were negative. Laboratory values at the time of diagnosis are summarized in Table 1.

The diagnosis of EGPA was established based on the presence of long-standing asthma, peripheral eosinophilia, chronic rhinosinusitis with nasal polyposis, and histopathological evidence of small-vessel vasculitis on skin biopsy. In addition, in patients with histopathologically confirmed small-vessel vasculitis, the disease was shown to meet the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for EGPA. Immunosuppressive therapy was initiated with methylprednisolone at a dose of 40 mg/day. The corticosteroid dose was gradually tapered to 6 mg/day; however, attempts to reduce the dose below this level resulted in asthma exacerbations. Maintenance therapy was therefore continued at 6 mg/day. During follow-up, further reduction of the dose to 4 mg/day led to recurrence of both asthma symptoms and cutaneous lesions, necessitating a return to the 6 mg/day maintenance dose.

The patient remained on low-dose corticosteroids for a total of two years. Due to corticosteroid-related adverse effects, including striae and hirsutism, mepolizumab was initiated. During mepolizumab therapy, methylprednisolone was successfully reduced to 4 mg/day without asthma exacerbations or recurrence of skin lesions. However, asthma control deteriorated when the dose was reduced below 4 mg/day. Consequently, maintenance therapy was continued for two years with methylprednisolone 4 mg/day in combination with subcutaneous mepolizumab 150 mg every four weeks. Because of systemic steroid-related adverse effects and the inability to further taper the steroid dose, treatment was switched from mepolizumab to benralizumab. Under benralizumab therapy, systemic steroids were gradually discontinued over four months without loss of asthma control or recurrence of skin lesions. However, in the eighth month of benralizumab treatment, pruritic, erythematous papular¬–plaque skin lesions developed and were unresponsive to

high-dose antihistamines, despite preserved asthma control. Laboratory evaluation demonstrated a normal eosinophil count; however, previously negative myeloperoxidase-ANCA (p-ANCA) results had converted to positive. Repeat testing confirmed persistent p-ANCA positivity.

Given the new onset of ANCA positivity and recurrent skin lesions during benralizumab therapy, methylprednisolone was reintroduced into the treatment regimen. Following the reinitiation of corticosteroids, the skin lesions resolved rapidly.

This case underscores the potential for ANCA seroconversion and disease flare following corticosteroid withdrawal in patients with EGPA undergoing benralizumab therapy. It highlights the importance of close monitoring of ANCA status and cutaneous manifestations in cases in which systemic steroids can be completely discontinued under benralizumab treatment.

DISCUSSION

Anti-neutrophil cytoplasmic antibodies are detected in approximately one-third of patients with EGPA and are associated with a distinct clinical phenotype. ANCA-positive patients more commonly present with manifestations of small-vessel vasculitis, including palpable purpura, glomerulonephritis, and mononeuritis multiplex. In contrast, ANCA-negative patients more frequently exhibit clinical features related to eosinophilic infiltration, particularly involving the respiratory, cardiac, and gastrointestinal systems.[3,4] Although these phenotypic differences between ANCA-positive and ANCA-negative EGPA are well recognized, it remains uncertain whether they influence therapeutic responses to maintenance treatments. The primary goal in the management of EGPA is to induce and maintain remission while minimizing cumulative exposure to systemic glucocorticoids and other immunosuppressive agents. In cases of life- or organ-threatening disease, induction therapy typically consists of systemic glucocorticoids in combination with cyclophosphamide or rituximab. For maintenance therapy, methotrexate, azathioprine, rituximab, or anti-IL-5/IL-5R agents may be used.[2]

In our case, the patient did not exhibit life- or organ-threatening disease; however, corticosteroid-related adverse effects developed during follow-up. Therefore, maintenance therapy was transitioned to mepolizumab and subsequently to benralizumab. While systemic steroids could be completely discontinued under benralizumab treatment, the patient subsequently developed cutaneous lesions, and p-ANCA seroconversion was observed during follow-up. Speculatively, this may suggest that systemic glucocorticoids play a broader role in suppressing the vasculitic component of EGPA beyond their eosinophil-lowering effects, whereas anti-IL-5R therapy alone may be insufficient to control vasculitic manifestations.

In our patient, the emergence of p-ANCA positivity was temporally associated with the appearance of skin lesions on the lower extremities, despite the absence of peripheral eosinophilia. Although firm conclusions cannot be drawn from a single case, we hypothesize that while benralizumab effectively controls eosinophil-mediated disease manifestations, it may have limited efficacy in suppressing ANCA-associated vasculitic processes.

Based on a single observation, it is not possible to establish a causal relationship between benralizumab therapy and ANCA seroconversion, particularly in the context of concurrent systemic glucocorticoid treatment. In this patient, MPO/p-ANCA positivity became evident following glucocorticoid discontinuation, suggesting that steroid withdrawal may have contributed to the unmasking of underlying vasculitic activity. Anti–IL-5 and anti–IL-5 receptor agents markedly reduce peripheral eosinophil counts, which may obscure clinical disease activity. Recent reports have described the development or relapse of EGPA during benralizumab therapy in the absence of eosinophilia. These observations indicate that vasculitic manifestations and ANCA positivity may occur despite apparently controlled eosinophil levels during biologic maintenance therapy, highlighting the importance of careful clinical monitoring.[2,5,6]

Consistent with our observations, a previously published case report also described a vasculitic relapse in an EGPA patient treated with mepolizumab despite persistently normal peripheral eosinophil counts. In that case, clinical improvement was achieved only after the reintroduction of high-dose systemic corticosteroids.[6] However, ANCA seroconversion was not reported.

CONCLUSION

Although similar cases are scarce in the literature, this report describes an EGPA patient with negative baseline ANCA who developed p-ANCA positivity and cutaneous lesions while receiving maintenance therapy with benralizumab. These findings raise important considerations regarding the need for continued ANCA monitoring during anti-IL-5R therapy and highlight potential limitations of such treatments in controlling the vasculitic component of EGPA.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Conflict of Interest: The authors have no conflicts of interest to declare.

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