

Eosinophilic Granulomatous Polyangiitis Emerging After Omalizumab Administration: An Asthma Patient Without Systemic Corticosteroids Develops Mononeuritis Multiplex After 22 Days

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Abstract

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody used to treat severe allergic asthma. Although most of the reported cases of omalizumab-associated eosinophilic granulomatous polyangiitis (EGPA) are attributed to the accompanying glucocorticoid reduction, a patient who met the 2022 American College of Rheumatology diagnostic criteria for EGPA yet had no history of systemic glucocorticoid treatment is described. This individual developed limb numbness accompanied by eosinophilia ($14.24 \times 10^9/L$) within 22 days after initiating omalizumab therapy. Critical warning: In asthmatic patients treated with omalizumab, if persistent eosinophilia or new neurological symptoms occur, the possibility of EGPA should be highly vigilant and evaluated.

Keywords: Asthma, eosinophilic granulomatosis with polyangiitis, mononeuropathies, omalizumab

Introduction

Eosinophilic granulomatous polyangiitis (EGPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis characterized by asthma, eosinophilia, and multisystem involvement. Omalizumab, an anti-IgE monoclonal antibody, is commonly used to treat severe allergic asthma. It is generally believed that omalizumab-associated EGPA is mostly related to the “unmasking” of the disease following glucocorticoid tapering, rather than being directly caused by the drug. However, this paper reports a case of a steroid-naïve asthma patient who developed rapidly progressive mononeuritis multiplex and significant eosinophilia within just 22 days after initial omalizumab treatment, meeting the 2022 American College of Rheumatology (ACR) classification criteria for EGPA. The exceptionally short onset interval in this case suggests that omalizumab may potentially directly induce EGPA through an underlying mechanism, war-ranting significant clinical attention.

Case Presentation

The chronological sequence of disease onset and key clinical events is summarized in Figure 1.

A 34-year-old woman with no smoking history was diagnosed with asthma, presenting with symptoms of coughing, wheezing, and chest tightness. The diagnosis was supported by a positive bronchodilator test, elevated fractional exhaled nitric oxide, and increased IgE levels. No other major systemic comorbidities were reported. At age 39, she underwent surgery for chronic sinusitis, otitis media, and nasal polyps. Postoperative pathology revealed necrotic debris and neutrophil infiltration, without evidence of eosinophilic infiltration.

A few months later, due to recurrent asthma exacerbations that remained poorly controlled with conventional medications—including a salbutamol inhaler and salmeterol/fluticasone inhaler—the patient was initiated on omalizumab therapy. Prior to treatment, laboratory findings revealed a baseline eosinophil count of $1.33 \times 10^9/L$ and an IgE level exceeding 1190 IU/mL. She was treated with omalizumab injections of 375 mg on September 12, 2019, and September 26. On October 4, 8 days after the last dose (September 26) and 22 days after the first dose (September 12) of omalizumab, the patient suddenly developed numbness at the distal ends of the limbs, with more severe symptoms in the left lower limb and right upper

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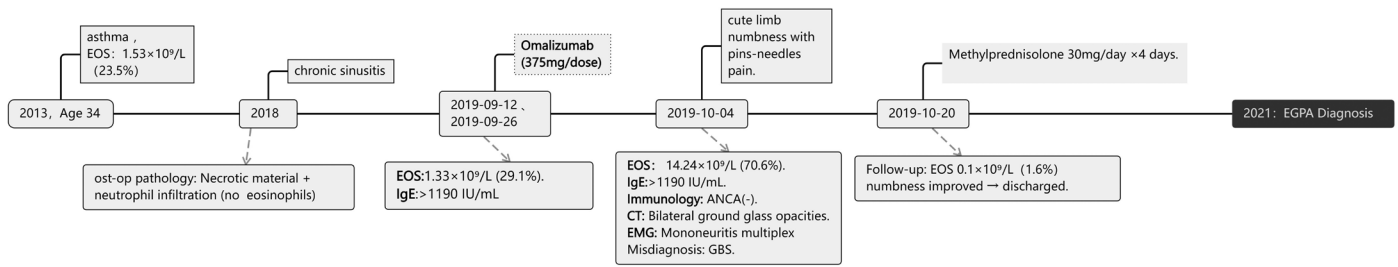


Figure 1. Chronological sequence of disease onset and critical events in the index case.

limb, accompanied by a tingling pain; physical examination showed disappearance of the biceps reflex in the right upper limb.

Laboratory investigations on October 15 demonstrated a markedly elevated eosinophil count of $14.24 \times 10^9/L$ (70.6%). The erythrocyte sedimentation rate was also noted to be elevated at 49 mm/h. Antineutrophil cytoplasmic antibody panel and autoimmune antibody panel were both negative. Other hematological indicators, including infection parameters, showed no abnormalities. On October 21, lumbar puncture was performed, and the routine, biochemical, cytological, and microbiological analysis of cerebrospinal fluid (CSF) were all normal. Further examinations, including magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the head, and lumbar spine MRI, were unremarkable except for severe sinusitis. Chest computed tomography showed scattered multiple ground-glass opacities in both lungs; electromyography testing indicated changes consistent with multiple mononeuropathy, in line with the reported characteristics of EGPA vasculitis.¹ However, at that time, she was diagnosed with Guillain-Barré Syndrome (GBS).

Highlights

- Highlights steroid-naïve context: Acute eosinophilia ($14.24 \times 10^9/L$) and mononeuritis developed within 22 days post-omalizumab without prior systemic steroids, a potential drug-associated eosinophilic granulomatous polyangiitis (EGPA).
- Integrated mechanism suggests: Omalizumab-associated antineutrophil cytoplasmic antibody (ANCA)(-) mononeuritis multiplex may involve eosinophil-driven intraluminal occlusion (vs. ANCA(+) vasculitis).
- New-onset neurological symptoms (especially limb numbness/pain) with persistent eosinophilia post-omalizumab mandates urgent EGPA evaluation in ANCA(-) cases.

From October 16 to October 19, she underwent a 4-day course of steroid therapy (methylprednisolone 30 mg IV, once daily). On October 20, a follow-up complete blood count showed normalization of white blood cells and eosinophils (eosinophils 0.15×10^9 , accounting for 2.6%). Her limb numbness improved and she was discharged in good condition on October 28.

At the age of 41, the patient was readmitted due to an asthma exacerbation. Routine examinations revealed a significantly elevated eosinophil count (eosinophils 12.24×10^9 , accounting for 70%). Subsequent bone marrow aspiration, biopsy, and flow cytometry showed no abnormalities. Upon retrospective review of the patient's medical history, GBS was ruled out as the cause of the polyneuritis episode in 2019 based on the following test results obtained at that time: normal CSF analysis without albuminocytological dissociation, negative oligoclonal bands in both CSF and serum, and negative anti-ganglioside antibodies. Furthermore, the observed asymmetric neuropathy presenting as mononeuritis multiplex, accompanied by pronounced peripheral eosinophilia, was more consistent with vasculitic neuropathy rather than GBS. A comprehensive 7-year medical review identified key features satisfying the 2022 ACR diagnostic criteria for EGPA: Peripheral eosinophilia (peak count $\geq 1 \times 10^9/L$; +5 points), Obstructive airway disease (confirmed asthma; +3 points), Nasal polyposis (radiologically/histologically verified; +3 points), Mononeuropathy multiplex (electrophysiologically confirmed, excluding radiculopathy; +1 point).¹ The total score of 12 points exceeded the diagnostic threshold (≥ 6 points), with this criterion demonstrating 85% sensitivity (95% CI 77%-91%) and 99% specificity (95% CI 98%-100%) in validation studies. Following multidisciplinary consensus, EGPA was definitively diagnosed.¹ The patient was treated with methylprednisolone (40 mg/day for 4 days), which led to the resolution of respiratory symptoms and normalization of eosinophil counts. She was discharged in an improved condition and placed on a

maintenance oral regimen of prednisone (25 mg/day). During the 4-year follow-up, her asthma remained well-controlled with no recurrence of sinusitis or neuropathy, and she required no further hospitalizations due to EGPA exacerbation.

Discussion

This case highlights concerns regarding the temporal association between omalizumab initiation and the development of GBS-like symptoms in 2019. Currently, literature documents that some asthma patients developed multisystem symptoms following omalizumab administration, ultimately diagnosed as EGPA.²⁻⁴ In the European EGPA Study Group cohort, among 529 patients with severe asthma, 30 (5.7%) developed EGPA during treatment targeting type 2 inflammation, with approximately half of these cases (14 patients) involving omalizumab therapy.⁵ These cases were largely attributed to the tapering of concomitant asthma-controlling medications (e.g., glucocorticoids) during omalizumab therapy. However, in the present case, the patient used only inhaled agents without oral corticosteroids for asthma control prior to omalizumab initiation. Moreover, the temporal association between symptom onset and omalizumab treatment was highly suggestive of a possible link. Regarding EGPA, to the authors' knowledge, only 4 cases of neuritis occurring during omalizumab treatment have been reported in the literature that were subsequently diagnosed as EGPA, as summarized in Table 1.

Eosinophilic granulomatous polyangiitis is considered an immune-inflammatory disorder based on the profound immunological dysregulation of both the innate and adaptive immune systems, including T and B lymphocytes, eosinophils, and neutrophils. In addition, genetic pre-dispositions have been reported.⁶ Neurological involvement is present in 42%-76% of patients with EGPA, depending on the study series. Both the peripheral and central nervous systems (CNS), as well as cranial nerves, can be affected in EGPA. Peripheral nervous system involvement is the most frequent

Table 1. Reported Cases of Omalizumab-Associated Eosinophilic Granulomatous Polyangiitis–Related Neuritis in Asthma Patients

Case	Carson et al ¹⁷	Bekçi̇başı et al ¹⁸	Jachiet et al ³	Jachiet et al ³	Pu�chal et al ¹⁹
Age, years	60	31	46	53	77
Sex	Male	Male	Female	Male	Male
Past medical history	A 40-year history of asthma and sinusitis	Nasal polyps and asthma	Severe and corticosteroid-dependent asthma	Severe and corticosteroid-dependent asthma	Nasal polyps and asthma
Eosinophil count before the use of omalizumab, cells/mm ³ , (%)	620	–	–	–	750
IgE before the use of biological-agents, KU/L	257	–	–	–	1449
The usage regimen of omalizumab	Omalizumab (600 mg/4 weeks)	Omalizumab	Omalizumab with prednisone	Omalizumab combined with prednisone and azathioprine	Omalizumab (375 mg/2 weeks)
Time from first omalizumab dose to EGPA onset	10 weeks	–	15 months (allowing tapering of prednisone from 30 mg/day to 5 mg/day)	12 months	6 weeks
New neurological manifestations after omalizumab	Elevation of the left hemidiaphragm was observed, with preserved strength in all 4 limbs and sensory deficit corresponding to the L5/S1 nerve root distributions, leading to a diagnosis of phrenic nerve palsy and mononeuritis multiplex	Hyperesthesia and pain in both lower limbs	Rapidly progressive bilateral visual impairment, eye examination, and visual evoked potential tests were consistent with a diagnosis of retrobulbar optic neuritis	Progressive visual impairment in his left eye; examinations were consistent with a diagnosis of retrobulbar optic neuritis.	A mild confusional state, wasting of the right hand and extensor plantar responses
Laboratory test results after omalizumab administration	IgE, IU/mL ANCA Eosinophil count (cells/mm ³)	1080 Negative 6990 (45)	– – 1300	– – 200	– Negative 5300
Prognosis	Symptomatic improvement after 5-day methylprednisolone 60 mg, then tapered to 15 mg, with azathioprine initiation and steroid weaning, however with: persistent eosinophilia, exacerbation rate of 2/year, and repeated chest X-ray showing persistent left hemidiaphragm elevation	The patient was initiated on high-dose intravenous methylprednisolone (1 mg/kg). Significant clinical improvement was observed 5 days post-treatment initiation	No improvement was observed after treatment with methylprednisolone pulses followed by oral prednisone associated with azathioprine after 2 years of follow-up	No improvement was observed after treatment with methylprednisolone pulses followed by oral prednisone associated with intravenous cyclophosphamide	A dramatic improvement in signs and symptoms was observed

ANCA, antineutrophil cytoplasmic antibody; EGPA, eosinophilic granulomatous polyangiitis.

(60%-70%), followed by CNS manifestations (5%-15%), whereas cranial neuropathy is the least common (<5%).^{7,8}

In a sural nerve biopsy study of 82 patients with EGPA-associated neuropathy, Ryoji Nishi et al⁹ found that nerve damage resulted from vasculitis and eosinophilic infiltrates. In the myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA)-positive group, more frequent findings suggestive of vasculitis were observed, characterized by destruction of vascular structures with or without fibrinoid necrosis. Conversely, MPO-ANCA-negative patients exhibited prominent features including increased numbers of eosinophils within epineurial vessel lumina, occlusion of epineurial vessels by intraluminal eosinophils, and eosinophil extravasation into the endoneurial interstitium. The number of eosinophils in the vessel lumen was higher in the MPO-ANCA-negative group than in the MPO-ANCA-positive group (0.53 ± 0.74 vs 0.18 ± 0.33 per vessel, $P < .01$). These findings suggest that the pathogenesis of EGPA comprises at least 2 distinct mechanisms: ANCA-associated vasculitis predominates in MPO-ANCA-positive patients, whereas eosinophil-associated tissue damage appears to play a major role in MPO-ANCA-negative patients. This mechanistic stratification directly corroborates prior hypotheses that EGPA comprises 2 discrete entities—ANCA-driven and eosinophil-driven disorders—with distinct organ involvement profiles.¹⁰

Baseline eosinophil count fails to effectively predict omalizumab treatment response in severe asthmatics.¹¹ However, Sposato et al¹² demonstrated that in patients undergoing long-term omalizumab treatment (≥ 1 year), those with persistent high blood eosinophils (BE $> 300/\mu\text{L}$) showed significantly inferior outcomes compared to the low-BE group (BE $\leq 300/\mu\text{L}$) in terms of lung function, asthma control test scores, and maintenance doses of glucocorticoids. While current evidence demonstrates that omalizumab reduces blood eosinophil levels, a post-marketing analysis of the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database revealed transient eosinophilia in 36% of patients (N=270/749) following omalizumab administration, suggesting this eosinophilic response may represent a potential adverse drug event.^{13,14} The mechanism underlying eosinophil elevation following omalizumab treatment remains incompletely elucidated. Notably, in the few reported cases of omalizumab-induced neuritis in EGPA patients, all

exhibited ANCA-negative status alongside similarly marked eosinophilia.

It is hypothesized that this phenomenon may be initiated by a severe immune-dysregulation-mediated disease flare reaction, ultimately driving pathological hyperproliferation and activation of eosinophils. Nevertheless, given the limited number of documented cases, it remains unclear whether this represents a coincidental finding or a potential mechanistic association, warranting further investigation. Moreover, EGPA's natural history—progressing from a prodromal phase (asthma/allergic rhinitis) through an eosinophilic stage (peripheral eosinophilia $>10\%$ with tissue infiltration) to vasculitis—may predate drug exposure; in this particular case, the vasculitic progression could reflect natural disease evolution rather than a direct drug effect. Nevertheless, it is noteworthy that the association between omalizumab and EGPA remains unsettled. Several studies have reported that EGPA patients with severe asthma showed improvement in asthma symptoms, a reduction in blood eosinophil counts, and no increase in EGPA disease activity following omalizumab treatment.^{2,4,15,16} Regardless of underlying mechanisms, vigilant monitoring of eosinophil counts in severe asthmatics with eosinophilia receiving omalizumab is strongly advised. Particularly crucial in MPO-ANCA-negative patients, persistent eosinophilia should prompt immediate reassessment of therapeutic risk-benefit balance. Importantly, emergent neurologic symptoms (e.g., limb paresthesia, visual acuity decline, or blurred vision) necessitate urgent evaluation for EGPA.

Conclusion

Omalizumab therapy may potentially trigger or exacerbate EGPA. It may induce pathological eosinophilia in susceptible patients—particularly ANCA-negative individuals with elevated baseline eosinophilia—potentially triggering de novo EGPA or accelerating subclinical disease progression, where excessive eosinophilic infiltration into the epineurial vasculature directly causes mononeuritis multiplex. Consequently, in ANCA-negative asthmatics receiving omalizumab, concomitant eosinophilia and neuritis symptoms (e.g., distal limb numbness, neuropathic pain, or paresthesias) must prompt urgent EGPA evaluation. However, this study has several limitations. Firstly, the patient had pre-existing asthma and nasal polyposis, and the progression of EGPA from the prodromal phase to vasculitis may have predated drug exposure; thus, the disease may have progressed independently of omalizumab. Secondly, the absence of

histopathological confirmation of vasculitis and the limited number of similar reported cases obscures the distinction between natural progression and omalizumab-triggered vasculitis. This urgently warrants large-scale, population-based mechanistic studies for clarification.

Key Clinical Takeaways

1. Monitor high-risk patients: Closely watch ANCA-negative asthmatics with high baseline eosinophilia on omalizumab.
2. Act on red flags: Urgently evaluate for EGPA if persistent eosinophilia and new neurological symptoms (e.g., numbness, pain) develop.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was not required for the study.

Informed Consent: Written informed consent was obtained from the patient who agreed to take part in the study.

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