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Case Based Review

Three cases of relapsed eosinophilic sinusitis without eosinophilia during mepolizumab maintenance therapy for eosinophilic granulomatosis with polyangiitis

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Author contributions

KN, YU and JS wrote the manuscript. KN, YU, MI, MI, GK and JS contributed towards patient medical history. All authors were involved in critical review, editing, revision and approval of the final manuscript.

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Abstract

We present three cases of eosinophilic granulomatosis with polyangiitis (EGPA) where patients experienced relapse of eosinophilic sinusitis without peripheral eosinophilia while on remission maintenance therapy with mepolizumab (MPZ), an anti-interleukin (IL)-5 monoclonal antibody. Despite the initial control of symptoms with high-dose prednisolone (PSL) and MPZ, patients experienced relapse of nasal obstruction and eosinophilic infiltration in nasal mucosal biopsies. Notably, relapses occurred despite normal peripheral eosinophil counts, indicating the localized nature of eosinophilic inflammation. While IL-5 inhibitors effectively reduce peripheral blood eosinophils, eosinophilic sinusitis may persist due to local factors such as IL-4-mediated inflammation. IL-4 has been implicated in promoting eosinophil migration into nasal tissues, suggesting that IL-5 inhibitors alone may not sufficiently suppress eosinophilic infiltration in such cases. These findings highlight the importance of considering the possibility of eosinophilic sinusitis relapse in EGPA patients treated with IL-5 inhibitors and reduced glucocorticoid doses. Further research is warranted to elucidate the mechanisms underlying local eosinophilic inflammation and optimize treatment strategies for EGPA patients.

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a syndrome characterized by eosinophilic inflammation, necrotizing systemic vasculitis, and granulomatous formation. In EGPA, an allergic phase, including bronchial asthma and chronic sinusitis, precedes the eosinophilic phase, which then progresses to the vasculitic phase, exhibiting a characteristic clinical course [1, 2, 3]. Eosinophils are thought to play a central role in the pathology of EGPA. The introduction of mepolizumab (MPZ), a humanized monoclonal antibody against interleukin (IL)-5, a cytokine involved in the differentiation, proliferation, and activation of eosinophils, has significantly changed the therapeutic strategy for EGPA. The MIRRA trial reported that the use of MPZ in relapsing/refractory EGPA improved outcomes, including glucocorticoid tapering [4]. Furthermore, there have been reports of cases in which glucocorticoids could be discontinued with the concomitant use of MPZ [5]. We report three cases of EGPA, with relapse of eosinophilic sinusitis without eosinophilia, under remission maintenance therapy with MPZ, an anti-IL-5 monoclonal antibody. We obtained written consent for case reporting from all patients following the Ethical Committee of Hyogo Prefectural Amagasaki General Medical Center.

Case presentation

Patient 1. A 56-year-old woman presented with wheezing, nasal obstruction, numbness, and weakness of both lower extremities. She exhibited severe bilateral wrist and foot drop with a manual muscle test score of 0 to 1 out of 5, along with severe sensory disturbances in her extremities, distally from the elbows and knees. Her activities of daily living (ADL) were severely compromised, leaving her bedridden. Nerve conduction studies (NCS) of

her extremities revealed the pattern of mononeuritis multiplex which implied vasculitis. Anti-neutrophil cytoplasmic antibody (ANCA) was negative, and her maximum eosinophil count was 30,504 /μL (Figure 1B). Hematologic malignancy was considered unlikely after consultation with a hematologist, as no morphological abnormalities were observed in the peripheral blood. Whole-body CT revealed bilateral sinusitis and ground-glass opacity at the lung apex, suspicious of eosinophil infiltration, but biopsies were not performed. She was diagnosed with EGPA, and her severe peripheral neuropathy was considered an organ-threatening manifestation, prompting the initiation of high-dose prednisolone (PSL) and intravenous cyclophosphamide. About two months after, her neurological symptoms persisted with little change, and follow-up NCS showed no improvement. Therefore, MPZ was added on. After starting MPZ, her ADL gradually improved to the point where she could walk with a cane, and the area of numbness decreased. Eventually, she achieved complete remission. Ten months after the initiation of remission induction therapy, her nasal obstruction relapsed. Despite no elevation of the eosinophil count, a nasal mucosal biopsy showed eosinophilic infiltration. For the treatment of eosinophilic sinusitis, we closely monitored her condition in collaboration with an otolaryngologist, considering an increase in the dosage of glucocorticoids or a switch from MPZ to dupilumab. However, five months later, a relapse of EGPA was diagnosed due to the onset of fever, wheezing, and worsening numbness in her extremities, along with the increased inflammatory markers and eosinophil count in laboratory data. She was successfully treated with an increased PSL dosage of up to 5 mg/day, inhaled corticosteroids/long-acting beta-2 agonist, and high-dose intravenous immunoglobulin therapy, along with the continuation of MPZ.

Patient 2. A 52-year-old woman presented with wheezing, nasal obstruction, and purpura in her lower extremities. She was diagnosed with necrotizing vasculitis on biopsy. ANCA was negative, and her maximum eosinophil count was 1,320 /μL (Figure 1C). Her initial symptoms were well controlled with high-dose PSL. Eleven months after PSL initiation, the patient developed olfactory loss accompanied by eosinophilia. This subsided with an increase in PSL and the addition of azathioprine. Eleven months later, MPZ was initiated because of a relapse of olfactory loss and eosinophilia. Eleven months after MPZ initiation, nasal obstruction, wheezing, and purpura in her lower extremities relapsed. Her peripheral eosinophil count remained within the normal range. A nasal mucosal biopsy showed eosinophilic infiltration. Her various symptoms were well controlled by increasing the PSL dosage to a maximum of 15 mg/day, combined with continued MPZ.

Patient 3. A 60-year-old man with a history of allergic rhinitis, eosinophilic sinusitis, and asthma presented with fever, wheezing, nasal obstruction, numbness in his extremities, and a spermatic cord mass. Inguinal orchiectomy revealed massive infiltration of eosinophils. ANCA was negative, and his maximum eosinophil count was 10,675 /μL (Figure 1D). His initial symptoms were well-controlled with a combination therapy of high-dose PSL and MPZ. Seven months after therapy initiation, nasal obstruction recurred despite the lack of eosinophilia. Relapse of the eosinophilic sinusitis was diagnosed based on the biopsy specimen obtained during sinus surgery. After this course, no symptoms of systemic vasculitis were observed with maintenance therapy using MPZ without regular glucocorticoids. His nasal obstruction was managed by the otolaryngologist with intermittent oral betamethasone at 1 mg/day for up to 7 days.

Discussion

All three patients met the Lanham criteria [6], the 1990 ACR classification criteria for EGPA [7], and the 2022 ACR/EULAR scoring classification criteria for EGPA [8]. In all cases, nasal obstruction and/or a history of eosinophilic sinusitis existed at the initial presentation of EGPA. During the remission maintenance therapy with MPZ and reduced dose of PSL, eosinophilic sinusitis relapsed despite the lack of peripheral eosinophilia (Figure 1A). At our institution, the most commonly affected organs in relapses were the sinuses in MPZ-treated patients and peripheral nerves in those not treated with MPZ. Based on our cases, we believe that particular attention should be paid to the recurrence of sinusitis in EGPA patients undergoing treatment with MPZ, even in the absence of eosinophilia. However, the relapse of sinusitis might go undetected without close monitoring by otolaryngologists, as implemented at our institution. Additionally, in two out of three cases, systemic vasculitis relapse followed the relapse of sinusitis. Close cooperation between rheumatologists and otolaryngologists may enable the early detection of eosinophilic sinusitis relapse and, consequently, the relapse of EGPA in some cases.

Eosinophils differentiate and proliferate in the bone marrow [9]. These are stimulated by IL-5, and are mobilized into the blood [10, 11]. IL-5 inhibitors suppress eosinophilic differentiation, proliferation, and mobilization, resulting in a rapid decrease in the peripheral blood eosinophil count [12]. On the other hand, eosinophilic sinusitis, especially in cases of nasal polyps, is associated with a type 2 inflammation [13, 14]. In particular, chronic rhinosinusitis associated with EGPA is characterized by significant eosinophilic infiltration and tends to follow a chronic relapsing course despite surgery and medical therapy [15]. Allergens sensitize Th2 cells, group 2 innate lymphoid cells

(ILC2), and cytokines, such as IL-4, IL-13, and IL-5. Studies have reported the role of IL-4 in eosinophil infiltration into nasal tissues. IL-4 promotes eosinophil migration into tissues by increasing VCAM-1 expression in nasal polyp fibroblasts [16, 17]. Toll-like receptor ligands and IL-4 contribute to eosinophil infiltration specific to nasal polyp formation via MCP-4 release [18]. These studies suggest that IL-4 plays an essential role in the infiltration of eosinophils into nasal tissues, and IL-5 inhibitors may be insufficient to suppress eosinophil infiltration into nasal tissues.

In conclusion, although IL-5 inhibitors are effective in sparing glucocorticoids and preventing relapse in EGPA, our cases suggest that local infiltration of eosinophils may occur despite the suppression of eosinophils in the peripheral blood. In particular, relapse of eosinophilic sinusitis should be considered in patients undergoing treatment with an IL-5 inhibitor and a reduced dose of glucocorticoids.

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	Patient 1	Patient 2	Patient 3
At the initial presentation of EGPA			
Age [years]	56	52	60
Sex	F	F	M
Asthma	+	+	+
Sinusitis / nasal obstruction	+	+	+
Other symptoms / organ involvements	numbness weakness	purpura	fever swelling of spermatic cord
ANCA-IFT	negative	negative	negative
Anti-MPO (IgG) [U/mL]	<3.5	<3.5	<3.5
Anti-PR3 (IgG) [U/mL]	<3.5	<3.5	<3.5
At the timing of sinus biopsy / surgery			
Eosinophils [/μL]	0	38.5	9.4
GC therapy [mg/day] (PSL equivalent)	1.5	2.5	0

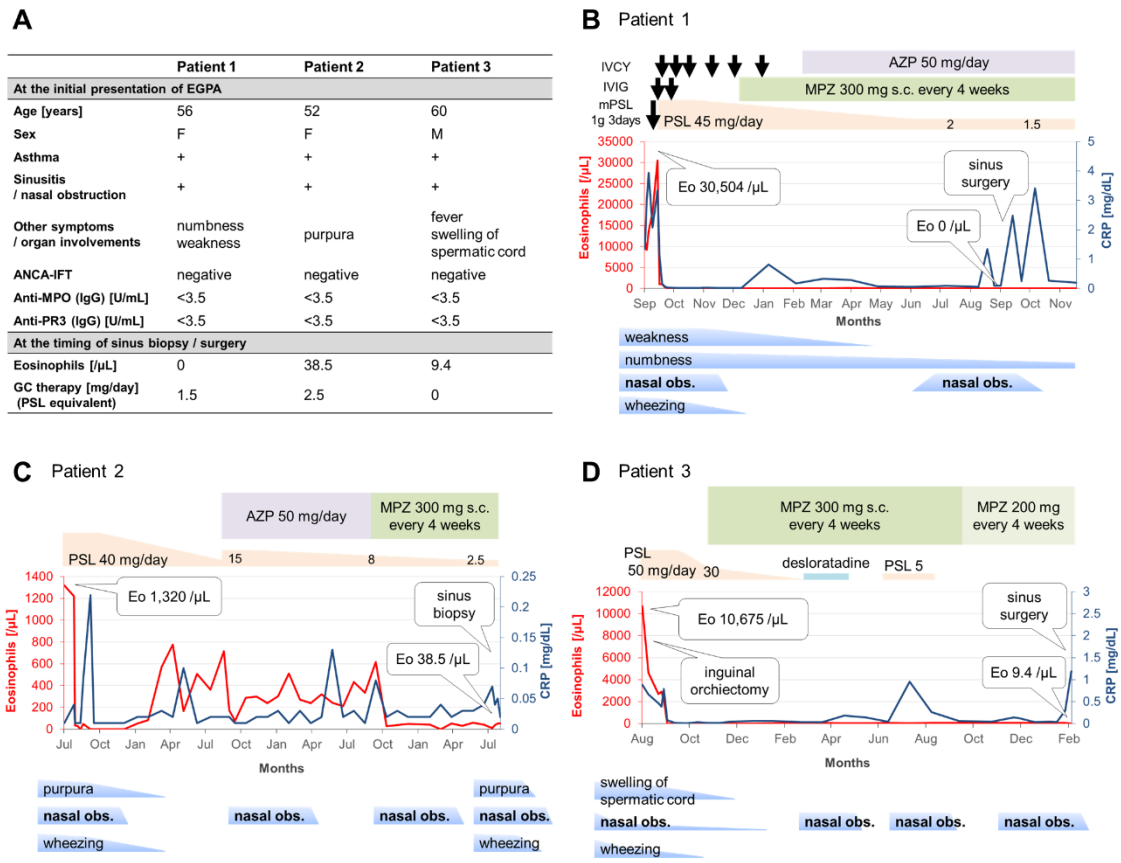


Figure Legend

Figure 1. Patient characteristics with clinical features at the initial presentation and at nasal biopsy or surgery (A). Graphical summary of treatment timeline of the first (B), second (C), and third case (D).

ANCA, anti-neutrophil cytoplasmic antibody; AZP, azathioprine; CRP, C reactive protein; EGPA, eosinophilic granulomatosis with polyangiitis; Eo, eosinophil; GC, glucocorticoid; IFT, immunofluorescence test; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; MPO, myeroperoxidase; MPZ, mepolizumab; nasal obs., nasal obstruction; PR3, proteinase3; PSL, prednisolone; s.c., subcutaneous.