

[CASE REPORT]

Eosinophilic Granulomatosis with Polyangiitis Presenting with Central Retinal Artery Occlusion During Treatment with Anti-interleukin-5 Receptor Monoclonal Antibody

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Abstract:

Eosinophilic granulomatosis with polyangiitis (EGPA) is an anti-neutrophilic cytoplasm antibody (ANCA)-associated vasculitis characterized by asthma and eosinophilia. Although EGPA involves multiple organs, ocular involvement is infrequent and often carries a poor visual prognosis. We herein report a rare case of EGPA presenting with central retinal artery occlusion (CRAO) in which visual loss developed during treatment with anti-interleukin (IL)-5 receptor monoclonal antibody, and improvement in visual outcomes was attained after treatment combining high-dose oral corticosteroids, cyclophosphamide and an anticoagulant. Physicians should consider CRAO as an ophthalmic manifestation of EGPA in patients with severe eosinophilic asthma.

Key words: eosinophilic granulomatosis with polyangiitis, central retinal artery occlusion, anti-neutrophil cytoplasmic antibody, asthma, eosinophilia

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis affecting small- to medium-sized vessels and is characterized by asthma and eosinophilia (1). Although EGPA involves multiple organs, ocular involvement is infrequent and often carries a poor visual prognosis (2, 3).

We herein report a rare case of EGPA presenting with central retinal artery occlusion (CRAO) in which visual loss developed during treatment with an anti-interleukin (IL)-5 receptor monoclonal antibody, and improvement in visual outcomes was attained after treatment combining high-dose oral corticosteroids, cyclophosphamide and an anticoagulant.

Case Report

A 53-year-old French man had been diagnosed with asthma 3 years ago and was treated with inhaled corticosteroids (ICSs) and long-acting β_2 -agonist (LABA) combination at a primary care clinic. Despite high-dose ICS/LABA treatment, the patient often experienced asthma exacerbations. The patient was therefore referred to our respiratory clinic 10 months ago.

Even with step 5 treatment of the Global Initiative for Asthma guideline, which includes high-dose ICS/LABA, a leukotriene receptor antagonist, theophylline and maintenance oral corticosteroids (OCSs), the patient's asthma remained poorly controlled. As a result of having nasal congestion and dysosmia, the patient was diagnosed with chronic rhinosinusitis with nasal polyps as a comorbidity of

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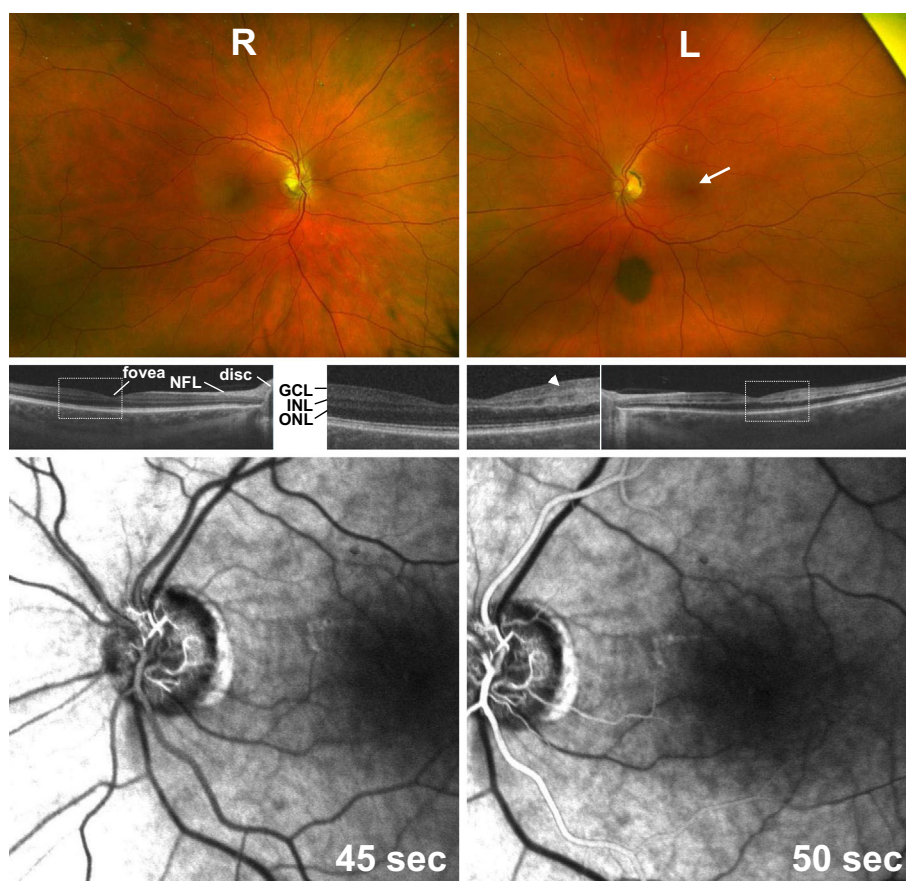


Figure 1. (top) Wide-field fundus photographs depict retinal whitening and a cherry-red spot on the left eye (arrow), which is not distinct but is identifiable compared with the fundus of the right eye. (middle) Optical coherence tomography shows hyperreflectivity of the inner retina (arrowhead) reflecting retinal whitening. Magnified images are consistent with the area of the white dotted rectangles. (bottom) Fluorescein angiograms of the left eye show a filling delay of the retinal artery with an arm-to-retina circulation time of over 45 seconds. GCL: ganglion cell layer, INL: inner nuclear layer, NFL: nerve fiber layer, ONL: outer nuclear layer

severe asthma. Despite intranasal corticosteroids, the patient's asthma did not improve. Two months ago, the patient suddenly complained of acute diplopia due to limited abduction of the right eye. No abnormalities were detected on magnetic resonance imaging of the brain and orbits. Laboratory tests showed blood vitamin B12 deficiency and eosinophilia (3,444/ μ L). Abducens nerve palsy was presumed to cause diplopia. To treat diplopia and eosinophilic severe asthma, vitamin B12 tablets and an anti-IL-5 receptor monoclonal antibody benralizumab (30 mg) were administered. Despite improvement in his diplopia, respiratory symptoms and blood eosinophilia (0/ μ L), the patient complained of acute vision loss without ocular pain in the left eye and bilateral lower leg pain and weakness.

On admission, the patient's vital signs were as follows: body temperature, 37.3 °C; oxygen saturation on room air, 95%; and heart rate, 95 beats/min. Expiratory wheezes were heard on lung auscultation. Skin purpura were observed on the bilateral lower legs. A neurological examination showed that pupils, light reflex, and extraocular movement of both eyes were normal. The best-corrected visual acuity was 20/

200 in the left eye and 20/13 in the right eye. Muscle weakness in the right lower leg and surface sensory disturbance in the bilateral lower legs were observed.

Chest computed tomography and brain magnetic resonance imaging showed no abnormalities. Laboratory data showed a white blood cell count of 9,500/ μ L (eosinophils 0%), C-reactive protein of 6.79 mg/dL, D-dimer of 2.1 μ g/mL, rheumatoid factor of 58 IU/mL, and a positive result for myeloperoxidase (MPO)-ANCA (61.8 U/mL). Additional tests, such as ophthalmological and neurological examinations, were performed. The intraocular pressures were normal. Fundoscopy revealed retinal whitening in the left eye (Fig. 1), which corresponded to hyperreflectivity of the inner retina on optical coherence tomography. A fluorescein angiogram showed delayed arterial filling with an extended arm-to-retina circulation time in the left eye (Fig. 1), confirming the diagnosis of CRAO. Echocardiography and ultrasonography of the internal carotid artery were normal. A nerve conduction study of the lower extremities revealed markedly decreased amplitudes in the multifocal sensorimotor nerves with slight decreased conduction velocities, sug-

Table. Nerve Conduction Study.

Motor nerves (Right/Left)		MCV, m/s	Latency, ms	Duration, ms	Amplitude, mV
Tibial	Ankle	40.8/37.0	3.87/4.11	4.86/6.30	0.15/0.05
	Pop. Fossa		14.52/16.53	5.67/5.67	0.10/0.03
Peroneal	Ankle	37.9/37.9	5.31/5.40	5.82/7.08	1.4/0.82
	Fibula head		15.33/14.94	6.00/7.95	1.2/0.76
	Fibula head	37.6/40.3	15.33/14.94	6.00/7.95	1.2/0.76
	Pop. Fossa		17.19/16.80	6.12/7.77	1.3/0.75

Sensory nerves (Right/Left)		SCV, m/s	Latency, ms	Amplitude, μ V
Peroneal	Ankle	36.5/39.5	3.84/3.54	1.2/0.9
Sural	Lower leg	N.E./35.4	N.E./3.96	N.E./0.8

MCV: motor conduction velocity, Pop: popliteal, SCV: sensory conduction velocity, N.E.: not evoked

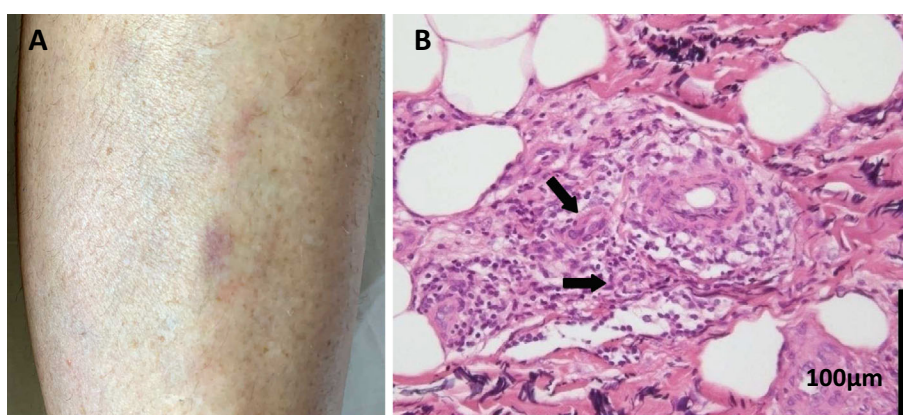


Figure 2. A) Purpura on the left lower leg. B) The result of a skin biopsy of the purpura with Elastica van Gieson staining shows infiltration of neutrophils, lymphocytes, macrophages, and multinucleated giant cells (arrows) but few eosinophils in extravascular areas.

gesting axonal multiple mononeuropathy (Table). A skin biopsy of the purpura revealed small-vessel vasculitis with neutrophils, lymphocytes, macrophages, and multinucleated giant cells but few eosinophils (Fig. 2). The patient met four of the six American College of Rheumatology 1990 criteria for EGPA (4) and all three criteria of Lanham (1), so the patient was diagnosed with EGPA.

High doses of oral prednisolone (80 mg/day) and 12 bi-weekly regimens of cyclophosphamide pulse therapy (800 mg/day) were administered to treat EGPA. Anticoagulants (4 days of intravenous argatroban hydrate followed by 10 days of intravenous heparin) were initiated to treat CRAO. The patient's respiratory symptoms of asthma rapidly improved, and his lower leg pain and weakness gradually improved. During oral prednisolone gradual tapering, treatment with benralizumab (30 mg administered subcutaneously every 4 weeks) was replaced by an anti-IL-5 monoclonal antibody, mepolizumab (300 mg every 4 weeks). After 5 months of treatment, the best-corrected visual acuity of the left eye improved to 20/28, and oral prednisolone was reduced to 5 mg/day.

Discussion

To our knowledge, this is a rare case of EGPA presenting with CRAO in which visual recovery was attained. Our case was the first to develop ophthalmic presentation during anti-asthma treatment including an anti-IL-5 receptor monoclonal antibody.

EGPA most frequently involves the peripheral nerves and upper and lower airways (1). Although ocular involvement is infrequent, it often carries poor visual outcomes. In previous reviews (2, 3), ocular manifestation was divided into two types: idiopathic orbital inflammation and ischemic vasculitis. Idiopathic orbital inflammation, including conjunctival nodules, has a chronic onset, orbital abnormalities on imaging studies, negative ANCA, and good visual outcomes in response to corticosteroid therapy (2). This type of patient most frequently presents with redness and ocular pain (3). The differential diagnosis for disorders of extraocular movement may be important to exclude causal orbital inflammation. The ischemic vasculitis type, including CRAO, has a sudden onset, no abnormalities on orbital imaging studies,

and positive ANCA findings (2). This type of patient most frequently presents with acute-onset vision loss and poor visual outcomes despite treatment (3). Given the above, our patient was classified as having the ischemic vasculitis type.

Thus far, 17 cases of EGPA presenting with CRAO have been reported (3, 5-9); however, no case developed vasculitis symptoms during treatment with an anti-IL-5 receptor monoclonal antibody. Improvement in visual acuity was obtained in only four cases (5-7). Three of those four cases were treated immediately with a combination of steroid pulse therapy and cyclophosphamide. Our patient was also treated with a combination of high-dose OCS, cyclophosphamide pulse therapy, and an anticoagulant. Early intensive treatment combining high-dose glucocorticoids and immunosuppressants may be effective for EGPA with ophthalmic involvement.

The precise pathogenesis of EGPA remains unknown. Eosinophilic inflammation is a cardinal feature of EGPA. Eosinophils are abundant both in the periphery and in EGPA lesions. Activated tissue eosinophils secrete cytotoxic granule proteins that contribute to tissue damage and inflammation (1). ANCA is also an important component of EGPA. Clinically, *in vitro* experimental and animal model observations strongly support the role of ANCA in the pathogenesis of ANCA-associated vasculitis, including EGPA (10). ANCA activates neutrophils, and activated neutrophils penetrate and attack vessel walls by releasing proteolytic enzymes and forming neutrophil extracellular traps (1, 11). In our patient, vasculitis symptoms, including CRAO and peripheral neuropathy, developed during treatment with an anti-IL-5 receptor monoclonal antibody, despite the fact that few eosinophils were present in the blood and skin lesions at the time of the diagnosis of EGPA. Serum levels of MPO-ANCA were elevated. ANCA as well as eosinophils might be involved in the development of CRAO and peripheral neuropathy. Controlling eosinophilic inflammation alone was unable to inhibit the development of vasculitis from impending forme fruste of EGPA, and ANCA might also have contributed to the development of EGPA in our patient.

We herein report a rare case of EGPA presenting with CRAO in which visual loss developed during anti-asthma treatment including an anti-IL-5 receptor monoclonal antibody and visual recovery was attained after treatment with high-dose glucocorticoids, immunosuppressants, and an anti-

coagulant. Physicians should consider CRAO as an ophthalmic manifestation of EGPA in patients with severe eosinophilic asthma. A team approach involving ophthalmologists, rheumatologists, and internists is also important in the diagnosis and management of EGPA.

The authors state that they have no Conflict of Interest (COI).

References

1. Furuta S, Iwamoto T, Nakajima H. Update on eosinophilic granulomatosis with polyangiitis. *Allergol Int* **68**: 430-436, 2019.
2. Takanashi T, Uchida S, Arita M, Okada M, Kashii S. Orbital inflammatory pseudotumor and ischemic vasculitis in Churg-Strauss syndrome: report of two cases and review of the literature. *Ophthalmology* **108**: 1129-1133, 2001.
3. Akella SS, Schlachter DM, Black EH, Barmettler A. Ophthalmic eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome): a systematic review of the literature. *Ophthalmic Plast Reconstr Surg* **35**: 7-16, 2019.
4. Masi AT, Hunder GG, Lie JT, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). *Arthritis Rheum* **33**: 1094-1100, 1990.
5. Bastiaensen LA. Chronic progressive external ophthalmoplegia. *Bull Soc Belge Ophthalmol* **237**: 381-423, 1989.
6. Kamata Y, Hashizume K, Kaneko M, Kurosaka D. A case of Churg-Strauss syndrome and central retinal artery occlusion with good visual recovery. *Indian J Ophthalmol* **61**: 178-179, 2013.
7. Reddy AK, Lau MK, Sieck EG, Kolffenbach JR, Palestine AG. Retinal artery occlusion followed by contralateral amaurosis fugax in association with eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Am J Ophthalmol Case Rep* **18**: 2020. published Online First.
8. Man BL, Fu YP, Shum KS, Mok CC. Bilateral central retinal artery occlusion in a patient with Churg-Strauss vasculitis. *Clin Exp Rheumatol* **29**: S137, 2011.
9. Asako K, Takayama M, Kono H, Kikuchi H. Churg-Strauss syndrome complicated by central retinal artery occlusion: case report and a review of the literature. *Mod Rheumatol* **21**: 519-523, 2011.
10. Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. *Curr Opin Nephrol Hypertens* **20**: 263-270, 2011.
11. Fagni F, Bello F, Emmi G. Eosinophilic granulomatosis with polyangiitis: dissecting the pathophysiology. *Front Med* **8**: 627776, 2021.

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