Respiratory Medicine Case Reports 47 (2024) 101980

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case Report

Intravenous cyclophosphamide and immunoglobulin ameliorated visual field defects in a patient with eosinophilic granulomatosis with polyangiitis

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ARTICLE INFO

Keywords:
ANCA-Associated vasculitis
Cyclophosphamide
Eosinophilic granulomatosis with polyangiitis
IVIG
Optic neuritis
Visual field defects

ABSTRACT

Treating ocular involvement in eosinophilic granulomatosis with polyangiitis (EGPA) can be challenging. We present the case of a 37-year-old woman with EGPA who had severe bilateral visual field defects. Laboratory results showed leukocytosis (17,500 WBC/μL, 25.8 % eosinophils), negative MPO-ANCA titer, and elevated PR3-ANCA level (33.2 IU/mL). Diffusion-weighted MRI revealed bilateral hyperintense occipital lesions, which were more prominent on the left. Her therapy initially included a steroid pulse, followed by daily prednisolone, but her visual field defects remained refractory. The addition of intravenous cyclophosphamide (5 courses) and intravenous immunoglobulin decreased her optic neuropathy and resolved her visual field defects.

1. Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is a vasculitis characterized by an abnormally high number of eosinophils in the peripheral blood and tissues [1]. Patients with EGPA manifest several types of ocular lesions, including occlusion of the central retinal artery or vein, ischemic optic neuropathy, conjunctival nodules, orbital myositis, ptosis, and dacryocystitis. In one study, 11.1 % (30/270) of patients presented with eye lesions [2]. Among those patients, 30 % (9/30) had visual field defects, and 13.3 % (4/30) had loss of vision. In a second report, 67 % (18/27) of patients with EGPA had persistent visual field defects even after treatment with steroids and immunosuppressants [3]. In another study, EGPA patients with ischemic ocular vasculitis failed to respond to immunosuppressive therapy beyond steroids [4]. These previous studies collectively indicate that ocular involvement in EGPA can be challenging to treat.

Here we report a patient with EGPA and steroid-resistant optic neuropathy whose visual field defects responded dramatically after we added intravenous cyclophosphamide (IVCY) and intravenous immunoglobulin (IVIG) to an increased dose of corticosteroids. Our

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https://doi.org/10.1016/j.rmcr.2024.101980
Received 10 September 2023; Received in revised form 31 December 2023; Accepted 6 January 2024
Available online 9 January 2024

case illustrates that, for patients with visual field disorders, improving their visual field improves their quality of life, which more valuable than prolonging their lifespan.

2. Case

A 37-year-old woman presented to our hospital with a 3-kg weight loss that had occurred gradually over the previous 3 months, generalized fatigue, blurry or decreased peripheral vision (especially on the left), dyspnea on exertion, abdominal pain, and diarrhea. She also noted arthralgias, purpura, difficulty walking, numbness in the fingertips of both hands, and muscle weakness in the right hand and both lower limbs. Her previous medical history was noteworthy for asthma, which had been diagnosed 3 years previously (at age 34) and was treated with budesonide–formoterol and a leukotriene antagonist. In addition, she was never a smoker and was employed as an office worker. In summary, the patient's main complaints at the time of examination were left hemiplegia, diarrhea, abdominal pain, and visual field disturbance in the left hemianopia.

Physical examination findings included normal breath sounds on auscultation. The abdomen was soft on palpation, with no muscular guarding and with normal bowel sounds. Indicating a peripheral neuropathy, the muscle strength of the left fingers and during dorsiflexion, dorsiextension, and abduction of the left foot were all at a Manual Muscle Test (MMT) level of 4. Our patient's eye examination revealed severe visual field defects on both sides, especially in the lower left region. In particular, her visual findings included central scotoma in the lower left quadrant in left eye, and 1/4 hemianopia in the lower left quadrant of right eye.

Her laboratory test results showed leukocytosis of 17,500 WBC/μL, 25.8 % of which were eosinophils; C-reactive protein concentration of 16.2 mg/dL; erythrocyte sedimentation rate of 42 mm in 2 h; a negative anti-myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) titer; and an elevated anti-proteinase 3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) level of 33.2 IU/mL (normal, 3.5 IU/mL or less). Rheumatoid factor and immune complex assays were negative. The total serum IgE level via radioimmunosorbant test (RIST; 91.4 IU/mL) was within the normal range, and the IgE radioallergosorbant test (RAST) for house dust mites was positive.

A computed tomography scan of the sinuses showed right maxillary sinusitis. Brain MRI diffusion-weighted images (DWI) showed bilateral occipital hyperintense lesions, more prominent on the left than the right (Fig. 1(a)). Given our patient's clinical, laboratory, and radiologic findings, we diagnosed acute cerebral infarction associated with EGPA.

We performed additional tests to evaluate the extent of multisystem involvement in her disease. Lower gastrointestinal endoscopy revealed erosions and dark-red lesions, which are characteristic endoscopic mucous membrane findings in patients with EGPA [5]. A biopsy sample from the ascending colon revealed submucosal eosinophil infiltration. Echocardiography showed an ejection fraction of 74 %, whereas cardiac scintigraphy with ^{123}iodine-labeled metaiodobenzylguanidine (^{123}I-MIBG) revealed spotty accumulation of MIBG in the anterior septum to the apex, consistent with mild cardiomyopathy, and an elevated washout rate of 37.1 %, suggestive of cardiac dysfunction.

Given the extent and severity of the organ system involvement in her disease process, we administered a methylprednisolone pulse (1000 mg intravenous injection daily for 3 consecutive days) and treated her with oral prednisolone (PSL), 30 mg daily for 1 month, tapered monthly by 5–10 mg to 2.5 mg daily. Her abdominal pain, arthralgias, purpura, and multiple polyneuropathies decreased, but her visual field defects, dyspnea on exertion, and fatigue did not respond. On subsequent fluid-attenuated inversion recovery (FLAIR) and DWI MRI scans 3 months after starting corticosteroids, the high-intensity lesions in the optic nerve region of the occipital lobe had decreased in size, whereas the T2-weighted images (T2WI) indicated an old infarction at the same site (Figs. 1(b)–Fig. 3). Visual field testing at this time revealed the left half of the visual field was severely deficient in both the right (Fig. 2(a), Fig. 3) and left eyes, particularly in the left lower quadrant of the left eye (Figs. 2(b)–Fig. 3).

Due to the persistence of our patient's ocular lesions, we increased her PSL dose to 10 mg daily, added 700 mg of intravenous cyclophosphamide (IVCY) every 3 weeks for 5 courses, and administered the first dose of IVIG after the third course of IVCY (Fig. 3). Her steroid-resistant optic neuropathy responded favorably to the revised treatment, and her visual field defects decreased. The high-intensity lesions were barely visible on FLAIR and DWI and were decreased on T2WI images (Figs. 1(c)–Fig. 3). A second visual field test (Fig. 2(c) right (d) left, Fig. 3), was performed 4 months after the first. After the IVCY and second IVIG, the 2 hyporeflective lesions in the lower left half had decreased modestly in size, all but one dark spot had faded and regressed, and many scotomas disappeared. As her vision improved, our patient was able to walk without looking down. In addition, her dyspnea on exertion and fatigue resolved, and the cardiothoracic ratio decreased from 43.7 % at diagnosis to 33.6 %.

The IVCY dose was tapered to 600 mg every 4–5 weeks for 7 courses, and the PSL dose was reduced by 2.5-mg decrements from 10 mg to 5 mg daily without recurrence of the visual field defects or cardiac symptoms.

The ethics committee at the Yokohama Medical Center approved the study (No. 2022–6) in 2022, and written informed consent was obtained from this patient.

3. Discussion

Our patient followed the characteristic clinical course of EGPA patients as outlined in the Japanese Ministry of Health, Labor, and Welfare diagnostic criteria for “allergic granulomatosis angiitis/Churg–Strauss syndrome (AGA/CSS)” [6], as EGPA was known formerly. Her vasculitis, polyneuritis, central nervous system involvement, mild cardiomyopathy, eosinophilic colitis, arthritis, and purpura followed the onset of asthma and elevated peripheral blood eosinophil levels [7].

We consider a thorough multi-component assessment necessary even when patients describe symptoms strongly indicative of EGPA as their chief complaints. First, patients cannot convey to their doctors descriptions that are sufficiently detailed for diagnosis. Second, vasculitis can present with few, often subjective, symptoms. For these reasons, we find a robust combination including med-

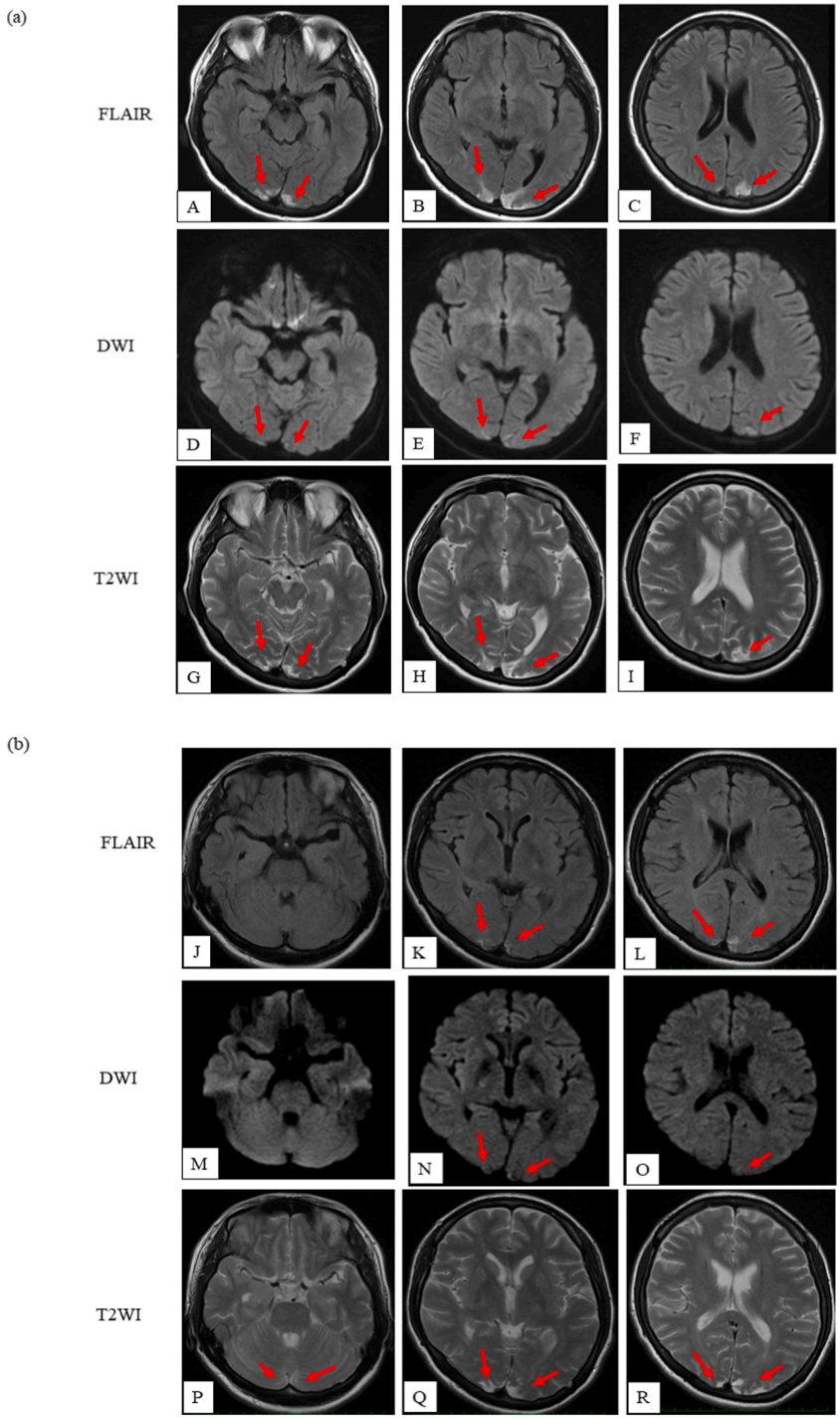

Fig. 1. Axial brain MRI images before, during, and after treatment with PSL, IVCY, and IVIG.
Pretreatment images (a) show high-intensity lesions (red arrows) in the optic nerve region of the occipital lobes on FLAIR (A, B, C), DWI (D, E, F), and T2WI (G, H, I), confirming acute cerebral infarction at diagnosis. Axial MRI images 3 months after starting PSL (b). The high-intensity lesions (red arrows) in the occipital lobe optic nerve region decreased in size on FLAIR (J, K, L) and DWI (M, N, O), whereas the T2WI images (P, Q, R) indicated an old infarction at the same site. Seven months after starting PSL, 1 month after the 5th IVCY dose, and 2 months after IVIG (c), the high-intensity lesions were barely visible (red arrow) on FLAIR (S, T, U) and DWI (V, W, X) and decreased (red arrows) on T2WI (Y, Z, AA) images.

Fig. 1. *(continued)*
Abbreviations: DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; PSL, prednisolone; T2WI, T2-weighted image. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

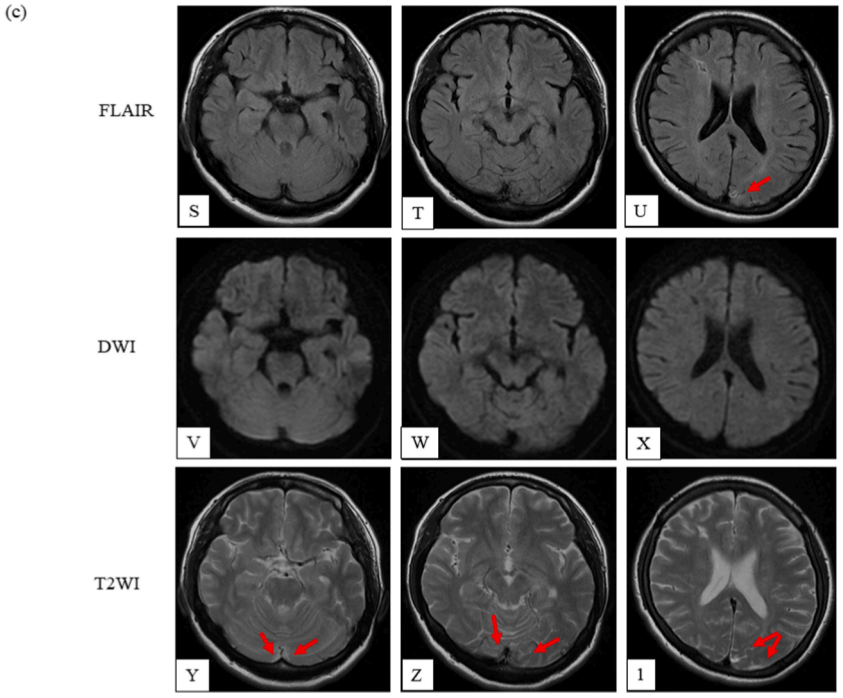

Fig. 1. (*continued*)

ical history, clinical examination, clinical pathology, and radiographic imaging important for accurate diagnosis of EGPA. We applied this practice rationale to the patient whose case we present here.

The visual field defects in patients with EGPA may persist despite treatment with steroids and immunosuppressants [3]. Among 46 patients with ocular symptoms associated with EGPA, ischemic optic neuropathy was the second most common cause of central retinal artery and vein vasculitis. Cases of ischemic vasculitis require intense immunosuppressive therapy and are unlikely to show improvement on steroid therapy alone [4].

Although IVIG has been used effectively to treat peripheral neuropathy and cardiac dysfunction in patients with EGPA [8], our review of the literature did not yield any reports regarding its effectiveness in patients with optic neuritis. However, IVIG has been shown to be effective in neuromyelitis optica [9], facial paralysis [10], and vasculitis-associated cerebral infarction [11]. In patients with facial paralysis and cerebral infarction, their symptoms resolved only after IVIG was added to steroids and cyclophosphamide. Likewise, in the patient we report here, the visual field defects persisted even though we increased her steroid dose (indicating that her optic neuropathy was steroid resistant) and resolved only after we added cyclophosphamide at an initial treatment and included IVIG. We previously reported an increase in FOXP3+ frequency among $CD4^+$ regulatory T cells and improved peripheral and central neuropathy symptoms and cardiac function in a cohort of patients with EGPA for whom IVIG was added to standard therapy [12]. We also demonstrated that adding IVIG could reduce the PSL maintenance dose [12] and showed that IVIG might improve the prognosis of patients with EGPA with cardiac involvement [13]. Our current findings support similar inclusion of IVIG in EGPA patients with ocular lesions.

In conclusion, adding intravenous cyclophosphamide and IVIG to corticosteroids substantially ameliorated visual field defects in our patient with steroid-resistant EGPA-associated optic neuritis. Additional clinical trials are needed to establish this promising triple-drug combination as a treatment for patients with EGPA and refractory multisystem involvement.

4. Bullet points

1. 11.1 % (30/270) of patients presented with eye lesions in EGPA patients. Among those patients, 30 % (9/30) had visual field defects, and 13.3 % (4/30) had loss of vision.
2. The visual field defects in patients with EGPA may persist despite treatment with steroids and immunosuppressants
3. Optic neuropathy responded favorably and her visual field defects resolved by treatment of IVIG was added to steroids and cyclophosphamide.

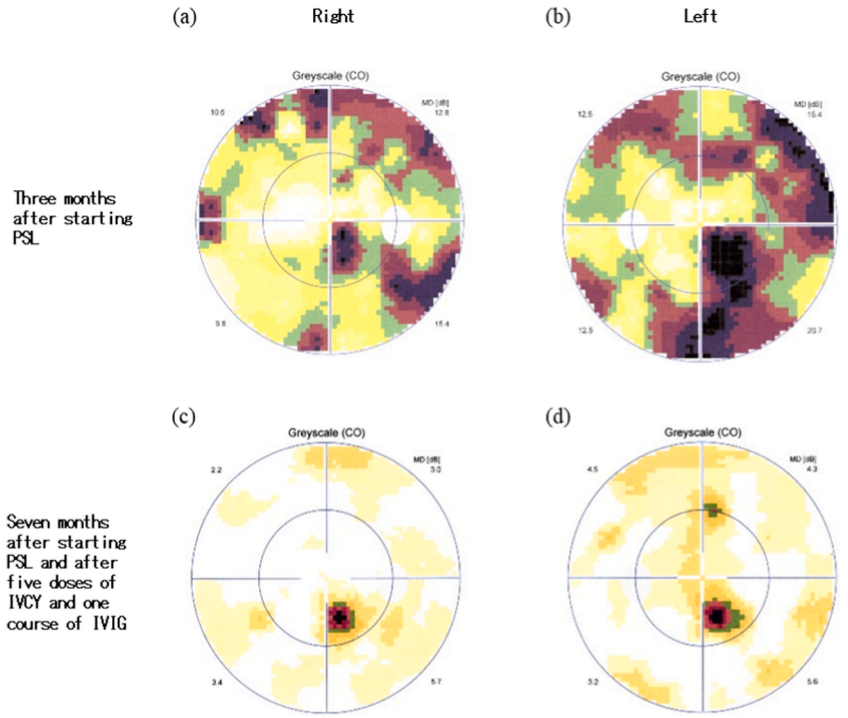

Fig. 2. Visual field tests by Optical Coherence Tomography of the Peripapillary Retina and ON-Hogging Vessels in Glaucoma Suspects (OCTOPUS) at 3 and 7 months after treatment initiation.
The visual field test at 3 months coincides with the brain MRI in Fig. 1(b). The left half of the visual field was severely deficient in both the right (a) and left (b) eyes, particularly in the left lower quadrant of the left eye (b). The second visual field test (c, right; d, left), performed 4 months after the first, coincides with the brain MRI in Fig. 1(c). After the second IVCY course, the 2 hyporeflective lesions in the lower left quadrant were decreased in size, and after IVIG therapy, all but one dark spot had faded and regressed, and many scotomas had disappeared.
Abbreviations: IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; PSL, prednisolone.

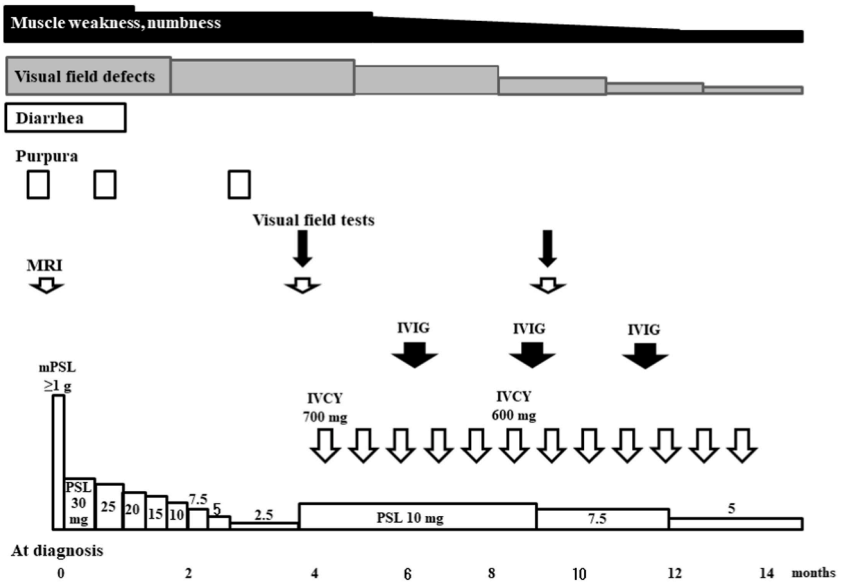

Fig. 3. Clinical course of our patient from diagnosis of eosinophilic granulomatosis with polyangiitis until clinical remission. Abbreviations: IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; PSL, prednisolone.

CRediT authorship contribution statement

Yuto Motobayashi: Writing – original draft, Investigation. **Chiyako Oshikata:** Methodology, Investigation. **Yuka Kodama:** Investigation. **Kosuke Terada:** Visualization, Investigation. **Yuga Yamashita:** Investigation. **Ryo Nakadegawa:** Investigation. **Hinako Masumitsu:** Investigation. **Reeko Osada:** Investigation. **Hirokazu Takayasu:** Investigation. **Nami Masumoto:** Investigation, Data curation. **Saki Manabe:** Investigation. **Takeshi Kaneko:** Visualization, Methodology. **Akira Shiraishi:** Visualization, Supervision, Conceptualization. **Naomi Tsurikisawa:** Writing – review & editing, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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