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Polyarteritis nodosa initially presenting as ocular motility impairment and diplopia with subsequent development of bilateral central retinal artery occlusion: A case report

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ABSTRACT

Purpose: Polyarteritis nodosa (PAN) is a systemic vasculitis of unknown etiology affecting medium- and small-sized arteries and can present with varied organ involvement, including ocular manifestations. Here, we report a unique case of PAN that initially presented with diplopia and ocular motility impairment, with subsequent development of bilateral central retinal artery occlusion (CRAO), a rare ocular manifestation of PAN.

Observations: A 58-year-old man presented with left abduction impairment and diplopia, which initially improved without intervention. However, similar symptoms recurred in the right eye later. The patient presented to the ophthalmology department and was initially suspected of having orbital myositis related to IgG4 disease owing to elevated IgG4 levels. Subsequently, the patient developed bilateral CRAO, confirmed using fundus fluorescein angiography, resulting in remarkable visual loss. Despite negative autoantibodies, a high inflammatory response, and symptoms suggestive of systemic involvement (myalgia, hematuria, muscle weakness, and gastrointestinal symptoms), PAN was diagnosed following laparotomy for intestinal perforation, revealing vasculitis in the medium-to-small arteries.

Conclusions and importance: This case underscores the importance of considering a possible diagnosis of PAN in patients with ocular motility impairments and diplopia, even in the absence of classic systemic symptoms. PAN can rapidly progress to severe visual dysfunction, including bilateral CRAO, as observed in this case. Consequently, early recognition and treatment of PAN are crucial, given its potentially severe complications and poor prognosis. Further, this report contributes to the limited literature on PAN, emphasizing the need for awareness of the rare ocular manifestations of systemic vasculitis

1. Introduction

Polyarteritis nodosa (PAN) causes necrotizing vasculitis of unknown cause, characterized by fibrinoid necrosis in multiple organs throughout the body (vasculitis syndrome), resulting in inflammation of the vessel walls of medium and small arteries and perivascular inflammatory cell infiltration.[1] PAN presents with a variety of symptoms throughout the body, including in the ocular tissue. Notably, untreated PAN has a poor prognosis. It occurs more frequently in men than in women and is found in all ethnic groups. The average age of onset is approximately 50 years, with a peak incidence in the fifth and sixth decades of life.[2]

Ocular involvement in PAN occurs in 10–20 % of cases and includes scleritis, peripheral ulcerative keratitis, non-granulomatous uveitis, retinal vasculitis, orbital pseudotumor, anterior ischemic optic neuropathy, and central retinal artery occlusion (CRAO).[3] However, few studies have reported that diplopia due to cranial nerve impairment may be a precursor symptom of PAN. Furthermore, CRAO is a less known complication of PAN.

Here, we present a case of bilateral retinal artery occlusion, initially presenting with diplopia and ocular motility impairment, followed by a diagnosis of PAN.

2. Case report

A 58-year-old man first presented to the neurologist at our institution in early 2020 with diplopia and an abduction impairment in the left eye,

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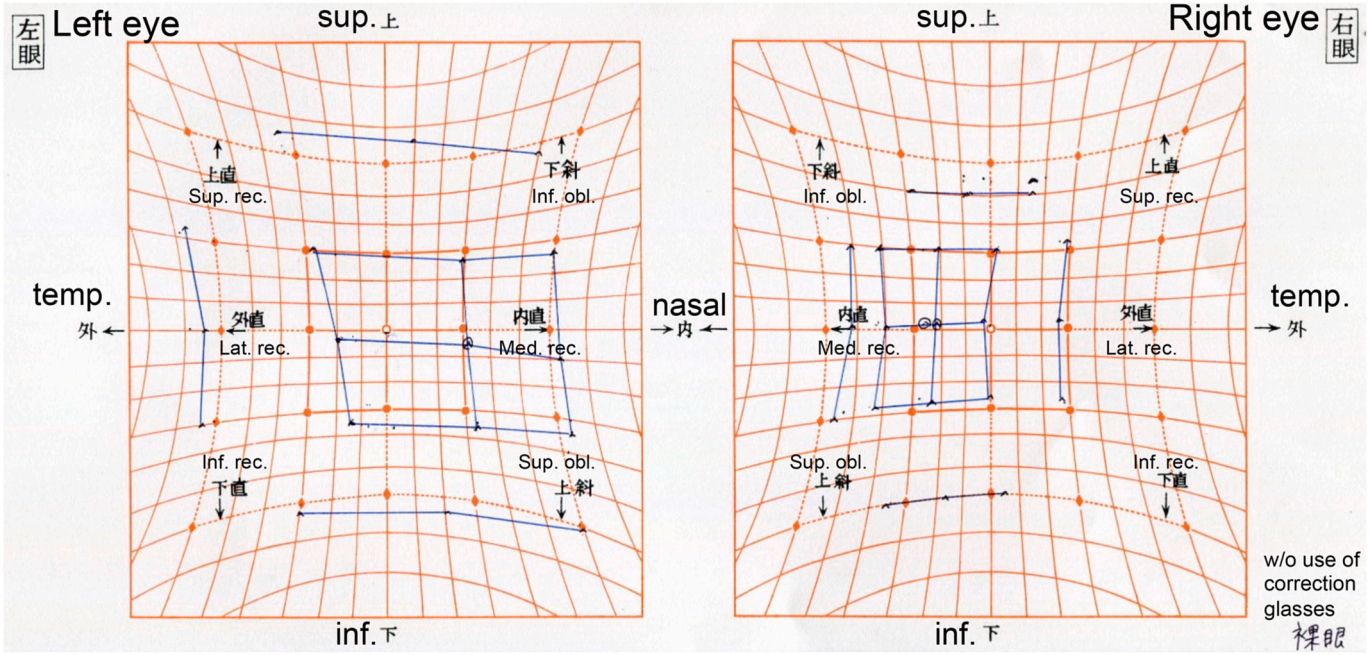

Fig. 1. Hess chart. The patient had an impairment of the adduction, abduction, and elevation in the right eye.

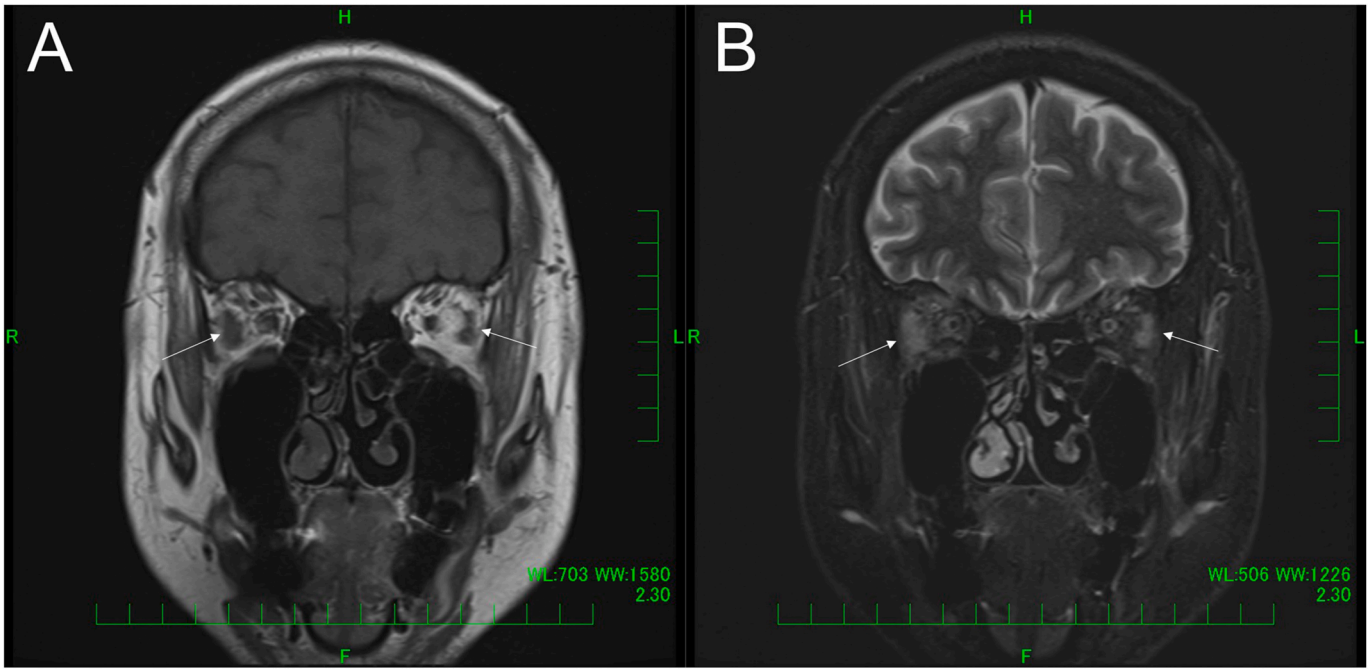

Fig. 2. Magnetic resonance imaging of the head shows slight enlargement of the bilateral lateral rectus muscles (A, arrows), particularly the lateral rectus muscle of the right eye. Short tau inversion recovery shows a slightly high signal in the lateral rectus muscles of both eyes (B, arrows).

which later improved without treatment. Subsequently, he exhibited an abduction impairment of the right eye, which improved without treatment. Autoantibody test results, including those for anti-SS-A antibodies, anti-SS-B antibodies, anti-acetylcholine receptor antibody, anti-double-stranded DNA antibodies, anti-nuclear antibody, *anti*-cardiolipin antibodies, C-ANCA, and MPO-ANCA, were negative, except for a slightly elevated lupus anticoagulant ratio of 1.38 (reference: <1.2) and elevated IgG4 level of 178 mg/dL (reference: 11.0–121.0 mg/dL). The patient presented to the ophthalmology department a few months later for suspected orbital myositis associated with IgG4-related disease. Around this time, the myalgia in both lower extremities, which had been present for a few weeks, gradually worsened; hematuria was also observed. Best correct visual acuity (BCVA) was within the normal range (1.2, decimal) in both eyes. The eyes had 18 prismatic esotropia at near and 30 prismatic esotropia at distance. Slight ptosis was observed in the right eye, the relative afferent pupillary defect was negative, and the light reflex was unremarkable. However, the right eye exhibited adduction, elevation, and abduction impairments (Fig. 1), and the lateral rectus muscle was slightly enlarged, particularly in the right eye (Fig. 2). In addition, short tau inversion recovery of magnetic resonance imaging (MRI) showed a slightly high signal in the lateral rectus muscles of both eyes (Fig. 2). No lacrimal or salivary gland swelling was

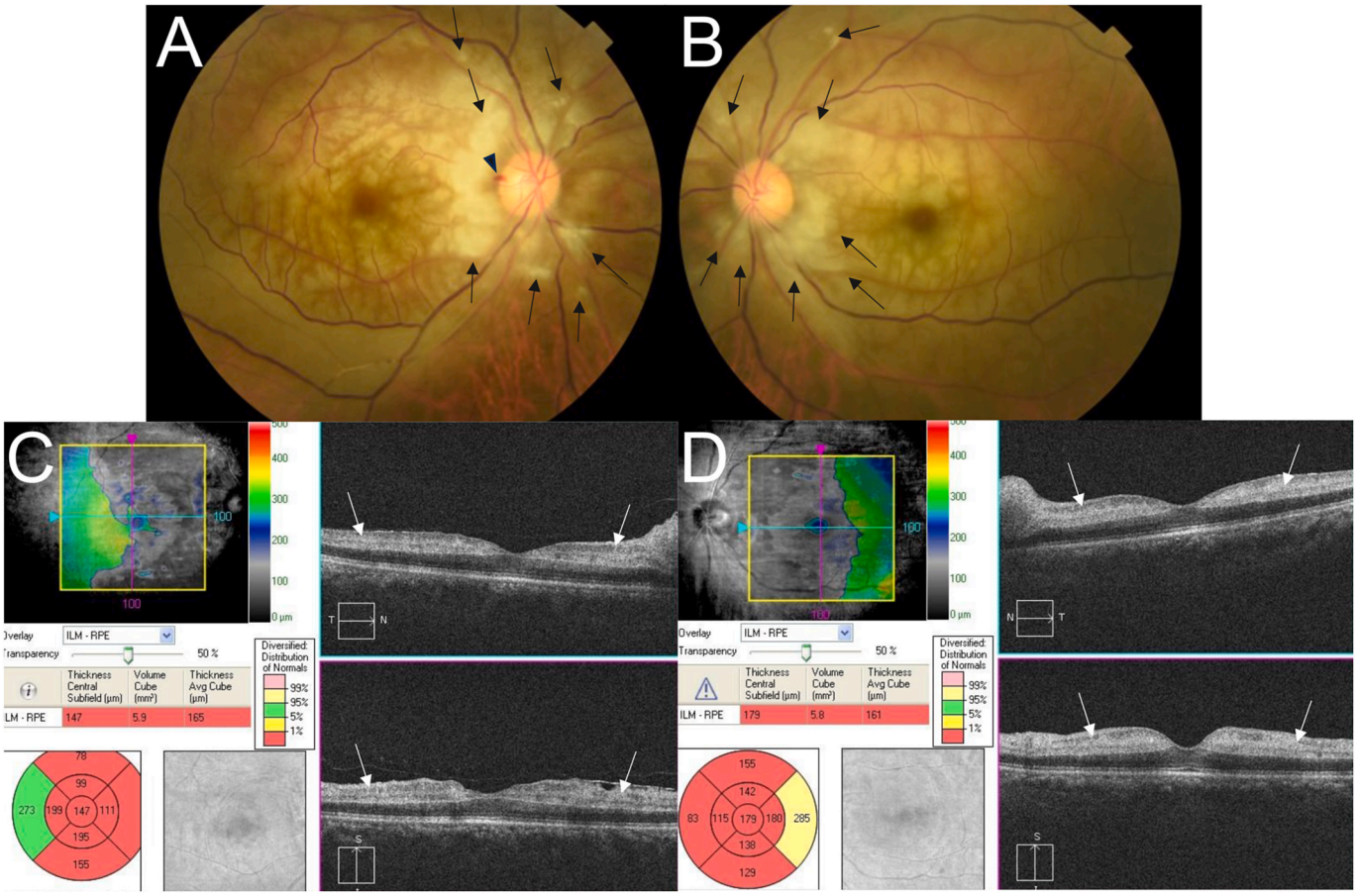

Fig. 3. Fundus photograph (A, B) 5 days after significant loss of vision in both eyes. Cotton wool spots (A, B, arrows), retinal pallor, retinal edema, and cherry red spots are seen in both eyes. Papillary hemorrhage is also seen in the right eye (A, arrow head).
Optical coherence tomography findings obtained on the same day (C, D) demonstrate a highly reflective zone (arrows) within the inner retinal layers. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

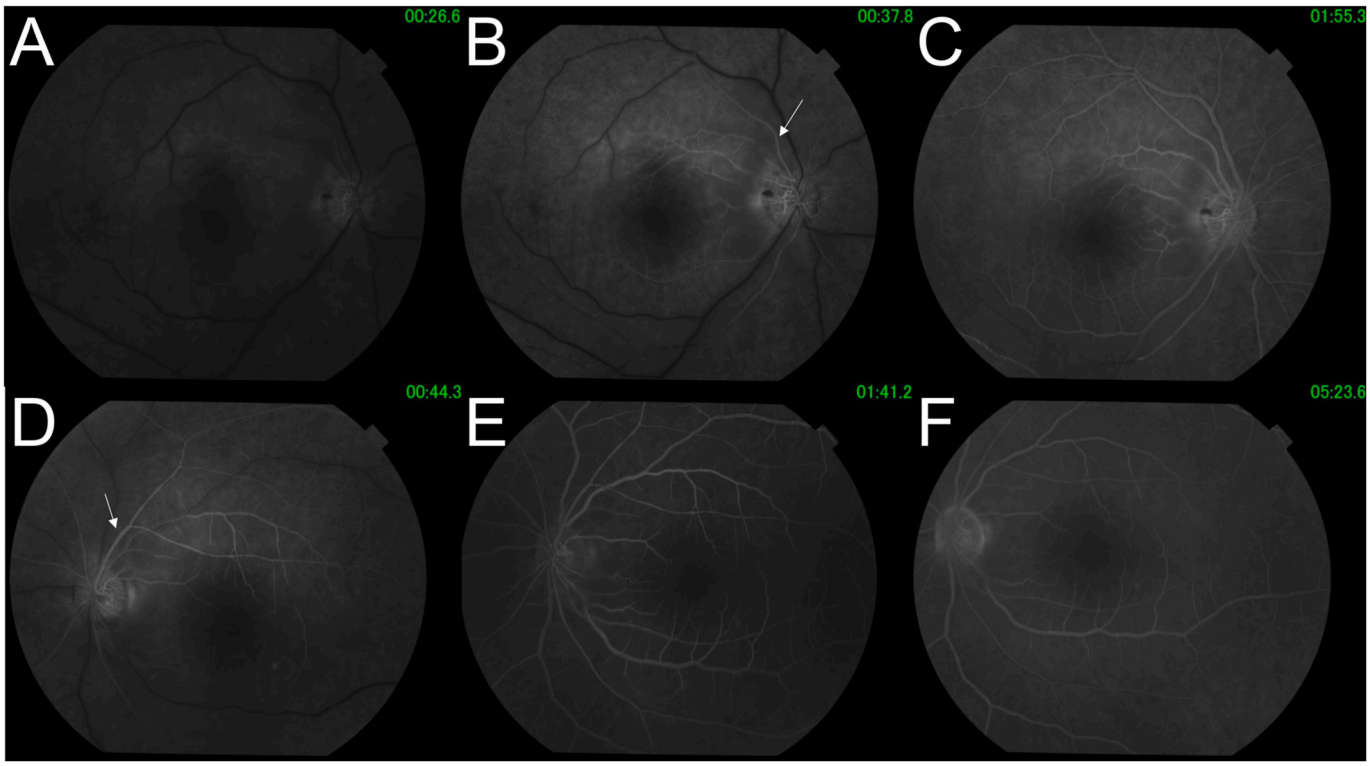

Fig. 4. Fundus fluorescence angiography. Right eye (A, B, and C): no retinal artery contrast is observed until 26 s after the start of contrast (A), showing delayed circulation; 37 s after the start of contrast (B), perfusion of the upper retinal artery is seen (B, arrow), as well as delayed venous phase (C). Left eye (D, E, and F): similarly, the left eye clearly shows circulatory delay with only perfusion of the superior retinal artery at 44 s of contrast (D, arrow), and a delayed venous phase is observed (E, F).

observed. No intraorbital inflammation or mass was noted. MRI findings were not typical enough for IgG4-related disease.

The patient reported experiencing intermittent foggy vision and fluctuating visual acuity in the right eye, with symptoms that alternately improved and then worsened. After a few days, the patient's condition had deteriorated. The same pattern of symptoms was noted in the left eye and continued to worsen. Shortly thereafter, the patient experienced weakness in the extremities (especially in both hands and the distal muscles of the left lower extremity), numbness in both hands, pain in both thighs and lower legs, stuttering, loss of appetite, and lost control of bowel movements and gas emissions. The patient visited the Ophthalmology and Neurology outpatient clinics. At the time of presentation, the right and left eye decimal BCVA was 0.02 and 0.01, respectively, the ocular position was ortho, and oculomotor examination showed a slight limitation in right eye abduction. Anterior segment slit-lamp examination was normal, and the intraocular pressure was 14 mmHg each in both eyes. However, posterior segment examination revealed remarkable retinal clouding and edema with papillary hemorrhage, cottony white spots, and cherry-red spots in both eyes (Fig. 3). Optical coherence tomography (OCT) detected a highly reflective zone extending from the inner retinal layers (Fig. 3). Further, fundus fluorescein angiography revealed delayed contrast in the retinal arteries, with no visible perfusion until 26 s and only superior retinal artery perfusion at 37 s, indicating circulatory and venous phase delays in the right eye (Fig. 4). In the left eye, perfusion of the superior retinal artery was noted at 44 s, with pronounced circulatory and venous phase delays (Fig. 4). These observations were indicative of bilateral CRAO.

The blood pressure was 166/101 mmHg. Blood test results revealed a high leukocyte count of 22,530 cells/μL (reference: 3900–9800 cells/μL), blood sedimentation rate of 88 mm/h (reference: 2–10 mm/h), c-reactive protein level of 30.90 mg/dL (reference value: ≤0.14 mg/dL), a high inflammatory response, hypoalbuminemia, elevated hepatobiliary enzymes, and hematuria on urinalysis, with no elevation in creatine kinase level. Other findings were as follows: IgG4, 178 mg/dL (reference: 11.0–121.0 mg/dL); IgG, 821 mg/dL (reference: 870–1700 mg/dL); lupus anticoagulant, 1.38 ratio (reference: ≤1.2); and sIL-2R, 2090 U/mL (reference: 157–474 U/mL). Other autoantibody levels were not abnormal; tests for hepatitis B/C were negative. Moreover, MRI revealed a new fluid-attenuated inversion recovery high signal, high diffusion-weighted imaging, and low apparent diffusion coefficient in the left thalamus, bilateral occipital lobes, and left corpus callosum of the head, suggesting multiple cerebral infarctions. The peripheral neuropathy was diagnosed as mononeuritis multiplex.

We suspected vasculitis and IgG4-related disease due to the high degree of inflammation, multisystemic nature of the symptoms, particularly strong ocular symptoms, and high IgG4 level (178 mg/dL). Therefore, on the same day, methylprednisolone infusion (1 g/day) was initiated and administered for 3 days, followed by steroid pulse therapy. The patient was started on a 1 mg/kg dose of oral medication. However, within a couple of weeks, the patient developed acute abdominal pain and gastrointestinal tract perforation; therefore, he was referred to the department of surgery and underwent an emergency laparotomy on the same day. The small intestine was perforated. Consequently, the affected segment of the intestinal tract was surgically resected. Histopathological examination revealed ischemia and perforation of the small intestine due to vasculitis of the medium-sized major arteries to some small arteries (Fig. 5) and no abnormalities of autoantibodies, including ANCA. Consequently, the patient was diagnosed with PAN.

Treatment with cyclophosphamide pulse therapy at 500 mg/dose every 3 weeks, with concomitant tapering of prednisolone, was initiated. Four courses of cyclophosphamide pulse therapy were administered. The swelling of the lateral rectus muscle showed improvement. OCT demonstrated marked atrophy of the inner retinal layers (Fig. 6). Unfortunately, there was no improvement in visual acuity, and the decimal BCVA after 3 years was perception of light (PL) in the right eye and 0.03 in the left eye.

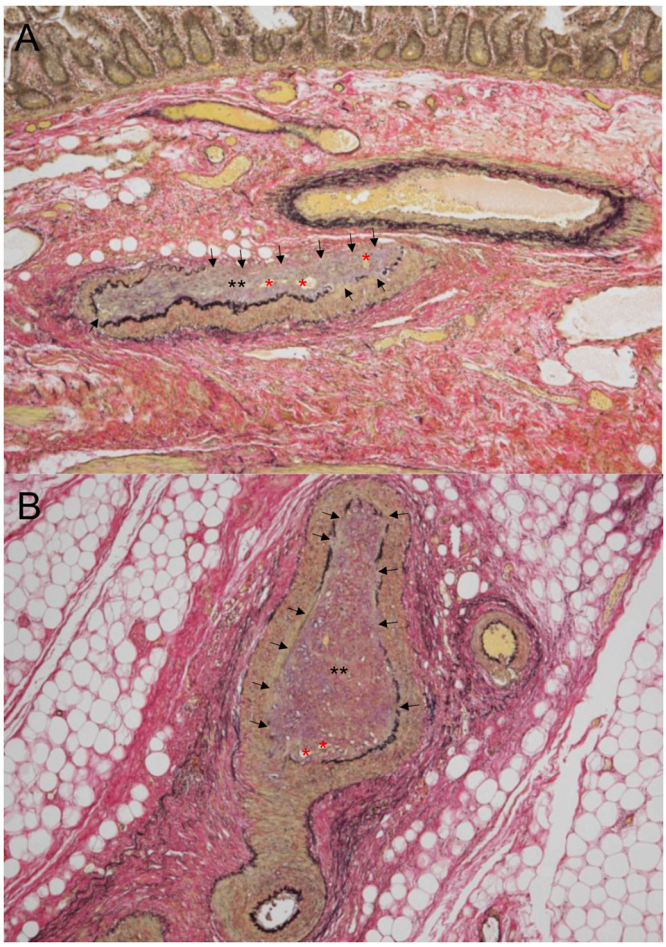

Fig. 5. Histopathology images demonstrating arteritis affecting medium-sized and small arteries within the intestinal wall (A) and mesenteric adipose tissue (B), stained with Elastica van Gieson (EVG). The images show luminal narrowing caused by organized thrombi (double asterisks) and recanalization (red asterisks) of organized thrombi. EVG staining reveals disruption of the internal elastic lamina (arrows). Magnification: 40x (objective 4x). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3. Discussion

Here, we described a case wherein the patient initially presented with diplopia and ocular motility impairment. Orbital myositis due to IgG4-related disease was suspected; however, the patient developed bilateral CRAO, which was subsequently diagnosed as PAN. This case highlights that systemic vasculitis, such as PAN, should be strongly suspected in patients presenting with diplopia or bilateral CRAO, particularly when accompanied by systemic symptoms.

The diagnostic criteria for IgG4-related ophthalmic disease include clinical examination findings such as characteristic swelling or masses in ophthalmic tissues, elevated serum IgG4 levels (≥135 mg/dL), and histopathological evidence of lymphoplasmacytic infiltration with IgG4+ plasma cells, meeting specific ratio and cell count thresholds.[4,5] In this case, we observed enlargement of the lateral extraocular muscles and an elevated IgG4 level (175 mg/dL), indicating that this case is only considered a "possible" case of IgG4-related ophthalmic disease.

Miteva et al.[6] reported the case of a 67-year-old man with a diagnosis of PAN initially presenting with diplopia, abnormal muscle pain in the lower extremities, and gait disturbance. In our case, the presence of lower extremity pain and walking difficulties aligns with the findings reported by Miteva et al.[6] Visual and oculomotor symptoms are considered rare findings in PAN[6,7]; however, diplopia may be a precursor symptom of systemic PAN.[6] In the case of Miteva et al. the diplopia preceded the onset of cutaneous symptoms by 2–3 months and was transient.[6] In our case, diplopia also preceded the onset of the bilateral CRAO and walking difficulties and was transient. The potential etiology of the ocular motility impairment could be cranial nerve lesions, such as oculomotor and abducens nerve palsy, attributable to PAN. Cranial nerve involvement in PAN is uncommon and occurs less frequently than central nervous system lesions or peripheral neuropathy. A literature review indicates that the optic (II), oculomotor (III), trochlear (IV), and abducens (VI) nerves are the affected cranial nerves in PAN cases.[6,8] Moreover, oculomotor nerve palsy is the first reported manifestation of PAN, although it is rare.[8] Destructive involvement of the arterial walls of the vasa nervorum of these nerves can cause extraocular muscle paralysis and failure of simultaneous eye rotation.[6,8]

Other possible causes of diplopia due to PAN include ischemia and extraocular muscle dysfunction, resulting in ocular paralysis and diplopia.[9] PAN can cause diffuse orbital inflammation, leading to ectropion, limited ocular movement, conjunctival hyperemia, and decreased visual acuity. There have been a few reports on PAN-related ectropion and orbital inflammation.[9–13] However, all these signs and symptoms are secondary to the mass effect of vasculitis occurring in the orbit. Nonetheless, in our case, there was no evidence of intraorbital inflammation or mass. Moreover, there were no inflammatory findings in the external or anterior ocular areas in our case.

Posterior ocular findings of PAN include branch retinal and CRAOs, ischemic retinopathy, and anterior or posterior ischemic optic neuropathy.[14] In contrast, the presence of CRAO is uncommon; however, one study described the case of a 70-year-old woman with PAN who presented with CRAO in the right eye and anterior ischemic optic neuropathy with choroidal infarction in the left eye.[15] This is the first reported case of anterior ischemic optic neuropathy coexisting with CRAO in association with PAN.[16] Emad et al.[17] reported another case of unilateral CRAO and ischemic optic neuropathy associated with PAN in a 23-year-old woman. Conversely, in our case, the central retinal arteries of both eyes were involved, and marked retinal ischemia and visual loss were observed in both eyes. To our knowledge (search terms: "bilateral central retinal artery occlusion polyarteritis nodosa" in PubMed on October 6, 2024), only two cases of bilateral CRAO associated with PAN have been previously reported.[18,19]

PAN can extend to the central retinal artery, leading to CRAO through the following mechanisms. Vasculitis causes inflammation and necrosis of the arterial wall, resulting in endothelial damage and dysfunction.[20] This damaged endothelium promotes thrombosis within the lumen of the central retinal artery.[21] Additionally, inflammation can thicken the vessel wall, narrowing the lumen and restricting blood flow.[22] Thrombi formed in larger arteries affected by PAN can also embolize and occlude the central retinal artery.[20]

4. Conclusion

This case demonstrates that PAN can cause diplopia and ocular motility impairments, which may serve as early indicators of the disease. The rare occurrence of bilateral CRAO associated with PAN underscores the need to consider systemic vasculitis as a possible cause in cases of ocular motility impairment, particularly when accompanied by constitutional symptoms. Early recognition and treatment of PAN are essential for preventing severe ocular complications and preserving vision.

CRediT authorship contribution statement

Suguru Nakagawa: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Shigeo Akiyama:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Shuji Hino:** Writing – review & editing, Supervision, Data curation,

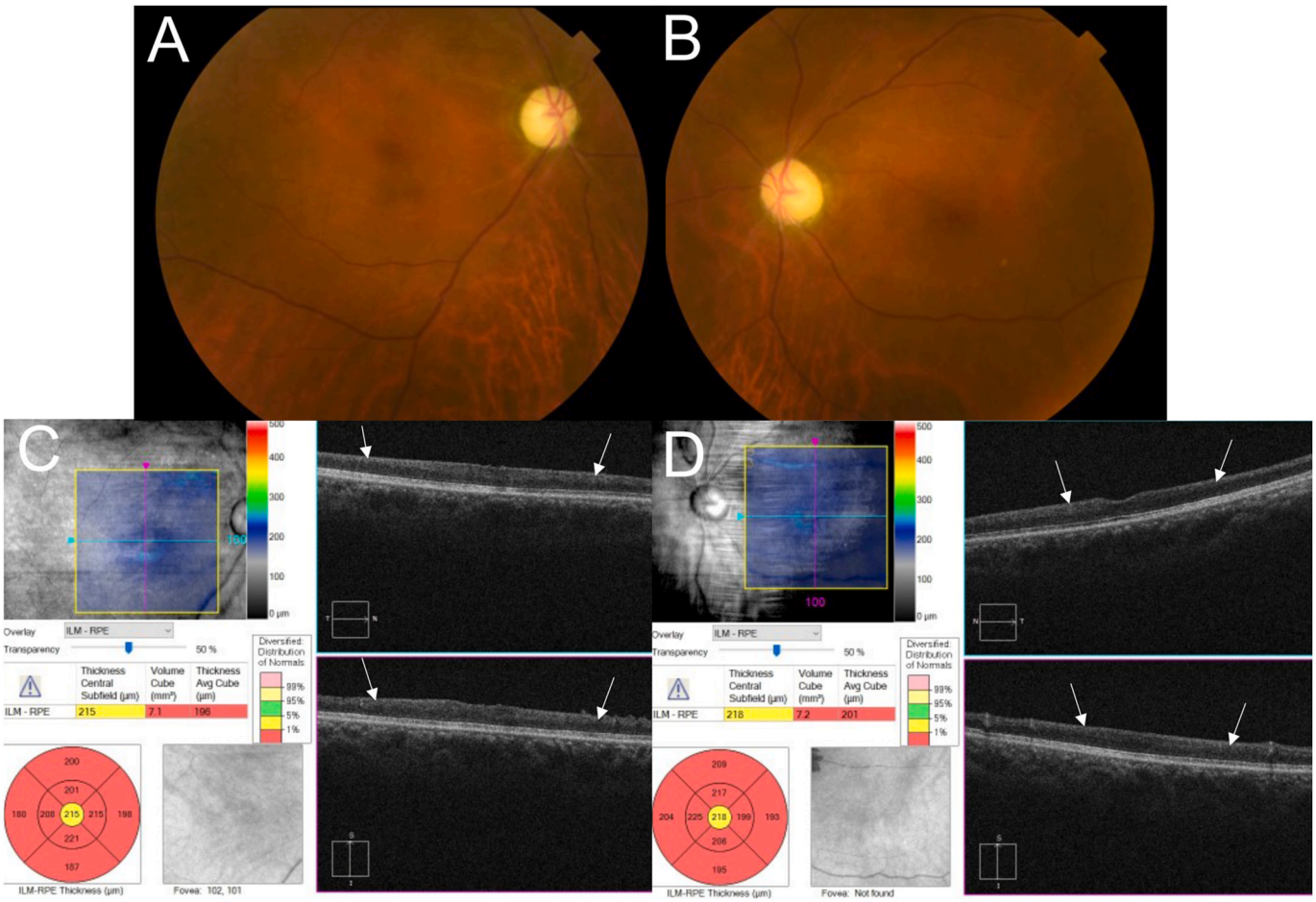

Fig. 6. Fundus photograph (A, B) and optical coherence tomography (OCT) findings (C, D) two years after onset. OCT shows marked atrophy of the inner retinal layers (C and D, arrows).

Conceptualization. **Kiyoshi Ishii:** Writing – review & editing, Supervision, Data curation.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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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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