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Case report

# Vasculitis with superior ophthalmic vein thrombosis compatible with neuro-neutrophilic disease

Mari Sakamoto[a], Takuji Kurimoto[a,*], Sotaro Mori[a], Kaori Ueda[a], Yukako Keshi[a], Yuko Yamada[a], Atsushi Azumi[b], Taro Shimono[c], Makoto Nakamura[a]

[a] Division of Ophthalmology, Department of Surgery, Kobe University Graduate, School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, 650-0017, Japan
[b] Kobe Kaisei Hospital, 3-11-15 Shiohara Kitamachi, Nada-ku, Kobe, 657-0068, Japan
[c] Department of Diagnostic and Interventional Radiology, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka, 545-8585, Japan

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ABSTRACT

*Purpose:* To present a unique case of neuro-neutrophilic disease with inflammation and thrombosis of the superior ophthalmic vein (SOV).

*Observations:* A 43-year-old Japanese man with past histories of oculomotor paralysis, auditory disorder, ischemic enteritis, and recurrent oral ulceration was referred to our hospital because of blurred vision in his right eye. Ophthalmic examination revealed decreased best corrected visual acuity and central scotoma in his right eye. Orbit magnetic resonance imaging (MRI) revealed an enlarged SOV in the right eye, with Gadolinium (Gd) enhancement in the wall of the vein but not inside the vein, indicating thrombosis. Multiple Gd-enhanced hyperintense lesions were also observed in the juxtacortical area of the brain. We diagnosed the patient with vasculitis in the right SOV that was adversely affecting the optic nerve. We ruled out systemic thrombophilia, infections, and malignancy by systemic examinations. The human leukocyte antigen (HLA) typing was Cw1-, B54-, B61-, A2-, A24-, and DR4-positive and B51-negative. We treated the patient with systemic steroid and anticoagulant therapy. After three courses of steroid pulse therapy, his symptoms and the MRI findings of the right SOV and brain improved; therefore, we decided to discontinue the anticoagulant therapy. One month after anticoagulant cessation, MRI revealed recurrence of the thrombus and enlargement of the right SOV despite the lack of vision worsening. We restarted the anticoagulant therapy while continuing the oral prednisolone treatment. At the final visit, 14 months after the onset of the disease, the patient was still receiving oral anticoagulation with warfarin potassium and prednisolone (5 mg/day). His symptoms and the right eye's visual function remained normal with a mildly enlarged SOV; there was less Gd enhancement and no brain lesions on MRI.

*Conclusions and importance:* We treated a unique case of possible neuro-neutrophilic disease that presented visual disturbances due to right SOV inflammation and thrombosis. Anticoagulation and systemic steroid therapies were required to reduce the inflammation and to prevent the recurrence of thrombosis.

## 1. Introduction

Neuro-neutrophilic diseases include neuro-Behçet disease (NBD) and neuro-Sweet disease (NSD) that are characterized by aseptic inflammatory lesions of the central nervous system (CNS).[1] Here, we present a unique case of neuro-neutrophilic disease with inflammation and thrombosis of the superior ophthalmic vein (SOV).

## 2. Case report

A 43-year-old Japanese man was referred to our hospital with the complaint of blurred vision in his right eye. He had past histories of oculomotor paralysis and auditory disorder at the age of 15 and 37 years, respectively, both of which recovered with systemic corticosteroid therapy. He had suffered from ischemic enteritis at the ages of 33 and 42 years. He also had episodes of recurrent oral ulcerations.

Ophthalmic examination revealed best corrected visual acuities (BCVAs) of 0.5 and 1.2 and intraocular pressures of 18 mmHg and 17 mmHg in the patients' right and left eyes, respectively. His pupils were isocoric and the light reflex was normal in both eyes with no afferent pupillary defects. No abnormal findings were observed in the lids, anterior segments, and fundi (Fig. 1A) of either eye. Fluorescein

* Corresponding author.
*E-mail address:* kuritaku12011201@yahoo.co.jp (T. Kurimoto).

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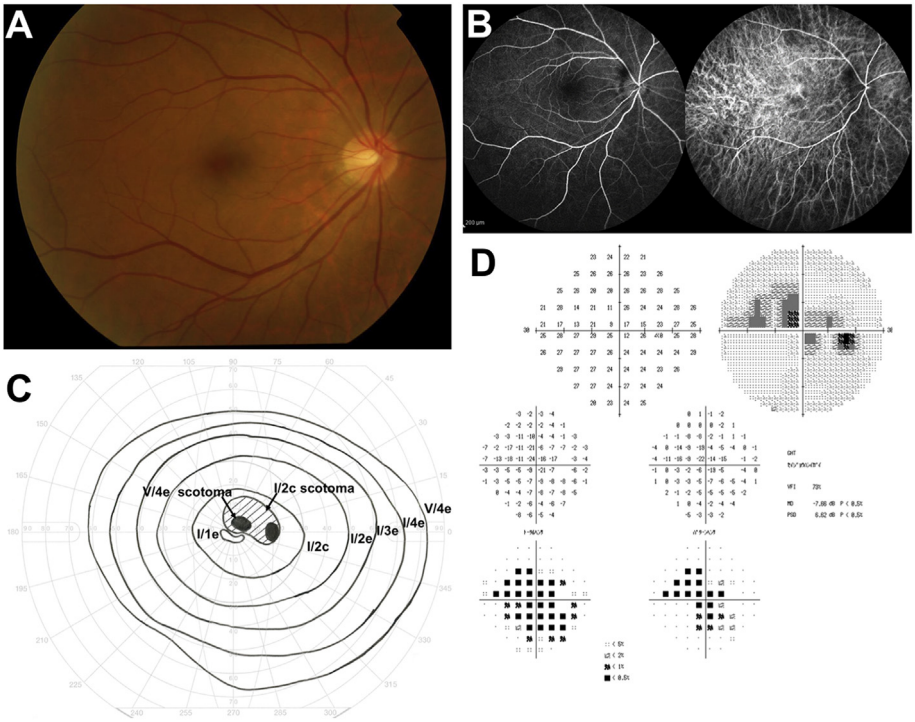


**Fig. 1. Ophthalmic tests of the patient's right eye on the first visit.**
Funduscopy (A) and fundus angiography (B) show no abnormality. Goldmann kinetic visual field test (C) and Humphrey visual field test (D) showing central scotoma.

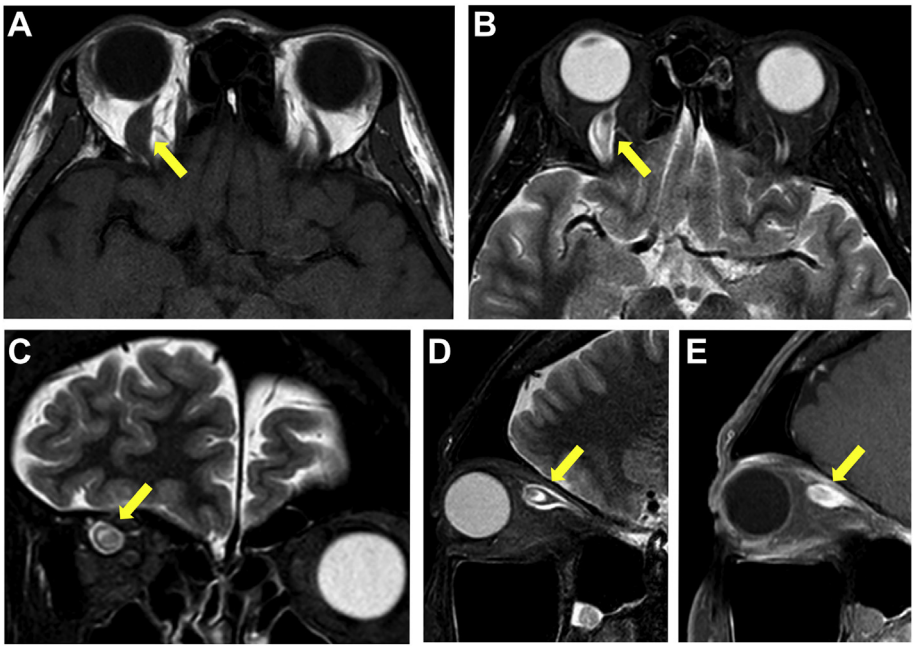


**Fig. 2. Magnetic resonance imaging of the right orbit before treatment.**
T1-weighted orbit magnetic resonance imaging MRI (A) revealed an enlarged superior ophthalmic vein (SOV) (arrow) in the right eye. Short-T1 inversion recovery (STIR) of the cross-sectional image of SOV showed a thickened wall with a high signal intensity, an intermediate zone with a low signal intensity, and a central spot with a high signal intensity (B–D) (arrow). SOV showed Gadolinium (Gd) enhancement in the wall of the vein but not inside the vein corresponding to the central spot in the STIR image (E) (arrow), and indicating thrombosis in the inflamed SOV.

and indocyanine green angiography (Fig. 1B), optical coherent tomography, and multi-focal electroretinogram findings were also normal for both his eyes. Visual field (VF) tests showed central scotoma in the right eye (Fig. 1C and D). BCVA in the right eye further declined to 0.1 3 weeks after the referral. T1-weighted orbit magnetic resonance imaging (MRI) revealed an enlarged SOV in the right eye (Fig. 2A). Short-T1 inversion recovery (STIR) showed an owl's eye-appearance of the cross-sectional image of SOV, i.e., a thickened wall with a high signal intensity, an intermediate zone with a low signal intensity, and a central spot with a high signal intensity (Fig. 2B–D). The right eye SOV also presented Gadolinium (Gd) enhancement in the wall of the vein but not inside the vein corresponding to the central spot in the STIR image (Fig. 2E), indicating thrombosis in the inflamed SOV. We found no abnormal MRI findings in the optic nerves. However, juxtacortical hyper-intensity lesions with Gd enhancement were also observed in the left temporal and insular lobes (Fig. 3A). Magnetic resonance angiography findings were unremarkable (data not shown); however, magnetic resonance venography revealed stenosis of the left transverse sinus with collateral vascular flow, indicating a chronic disturbance of the venous return (Fig. 4A and B). We diagnosed the patient as having vasculitis with a thrombus in the right SOV that was affecting the optic nerve and resulted in visual disturbance; we admitted him to our

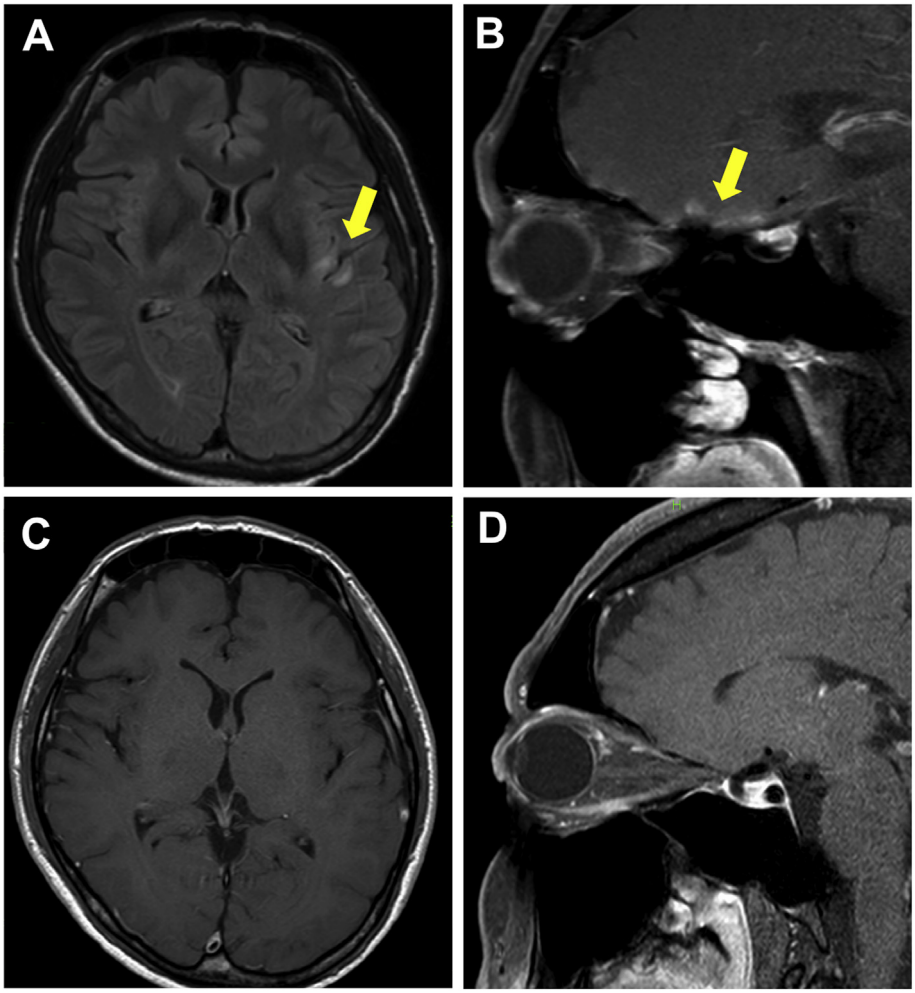


**Fig. 3. Multiple brain lesions on magnetic resonance imaging**.
Fluid-attenuated inversion recovery imaging shows juxtacortical hyperintense lesions (arrow) in the left temporal and left insular lobes (A). Multiple Gd-enhancing lesions (arrow) are seen in the base of the right frontal lobe after the second course of steroid therapy (B). Brain lesions disappeared after the third course of steroid therapy (C and D).

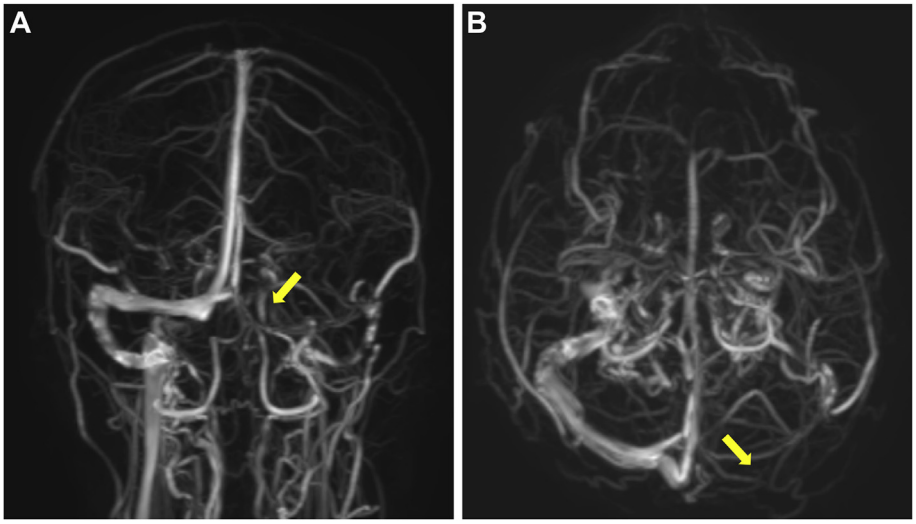


**Fig. 4. Magnetic resonance venography**.
Magnetic resonance venography revealed stenosis of left transverse sinus with collateral vascular flow (arrow) (A and B).

hospital for further investigation.

Most laboratory findings were normal, except for a mild elevation in the white blood cell count (11600 cells/μl). Serum C-reactive protein, immunoglobulin G4, interleukin-2-receptor, protein-C, protein-S, anti-cardiolipin antibody, anti-neutrophil cytoplasmic antibody, and anti-nuclear antibody were all within normal levels. Positron emission tomography and computed tomography (PET-CT) revealed no abnormal lesions (data not shown). The patient was referred to a cardiologist and found to have no systemic thrombophilia. Although an ileocecal ulcer was found the last time the patient suffered from ischemic enteritis (8 months before the referral), no pathological changes suspicious of Behçet's disease (BD) were found at that time. We performed colonoscopy again and found no abnormalities. The patient's human leukocyte antigen (HLA) typing was Cw1-, B54-, B61-, A2-, A24-, and DR4-positive and B51-negative.

We initiated treatment with methylprednisolone (mPLS) mini-pulse therapy (500 mg/day for 3 days) and an anticoagulant therapy, including an intravenous injection of heparin sodium, followed by oral administration of warfarin potassium, whose dosage was adjusted to maintain the prothrombin time-international normalized ratio within 1.6–2.6. Although BCVA in his right eye promptly recovered to 0.8 and the SOV MRI findings improved, the central scotoma remained. So, we prescribed additional full-pulse mPLS therapy (1 g/day for 3 days). The central scotoma was reduced and BCVA returned to 1.0 with further improvement of the SOV MRI findings (Fig. 5A–C). However, the brain lesions in the left temporal and insular lobe cortexes were still seen together with other multiple hyperintense Gd-enhanced lesions in the right frontal lobe base (Fig. 3B). Neurological examination revealed no abnormalities and the cerebrospinal fluid (CSF) had a slightly increased protein concentration (48 mg/dl) not suggestive of infection. We decided to add a third course of steroid pulse therapy (1g/day for 3 days) and the patient's symptoms improved further. Finally, the MRI findings of multiple brain lesions and the right SOV improved (Fig. 3C, D, and 5D-F). The patient was then discharged and followed up at the outpatient clinic with oral prednisolone (30 mg/day) and warfarin potassium (3–3.5 mg/day).

Symptoms in the right eye disappeared, but the patient noticed blurred vision episodes every time his body temperature increased, such as after taking a bath or during intense exercise. We recommended tapering the oral prednisolone and discontinued the anticoagulant. One month after anticoagulation discontinuation (3 months after the disease onset), a regular MRI check-up revealed the recurrence of thrombus and right SOV enlargement (Fig. 5G and H), despite a lack in the worsening of vision or brain lesions (Fig. 5I). We restarted the anticoagulant therapy (warfarin potassium) and continued the oral prednisolone (15 mg/day). At the final visit, 14 months after the disease onset, the patient continued to take oral anticoagulation (warfarin potassium, 3.5mg/day) *and* prednisolone (5 mg/day). The visual function in his right eye stayed normal with a BCVA of 1.5 bilaterally (Fig. 5L). The last MRI taken 9 months after the disease onset showed a mildly enlarged SOV with lesser enhancement than the first MRI (Fig. 5J and K) *and* no brain lesions.

## 3. Discussion

The present case had oral aphthosis, CNS lesions, and vasculitis but

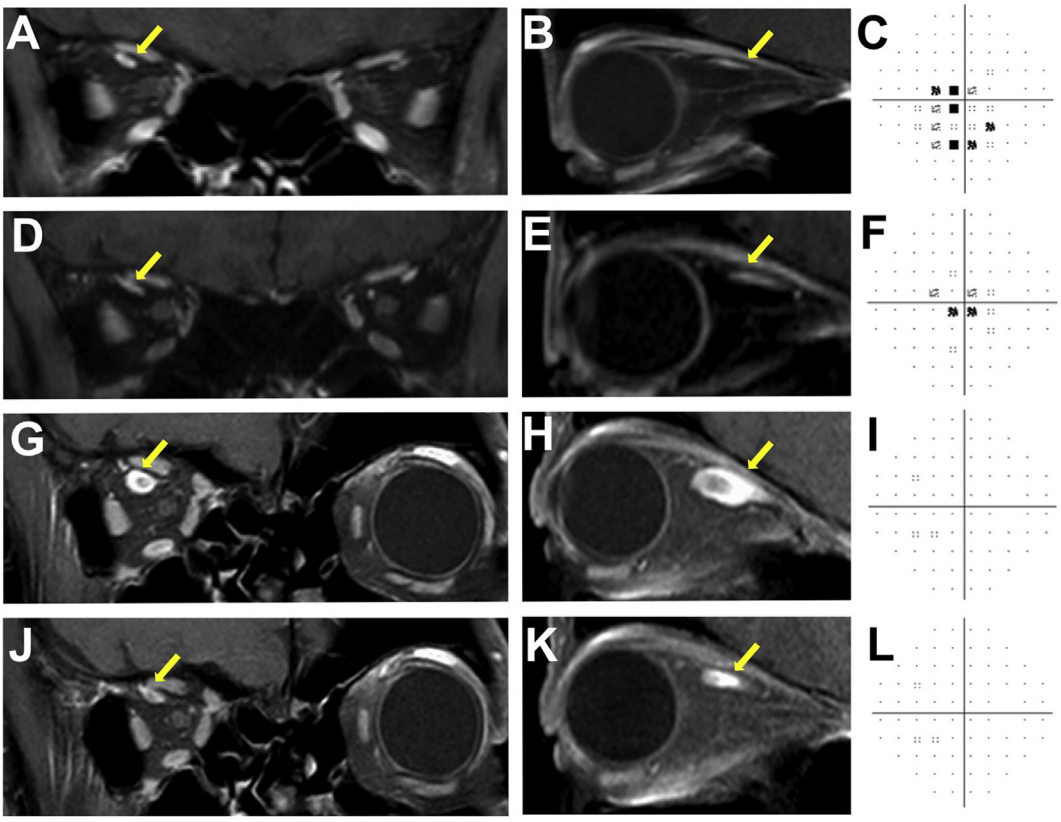


**Fig. 5. Temporal changes of right superior ophthalmic vein findings on Gd-enhanced magnetic resonance imaging and Humphrey visual field test.** Enlargement of the right superior ophthalmic vein (SOV) (arrow) and Gd enhancement improved after two courses of steroid pulse therapy (A and B), but the central scotoma remained (C). Magnetic resonance imaging (MRI) findings (D and E) (arrow) and visual field (VF) test (F) show further improvement after the third course of steroid therapy. One month after warfarin potassium discontinuation, MRI showed recurrence of vasculitis in the right SOV with a large thrombus formation (G and H) (arrow), but the VF test kept improving (I). The latest MRI showed mildly enlarged right SOV with a smaller thrombus in the middle of the vein and a less enhanced wall (J, K) (arrow) without visual field disturbance (L). A, D, G, and J: Gd-enhanced coronal MRI. B, E, H, and K: the sagittal section of orbital MRI. C, G, I, and L: the pattern deviation of Humphrey field analysis.

did not have skin lesions, genital aphthosis, and intraocular abnormalities such as uveitis. According to the international consensus recommendation criteria for NBD diagnosis, our patient might have been diagnosed as having a probable NBD. NBD is classified into two categories: parenchymal and nonparenchymal. The most characteristic sign in parenchymal NBD is brainstem involvement, whereas the major event in nonparenchymal NBD is cerebral venous thrombosis. Our patient's medical histories indicated signs of both types of NBD because the patient's oculomotor paralysis and auditory disorder may have been due to brainstem symptoms of parenchymal NBD, but the SOV vasculitis with thrombosis, the multiple asymptomatic brain lesions, and the dural venous sinus stenosis with collateral circulation may have been construed as signs characteristic of nonparenchymal NBD. We found no literature reports on SOV thrombosis; however, it is not surprising to see SOV thrombosis in patients with NBD given that all sizes and vessel types can be involved in BD.[2,3] Lower extremity vein thrombosis is the most frequent vascular manifestation in BD, followed by vena cava thrombosis, pulmonary artery aneurysms, Budd–Chiari syndrome, peripheral artery aneurysms, dural sinus thrombosis, and abdominal aorta aneurysms.[2]

Conversely, Sweet's disease (SD) is an acute febrile neutrophilic dermatosis, characterized by painful erythematous plaques. Aseptic neutrophilic inflammation occurs in the dermis as well as in the eyes, lungs, liver, kidneys, gastrointestinal tract, bone marrow, muscle, and brain; these manifestations can occur without skin lesions. Encephalomeningitis seen in patients with SD is called NSD.[4,5] Although both NBD and NSD are neutrophil-associated pathologies that can involve CNS, Hisanaga et al.[5] found five differences between the two: (1) There is no gender predilection in NSD, whereas men are predominantly affected in NBD; (2) NSD displays a broader distribution of age at onset ranging from 30 to 70 years, whereas NBD affects a younger population preferentially aged 20–40 years; (3) NSD can affect any region of CNS, whereas NBD involves the basal ganglia and brainstem; (4) episcleritis and conjunctivitis are seen in some patients with NSD, whereas uveitis is common in patients with NBD; and (5) there is a strong HLA-Cw1 and B54 association in NSD, whereas there is a high frequency of HLA-B51 in NBD. Our case showed some NSD aspects such as the HLA typing of Cw1 and B54 positivity with B51 negativity, the history of neurologic manifestations, brain lesions outside of brain ganglia and brainstem, and the absence of typical uveitis.

However, previous studies reported an NBD case with the HLA Cw1/B54[6] and an NSD case with the negative typing of HLA Cwl/B54/B51[7]. Because the clinical features of NSD and NBD overlap, it is difficult to differentiate the two unless a skin lesion is present and the skin biopsy is obtainable. Hisanaga[1] coined the term “neuro-neutrophilic disease” as a tentative diagnosis for cases without skin lesions, wherein NSD is thought to be a relatively benign type and NBD a relatively malignant type. From this viewpoint, our case should be clinically diagnosed as a neuro-neutrophilic disease, where longer follow-up could demonstrate future skin lesion development.

We chose not to perform a brain biopsy because the initial steroid therapy improved the visual function and the SOV MRI findings, and because the CSF and PET-CT findings ruled out infection and malignancy. The good response to steroid therapy, the lack of systemic thrombophilia, and the MRI findings of the vessel wall enhancement indicated that the primary pathology of SOV in the present case was vasculitis, although there was thrombus formation. This idea is in accordance with reports that systemic inflammation rather than thrombophilic factors is responsible for thrombosis in patients with BD.[2,8,9] Despite the presence of a thrombus, our patient did not show any signs of increased SOV pressure such as elevated intraocular pressure or episcleral vein congestions. This may be because the space between the thrombus and the vessel wall, demonstrated by the intermediate zone on the STIR image, allowed for the blood to flow.

In our case, MRI findings showed no obvious evidence of inflammation in the optic nerve itself throughout the course; therefore, the pathological mechanism of optic nerve involvement remains inconclusive. However, we may postulate that visual decline on presentation could be thought as one of the multicentric involvement of the disease rather than the result of adjacent inflammation of SOV. The fact that the visual function was not totally affected when the thrombus in SOV recurred may support the speculation even though oral prednisolone (15 mg/day) was taken when thrombus recurred.

The use of anticoagulants for the management of thrombosis in BD is controversial,[8–11] and it has not been evaluated in a controlled study yet. In our case, the thrombus in SOV recurred after oral anticoagulant cessation and decreased following the re-initiation of the therapy, during treatment with a constant dose of oral prednisolone. This indicates that the systemic corticosteroid therapy reduced the inflammation as it does in NSD cases,[1,5] but it did not prevent thrombus formation.

There are no controlled data for management of NBD or NSD. Corticosteroids, azathioprine, cyclophosphamide, methotrexate, and TNFα antagonists are used for parenchymal involvement in BD, and corticosteroids are recommended for dural sinus thrombosis.[9] Corticosteroids are reported to be effective for NSD; however, recurrences are seen in some cases and prevention therapies have not been established. Use of indomethacin, colchicine, and potassium iodide together with corticosteroids have been reported.[5] The patient continued to take oral warfarin and prednisolone (5 mg/day) at the final visit 14 months after disease onset. Careful follow-up is needed for further management of residual thrombus in SOV with minimum dose of corticosteroid and anticoagulation therapy, and the use of alternative immunosuppressants mentioned above is need for consideration.

## 4. Conclusion

In all, we report a unique case of possible neuro-neutrophilic disease that presented visual disturbance due to right SOV inflammation and thrombosis. Anticoagulation and systemic steroid treatments were required to reduce the inflammation and to prevent the recurrence of thrombosis.

## Patient consent

The patient consented to publication of the case in writing.

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*Conflicts of interest*

The authors have no financial disclosures.

*Authorship*

All authors attest that they meet the current ICMJE criteria for Authorship.

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