

Refractory optic perineuritis due to granulomatosis with polyangiitis successfully treated with methotrexate and mycophenolate mofetil combination therapy

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Abstract

Optic perineuritis is an uncommon inflammatory disorder of the optic sheath that causes visual loss or eye pain. There are few case reports of optic perineuritis associated with granulomatosis with polyangiitis. Herein we report the case of a 37-year-old male with granulomatosis with polyangiitis and who presented with headache, blurred vision in the right eye, diplopia, and numbness in the right forehead. Brain magnetic resonance images (MRI) findings revealed hypertrophic pachymeningitis and refractory optic perineuritis. These were manageable only by means of weekly methotrexate and mycophenolate mofetil combination therapy but not with methotrexate, mycophenolate mofetil, intravenous cyclophosphamide, rituximab, azathioprine, or cyclosporine individually.

Keywords: Granulomatosis with polyangiitis, optic perineuritis, hypertrophic pachymeningitis, methotrexate, mycophenolate mofetil

Introduction

Central nervous system (CNS) involvement in patients with granulomatosis with polyangiitis (GPA) is relatively rare, occurring in only 7-11% of patients (1). The predominant phenotype of CNS involvement is hypertrophic pachymeningitis (HP), of which 46% of cases are CNS-GPA (1). Optic perineuritis (OPN), another much less common manifestation of CNS-GPA, is an inflammatory disorder of the optic sheath, which can be diagnosed via magnetic resonance imaging (MRI) by enhancing the optic nerve sheath while sparing the optic nerve parenchyma (2). Herein we report the case of a patient with GPA who presented with HP and refractory OPN, which was manageable only by means of weekly methotrexate (MTX) and mycophenolate mofetil (MMF) combination therapy, but not with MTX, MMF, intravenous cyclophosphamide, rituximab, azathioprine, or cyclosporine individually.

Case Presentation

A 37-year-old male presented to our clinic at Teikyo University Hospital with a three-month history of general malaise, pain in the bilateral cheeks, and nasal congestion. Physical examination and laboratory test results revealed otitis media, sinusitis, proteinuria, and microscopic hematuria. Proteinase-3 anti-neutrophil cytoplasmic antibody (PR3-ANCA) was above the upper normal range (10 EU/mL) at 88 EU/mL. Renal biopsy showed pathological findings consistent with crescentic glomerulonephritis. T2-weighted magnetic resonance images revealed multiple high-intensity lesions in the cerebrum and HP. GPA was diagnosed, and the patient was treated with 60 mg prednisolone (PSL) daily (Predonine; Sionogi, Osaka, Japan) and 100 mg oral cyclophosphamide (CYP) (Endoxan; Sionogi, Osaka, Japan). All GPA manifestations, including those of the middle ear, upper respiratory tract, kidney, and CNS, responded favorably to treatment. Proteinuria and hematuria resolved, and the patient's renal function normalized. Further, the patient became negative for PR3-ANCA. PSL was tapered gradually, and oral CYP was discontinued after six months due to the favorable response of the affected organs to treatment.

Six months after the discontinuation of CYP, the patient complained of a headache, blurred vision in the right eye, and numbness in the right forehead. PR3-ANCA levels were elevated again, but otitis media and glomerulonephritis did not recur. On the other hand, magnetic resonance imaging showed a recurrence of HP and an enhancement and a thickening of tissue from the meninges near the right optic canal to the right optic nerve sheath (Figure 1). PSL dosage was increased from 22.5 to 60 mg daily, and intravenous cyclophosphamide (IVCY) pulse therapy (Endoxan; Sionogi, Osaka, Japan) was initiated at 750 mg monthly. After the remission of GPA was achieved again, PSL was gradually tapered to 10 mg daily, and IVCY pulse therapy was discontinued after 8 months and replaced with MTX (20 mg/week) (Rheumatrex; Pfizer, New York, USA) as maintenance therapy.



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After four years of maintenance therapy with PSL and MTX at the dosages indicated above, GPA recurred with an accompanying fever, headache, and exacerbated sinusitis. A chest computed tomography scan showed multiple lung nodules in the upper quadrant of the right lung. A brain MRI revealed multiple enhanced nodules in the cerebrum with no indication of OPN recurrence. PSL dosage was increased to 60 mg daily, and IVCY pulse therapy was administered again. One month after increasing the PSL dosage, bilateral ocular pain, diplopia, blurred vision, and numbness in the right forehead occurred, indicating the recurrence of bilateral OPN and the development of right V and VI cranial nerve palsy. PR3-ANCA levels were elevated to 23 EU/mL. Methylprednisolone (mPSL) pulse therapy (1 g/day for three days) (Solu-Medrol; Pfizer, NY, USA) was administered, followed by PSL (60 mg/day).

After several days, eye involvement showed rapid improvement. Rituximab (375 mg/m²/week for four weeks) (Rituxan; Zenyaku Kogyo, Tokyo, Japan) and subsequently, 50 mg azathioprine daily (Imuran; GlaxoSmithKline, London, UK) were administered, and PSL was tapered. A month later, after PSL dosage was tapered to 30 mg daily, bilateral OPN recurred. mPSL pulse therapy was administered again, resulting in rapid improvement. Cyclosporine 200 mg daily (Neoral; Novartis, Basel, Switzerland) was administered in combination with a corticosteroid, but after three months, they failed to prevent the patient from relapsing when PSL dosage was tapered to 22.5 mg daily. mPSL pulse therapy was therefore restarted.

Mycophenolate mofetil 2 g daily (Cellcept; Chugai, Tokyo, Japan) was next chosen for remission induction therapy, but it was un-

successful in preventing the elevation of PR3-ANCA levels to 107 U/mL (the measuring system was changed and the PR3-ANCA upper normal range was 4 U/mL), while the PSL dosages were being tapered to 25 mg daily. The addition of MMF was approved by the clinical ethics committee of Teikyo University Hospital, and written informed consent was obtained from the patient. Weekly MTX (20 mg/week) was added to MMF and PSL because MTX combined with PSL was effective in maintaining the longest period of remission. MRI showed an improvement in the HP and a decrease in the enhancement of the optic nerve sheath. PSL was tapered to 10 mg daily, and remission has been maintained thus far for three years with no adverse events.

Discussion

The pathomechanism in this case is explainable either by direct compression of the optic nerve by the thickened meninges or by the infiltration of the inflammatory cells into the perineurium (3). OPN in our patient was thought to have the same pathomechanism as HP, because the thickened dura adjoined the affected optic nerve sheath. Anatomically, the optic nerve is surrounded by the meningeal sheath, which consists of the dura mater, arachnoid mater, pia mater, and cerebrospinal fluid in the subarachnoid space. In addition, the OPN did not recur after the improvement of HP in the present case. There are few case reports of OPN associated with GPA (Table 1) (2-6). Seven of nine OPN cases associated with GPA presented HP, and several cases presented

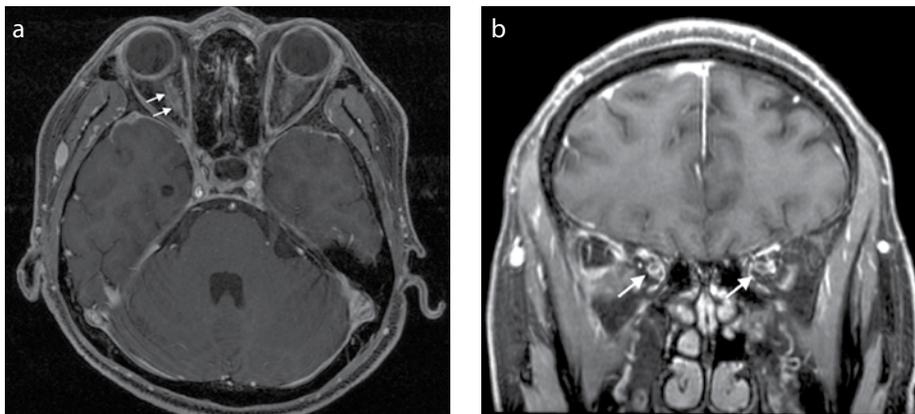


Figure 1. a, b. Axial (a) and coronal (b) gadolinium-enhanced T1-weighted MRI showing enhancement of the bilateral optic nerve sheath with sparing of the optic nerve parenchyma (arrow)

Table 1. Optic perineuritis associated with granulomatosis with polyangiitis

	Age/sex	Ocular symptom	Organ involvement	HP	ANCA	Treatment	OPN relapse
Takazawa et al. (2)	74/M	Loss of vision, visual field disturbance	Eye, upper airway, lung	(+)	PR3-ANCA	PSL	(+)
	72/M	Loss of vision, visual field disturbance	Eye, nasal sinus, ear, lung	(+)	PR3-ANCA	PSL, CYC	(-)
Shunmugam et al. (3)	63/F	Loss of vision	Eye, lung, ear	(-)	c-ANCA	PSL, MTX, CYC, Rituximab	(+)
Belden et al. (4)	55/F	Loss of vision, visual field disturbance	Eye, nasal sinus, lung, skin, colon	(+)	c-ANCA	PSL, CYC	(+)
Purvin and Kawasaki (5)	73/F	Diplopia, loss of vision	Eye, nasal sinus, ear	(-)	p-ANCA	PSL, MTX	(-)
	64/F	Eye pain, loss of vision	Eye, kidney, brain	(+)	p-ANCA	PSL, CYC	(+)
	53/M	Eye pain, loss of vision, visual field disturbance, color blindness	Eye, lung	(+)	c-ANCA	PSL, CYC	(+)
Nagaoka et al. (6)	71/M	Loss of vision, visual field disturbance	Eye, lung	(+)	PR3-ANCA	Not described	Not described
Present case	38/M	Loss of vision, visual field disturbance	Eye, nasal sinus, ear, lung, kidney, brain	(+)	PR3-ANCA	PSL, CYC, MTX, CSA, Rituximab, AZA, MMF	(+)

HP: hypertrophic pachymeningitis; OPN: optic perineuritis; M: male; F: female; mPSL: methylprednisolone; PSL: prednisolone; CYC: cyclophosphamide; IVCY: intravenous cyclophosphamide; MTX: methotrexate; AZA: azathioprine; CSA: cyclosporine A; MMF: mycophenolate mofetil

continuous lesions extending from the thickened meninges to the optic nerve sheath, indicating the close association of HP with OPN in GPA patients. While almost all cases presented upper and/or lower airway involvement, only two cases presented renal involvement, suggesting that granuloma formation is one form of OPN pathogenesis in GPA. In terms of treatment, OPN with GPA responds to high-dose corticosteroid therapy very well, and the ophthalmological prognosis is mostly favorable in the short term. However, patients in whom high-dose corticosteroid treatment was delayed for a long period after the onset of symptoms experienced an irreversible loss of vision (2, 4). High-dose corticosteroid therapy should therefore be administered as soon as possible after onset to minimize the possibility of vision loss. In most cases having OPN with GPA, remission was achieved and maintained using a combination treatment of corticosteroid with CYP or MTX. However, in a case reported by Shunmugam et al. (3), this treatment was unable to prevent recurrence, and in that case only rituximab was found to be useful in controlling the disease.

Granulomatosis with polyangiitis often recurs during the tapering of corticosteroids, and it is generally accepted that in cases of GPA accompanied by major organ pathology, initial glucocorticoid therapy should be introduced with cyclophosphamide or rituximab, and then followed by maintenance therapy with azathioprine or MTX (7). In refractory cases, rituximab is effective for remission induction. However, relapses are frequent in patients treated with only rituximab (8). It was reported that routine

re-treatment with rituximab alone, or in combination with azathioprine or MTX, was effective in preventing relapses (8, 9). In our case, the induction therapy with rituximab and azathioprine with PSL 60 mg daily was ineffective, and resulted in the recurrence of OPN after a month. The long-term contribution of rituximab to subsequent remission induced with MTX and MMF is unclear, but the probability of such a contribution is less likely due to the elevated PR3-ANCA levels. The present case illustrates the possibility of combining MTX with MMF as maintenance therapy in refractory cases of optic perineuritis due to granulomatosis with polyangiitis.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Teikyo University School of Medicine.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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