

## Case Report

# Optic neuropathy from connected intra- and extraorbital lesions in IgG4-related disease

Tsuneaki Yoshinaga, M.D., Ph.D.<sup>1)2)\*</sup>, Toru Kurokawa, M.D., Ph.D.<sup>3)</sup>, Takeshi Uehara, M.D., Ph.D.<sup>4)</sup>, Junpei Nitta, M.D., Ph.D.<sup>5)</sup>, Tetsuyoshi Horiuchi, M.D., Ph.D.<sup>6)</sup> and Yoshiki Sekijima, M.D., Ph.D.<sup>1)2)</sup>

**Abstract:** We present the case of a 74-year-old woman complaining of blurred vision in the left eye who was found to have a unilateral, continuous lesion of the optic nerve and nerve sheath accompanied by an intracranial mass next to the cavernous sinus and meninges. Surgical decompression of the left optic nerve in the optic canal and partial resection of the mass followed by prednisolone administration were successful. Immunohistochemical analysis disclosed abundant infiltration of IgG4-positive plasma cells at >10 cells/high power field. These findings indicated a new pattern of compressive optic neuropathy with confirmed IgG4 histopathological findings. Such an extensive lesion may produce visual disturbance.

(*Rinsho Shinkeigaku (Clin Neurol)* 2019;59:746-751)

**Key words :** IgG4-related disease, IgG4-ophthalmic disease, IgG4-related hypertrophic pachymeningitis, optic neuropathy

### Introduction

Optic nerve involvement has been reported in IgG4-related ophthalmic disease (IgG4-ROD)<sup>1)</sup>, IgG4-related hypertrophic pachymeningitis (IgG4-HP)<sup>2)</sup>, and other forms of IgG4-related disease (IgG4-RD), occasionally with severe visual impairment. We recently encountered the case of a unilateral, continuous lesion of the optic nerve and nerve sheath along with an intracranial mass next to the cavernous sinus and meninges in which optic neuropathy was mainly caused by a compressive mechanism. Such an extensive lesion has not been reported to date.

We herein describe the pathology and clinical outcome of a patient with IgG4-RD and large continuous mass lesion causing optic nerve involvement.

### Case report

A 74-year-old woman complaining of blurred vision in the left

eye that had persisted for three months was referred to our hospital. Physical examination revealed no exophthalmos, lymph node swelling, or rash. Her best corrected visual acuity (BCVA) was 1.2 OD and 0.2 OS and intraocular pressure was normal. Ptosis was not evident and eye movement was normal bilaterally. Anisocoria was absent under both dark and light conditions, although a relative afferent pupillary defect was apparent in the left eye. Critical flicker frequency (CFF, an evaluation method for optic nerve function) was 35 Hz in the right eye and 14 Hz in the left eye. Optic disc swelling in the left eye was detected by ophthalmoscopy and optical coherence tomography (OCT) (Fig. 1A and B). The right fundus was apparently normal. Goldmann perimetry testing of the left eye disclosed decreased sensitivity from the center to the lower field (Fig. 1C).

Hematological studies revealed elevated IgG (1,802 mg/dl, normal: 870–1,700 mg/dl) and normal IgG4 (98 mg/dl, normal: <135 mg/dl). Her serum IgG4/IgG ratio was normal at 5% (normal: <6%). Other blood parameters, including anti-myeloperoxidase,

\*Corresponding author: Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine [3-1-1 Asahi, Matsumoto 390-8621, Japan]

<sup>1)</sup>Department of Medicine (Neurology and Rheumatology), Shinshu University School of Medicine

<sup>2)</sup>Department of NeuroHealth Innovation, Institute for Biomedical Sciences, Shinshu University

<sup>3)</sup>Department of Ophthalmology, Shinshu University Hospital

<sup>4)</sup>Department of Biomedical Laboratory Medicine, Shinshu University Hospital

<sup>5)</sup>Department of Neurosurgery, Kobayashi Neurosurgical Hospital

<sup>6)</sup>Department of Neurosurgery, Shinshu University Hospital

(Received July 9, 2019; Accepted August 16, 2019; Published online in J-STAGE on October 26, 2019)

doi: 10.5692/clinicalneurol.cn-001342

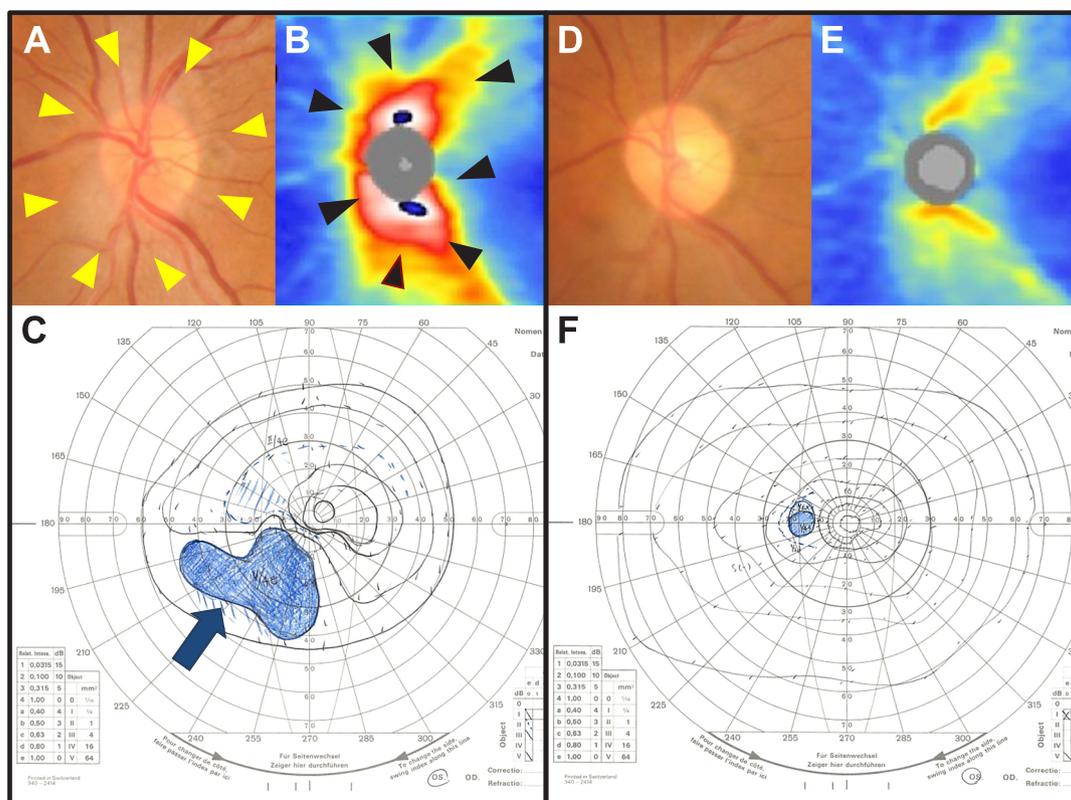


Fig. 1 Left fundus images and Goldmann perimetry at the initial examination (A–C) and one year after removal of the lesion (D–F). A: Magnified photograph shows a swollen optic disc (arrowheads). B: Maps of retinal nerve fiber layer thickness around the optic disc taken by optical coherence tomography (arrowheads). This image represents thickened retinal nerve fiber layer and clearly show the swollen optic disc. C: Goldmann perimetry. A large scotoma from the center to the lower visual field is apparent in the left eye (arrow). The swollen left optic disc had resolved completely (D and E) and Goldmann perimetry showed no relapse of the visual field defect (F).

anti-proteinase 3, anti-neutrophil cytoplasmic antibodies, rheumatoid factor, angiotensin-converting enzyme, soluble interleukin-2 receptor, and C-reactive protein, were within normal limits apart from slightly elevated Erythrocyte sedimentation rate (22 mm/hr; normal: <8 mm/hr). Antinuclear antibody titer was normal. Cerebrospinal fluid examination indicated a normal cell count (1/3 monocytes), total protein of 55 mg/dl, glucose of 53 mg/dl, immunoglobulin G of 10.3 mg/dl, and IgG index of 1.1.

Orbital MRI revealed an enhanced lesion along the left optic nerve to the cavernous sinus through the left optic canal (Fig. 2). No enlargement of the lacrimal glands, extraocular muscles, or infraorbital nerves were apparent. Contrast-enhanced whole-body computed tomography demonstrated no other swelling or enhanced lesions.

#### Outcome and management

The patient underwent surgical decompression of the left optic nerve in the optic canal and partial resection of the mass in another neurosurgical hospital. After the operation, 1 cycle of steroid pulse therapy of 1 g intravenous methyl prednisone

(PSL) for 3 days was administered. One month afterwards, her left BCVA and CFF had improved to 1.2 and 29 Hz, respectively. Her swollen optic disc had ameliorated slightly and decreased left-eye visual field sensitivity was improved.

Histopathological study of a specimen obtained from the lesion disclosed marked infiltration of lymphocytes and plasma cells along with storiform fibrosis (Fig. 3). No atypical lymphocytes or non-necrotizing epithelioid granulomas were apparent. Immunohistological analysis revealed abundant infiltrating IgG4-positive plasma cells at >10 cells/high power field. Analysis by the polymerase chain reaction (PCR) of paraffin-embedded biopsy sections disclosed no evidence of monoclonal immunoglobulin gene rearrangement. The patient satisfied the criteria for probable IgG4-ROD (2015)<sup>1</sup>. Other diseases were ruled out by systemic examination, blood testing, pathological study, and analysis of monoclonality. Based on the diagnosis, oral PSL of 20 mg/day (0.3 mg/kg/day) was commenced with her consent by a neurosurgeon during follow-up. One year after surgery, her left BCVA was 1.0 and CFF was normal at 35 Hz. The swollen optic disc had improved completely (Fig. 1D and E) and decreased left-eye visual field sensitivity was improved (Fig. 1F) under daily PSL of

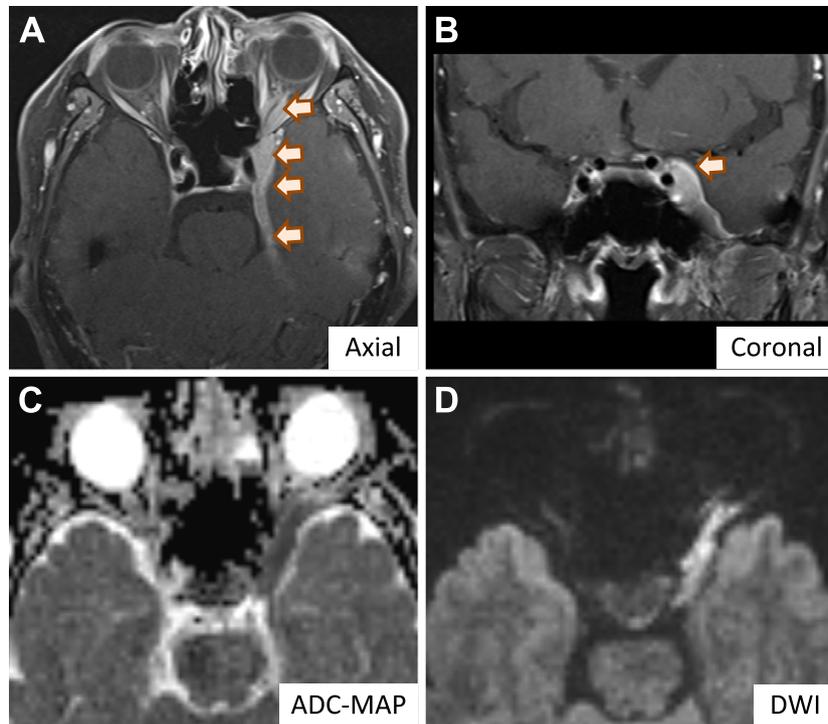


Fig. 2 A and B: Contrast-enhanced fat-suppressed axial and coronal orbital magnetic resonance imaging (TR: 600 ms, TE: 12 ms). The axial image shows an enhanced lesion along the left optic nerve extending to the cranium (arrows). C and D: ADC mapping and DWI (TR: 5,000 ms, TE: 82 ms) include fluid diffusion disturbances. The cavernous sinus is also enhanced.

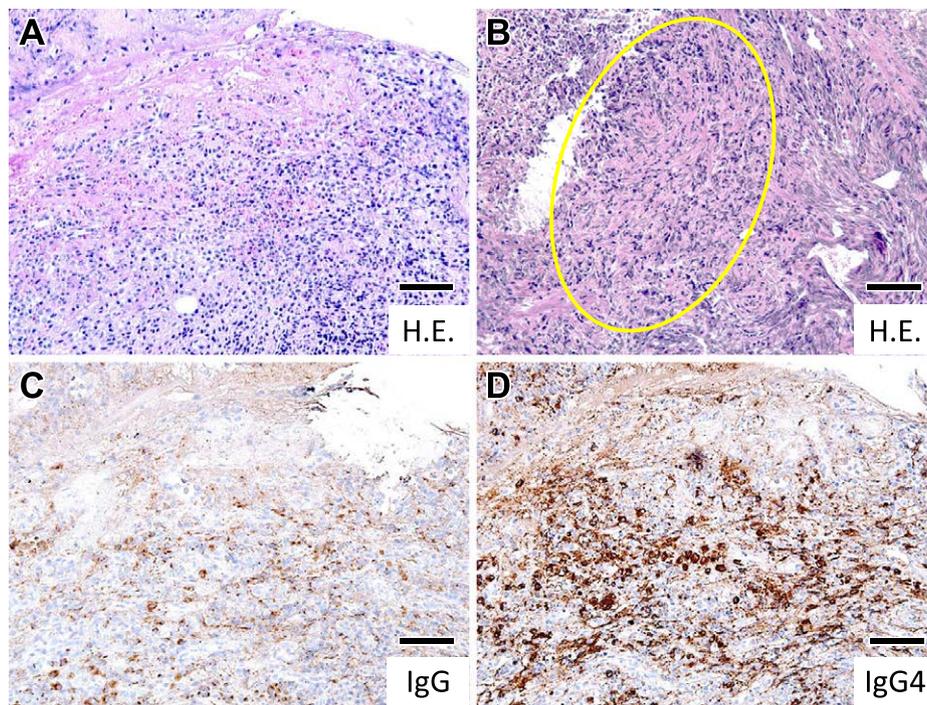


Fig. 3 Histopathological studies.

A and B: Hematoxylin and eosin (H.E.) staining; A, low magnification ( $\times 200$ ); B, low magnification ( $\times 200$ ). Lymphoplasmacytic infiltration (A and B) and storiform fibrosis (circle in B) are evident. C and D: Immunoperoxidase staining. IgG-positive plasma cells (immunoperoxidase staining,  $\times 100$ ). IgG4-positive plasma cells (immunoperoxidase staining,  $\times 100$ ). The IgG4/IgG ratio is  $>40\%$ . Scale bars = 50  $\mu\text{m}$ .

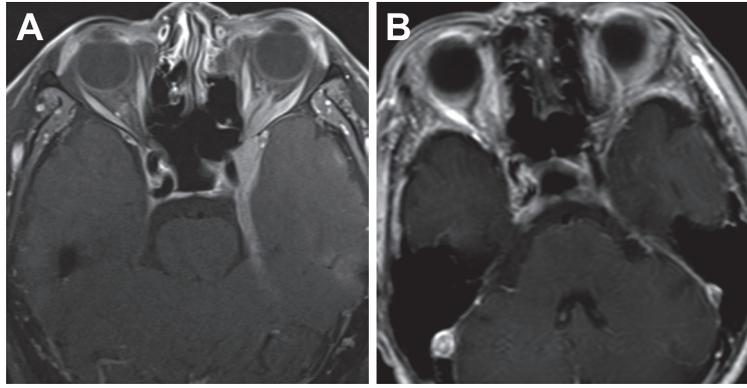


Fig. 4 A and B: Contrast-enhanced orbital MRI.

A: An axial orbital MRI (TR: 600 ms, TE: 12 ms) before surgery. B: An axial cranial MRI (TR: 483 ms, TE: 10 ms) three years after surgery. The axial image shows no relapse of mass lesions.

Table 1 Reported cases of optic neuropathy in IgG4-RD.

Case	Age (yrs)/Sex	Cause of optic nerve involvement	Systemic (S) or localized (L) orbital lesion	Serum IgG4 (mg/dl)	Reference
1	78/M	Orbital soft tissue	S	162	5
2	39/M	Orbital soft tissue	L	883	6
3	58/M	Enlargement of infraorbital nerve, enlargement of extraocular muscle	S	1,830	7
4	70/M	Enlargement of extraocular muscle	S	484	8
5	54/F	Orbital soft tissue	S	251	9
6	36/M	Not determined	L	1,440	10
7	62/M	Enlargement of extraocular muscle, orbital soft tissue	L	1,850	11
8	68/F	Enlargement of extraocular muscle, lacrimal gland swelling	S	2,170	12
Present	74/F	Intra- and extraorbital lesions	L	98	—

Notes: 'Systemic' means a case with other IgG4-related organ involvements, such as pancreatitis, peritoneal fibrosis, nodular lung, prostate swelling, lymph node swelling, and/or cholangitis.

5 mg. Eighteen months after surgery, the patient was able to discontinue PSL. Three years after surgery, her left BCVA was 1.2 without evidence of relapse on MRI.

### Discussion

In the reported case, the optic nerve involvement was considered to be IgG4-ROD rather than IgG4-HP. IgG4-ROD is a distinct clinicopathological entity characterized by elevated serum IgG4 levels and IgG4-positive lymphoplasmacytic orbital infiltration. Typical IgG4-ROD phenotype cases exhibit multiple simultaneous lesions most commonly in the lacrimal gland, extraocular muscle swelling, trigeminal nerve swelling, autonomic pancreatitis and other systemic lesions, and serum IgG4 level elevation ( $>500$  mg/dl<sup>3</sup>). Optic nerve involvement is uncommon in IgG4-ROD, with approximately 10% of patients complaining

of visual disturbance<sup>4</sup>. To date, there have been eight reported cases of optic neuropathy in IgG4-ROD that showed similar characteristics of chronic, bilateral manifestation and other organ involvement (Table 1)<sup>5-12</sup>. On the other hand, our case exhibited chronic unilateral ophthalmic neuropathy without other organ involvement.

The mechanism of optic neuropathy by IgG4-RD in previous reports can be broadly classified into several types: orbital mass in the orbital area, infraorbital nerve enlargement, extraocular muscle swelling and lipid mass in the orbital area, and orbital ganglia of vascular or neural structures<sup>13</sup>. In the present case, fossa or cavernous lesion enlargement presumably induced optic involvement by compression, although ischemia of a micro lesion, inflammation, and/or cell infiltration might also have been involved. The patient's radiological findings disclosed a homogenous lesion from the intra-extraorbital area through the

optic canal. Hence, it is plausible that the optic involvement may have been caused by infiltrating IgG4-positive cells or inflammatory processes in addition to compressive mechanisms.

IgG4-HP is a distinct clinicopathological entity characterized by elevated serum IgG4 levels and IgG4-positive lymphoplasmacytic infiltration in meningeal lesions<sup>2)</sup>. Multiple cranial nerve involvements with diffuse areas of hypertrophic meninges may also be present, although optic nerve involvement is rare. Wallace identified three cases of IgG4-RD among 43 cases of idiopathic HP by histopathological findings in the absence of serum IgG4 elevations<sup>2)14)</sup>. A retrospective, multi-center Japanese nationwide survey from 2005 to 2009 revealed 14 cases (8.8%) of IgG4-RD in 159 HP cases<sup>15)</sup>.

Some patients with IgG4-HP may display visual deficits. Lu reviewed 21 IgG4-HP case reports and observed that some reflected mechanical compression of vascular or neural structures, leading to functional deficiencies because of middle fossa area lesions<sup>2)</sup>. In the present case, a dura-like mass around the cavernous sinus produced visual deficits, which resembled symptoms of Tolosa-Hunt syndrome but with no headache or retro-orbital pain.

The origin of the mass in this case was presumed to be around the optic nerve canal, because the shape of the mass resembled that of a dumbbell through the optic nerve canal and resembled a schwannoma. If the mass had originated from the cavernous sinus, there would have likely been no infiltration into the superior orbital fissure and impairment of other cranial nerves. The reason why serum IgG4 was not elevated in this case may have been due to the lesion's localization<sup>16)</sup>.

Although histological findings in the present case suggested IgG4-RD, two other conditions were carefully considered during differential diagnosis. The first was meningioma of the optic nerve sheath since contrast-enhanced MRI showed optic nerve swelling with an enhanced lesion along the left optic nerve. In such a lesion, however, we would not have distinguished the optic nerve sheath from optic nerve edema by compressive neuropathy. It also would not have been a vein in the fundus or epithelial membrane antigen stain-positive in specimens, which would imply meningeal histopathology. Thus, we ruled out meningioma. The second consideration was malignant lymphoma, such as mucosa-associated lymphoid tissue lymphoma (MALT lymphoma). We also suspected lymphoma based on radiological MRI, but pathological testing showed no abnormalities and B cell analysis revealed no monoclonal cells. A Japanese study identified 44 orbital MALT lymphoma cases with IgG4-positive cell infiltration<sup>17)</sup>. MALT lymphomas usually respond quickly to steroid therapy. However, in our patient, the lesion responded gradually and continuously to steroids and analysis by PCR disclosed no evidence of monoclonal immunoglobulin gene rearrangement.

Based on the above, we encountered a new pattern of compressive optic neuropathy with histopathological findings of IgG4 involvement. This extensive lesion appeared to cause visual disturbance.

## Conclusion

The present case displayed a connected optic nerve and nerve sheath lesion and intracranial mass next to the cavernous sinus with meningeal involvement. The patient's resulting optic neuropathy may have been caused by infiltration of IgG4-positive plasma cells and/or inflammation by a compressive mechanism. To date, such an extensive lesion from the intrafossa to the extraorbital area has not been reported, and may represent a new pattern of IgG4-RD/ROD causing optic nerve involvement.

Abstract of this work was presented at the 221st Kanto-Koshinetsu Regional Meeting of the Japanese Society of Neurology and recommended by the conference chairperson for the publication to *Rinsho Shinkeigaku*.

**Acknowledgments:** The authors would like to thank Trevor Ralph for his English editorial assistance.

※The authors declare there is no conflict of interest relevant to this article.

## References

- 1) Goto H, Takahira M, Azumi A, et al. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol* 2015;59:1-7.
- 2) Lu LX, Della-Torre E, Stone JH. IgG4-related hypertrophic pachymeningitis: clinical features, diagnostic criteria, and treatment. *JAMA Neurol* 2014;71:785-793.
- 3) Inoue D, Zen Y, Sato Y, et al. IgG4-related perineural disease. *Int J Rheumatol* 2012;2012:401890.
- 4) Sogabe Y, Ohshima K, Azumi A, et al. Location and frequency of lesions in patients with IgG4-related ophthalmic disease. *Graefes Arch Clin Exp Ophthalmol* 2014;252:531-538.
- 5) Hwang G, Jin SY, Kim HS. IgG4-related disease presenting as hypertrophic pachymeningitis and compressive optic neuropathy. *Joint Bone Spine* 2016;83:601-602.
- 6) Noshiro S, Wanibuchi M, Akiyama Y, et al. IgG4-related disease initially presented as an orbital mass lesion mimicking optic nerve sheath meningioma. *Brain Tumor Pathol* 2015;32:286-290.
- 7) Haraguchi A, Ando T, Ueki I, et al. A case of compressive optic neuropathy putatively caused by IgG4-related idiopathic orbital inflammation. *Acta Med Nagasaki* 2012;57:29-32.
- 8) Nakata R, Yoshimura T, Motomura M, et al. IgG4-related disease with cavernous sinus and intra-orbital lesions diagnosed by nasal mucosa biopsy. *Rinsho Shinkeigaku (Clin Neurol)* 2016;56:637-640.
- 9) Kosakai A, Ito D, Yamada S, et al. A case of definite IgG4-related pachymeningitis. *Neurology* 2010;75:1390-1392.
- 10) Behbehani RS, Nomas HS, Herz AA, et al. Bilateral intracranial optic nerve and chiasmal involvement in IgG4-related disease. *J*

- Neuroophthalmol 2015;35:229-231.
- 11) Takahashi Y, Kitamura A, Kakizaki H. Bilateral optic nerve involvement in immunoglobulin G4-related ophthalmic disease. *J Neuroophthalmol* 2014;34:16-19.
  - 12) Higashiyama T, Nishida Y, Ugi S, et al. A case of extraocular muscle swelling due to IgG4-related sclerosing disease. *Jpn J Ophthalmol* 2011;55:315-317.
  - 13) Kashii S. IgG4-related disease: a neuro-ophthalmological perspective. *J Neuroophthalmol* 2014;34:400-407.
  - 14) Wallace ZS, Carruthers MN, Khosroshahi A, et al. IgG4-related disease and hypertrophic pachymeningitis. *Medicine* 2013;92:206-216.
  - 15) Yonekawa T, Murai H, Utsuki S, et al. A nationwide survey of hypertrophic pachymeningitis in Japan. *J Neurol Neurosurg Psychiatry* 2014;85:732-739.
  - 16) De Virgilio A, de Vincentiis M, Inghilleri M, et al. Idiopathic hypertrophic pachymeningitis: an autoimmune IgG4 related disease. *Immunol Res* 2017;65:386-394.
  - 17) Aihara Y, Azumi A, Furuta M, et al (Japanese study group of IgG4-related ophthalmic disease). A prevalence study of IgG4-related ophthalmic disease in Japan. *Jpn J Ophthalmol* 2013;57:573-579.