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Immunoglobulin G (IgG)4-related disease is a recently defined disease entity that is characterized by elevated serum IgG4 levels and abundant infiltration of IgG4-positive plasma cells and high-grade sclerosis of the affected region.¹ This disease includes autoimmune pancreatitis, Mikulicz disease, pseudotumor of the lung, tubulointerstitial nephritis, and Riedel thyroiditis,² but the only CNS involvement that has been reported so far is hypophysitis.³

In this report, a case of intracranial IgG4-related pachymeningitis, IgG4-related disease involving the dura mater, is reported. This is a definite case of pachymeningitis that was both serologically and histologically proven, and whose clinical course and serum IgG4 levels with treatment were followed.

Classification of evidence. This study provides Class IV evidence that IV methylprednisolone followed by oral prednisolone is effective in improving the symptoms and signs of IgG4 disease affecting the CNS.

Case report. A 54-year-old woman with anterior uveitis and scleritis of the left eye, left perceptive deafness, and hypothyroidism was treated with steroid and levothyroxine. Bilateral uveitis relapsed repeatedly, and her vision gradually deteriorated. When she was 56 years old, she had pain, bulging, ptosis, and ophthalmoplegia involving her left eye, sensory impairment of her left forehead, right perceptive deafness, left temporo-occipital headache, and fever, and ophthalmectomy was performed in our hospital (figure e-1 on the *Neurology*[®] Web site at www.neurology.org). However, her vision on the right was also subsequently impaired. Blood examination revealed high serum IgG (2,188 mg/dL) and IgG4 (251 mg/dL) levels (table e-1). Antinuclear antibody and antineutrophil cytoplasmic antibody (ANCA) were negative, and

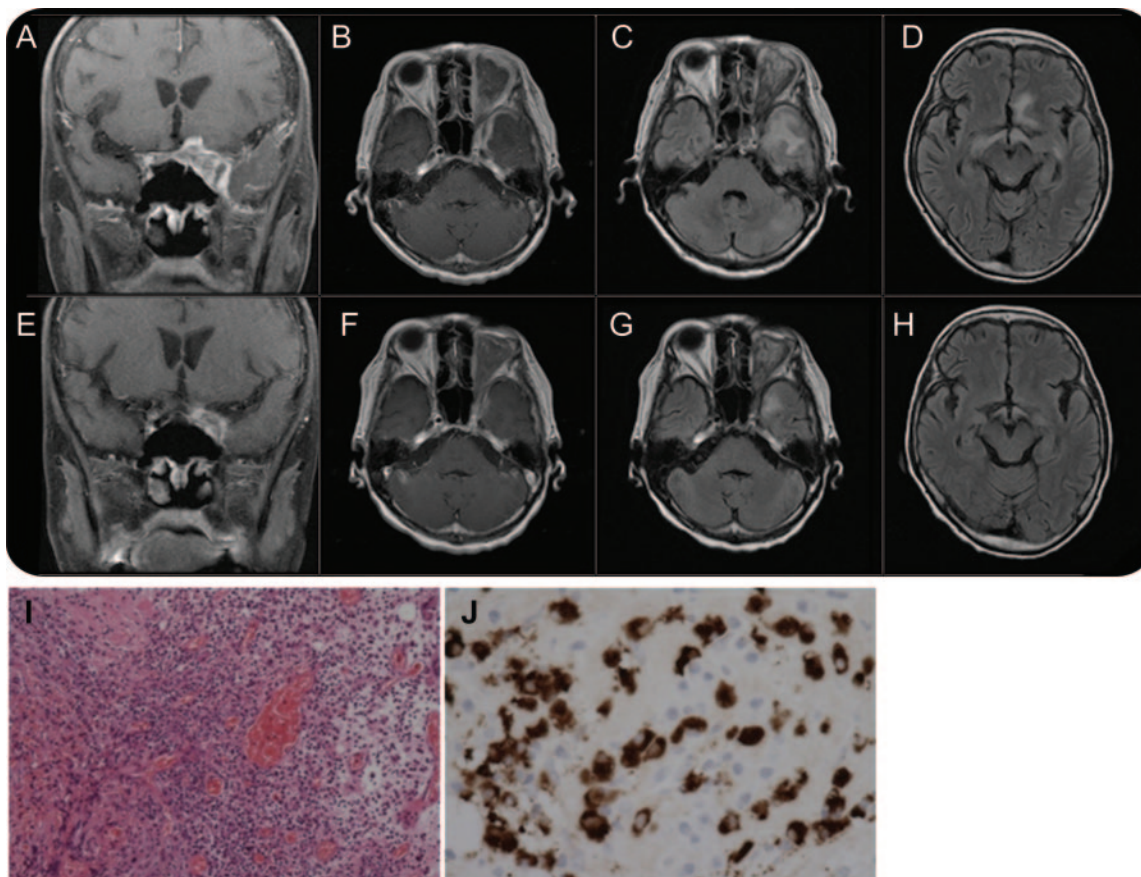
angiotensin-converting enzyme (ACE) was normal. Thyroid hormone was within the normal range, but thyroglobulin antibody and thyroid peroxidase antibody were positive. Urinalysis showed proteinuria and increased N-acetyl- β -D-glucosaminidase, indicating interstitial nephritis. A spinal tap revealed pleocytosis (112/ μ L: mononuclear 100/ μ L, polymorphonuclear 12/ μ L). Brain MRI showed thickening and enhancement of the left orbital wall and dura mater of the orbital apex, from the parasellar area to the middle skull base (figure 1, A–D), and the left ICA was occluded at the siphon (figure e-2). A nodular lesion was seen in the right lung (figure e-3). Enhanced gallium accumulation was seen in the left orbit (figure e-4).

On pathology, the left orbital wall showed chronic inflammation and fibrosis, and many plasma cell infiltrations were seen. Both κ - and λ -positive plasma cells were present, suggesting that the plasma cell infiltrations were polyclonal. On immunohistochemistry, the majority of plasma cells were IgG4-positive (figure 1, I and J). The patient was diagnosed with IgG4-related disease, and treatment was started with methylprednisolone 1 g/d for 3 days, followed by oral prednisolone 40 mg/d. Thereafter, right visual acuity, headache, and fever improved immediately, and deafness improved gradually. Serum IgG4 level (170 mg/dL) also decreased (table e-1). After 1 month of treatment, the dural lesions (figure 1, E–H), lung nodular lesion, and proteinuria also improved dramatically.

Discussion. A case of IgG4-related pachymeningitis with orbital pseudotumor, a nodular lung lesion, interstitial nephritis, and hypothyroidism is presented. The organ damage showed a very rapid response to steroid therapy, as in past reports of IgG4-related disease. Other systemic diseases, such as sarcoidosis and ANCA-associated vasculitis, including Wegener granulomatosis, can be excluded by the histology, high serum IgG4 levels, and negative serologic markers such as ANCA and ACE.

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Postoperative brain MRI before steroid treatment (A–D) and 1 month after steroid treatment was begun (E–H). (A, E) Gadolinium-enhanced coronal T1-weighted imaging and (B, F) axial T1-weighted imaging. (C, D, G, H) Axial fluid-attenuated inversion recovery images. The entire lesion from the left orbital wall and dura mater of the orbital apex, from the parasellar area to the middle skull base, is enhanced with gadolinium. The white matter is edematous near the left temporal leptomeningeal enhancement. Note that these lesions improved rapidly with steroid treatment. (I) Hematoxylin-eosin staining of the orbital tissue. Infiltration of lymphocytes and plasma cells is detected. (J) Immunohistochemistry of the orbital tissue using anti-immunoglobulin G (IgG)4 antibody. The proportion of IgG4/IgG-positive plasma cells is greater than 50%.

To date, there have been 2 cases reported with infiltration of IgG4-positive plasma cells to the dura mater on pathologic examination.^{4,5} The first case was spinal pachymeningitis complicated with sialadenitis.⁴ The other case was intracranial pachymeningitis, with no other organs affected.⁵ However, in both of these cases, only histologic analysis of the dura mater was available; the serum IgG4 levels, other complications, and detailed clinical courses were not available. Therefore, the clinical data available for these cases are inadequate to consider them definite IgG4-related disease.

There are currently no well-established criteria for systemic IgG4-related disease. Based on the investigation of reported cases, including other IgG4-related disease, we suggest the following points as being important for making the diagnosis of IgG4-related pachymeningitis: 1) high serum IgG and IgG4 levels; 2) infiltration of

IgG4-positive plasma cells into the lesion; 3) involvement of other organs possibly involved in IgG4-related disease; 4) exclusion of other diseases associated with high serum IgG4 levels, such as atopic dermatitis, parasitic infections, and pemphigus; 5) exclusion of other diseases that could cause pachymeningitis; and 6) good response to steroid therapy.

Finally, the present case suggests that IgG4-related disease can cause pachymeningitis, meaning that serologic and histologic examinations for IgG4-positive plasma cells and investigations for systemic complications must be performed to diagnose the etiology of pachymeningitis. However, at present, reports of patients with IgG4-related pachymeningitis have been restricted to Asia. Further cases need to be investigated to establish this disease concept and determine the long-term prognosis of this disease with treatment.

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Figure e-1

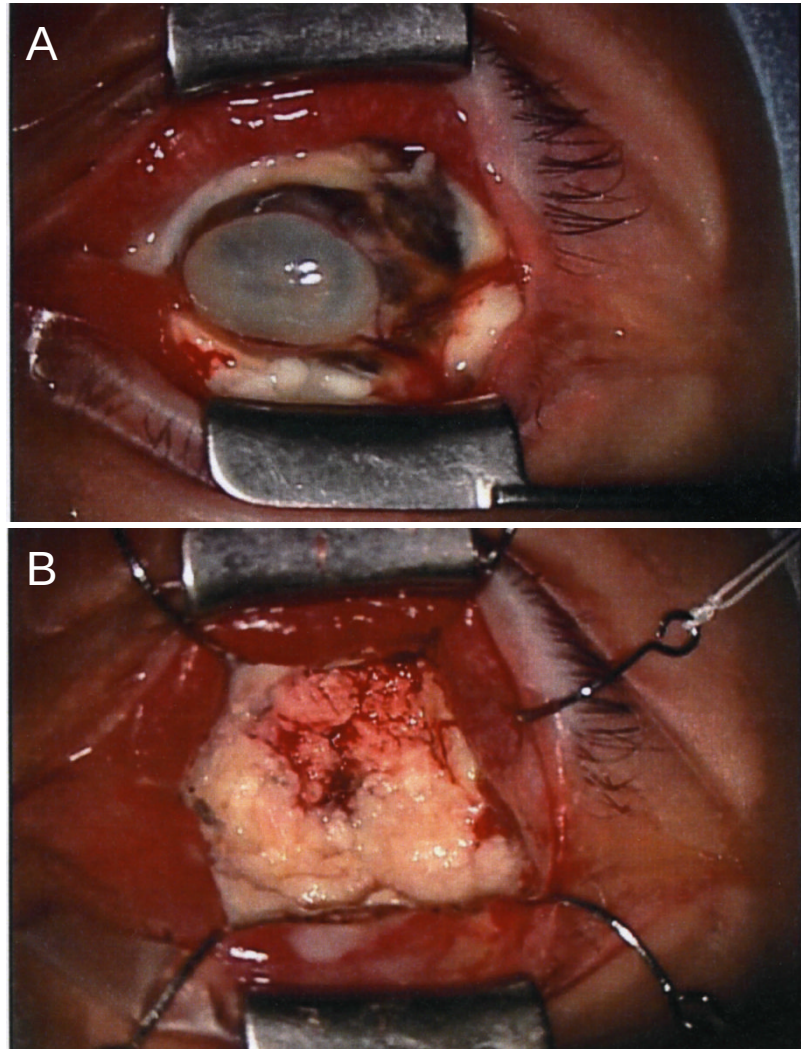


Figure e-1. Macroscopic observations of the patient's left eye.

The bulbar conjunctiva is not identified, the sclera is melted, and the uvea is barely identified. The other tissues are replaced by a white mass. (A) Before operation. (B) After operation.

Figure e-2

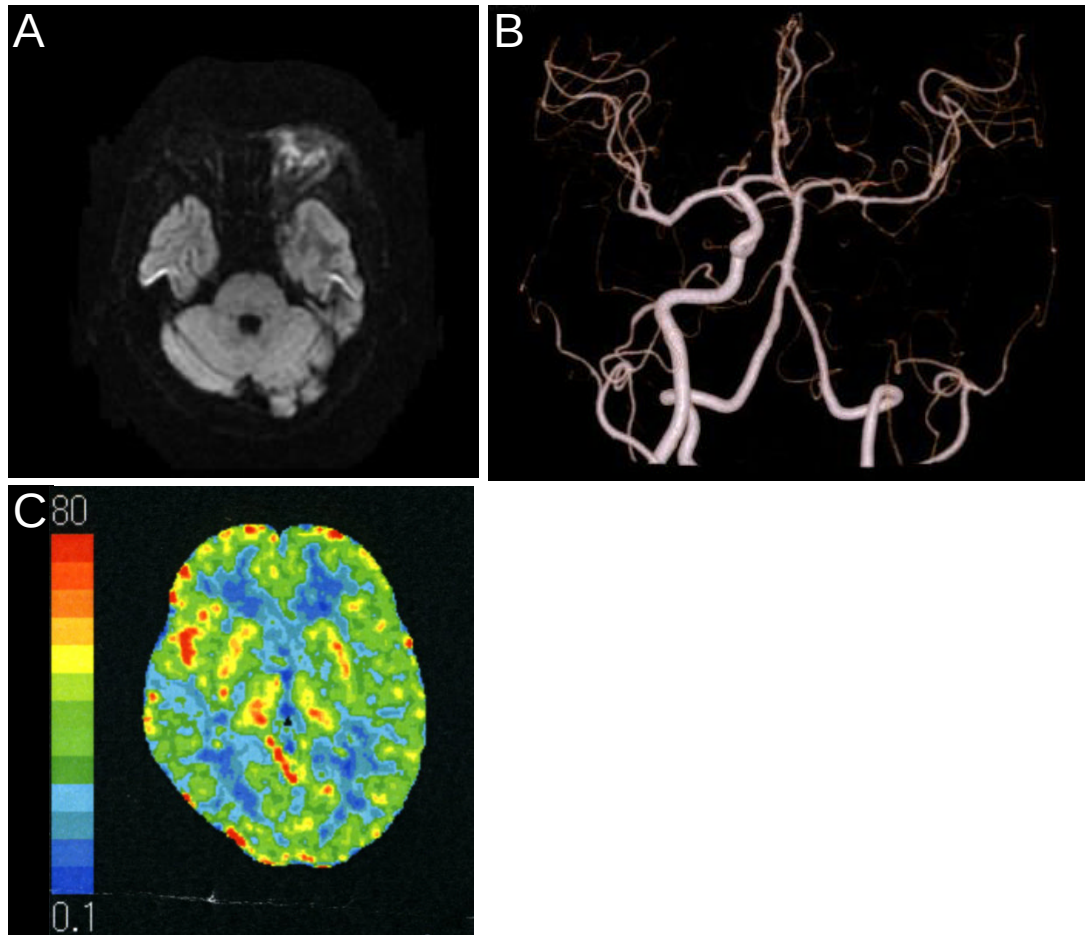


Figure e-2. Diffusion MRI and cerebral perfusion.

(A) There is no ischemic lesion on DWI. (B) 3D-CT angiography shows that the left ICA is occluded at the siphon. However, the left MCA is well detected via the anterior and posterior communicating arteries. (C) Xenon CT demonstrates the low blood flow of the left MCA area.

Figure e-3

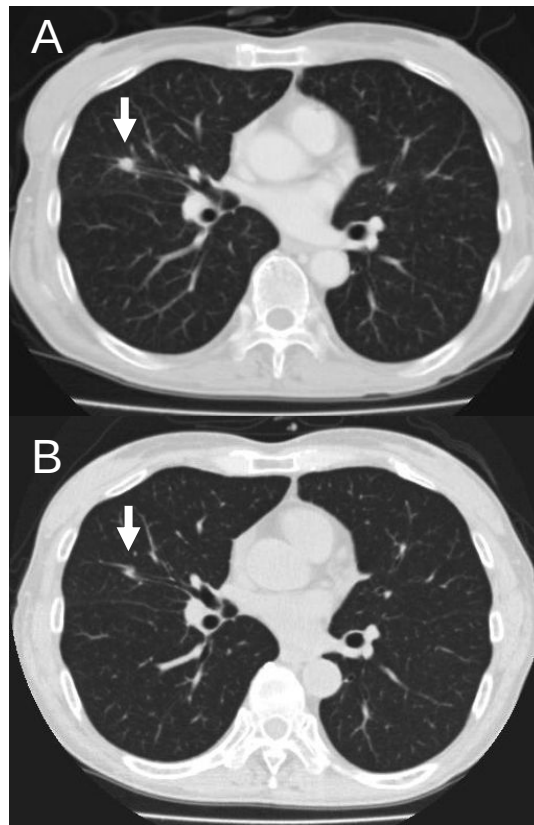


Figure e-3. The lung nodular lesion.

The figure shows the chest CT before (A) and 1 month after steroid treatment (B). (A) There is a nodular lesion (10 mm in diameter) in the right S4. (B) The nodular lesion in the S4 is fainter and smaller after treatment.

Figure e-4

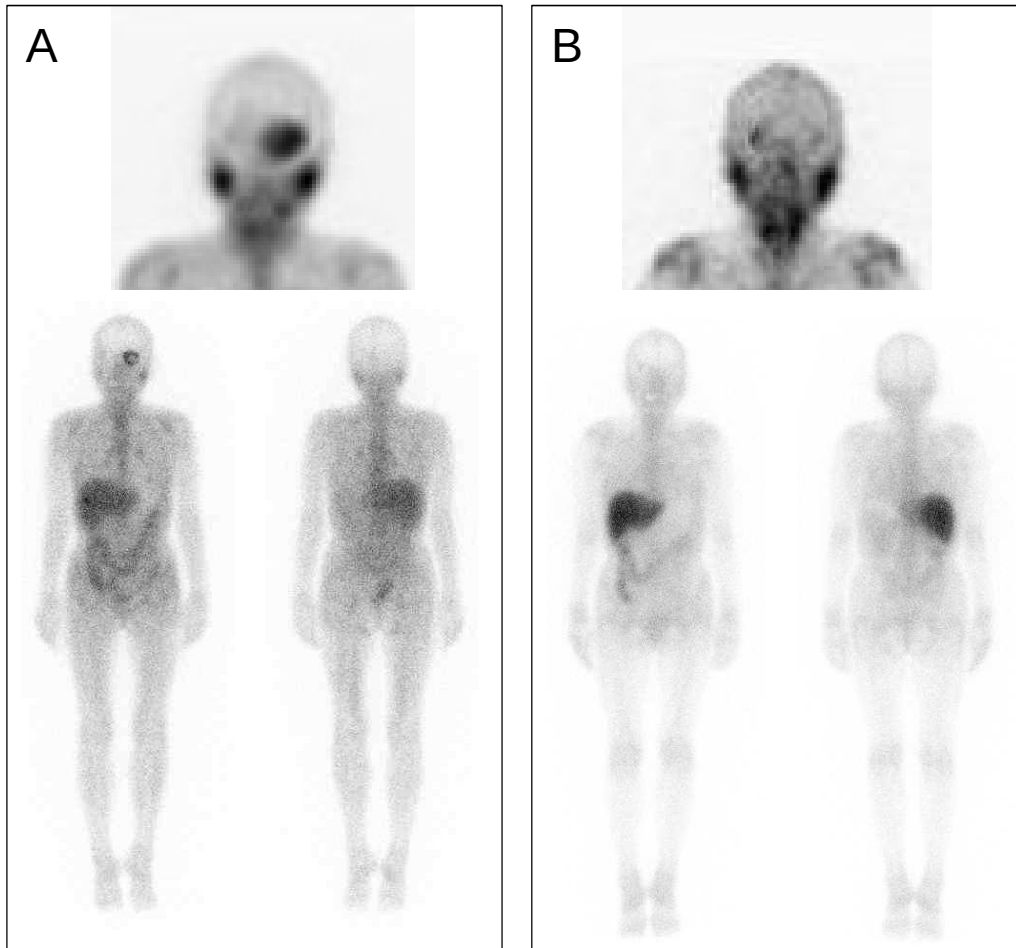


Figure e-4. Gallium scan.

Enhanced accumulation of gallium is shown in the left orbit, but there is no other abnormal accumulation in the whole body. After steroid treatment, the abnormal accumulation can be seen to have improved dramatically. (A) Before treatment. (B) After treatment.

Table e-1

Clinical chemistry tests before and after steroid treatment

	Before treatment	One month after treatment	Normal range
Serum			
IgG4 (mg/dl)	251	170	4.8-105
IgG (mg/dl)	2188	1113	870-1700
Total-IgE (IU/ml)	220	92	0-170
CRP (mg/dl)	2.68	0.01	0.00-0.35
MPO-ANCA (EU)	<10		0-19
C-ANCA (EU)	<10		0-9
ACE (IU/l)	6.2		7.7-29.4
ANA	(-)		
Anti-SSA Ab (Index)	<5.0		0.0-9.9
Anti-SSB Ab (Index)	<5.0		0.0-14.9
F-T3 (pg/ml)	3.3	1.4	2.0-4.5
F-T4 (ng/dl)	1.8	1.9	0.7-1.8
TSH (mIU/ml)	0.09	0.15	0.30-4.50
TPOAb (IU/ml)	2367	993	0-5
TGAb (IU/ml)	515.6	90	0-21
sIL2R (U/ml)	296		142-500
Urine collection			
Total protein (g/day)	0.24	not detectable	
β 2 microglobulin (μ g/day)	26.708	13.054	
NAG (IU/l)	9.6	6.9	0.0-5.0
Creatinine (g/day)	0.54	0.67	
Cerebrospinal fluid			
IgG4 (mg/dl)	<3.0		
Total cells (/ μ l)	112	8	
Polymorphonuclear (/ μ l)	12	1	
Mononuclear (/ μ l)	100	7	
Total protein (mg/dl)	186	69	
Glucose (mg/dl)	64	80	

MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, C-ANCA: cytoplasmic anti-neutrophil cytoplasmic antibody, ACE: angiotensin-converting enzyme, ANA: antinuclear antibody, TPOAb: thyroid peroxidase antibody, TGAb: thyroglobulin antibody, sIL2R: soluble IL-2 receptor, NAG: N-acetyl- β -D-glucosaminidase,