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Neuropathology Education

Intracranial mass-forming lesion associated with dural thickening and hypophysitis

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CLINICAL COURSE

A 78-year-old man presented with several months' history of blurred vision in the left eye. Physical examination revealed a left superior quadrantanopia**.** Laboratory investigations were within normal range, including renal, hepatic and pancreatic enzymes. MRI with contrast revealed two mass-forming lesions located in the falx cerebri (15×10 mm) and tentorium cerebelli (20×15 mm). In addition, slightly thickened falx cerebri and tentrium cerebelli were noted (Fig. 1a,b). Moreover, MRI revealed a swollen pituitary infundibulum, posterior hypophysis, and thickened dura which extended to the suprasellar region and compressed the optic nerve (Fig. 1c). Arteriography showed no obvious arterial supply to the lesion. The patient underwent excisional biopsy of the falx cerebri frontal mass and the frontal thickened dura. The lesions were hard and yellowish and rich in blood vessels.

PATHOLOGICAL FINDINGS

Microscopic examination of the surgical specimens revealed prominent plasmacytic infiltration with many lymphocytes, several lymphoid follicles, wide areas of sclerosis (Fig. 2a), and perivascular lymphocytic infiltration resembling phlebitis (Fig. 2b). In both specimens, neither neutrophilic or histiocytic infiltration nor granulomatous inflammation was observed. The plasma cells showed no atypia (Fig. 2c) and Gram, Grocott and Ziehl-Neelsen stains did not reveal the presence of microorganisms. Immunohistochemically, an increased number of IgG4-positive plasma cells were present, averaging 78 cells per five high power fields (HPF) (Fig. 2d). The proportion of IgG4-positive plasma cells to IgG-positive plasma cells was approximately 65%, which was demonstrated by double immunohistochemistry for IgG (Permablue, blue/AP, Diagnostic Bio Systems, Pleasanton, CA, USA) and IgG4 (diamino benzedine, brown) (Fig. 2e). Also, infiltrated mononuclear cells included many Foxp3-positive regulatory T cells (Fig. 2f). The highest ratio of FoxP3-positive cells to total mononuclear cells was 0.21.

DIAGNOSIS

Intracranial mass-forming IgG4-related pachymeningitis

Three weeks after steroid treatment, MRI showed remarkable shrinkage of both the affected dura mater and the infundibulo-hypophyseal lesion. At 12 months of follow-up, the patient was free of recurrence.

DISCUSSION

IgG4-related disease, also called "IgG4-related sclerosing disease",[1] is a recently described systemic fibroinflammatory disease associated with or without elevated circulating levels of IgG4. Although initial descriptions of this disorder concentrated on its pancreatic presentation as an "autoimmune pancreatitis,"[2] it has become apparent that IgG4-related disease is a systemic disease accompanied by

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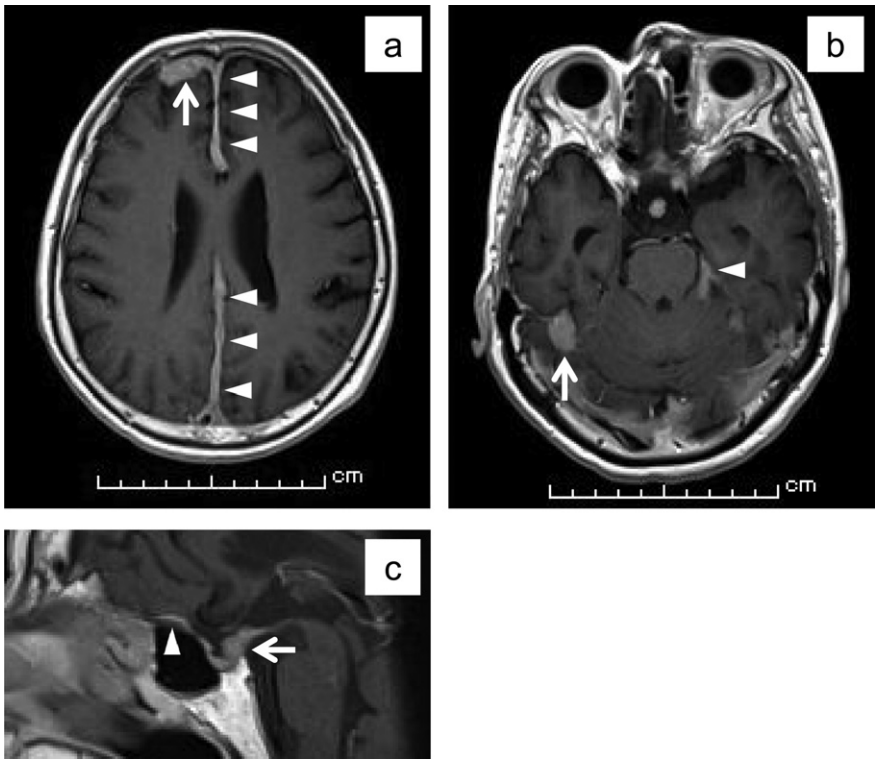

Fig. 1 Pretreatment brain MRI images (a–c). Before the steroid treatment, horizontal gadolinium (Gd)-enhanced T1-weighted MRI images show homogenously enhanced masses on the falx cerebri (a, arrow), right tentorium cerebelli (b, arrow). In addition, slightly thickened falx cerebri (a, arrow heads) and tentorium cerebelli (b, arrow head) are noted. Sagittal view shows Gd-enhanced swollen pituitary infundibulum, posterior hypophysis (c, arrow) and thickened sellar diaphragm (c, arrow head).

extrapancreatic inflammatory lesions. In 2009, IgG4-related pachymeningitis was first described as an epidural mass of the thoracic spine complicated with sialadenitis.[3] Subsequently, several cases of IgG4-related pachymeningitis have been reported (Table 1).[3–6] It has been suggested that a subset of idiopathic pachymeningitis may correspond to IgG4-related pachymeningitis.[6] In addition, an involvement of the pituitary gland has been recognized as another possible extra-pancreatic manifestation of the disease.[7] In the present case, the patient showed both IgG4-related pachymeningitis and infundibulo-hypophyseal lesions, simultaneously. We couldn't examine the infudibulo-hypophyseal lesion histologically; however, the shrinkage of the lesions by steroid therapy was consistent with the manifestation of IgG4-related disease.

In 2012, an international consensus meeting for pathological diagnosis of IgG4-related disease proposed "Boston criteria", in which the three major histopathological features, such as dense lymphoplasmacytic infiltrate, a striform type fibrosis, and obliterative phlebitis accompanied by IgG4+/IgG+ over 40% were required. However, the threshold number of IgG4+ plasma cells/HPF varies depending on the affected organs.[8] In the present case, we could confirm 78 IgG4+ cells/HPF and 65% of IgG4+/IgG+ cells by masking double immunostaining. High ratio of IgG4/IgG was sometimes noted in infectious pachymeningitis, including tuberculosis, *Staphylococcus aureus* and Lagerhans cell histiocytosis. Therefore, a combination of clinical and pathological features such as imaging and histopathological findings with exclusion of infectious disease is needed for the diagnosis of IgG4-related pachymeningitis.

The pathogenesis of IgG4-related disease is still unknown. IgG4 plays a major role in pathogenesis; however, the trigger for IgG4 elevation has not been clearly established. Recently, prominent infiltration of CD4+CD25^{high} Foxp3^{+} regulatory T-cells (Foxp3^{+}Tregs) in the pancreas of patients with autoimmune pancreatitis has been reported. Okazaki *et al*. suggested Foxp3^{+} Tregs may produce IL-10 and TGFβ, followed by switching B cells to produce IgG4 and fibrosis, respectively, in this disease.[9] In the present case, prominent infiltration of Foxp3^{+} Tregs in the dural mass was observed, which suggests that these cells play a pivotal role in the pathogenesis of IgG4-related pachymeninigitis.

In summary, we represented a case of mass-forming IgG4-related pachymeningitis with infundibulo-hypophyseal lesions. For appropriate diagnosis and management, it is important to recognize the entity, that is, IgG4-related pachymeningitis and hypophyseal lesions as differential diagnoses of meningeal thickening or hypophyseal lesions.

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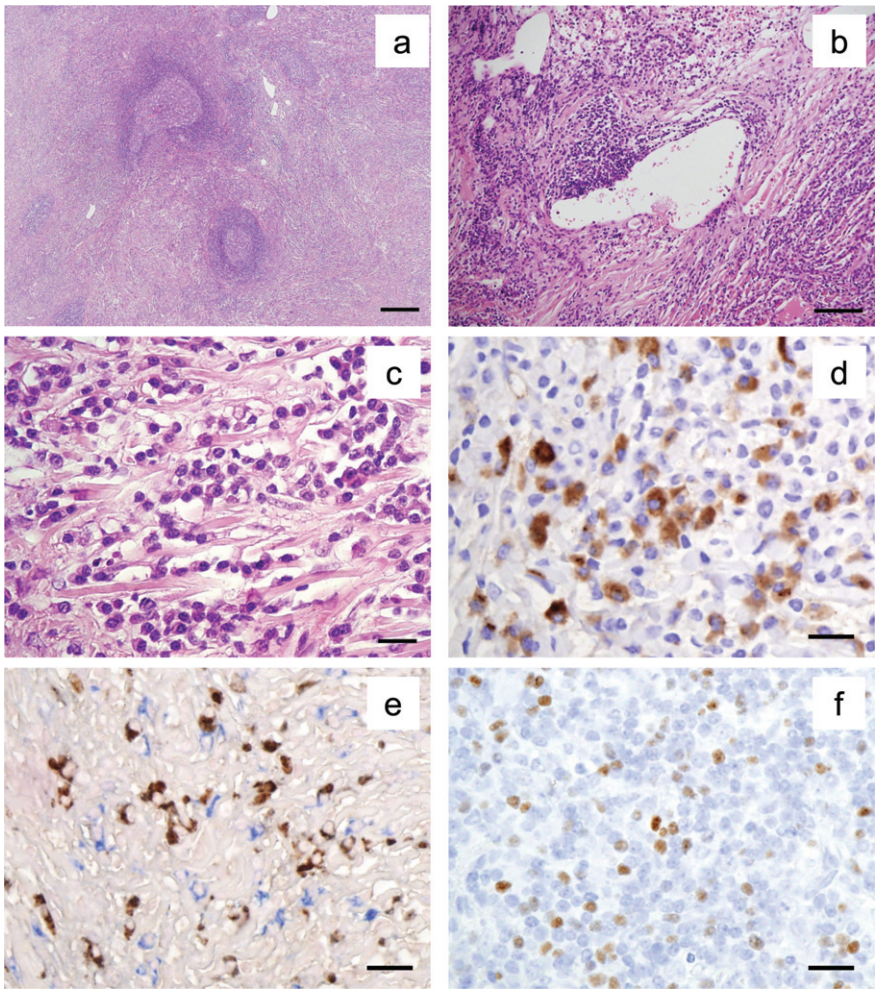

Fig. 2 Histological appearance of lesion of falx cerebri. HE staining shows fibro-inflammatory lesions consisting of lymphoid follicle formations (a), phlebitis (b), sclerosis and numerous plasmacytic infiltrations with many lymphocytes (c). The immunohistochemistry for IgG4 shows prominent IgG4+ cell infiltration (d). By using double immunohistochemistry for IgG (Permablue, blue) and IgG4 (DAB, brown), IgG+ and IgG4+ cells are clearly demonstrated (e). The average IgG4+ cell count was 78 per five high power fields (HPF), and the proportion of IgG4+ to IgG+ plasma cells was 65%. There are many Foxp3+ regulatory T cells (f). Scale bars indicate 200 µm (a), 50 µm (b) and 10 µm (c–f). (a–c: HE, d: IgG4, e: IgG-blue, IgG4-brown, f: Foxp3).

Table 1 Review of IgG4-related pachymeningitis

No	Age	Sex	MRI findings	Other involvement	Serum IgG4 (mg/dL)	IgG4+ cells/HPF	IgG4+/IgG+ (%)	Treatment	Reference
1	37	M	Epidural mass of T5–10	Salivary gland	NA	310	70	Steroid	(3)
2	46	F	Epidural mass of T9–11	None	90 after steroid therapy	>20	NA	Steroid	(4)
3	56	F	Dural thickening with orbital tumor	Lung, kidney, thyroid	251	NA	>50	Steroid	(5)
4	55	M	C3–C7 mass	NA	NA	46.6	60	Steroid+radiation	(6)
5	60	F	Dural thickening	NA	NA	41.6	24	Steroid+TNF-blocker	(6)
6	63	M	C2–3 mass	NA	NA	11.8	30	Unknown	(6)
7	53	M	Posterior fossa tumor	NA	NA	26.8	NA	Steroid	(6)
8	78	M	Dural mass and thickening	Infundibulo-hypophyseal lesion	NA	78	65	Steroid	Present case

HPF; high power field, NA; not available, T; thoracic, C; cervical.

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CONFLICT OF INTEREST

The authors declare that they have no competing financial interests.

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