



IgG4-related inflammatory pseudotumor of the brain parenchyma: a case report and literature review

Zhuqing Zhang¹ · Weiwei Fu² · Minghui Wang¹ · Lei Niu¹ · Bin Liu³ · Yingbin Jiao⁴ · Xuejun Liu¹

Received: 9 June 2018 / Accepted: 5 October 2018
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Abstract

A 29-year-old male with a 4-month history of binocular temporal visual field defect, 1-month history of memory loss and 5-day history of headache was admitted to our hospital. Brain MRI showed progressive signal abnormalities in the brain parenchyma. His laboratory tests showed elevated serum IgG4 and liver dysfunction. Abdominal CT, ultrasound and liver biopsy showed chronic liver disease. According to the diagnostic criteria of IgG4-related disease, IgG4-related inflammatory pseudotumor of brain parenchyma was considered. After methylprednisolone treatment, his symptoms improved and brain lesion reduced. This is the second reported case of a tumefactive lesion of the brain with serum IgG4 elevation, which was responsive to steroid treatment. Coincidentally, his mother had similar medical history and imaging findings, and was subspecialty diagnosed with the same disease, but without pathological and immunohistochemical confirmation. This suggests that the disease may be hereditary. It is important to recognize IgG4-related inflammatory pseudotumors of the brain parenchyma so that patients do not undergo unnecessary surgical or other procedures.

Keywords IgG4 · Inflammatory pseudotumor · Brain parenchymal · Calcification

Introduction

IgG4-related disease (IgG4-RD) is an autoimmune disorder characterized by elevated serum IgG4 levels and infiltration of IgG4-positive plasma cells in various tissues or organs. The organs involved in the reported IgG4-RD cases have included the biliary tree, pancreas, salivary glands, kidneys, lungs, lymph nodes, etc. [1]. IgG4-RD, is a rare nervous system disease, which occurs mostly in the dura, ventricles, orbit, pituitary, and around a cranial nerve. The IgG4-related inflammatory pseudotumor, which develops in the brain

parenchyma, is exceedingly rare, with no apparent specificity of the imaging and clinical manifestations. To the best of our knowledge, only one case has been reported to date. Recently, a patient with an IgG4-related inflammatory pseudotumor, which was confirmed and highly suspected to be familial hereditary, was admitted to our hospital. Herein, we present the case report and discuss the possibility of heredity of the disease, which mimicked glioblastoma or demyelinating pseudotumor.

Case report

A 29-year-old male underwent an MRI scan for evaluation of a binocular temporal visual field defect on December 13, 2016 in a local hospital (Fig. 1). Multiple lesions were found in the brain parenchyma without obvious mass effect (Fig. 2). A clinical diagnosis of “inflammatory lesions” was made. After symptomatic treatment, the patient’s symptoms were relieved and he was discharged.

Four months later, the patient was admitted to our hospital on April 12, 2017, with complaints of “memory loss for 1 month, headache for 5 days after drinking alcohol, and no relief after resting” (Fig. 1). Memory loss involved

✉ Xuejun Liu
bncz@sina.com
Zhuqing Zhang
nysx_zzq@126.com

¹ Department of Radiology, The Affiliated Hospital of Qingdao University, Qingdao, China
² Department of Pathology, The Affiliated Hospital of Qingdao University, Qingdao, China
³ Department of Rheumatology, The Affiliated Hospital of Qingdao University, Qingdao, China
⁴ Department of Neurosurgery, The Affiliated Hospital of Qingdao University, Qingdao, China

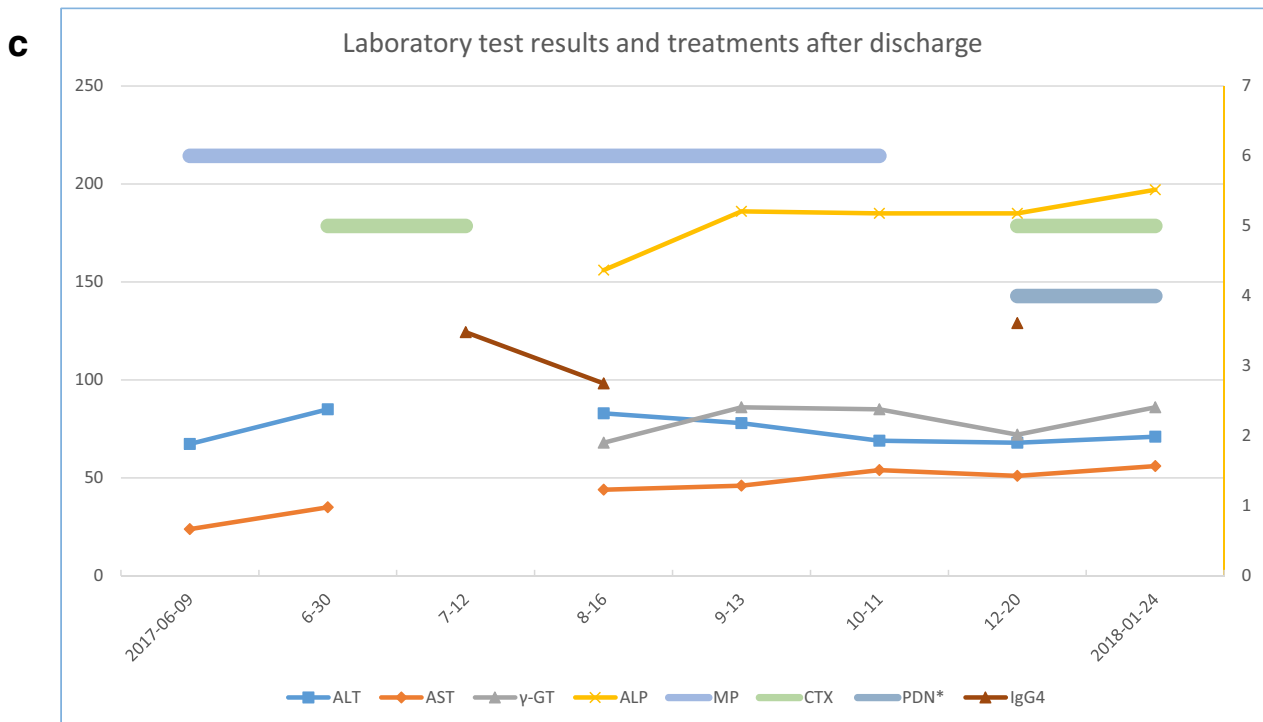
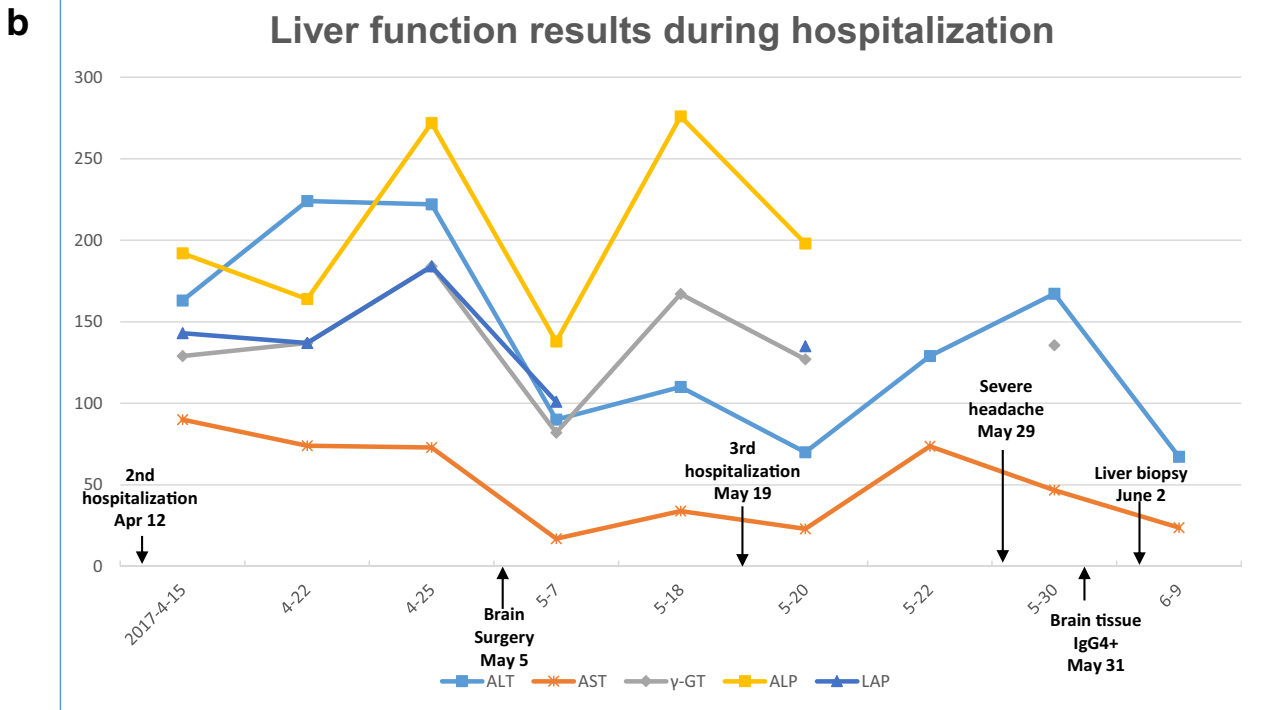
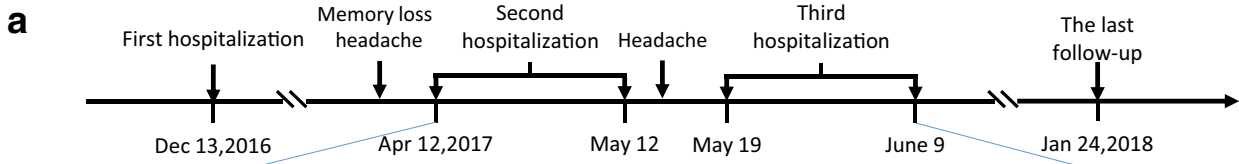


Fig. 1 Clinical course of the case. **a** Shows a timeline beginning with the patient's first hospitalization in December 2016 and ending after his last follow-up in January 2018. The major events and symptoms during the course of the patient's illness are indicated by arrows. **b** Displays the laboratory values and major treatment administered during the patient's second and third hospitalizations. **c** Lists the laboratory values obtained and the pertinent medications administered during the patient's 7-month follow-up. The horizontal thick gray lines indicate the medications administered. *MP* methylprednisolone, *CTX* cyclophosphamide, *PDN* prednisone. In **b** and **c**, the liver function and the serum IgG4 level are displayed through a set of line charts

forgetting mainly recent events without paresis or dysarthria. The patient was healthy, and his family history showed that the family members were healthy, except for his mother, who was diagnosed with glioblastoma and survived after radiotherapy (Fig. 3). There were no obvious abnormalities on PE. The MRI scan performed on the next day showed that the brain lesion was larger than before, especially the one in the left frontal lobe. Of note, the MR Gd-enhanced scan showed the lesion in the left frontal lobe was enhanced and characterized by a "flower ring", whereas the lesion in the left parietal lobe had not significantly changed (Fig. 4). Glioblastoma was suspected. No obvious abnormalities were found in the physical examination. The laboratory examinations on April 15 indicated a mild abnormality in the liver function (Table 1), but no obvious abnormality was found in other laboratory tests.

On April 17, liver ultrasound showed slight hepatomegaly with an increased echostructure of the liver, and thus hepatitis was considered. Further, on April 21, abdominal CT scan showed fullness of the left lobe of the liver (Fig. 5). After hepatoprotective and other symptomatic treatments, the liver function test was still abnormal on April 22 (Table 1), which was accompanied by continued dehydration. The hepatoprotective treatment continued.

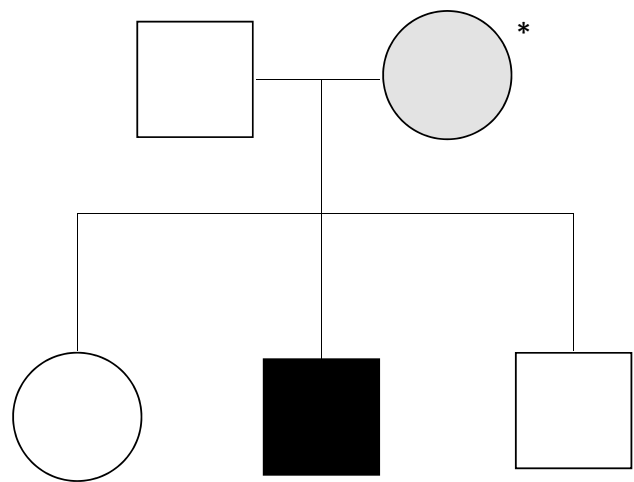


Fig. 3 Family tree of the patient's family. The patient and his mother were ill, but the other family members were healthy. *The mother's disease was not pathologically confirmed

The symptoms were not significantly relieved after 2 weeks of treatment; the headache without convulsions and the upper abdominal pain persisted (Fig. 1). A repeat brain MRI was performed on April 25, which showed no obvious changes in the lesions (images not shown). The liver function was persistently abnormal. On April 29, the patient had a severe headache. A brain CT on the next day (April 30) showed hypodensity of the lesion with punctate calcification (Fig. 4b, c). Based on these findings and the MRI results, non-tumorous lesions were considered while an inflammatory pseudotumor could not be excluded. To further clarify the nature of the lesion, intracranial lesion excision was performed on May 5 (Fig. 1), and a pathological diagnosis was made of demyelinating pseudotumor (Fig. 6). On May 12, serum immunoglobulin showed IgE 607.30 IU/mL (normal range 0–100), IgG 9.82 g/L (normal range 7–16), and IgG4

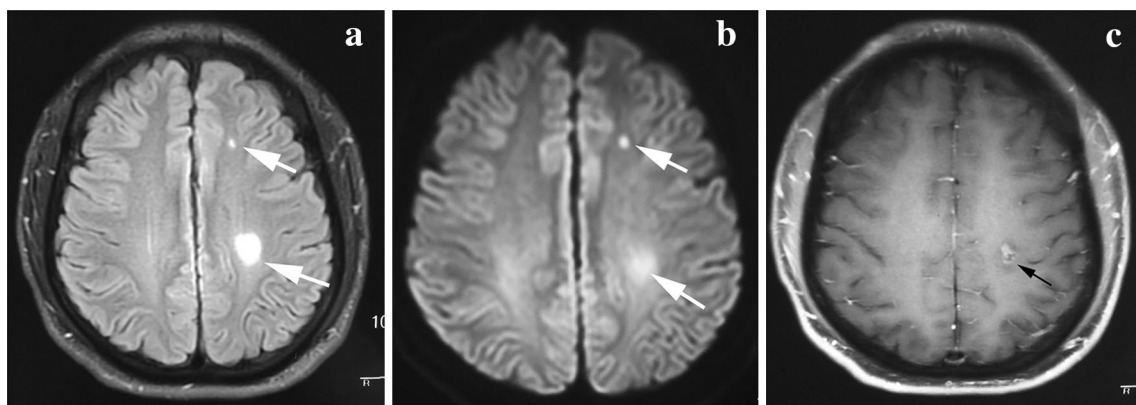


Fig. 2 The first time MR examination. FLAIR (**a**) and DWI (**b**) showed multiple abnormal signals in the brain parenchyma (arrow), without an obvious mass. Gd-enhanced T1WI (**c**) MRI revealed an apparently enhanced left parietal lobe lesion (black arrow)

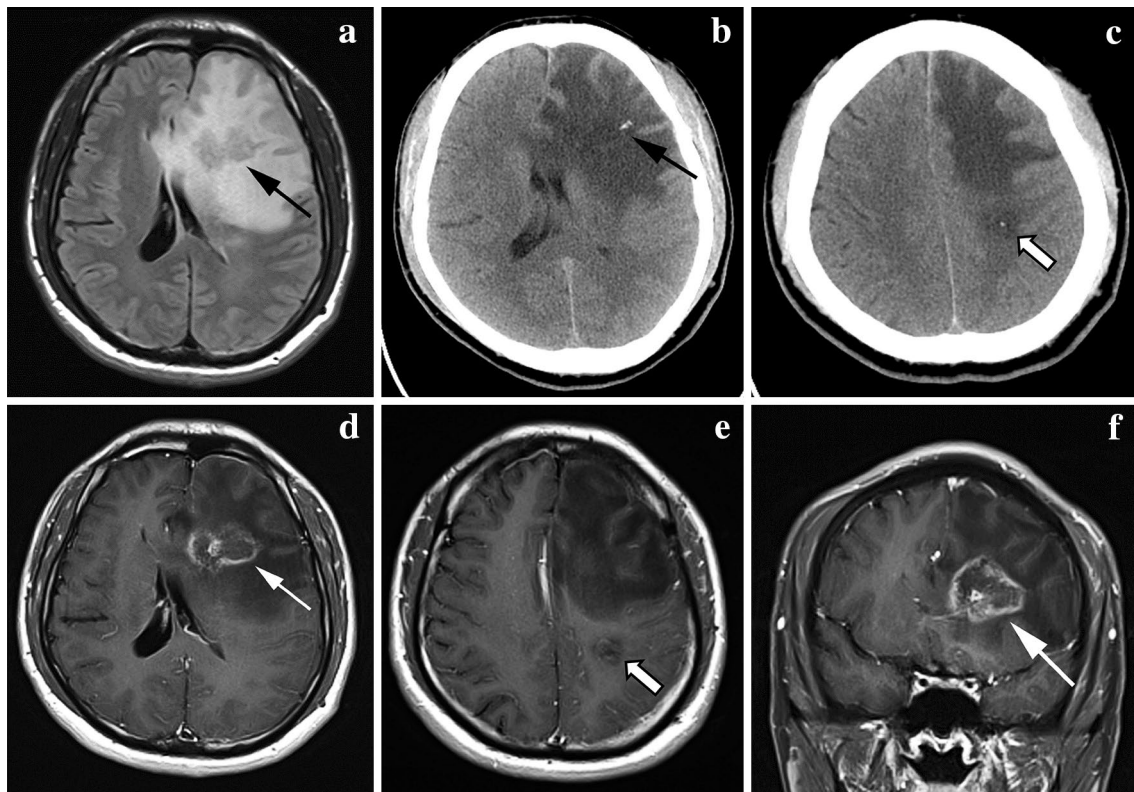


Fig. 4 MR examination of the second admission. The lesion of the left frontal lobe (black arrow) was significantly progressive than before, and the signal was heterogeneous, and surrounded by finger-like edema signals. Gd-enhanced MRI showed the flower ring-like

enhancement (white arrow), with an obvious mass effect. The left parietal lesion (hollow arrow) had not significantly changed than the first MR examination

Table 1 Liver function results during hospitalization

	Normal range (U/L)	Liver function values								
		2017-4-15	4-22	4-25	5-7	5-18	5-20	5-22	5-30	6-9
ALT	9–50	163	224	222	90	110	70	129	167.2	67.3
AST	15–40	90	74	73	17	34	23	73.7	46.7	23.8
γ -GT	10–60	129	137	184	82	167	127		135.6	
ALP	45–125	192	164	272	138	276	198			
LAP	30–70	143	137	184	101		135			

3.04 g/L (normal range 0.03–2.01). The patient's symptoms were relieved, and he was discharged.

On May 19, the patient was admitted to the hospital for the third time with a complaint of headache for 4 days (Fig. 1). No abnormalities were observed on physical examination. The patient was treated with mannitol to decrease his intracranial pressure and with methylprednisolone for anti-inflammation (80 mg mid iv), which relieved his symptoms. On May 23, the methylprednisolone dosage was changed to 40 mg mid iv. On May 22, the IgG4 concentration decreased to 2.25 g/L. Autoimmune encephalopathy was suspected at that point due to the elevated serum level of immunoglobulin. The liver function remained abnormal on reexamination.

On May 23, weakly positive antinuclear antibody (ANA) and 2+ positive sp100 protein were found in hepatopathy-related autoantibody tests, with no other abnormalities. A reexamination of the liver function on May 30 showed aggravation evident by the increased ALT and γ -GT concentrations (Table 1). Given the elevated serum level of IgG4, the lesion in the brain parenchyma, the persistently abnormal liver function, and the imaging abnormality of the liver, IgG4-RD involving the liver was suspected. On May 31, IgG4-RD immunohistochemical examination of brain tissue showed approximately 10–15 IgG4-positive plasma cells per HPF, the ratio of IgG4 and IgG was approximately

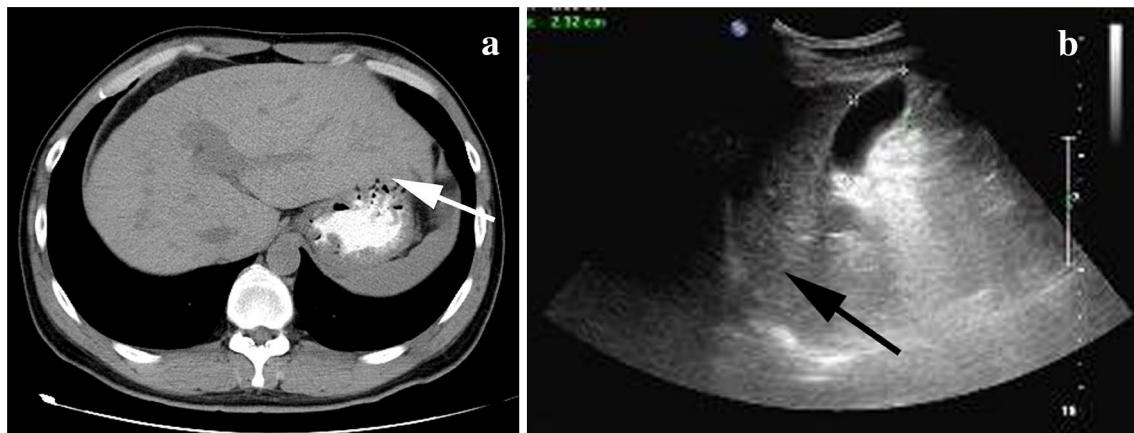


Fig. 5 Abdominal CT and ultrasound. **a** CT showed a full liver left leaf shape (white arrow), **b** rough echo of the liver (black arrow)

50% (Fig. 7). The final diagnosis was IgG4-related inflammatory pseudotumor of the brain parenchyma.

On June 2, the liver biopsy showed “chronic liver disease” (Fig. 8). However, the results of the immunohistochemical tests were negative for IgG and IgG4. The hepatoprotective therapy was continued. After the treatment, on June 9, the transaminase level was significantly lower than before (Table 1). The steroid therapy was switched to oral administration (32 mg po) for treatment continuation, and the patient was discharged (Table 2). The MRI performed on 24 Jan 2018, after 7 months of anti-inflammatory treatment (methylprednisolone and prednisone) and anti-immunotherapy (cyclophosphamide), showed improvement in the brain lesions (Fig. 9), and stable liver function indices (Table 2). During the follow-up in the clinic, the patient reported no headaches or other symptoms.

Discussion

Inflammatory pseudotumor (IPT), also known as inflammatory myofibroblastic tumor and plasma-cellular granuloma, is a rare soft-tissue inflammatory lesion. The pathological features of IPT are infiltration of lymphocytes, plasma cells, macrophages, and foam cells in the lesion. IPT can affect all organs, such as the lungs, lymph nodes, pancreas, liver, retroperitoneum, etc. [2]. Normal orbits are observed when IPT occurs in the head and the neck. It is noteworthy that IPT develops rarely in the central nervous system: only 70 cases have been reported worldwide, most of which in the saddle area, next to the saddle, choroid plexus, brain parenchyma, etc. IPT is aggressive and often causes symptoms such as skull bone destruction and nerve palsy. The pathogenesis of IPT remains unclear and is considered secondary to other diseases, such as trauma, acute infection (EBV, bacteria, fungi, etc. [3]), abnormal immune response and prolonged

reparative process [4]. Additionally, IPT is thought to have a genetic tendency, and approximately 50% of the cases may be related to the ALK gene rearrangement in 2p23 [2].

IgG4-related disease (IgG4-RD) is an infrequent autoimmune disease, whose underlying mechanism remains unclear. It is characterized by an elevated serum IgG4 level, infiltration of IgG4-positive plasma cells in multiple tissues or organs. The disease was first identified in 2001 and characterized by chronic pancreatitis [5]. IgG4-RD can be developed in any organ or tissue in the human body [6] but is the most common in the pancreas, salivary glands, and lacrimal gland. The nervous system could also be affected, but the predominant manifestations in most cases are hypertrophic pachymeningitis and hypophysitis [7], with or without other organ involvement [8]. Currently, the most widely recognized diagnostic criteria of IgG4-RD are those proposed by Japanese scholars [9]. Comprehensive clinical diagnostic criteria for IgG4-RD include: (1) clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; (2) hematological examination showing elevated serum IgG4 concentrations (135 mg/dL); (3) histopathological examination showing: (1) marked lymphocyte and plasmacyte infiltration and fibrosis, (2) infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells > 40% and > 10 IgG4+ plasma cells/HPF. Definite diagnosis: 1 + 2 + 3, probable: 1 + 3, and possible: 1 + 2.

In this case, the serum level of IgG4 was 3.04 g/L, the immunohistochemistry showed infiltration of numerous lymphocytes and plasma cells (Fig. 6b), and perivascular IgG4+ plasma cells were approximately 10–15/HPF. In addition, IgG4+/IgG+ was about 50% (Fig. 7), and the imaging examination suggested a mass in the brain parenchyma. Based on the diagnostic criteria, this case was finally diagnosed as IgG4-related IPT of the brain parenchyma. To our knowledge, this is the second reported case of IgG4-related IPT of the brain parenchyma [10]. IgG4-RD was sensitive

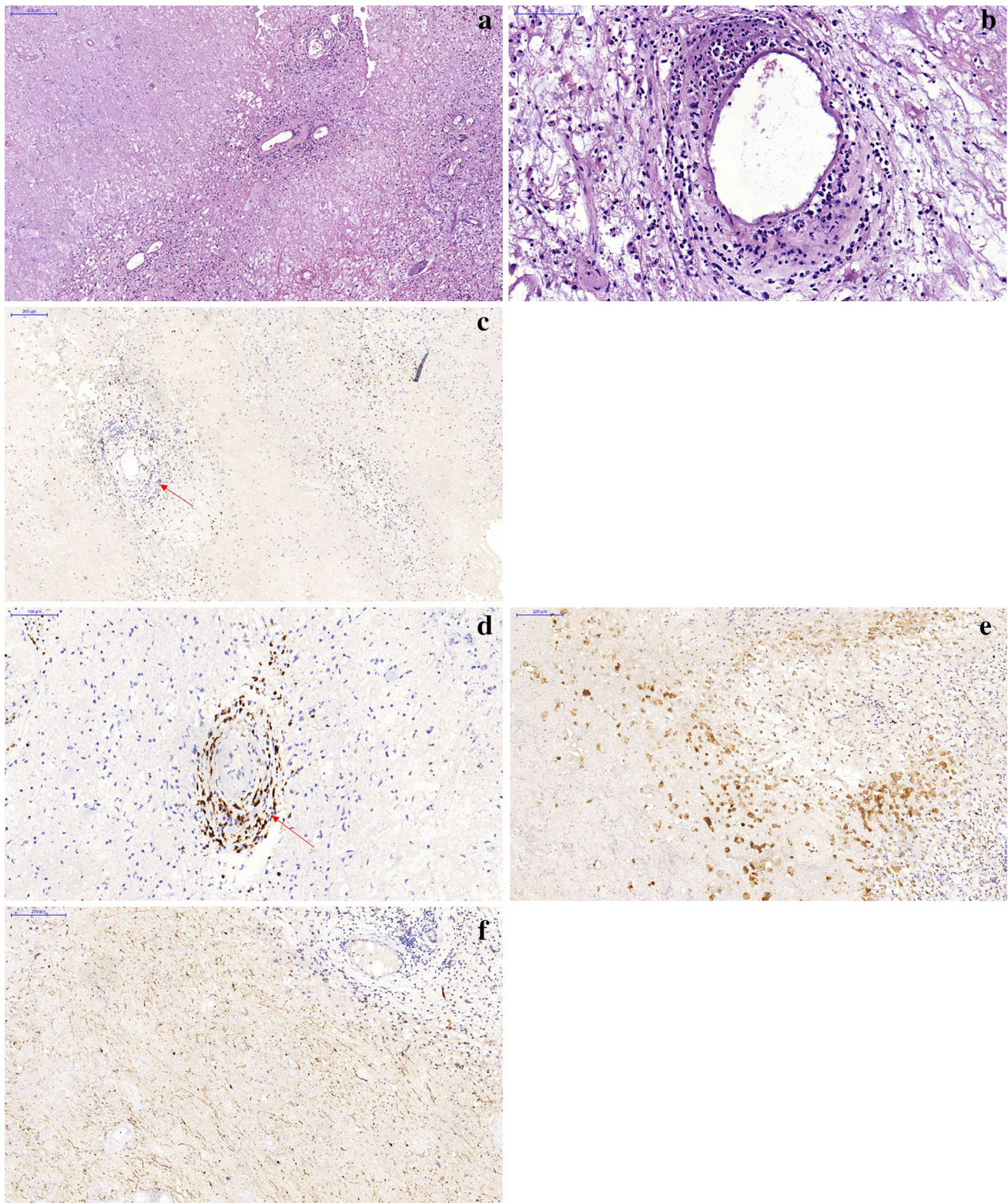


Fig. 6 Pathological findings of the patient's brain tissue. **a** Large necrosis in brain tissue and the aggregation of phagocytes (HE 100×); **b** numerous lymphocytes and plasma cells were noted around the walls of the blood vessels (HE 200×); **c** CD3 showed scattered

T cells; **d** CD38 showed plasma cells around the vessels; **e** CD68 showed phagocytes surrounding necrosis; **f** NF showed nerve fiber damage

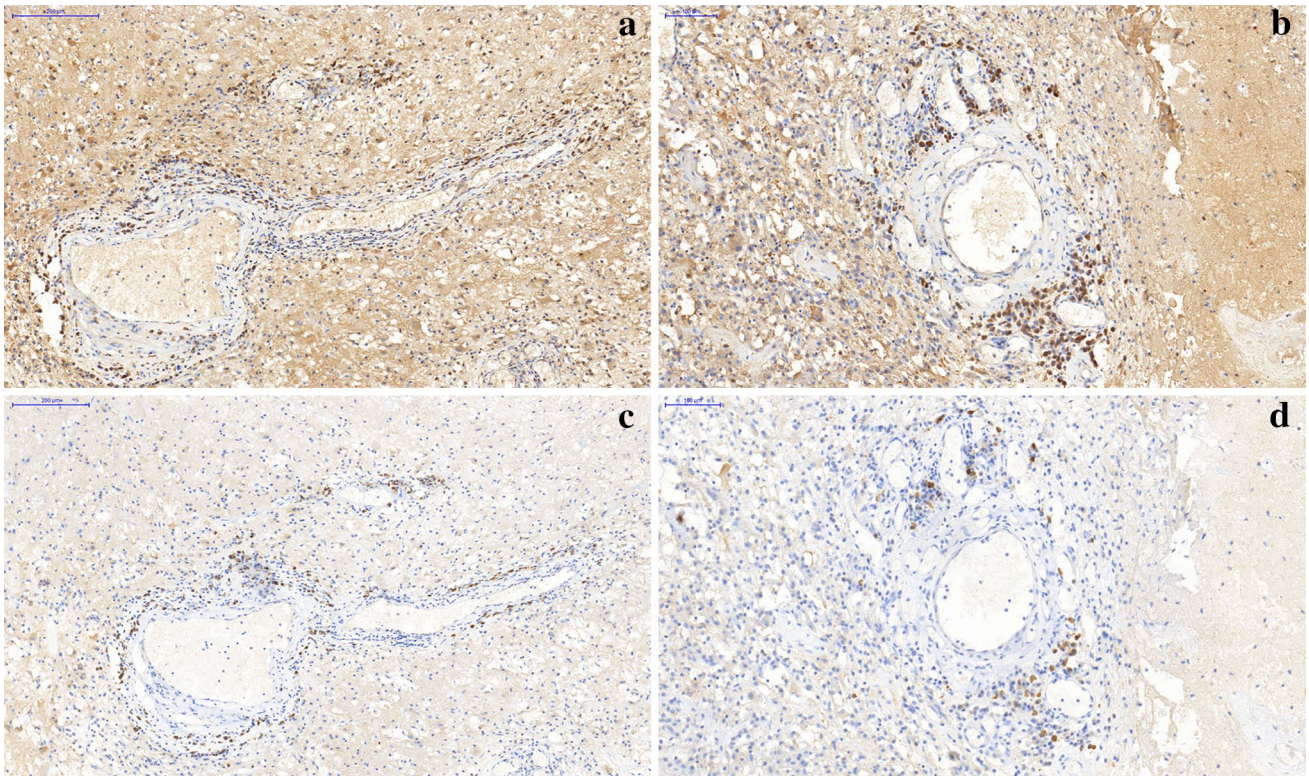


Fig. 7 Immunohistochemical results of the brain tissue. **a, b** IgG, **c, d** IgG4; the ratio between IgG and IgG4 was >40%, IgG4+ plasma cells were approximately 10–15 per HPF

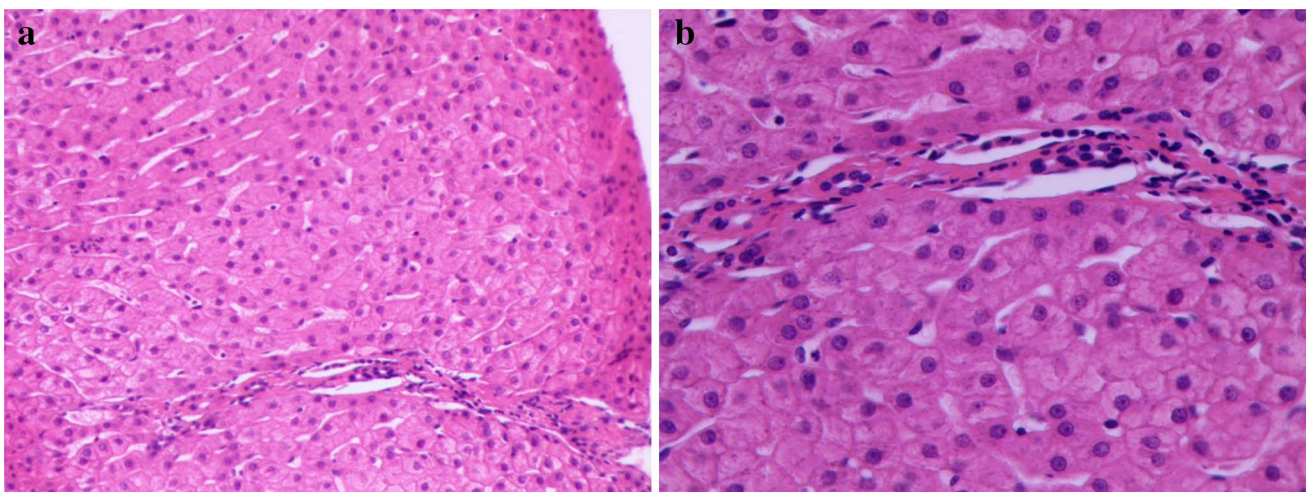


Fig. 8 Biopsy pathology of the liver. Hepatic cell turbidity, fatty degeneration of few hepatocytes, and few inflammatory cells infiltrated into the reservoir area

to glucocorticoid¹⁴, and the symptoms of this patient were relieved after methylprednisolone therapy.

We believe that the liver dysfunction was caused by autoimmune hepatitis, which may be primary biliary cholangitis

(PBC). The following evidence supported the diagnosis [11]: elevated serum ALP level (276 U/L on 18 May 18 [> 2 times normal]; Table 1); AMA negative, but ANA positive; 2+ positive sp100 antibodies; and the liver biopsy results.

Table 2 Laboratory test results and treatments after discharge

	Normal range	Laboratory test values and treatments									
		2017-06-09	6-30	7-12	8-16	9-13	10-11	11-8a	12-20	2018-01-24	
ALT	9–50 U/L	67.3	85		83	78	69			68	71
AST	15–40 U/L	23.8	35		44	46	54			51	56
γ-GT	10–60 U/L				68	86	85			72	86
ALP	45–125 U/L				156	186	185			185	197
Serum IgG4	0.03–2.01 g/L			> 3.48	2.75					> 3.61	
Treatments (doctor's prescription)		MP 32 mg qd	MP 28 mg qd, CTX 100 mg qod	MP 24 mg qd	MP 16 mg qd	MP 8 mg bid	MP 16 mg qd	MP 48 mg qd, CTX 100 mg qod	MPN 10 mg qd, CTX 50 mg qd	MPN 10 mg qd	MPN 10 mg qd

The first five lines represent the laboratory test results during the follow-up. The “treatment (doctor's prescription)” represents the doctor's prescription for the next period

MP methylprednisolone, CTX cyclophosphamide, PDN prednisone

^aThe results of the laboratory test on Nov 8 were not available by some reason

In this case, the relationship between autoimmune hepatitis and IgG4-RD was not confirmed by liver biopsy, which might have included false negatives. The accumulation of a greater number of similar reports would be helpful to further elucidate the underlying mechanism.

Certain genes are involved in the pathogenesis of autoimmune diseases such as autoimmune pancreatitis [12], but there is no report on familial IgG4-RD. Coincidentally, the patient's mother had been admitted to hospital 10 years ago with a highly similar medical history as that of her son. Their brain parenchyma lesion findings were also exceedingly similar. The CT scan showed a low-density mass with punctate calcification, MRI revealed a mass with flower ring-like enhancement that rapidly progressed, and a diagnosis was subsequently made of “high-grade glioma”. The patient refused surgical treatment, and underwent only palliative radiation therapy (dose not detailed), achieving “good effect” after the treatment. Imaging examination showed that the lesion almost completely disappeared, and the patient survived with no obvious sequelae (Fig. 10). Given the limited diagnostic conditions, the patient's mother failed to obtain a final diagnosis based on laboratory and histopathological examinations, but the excellent prognosis of this “high-grade glioma” was obviously highly questionable. Therefore, according to the high approximate imaging manifestations of the mother and the son, and the nearly complete remission after the treatment, we suspected that the mother and the son were likely to have had the same genealogical disease. Hence, IgG4-RD is likely to have a certain genetic heredity, but more familial cases and genetic examinations are needed to confirm this hypothesis.

The imaging findings of IPT in the brain parenchyma are atypical: parenchyma mass lesions and presence or absence of surrounding edema and parenchyma invasion, which hampers the fast and definitive identification of the tumor. Due to its rarity and non-specificity in imaging, the final diagnosis of IgG4-related IPT in the brain parenchyma relies on pathological examination. The lesions in the patient were initially misdiagnosed as high-grade gliomas or demyelinating pseudotumor due to their typical flower-ring enhancement. Given the close arrangement of the tumor cells, high-grade gliomas usually show iso- or hyperdensity in CT, but rarely calcification. In contrast, IPTs, which are characterized by inflammatory cell infiltration in histopathology, are usually iso- or hypodense, with or without calcification [3]. According to the characteristics of the CT scan images of the patient and his mother, which revealed a significantly low density with calcification, they had non-tumor lesions, not high-grade glioma. The non-tumor lesions need to be distinguished from tumefactive demyelinating lesions (TDLs, also called tumor-like inflammatory demyelinating disease, TIDD or

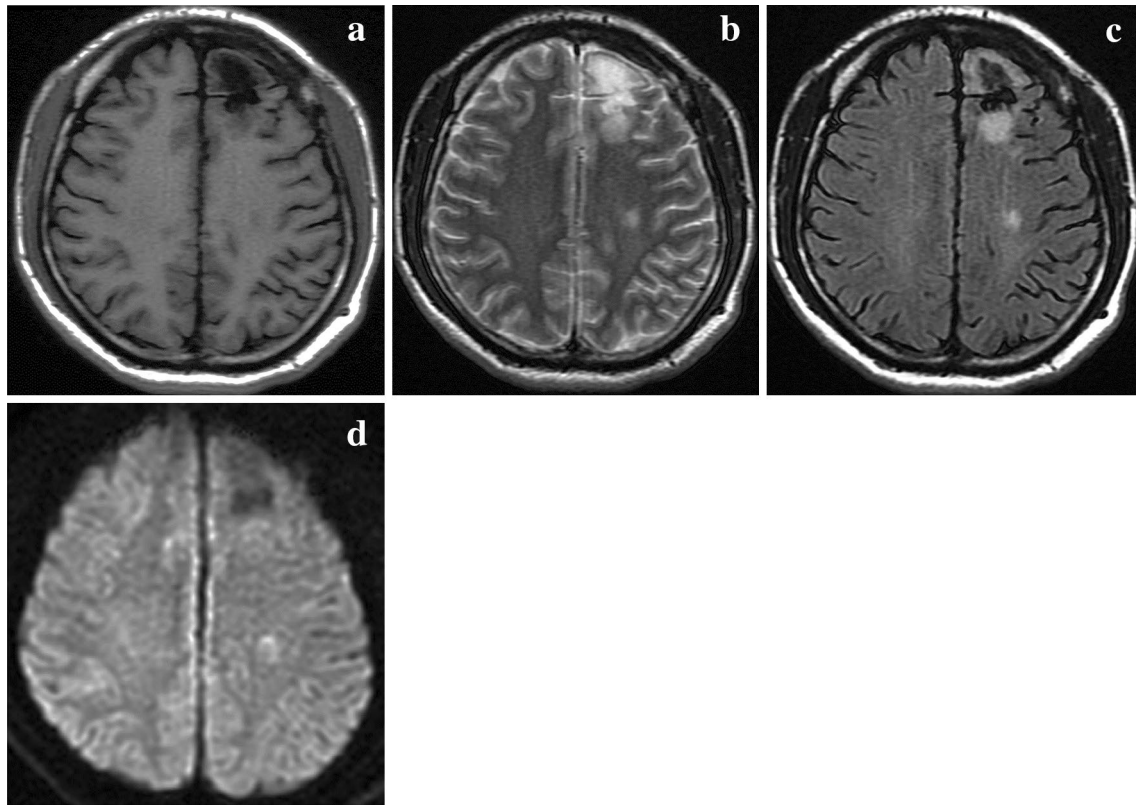


Fig. 9 Brain reexamination after 7 months of methylprednisolone treatment. **a–d** T1WI, T2WI, FLAIR, and DWI. The left parietal lobe lesion was smaller, and left frontal lobe showed gliosis after surgery

demyelinating pseudotumor, DPT). It is difficult to distinguish between the two by MRI due to the similarity of their imaging manifestations and the few reports of calcification in tumor demyelinating lesions [13]. The intracranial parenchyma lesions in the patient were characterized by a low density with punctate calcification, calcification on CT images was found in a few of the reported cases of IPT [3, 14]. Moreover, the psammoma bodies (PBs) of IPT (or plasma-cellular granuloma) can also be distinguished by their histopathological features [14], which suggests that calcification is an important criterion in the imaging diagnosis of IPT. Nevertheless, these features in IgG4-related IPT of the brain parenchyma require investigations of more cases for definitive confirmation.

The differentiation between tumor and non-tumor lesions determines the differences in the treatment regimens, which is of critical significance for the prognosis

and post-treatment quality of life of patients. CT is highly valuable in the differentiation of tumor and non-tumor lesions.

The genetic mechanisms of IgG4-RD also require more clinical and genetic studies. No standardized treatment exists for IgG4 disease. Nonetheless, many guidelines emphasize the therapeutic effect of glucocorticoids as a first-line therapy, with a large number of reports of symptomatic relief after glucocorticoid treatment. A retrospective analysis of the reported cases found that the recurrence rate after glucocorticoid therapy was as high as 72% [15], and the toxic side effects of glucocorticoids were more prominent in patients over 60 years of age [16]. Therefore, immunosuppressants and targeted immune modulators are critical for reducing or replacing the use of glucocorticoids in elderly patients.

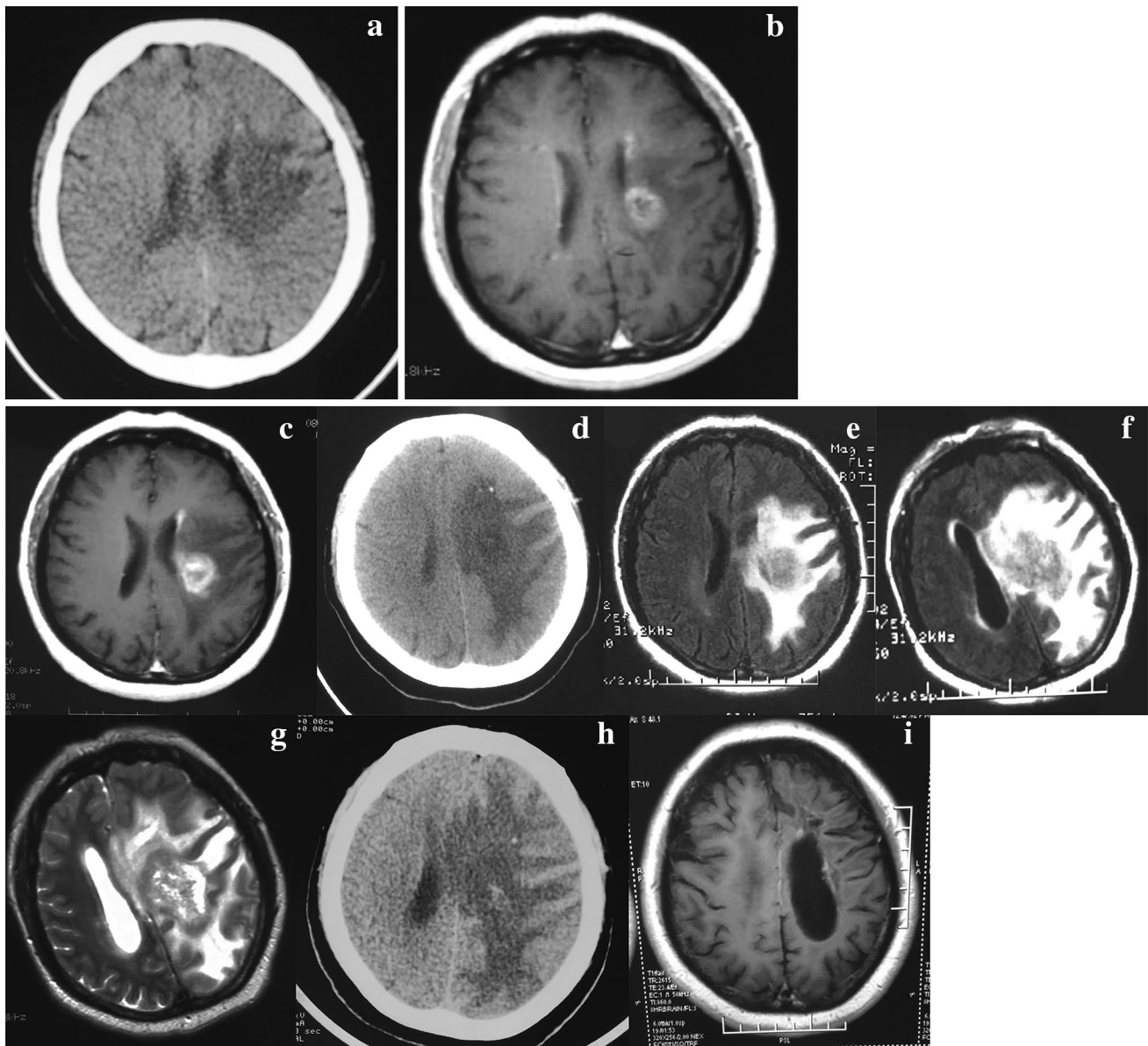


Fig. 10 CT and MR examinations of the patient's mother. **a, b** First examination (2007.12.5). **a** CT scan showed low density lesion with punctate calcification; **b** MRI showed the floral ring enhancement in the left radial crown area; **c–i** Progression of the lesion after 1 month

(**c, d**), 3 months (**e**), 6 months (**f, g**), 9 months (**h**), considered as “high-grade glioma” (**i**). The reexamination showed that the lesion was significantly reduced 1 year after radiotherapy

Acknowledgements The authors would like to express their gratitude to Qingdao people's livelihood science and technology Project [17-3-3-18-nsh] for the financial support provided.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standards The authors declare that they acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent Informed consent for publication was obtained from the patient.

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