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REVIEW

Immunoglobulin G4-related disease: case report and literature review

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Abstract

Immunoglobulin (Ig) G4-related disease (IgG4-RD) is a rare and chronic progressive clinical entity, characterized by elevated serum IgG4 along with tissue infiltration by IgG4 + plasma cells. It is an immune-mediated fibro-inflammatory condition that can affect virtually any organ and tissue. IgG4-related lung disease (IgG4-RLD) occupies 14% of all IgG4-RD, with nonspecific symptoms and various abnormal radiographic patterns. Published data on IgG4-related hypertrophic pachymeningitis (IgG4-RHP), an increasingly recognized central nervous system manifestation of IgG4-RD, is also limited. Both lung and cranial dura involvement have not yet been reported until now. We further entail a review of the literature on the clinicopathologic features and differential diagnosis of this uncommon disease. We herein report an interesting case of a 70-year-old male patient admitted due to headache and fever. A magnetic resonance imaging (MRI) of the brain revealed extensive dural thickening with marked enhancement. Chest computed tomography (CT) scan showed nodular or mass-like consolidation and focal interstitial change. Thoracoscopic lung biopsy and lumbar puncture were conducted. After careful histopathological observation and consideration of alternative differential diagnoses, he was diagnosed with IgG4-related disease with lung and cranial dural involvement based upon significant elevation of serum and cerebrospinal fluid (CSF) IgG4 concentration. The patient was started on oral prednisolone 60 mg/day (1.0 mg/kg/day) for 14 days, and a tapering dose of 5 mg every 2 weeks followed by maintenance therapy at low dose for 3 months. His clinical manifestations, and serologic and imaging findings improved with steroid treatment. Currently, the patient remains well without disease progression. IgG4-RD should be considered as a differential when diagnosing other similar multisystemic lesions. Clinical examination, careful histological observation, and immunostaining for appropriate markers are essential in establishing the diagnosis. Clinicians should become familiar with this alternative differential diagnosis.

Keywords IgG4-related disease · Lung disease · Pachymeningitis · Diagnosis · Pathologic features

Introduction

IgG4-RD was described as elevated serum IgG4 concentrations in patients with sclerosing pancreas infiltration into the tissue. Thereafter, many cases of IgG4-RD with various clinical patterns have been reported [1–3]. The involved organs share a number of core pathologic features and striking clinical and serologic similarities. Before its recognition as a unified disease in the early 2000s, the seemingly disparate manifestations had been presumed to be unrelated, single-organ disorders. Its diagnosis is based upon the combination of characteristic histopathologic, clinical, serologic, and radiologic findings [4, 5]. IgG4-RLD can involve the parenchyma, airways, pleura, and mediastinum and is known to present with various abnormal radiographic patterns. So, it is challenging to recognize and differentiate it from the many disorders it mimics, such as infections, other autoimmune

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conditions, and malignancy. A biopsy is often required for the final diagnosis [6, 7]. Hypertrophic pachymeningitis is an uncommon disorder that causes localized or diffuse thickening of the cranial dura. It represents one of the most challenging manifestations of IgG4-RD. Diagnosis relies primarily on magnetic resonance imaging, cerebrospinal fluid analysis, and meningeal biopsy [8, 9]. A PubMed search, with the terms IgG4, pachymeningitis, IgG4-related pachymeningitis, IgG4-related disease, IgG4-related lung disease, suggests that both lung and cranial dura mater involvement had not been reported yet. We herein report an interesting case of a 70-year-old male patient admitted due to headache and fever, with nonspecific computed tomography (CT) scan findings. Malignant tumor, cryptococcal infection, and infectious meningitis were considered firstly. Lumbar puncture showed increased intracranial pressure with no evidence of infection. MRI showed extensive cranial dura mater thickening with marked enhancement. The diagnosis was finally confirmed by pathological examination obtained by lung biopsy in combination with significant elevation of serum and CSF IgG4 concentration. We also provide a review of the literature to raise awareness of this clinically important disease, with an emphasis on describing the clinical features and differential diagnosis.

Case report

A 70-year-old previously healthy male patient presented to our clinic complaining of recurrent left posterior headache for 20 days and fever for 1 week. No particular personal or family history was reported. Physical examination did not reveal any significant findings. His neck was supple and nontender with negative Kernig and Brudzinski signs. Neurological examination revealed grossly intact cranial nerves II–XII with no facial droop or speech impairment. Motor examination showed normal tone, bulk and strength, and unaltered sensory perception to light touch and temperature. Physiological reflexes were existent without any pathological ones. Before admission, the brain CT scan in another clinical center was normal and the patient was treated with antibiotics without improvement in symptoms.

Blood examination in our center showed white blood cell (WBC) 8.95×10^9/L, procalcitonin (PCT) 0.1 ng/mL, C-reactive protein (CRP) 118 mg/L, ESR 115 mm/H, and normal levels of IgA, IgM, G test, and GM test. Antinuclear antibodies and anti-neutrophil cytoplasm antibodies were negative.

Lumbar puncture following admission revealed elevated CSF pressure of 29 cm H_2O (normal CSF pressure is between 18 and 20 cm H_2O). The CSF laboratory test showed 8WBCs/mm^3 and protein concentration of 22 mg/dL (normal, 10–44 mg/dL). Stains and cultures for acid-fast bacilli, bacteria, cryptococcus, and parasites organisms were all negative. A detailed infectious workup of the CSF was unrevealing. In addition, CSF cytopathology was negative for malignant cells. The serum and CSF concentrations of angiotensin-converting enzyme were normal. Brain MRI showed extensive pachymeningeal thickening and enhancement, predominantly over the posterior portion of the right hemisphere and extending to the right skull base (Fig. 1A–C). The possible diagnosis of idiopathic hypertrophic pachymeningitis (HP) was considered at that time.

He was then followed with chest CT, which revealed multifocal areas of consolidation and subpleural nodules in both lungs (Fig. 2A–D). We considered initial differential diagnosis as follows: auto-immune disease was excluded because of no associated symptoms such as arthralgia or skin rash, and there was no remarkable abnormality of autoimmune markers. Pulmonary infection including tuberculosis was also unlikely due to no infection sign, and negative sputum culture and acid-fast stain. Cryptococcosis was excluded based on a negative serologic cryptococcus capsular antigen and CSF India ink staining. The detection of pathogens from bronchoalveolar lavage fluid by metagenomic next-generation sequencing (BALF mNGS) was also negative.

CT-guided percutaneous lung biopsy of the lesions was performed and revealed massive lympho-plasma cell infiltration, interstitial fibrosis. Staining for PAS and TB-DNA detection were negative. Immunohistochemistry of the specimens stained positive for IgG, and was partially positive for IgG4. The IgG4/IgG-positive plasma cell ratio was > 40% (Fig. 3). Immunofixation electrophoresis revealed no monoclonal immunoglobulin. The serum concentrations of IgG4 (5.34 g/L; normal range, 0.03–2.01 g/L) also showed remarkable elevation. The blood test showed normal levels of IL-6 (5.1 pg/ml, normal range < 6.0 pg/ml). These findings supported the diagnosis of IgG4-RLD. Biopsy of the dural lesion was being offered; however, this was refused by the patient. Arrangements for repeat lumbar puncture were then considered. The IgG4 level of CSF was elevated (3.56 mg/dL; upper limit of normal range 0.32 mg/dL). The abdominal CT and magnetic resonance cholangiopancreatography (MRCP) scan did not reveal pancreatitis or abnormal finding in other organ. There were also no symptoms involving the salivary or lacrimal glands. Immunoglobulin G4-related disease with lung and cranial dura involvement was confirmed.

The patient was started on oral prednisolone 60 mg/day (1.0 mg/kg/day) for 14 days, and a tapering dose of 5 mg every 2 weeks followed by maintenance therapy at low dose for 3 months. After 1 month of treatment, the headache was relieved. The serum level of IgG4 became normal and the CT showed significant improvement in the areas of consolidation and nodules (Fig. 2E–H). Additionally, a follow-up MRI showed resolving pachymeningitis (Fig. 1D–F).

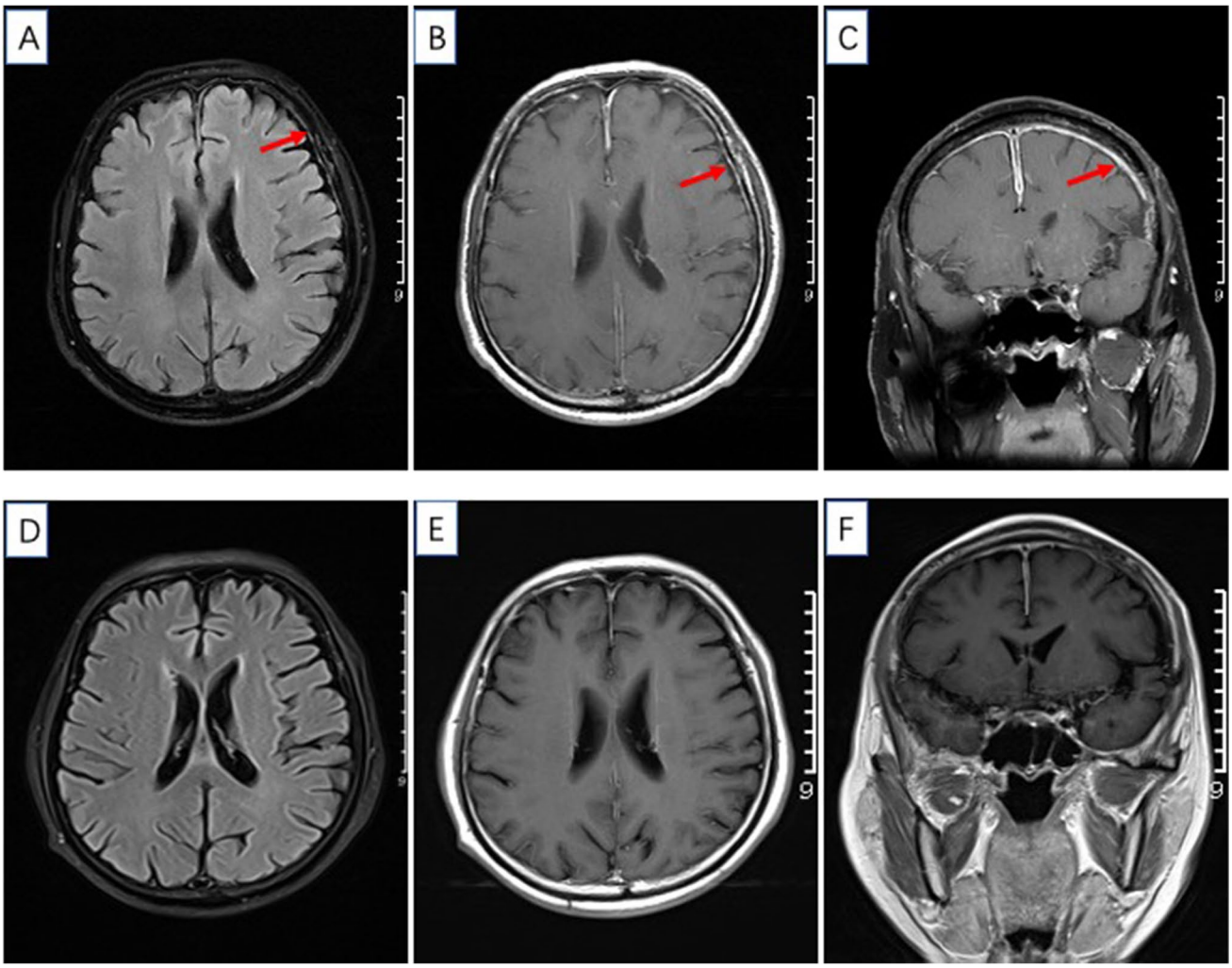

Fig. 1 **A–C** Brain MRI findings before therapy. **A** Axial MRI brain T2 FLAIR image. **B** and **C** Axial and coronal T1 post-gadolinium MRI brain images. The dura mater was diffusely thickened and obviously enhanced with gadolinium (arrow), indicating hypertrophic pachymeningitis. **D–F** Brain MRI obtained after steroid therapy showed a notable improvement in the lesions

Currently, the patient remains well without disease progression. Written informed consent was obtained from the patient for publication of the article.

Discussion

IgG4-RD was first identified as a multisystemic disease in 2003, in patients with autoimmune pancreatitis (AIP) [10]. Over the last decade, a group of various independent studies described the condition affecting different extrapancreatic organs including the biliary tract, gastrointestinal tract, lacrimal and salivary glands, lung, kidney, and lymph nodes. Common features in these reports were elevated serum levels of IgG4, histology showing IgG4-positive plasma cells, and resolution of illness following steroid therapy [3, 5, 11]. As for the epidemiology of the disease, it is insufficiently described and difficult to determine as it depends on the primary organ at presentation. Only studies of autoimmune pancreatitis in Japan demonstrated IgG4-RD as a rare entity with an estimated incidence of 0.28–1.08 per 100,000 population, accounting for 6% of the total cases of chronic pancreatitis. Most patients are males over 50 years of age with a male/female ratio of 3:1 [12, 13]. The disease is often mistaken for cancer, infection, or immune-mediated condition, such as granulomatosis with polyangiitis or giant cell arteritis. The most accurate assessment of IgG4-RD is based on a full clinical history, physical examination, selected laboratory investigation, appropriate radiology studies, and biopsy. Histopathologic studies are essential for differential diagnosis. It should be noted that infiltration of IgG4-positive plasma cells may occur in numerous inflammatory conditions and is, therefore, not diagnostic of IgG4-RD. Each

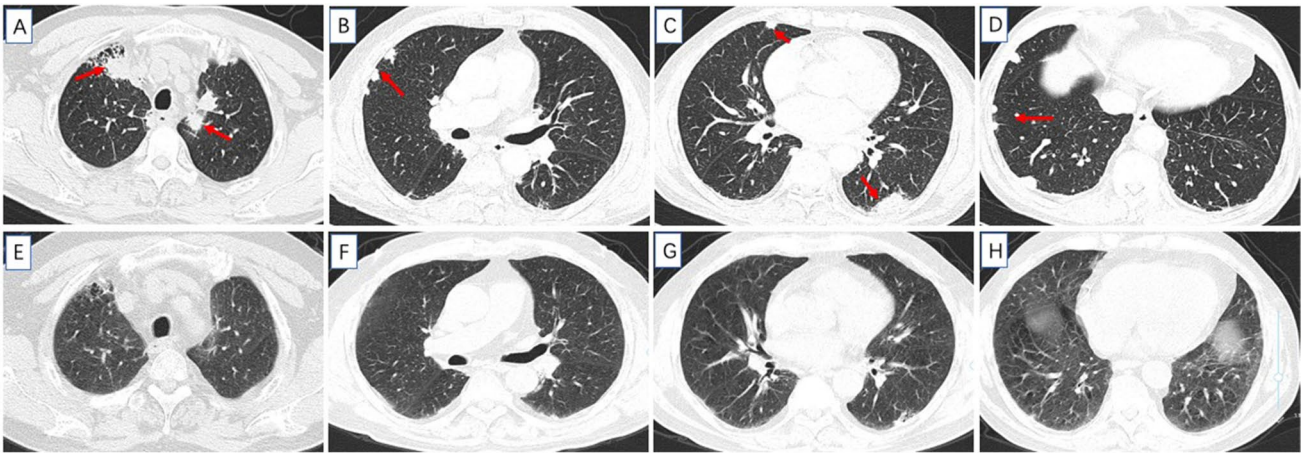

Fig. 2 **A–D** CT images at admission. CT scan showed multifocal areas of consolidations, subpleural nodules, and ground-glass opacities in both lungs (arrow). **E–H** CT images after glucocorticoid treatment. We diagnosed the case as IgG4-RD. The patient was started on oral prednisolone 60 mg/day for 14 days, and then was gradually tapered. After 1 month of treatment, CT showed significant improvement in the areas of consolidations and nodules

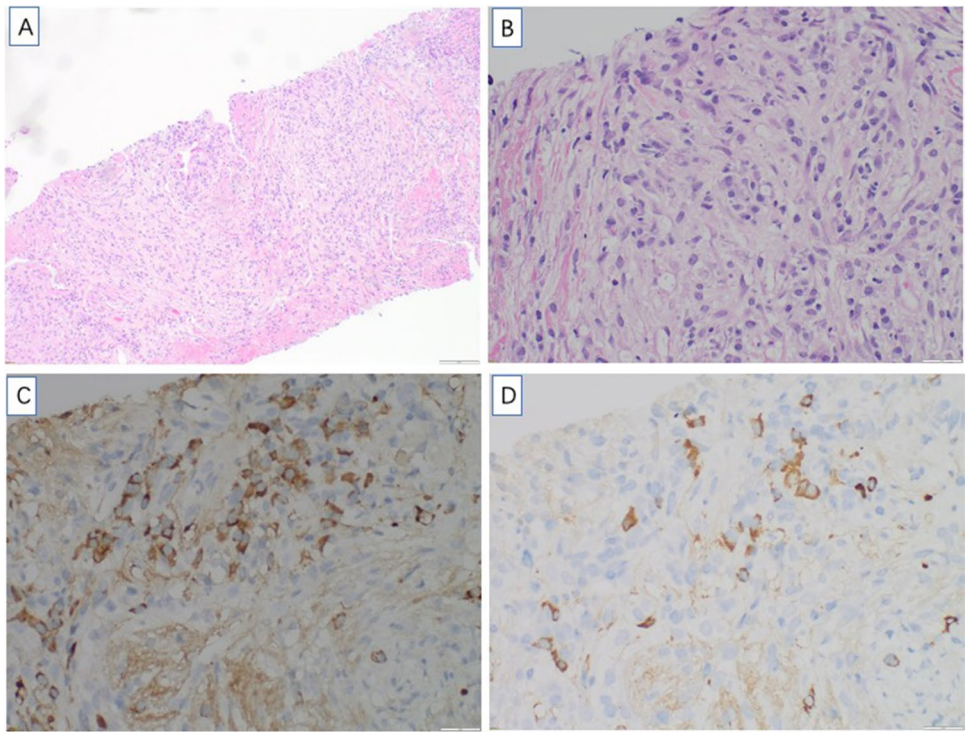

Fig. 3 The pathological features of the lung biopsy tissue. The hematoxylin–eosin staining (HE) of the specimen disclosed infiltration with plasma cells and interstitial fibrosis (**A**, original magnification 100; **B**, original magnification 400). The immunohistochemistry (IHC) showed a IgG4/IgG-positive plasma cell ratio of > 40% (**C**, IHC for IgG original magnification 400; **D**, IHC for IgG4 original magnification 400)

organ has its own criteria for IgG-RD and it might have its own cutoff numbers per HPF for IgG4 + plasma cells, although these numbers have not been verified. Typical histopathology is lymphoplasmacytic infiltration of IgG4-positive plasma cells, storiform-type fibrosis, and obliterative phlebitis. A ratio of IgG4 + /IgG + plasmacytes > 40% and IgG4-positive plasmacytes > 10 per high power field (HPF) in involved tissues contribute to the diagnosis of IgG4-RD [14–17]. In addition, the presence of granulomas, although an unusual finding, should not preclude a diagnosis of IgG4-RD in the appropriate clinicopathological context [18].

Elevated serum levels of IgG4 may provide an opportunity to identify IgG4-RD. In 2001, Hamano et al. found elevated serum levels of IgG4 in patients with autoimmune sclerosing pancreatitis among the Japanese population and described it as an immunoglobulin G4-related disease (IgG4-RD) [2]. At present, high serum IgG4 concentrations

Table 1 A review of the manifestations of IgG4-related disease that affects pulmonary, head

Pulmonary		Head	
Airway	Central airway stenosis	Nervous system	Hypertrophic pachymeningitis
	Bronchial thickening		hypophysitis
Lung parenchyma	Pulmonary nodules		Spinal pachymeningitis
	Consolidation		Sinus-venous thrombosis
	Solitary mass		Pseudotumor-like mass
	Interstitial lung disease		Perineural disease
	Ground-glass opacity		Brain parenchymal invasion
	Hilar lymohadenopathy		Skull hyperostosis
	Combined pulmonary fibrosis with emphysema	Ocular adnexal	Orbital myositis
	Organic pneumonia		Orbital pseudotumor
Pleura	Pleura effusion		Lacrimal gland enlargement
	Pleura thickening		Chronic sclerosing sialadenitis
	Spontaneous hemothorax	Salivary gland	Sublingual, submandibular gland, parotid enlargement
Pulmonary vascular	Pulmonary arteritis		
	Pulmonary artery aneurysm		
	Pulmonary artery stenosis		
	Pulmonary embolism		
Mediastinum	Mediastinal lymphadenopathy		
	Sclerosing mediastinitis		

are recognized as a vitally important diagnostic criterion for IgG4-RD. In a meta-analysis conducted by Hao et al., the pooling accuracy of serum IgG4 levels of > 135–144 mg/dL yielded a sensitivity of 87% and specificity of 83% for the diagnosis of IgG4-RD [19]. In addition, it was reported that the serum IgG4 concentrations were closely associated with disease activity. To some extent, the detection of serum IgG4 levels after treatment can reflect the therapeutic effects and recurrence of IgG4-RD [20, 21].

However, serum IgG4 level may also increase in other diseases, for instance, pancreatic carcinoma, cholangiocarcinoma, and sclerosing cholangitis. Besides this, a few patients with elevated serum IgG4 levels have been reported who suffered from allergic dermatitis, asthma, and Castleman disease. In addition, about 20–40% of patients with biopsy-confirmed IgG4-RD have been found to have serum IgG4 levels that were within the normal range. Therefore, serum IgG4 concentration is a useful screening tool while a diagnosis of IgG4 disease cannot only be dependent on the detection of elevated serum IgG4 levels [22, 23]. In our case, the elevated serum IgG4 level was an important diagnostic clue, which was arranged via immunohistochemistry for IgG4 and IgG in lung tissue.

As an increasingly recognized manifestation of IgG4-related disease, the epidemiology of IgG4-RLD is still not well understood. A retrospective study of 90 patients with autoimmune pancreatitis revealed that 54% of patients had lung lesions, but another study of 116 patients with biopsy-proven IgG4-RD revealed that biopsy-proven IgG4-RLD accounted for only approximately 10% of cases. Another study also showed lung involvement in 78 (23.4%) of 334 patients with IgG4-RD [24–26]. About 50% of patients with IgG4-RLD exhibit respiratory symptoms such as cough, dyspnea on exertion, and chest pain, while the remaining 50% display only radiographic abnormalities [27]. There exists many challenges in differentiating this disease from the other disorders it mimics. Four patterns are observed in IgG4-RLD: mediastinal, parenchymal, pleural, and airway involvement. Mediastinal and hilar lymphadenopathy are the most common pulmonary patterns [6]. In some studies, lung involvement was defined as clinically or radiographically detectable manifestations in the bilateral pulmonary area with the degree of involvement higher when mediastinal/bronchial manifestations are included. In our case, parenchymal involvement included nodules, masses, consolidation, reticular opacities, and bronchovascular thickening which was consistent with previous literature [6] We performed a systematic literature review of IgG4-related disease that affects pulmonary and/or head with additional manifestations summarized (Table 1) [14, 18, 28–37].

Hypertrophic pachymeningitis (HP) refers to inflammation leading to a localized or diffuse thickening of the cranial or spinal cord dura mater. Cases in which the pachymeningitis has no known etiology are termed “idiopathic” HP. IgG4-related disease accounts for an increasing proportion of cases of idiopathic hypertrophic pachymeningitis [8, 9]. The diagnostic process of IgG4-RHP cases involves laboratory investigations of both blood and CSF samples, magnetic

resonance imaging, and pachymeningeal biopsies. Signs and symptoms vary among patients. In addition to headache and fever, patients can present with multiple cranial nerve palsies including dysesthesia, deafness, ptosis, and ophthalmoplegia. Contrast-enhanced MRI is valuable in identifying the lesion. If the inflammatory response appears diffuse, pachymeningitis would be the diagnosis. A local response suggests inflammatory pseudotumor. But the radiologic appearance of the lesions varies considerably from case to case and is not diagnostic of any particular disease entity. The current study was too small to establish any single MRI pattern as highly characteristic of IgG4-RD [30, 33, 38].

Della Torre et al. suggested that IgG4 levels could be a surrogate marker for neurologic IgG4-RD when biopsy of an involved organ could not be performed. Histopathological findings are never diagnostic alone of IgG4-RD [39]. But it should be noted that diagnostic confirmation by biopsy is strongly recommended. In our case, after ruling out sarcoidosis, tumors, meningioma, infections (syphilis, tuberculosis, Lyme disease), and autoimmune diseases (rheumatoid arthritis, Sjogren's syndrome, granulomatosis with polyangiitis) by a thorough clinical examination and lumbar puncture, IHP was considered initially. However, his significantly elevated serum and CSF levels of IgG4 suggested otherwise. Our patient's clinical manifestations, serologic, and imaging findings improved with steroid treatment. All the affected organs responded similarly to corticosteroids. Although no dural biopsy was performed, the diagnosis of IgG4-RHP was confirmed via response to steroid therapy. Prompt improvement after starting glucocorticoid treatment is often interpreted as a useful diagnostic sign in patients with an unclear diagnosis. Clinicians should become familiar with this alternative differential diagnosis because a prompt therapeutic approach may avoid long-term neurological complications.

IgG4-RD typically responds well to treatment with glucocorticoids while no randomized controlled studies for the treatment of IgG4-RD have been done to date. The urgency of treatment depends on the involvement of vital organs and the risk of organ damage. In patients with advanced organ dysfunctions like the presence of portal hypertension, chronic salivary and lacrimal gland dysfunction, or orbital pseudotumors leading to vision loss, supportive management is advocated. Relapse is relatively common and treatment with a steroid-sparing agent or rituximab may be required. In patients with IgG4-RD refractory to steroid or other immunosuppressive agents, rituximab, a mono-clonal antibody directed against CD20 antigen on B lymphocytes, is useful as an alternate therapeutic option. Clinical response is associated with radiological, biochemical, and serological improvement. The response usually starts in 2 to 4 weeks. At least a 3- to 6-month duration of treatment is usually recommended. The maintenance of glucocorticoids is associated with a lower relapse rate in comparison to complete cessation of steroid [3, 4]. Further prospective studies are necessary to define optimal treatment strategies. Future research directions are the elucidation of possible antigenic triggers initiating IgG4-RD and B- and T-cell interactions, including the mechanisms ultimately leading to fibrosis.

In conclusion, we report a very unusual case of IgG4-RD with lung and meningeal involvement. IgG4-RD should be considered as a differential when diagnosing other similar multisystemic lesions. Clinical examination, careful histological observation, and immunostaining for appropriate markers are essential in establishing the diagnosis. Further prospective study is needed for more detailed understanding of IgG4-RD, including the role of serum IgG4 and CSF IgG4 levels and identification of more specific disease markers.

Abbreviations CSF: Cerebrospinal fluid; CT: Computed tomography; MRI: Magnetic resonance imaging; IgG4-RD: Immunoglobin G4-related disease; IgG4-RLD: IgG4-related lung disease; IgG4-RHP: IgG4-related hypertrophic pachymeningitis; PCT: Procalcitonin; WBC: White blood cell; G/GM: 1,3-β-D-glucan/galactomannan tests; BALF: Bronchoalveolar lavage fluid; mNGS: Metagenomic next-generation sequencing; FLAIR: Fluid-attenuated inversion recovery; HE: Hematoxylin–eosin staining; IHC: Immunohistochemistry

Author contribution All the authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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Data Availability The data used to support the findings of this study are included within the article. The data and materials in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication All the authors consent to submit the manuscript for publication.

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

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