

## CASE REPORT

# The great imposter: A case report of IgG4-RD hypertrophic pachymeningitis with skull lytic lesion and pulmonary nodules

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## Abstract

Immunoglobulin G4-related disease (Ig4RD) is an inflammatory condition with unique clinical, serological, and pathological features. In this study, we report a challenging diagnostic clinical case of Ig4RD diagnosed based on histopathology. This unique imitating nature reinforces that it is crucial to consider the diagnosis of IgG4-RD in those presenting with pachymeningitis.

## KEYWORDS

hypertrophic pachymeningitis, immunoglobulin G4-related disease, lung nodules, seizures, skull lytic lesion, subdural hematoma

## 1 | INTRODUCTION

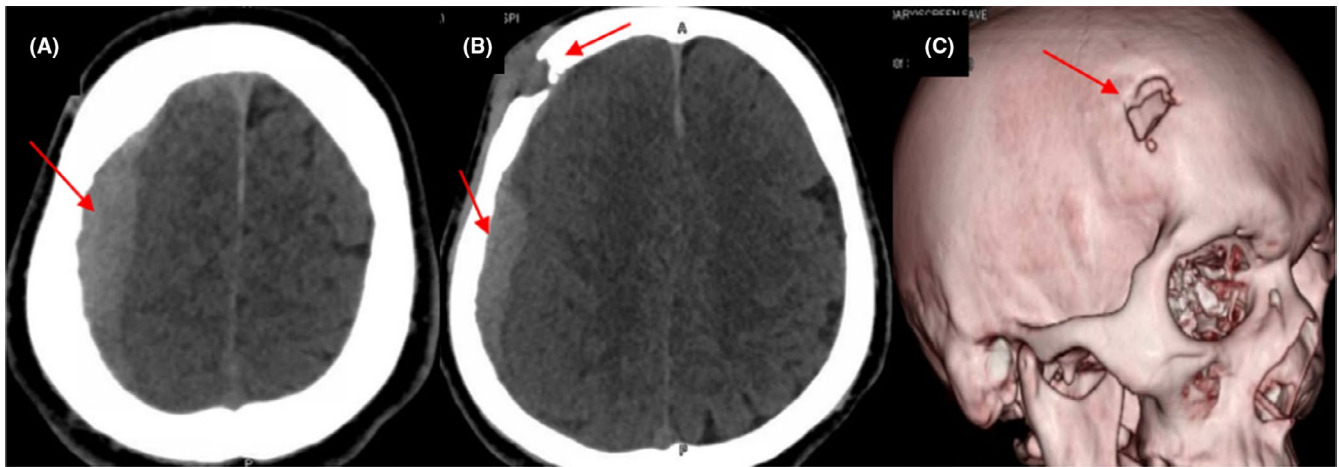
Immunoglobulin G4-related disease (IgG4-RD) is recently recognized as a multisystemic syndrome characterized by an immune-mediated fibroinflammatory condition with unique clinical, serological, and pathological features. It can involve any organ and form multiple stupefactive lesions.<sup>1</sup> It was first reported in the pancreas in early 2000, but gradually it has been reported in other sites,<sup>2,3</sup> particularly in salivary, bile duct, and lacrimal glands. Diagnosis of IgG4-RD requires the identification of characteristic findings upon biopsy of affected tissue, which is interpreted in the context of clinical, serologic, and radiologic

data. IgG4-RD is a steroid-responsive disease, and early recognition and treatment are essential because of the indolent nature of the condition and the risk of progression from an inflammatory stage to poorly responsive fibrotic disease and ultimately severe organ damage. Most patients experience disease flares during or after glucocorticoid tapers.<sup>4</sup> Thus, additional immunosuppressive therapy may also be required.

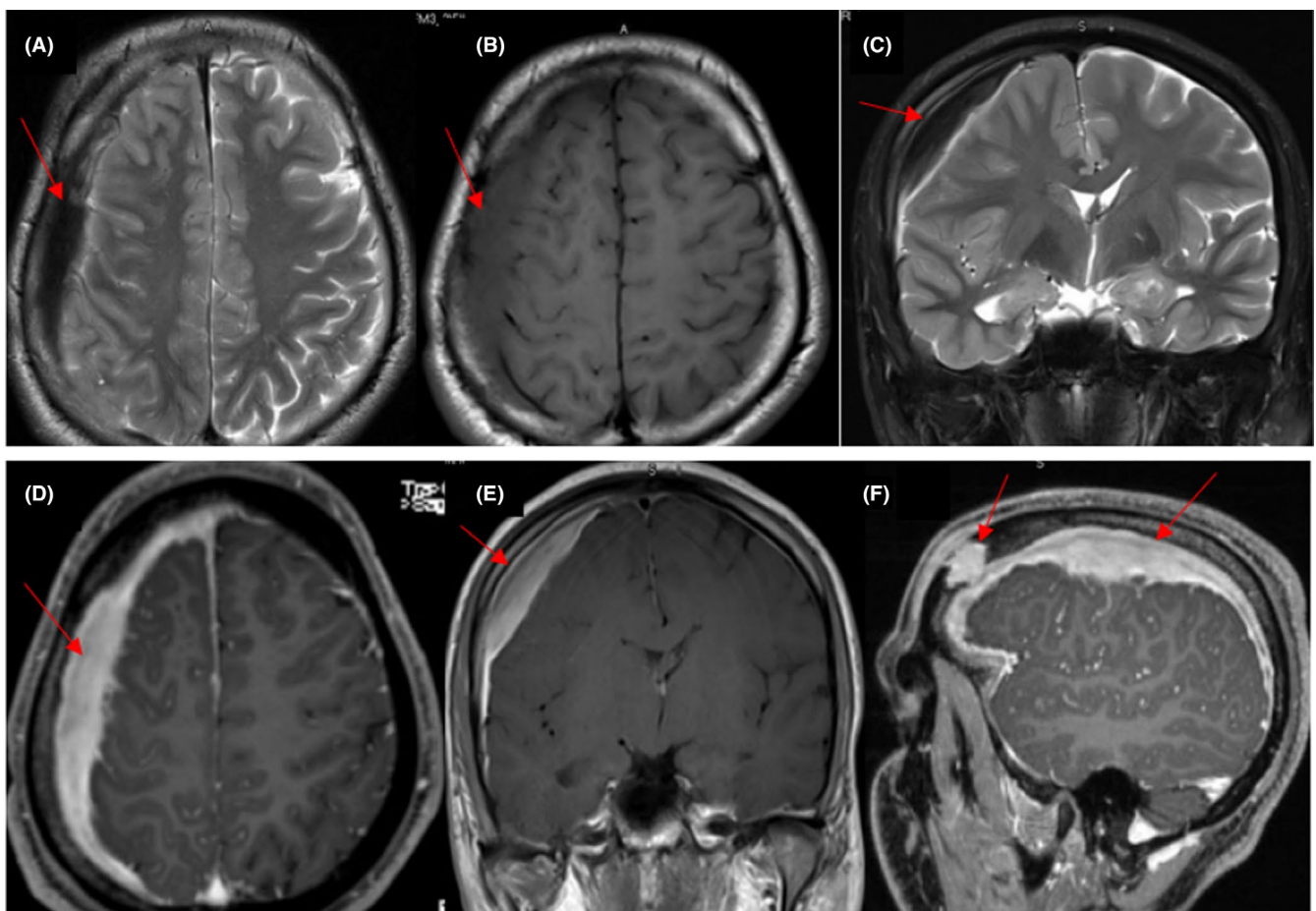
Neurological presentation is less common and usually presents as hypophysitis followed by hypertrophic pachymeningitis (HP),<sup>3</sup> which is a rare inflammatory disorder that causes localized or diffuse thickening of intracranial dura mater. Therefore, it has a broad range of neoplastic,

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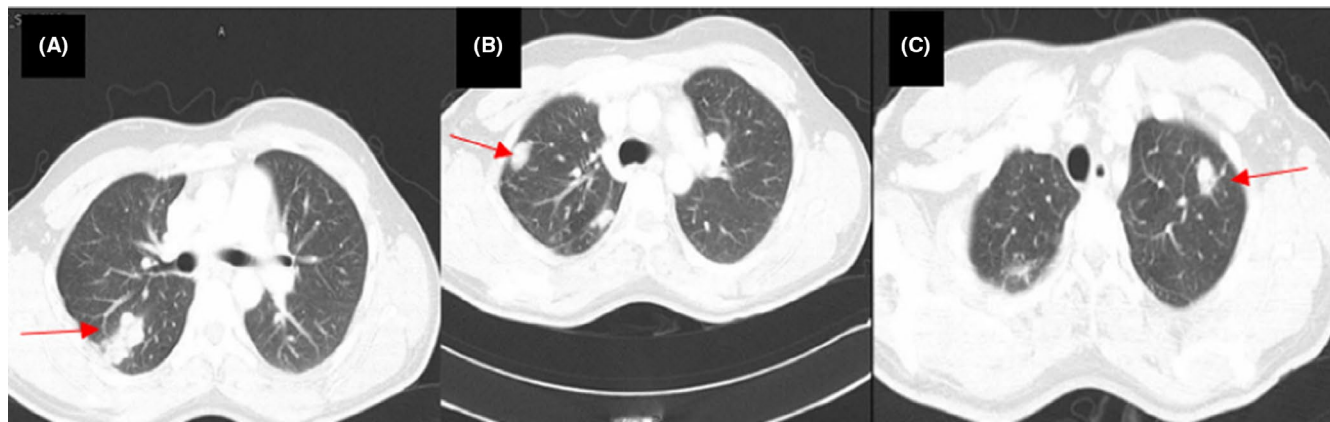
**FIGURE 1** Noncontrast head CT scan showed right-side extra-axial hyperdensity along frontoparietal convexity of 12–13 mm in maximum thickness with effacement of the adjacent sulci and 5 mm midline shift to the left (A and B). An osteolytic lesion in the right frontal bone (B and C)



**FIGURE 2** MRI of head with contrast showed right extra-axial hemispheric crescentic-shaped mass lesion with intense postcontrast enhancement and underlying dural involvement (as shown in A–E)-associated irregularity of the adjacent inner skull table with right frontal focal full-thickness bony defect, underlying diploic and extracranial enhancing swelling (F). Partial effacement of the right cerebral frontoparietal cortical sulci with mild compression of the right lateral ventricle and midline shift to the left side of about 5 mm

chronic inflammatory, infectious, and hemorrhagic conditions associated with it, which can be a diagnostic challenge.<sup>1,3</sup> When no cause is found, it is termed idiopathic

hypertrophic pachymeningitis. A dural biopsy is usually essential for a definitive diagnosis. Clinical manifestations of the disease are subject to localization or complications



**FIGURE 3** Pan CT scan showed multiple enhancing pulmonary nodules of both lungs, predominantly in the upper lung lobe with no other abnormality in abdomen and pelvis

due to the compression and infiltration of neurologic and vascular adjacent structures. It has been suggested that IgG4-related sclerosing disease represents a subset of cases previously diagnosed as idiopathic hypertrophic pachymeningitis. Headache, cranial nerve palsy, and ataxia are the most common presentations. Seizures as chief presentations are uncommonly reported in the literature.<sup>5,6</sup>

Here, we report highlights of a unique, intricate case of a young man presented to our hospital with presentations imitating various pathological conditions. After undergoing a diagnostic workup, he was eventually diagnosed with histologically proven IgG4-RD systemic disease with meningeal involvement, a rare entity.

## 2 | MATERIAL AND METHOD

### 2.1 | Case presentation

A 25-year-old South Asian gentleman with no past medical illness was admitted to the hospital with a seizure complaint developed during an air flight. The event started with jerky movements on the left side of his body, predominantly in the face and upper limb, and numbness, followed by shaking of the whole body and loss of consciousness lasting for a few minutes. According to the patient, these attacks were started 1 year ago, with the last episode 2 months ago. He also had a mild nonspecific headache and right frontal scalp swelling for 2 months without any fever, cough, weight loss, and night sweats. There was no history of postictal focal weakness, blurring or loss of vision, and unsteady gait. He denied any history of joint pain, dry eyes, or mouth, skin rash, and oral ulcers. A review of the system was negative for any respiratory, gastrointestinal, and urinary symptoms. He did not take any medical treatment for these events. He had no history of smoking, alcohol, use of illicit recreational drugs, and

family history for epilepsy or other neurological diseases. He was working as a cobbler in a leather factory with no history of sick contact.

Neurologic and systemic examinations were unremarkable, and vital signs were stable. He was started on phenytoin as an antiseizure agent. Initial blood work, including complete blood count, coagulation profile, blood chemistry, and renal and liver function tests, did not show any significant abnormality. His chest X-ray showed hazily; ill-defined shadows present in the right upper zone and to a lesser extent at the left upper zone and the right base. Noncontrast head CT scan showed right-side extra-axial hyperdensity along frontoparietal convexity of 13 mm in maximum thickness with effacement of the adjacent sulci and 5 mm midline shift to the left (Figure 1A,B) and reported as subdural hematoma. An osteolytic lesion is reported in the right frontal bone (Figure 1B,C). However, there was no history of any trauma or bleeding disorder. MRI of the head with contrast showed a right-side extra-axial hemispheric crescentic-shaped mass lesion showing low signal in T2, FLAIR, and T1 sequences with intense postcontrast enhancement and underlying dural involvement having a maximum thickness of 13 mm (Figure 2A–E). There was the associated irregularity of the adjacent inner skull table with right frontal focal full-thickness bony defect, underlying diploic and extracranial enhancing swelling, and right frontal bone marrow signal abnormality (Figure 2F). Partial effacement of the right cerebral frontoparietal cortical sulci with mild compression of the right lateral ventricle and midline shift to the left side of about 5 mm was seen (Figure 2E).

The working differential diagnosis at the stage based on the clinical and imaging findings was an infective process (TB and fungal infections), neoplastic lesion (carcinomatosis, lymphoma, and leukemia), histiocytosis, and inflammatory granulomatous processes like sarcoidosis and Wegener granulomatous. Further workup was

tailored accordingly based on the differential. CT scan of chest, abdomen, and pelvis showed multiple enhancing pulmonary nodules of both lungs, in the upper lung lobe (Figure 3A–C). Erythrocyte sedimentation rate was high 67 (reference 5–28), C-reactive protein (CRP) 129 (reference 1–5), and procalcitonin was normal, while TB PCR from histopathology section was negative. The serum and urine protein electrophoresis were unremarkable. The flow cytometry indicated no definitive immunophenotypic evidence of a monotypic B-cell population. ANA and ANCA were negative.

He underwent right-side craniotomy for right frontal skull osteolytic lesion with dural thickening. Resection and repair of the thickened dural area and skull defect were performed. A frozen section diagnosis of the skull lesion with intracranial subdural collection showed aggregates of chronic inflammatory cells, plasma cells, and lymphocytes, while that of thickened dura had dense fibrous tissue with a focal aggregate of chronic inflammatory cells. Histopathologic sections show sclerosed fibrous tissue in storiform pattern and patchy chronic inflammatory cell infiltrate, including lymphocytes, plasma cells, and a few histiocytes and eosinophils. Few neutrophils were also noted. The inflammatory cells aggregated around blood vessels with no granuloma, necrosis, or atypia. Ancillary immunohistochemistry studies with appropriate controls show the following results: CD138: positive and highlighting an enormous number of plasma cells. IgG: positive in plasma cells. IgG4: positive in plasma cells (more than ten positive cells/HPF). Kappa and Lambda: polyclonal. Alk-1: negative. S-100: negative. Based on these findings, a definite diagnosis was an inflammatory sclerosing pseudotumoral lesion compatible with IgG4-related meningeal disease. Histopathology from CT-guided right lung biopsy was also consistent with IgG4-related pulmonary disease.

Serum immunoglobulin measurement was positive for elevation in total IgE with a level 263 k units/L (reference range between 0 and 114) and in IgG4 (223 mg/dl with a reference range of 3–201). C3 and C4 levels (194 and 193) were also elevated. Final cultures were negative for mycobacterium, fungal, and other bacterial organisms.

During his hospital stay, the patient had experienced episodes of sudden left-side jerky movement with facial twitches followed by loss of consciousness. Levetiracetam was added as a second AED. After the final diagnosis of IgG4-related disease, he was treated on oral steroids sixty milligrams once daily, and IV 1 gram rituximab was given, followed by a second dose in 14 days in his home country. Azathioprine 100 mg once daily was also prescribed on discharge. He did not have further seizures but only

reported episodic mild numbness of the left side with minor jerky movements. Inflammatory markers showed that CRP decreases to fifty-three. He was repatriated to his home country as he was a transit passenger.

### 3 | DISCUSSION

Meningeal involvement of IgG4-RD is rare and was first described in 2009.<sup>7,8</sup> Based on prior studies, it is estimated to be slightly above 2% of overall clinical manifestations.<sup>9</sup> Fewer than eighty patients IgG4 related to HP have been described in the literature.<sup>1</sup> It can mimic various inflammatory, infective, neoplastic, and hemorrhagic conditions. IgG4-RD-HP-related diagnoses can be a diagnostic dilemma, despite a thorough clinical, laboratory, and imaging investigation.

Tissue biopsy remains the gold standard for the final diagnosis. Early diagnosis is relevant to decisions about therapy. IgG4-HP closely follows granulomatosis with polyangiitis (GPA) as a leading cause of inflammatory HP. Other diagnoses to consider are lymphoma, sarcoidosis, tuberculosis, rheumatoid arthritis, and Langerhans cell histiocytosis.<sup>9</sup>

There have been two from IgG4-RD HP described in the literature.<sup>9,11</sup> Isolated IgG4-HP was characterized by the absence of extra-meningeal organ involvement (including the pituitary gland). Mutually exclusive brain or spinal cord lesions are defined as “single-organ pachymeningitis.” When extra-meningeal involvement was reported, IgG4-HP was defined as systemic IgG4-RD. Nonspecific IgG4-HP was retained when data were lacking for classification. Our case can be classified as systemic IgG4-RD.

IgG4-RDs occur, reported in men aged between 50 and 60 years,<sup>10</sup> although our patient is much younger than that. The finding of an elevated serum IgG4 concentration is supportive of IgG4-RD but is not a constant finding.<sup>12</sup> It can also increase in cancer, allergic, autoimmune disorders, and other conditions. It should not be used as diagnostic criteria and evidence for starting empiric treatment. IgG4 levels are closely related to disease activity and the extent of organ damage.<sup>13</sup> Therefore, it is essential to ascertain extra-neurologic organ involvement in patients with IgG4-HP presenting with high serum IgG4 levels and elevated plasma inflammatory markers. In such circumstances, PETCT is of diagnostic value.<sup>9</sup>

Cerebrospinal fluid (CSF) alone is not a reliable parameter for the diagnosis of IgG4-HP. It is common to find lymphocytic meningitis. A moderate increase in CSF proteins with intrathecal synthesis of IgG with oligoclonal bands and increase in intrathecal IgG4 levels could be a surrogate marker for neurologic IgG4-RD when tissue biopsies could not be performed.<sup>13</sup>

Intracranial hypertrophic pachymeningitis rarely accompanies subdural hygroma or hematoma. Only three cases have been reported in the literature, of which two cases involved a diagnosis of IgG4-RDs.<sup>14–16</sup> Our case presented as an SDH mimic, which is also rarely reported with HP.<sup>1,17</sup> Skull involvement with IGG4-RD HP has been reported in a few cases.<sup>6,18</sup> These skull lesions are described as hyperostosis or thickening, while our case is unique in that it has lytic skull lesions.

Pulmonary involvement occurs in 12–50% of patients with IgG4-related disease. It takes the form of various sizes of lung nodules, lung masses, patchy ground-glass opacities, infiltrates resembling consolidation, reticular opacities, thickened bronchovascular bundles, central airway stenosis and obstruction, bronchiectasis, pleural effusion, nodular pleural lesions, and interstitial lung disease.<sup>19</sup> In our case, however, the involvement of meningeal disease with pulmonary nodules has been uncommon. In one report, a 48-year-old man presenting with a headache was found to have HP along with incidental bilateral pulmonary nodules. He had systemic features of both GPA and IgG4-related disease and seropositivity for both cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and IgG4.<sup>20</sup> He was treated with prednisone and rituximab with improvement in his symptoms.

Steroids remain the first-line treatment.<sup>4</sup> Short-term response to surgery in single-organ IgG4-HP is good and, in some cases, maybe sufficient to achieve remission.<sup>9</sup> However, all patients with IgG4-RD respond to glucocorticoids, approximately 40% of those that fail to achieve complete remission relapse within 1 year.<sup>21</sup> Patients with multiorgan disease or an extremely high serum IgG4 will require an agent other than glucocorticoids alone. Rituximab is preferred over other glucocorticoid-sparing medications. It has been shown in IgG4 studies frequently as an excellent treatment for IgG4-RD and IG-HP, among other immunosuppressive drugs.<sup>22,23</sup> Our patient had multisystem involvement, so it was deemed appropriate to start rituximab without waiting for steroid response. It is essential to follow this disease to look for new organ involvement and recurrence.

## 4 | CONCLUSIONS

We describe a unique case of a 25-year-old man with seizures whose clinical presentation was imitating various diseases, making it a diagnostic challenge. Histopathology from two sites was performed; this aided in confirming the diagnosis of an IgG4-related disease. This case reinforces that it is crucial to consider the diagnosis of IgG4-related disease in those presenting with

pachymeningitis. A tissue diagnosis is imperative in this circumstance to commence the appropriate management and avoid complications.

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## CONFLICT OF INTEREST

No conflict of interest.

## AUTHOR CONTRIBUTIONS

Muhammad Faisal Wadiwala contributed to case description, acquisition of data, analysis, and interpretation. Liaquat Ali contributed to acquisition of data, analysis, and interpretation. Adnan Khan contributed to critical revision of the manuscript for important intellectual content. The author(s) proofread and approved the final manuscript. Mohammad Alhatou contributed to critical revision of the manuscript for important intellectual content. The author(s) proofread and approved the final manuscript.

## ETHICAL APPROVAL

The case report was approved by the Medical Research Centre of Hamad Medical Corporation (ABHATH) on June 16, 2021. Protocol ID MRC-04-21-559.


## CONSENT

The patient gave written consent for their personal or clinical details along with any identifying images to be published in this study.

## DATA AVAILABILITY STATEMENT

Not applicable as no new data generated.

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