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CASE REPORT

Large dural-based mass with bony hyperostosis in a 16-year-old male: IgG4-related disease mimicking lymphoplasmacyte-rich meningioma

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Abstract

Background: IgG4-related disease is an autoimmune process that presents with tumefactive lesions characterized by storiform fibrosis, a dense lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, obliterative phlebitis, and often elevated serum IgG4 levels. Central nervous system IgG4-related disease is very rare and usually occurs in the form of hypertrophic pachymeningitis or hypophysitis. Presentation as a large solitary meningioma-like mass with overlying hyperostosis in a young adult has not been reported before. Case summary: A 16-year-old male presented with focal seizures for 5 months. Imaging showed a large, extra-axial, and contrast-enhancing mass lesion in the left frontoparietal region with focal calvarial thickening. Histopathology revealed a fibrosclerotic lesion involving dura with a polymorphic infiltrate of plasma cells, mature lymphocytes, histiocytes, and occasional eosinophils. Immunohistochemical workup excluded the possibilities of meningioma, lymphoproliferative neoplasms, and histiocytic lesions. Majority of plasma cells were IgG4+ rendering a diagnosis of IgG4-related disease. Further serological and imaging workup did not reveal any evidence of systemic involvement. His serum IgG4 levels were normal. Considering a gross total resection of the lesion, no further treatment was given and the patient has been asymptomatic since. Conclusion: IgG4-related lesions of the CNS are under-recognized and accurate diagnosis, especially in those with isolated CNS disease and normal serum IgG4 levels, necessitates robust histopathological and laboratory workup to exclude mimics. They may occur as large dural masses with hyperostosis and differentiation from lymphoplasmacyte-rich meningiomas, in particular, can be challenging. While steroids are the mainstay of treatment in IgG4-related disease, surgical resection may be curative in solitary lesions presenting with compressive symptoms.

Keywords IgG4 · Hypertrophic pachymeningitis · Hyperostosis · Meningioma · Pediatric

Introduction

First described in the pancreas, IgG4-related autoimmune disease (IgG4-RD) is a multi-system disorder of unknown etiology that can involve a variety of extra-pancreatic sites. Central nervous system (CNS) involvement is documented in < 2% of patients with IgG4-RD and commonly takes the form of hypertrophic pachymeningitis (HP) or hypophysitis. IgG4-related HP lesions (IgG4-HP) present as diffuse or nodular thickenings of the cranial and/or spinal dura [1]. In rare instances, they may form tumefactive pseudotumoral masses resembling meningiomas [1, 2], and especially when occurring in the absence of extra-CNS organ involvement, such lesions present a formidable diagnostic challenge.

Clinical summary

A 16-year-old male presented with complaints of focal seizures involving the right side of the body for 5 months. Imaging revealed a large extra-axial contrast-enhancing lesion in the left frontoparietal region with calvarial bone remodeling (Fig. 1). Pre-operative diagnosis was atypical meningioma. The patient underwent left fronto-temporo-parietal craniotomy and tumor excision. Intra-operatively, the tumoral mass was grayish white,

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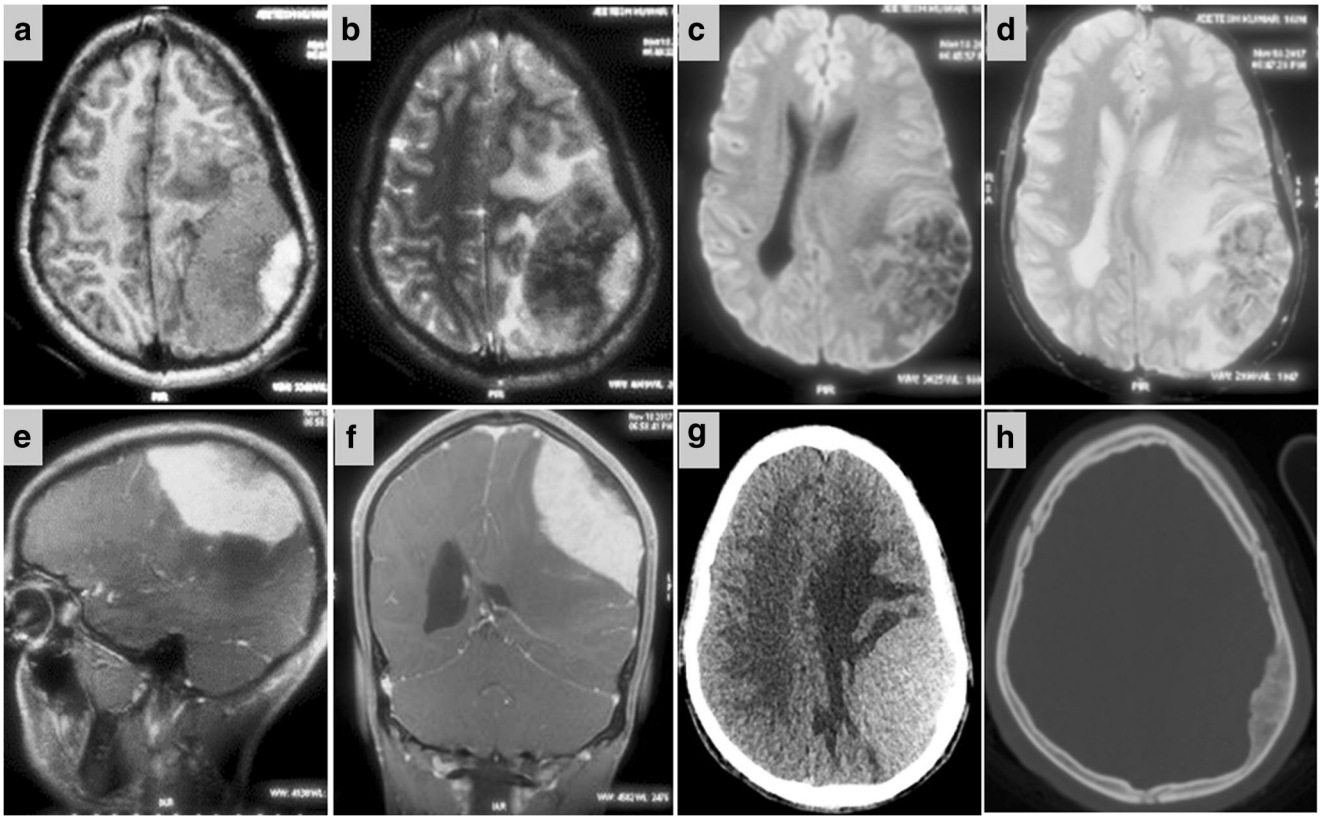

Fig. 1 Radiological features of the tumor: magnetic resonance imaging shows a large extra-axial mass in left frontoparietal region with mass effect and midline shift (**a** axial T1W, **b** axial T2W, **c** axial diffusion-weighted image, **d** axial gradient ECHO). The lesion shows uniform contrast enhancement (**e** sagittal and **f** coronal post-gadolinium T1W). Hyperostosis is seen in the overlying calvarium on computed tomography images (**g**), with bony remodeling better appreciated on the bone window (**h**)

firm, and moderately vascular, with poor plane of separation from brain. A gross total excision was achieved. Tumor tissue was processed entirely for histopathology.

Microscopy revealed thickened and sclerotic dura infiltrated by plasma cells, mature lymphocytes, and occasional eosinophils. In some areas, storiform fibrosis was evident; however, there was no phlebitis. The inflammatory infiltrate was denser along the dura–brain interface and predominated in histiocytes. Occasional entrapped meningothelial nests were seen adjacent to the brain interface. Lymphoid follicles, emperipolesis, Touton-type giant cells, nuclear grooves in histiocytes, granulomas, giant cells, atypical spindle cells, mitotic activity, or necrosis was not seen. Plasma cells did not show light chain restriction on kappa and lambda immunohistochemistry. The histiocytes were CD68 positive but immunonegative for CD1a, langerin, and S100. Immunostaining for smooth muscle actin and anaplastic lymphoma kinase protein was negative. There was diffuse increase in IgG4-positive plasma cells (30–35/high-power field) with IgG4/IgG ratio of 80% clinching the final diagnosis of IgG4-RD (Fig. 2).

On further workup, hemogram, renal function tests, liver function tests, erythrocyte sedimentation rate, autoimmune antibody profile (anti-double stranded DNA, anti SS-A and SS-B, ANA, ANCA, rheumatoid factor), viral markers (HBV, HCV, HIV), Mantoux test, and post-operative serum IgG4 levels (1.29 g/L; biological reference range, 0.049–1.985) were found to be within normal limits. Whole-body imaging did not reveal any abnormality. Contrast MRI performed 4 months after surgery showed no residual lesions. Patient is under close follow-up since then for the last 16 months and is asymptomatic.

Discussion

IgG4-RD presenting with tumefactive masses is well-known, and such lesions are most commonly described in the orbit, salivary glands, lungs, kidneys, lymph nodes, and retroperitoneum [1]. Intracranial IgG4-related pseudotumors are exceptional and may occur as intracranial/spinal dural-based, sellar, intraventricular, and even intra-parenchymal masses [1]. Meningioma-like masses, including the one in our patient, likely fall within the spectrum of IgG4-HP. While IgG4-HP usually present as diffuse dural thickening raising suspicion for vasculitic disorders, rheumatoid arthritis, sarcoidosis, lymphomatous neoplasms, and tuberculosis [3], presentation as single or multiple nodular meningioma-like masses are also reported [1, 2].

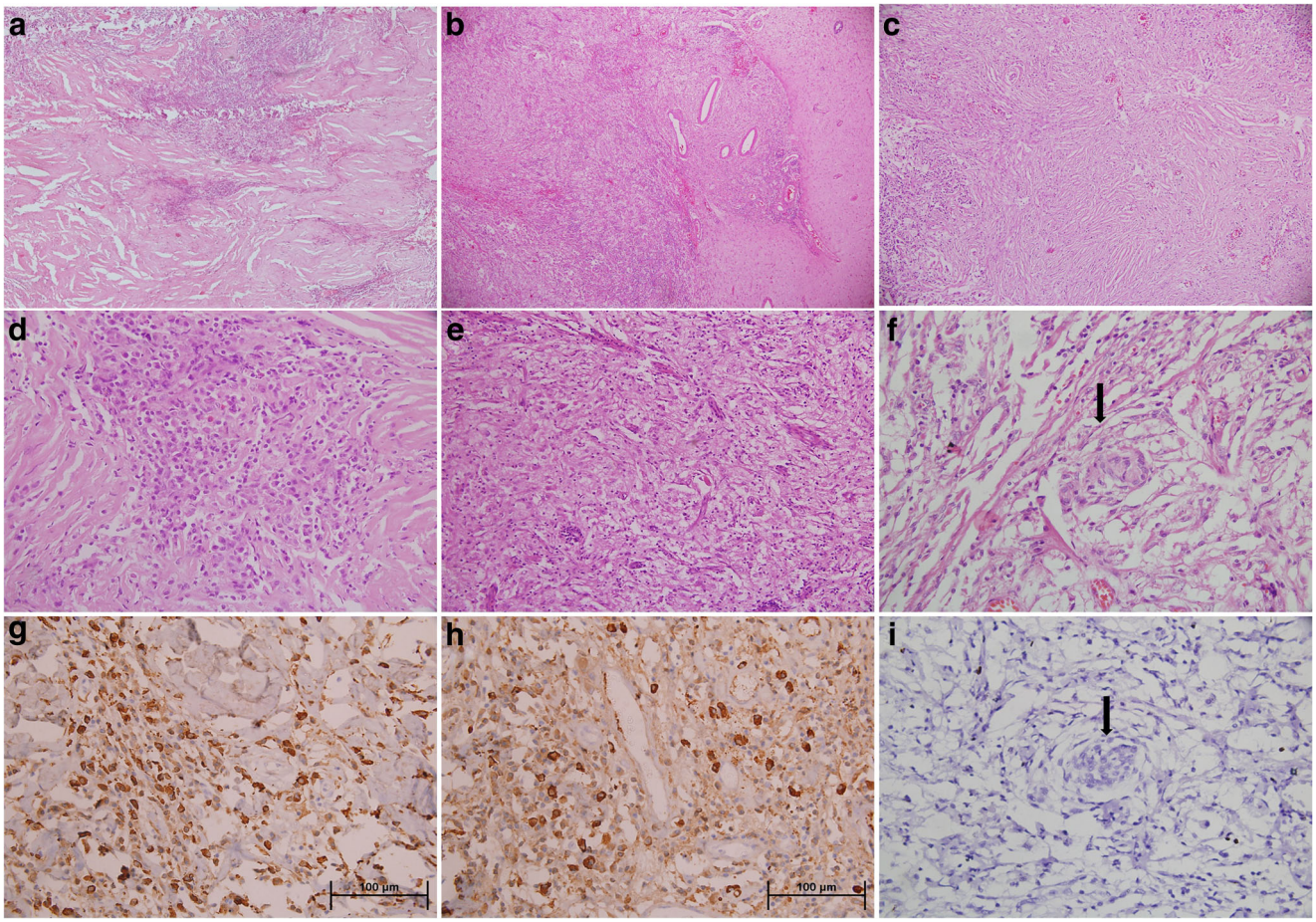

Fig. 2 Histopathological features of the tumor: microscopy shows thickened, sclerotic dura (**a** hematoxylin and eosin (H&E), × 40), and leptomeninges and superficial brain cortex (**b** H&E, × 40) with a mixed inflammatory infiltrate. Focal storiform fibrosis is seen (**c** H&E, × 100). The infiltrate is composed of plasma cells, lymphocytes, and occasional eosinophils (**d** H&E, × 400), with prominence of foamy histiocytes along the brain–dura interface (**e** H&E, × 200). Very rare meningothelial cells are seen (arrow, **f** H&E, × 400). There is diffuse increase in IgG4+ plasma cells in both dural (**g** IHC, × 400) and leptomeningeal (**h** IHC, × 400) components. The reactive meningothelial nests do not label for MIB-1 (arrow, **i**, IHC, × 400)

IgG4-HP is being increasingly recognized [3, 4] and emerged as the second most common etiology of HP following ANCA-related vasculitic disorders in a recent Japanese study [1]. IgG4-HP predominates in males (male/female ratio, 10:1) and occurs at a mean age of 56 years [1], ranging from as young as 19 years [5] to as old as 78 years [6]. Our patient is the youngest patient diagnosed with CNS IgG4-RD. Up to 30% of patients lack evidence of systemic involvement at presentation, and up to 45% patients do not show elevations in serum IgG4 levels [1]. Although recent observations have found that intrathecal IgG4 level estimation may be a more sensitive diagnostic marker for IgG4-HP [7], most patients invariably undergo biopsy or surgical excision for a definitive diagnosis.

The classic histopathological triad of IgG4-RD includes lymphoplasmacytic infiltration, storiform fibrosis, and obliterative phlebitis [4]. Among these, phlebitis has been observed less commonly in IgG4-HP and was absent in our case [1]. IgG4+ plasma cells are essential for diagnosis and according to the latest consensus, presence of > 10 IgG4+ plasma cells/high-power field along with one or more of the triad of classical histological features can provide a probable diagnosis of IgG4-related HP [4]. However, one must bear in mind that IgG4+ plasma cells are not specific for IgG4-RD and have been noted in other inflammatory and infectious conditions, including ANCA-related vasculitis, tuberculosis, and Rosai–Dorfman disease (RDD) [1, 8]. Thus, additional clinical, serological, and radiological evidences in the form of other organ involvement and an elevated serum IgG4 level are required for confirmation of IgG4-HP. Consequently, in patients with normal serum IgG4 and without systemic involvement, a robust histopathological and laboratory workup would be necessary.

The histopathological differential diagnosis of dural-based masses with rich inflammatory infiltrates includes lymphoplasmacyte-rich/chordoid meningiomas, RDD, and inflammatory myofibroblastic tumor. As detailed in Table 1, histopathological and immunohistochemical assessment in

Table 1 Differential diagnosis of dural-based tumor and tumor-like masses with extensive inflammatory cell infiltrates

Entity	Incidence	Age distribution	Associated systemic manifestations	Presentation as dural mass	Specific radiological features
Lymphoplasmacyte-rich meningioma[a]	Very rare; < 1% of all meningiomas	Mean age ~ 40 years (9–79); M = F	Hypergammaglobulinemia and iron refractory anemia in ~ 20% cases, particularly in younger adolescent patients [9]	Typical	Contrast enhancing, T2-hyperintense with severe vasogenic edema [9]
CNS-Rosai–Dorfman disease [11]	Very rare (~ 200 cases reported)	20–40 years, M > F	~ 20% show systemic involvement in the form of extra-CNS lesions	~ 90% present as leptomeningeal masses mimicking meningiomas	Contrast enhancing, T2 hypointense masses with surrounding vasogenic edema
CNS-inflammatory myofibroblastic tumor, plasma cell granuloma-like variant [12]	Very rare (~ 100 cases reported)	Wide age range (< 1–74 years)	Usually absent	~ 70% present as dural-based nodular or en-plaque masses mimicking meningioma	Contrast enhancing, T2 hypointense masses with edema
Langerhan cell histiocytosis (LCH) [14]	Rare, incidence of 0.2–2/10,000 children < 15 years	Pre-adolescents and young adolescents	Usually present; endocrine disturbances (hypothalamic-pituitary axis) usually seen	~ 30% of systemic LCH patients harbor meningeal lesions associated with other CNS bony/parenchymal lesions; presentation as isolated dural mass extremely rare [15]	Contrast enhancing, T1/T2 intermediate intensity lesions with overlying calvarial bony defects
CNS-Erdeim–Chester disease (ECD) [16]	Rare (CNS involvement seen in < 30% of ECD patients)	40–60 years	Nearly always present; diabetes insipidus and skeletal abnormalities most common	30–50% of cases harbor dural lesions, in the form of thickening or nodular masses, usually multiple associated with/without infiltrative parenchymal lesions	Contrast-enhancing masses
CNS-IgG4-related hypertrophic pachymeningitis [1]	Extremely rare (CNS involvement seen in < 2% of IgG4 RD)	Mean age ~ 56 years (M > F)	~ 48% show systemic manifestations	Meningeal involvement is usually in the form of diffuse thickening and less commonly as pseudotumoral masses	T2-hypointense masses with foci of hyperintensity corresponding to inflammation

Histopathology	Storiform fibrosis/ phlebitis	Composition of inflammation	Increase in IgG4 plasma cells	Treatment and prognosis
Meningiothelial tumor cell nests intermixed with or surrounded by dense obscuring inflammation	Not seen; nondescript fibrosis may be seen [9, 10]	H, PC, L usual; Eo, lymphoid follicles or granulomas rarer [10]	Rare, occasional examples show IgG4/IgG ratios up to 30%, albeit focally [10]	Surgery is main stay of treatment; usually WHO grade I tumor
Large and small–medium-sized foamy histiocytes exhibiting at least focal emperipolesis and S100 positivity; admixed inflammatory cells	Not seen; thickened and fibrotic dura with collagen deposition usual	PC, L	Common with ~ 50% cases including dural examples showing IgG4/IgG ratios > 40% [8]	Symptomatic management, usually surgery with or without adjuvant radiotherapy; prognosis usually good
Spindle-shaped myofibroblastic tumor cells that express smooth muscle actin admixed with inflammation	Not seen; dural thickening and collagen deposition can be seen	PC, L, Eo	Not known; occasional extra-CNS IMTs found to harbor IgG4/IgG ratios up to 15% [13]	Surgery is the main stay of treatment; increased risk of recurrence in subtotal resection and in ALK expressing IMTs
S100 and CD1a positive histiocytes with longitudinally grooved nuclei admixed with inflammatory cells	Not seen; dural thickening may been seen [15]	Eo, L, PC, and neutrophils	Not known	Chemotherapy and cranial radiation; variable prognosis
CD68+, CD1a-, S100-lipid-laden Touton-type giant cells with scant inflammation	Not seen; classically shows dense fibrosis	L, PC	Not known	Scant data; surgery may be helpful in meningioma-like masses
Classical triad of lymphoplasmacytic infiltrate, storiform fibrosis, and phlebitis; phlebitis less common in CNS lesions	Storiform fibrosis is classical	PC, L, Eo	Elevated always and required for diagnosis	Scant data; steroids as first-line therapy

M male, *F* female, *CNS* central nervous system, *PC* plasma cells, *L* lymphocytes, *Eo* eosinophils, *H* histiocytes

[a] Chordoid meningiomas may also harbor prominent lymphoid follicles, chronic inflammatory cell infiltrate, focally elevated IgG4 plasma cells, manifest with anemia or Castleman disease, but show characteristic chordoma-like areas interspersed with varying amount of typical meningioma-like areas [10]

conjunction with clinical and radiological features help in differentiation. Notably, the young age of our patient, and the presence of bony remodeling and hyperostosis, hitherto described only once before with IgG4-HP [2], made differentiation from a lymphoplasmacyte-rich meningioma particularly difficult. However, the absence of a neoplastic meningothelial component and diffuse increase in IgG4+ plasma cells helped in ruling it out [10].

There are no consensus guidelines on the treatment of CNS IgG4-RD [1]. Glucocorticoids are the mainstay of treatment, with some patients receiving second-line steroid-sparing drugs or B cell-depleting agent rituximab in the face of steroid resistance/toxicity [1]. Surgical decompression may be required only in the presence of compressive symptoms, particularly common in spinal lesions. In instances such as ours with complete excision of lesion and absence of symptomatic systemic lesions, additional steroid therapy is not necessary [2].

To conclude, CNS IgG4-RD is extremely rare and most commonly manifest as HP. The latter may present as an isolated tumor-like mass with normal serum IgG4. Elevated IgG4+ plasma cells are necessary but not adequate for diagnosis, and a wide variety of inflammatory, infectious, and neoplastic conditions need exclusion. Accurate diagnosis, documentation, and long-term follow-up of CNS IgG4-RD is necessary for improved understanding of its biology.

Compliance with ethical standards

Conflict of interest Authors declare no conflict of interests for this article.

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