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IgG4 in Inflammation-Rich Meningioma

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Authors
Lal, Aseem
Dahiya, Sonika
Gonzales, Michael
et al.

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RESEARCH ARTICLE

IgG4 Overexpression Is Rare in Meningiomas with a Prominent Inflammatory Component: A Review of 16 Cases

Aseem Lal[1]; Sonika Dahiya[2]; Michael Gonzales[3]; Annie Hiniker[1]; Richard Prayson[4]; Bette K. Kleinschmidt-DeMasters[5]; Arie Perry[1,6]

[1] Department of Pathology and [6] Neurological Surgery, University of California San Francisco, San Francisco, CA.
[2] Department of Pathology, Washington University School of Medicine, St. Louis, MO.
[3] Anatomical Pathology Department, Royal Melbourne Hospital, Melbourne, Australia.
[4] Department of Anatomic Pathology, Cleveland Clinic Foundation, Cleveland, OH.
[5] Department of Pathology, University of Colorado Health Science Center, Denver, CO.

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Corresponding author:
Arie Perry, MD, Department of Pathology, University of California San Francisco, 505 Parnassus Avenue, Room M551, Box 0102, San Francisco, CA 94143-0102 (E-mail: *Arie.Perry@ucsf.edu*)

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Abstract

Meningiomas with prominent inflammation are traditionally classified as "lymphoplasmacyte-rich meningioma" (LPM). Both inflammatory and neoplastic meningeal proliferations have recently been linked to IgG4 disease, although a potential association with LPM has not been previously explored. Sixteen meningiomas with inflammatory cells outnumbering tumor cells were further characterized by CD3, CD20, CD68 and/or CD163, CD138, kappa, lambda, IgG and IgG4 immunostains. There were 11 female and 4 male patients, ranging from 22 to 78 (median 59) years of age. Tumors consisted of 10 World Health Organization (WHO) grade I, 5 grade II and 1 grade III LPMs. Immunohistochemically, the most numerous cell type was the macrophage in all cases followed by CD3-positive T cells and fewer CD20-positive B cells. Plasma cells ranged from moderate-marked (N = 5) to rare (N = 7), or absent (N = 4). Maximal numbers of IgG4 plasma cells per high power field (HPF) ranged from 0 to 32, with only two cases having counts exceeding 10/HPF. The IgG4/IgG ratio was increased focally in only two cases (30% and 31%). Additionally, plasma cells represented only a minor component in most examples, whereas macrophages predominated, suggesting that "inflammation-rich meningioma" may be a more accurate term. The inflammatory stimulus for most cases remains to be elucidated.

Abbreviations

CNS, central nervous system; IHC, immunohistochemistry; IPT, inflammatory pseudotumor; LPM, lymphoplasmacyte-rich meningioma.

INTRODUCTION

IgG4-related disease is a recently recognized distinct entity that may be associated with universal features including tumefactive lesions, IgG4-rich plasma cells in a dense lymphoplasmacytic inflammatory infiltrate, storiform fibrosis and often an elevated serum IgG4 level (34). In 2001, Hamano *et al* reported that patients with autoimmune pancreatitis had elevated serum levels of IgG4 compared with pancreatitis due to other causes (13). This was followed by the revelation of increased numbers of IgG4-positive plasma cells in the pancreas and surrounding tissues of the resected pancreatectomy specimens of autoimmune pancreatitis (17). Over the years, it has become evident that IgG4-related sclerosing disease can involve many other organs individually or in various combinations, without a requirement for pancreatic involvement (24).

As the spectrum of this disease continues to evolve and be better defined, the literature on central nervous system (CNS) involvement by this autoimmune disorder, including diagnostic criteria, remains scant. Lindstrom *et al* studied 10 cases of unexplained lymphoplasmacytic meningeal inflammation (previously diagnosed as idiopathic hypertrophic pachymeningitis) and evaluated these for IgG and IgG4 expression using immunohistochemistry (IHC) (24). Proposing a cutoff of greater than 10 IgG4-positive plasma cells per high power field averaged over 5 consecutive/high power fields (HPFs) to be IgG4 related, 5 of their 10 cases qualified as IgG4 disease (24). They also noted that their IgG4-positive cases often displayed other histological features commonly seen in this disorder, including dense fibrosis and phlebitis (24). They therefore concluded that a subset of dural-based chronic inflammatory lesions previously considered idiopathic might, in fact, represent IgG4-related meningeal disease. A review of the literature on CNS

involvement by this disease also reveals isolated case reports of IgG4 disease presenting as hypophysitis (14, 33), pachymeningitis with or without dural mass (3, 18, 36, 40), spinal cord involvement (3), or an orbital mass (38).

Interestingly, increased numbers of IgG4-positive plasma cells have also been noted in a spectrum of head and neck lesions designated as inflammatory pseudotumors (IPTs), suggesting that a subset of these may similarly fall under the family of IgG4-sclerosing disease. Once the neoplastic counterpart of ALK-associated inflammatory myofibroblastic tumor is excluded, CNS IPT (also called plasma cell granuloma/xanthogranuloma/histiocytoma) is the leading consideration. CNS IPT is a mass like, often dural-based lesion characterized by a non-clonal spindle cell proliferation of fibroblastic/myofibroblastic cells and a chronic inflammatory component comprised of lymphocytes, plasma cells and eosinophils in varying proportions (19). IgG4-related IPTs are well known to occur in some head and neck sites including the salivary gland, lacrimal glands and pituitary gland (19). Other reported sites include nose/paranasal sinus (15), intracranial/dural sites (25) and parapharyngeal space (26). IgG4-related IPT of the trigeminal nerve without involvement of other CNS sites has also been reported by Katsura *et al* (19). Most recently, increased numbers of IgG4-positive plasma cells were observed in a subset of dural-based marginal zone lymphomas, raising the possibility that IgG4 disease may even predispose to neoplastic transformation (37). Given that the spectrum of CNS lesions associated with IgG4 disease continues to evolve and expand, we sought to explore possible associations with another neoplastic disorder, meningioma, specifically those associated with marked chronic inflammation, commonly referred to as lymphoplasmacyte-rich meningioma (LPM). Furthermore, because IgG4-sclerosing disease has been known to respond well to corticosteroid therapy (24, 36), establishing a link between this entity and LPM could potentially have significant treatment implications.

MATERIALS AND METHODS

Case selection

A subset of meningiomas with a prominent inflammatory component, including LPMs, was retrieved from the archives of the authors' surgical pathology and consultation files. A total of 16 cases were identified from 15 patients. Information regarding neuroimaging features, recurrence and medical history of cancer or inflammatory conditions (especially thyroiditis and pancreatitis) was obtained from the medical records at the institution from which the case originated.

Morphological evaluation

All cases were morphologically evaluated and graded by one of the authors (AP) utilizing the World Health Organization (WHO) grading scheme for meningiomas (30). In order to qualify as a LPM, inflammatory cells had to outnumber tumor cells in at least portions of the mass; additionally, the predominant pattern of inflammation, that is, intratumoral vs. peritumoral, was also recorded. Degree of sclerosis (subjectively stratified into mild, moderate or marked) and presence or absence of perivascular inflammation/vasculitis/perivenular phlebitis and vascular thrombosis were also documented. Presence or absence of psammoma bodies, lymphoid follicles, eosinophils and granulomas was also evaluated.

IHC staining

IHC was performed on formalin-fixed, paraffin-embedded tissue sections using the streptavidin–biotin peroxidase method. Antibodies and dilutions used were epithelial membrane antigen (EMA) (DAKO; dilution 1:100), progesterone receptor (PR) (DAKO; dilution 1:100), Ki-67 (MIB-1 clone; DAKO; dilution 1:1000), CD20 (Leica; dilution ready to use/undiluted) CD3 (Leica; dilution ready to use/undiluted), CD68 (Leica; dilution ready to use/undiluted), CD163 (Leica; dilution 1:100), CD138 (Leica; dilution ready to use/undiluted), IgG (DAKO; dilution 1:600), IgG4 (Cell Marque; dilution-undiluted), kappa (Cell Marque; dilution 1:5) and lambda (Cell Marque; dilution 1:2). Antigen retrieval was achieved using either heat-induced epitope retrieval (DAKO Pascal pressure cooker) in 10 mM citrate buffer at pH 6.0 (EMA, Ki-67, kappa, lambda and IgG) or automated on the Leica Bond System in ER1 at pH 6.0 (PR, CD20, CD138 and CD163), ER2 at pH 9.0 (CD3 and CD68), or proteinase K (DAKO) (IgG4). The blocking step included incubation with 3% H_2O_2. The detection chromagen was 3,3′-diaminobenzidine tetrahydrochloride (DAB).

IHC scoring

All immunohistochemical stains were evaluated by three pathologists (AP, AL, AH). EMA and PR were scored as positive or negative. The Ki-67 labeling index (LI) was scored in a minimum of 500 cells as the maximal fraction of tumor cells showing nuclear positivity for this marker ("hot spots"), with results expressed as a percentage. Care was taken to exclude endothelial and inflammatory cells, although this was difficult in some cases. CD3, CD20, CD138, CD68 and CD163 positive infiltrates were scored subjectively as mild, moderate or marked based on cell densities (roughly defined as: mild = scattered immunoreactive cells; marked = over half of cells in multiple low magnification fields are immunopositive; moderate = cell densities of positive cells between those of mild and severe). Kappa and lambda stains were estimated by quantitative scoring as the maximal number of immunopositive plasma cells in any 5 consecutive HPFs. Based on criteria reported in literature, a kappa to lambda ratio greater than 4.0 (kappa restricted) or less than 0.5 (lambda restricted) was considered clonal (4, 27). Using these cutoffs, the results were reported as either polyclonal or monoclonal. IgG and IgG4 were similarly scored by calculating the maximal number of IgG- and IgG4-positive plasma cells in any consecutive 5 HPFs, and the results were expressed as a ratio of IgG4/IgG (percentage). More specifically, regions of interest were outlined using dotting pens in consecutive sections stained with IgG and IgG4 in order to ensure that the same areas were included in both counts, before ratios were determined. The final counts were divided by five in order to determine a final count/HPF. Final IgG4 counts >10/HPF and IgG4/IgG ratios >25% were considered significant.

RESULTS

The clinical details are highlighted in Table 1. There was a female predominance and most lesions were intracranial, except one case where the mass was spinal. All masses were single and four patients had recurrent tumors (either current presentation or subsequent). Associated significant systemic manifestations were not noted in most cases, except for a history of sarcoidosis (case 2), familial thyroid autoimmune disease (case 6) and chronic myeloid leukemia (case 9).

Detailed imaging studies were available in 12 cases, as highlighted in Table 1. The neuroimaging features generally appeared consistent with meningioma and no obvious features specific for LPM were found in the current study.

Morphologically, most cases were WHO grade I meningioma (10 of 16 cases), with five cases qualifying for WHO grade II and one qualifying as anaplastic (WHO grade III). Most cases had an intratumoral pattern of inflammation with intermingled meningothelial and inflammatory cells. However, two cases were characterized by mostly solid-appearing meningioma surrounded by dense chronic inflammation at the periphery of the tumor. Although, a perivascular inflammatory pattern was also noted in three cases, none of the cases showed clear features of vasculitis. Eosinophils were not prominent in any case. Lymphoid follicles were noted in a minority of cases, but none featured granuloma formation (Table 2).

Table 3 highlights the immunohistochemical features in all cases. EMA positivity was found in all cases where it was performed (12 of 12). There was variable PR expression in 10 cases and no staining in 2 cases. The Ki-67 proliferation index ranged from 1% to 40% and was mostly elevated (>4%) in higher grade examples. Characterization of the inflammatory infiltrate by IHC revealed the lymphocytes to be predominantly CD3-positive T cells with a variable, but consistently smaller number of CD20-positive B cells. All cases featured a dense (marked) infiltrate of CD68- or CD163-positive macrophages, such that the macrophage was consistently the most abundant inflammatory cell present (Figures 1 and 2). Plasma cells were characterized by CD138 staining and ranged from mild to marked infiltrates, although this was often not a prominent feature as they were scored as absent to only mild in 11/16 (69%) cases. In all but one case, kappa and lambda studies revealed a polyclonal phenotype. In one case (case

Table 1. Clinical features.

Case #	Age/ gender	Presenting signs and symptoms	Imaging details	Extent of surgery	Follow-up
1	45/F	NA	Parasagittal	NA	RF at 13 years
2	62/F	Incidental finding	1.7 cm, homogenously enhancing, left temporal	GTR	RF at 1 year
3	22/M	Seizure activity	Left posterior frontal	GTR	Recurred at 3 years
4	70/F	NA	Enhancing, extra-axial mass, left temporal	GTR	RF at 4 years
5	54/F	Seizure activity	Right parietal parafalcine	GTR	Recurred at 3 years (current tumor). RF 14 months later
6	50/F	NA	Suprasellar	GTR	RF at 14 months
7	61/F	Seizure activity, decreased concentration	6.6 cm, heterogeneously enhancing, extra-axial, left frontal falcine	GTR	Recurred at 50 months. Alive with residual tumor at 80 months
8	32/M	Numbness over right frontoparietal occipital region	4.7 cm, homogenously enhancing, extra-axial, left temporal	GTR	RF at 2 months; lost to follow-up
9	46/F	Facial weakness	2.5 cm, homogenously enhancing, left frontoparietal	GTR	RF at 1 year
10	65/F	Confusion, nausea and gait instability	Heterogeneously enhancing, extra-axial, bifrontal (left > right)	GTR	RF at 1 year
11	73/F	Slowly progressive lower limb weakness, bladder and bowel incontinence	Contrast enhancing, intradural, extramedullary lesion at T4/5	NA	NA
12	57/M	Disturbance of taste and smell, intermittent diplopia	Large, contrast enhancing, extra-axial, centered in left frontal pole	GTR	Recurred at 2 years (case 13)
13	59/M	NA	Left orbital recurrence (case 12)	GTR	RF at 16 months
14	78/F	Headaches, mild ataxia and left-sided tinnitus	Contrast enhancing, dural based, left cerebellopontine angle	GTR	RF at 13 months
15	63/M	Bilateral lower extremity weakness and hyperreflexia	6.9 cm, heterogeneously enhancing, extra-axial, right parasagittal	Near GTR	RF at 2 months
16	47/F	Seizure activity	4.6 cm, homogenously enhancing, extra-axial, posterior parietal	NA	NA

GTR = gross total resection; NA = not available; RF = recurrence free.

Table 2. Morphological features.

Case #	Grade	Dural invasion	Brain invasion	Other aggressive features	Mitoses per 10 HPF	Psammoma bodies	Lymphoid follicles	Granulomas	Pattern of inflammation	Perivascular inflammation, vasculitis, perivenular phlebitis	Associated vascular thrombosis	Eosinophils
1	II	NA	NA	Sheeting, small cells, hypercellularity, nucleoli	0	No	No	No	Intratumoral	No	No	No
2	I	Yes	NA	No	1	Yes	No	No	Intratumoral	No	No	No
3	II	No	Yes	Chordoid features	2	No	Yes	No	Peritumoral	Yes (perivascular inflammation)	No	Mild
4	I	NA	NA	No	0	No	No	No	Intratumoral	No	No	No
5	II	NA	Yes	Sheeting, nucleoli	1	No	No	No	Intratumoral	No	No	No
6	I	NA	NA	No	1	No	Yes	No	Intratumoral	No	No	No
7	I	NA	NA	No	1	No	No	No	Intratumoral	No	No	No
8	I	Yes	NA	No	0	No	Yes	No	Intratumoral	No	No	No
9	II	No	NA	No	5	Yes	Yes	No	Peritumoral	Yes (perivascular inflammation)	No	No
10	III	No	Yes	Nucleoli, necrosis, small cells, focally chordoid, sarcomatoid	29	No	No	No	Intratumoral	No	No	No
11	II	NA	NA	Necrosis	6	Yes	No	No	Intratumoral	Yes (perivascular inflammation)	No	No
12	I	NA	NA	Focally rhabdoid	1	No	No	No	Intratumoral	No	No	No
13	I	Yes	NA	Sheeting	1	Yes	No	No	Intratumoral	No	No	No
14	I	NA	NA	None	0	Yes	No	No	Intratumoral	No	No	No
15	I	NA	NA	None	ND	No	No	No	Intratumoral	Yes (perivascular inflammation)	No	No
16	I	NA	No	None	<4	Yes	No	No	Intratumoral	No	No	No

HPF = high power field; NA = not applicable (eg, no brain present); ND = not done.

14), monoclonality was suggested immunohistochemically, but there were no other morphologic, immunohistochemical or clinical features to suggest an underlying plasma cell dyscrasia or lymphoma. IgG-positive plasma cells ranged from 0 to 107 (median 7.5)/HPF and IgG4-positive plasma cells ranged from 0 to 32 (median 0)/HPF. However, only two cases had IgG4 numbers greater than 10/HPF (cases 9 and 14) and in both of these, this was only a focal finding. Calculation of the ratio of IgG/IgG4 as a percentage also revealed an increase in these same two cases, although again it was a focal feature (Figures 3 and 4). Four cases had no plasma cells and, therefore, no IgG, IgG4, kappa or lambda subclass staining.

DISCUSSION

LPM represents one of the least common and poorly characterized variants of meningioma. As such, there remains considerable controversy over diagnostic definitions, etiology, therapeutic implications and even whether or not this represents a distinct or clinically meaningful diagnosis. Specifically, what exact percentage of inflammatory cells needs to be present in a meningioma to qualify as LPM designation is unclear, and previous studies may have suffered from too lax, or too stringent criteria. For this reason, additional studies are sorely needed. We specifically attempted to confine our work to meningiomas where at least in one region of

Table 3. Immunohistochemical features.

Case #	EMA	PR	Ki-67 index (%)	CD20-positive B cells	CD3-positive T cells	CD68/CD163-positive macrophages	CD138-positive plasma cells	IgG4/ HPF	IgG/ HPF	IgG4/IgG (%)	Kappa/lambda
1	ND	ND	ND	Mild	Moderate	Marked	Mild	0	0	NA	Only rare staining
2	Positive	Positive	Low (per report)	Mild	Moderate	Marked	Mild	0	4	0	Polyclonal
3	Positive	Negative	ND	Moderate	Marked	ND	Mild	5	105	5	Polyclonal
4	Positive	ND	ND	Mild	Marked	Marked	Mild	0	4	0	Polyclonal
5	Positive	Negative	16	Moderate	Marked	Marked	Moderate	2	107	2	Polyclonal
6	ND	ND	ND	Moderate	Marked	Marked	Mild	1	6	4	Polyclonal
7	Positive	Positive	7	Mild	Marked	Marked	Mild	0	12	0	Polyclonal
8	Positive	Positive	3	Moderate	Marked	Marked	Marked	1	70	2	Polyclonal
9	Positive	Positive	17	Moderate	Marked	Marked	Moderate	32	103	31	Polyclonal
10	Positive	Positive	40	Mild	Marked	Marked	Marked	0	98	0	Polyclonal
11	Positive	Positive	8	Mild	Moderate	Marked	Mild	0	9	0	Polyclonal
12	Positive	Positive	4	Mild	Moderate	Marked	None	0	0	NA	No plasma cells
13	Positive	Positive	3	Mild	Moderate	Marked	None	0	0	NA	No plasma cells
14	Positive	Positive	3	Moderate	Moderate	Marked	Marked	27	92	30	Inconclusive†
15	ND	Positive	1	Mild	Mild	Marked	None	0	0	NA	No plasma cells
16	ND	ND	<8	Mild	Moderate	Marked	None	0	0	NA	No plasma cells

†Immunostains suggested kappa restriction in case 14, although there was no additional morphologic, immunohistochemical or clinical evidence to support a lymphoproliferative disorder.
EMA = epithelial membrane antigen; HPF = high power field; NA = not applicable because of lack of plasma cells; ND = not done; PR = progesterone receptor.

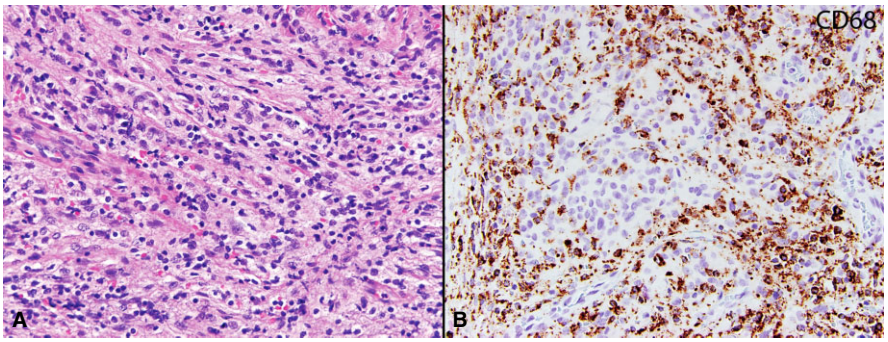

Figure 1. Case 13: WHO grade I meningioma with an intratumoral infiltrate of lymphocytes (original magnification 200x) **A.** Immunohistochemical stain for CD68 showing many macrophages within the tumor (original magnification 20x) **B.**

the tumor the inflammation predominated over the meningeal counterpart.

With these criteria, our study shows that the majority of LPMs have no clear association with IgG4 disease, but that there can occasionally be an increase in IgG4-positive plasma cells at least focally. Unfortunately, both of our "positive" cases were recent biopsies with limited follow-up times, such that it is difficult for us to determine any meaningful differences between these cases and either LPMs without IgG4 plasma cells or more typical meningiomas with limited inflammation. Nonetheless, there was no known systemic disease and only a single meningioma was present in these two patients rather than diffuse thickening or multifocal meningiomas. These two patients are currently being treated as standard surgical cases, that is, no differently than they would be for a conventional meningioma.

Associations between meningiomas and inflammatory responses or inflammatory disorders have not been thoroughly studied, although perhaps some overlap exists between LPM and some examples of chordoid meningiomas. In the original description, chordoid meningiomas were frequently associated with prominent lymphoplasmacytic infiltrates, lymphoid follicles, germinal center formation and systemic features of Castleman's disease, iron-resistant microcytic anemia and/or hypergammaglobulinemia that resolved after meningioma resection and recurred with tumor regrowth (20). Although larger series have failed to demonstrate a strong association of chordoid meningiomas with systemic manifestations, a mild-to-moderate inflammatory component was noted in approximately 60% of cases in one large series (8), whereas more pronounced inflammatory responses and systemic disorders continue to be reported in subsets by others (1, 12, 22, 23). This raises the question about the possibility of significant IgG4 plasma cell infiltrates in chordoid meningiomas with prominent inflammation. Our series includes one example (case 3) of a young man with chordoid meningioma containing prominent inflammation. This case revealed dense, mostly, peritumoral inflammation comprised of prominent lymphocytes and plasma cells, including germinal center formation and scattered eosinophils. Although many IgG-positive plasma cells were noted in this case, the ratio of IgG4/IgG failed to achieve significance. Nonetheless, further studies are needed in chordoid meningiomas to evaluate its association with IgG4 disease or other inflammatory/immune disorders. An additional possible link between chordoid meningiomas and LPMs is the fact that these two can be associated with systemic inflammatory disorders, while this is rarely reported with other meningioma subtypes (2). Up to 21% of LPMs have been associated with systemic manifestations such as hypergammaglobulinemia and/or anemia, especially in younger patients (42); this is highly reminiscent of the experience with chordoid meningiomas, as noted earlier.

The link between inflammation, meningioma and systemic disorders appears complex, but intriguing. In a recent study, Zhu *et al* reviewed the clinical, radiological and histological features of 19 LPMs along with 43 additional cases from the literature (42). The features are similar to those of conventional meningioma, although young age of onset, lack of female predilection, multifocality, diffuse growth pattern, heterogeneous contrast enhancement, cystic changes and peritumoral brain edema may be more commonly encountered. These features were not obvious in our current study, although it was limited to 15 patients, which is nonetheless large for a series on LPM, but underpowered for detection of clinic–radiologic associations. It should also be noted that although recurrence and survival rates have been mostly favorable,

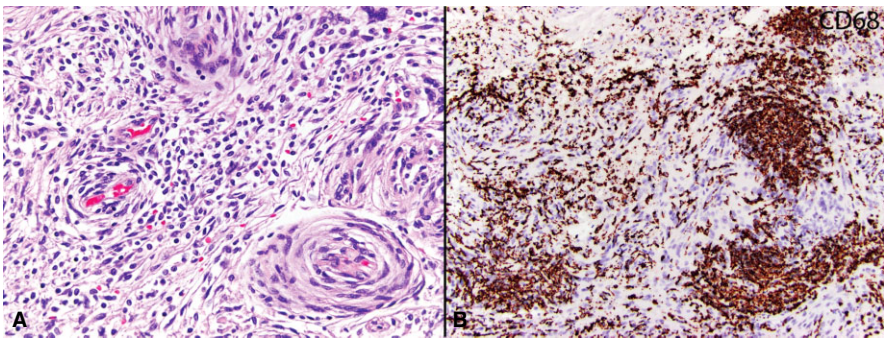

Figure 2. Case 15: WHO grade I meningioma with an intratumoral infiltrate of lymphocytes, including a focal perivascular distribution (original magnification 200x) **A.** Immunohistochemistry for CD68 reveals many macrophages within the tumor (original magnification 200x) **B.**

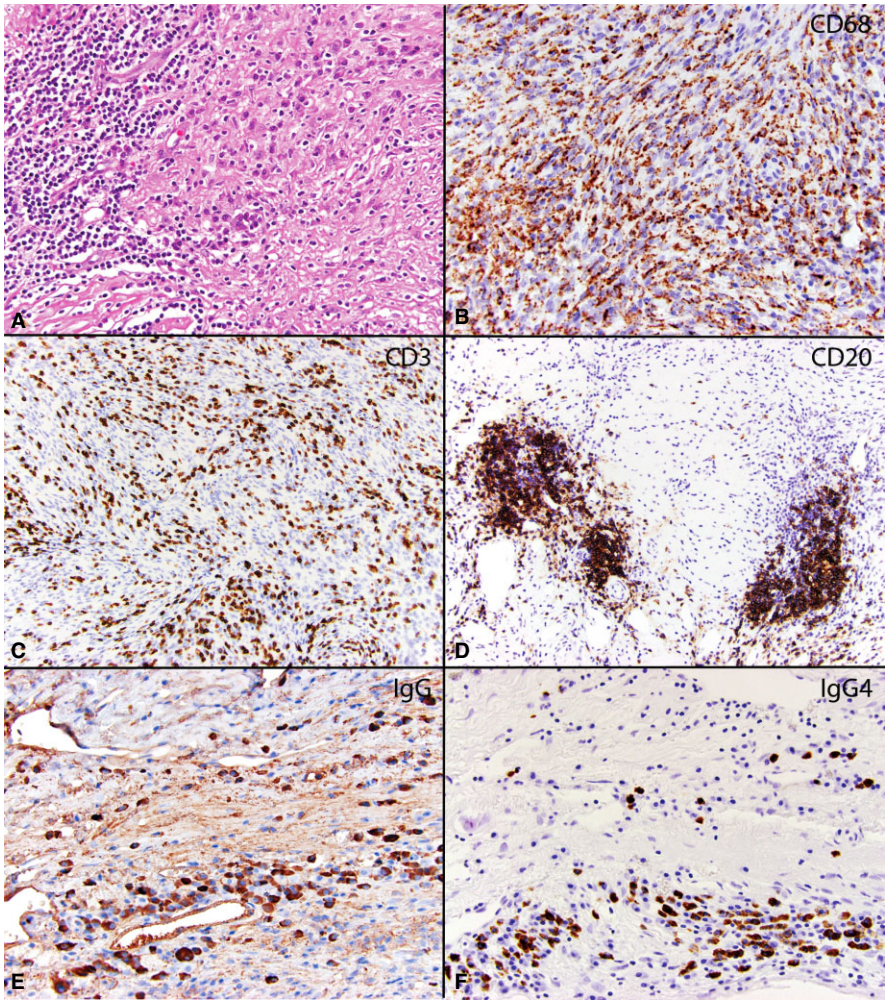

Figure 3. Case 9: Atypical (WHO grade II) meningioma surrounded by dense chronic inflammation with many admixed histiocytes. The inflammation is mostly at the edge of the tumor (original magnification 200X) **A.** Immunohistochemical stains for CD68 reveals numerous macrophages within the tumor (original magnification 200X) **B**, while CD3 reveals numerous T lymphocytes (original magnification 20X) **C** and CD20 reveals moderate numbers of B lymphocytes within the tumor, including occasional lymphoid follicle formation (original magnification 200X) **D.** An immunohistochemical stain for IgG reveals moderate numbers of IgG positive plasma cells within the tumor (103/hpf) (original magnification 200X). Inset: another field of view showing many IgG positive plasma cells (original magnification 100x) **E.** An immunohistochemical stain for IgG4 reveals clusters of IgG4 positive plasma cells, reaching up to 32/hpf (original magnification 200X) **F.**

clinical follow-up has been limited in the literature (>3 years in only 19 patients). It still remains unclear whether the inflammation is secondary to the meningioma or whether in some cases, the meningothelial proliferation is reactive to a primary inflammatory process (39).

Finally, our series was not only limited to WHO grade I LPMs, but also included higher grade examples. This therefore expands the known spectrum of LPM to include more atypical WHO grade II and anaplastic WHO grade III cases. In most of our cases, the evidence argued against any possible association with IgG4 disease. Additionally, the fact that significant IgG4 positivity was noted in a small subset of our cases is, in itself, not diagnostic of IgG4 disease. In a consensus statement by Deshpande *et al*, strict diagnostic criteria should be followed to diagnose IgG4-sclerosing disease (10). In our series, aside from the consistent presence of dense lymphoplasmacytic/macrophage inflammation, the other diagnostic features were either absent (perivenular phlebitis) or present, but not as classically reported (eg, fibrosis present, but not in a storiform fashion). In terms of diagnostic cutoffs for IgG4 disease in tissue, the literature is diverse and many different values have been offered (5, 9, 11, 16, 24, 29, 41). Lindstrom *et al* have suggested that the presence of more than 10 IgG4-positive plasma cells/HPF is indicative of IgG4 meningeal disease (24). At the international symposium on IgG4-related disease held in Boston in 2011, however, Deshpande and colleagues described cutoffs specific to each organ type, and for meninges, they felt that there was insufficient experience to provide definitive criteria (10). In terms of IgG4/IgG ratio, many researchers have suggested values greater than 40% as significant (6, 7, 32). This is mostly consistent with the study by Lindstrom *et al* where cases with IgG4-related meningeal disease had IgG4/IgG ratios in the range of 24%–60% (average 42%). However, the ratio should be considered significant only in corroboration with other features of IgG4 disease, as significant overlapping ratios may be seen in non-IgG4-related conditions (10). In the current study, the same two cases reached significance for both levels of IgG4/HPF and the IgG4/IgG ratio. As such, it is possible that rare examples of LPM are associated with IgG4 disease. However, caution should be used in interpretation of the findings of elevated IgG4-positive plasma cells in isolation, particularly when only qualifying focally as in our cases. Within the spectrum of IgG4-sclerosing disease, many cases may not fulfill or partially fulfill the criteria for this entity. Deshpande *et al* have therefore proposed classification into categories as highly suggestive, probable or insufficient evidence for IgG4 disease (10). Because the literature on CNS IgG4 disease is still limited, meningeal involvement is currently proposed as probable

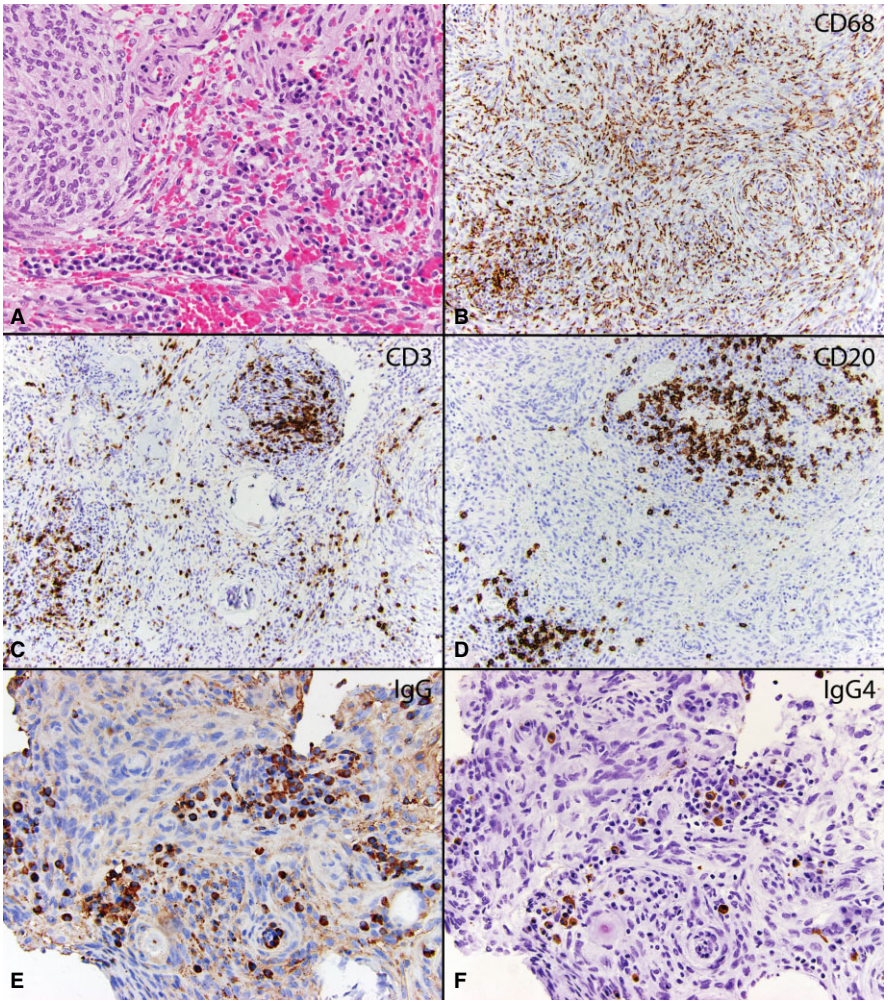

Figure 4. Case 14: WHO grade I meningioma with an intratumoral infiltrate of lymphocytes and plasma cells (original magnification 200X) **A.** Immunohistochemical stains for CD68 reveals numerous macrophages within the tumor (original magnification 200X) **B.** A stain for CD3 reveals moderate numbers of T lymphocytes (original magnification 200X) **C,** while CD20 reveals moderate numbers of B lymphocytes within the tumor (original magnification 200X) **D.** An immunohistochemical stain for IgG reveals clusters of IgG positive plasma cells (92/hpf) (original magnification 200X) **E** and IgG4 shows focally significant numbers of IgG4 positive plasma cells (27/hpf) (original magnification 200x) **F.**

IgG4-sclerosing disease (10). The CNS manifestations of IgG4 disease as well as the findings of our current study require further research to better understand and define this entity in this location.

Additionally, no marker is entirely specific, including serum IgG4 levels; indeed, these markers may be elevated to significant levels in non-IgG4-related conditions including inflammatory processes, as well as malignancies (9, 21, 28, 35, 41). There is therefore a need to define additional markers to add specificity to the diagnosis. FOXP3 (a marker for CD25-positive T-regulatory cells) has been well studied in immune-mediated processes (31). Its relevance in the context of IgG4-sclerosing disease lacks sufficient data and maybe a potential surrogate marker to be further evaluated.

This study also discovered the consistent presence of numerous macrophages (defined by either CD68 or CD163) in the entire series. This suggests that macrophages are a consistent accompanying population in LPMs. As such, it is possible that "inflammation-rich meningioma" is a more accurate term for these cases.

CONCLUSION

IgG4-positive plasma cells are rarely a component of meningiomas with a prominent inflammatory component. Their significance in this context is unclear and may require further research. In contrast, macrophages consistently form the most abundant cell type within inflammation-rich meningiomas.

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