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Surgical Neurology International

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SNI: Neuro-Oncology

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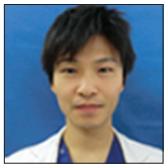
Case Report

Angiomatous meningioma associated with rapidly aggravated peritumoral leptomeningitis: A case report

Hideki Nakajima[1], Takuro Tsuchiya[1], Shigetoshi Shimizu[1], Tetsuya Murata[2], Hidenori Suzuki[3]

Departments of [1]Neurosurgery and [2]Pathology, Suzuka General Hospital, Suzuka, [3]Department of Neurosurgery, Mie University Graduate School of Medicine, Tsu, Japan.

E-mail: *Hideki Nakajima - zima0131@gmail.com; Takuro Tsuchiya - tkr01tcy@gmail.com; Shigetoshi Shimizu - shigeshimi322@icloud.com; Tetsuya Murata - dr.tetsuya.murata@miekosei.or.jp; Hidenori Suzuki - suzuki02@clin.medic.mie-u.ac.jp



***Corresponding author:**
Hideki Nakajima,
Department of Neurosurgery,
Suzuka General Hospital,
Suzuka, Japan.

zima0131@gmail.com

Received : 16 January 2023
Accepted : 20 April 2023
Published : 28 April 2023

DOI
10.25259/SNI_54_2023

Quick Response Code:

ABSTRACT

Background: A special type of meningioma is known to have infiltrated inflammatory cells within the tumor, associated with peritumoral inflammation. However, there have been no reports of meningioma with inflammatory response only around the tumor, without inflammatory cells within the tumor itself.

Case Description: A 70-year-old woman presented with transient right hemiparesis due to an extra-axial tumor on the left frontal convexity. The tumor appeared hypointense on T1-weighted magnetic resonance images and hyperintense on T2-weighted images without peritumoral edema, and was homogenously enhanced associated with the peritumoral leptomeningeal enhancement. Cerebrospinal fluid examination showed an increase in the number of inflammatory cells with a predominance of mononuclear cells. During the following 1 month, the tumor size was unchanged, but the peritumoral leptomeningeal enhancement was remarkably enlarged with uncontrolled focal seizures. The tumor was subtotally removed and semisolid substances in the subarachnoid space were biopsied. Pathological examination with immunostaining revealed angiomatous meningioma: the tumor had no inflammatory cell infiltration within it, but was associated with the infiltration of immunoglobulin G4-negative lymphocytes into the border zone between the tumor and the dura mater, as well as numerous neutrophils and fibrinous exudates in the peritumoral subarachnoid space. The tumor removal rapidly improved the leptomeningeal enhancement and inflammatory reactions.

Conclusion: The authors reported the first case of angiomatous meningioma associated with massive peritumoral inflammation without inflammatory infiltrates within the tumor itself.

Keywords: Anti-cyclic citrullinated peptide antibody, Arachnoid enhancement, Inflammation-rich meningioma, Leptomeningitis, Rheumatoid meningitis

INTRODUCTION

Meningiomas derive from meningeal cells of the arachnoid membrane and generally do not affect the subarachnoid space and the brain parenchyma except for those with central nervous system (CNS) World Health Organization (WHO) grade 2 or 3 of moderate or greater malignancy.[2,15] Although rare, even CNS WHO Grade-1 cases such as lymphoplasmacyte-rich meningiomas (LPMs) have been reported to affect the surrounding tissues, resulting in dural thickening, pachymeningitis, and peritumoral inflammation, and to cause systemic hematological abnormalities such as hyperglobulinemia and iron-refractory anemia.[4,6,13,19,24,26] Meningiomas

with immunoglobulin (Ig) G4-positive plasma cells were also reported to cause peritumoral inflammation.[12,13] However, all of the meningiomas had inflammatory cell infiltrates within the tumor itself, and there have been no reports of meningiomas causing peritumoral inflammation without inflammatory infiltrates within the tumor itself. The authors report the first case of angiomatous meningioma associated with severe peritumoral leptomeningitis without the infiltration of inflammatory cells into the tumor itself, which quickly improved after removal of the meningioma.

CASE PRESENTATION

A 70-year-old woman with no history presented to a local hospital with transient right hemiparesis 1 month earlier, where computed tomography (CT) of the head revealed an intracranial isodense tumor (30 mm in diameter) with no calcification on the left frontal convexity, being referred to our hospital. On admission, the patient was afebrile and had no neurological deficits. On brain magnetic resonance imaging (MRI), the tumor appeared hypointense on T1-weighted images [Figure 1a], and hyperintense on T2-weighted images [Figure 1b] without peritumoral edema. Gadolinium-enhanced T1-weighted images demonstrated a homogenously enhanced extra-axial tumor with peritumoral leptomeningeal enhancement [Figure 1c]. A whole spine MRI revealed no findings suggestive of meningeal dissemination. A whole-body contrast-enhanced CT showed a mass lesion in the left mammary gland, which was diagnosed as breast cancer by a needle biopsy. Positron emission tomography-CT revealed no mass lesions in the other organs. Blood laboratory examinations were within normal ranges including tumor markers (carcinoembryonic antigen, and carbohydrate antigen 19-9 and 125); white blood cell counts, 6800/μL; C-reactive protein, 0.09 mg/dL; and soluble interleukin-2 receptor, 342 U/mL. Cerebrospinal fluid (CSF) analyses disclosed a total protein level of 68 mg/dL, a glucose level of 45 mg/mL, and cell counts of 178 mononuclear cells/mm^3 and 70 polymorphonuclear cells/mm^3, but the cytology revealed no tumor cells. Both blood and CSF cultures were negative.

As a differential diagnosis, a solitary dural metastasis of breast cancer could not be ruled out, and close follow-ups were continued. As simple focal seizures of the right upper extremity developed, 1000 mg/day (500mg twice) of levetiracetam was administered. One-month post-admission MRI revealed that the tumor size was unchanged, but peritumoral leptomeningeal gadolinium enhancement was significantly expanded [Figures 2a-c]. Because focal seizures could not be controlled even by 3000 mg/day (1500 mg twice) of oral levetiracetam administration, tumor removal was performed. After the left frontal craniotomy, no lesions were revealed on the epidural space. When the dura mater was incised and turned over, a soft and reddish tumor was exposed [Figure 3a]. Peritumoral subarachnoid space was filled with yellowish semisolid substances [Figure 3b]. Most of the tumor was excised, but the semisolid substances in the subarachnoid space were only biopsied to avoid brain damage due to the removal [Figure 3c]. Postoperatively, seizures resolved, and 1-week postsurgery MRI revealed remarkable attenuation of the leptomeningeal enhancement [Figure 3d, *upper panel*]. CSF findings also improved to a total protein level of 68 mg/dL and cell counts of 4 mononuclear cells/mm^3 and 2 polymorphonuclear cells/mm^3. Serum markers of autoimmune diseases including IgG1 to IgG4, myeloperoxidase-antineutrophil cytoplasmic antibody (ANCA), proteinase 3-ANCA, anti-cyclic citrullinated peptide (CCP) antibody, rheumatoid factor, antinuclear antibody, anti-thyroglobulin antibody, anti-thyroid peroxidase antibody, and viral antibodies for herpes simplex virus, varicella zoster virus, cytomegalovirus, and Epstein-Bass virus were measured, and only an anti-CCP antibody level was high (1000 U/mL). However, the patient had no symptoms of rheumatoid arthritis (RA) and did not meet the criteria, being followed up. The patient was discharged

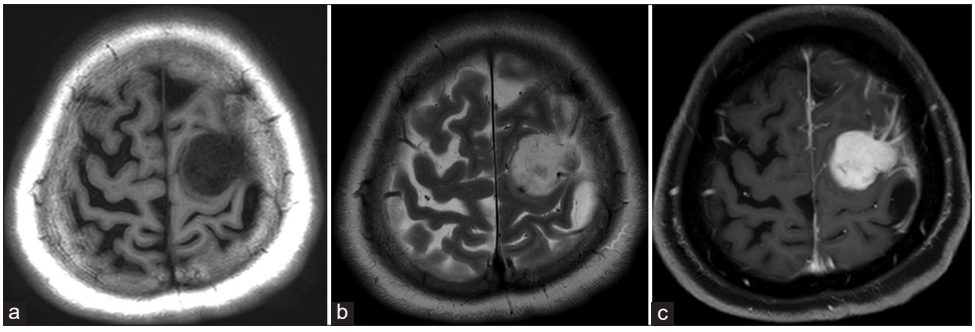


Figure 1: Magnetic resonance imaging (MRI) on admission (a-c). An extra-axial tumor on the left frontal lobe is hypointense on T1-weighted image (a) and hyperintense without peritumoral edema on T2-weighted image (b). Gadolinium-enhanced T1-weighted image shows a homogenously enhanced tumor with leptomeningeal enhancement around the tumor.

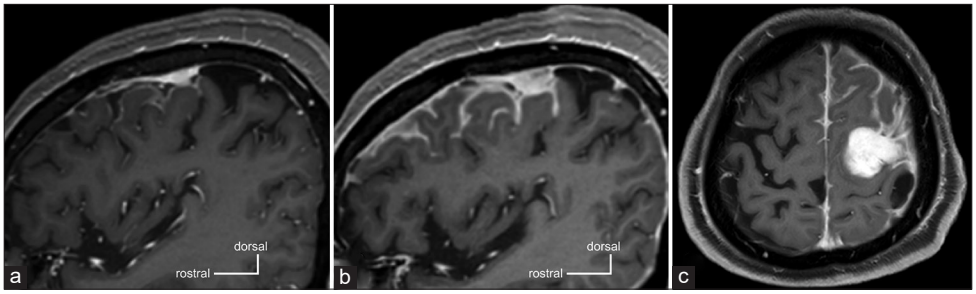


Figure 2: Magnetic resonance imaging on admission (a) and 1 month later (b and c). Gadolinium-enhanced T1-weighted sagittal image on admission shows leptomeningeal enhancement around the tumor (a), which is markedly enlarged 1 month later ([b], sagittal image; [c], axial image).

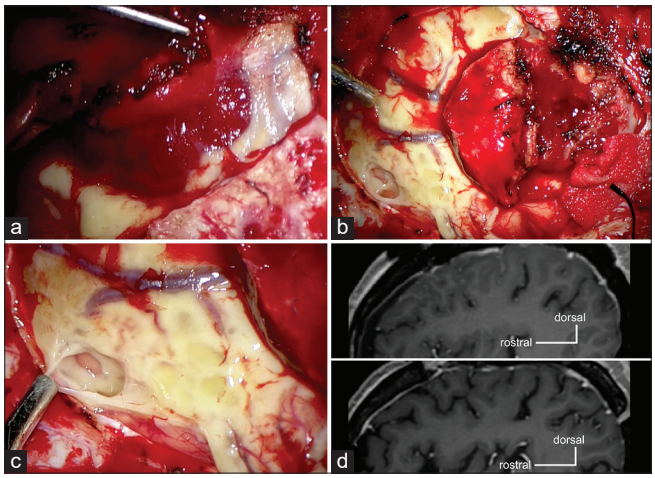


Figure 3: Intraoperative findings (a-c) and postoperative magnetic resonance imaging (MRI) (d-e). The tumor is soft and reddish (a). The subarachnoid space is broadly filled with yellowish semisolid materials (b), which are biopsied (c). Postoperative MRIs at 1 week (d, *upper panel*) and 3 years later (d, *lower panel*) demonstrate a rapid improvement of leptomeningeal enhancement and no recurrence of it.

with no neurological deficits and underwent resection of the breast cancer 3 months later. The patient has passed more than 3 years without recurrence of seizures, leptomeningitis [Figure 3d, *lower panel*], meningioma, and breast cancer.

Pathological findings

The convexity dural-based tumor [Figure 4a] consisted of angiomatous components with numerous small to medium-sized vascular channels [Figure 4b], and microcystic components with microcysts and cobweb-like background [Figure 4c], associated with some meningothelial cells. The tumor had neither malignant findings such as increased mitotic activity, nuclear atypia and brain invasion, nor inflammatory cell infiltration into the tumor. In the border zone between the convexity dural-based tumor and the dura mater, however, there were inflammatory infiltrates and formation of some lymph follicles [Figure 4d]. Infiltration of numerous neutrophils and fibrinous exudates was also observed in the subarachnoid space [Figure 4e].

Immunohistochemical study was performed using the Bench Mark ULTRA auto-stainer (Ventana, Tucson, AZ, USA) and the used antibodies were listed in Table 1. Tumor cells were positive for vimentin [Figure 4f] and slightly positive for epithelial membrane antigen [Figure 4g], and vascular endothelial cells were positive for CD34 [Figure 4h]. Glial fibrillary acidic protein was negative, and MIB-1 index [Figure 4i] was <1% in the convexity dural-based tumor. Based on the above findings, a histological diagnosis of angiomatous meningioma (CNS WHO Grade 1) was made for the tumor.

On the other hand, inflammatory cells infiltrating into the border zone between the tumor and the dura mater were positive for CD3 (T-cell-associated antigen; Figure 4j) and CD20 (B-cell-associated antigen; Figure 4k), and negative for CD15 (neutrophil-associated antigen; Figure 4l); and those around lymph follicles were positive for CD68 (histocyte-associated antigen; Figure 4m) and CD138 (plasma cell-associated antigen; Figure 4n). IgG-positive cells were abundant [Figure 4o], of which only 10% were IgG4 positive [Figure 4p]. In contrast, almost all inflammatory cells infiltrating into the subarachnoid space were positive for CD15 [Figure 4q], while almost no cells were positive for CD68 [Figure 4r], CD45 (lymphocyte-associated antigen; Figure 4s), CD20 [Figure 4t], and CD138 [Figure 4u]. Thus, the findings indicated that there were no inflammatory cells within the tumor itself, but the tumor was associated with peritumoral infiltration of inflammatory cells: lymphocytes mainly infiltrated into the border zone between the tumor and the dura mater, and neutrophils infiltrated into the peritumoral subarachnoid space with fibrinous exudates.

DISCUSSION

Meningiomas with inflammation are rare.[26] Although several types of meningiomas with inflammation have

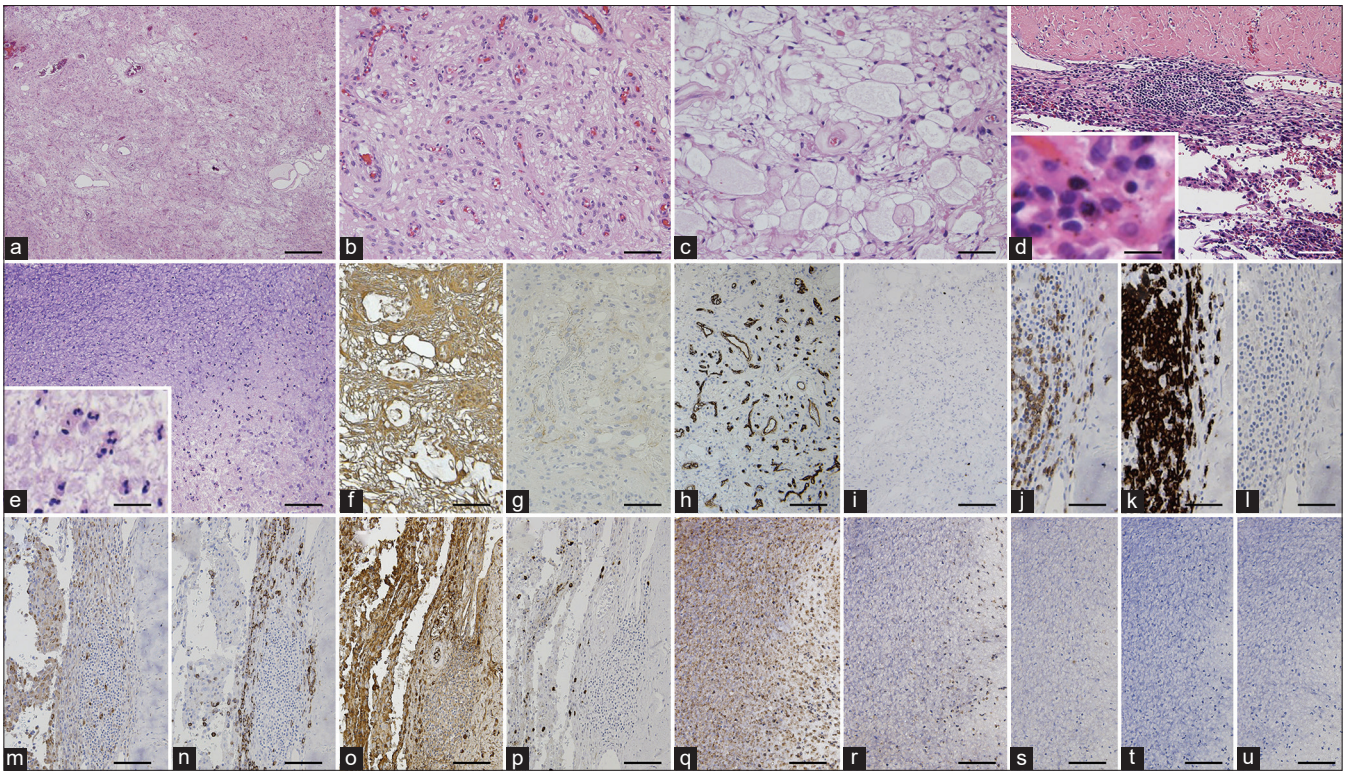


Figure 4: Histopathological (hematoxylin and eosin stain; [a-e]) and immunohistochemical (f-u) findings. The convexity dural-based tumor consists of angiomatous components with numerous small to medium-sized vascular channels (a, low-magnification, and b) and microcystic components with microcysts and cobweb-like background (c). Inflammatory infiltrates exist in the border zone between the tumor and the dura mater (d), and mainly consist of lymphocytes (*insert* of d). The lesion in the subarachnoid space consists of a cluster of neutrophils (*insert* of e) with fibrinous exudates (e). The tumor cells are reactive for vimentin (f) and slightly reactive for epithelial membrane antigen (g). Vascular endothelial cells were positive for CD34. MIB-1 index is <1%. Inflammatory infiltrates in the border zone between the tumor and the dura mater are reactive for CD3 (j) and CD20 (k), but almost non-reactive for CD15 (l), while those around lymph follicles are positive for CD68 (m) and CD138 (n). The inflammatory cells in the border zone are also broadly reactive for IgG, but those of <10% are reactive for IgG4. In contrast, inflammatory infiltrates in the subarachnoid space are reactive for CD15 (q) and not for CD68 (r), CD45 (s), CD20 (t), and CD138 (u). Bar = 0.5 mm (a), 100 μm (b-g and m-u), 12.5 μm (*insert* of d), 25 μm (*insert* of e), 200 μm (h and i), and 50 μm (j-l).

Table 1: Summary of antibodies used for immunohistochemistry.

Antibodies	Species, clonality	Clone	Dilution	Source
Vimentin	Mouse, monoclonal	V9	Prediluted	Roche, Indianapolis, IN, USA
EMA	Mouse, monoclonal	E29	Prediluted	Roche, Indianapolis, IN, USA
CD34	Mouse, monoclonal	QBEnd/10	Prediluted	Roche, Indianapolis, IN, USA
GFAP	Rabbit, monoclonal	EP672Y	Prediluted	Roche, Indianapolis, IN, USA
Ki67	Rabbit, monoclonal	30-9	Prediluted	Roche, Indianapolis, IN, USA
CD3	Rabbit, monoclonal	2GV6	Prediluted	Roche, Indianapolis, IN, USA
CD20	Mouse, monoclonal	L26	Prediluted	Roche, Indianapolis, IN, USA
CD68	Mouse, monoclonal	KP-1	Prediluted	Roche, Indianapolis, IN, USA
CD138	Mouse, monoclonal	B-A38	Prediluted	Roche, Indianapolis, IN, USA
IgG	Rabbit, polyclonal	Polyclonal	Prediluted	Roche, Indianapolis, IN, USA
IgG4	Mouse, monoclonal	MRQ-44	Prediluted	Roche, Indianapolis, IN, USA
CD15	Mouse, monoclonal	MCS-1	Prediluted	Nichirei, Tokyo, Japan
CD45 (LCA)	Mouse, monoclonal	RP2/18	Prediluted	Roche, Indianapolis, IN, USA

EMA: Epithelial membrane antigen, GFAP: Glial fibrillary acidic protein, IgG: immunoglobulin G

been reported, the pathophysiology remains unclear and appears to be heterogeneous.[13] LPMs are CNS WHO Grade-1 meningiomas with extensive intratumoral chronic inflammatory infiltrates,[15] but rarely cause pachymeningitis

and inflammation in the peritumoral tissues.[4,6,13,19,24,26] There are increasing numbers of reports of IgG4-related diseases in the CNS including idiopathic hypertrophic pachymeningitis and meningioma with high infiltrates of IgG4-positive plasma cells within the tumor.[4,6,8,12-14,24-26] Kuranari *et al*. reported a case of meningothelial meningioma with intraoperatively observed yellowish semisolid substances in the peritumoral subarachnoid space, in addition to extensive intratumoral infiltration of IgG4-positive plasma cells and eosinophils.[12] The present case was completely different from previous reports of meningioma with inflammation, because inflammatory cells were absent within the tumor itself. Our case was CNS WHO Grade-1 angiomatous meningioma, which grew slowly, but dramatically enhanced the peritumoral leptomeningeal inflammation in a month with poorly controlled epileptic seizures. Notably, the tumor removal rapidly improved the peritumoral leptomeningeal enhancement and inflammation, suggesting a link between the meningioma and the peritumoral inflammatory reactions. To the best of our knowledge, there are also no reports that other meningioma-mimicking dural-based masses were associated with the surrounding pachymeningeal or leptomeningeal inflammation without intratumoral inflammation.

Meningiomas have been reported to elicit inflammatory responses, but inflammatory cells are also known to exacerbate meningiomas.[9,20] According to Du *et al*., CNS WHO Grades-2 and -3 meningiomas with infiltration of inflammatory cells had lower numbers of CD3-positve T cells, CD4-positve T-helper cells, and CD8-positve cytotoxic T-lymphocytes while a higher number of regulatory T cells, compared with Grade-1 meningiomas.[5] More infiltrations of tumor-associated macrophages were observed in higher CNS WHO-grades meningiomas, and the ratio of M1-phenotype macrophages with anti-tumor activity to M2-phenotype ones (alternatively activated immunosuppressive cell types that may contribute to tumor progression) was decreased in higher grade meningiomas.[18,21] In addition, macrophages and mast cells have been reported to induce inflammation and contribute to peritumoral edema.[9,20,23] The present case was a CNS WHO grade-1 angiomatous meningioma with no surrounding edema, and the exacerbation of the leptomeningitis was not associated with the tumor progression.

Another interesting finding in the present case was the elevation in serum levels of anti-CCP antibody without the symptoms suggestive of RA. Anti-CCP antibodies are RA-specific serum biomarkers and are used for the diagnosis of RA according to the 2010 European League Against Rheumatism criteria.[7,10,17] RA rarely involves the CNS, and inflammation in RA preferentially occurs in the meninges, especially in the dura mater, rather than in the brain, reflecting an autoimmune response to collagen: [1] rheumatoid meningitis (RM) is an aggressive manifestation of RA.[3,11,17,22] Histopathologic findings of RM are characterized by pachymeningitis or leptomeningitis, rheumatoid nodules, and vasculitis.[16] Inflammatory infiltrates in the meninges in RM consist of mononuclear cells, especially plasma cells, while neutrophils are rarely seen.[25] In the present case, although clusters of plasma cells were observed on the border between the tumor and the dura mater, inflammatory infiltrates in the subarachnoid space were dominated by neutrophils. In addition, no rheumatoid nodule was observed, and therefore, RM was denied. However, elevated serum levels of anti-CCP antibodies suggested the existence of an autoimmune reaction. It is possible that the meningioma was recognized as a foreign body and triggered an inflammatory response in the present case.

CONCLUSION

Inflammation can be closely related to meningiomas, but the pathophysiology remains unclear. The present case is the first report of angiomatous meningioma associated with massive peritumoral inflammatory reactions without inflammatory cell infiltrations within the tumor itself. Further accumulation of similar cases is awaited to elucidate the pathophysiology and the relationships between meningioma and inflammation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Nakajima H, Tsuchiya T, Shimizu S, Murata T, Suzuki H. Angiomatous meningioma associated with rapidly aggravated peritumoral leptomeningitis: A case report. Surg Neurol Int 2023;14:159.