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Rhabdoid Meningioma with Infiltration of Igg4-Positive Plasma Cells and Eosinophils after Stereotactic Radiotherapy: A Case Report and Review of Literature

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Meningioma; Rhabdoid; Eosinophil; plasma cell; IgG4; Radiation therapy

1. Abstract

Meningiomas are a large group of predominantly benign, slow-growing tumors that develop in the meninges, and they are one of the most common types of intracranial tumors. However, meningiomas with plasmacytic or eosinophilic infiltration are extremely rare, with only isolated cases being reported. In this case, we present a 61-year-old woman who was diagnosed with a grade 3 rhabdoid meningioma. She underwent stereotactic radiation therapy as the first stage of treatment, followed by surgical treatment as the second stage. Upon histological examination, the meningioma was found to be infiltrated with lymphocytes, plasma cells (including IgG4+ forms), macrophages, and eosinophils. This infiltration may be attributed to both the tumor's invasion into the brain tissue, leading to activation of the local immune response, and the damaging effects of radiation therapy on the blood-brain barrier.

2. Introduction

Meningiomas are a large group of predominantly benign, slow-growing tumors that develop in the meninges (ICD-O coding 9530/0) [1]. The term "meningioma" and the anatomical classification still in use were proposed in 1922 by American neurosurgeon G. Cushing [2]. In the adult population, meningiomas account for 18-34% of all intracranial tumors, ranking second among all brain tumors. In terms of frequency, they are second only to gliomas [3-5]. According to the latest criteria from the World Health Organization (WHO, 2021), meningiomas are divided into 15 histological subtypes and are graded based on the degree of tumor anaplasia from benign grade 1 to anaplastic grade 3. Grade 1 meningiomas make up approximately 80% of all tumors [1, 3]. Meningiomas infiltrated by inflammatory cells, such as lymphocytes and plasma cells, are rare. The distinct grade 1 lymphoplasmocyte-rich meningioma is a relatively uncommon subtype characterized by fibrosis and infiltration of both plasma cells and lymphocytes. However, meningiomas with IgG4-positive plasmacytic or eosinophilic infiltration are extremely rare, with only isolated cases reported [6-9]. The mechanisms of the inflammatory response associated with meningiomas are not fully understood. Meningiomas are known to be susceptible to infiltration by peripheral immune cells because they are located outside the blood-brain barrier (BBB) [10-12]. It has been suggested that dysregulation of immune functions may play a critical role in the tumorigenesis and progression of meningiomas, especially malignant meningiomas. However, the immune landscape and key genes associated with immune cell infiltration in meningiomas are not fully understood.

3. Clinical Case

Patient K, 61 years old woman. According to the patient's medical history, they began experiencing double vision in 2019. An ophthalmologist recommended a magnetic resonance imaging (MRI)

of the brain, which revealed a meningioma measuring 14×30×31 mm in the anterior third of the superior sagittal sinus and falx on the right (June 2019). However, the diplopia was not initially associated with the presence of a space-occupying lesion. The patient underwent surgical ophthalmological treatment for paralytic strabismus, which successfully resolved the diplopia. In 2019, the patient received three sessions of stereotactic radiation therapy using a Cyber Knife G4 device in hypofractionation mode (1800 cGy in three fractions) (Figure 1).

The patient's condition stabilized after the treatment, and no further annual MRIs were performed. In September 2023, the patient's health deteriorated, experiencing increased fatigue and decreased performance. A follow-up MRI of the brain with contrast on November 09, 2023, showed an increase in tumor size to 29×56×44 mm, pronounced perifocal edema, and a displacement of the midline structures by 8 mm to the left (Figure 2). In November 2023, the patient visited the neuro-oncology clinic at the Polenov Neurosurgical Institute. Upon admission, the patient's condition was satisfactory with stable vital functions and hemodynamics. The neurological examination did not reveal any focal symptoms and the patient was right-handed. The pupils were equal in size and the patient had full eye movement without any nystagmus. There were no sensory disturbances on the face and the patient was able to close their eyelids completely, although there was slight asymmetry in the nasolabial folds. Swallowing was preserved and the tongue was in the midline. There were no signs of muscle weakness in the limbs and the muscle tone was normal. Deep reflexes were low in all extremities. The patient performed coordination tests satisfactorily and was stable in the Romberg position. According to the Karnofsky scale, the patient's functional status was at 90%.

The neuro-ophthalmologist reported that the patient's vision in the right eye was 1.0 and 0.8 in the left eye (with initial cataract in both eyes). The optic discs appeared pale pink with clear boundaries and there were no changes in the field of vision. The electroencephalography (EEG) results showed moderate diffuse changes with an irritative nature, a significant pathological process in the right frontotemporal region, and less pronounced changes in the left frontal region. There was also functional instability in the mid-trunk structures and possible epileptiform irritation in the medio-basal formations of the temporal lobes, primarily on the right side. The patient underwent surgical neurosurgical treatment, including an osteoplastic craniotomy in the frontal region on the right, microsurgical removal of the tumor (with a degree of radicality of Simpson I), and simultaneous plastic surgery of the dura mater with an artificial graft. During the tumor removal, the macroscopic picture was typical of a meningioma. In the postoperative period, there was no observed increase in cerebral or focal symptoms. A control computed tomography (CT) scan was conducted the day after surgery, which showed no evidence of intracranial pathological areas with contrast agent accumulation. However, perifocal edema of the right frontal lobe persisted (see Figure 3). The patient was discharged in a satisfactory and stable condition for outpatient treatment by a neurologist and oncologist at their place of residence. It is recommended that the patient undergo a course of radiation therapy and have a control MRI with contrast after 3 months, followed by a consultation with a neurosurgeon.

Biopsy material of tumor fragments was examined in the pathological department of the Polenov Neurosurgical Institute. The material was fixed in 10% buffered formalin, dehydrated in a standard manner and embedded in paraffin. Histological sections stained with hematoxylin and eosin (BioVitrum, Russia) were studied. For immunohistochemical studies, antibodies from Dako (USA) and the EnVision imaging system were used. Histological analysis and microphotography were carried out using a Leica Aperio AT2 scanning microscope and AperioImageScope image manager (Leica Microsystems, USA). The study was conducted in accordance with the Helsinki Declaration of Human Rights. Preoperative examination and surgical treatment of patients were carried out in accordance with the Clinical Guidelines of the Association of Neurosurgeons of Russia 2015. Histological examination confirmed the presence of an arachnoendothelial tumor (Figure 4). The tumor showed a lobular structure and moderate expression of cellular and nuclear polymorphism. Round cells with rounded vesicular nuclei were observed in part of the tumor structure, with most nuclei containing distinct, centrally located nucleoli (Figure 4A-B). The majority of the tumor consisted of round rhabdoid cells with abundant eosinophilic opalescent cytoplasm and an eccentrically located nucleus containing a distinct nucleolus. The tumor was found to have invaded brain tissue (Figure 4C). Angiomatosis and a few areas of micronecrosis were present in the tumor stroma, along with 12 mitotic figures in 10 fields of view at ×400 magnification. Additionally, the tumor stroma showed abundant infiltration of lymphocytes, plasma cells, and eosinophils (Figure 4D-F).

An immunohistochemical study of tumor cells revealed weak expression of epithelial membrane antigen (EMA) with large areas of loss, as well as loss of expression of somatostatin receptor type 2 (SSTR2) (Figure 5A). The level of Ki67/MIB1 proliferative activity was 15% (Figure 5B). Immunophenotyping of lymphoid cells showed diffuse expression of the CD45 marker, with some cells staining positive for the CD3 marker (Figure 5C). The expression of the CD5 marker was colocalized with CD3+ cells, and clusters of CD4+ and CD8+ cells were also detected. Additionally, some lymphoid cells were positively stained with antibodies to the CD79a marker (Figure 5D), indicating the formation of follicular lymphoid structures. However, CD20-positive cells were found to be single, while CD138+/CD38+ cells were numerous (Figure 5E). It was also observed that some plasma cells expressed IgG, and up to 1% of plasma cells were stained with the IgG4 marker (Figure 5F). Staining with the CD68 marker revealed large accu-

mulations of positive macrophage cells.

Therefore, the patient has a grade 3 rhabdoid meningioma with high proliferative activity and invasion into brain tissue. The tumor also showed diffuse lymphoplasmacytic infiltration with the presence of IgG4+ plasma cells, as well as diffuse infiltration of eosinophils.

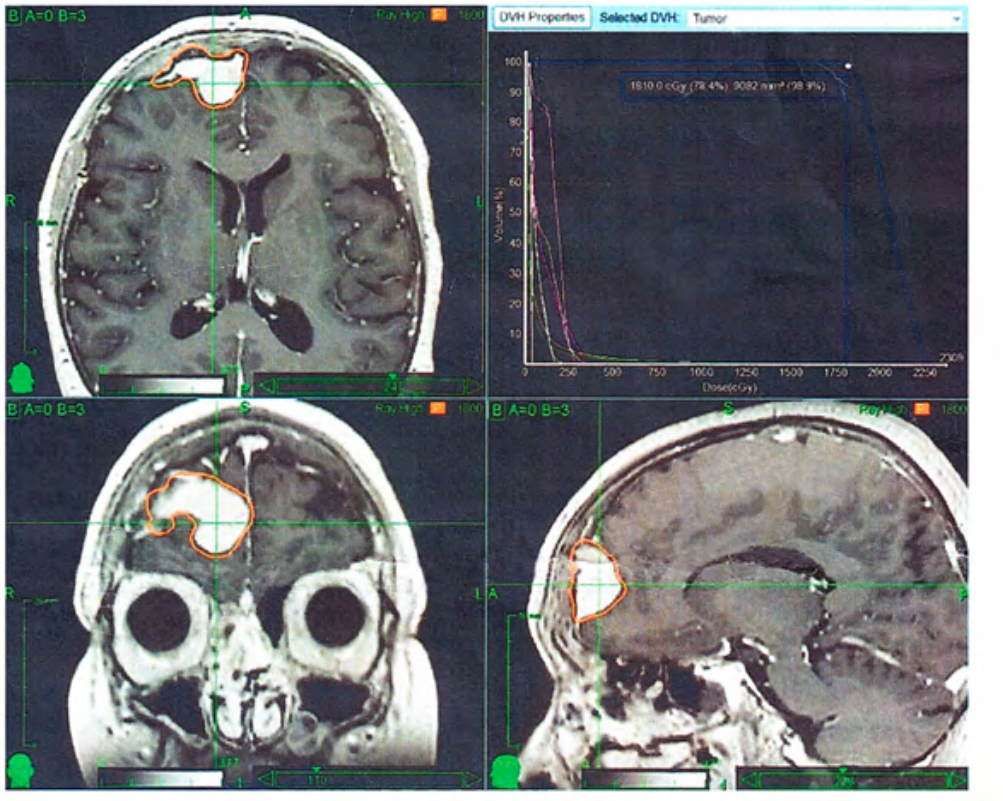

Figure 1: Plan for a stereotactic radiation therapy session (Cyber Knife).

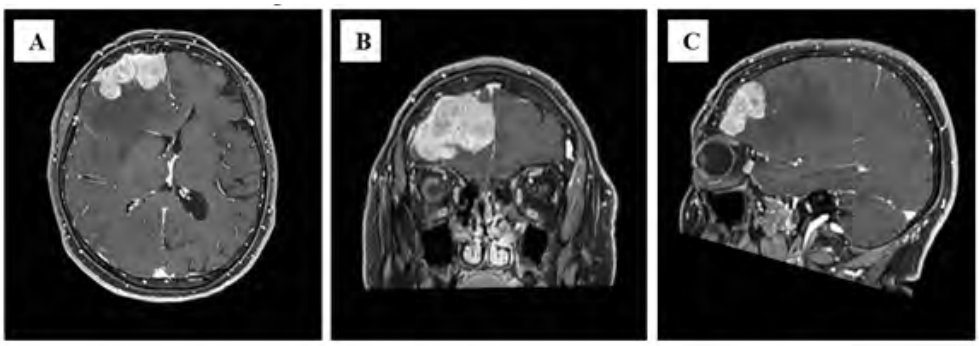

Figure 2: MRI of the brain in axial (A), coronal (B) and sagittal (C) projections. On T1-WI after contrast, a multinodular, extracerebral formation with clear, uneven contours is visualized, with a wide base adjacent to the dura mater, heterogeneously accumulating contrast.

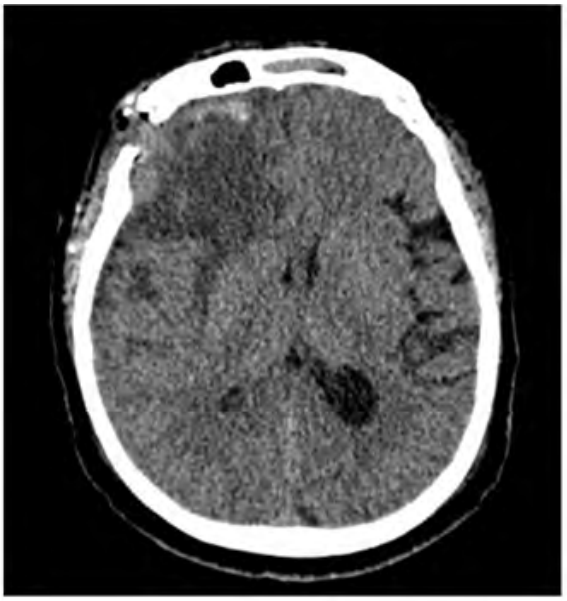

Figure 3: CT scan of the brain with contrast on the 1st day after surgery. The tumor was completely removed.

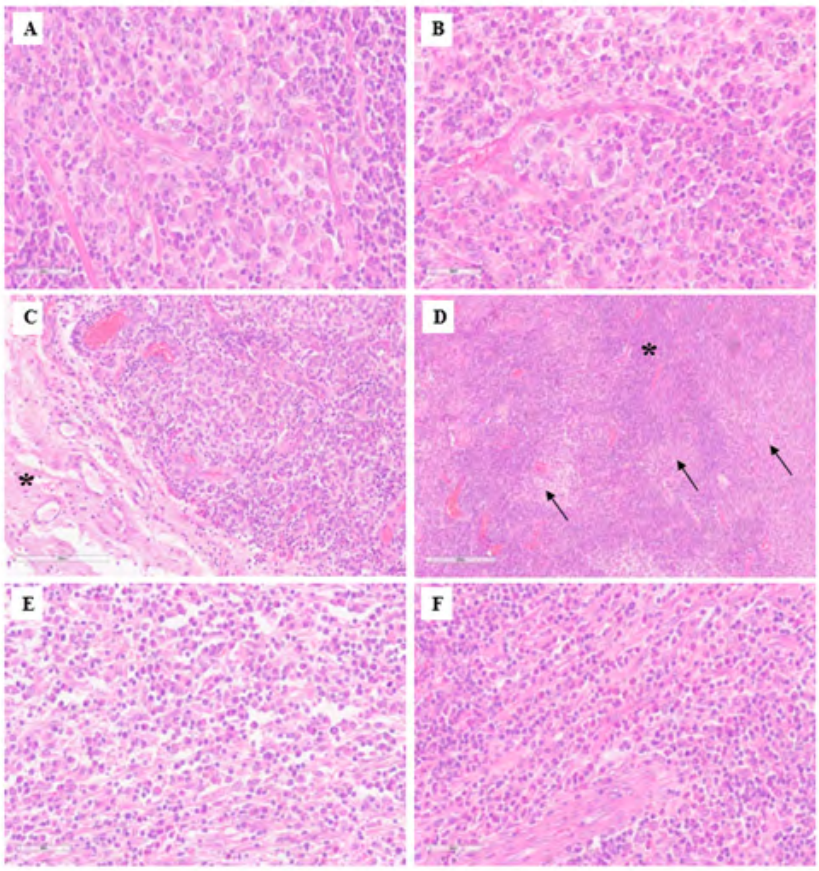

Figure 4: Results of histological examination of the resected tumor.
Hematoxylin and eosin staining.
A-B – Tumor from the arachnoid endothelium with a diffuse type of growth, the tumor consists of rhabdoid cells, ×400
C – Tumor cells infiltrate brain tissue (*); Lymphocytic infiltration is also present at the tumor-brain border, ×200
D – Diffuse lymphoid infiltration of the tumor (*), arrows indicate islands of tumor cells, ×100
E – Lymphoplasmacytic infiltration in the tumor, ×400
F – Eosinophilic infiltration in the tumor, ×400

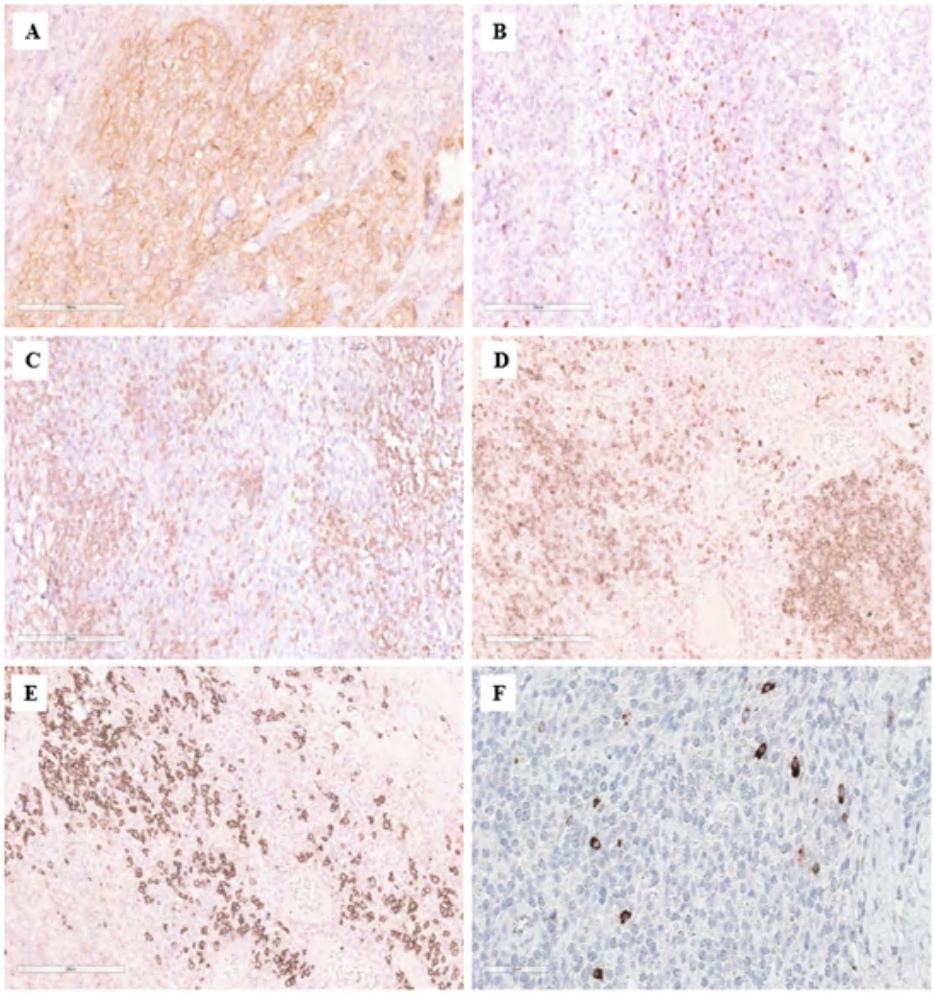

Figure 5: Results of immunohistochemical reactions.

A – Membrane and cytoplasmic staining of meningioma tumor cells with the SSTR2 marker, ×200

B – Level of proliferative activity for Ki67 up to 15%, ×200

C – Staining of numerous T-lymphocytes of the tumor stroma with the CD3 marker, ×200

D – Staining of numerous lymphocytes of the tumor stroma with the pan-B-cell marker CD79a, the formation of follicular structures is detected, ×200

E – Staining of numerous plasma cells of the tumor stroma with the CD38 marker, ×200

F – Some plasma cells were stained with an antibody to IgG4, ×400

4. Discussion

It has been established that macrophages are the most common type of immune cells in the immune environment, and their number is higher in grade 2 and 3 meningiomas [10]. Moreover, high-grade meningiomas have a large number of mast cells in the perivascular areas of the tumor, which has been found to contribute to tumor aggressiveness [11]. In addition, regulatory T cells, CD4+ helper and CD8+ cytotoxic T cells, as well as a small number of B cells were also observed in the microenvironment of meningioma tissues [13]. Regulatory T cells may also be involved in creating an immunosuppressive microenvironment by releasing cytokines to reduce the proliferation of CD4+ and CD8+ T cells in grade 2 or 3 meningiomas [14]. Also, Chen J et al found that plasma cells, M1 macrophages, M2 macrophages, neutrophils, eosinophils and activated NK cells were significantly different infiltrating immune cells in meningioma [15]. Based on the results of single-cell RNA sequencing (scRNA-seq) data for the identification of macrophages in meningiomas and normal meninges, it was found that in meningiomas the proportion of macrophages is significantly higher than in normal meninges, including new clusters of them [16], which in combination with the genetic module allowed the division of meningiomas into two subtypes with different clinical characteristics and characteristics of the tumor microenvironment (TME). It has been suggested that the inflammatory response associated with IgG4+ plasma cells may mediate inflammation in surrounding tissues, leading to thickening of the dura mater adjacent to the meningioma and severe headache [17].

The interaction between the blood-brain barrier (BBB), border glia, and meningiomas has not yet been studied, and the TME in meningiomas is not well understood. The BBB is a complex struc-

ture that consists of tight junctions between cells, specific transport mechanisms, and enzymes that metabolize molecules during transit. It is not a fixed barrier but can be modulated and regulated in both physiology and pathology [18–20]. However, the extent of possible reciprocal crosstalk between tumors and the brain in meningiomas and how it influences pathophysiology remains unknown. The authors found that infiltration of tumor-associated macrophages increases with increasing WHO grade, and invasion into the brain is required to induce an immune response in the brain parenchyma [21]. Meningiomas are located outside the blood-brain barrier [22] and are usually supplied by the external carotid artery [23], suggesting that the diffuse monocyte infiltrates in meningiomas represent blood-derived macrophages, while the monocyte response to the tumor-brain interface may contain microglia [24]. Additionally, it has been observed that tumor-associated astrocytes disappear during meningioma invasion into the brain [25], which is accompanied by a focal absence of the pial basement membrane and correlated with the absence of subpial astrocytes. The authors interpreted this finding as the "disappearance of astrocytes" after invasion and suggested that astrocyte survival is dependent on attachment to an intact basement membrane. The loss of astrocytes, one of the key components of the BBB, may result from degradation of the basement membrane, which can be mediated by matrix metalloproteases expressed by tumor cells in invasive and aggressive meningiomas [26]. Coexpression of MMP-9 with MIF-1 [27] and immunoregulatory T cells may promote brain invasion by attenuating the microglial response [28]. Several cytokines/chemokines, such as IL-6, CXCL12, and TGF-β, have been shown to form autocrine loops in meningioma cells. Such loops have been demonstrated as a signaling mechanism influencing tumor behavior [29–31]. Some chemokine/chemokine receptor pairs have also been found in endothelial cells and in the tumor-associated macrophages [32], implying that paracrine signaling also takes place in the TME. Whether and how microglia and astrocytes contribute to the cytokine milieu in meningiomas or whether TME mutually influences these glial cells has not been investigated.

Radiation therapy (RT) is the cornerstone of the treatment strategy for brain tumors. In addition to cytotoxicity, radiation therapy can cause disruption of the BBB, which leads to increased permeability of the surrounding brain parenchyma [33]. Although this effect is generally accepted, it remains unclear how and to what extent different irradiation regimens affect the integrity of the BBB. There is evidence that the integrity of the BBB is altered following the use of radiation therapy, resulting in both reversible and irreversible tissue damage to the patient. While early brain damage caused by radiation is largely reversible, later, more chronic damage, not present until three months after treatment, can cause (sometimes serious) problems for the patient [34]. It is assumed that cellular and vascular responses of the BBB to RT are mediated by astrogliosis and ultrastructural changes in the endothelium [35]. These changes in the BBB can ultimately lead to seizures, brain inflammation, and vascular leaks causing bleeding and/or stroke [36-37].

5. Conclusion

In this case of grade 3 rhabdoid meningioma, the presence of lymphocytes, plasma cells (including IgG4+ forms), macrophages, and eosinophils within the tumor may be attributed to both the tumor's invasion into brain tissue and the damaging effects of radiation therapy on the blood-brain barrier (BBB). Further research is needed to understand the role of brain tissue in the development of meningiomas and the type and extent of immune response in different types of tumors. Additionally, determining the permeability of the BBB in patients undergoing radiation therapy could aid in the development of effective chemotherapy treatments for aggressive meningiomas.

6. Conflict of Interest

The authors declares that there is no conflict of interest.

7. Financing

The study was conducted without any sponsorship.

8. Compliance with Patient Rights and Principles of Bioethics

The patient provided informed and voluntary consent for the study. The study was also conducted in accordance with the Helsinki Declaration of Human Rights.

9. Preoperativ Examination and Surgical Treatment

The patient underwent preoperative examination and surgical treatment in accordance with the Clinical Guidelines of the Association of Neurosurgeons of Russia 2015.

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