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Necrotizing Parasagittal Meningioma in Patient with Systemic Lupus Erythematosus after Treatments with Methotrexate and Hydroxychloroquine

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Abstract

Objective Meningiomas are the most common extra-axial tumors of the central nervous system. Meningiomas are particularly problematic when they invade deep or vital structures, causing the tumors to be inoperable. Nonsurgical adjunctive or salvage treatments to shrink a meningioma with multiple recurrences, located in deep-seated area or surgically unfit area, remain underexplored. The authors report a rare case of a spontaneously necrotic meningioma (World Health Organization [WHO] grade I) in a patient with systemic lupus erythematosus on chronic methotrexate and hydroxychloroquine.

Case Study A 29-year-old female with systemic lupus erythematosus had been treated with methotrexate and hydroxychloroquine for 7 years. She presented with episodes of seizures and hemiparesis. Neuroimaging revealed a possible necrotic meningioma in the left parietal parasagittal area. Subsequent intraoperative findings showed lytic tissue of the tumor, and by histopathology results the tumor was classified as WHO grade I with massive necrosis. After craniotomy with tumor removal, the patient's motor function fully recovered without recurrent seizures.

Discussions Necrotizing of small and benign meningioma is rarely found but otherwise interesting. The cause of this phenomenon is not yet understood thoroughly. In this case, we suspected various possible causes such as vasculitis interrupting blood supply, use of immunosuppressive drugs such as hydroxychloroquine or methotrexate, or, less likely, latent infections in the immunocompromised patient. Despite the lack of more evidence supports, this finding encourages further study of nonsurgical or salvage treatment of inoperable meningioma, so sequalae after refractory recurrences of meningioma can be prevented, and patient treatment outcomes can be improved.

Keywords

- necrotic meningioma
- salvage treatment
- hydroxychloroquine
- methotrexate
- nonsurgical treatments
- systemic lupus erythematosus

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Introduction

Around 35% of primary intracranial tumors are meningiomas.[1,2] Most are benign (grade I), but around 17% have atypical or anaplastic patterns.[3] Surgical treatments with total resections are the gold standard for meningiomas located in an accessible area.[2–4] If located in the skull base, ventricles, brain stem, or other critical neurovascular structures, total resection surgery may not be achievable.[3] In these cases, nonsurgical therapies such as radiation or chemotherapy can be used. Radiation plays an important role as an adjunctive treatment for World Health Organization (WHO) grade II and III meningiomas and is partially effective for WHO grade I meningiomas.[5] Mooney et al investigated the use of brachytherapy, after combined surgical and radiotherapy treatment, as a rescue treatment for meningiomas with malignant progression.[6] Chemotherapy options include hydroxyurea and somatostatin, but these are not standardized and lack strong evidences to support their use.[7,8] Progressions of many meningiomas after using these adjunctive therapies make patients suffer from progressive deteriorations of the disease. Furthermore, repeated surgeries often result in poor outcomes including a high tendency to have neurodeficits and sometimes poor cosmetic results.

This study thus aims to report the finding of a patient with systemic lupus erythematosus and a WHO grade I meningioma that showed massive necrosis, possibly due to vasculitis or long-term use of certain cytotoxic drugs (hydroxychloroquine and methotrexate). This case may be beneficial to future research investigating salvage treatment for meningiomas in difficult locations or resistant to other treatment strategies.

Case Study

A 29-year-old female with a history of systemic lupus erythematosus was admitted to the hospital due to sepsis and suspected relapse of disease. She had been treated with hydroxychloroquine, methotrexate, and prednisolone for 7 years. During admission, the patient experienced generalized tonic–clinic seizures with postictal right hemiparesis. Her vital signs were stable. There was no episode of hypotension or septic-shock. Under adequate antiepileptic treatment, the patient gained full consciousness, but right hemiparesis persisted.

Magnetic resonance imaging of the brain revealed a $3.7 \times 3.9 \times 2.4$ cm heterogenous ring-enhancing lesion in the left posterior parasagittal area. It occupied the left motor cortex and displayed leptomeningeal enhancement with mildly restricted diffusion in the diffusion-weighted image and suppression of the apparent diffusion coefficient (see ►**Fig. 1A–F**). Meningioma with atypical appearance was suspected, with differential diagnoses of a dural-based abscess or tumor necrosis due to her history of fever and her immunocompromised status. Surgical intervention was decided to confirm diagnosis and remove the lesion responsible for causing seizures and hemiparesis. Vascular access failed multiple times after skin incision was done due to severe vasculitis, so a craniotomy was designed to avoid the sagittal sinus and minimize the risk of hemorrhage. No evidence of peripheral tissue necrosis was observed. During the craniotomy, the lesion was observed with slough covering necrotic brain tissue (►**Fig. 2**). The tumor was removed, but the adhesion capsule attached to the motor area of the brain was left in situ. After the operation, the patient gained consciousness with no recurrence of seizure. Her motor function gradually returned to full strength after several months.

Tissue samples from the surgery were cultured and showed no growth of aerobic bacteria or tuberculosis. A pathological study revealed an epithelial meningioma (WHO grade I) with massive tumor necrosis. Immunohistochemistry was positive for vimentin, EMA, and S100. After surgery, the patient was seizure free. Her weakness improved gradually over several months. No recurrent tumor was seen on a follow-up magnetic resonance imaging (►**Fig. 3A–C**).

Discussions

Necrotic features in small, benign meningioma are uncommon. Necrosis is often found in large tumors that lack blood supply to the core.[9] They can also be found in aggressive, rapidly growing, and recurring tumors.[10,11] Necrosis, brain invasion, and perilesional edema are features of high-grade meningiomas, such as rhabdoid meningioma (WHO grade III). Necrosis is thought to be caused by high mitotic activity, which favors malignant behavior and is associated with poor patient outcomes.[10,12] Necrosis of large tumors can occur after chemotherapy.[13] It also can occur due to acute anemia from blood loss following hysterectomy.[9] Causes of necrosis in uncommon presentations, such as in a small or WHO grade I meningioma, may vary depending on concomitant factors and still under determined.

In this case, we suspect several factors contributing to the patient's condition. First, this patient had been taking immunosuppressant therapy for years, which might have led to necrosis in the small tumor. Methotrexate has long been used as a tumoricidal drug for aggressive malignant tumors, especially in higher doses. Side effects of using methotrexate alone are lower than in combination with chemotherapy.[14] Hydroxychloroquine is another agent used to treat tumors via its autophagy inhibitor mechanism. Autophagy plays a dichotomous role in cancer treatment. Many studies show that autophagy inhibitors augment the efficacy of chemotherapy.[15] Recently, hydroxychloroquine has been cited in several publications indicating that it prolongs the survival of intracranial tumors such as glioma, neuroblastoma, or prolactinoma.[16–19] It also shows some antitumor effects. In this patient, we cannot positively identify methotrexate, hydroxychloroquine, or a combined effect as the cause of her meningioma necrosis. Second, the patient had vasculitis. The inflammation of vessels often leads to ischemic events. It might be a possible cause of ischemic necrosis in tumors. However, several reports showed different effects.[20,21] It is found that the vasculitis was related to either enlargement of the meningioma, tumor necrosis, or both. Finally, infection

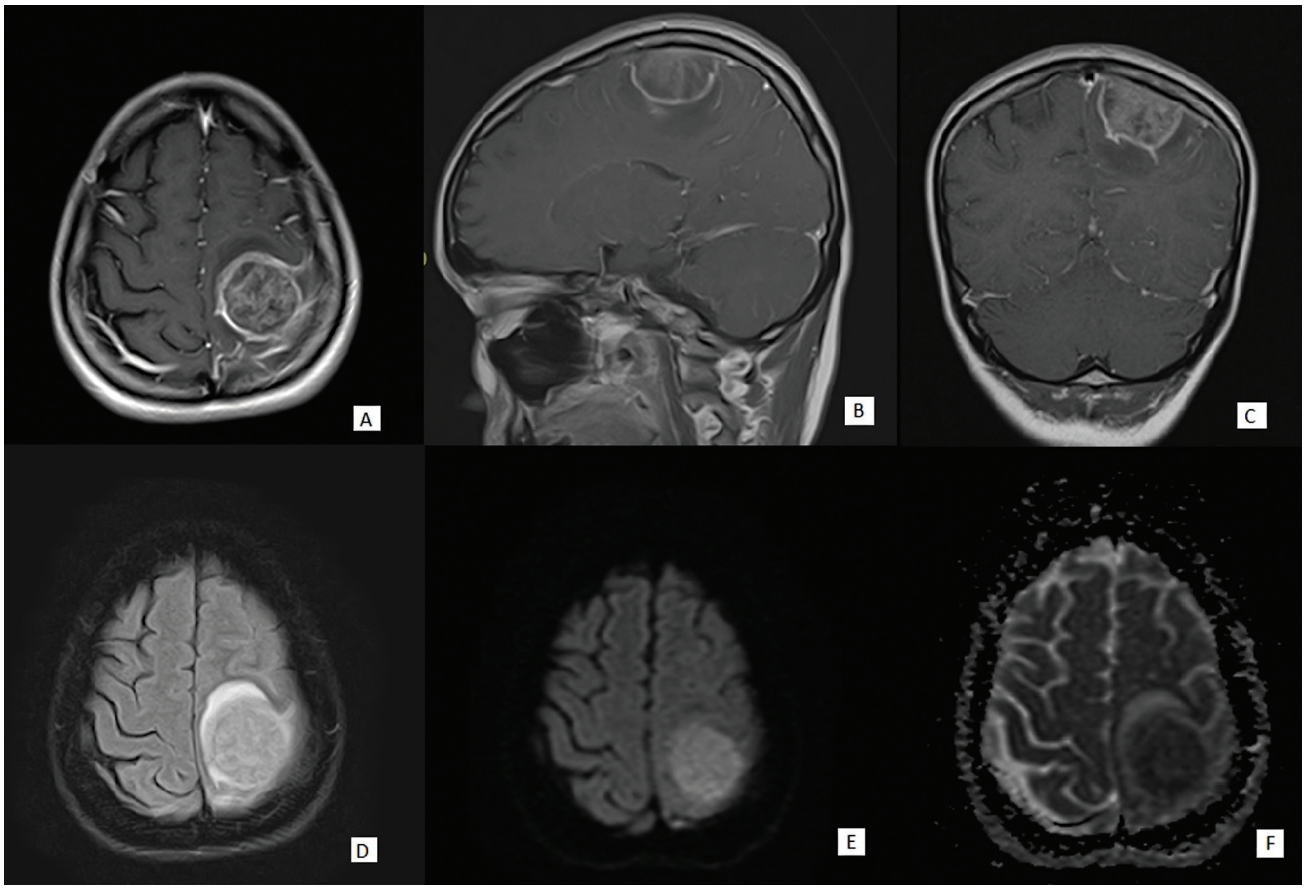

Fig. 1 Preoperative T1-weighted gadolinium enhancement magnetic resonance imaging of axial (**A**), sagittal (**B**), and coronal (**C**) views showing enhanced dural-base lesion with intralesional necrosis. Fluid-attenuated inversion recovery image (**D**) showing moderate edema around the lesion. Diffusion-weighted imaging (**E**) showing mild restricted diffusion. Apparent diffusion coefficient (**F**) showing suppression. These findings were compatible with necrotic lesions, but atypical infection could not be ruled out.

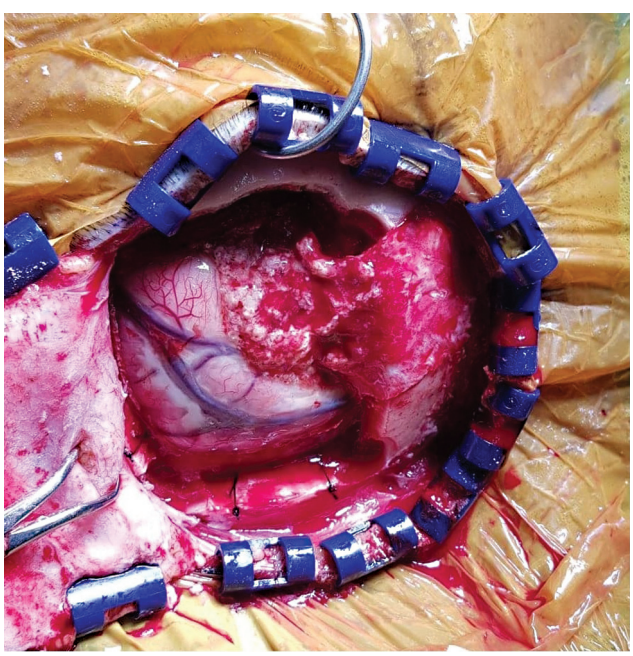

Fig. 2 Intraoperative finding showing massive necrosis of lytic tumor with no pus. Tumor was soft and suckable.

may be a possible cause of this patient's worsening condition. Even though initial investigations showed no organism but it could be other organisms such as anaerobic or Mycobacterium avium complex. However, she never had any signs of infection before. With the timing of fever and related symptoms, it was less likely to cause by infection process.

Conclusion

We believe this case offers insight into the study of spontaneous necrosis of meningioma, being a supportive data and initiate ideas to continue further studies about the use of hydroxychloroquine or methotrexate as an adjunct or salvage treatment, the concomitant effects of vasculitis, and the mechanism of necrosis and its implication in humans. Nonsurgical treatments for benign tumors can be effective for tumors located in inaccessible areas, in patients with unfavorable medical comorbidities, and may offer effective salvage treatment of refractory tumors. Nonsurgical methods also may be used to help shrink large tumors before surgical intervention to minimize operative time, prevent blood loss, and preserve tissue. Though now we still cannot conclude that methotrexate and hydroxychloroquine can be used as

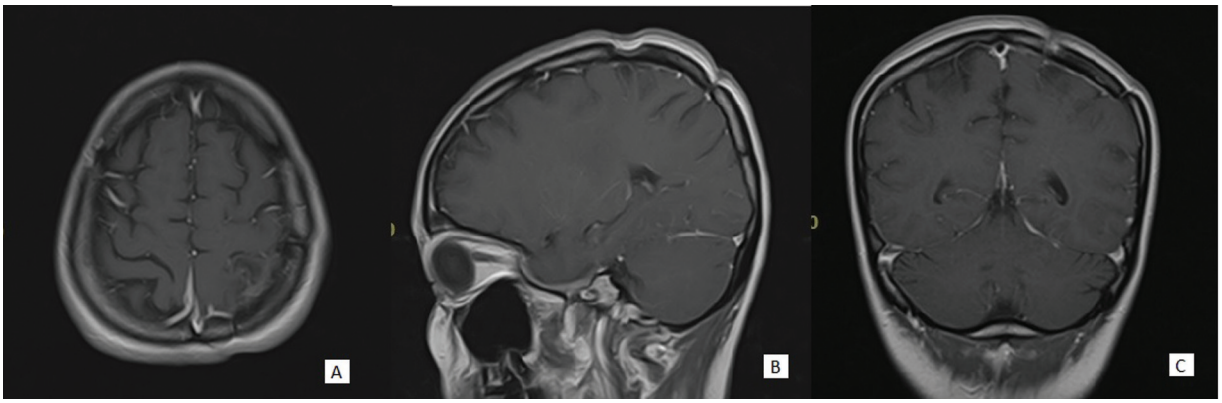

Fig. 3 Postoperative T1-weighted gadolinium enhancement magnetic resonance imaging of axial (**A**), sagittal (**B**), and coronal (**C**) views showing no residual tumor, without dural enhancement. Sinus was still intact.

salvage treatments for inoperable meningioma, the author thinks that this case report can provide a good supporting data for further research in this area as well.

Conflict of Interest
None declared.

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