Association Between Long-Term Progesteron Exposure and Intracranial Meningioma: A Case Report in a 44-Year-Old Woman

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ABSTRACT

Background: Meningioma is a common benign intracranial tumor originating from arachnoid cap cells and accounts for approximately one-third of all primary brain tumors. Its higher incidence in women suggests hormonal involvement, particularly from progesterone and progestogen exposure. Prolonged use of hormonal contraceptives, such as depo medroxyprogesterone acetate (DMPA), has been associated with the development and progression of meningioma. Objective: To describe the clinical presentation, neuroimaging findings, management, and possible association between long-term progesterone exposure and intracranial meningioma in a middle-aged woman.

Methods: We report the case of a 44-year-old woman with a history of long-term DMPA use who presented with progressive neurological symptoms. Clinical evaluation, neuroimaging studies, surgical treatment, and histopathological examination were performed and reviewed.

Results: The patient presented with recurrent severe headache, blurred vision, and a progressively enlarging right-sided scalp mass. She had received DMPA injections for more than 15 years. Contrast-enhanced brain CT demonstrated a well-defined right frontotemporal extra-axial mass consistent with meningioma. The patient subsequently underwent

craniotomy and complete tumor excision. Histopathological examination confirmed a WHO Grade I meningioma with mixed meningothelial and angiomatous patterns.

Conclusion: This case highlights a potential association between prolonged DMPA exposure and intracranial meningioma. Early recognition of neurological symptoms, timely neuroimaging evaluation, and appropriate surgical management are essential to optimize outcomes. Discontinuation of hormonal exposure should also be considered in patients with hormone-sensitive meningiomas.

Keyword: Meningioma; Hormonal contraception; Progesterone, Brain tumor

Introduction

Meningiomas are the most prevalent type of primary neoplasia in the central nervous system, accounting for about 33% of all primary tumors and about 50% of benign brain tumors. Meningiomas arise in the meninges, the tissue covering the brain and spine. Meningiomas are classified into three grades per the World Health Organization (WHO) classification of tumors of the central nervous system. Most meningiomas are grade I and benign, while a small percentage are more malignant (1-3%). The five-year survival rate in patients with malignant meningiomas is reported from 32% to 64%. Many factors have been proposed as risk factors for meningiomas, including genetic syndromes such as neurofibromatosis type 2, radiation exposure, use of hormone therapy, and family history of meningiomas[1].

Meningiomas comprise nearly one third of all primary central nervous system tumors, with incidence rates reported to be between 1.3 and 7.8 per 100,000 person-years. Women are diagnosed more often than men, with a reported female-to-male ratio of approximately 2:1. The incidence of meningiomas appears to increase with age; the greatest incidence occurs in the sixth and seventh decades of life. Over the span of the last few decades worldwide, the incidence of meningiomas has been steadily increasing, a phenomenon likely attributable to aging population demographics; enhanced availability and accuracy of diagnostic imaging, particularly magnetic resonance imaging (MRI) scans; and advancements in accurate tumor registration. Risk factors include prior exposure to ionizing radiation; genetic predisposition, including NF2 mutations; family history; and reproductive or hormonal factors[2].

Most meningiomas arise within the intracranial compartment, commonly along the parasagittal region, cerebral convexity, or sphenoid wing, with other less frequent sites

including the olfactory groove, tuberculum sellae, and spinal meninges. The clinical presentation largely depends on the tumor's size, growth rate, and anatomical location. As the lesion enlarges, it can compress adjacent brain tissue or cranial nerves, leading to progressive neurological deficits such as headaches, seizures, or focal impairments. Tumors located at the skull base, particularly near the sphenoid wing or parasellar region, often cause visual disturbances or cranial nerve palsies due to their close relationship with vital neurovascular structures and the limited intracranial space[3].

Beyond genetic predisposition, hormonal factors are believed to influence the development and progression of meningiomas. These tumors frequently express progesterone receptors, and occasionally estrogen or androgen receptors, suggesting that hormonal activity may contribute to their growth. This hormonal sensitivity may explain the higher incidence of meningiomas in women and their tendency to enlarge during periods of hormonal fluctuation, such as pregnancy, the luteal phase of the menstrual cycle, or hormone replacement therapy. Some studies have also reported an association between long-term use of hormonal contraceptives and an increased risk of meningioma formation or enlargement. Meningiomas are generally slow-growing, often remaining silent for years before producing symptoms. However, under hormonal influence, the rate of tumor growth may accelerate. leading to earlier clinical manifestation in individuals exposed to increased or prolonged hormonal stimulation[3].

Presentation of meningiomas is highly variable depending on tumor size, location, and the degree of compression on adjacent neural structures. The vast majority of cases are asymptomatic or present with vague complaints similar to headaches or nonspecific focal neurologic deficits, such as weakness of limb(s), sensory changes, or seizures. Tumors located at the skull base or near cranial nerve(s) can lead to visual complaints, diplopia, anosmia, or other cranial nerve dysfunction. Spinal meningiomas tend to present with more localized back pain, radiculopathy, progressive motor weakness, gait disturbance, or sphincter dysfunction. Larger tumors or tumors associated with peritumoral edema can lead to signs of increased intracranial pressure such as nausea, vomiting, and papilledema[3].

The diagnosis of meningioma is primarily based on modern neuroimaging, with contrast-enhanced MRI serving as the preferred tool. Typical radiological hallmarks include a sharply circumscribed extra-axial lesion with dural attachment, uniform contrast enhancement, and occasionally the presence of a "dural tail." CT imaging is complementary, particularly valuable in detecting calcification and assessing hyperostosis of the skull. More advanced imaging methods, such as diffusion and perfusion MRI or somatostatin receptor

PET, may provide additional information regarding tumor grading, brain invasion, or treatment response. Nevertheless, a conclusive diagnosis requires histopathological confirmation obtained from surgical tissue samples, often supplemented by immunohistochemistry, including proliferation markers such as Ki-67[4].

Case Illustration

A 44-year-old Indonesian woman presented to the emergency department with the chief complaint of a severe, unbearable headache causing her to cry, which had persisted for three hours prior to admission. The headache, described as a throbbing pain, had been present intermittently since 2020, with episodes becoming more frequent and intense since 2023. The patient reported noticing a lump on the right side of her head for the first time in 2020, which gradually increased in size over the next three years and was accompanied by recurrent headaches. While experiencing headache episodes, she regularly noted nausea without vomiting. Since 2023, she noted blurred vision; however, she stated that she had not experienced hearing problems or seizures. For the past two months, she reported weakness in the soles of her feet, and she experienced frequent episodes of dizziness along with elevated blood pressure despite not having a history of hypertension. Her headache typically arose or became worse after engaging in long periods of activity or when she was on her mobile phone for multiple hours.

The patient denied a history of head tumors, epilepsy, hypertension, diabetes mellitus, or vertigo but did have an appendectomy in 2020 without complication. Approximately one month prior to this hospitalization, the patient presented to the neurosurgery outpatient clinic with similar complaints. A head CT scan with contrast was ordered after that visit, and meningioma was noted in the finding, with a recommendation for surgical treatment (Figure 1). However, the patient postponed the procedure as she was not yet ready and planned to return for follow-up the following month. During the past month, she had visited the Emergency Department (ED) three times with the same complaint. Each time, her symptoms temporarily improved after receiving medication but later recurred. To alleviate the pain, she frequently applied warm compresses and gentle massage to her head. Following these recurrent episodes, the patient eventually agreed to undergo surgical treatment.

From the neurosurgery clinic, she was prescribed betahistine 6 mg, citicoline 500 mg, and novagesic forte 650 mg, which provided only temporary relief. She also reported seeking treatment at another hospital between 2024 and 2025, where she underwent radiotherapy twice weekly for one year, targeting her neck, back, and posterior head region. However,

there was no significant improvement, prompting her to change hospitals for further management.

There was no family history of similar symptoms, brain tumors, or malignancy. Further history revealed long-term use of three-month injectable hormonal contraception (depot medroxyprogesterone acetate). The patient is a mother of four children, born in 2003, 2012, 2014, and 2021. The patient had used this contraceptive intermittently across three periods: from 2003 to 2011, again from 2014 to 2020, and most recently from 2021 to August 2025. Throughout her contraceptive use, she experienced amenorrhea and no adverse effects. Prolonged exposure to progestogen-based hormonal contraception is considered a potential risk factor for meningioma development, as several epidemiological studies have demonstrated an association between long-term progestogen exposure and an increased incidence of intracranial meningioma[1,2].

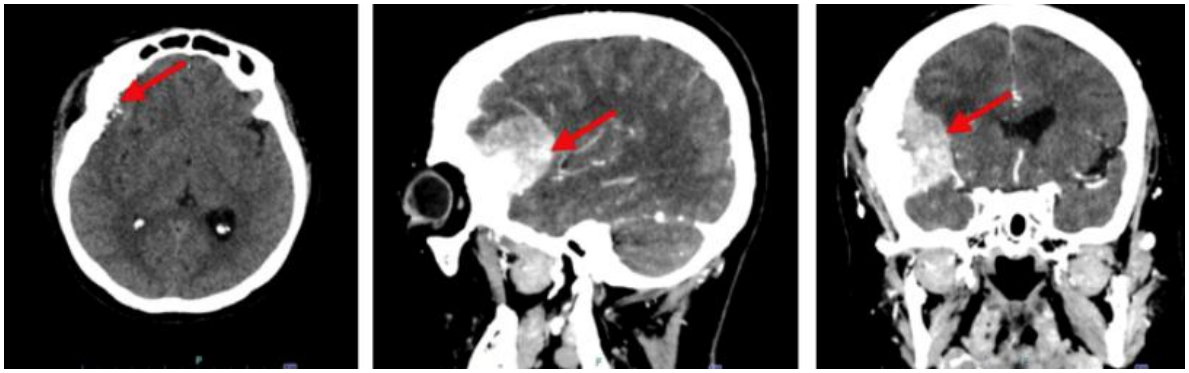

Figure 1. Cervical CT scan with contrast

Neuroimaging was performed to confirm the suspected intracranial lesion and to better evaluate its characteristics and extent. A contrast-enhanced head CT scan, obtained in axial, coronal, and sagittal planes, demonstrated an isodense extra-axial mass in the right frontotemporal region, measuring approximately 31 × 41 × 63 mm. The mass appeared well-circumscribed, with a broad-based attachment to the dura and focal hyperostosis of the adjacent skull bone, both of which are typical features of meningioma. The lesion showed a pre-contrast density of 32 Hounsfield Units (HU) and enhanced to 64 HU after contrast administration, indicating strong, homogeneous enhancement consistent with a solid and highly vascular tumor.

Associated findings included vasogenic edema in the right frontal white matter, resulting in mild compression of the right lateral ventricle and a slight midline shift toward the left. These alterations indicate a significant mass effect on neighboring brain tissue. The

delineation between cortical and medullary regions remained intact, suggesting no deep parenchymal invasion. The brainstem, cerebellum, and retrobulbar areas were considered normal, and there did not appear to be any erosion or destruction involving the bony structures of the skull. Very much suggestive of a right frontotemporal meningioma.

In summary, these imaging characteristics, including an extra-axial, well-circumscribed mass with markedly homogeneous enhancement, dural attachment, skull hyperostosis, and perilesional edema, are very suggestive of a right frontotemporal meningioma. In conclusion, the radiological findings are highly in favor of the diagnosis of a high-grade meningioma, having a characteristic imaging appearance and mass effect closely correlating with the patient's progressive neurological symptoms and clinical course. Chest X-ray findings show no pulmonary abnormalities but indicate cardiomegaly and elongation of the aorta, with no sign of active involvement from pulmonary tuberculosis (Figure 2).

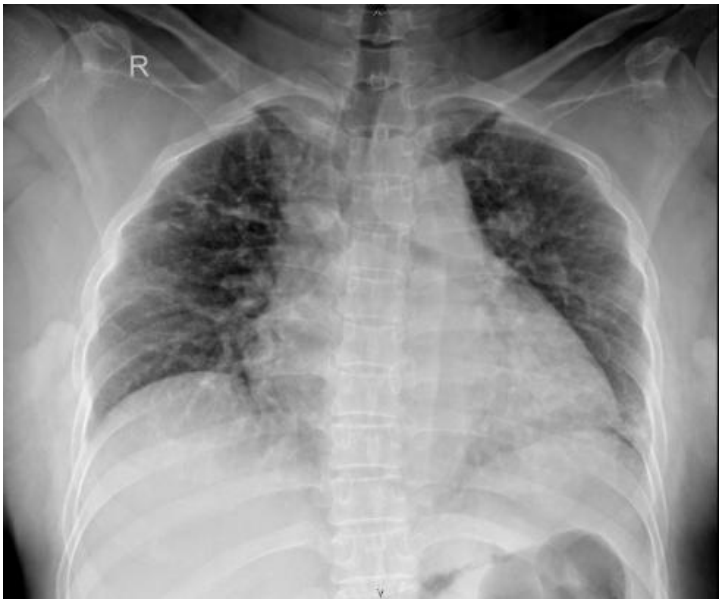

Figure 2. Chest X-ray (September 21, 2025)

On September 22, 2025, a craniotomy was performed for the excision of the tumor (Figure 3). The top of the scalp was incised and a bone flap was elevated in a routine manner to create an operative field where a well-defined intracranial mass was found. Tumor excision was performed under 8× loupe magnification to provide an adequate view of tumor margins. The dura was intact with no evidence of tumor invasion. A small portion of the tumor was removed and submitted for histopathologic characteristics and confirmation of diagnosis. Resection was continued until the entire tumor had been completely excised. After tumor excision, the surrounding bone surface was drilled down to healthy bone margins to

ensure clearance of any remaining pathological tissue. Bleeding was controlled appropriately, and the wound was closed in anatomical layers. The histopathological examination demonstrated features consistent with a *meningioma*, showing mixed meningothelial and angiomatous patterns (WHO Grade 1), indicating a benign lesion with slow growth potential.

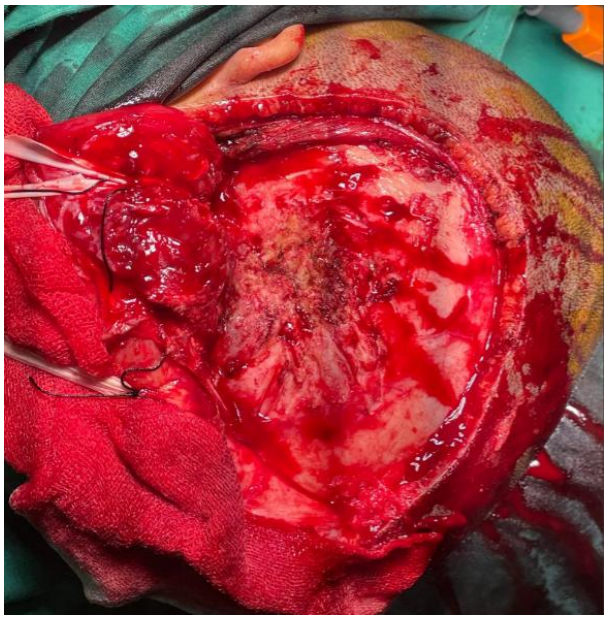

Figure 3. Craniotomy meningioma remover (September 22, 2025)

Discussion

Meningioma is a slow-growing, extra-axial tumor that originates from arachnoid cap cells in the meninges, representing approximately 30-40% of all primary intracranial tumors[5]. Clinical complaints are usually dependent on tumor location, size, and inflammatory mass effect of adjacent neural structures[6]. In our case, the patient reported chronic headache in a throbbing nature that had progressively worsened since 2022, as well as nausea and intermittent visual disturbance. These symptoms correlate with the most common clinical presentation of intracranial meningiomas, including headache, visual impairment, seizures, and focal neurologic deficit due to local compression[7]. Progressive enlargement of a right-sided scalp mass, development of visual blurring, and lower extremity weakness suggests a mass creating elevated intracranial pressure or local cortical compression.

Meningiomas are typically benign (WHO Grade I); however, even benign tumors can be associated with high morbidity when in close proximity to key neurovascular structures[8]. Headache in meningioma is often due to mass effect (either related to the tumor's expansion

that stretches sensory dura or compresses pain-sensitive structures). Visual symptoms, similar to that experienced by this patient, are common in tumors of the sphenoid wing or parasellar regions[9]. The absence of seizure activity may suggest a lesion distant from the motor cortex. Progressive lower limb weakness, although less common, may indicate chronic mass effect on the parasagittal region involving the motor area for lower extremities or compression of the falx cerebri region[10].

The histopathological examination demonstrated features consistent with a meningioma, showing mixed meningothelial and angiomatous patterns (WHO Grade I), indicating a benign lesion with slow growth potential. This finding aligns with the clinical history of long-term exposure to exogenous progesterone through three-monthly depot medroxyprogesterone acetate (DMPA) injections. Progestogen-based hormonal contraceptives, such as DMPA, have been shown to stimulate tumor cell proliferation through activation of progesterone receptors commonly expressed in meningioma tissues. In this patient, continuous hormonal exposure for over 15 years may have contributed to tumor initiation or accelerated its growth, as supported by several epidemiological and pathological studies linking prolonged progesterone stimulation with meningioma development. The benign histological pattern and slow-growing behavior observed in this case are consistent with hormonally influenced meningiomas, which often stabilize or regress following discontinuation of exogenous hormone therapy.

According to the World Health Organization (WHO) 2021 classification, meningiomas are graded into three categories based on histopathological and molecular features. Grade I (Benign): Represents 80–85% of all meningiomas. These tumors exhibit low mitotic activity (<4 mitoses per 10 high-power fields) and lack brain invasion. Common subtypes include meningothelial, fibrous, and transitional meningioma. Grade II (Atypical): Characterized by higher mitotic activity (4–19 mitoses per 10 HPF), focal brain invasion, or at least three of five specific histologic features (increased cellularity, prominent nucleoli, patternless growth, small cell change, or spontaneous necrosis). These tumors account for 15–18% of cases and show a higher risk of recurrence. Grade III (Anaplastic/Malignant): Defined by >20 mitoses per 10 HPF or frank malignant morphology. These account for about 2–3% of cases and are associated with aggressive behavior, local invasion, and poor prognosis[10,11].

Although this patient's histopathological grade was not yet determined, the chronic and progressive course without metastasis is consistent with a WHO Grade I meningioma. Long-term hormonal stimulation, particularly from progestogen exposure, has been linked

to tumor proliferation and may contribute to progression from benign to atypical histology[12].

Several environmental, hormonal, and genetic factors contribute to meningioma development. Among these, hormonal exposure, particularly prolonged use of progestogen-based contraceptives, has been increasingly recognized as a major risk factor[11]. The patient's history of long-term use of depot medroxyprogesterone acetate (DMPA) injections for more than 15 years cumulatively aligns with findings from recent studies showing that chronic exposure to synthetic progestogens increases meningioma risk, particularly at the skull base and parasagittal regions[12].

The hormone progesterone is believed to stimulate meningioma growth through activation of progesterone receptors (PR) expressed in up to 70–90% of meningioma cells[13]. Studies have shown that long-term use of high-dose progestins such as cyproterone acetate, chlormadinone acetate, and DMPA is associated with an elevated risk of intracranial meningioma that may regress after cessation of hormonal exposure. Tumor regression following hormonal discontinuation has been reported predominantly in WHO Grade I meningiomas, particularly those strongly expressing progesterone receptors and associated with prolonged exposure to exogenous progestogens. These tumor are generally slow-growing and hormonally responsive, allowing stabilization or reduction in tumor volume after withdrawal of hormonal stimulation. In contrast, spontaneous regression is less commonly observed in atypical (WHO Grade II) or anaplastic (WHO Grade III) meningiomas, which are characterized by more aggressive biological behaviour, higher proliferative activity, and reduced dependence on hormonal signaling. Therefore, hormonal withdrawal is most likely to be beneficial in benign, hormone-sensitive meningiomas and should be considered as part of the management strategy in appropriately selected patients[11,14]. The absence of family history of brain tumors or malignancy in this patient further supports the hypothesis that exogenous hormonal exposure was a significant contributing factor.

Diagnosis of meningioma is established through neuroimaging and histopathological confirmation. Contrast-enhanced MRI remains the gold standard, revealing a well-circumscribed, extra-axial mass with homogenous enhancement and a dural tail sign, typical features of meningioma[15]. In this patient, CT-scan imaging had previously demonstrated a right-sided intracranial mass consistent with meningioma. MRI could further delineate tumor extent, dural attachment, and potential invasion into adjacent structures, providing crucial information for surgical planning[16].

Laboratory investigations are usually nonspecific but may be useful for ruling out

secondary causes of headache or metabolic abnormalities. Differential diagnoses for this presentation include metastatic brain lesions, gliomas, and pituitary adenomas, which can mimic meningioma radiologically[17]. Clinical correlation with patient history and imaging patterns remains essential.

The cornerstone of meningioma management is surgical resection, which aims for complete tumor removal and dural excision when feasible[18]. The extent of resection directly correlates with recurrence rates, and the Simpson grading system remains a widely used predictor of prognosis[19]. However, in patients who decline surgery or have contraindications due to tumor location or comorbidities, radiotherapy or stereotactic radiosurgery (SRS) serves as an effective alternative[20].

In this case, the patient underwent radiotherapy twice weekly for one year, directed to the posterior head, neck, and back regions. This regimen aligns with current practice for partially resected or unresectable meningiomas. However, the absence of significant clinical improvement suggests either a radioresistant tumor subtype or inadequate dosing parameters. Medical therapy with citicoline, betahistine, and analgesics was prescribed for symptomatic management, though such treatments only provide temporary relief without addressing tumor growth. Future management should include re-evaluation with MRI and reconsideration of surgical intervention depending on the tumor's anatomical accessibility and the patient's functional status[21].

If untreated or inadequately managed, meningiomas can cause several neurological and systemic complications. Chronic intracranial hypertension is common due to space-occupying mass effect, leading to persistent headache, papilledema, and potential optic atrophy[22]. Compression of cranial nerves may result in visual loss, diplopia, facial numbness, or hearing deficits, depending on the tumor's location[23]. Large or recurrent meningiomas can cause seizures, motor weakness, or cognitive impairment due to cortical compression. In rare instances, malignant transformation can occur, particularly in hormonally influenced or irradiated tumors[24].

In this patient, symptoms such as progressive visual blurring, headache, and limb weakness likely represent neurological compromise from chronic mass effect. Prolonged untreated cases risk permanent neurological disability, underscoring the need for definitive therapy and long-term monitoring.

The prognosis for meningioma is generally favorable, with a 10-year survival rate exceeding 80–90% for WHO Grade I tumors after total surgical resection[25]. However, recurrence remains a concern, particularly for tumors with incomplete resection or hormonal

dependence. Clinical and radiological follow-up every 6–12 months is recommended to monitor for recurrence or growth[27]. From a preventive perspective, women receiving long-term progesterone or progestogen-based therapies should undergo periodic clinical assessment and regular re-evaluation of the need for continued hormonal treatment. Recent epidemiological evidence suggests that the risk of intracranial meningioma increases with prolonged exposure to certain progestogens, including medroxyprogesterone acetate (DMPA), particularly after extended use exceeding one year and with increasing cumulative exposure. However, a universally accepted maximum safe duration of progesterone exposure has not yet been established. Therefore, clinicians should prescribe the lowest effective duration necessary and consider alternative non-hormonal contraceptive methods when appropriate. Patients should also be educated regarding early warning symptoms of meningioma, such as persistent headaches, visual disturbances, seizures, hearing impairment, or focal neurological deficits, which warrant prompt neuroimaging evaluation. In patients diagnosed with meningioma, discontinuation of exogenous progestogen therapy is recommended because tumor stabilization or regression has been reported following withdrawal of hormonal exposure[28-29].

Discontinuation of hormonal contraception is critical in hormonally driven cases. Several reports have documented spontaneous regression or stabilization of meningioma after withdrawal of exogenous progesterone therapy, supporting a hormone-dependent mechanism[27]. Thus, in this patient, cessation of DMPA, combined with re-evaluation for surgical candidacy, may offer the best therapeutic outcome.

Conclusion

This case highlights the significance of early recognition and comprehensive management of meningioma to prevent progressive neurological deficits and irreversible disability. Although meningiomas are often benign and slow-growing, prolonged hormonal exposure, such as long-term depot medroxyprogesterone acetate (DMPA) use, may contribute to tumor progression. Accurate diagnosis with MRI and timely surgical resection remain the cornerstone of therapy, while radiotherapy or radiosurgery provides effective alternatives in inoperable cases. The prognosis for WHO Grade I tumors is generally favorable, but recurrence risk underscores the importance of discontinuing exogenous hormonal therapy and maintaining long-term clinical and radiological follow-up.

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