Coexistence of meningioma and other intracranial benign tumors in non-neurofibromatosis type 2 patients: A case report and review of literature

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Abstract

BACKGROUND
The coexistence of meningioma and other intracranial primary benign tumors is rare, especially in non-neurofibromatosis type 2, and there is limited guidance for the management of such patients. Here, we report a series of 5 patients with concomitant meningioma and other intracranial benign tumors, including subependymoma and pituitary adenoma.

CASE SUMMARY
Five non-neurofibromatosis type 2 patients with simultaneous occurrence of meningioma and other intracranial benign tumors were retrospectively reviewed. The patients had no history of previous irradiation. The clinical features, pre- and postoperative imaging, surgical procedure and pathological findings were extracted from electronic medical records. There were 4 female patients (80%) and 1 male patient (20%). The mean age was 42.8 years (range: 29-52 years). The coexisting tumors included subependymoma in 1 case (20%) and pituitary adenoma in 4 cases (80%). The most common clinical symptom was headache (3/5, 60%). Four patients (80%) underwent craniotomy. One patient (20%) underwent transsphenoidal surgery followed by transcranial operation. All tumor diagnoses were confirmed by histopathological examination. The mean follow-up was
38.8 mo (range: 23-96 mo), and all 5 patients were in a stable condition at the last follow-up.

CONCLUSION
The simultaneous occurrence of meningioma and other intracranial benign tumors is a rare clinical event. Histological examination is necessary for the accurate diagnosis. Neurosurgeons should select the appropriate surgical strategy according to the clinical features of each patient, which may provide a more favorable prognosis for individual patients.

INTRODUCTION
Meningioma is the most frequent intracranial benign tumor, accounting for 37.1% of tumors overall[1]. However, the concomitant occurrence of meningioma and other intracranial benign tumors is extremely rare[2]. Only a few coexisting meningioma and other intracranial benign tumor cases have been reported in previous publications, such as pituitary adenoma[3,4], craniopharyngioma[5] and vestibular schwannoma[6-9]. It is well-recognized that the occurrence of multiple nervous system tumors in the same patient is a characteristic of neurofibromatosis type 2 (NF2)[8]. Patients are diagnosed with NF2 when they meet the Manchester criteria (Supplementary Table 1)[10,11]. However, clinical and pathological features of non-NF2 patients with collision-tumors remain unclear. Here we report the clinical presentation, radiological features, surgical management and outcomes in our series of 5 non-NF2 patients with concomitant meningioma and other intracranial benign tumors, including one subependymoma, which was reported for the first time, and four pituitary adenomas. In addition, we also reviewed the available literature.

CASE PRESENTATION
Chief complaints
Case 1: A 45-year-old female patient presented with a sudden night epileptic seizure 10 d prior.
Case 2: A 40-year-old female patient presented with dizziness and headache for 1 mo.
Case 3: A 48-year-old male patient presented with frontal and bilateral temporal headache for 1 mo.
Case 4: A 52-year-old female patient presented with left progressive blurred vision for 6 mo and headaches for 2 mo.
Case 5: A 29-year-old female patient presented with menstrual disorder for 2 years and intermittent headache for 3 mo.

History of present illness
Case 1: The patient suffered a sudden epileptic seizure 10 d ago at night, which lasted for a few minutes.
Case 2: The patient had dizziness and headaches for 1 mo.
Case 3: The patient had a headache for 1 mo. The headache took place at night and affected his sleep.
Case 4: The patient had progressive vision loss in the left eye for 6 mo. She suffered from headache from 2 mo.
Case 5: The patient had menstrual disorder for 2 years. She developed amenorrhea and intermittent headaches 3 mo ago.

History of past illness
All patients had no history of specific illnesses.

Personal and family history
All patients had no special personal and family history.

Physical examination
Case 1, 2, 3 and 5: Neurological examination of the patient found no positive signs.
Case 4: There was only slight sensation in her left eye when she was admitted.

Laboratory examinations
Case 1, 3 and 4: Preoperative endocrine examination showed no abnormal changes.
Case 2: Endocrine examination indicated that prolactin levels were moderately elevated (61.19 ng/mL).
Case 5: Preoperative endocrine examination showed that prolactin levels were slightly elevated (59.17 ng/mL).

Imaging examinations
Case 1: Brain computed tomography at the local hospital suggested an intracranial space-occupying lesion in the left parietal lobe. Brain contrast-enhanced magnetic resonance imaging (MRI) showed a well-circumscribed mass (3.6 cm × 2.7 cm × 2.7 cm) in the left parietal parafalcine and a mass (1.9 cm × 1.2 cm × 1.1 cm) in the left lateral ventricle.
Case 2: MRI showed a mass (3.0 cm × 2.3 cm × 2.5 cm) in the right middle cranial fossa and a mass (0.5 cm × 0.5 cm × 0.5 cm) in the sellar region.
Case 3: Brain MRI showed lesions located in the planum sphenoidale and sellar regions.
Case 4: There was a well-circumscribed mass (3.5 cm × 3.2 cm × 2.7 cm) surrounded with brain edema in the left sphenoid ridge and a mass (2.8 cm × 2.5 cm × 2.5 cm) encasing the internal carotid artery in the sellar and suprasellar regions, as determined by radiological examination.
Case 5: MRI showed a mass (5.7 cm × 3.3 cm) encasing the internal carotid artery located in the left petrodival region and a mass (maximum diameter 1.0 cm) located in the sellar region.

Final Diagnosis
Case 1: Postoperative histopathological examination showed meningioma and subependymoma (Figure 1).
**Case 2:** Histopathological examination showed a meningioma and non-functioning pituitary adenoma (Figure 2).

**Case 3:** Histopathological examination showed a meningioma and non-functioning pituitary adenoma (Figure 3).

**Case 4:** Histopathological examination showed a meningioma and non-functioning pituitary adenoma (Figure 4).

**Case 5:** Postoperative histopathological examination showed a meningioma and non-functioning pituitary adenoma (Figure 5).

**TREATMENT**

**Case 1:** After this discovery, she underwent craniotomy, and the two neoplasms were removed in one session.

**Case 2:** First, endonasal transsphenoidal surgery was performed for resection of the intrasellar mass. Then, the right middle cranial fossa mass was removed (Simpson grade II) by transcranial surgery.

**Case 3:** The patient underwent transcranial resection for the two tumors through the right transtemporal approach.

**Case 4:** A single transcranial procedure was performed for removal of the sphenoid ridge mass (Simpson grade II) and sellar region mass. The pituitary tumor underwent subtotal resection.

**Case 5:** The patient underwent craniotomy for the two tumors. The petroclival tumor was hard in consistency and rich in blood supply with internal carotid artery encasement. The tumor was also close to cranial nerves II-VI and compressed the brain stem. A subtotal resection was performed (Simpson grade IV) for the petroclival tumor. Then the intrasellar tumor was removed.

**OUTCOME AND FOLLOW-UP**

Between January 2011 and January 2019, 2922 consecutive patients were diagnosed with meningioma in our institution. There were 5 meningioma patients (~0.17%) with different
intracranial benign tumors, and none of them were diagnosed with NF2. They had no history of previous irradiation. Clinical data were obtained and analyzed through retrospective medical history reviews, neuroimaging information, histopathological examination and follow-up. This retrospective study was approved by the institutional review board. Written consent was obtained from each patient for the use of their clinical data for research.

There were 4 female patients (80%) and 1 male patient (20%) with concomitant meningioma and other intracranial benign tumors. The mean age was 42.8 years (range: 29-79 years). The coexisting tumors included subependymoma in 1 case (20%) and pituitary adenoma in 4 cases (80%, four non-functional pituitary adenomas). The mean follow-up time was 38.8 mo (range: 23-96 mo). The clinical information of these cases is summarized in Table 1.

Case 1: The patient was followed up for 27 mo with no evidence of recurrent disease.
Case 2: The patient was followed up for 24 mo, and she was in good health.
Case 3: He was treated by hormone replacement therapy because of postoperative hypopituitarism. The patient was followed up for 23 mo. He took LT4 regularly and is currently in good health.
Case 4: Four months after the surgery, MRI reexamination revealed the growth of residual pituitary tumor. Subsequently, she underwent radiotherapy. The patient was in good health at the 24-mo follow-up.
Case 5: As of this writing, the patient had been in stable condition for 96 mo.

DISCUSSION
The coexistence of meningioma and other intracranial benign tumors is a rare phenomenon that nevertheless deserves our attention. The most frequent coexistence of simultaneous benign tumors is pituitary adenoma with meningioma and schwannoma with meningioma [12]. The co-occurrence of meningioma and schwannoma is more likely to occur in patients with NF2, which has been well described previously. However, the clinical characteristics of non-NF2 patients with coexisting tumors are largely unknown.
To the best of our knowledge, we present the first case of concomitant meningioma and intracranial subependymoma. Subependymomas are rare, benign, slow-growing tumors and represent only 0.2% to 0.7% of intracranial tumors[^13-16]. These tumors most often arise in the fourth ventricle (50%-60%) and the lateral ventricles (30%-40%)[^14,15]. Most patients present with hydrocephalus as a consequence of ventricular obstruction or less commonly focal neurological dysfunction and seizures caused by mass effects[^14,17]. The main purpose of surgery is to maximize the removal of the tumor[^18]. In the published case series, there were satisfactory postoperative mortality and morbidity rates from supratentorial subependymomas[^13-18]. In our case 1, resection of the left parietal meningioma and supratentorial subependymoma was accomplished via a single procedure. In a recent long-term outcome study of subependymoma, no patients exhibited a deterioration of performance status or tumor recurrence at medium to long-term follow-up[^16]. As with the single subependymoma, the patient in our case also had a good prognosis after operation, and there was no evidence of recurrence at the last follow-up. Although the extremely rare coexistence of meningioma and subependymoma in our case may be an incidental event, the intrinsic relationship of these two tumors might require future investigation.

Until now, our understanding of the coexistence of meningioma and pituitary adenoma is based on occasional case reports[^2-4,12,19-34]. We reviewed all the reported cases that were available to us, and the information was summarized in Table 2. The mean age of patients was 54.6 years (range: 26-82 years), and there were 39 women and 14 men among the published cases (female:male = 2.79:1). Our 4 cases also showed a female tendency (female:male = 3:1), and the mean age was 42.8 years (range: 29-52 years). A preference for parasellar, suprasellar and sphenoid ridge localization was found with 27 reported cases (50.94%)[^2-4,20-23,25,26,30,32-37,42,47-49,51,54]. Consistently, the meningioma of our cases was in the petroclival, sellar and sphenoid wing regions.

The most common type of pituitary adenoma with coexisting meningioma among reported cases was a non-secreting tumor (21/53, 39.62%) followed by growth hormone-producing tumor (17/53, 32.08%). In this paper, all 4 cases were non-functioning pituitary
adenoma, representing the most common type. Although prolactinomas are the most frequent pituitary adenomas in general, the higher prevalence of acromegaly in patients with coexisting meningioma has led some authors to propose an association between growth hormone-producing adenomas and meningioma\textsuperscript{[29,34,40,42,49]}. They suggested that persistently elevated growth hormone might stimulate arachnoid cap cells to play a role in the development of meningioma\textsuperscript{[24,39,51]}. A recent study suggested that patients with acromegaly were at increased risk of meningioma\textsuperscript{[55]}.

Some researchers have tried to explore the association between meningiomas and pituitary tumors. The early reports suggested that this phenomenon was related to history of irradiation for pituitary tumors\textsuperscript{[2]}. However, many cases with no history of radiotherapy were reported as well\textsuperscript{[24,27,29,48,49]}, including our cases. Therefore, Curto et al\textsuperscript{[40]} suggested that the coexistence of meningioma and pituitary adenoma was a coincidental phenomenon. However, there was a higher proportion of involvement of chromosome 14 and 22 in estrogen receptor positive de novo meningiomas\textsuperscript{[56]}. Similar genetic changes shared by two unrelated tumors found on the same chromosome may explain their coexistence\textsuperscript{[12]}.

Moreover, due to the indolence of benign tumors, a significant portion of this coexisting tumor population may remain undiagnosed\textsuperscript{[12]}. MRI is useful for the diagnosis of the coexistence of two intracranial tumors but has limited significance for adjacent pituitary adenoma and meningioma\textsuperscript{[4]}. Histological results are necessary for diagnosis because other preoperative findings cannot support accurate diagnosis\textsuperscript{[54]}. For example, some reported cases were coexisting sellar meningioma and pituitary adenoma\textsuperscript{[4,42,47-49,54]}. Because of the close location of the two tumors, it is difficult to produce an accurate diagnosis by preoperative imaging, as in our case 3. It deserves special attention because the two different types of tumors were not definitely diagnosed before surgery but later when the pathologist’s results were obtained. The patient in case 3 developed hypopituitarism after the operation, and this complication was also reported in other similar cases\textsuperscript{[47,49]}.
Traditionally, the treatment of these two coexisting tumors required one craniotomy\textsuperscript{[30,31,33]} or two separate operations using two different approaches\textsuperscript{[2,32,35,39]}. Prevedello \textit{et al}\textsuperscript{[42]} performed a single endoscopic expanded endonasal approach in patients with coexisting tuberculum sellae meningiomas and pituitary adenoma. In our opinion, surgical strategies should be decided according to the characteristics of the coexisting tumors (e.g., location, size and adjacent neurovascular structures) and the clinical features of individual patients (e.g., symptoms and systemic conditions). Like the single pituitary adenoma, the patient with coexisting meningioma and pituitary adenoma had a favorable prognosis using the retrospective case reports. Postoperative endocrine reexamination should be periodically monitored at the endocrinology outpatient department, especially in patients with postoperative hormone imbalance after surgery. However, as this study is a retrospective analysis and the case numbers are limited, we cannot draw strong conclusions.

**CONCLUSION**

The simultaneous occurrence of meningioma and other intracranial benign tumors is a rare clinical event, and histological examination is necessary for their accurate diagnosis. Neurosurgeons should select the appropriate surgical strategy according to the clinical features of individual patients, which may provide the patient with a more favorable prognosis.
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