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Mirror, mirror on the wall, who's the fairest of them all? Atypical meningioma associated with multiple meningiomas

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Abstract: The incidence of multiple meningiomas (MMs) without stigmata of neurofibromatosis or family history of meningiomatosis is rare. MMs with atypical histology are even rarer, since most of them have benign histology. The authors report three cases of MMs, of which the symptomatic meningioma removed was an atypical meningioma (AM). We also review their possible pathogenesis and histopathology. Although there has not been established any MMs management and therapy strategy so far, our recommendation is to treat symptomatic and accessible lesions or growing tumours and also to prefer a conservative approach consisting of the imaging follow-up of asymptomatic lesions.

Key words: atypical meningioma, multiple meningiomas, meningiomatosis, WHO grade II meningiomas

Introduction

The first description of a multiple intracranial meningiomas dates back to 1889 and was made by Anfimov and Blumenau, who had found one large and four small tumours on an autopsy that they performed (1). Later on, in 1938, Harvey Cushing and Louise Eisenhardt explained the pathology of this entity and used the term "multiple meningiomas" to refer to the case of a patient who had "more than one meningioma and less than a diffusion of them" (7).

Meningiomas represent about one third of all primary brain tumours in adults (8, 11), with an incidence that has increased in recent years (10, 35). Majority of meningiomas are solitary (33), and MMs are defined as the presence of ≥ 2 spatially separated metachronous or synchronous meningiomas and represents up to 10% of all meningiomas (18, 20). They may be sporadic, radiation induced or familial, when they occur as type 2 neurofibromatosis or familial meningiomatosis (33).

Nowadays, the term MMs is used to

describe a condition in which a patient has the simultaneous or sequential appearance of two or more independent meningiomas, whether the tumours have the same pathologic subtypes or not (13). Nonetheless, Borovich et al. considers that MMs might be truly multiple when tumours from the same patient have different histological subtypes and multicentric when tumours have the same histology (3).

The pathophysiologic mechanisms underlying the occurrence of MMs have not yet been fully understood and thus two different hypotheses have been suggested so far (16, 34, 37). According to the first theory, multiple lesions originate from multicentric neoplastic foci and grow independently under the stimulation of a supposed tumour-producing factor. The second theory argues that a signal transforming event occurs and an original clone of neoplastic meningothelial cells spreads throughout the meninges or along the cerebrospinal fluid, leading to the formation of multiple clonally tumours (13, 16, 34, 37). Nevertheless, the tumour histology and dynamics of histopathological changes undergone by these multiple lesions in time have not been fully understood.

MMs also give rise to special treatment problems, the most important of which are as follows: which lesion is symptomatic, which lesion needs to be treated and what is the best therapeutic approach, what is the best treatment option and how should incidental MMs be managed? Due to these aspects, and also to their relative rarity, unclear aetiology and issues related to management strategy (29), MMs have raised the specialists' interest and they should constitute a priority in meningiomas treatment.

Methods

We followed the 3 years evolution of three patients with MMs who underwent surgery in the "Profesor Dr. Nicolae Oblu" Emergency Clinical Hospital of Iasi in 2010, 2012 and 2013, respectively. The inclusion criteria were adult patients (>18 years) with diagnosis of ≥ 2 separate meningiomas on MRI examination, one of which removed by surgery and diagnosed with AM (WHO grade II). The exclusion criteria were patients with type 2 neurofibromatosis, history of radiotherapy or familial types.

Results

The 3 cases of MMs with AM are shown in Table 1.

Case 1. A 64-year-old male patient has had slowly progressing vision disorders for about 2 years, which were examined by several ophthalmologists. He had decreased visual acuity in both eyes. The MRI examination reveals three MMs: one diaphragm sellae meningioma with a right parietal meningioma and a left parietal meningioma (Figure 1). Through a left fronto-temporal approach the meningioma of the diaphragm sellae was completely resected with good optic chiasma and pituitary stalk decompression (Figure 1). Postoperative ophthalmologic exam reveald that visual acuity of right eye was 6/6 and left eye - 1/500 BCVA. Also, the fundus examination revealed normally coloured and regular edges of the optic disc, C/D ratio 0.3 for right eye and 0.4 for left eye.

Case 2. A 65-year-old female patient is hospitalized for intracranial hypertension syndrome with cerebellar syndrome. The MRI

scan reveals the presence of a left transverse sinus meningioma (Figure 2. A) with an associated left parasagittal meningioma (Figure 3). The left transverse sinus meningioma was resected through a paramedian suboccipital approach (Figure 2. B.). Total 0.9 Gy irradiation is also performed, both for the remaining tumour on the left transverse sinus and for the left frontal parasagittal meningioma.

Case 3. A 73-year-old female patient was admitted for gait disorders that have set in 2 years before and have progressively worsened and for 1-month-old intracranial hypertension syndrome. The MRI scan reveals superior sagittal sinus meningiomatosis. The surgical procedure, performed through a parieto-occipital approach, consists of intracapsular tumour resection and partial sinus and infiltrated falx cerebri resection (Figure 4).

In all three patients, both the meningiomas resected and the other meningiomas were followed by yearly MRI scan. The follow-up revealed that, 3 years later, the MMs had not increased in size. As concerns AM recurrence, a 0.1 cm increase of left transverse sinus meningioma was noted in case 2 after one year.

TABLE I

Clinical data of patients with multiple meningiomas, of which one was atypical meningioma

	Case 1	Case 2	Case 3
Location (AM)	diaphragm sellae meningioma	left transverse sinus meningioma	parieto-occipital meningioma
Location of the other meningiomas	right parietal left parietal	left parasagittal	superior sagittal sinus meningiomatosis
Age, sex	M, 64 years	F, 65 years	F, 73 years
Symptoms	visual acuity decreased visual acuity in both eyes	intracranial hypertension syndrome, cerebellar syndrome	spastic paraparesis, intracranial hypertension syndrome
Ki - 67	4%	4.7%, with 7.59% on a field	6%

Discussion

Demography. As concerns the patients' demographic data, our findings are in accordance with other research shown in literature, which proves that the mean age of presentation with MMs is the 6th decade of life and it is the same as for patients with solitary meningioma (12, 13, 26, 27, 33).

MMs occur much more frequently in females than in males, and their predilection for the female gender is considerably higher than for the male gender, studies showing a significantly higher F: M ratio of 3.5:1 in MMs

(12, 13, 27). However, it is still unclear why female preponderance is much higher in MMs than in solitary meningiomas, yet according to a recent hypothesis, hormonal dependency may be higher, which may be accounted for by the stronger progesterone expression in these tumours compared with their solitary counterparts (13, 32, 33). Moreover, Tsermoulas et al. argue that genetic factors may enhance the potential for tumorigenesis in women (33). Our case series also exhibited a female predilection, as two of the three patients were women.

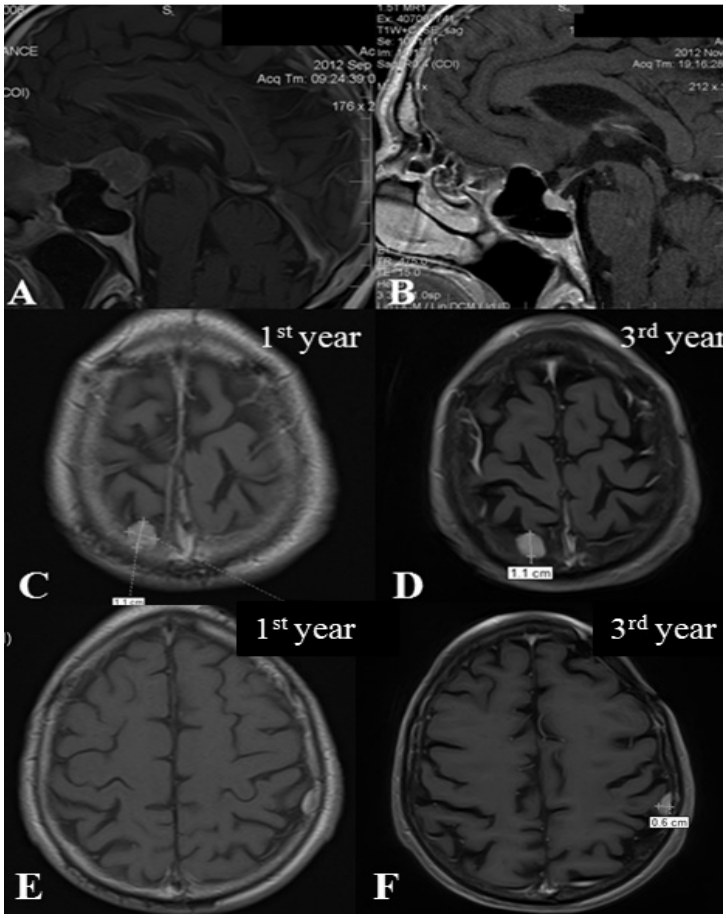

Figure 1 - (Case 1) Preoperative (A) and postoperative (B) sagittal T1-weighted images with contrast. Multiple meningiomas with one right parietal meningioma (C) and one left parietal meningioma (E)

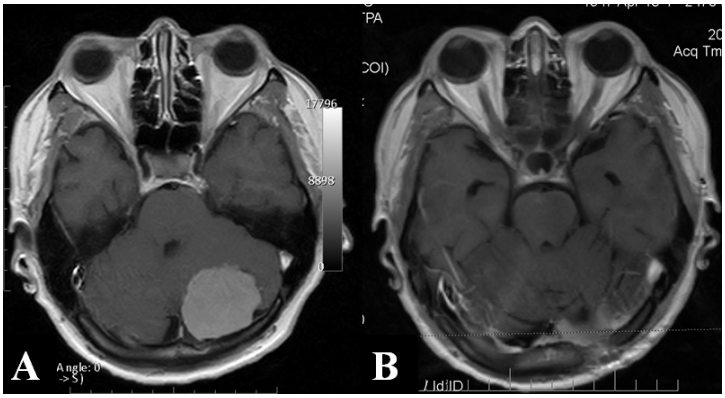

Figure 2 - (Case 2) Preoperative (A) and postoperative (B) axial T1-weighted images with contrast of a left transverse sinus meningioma

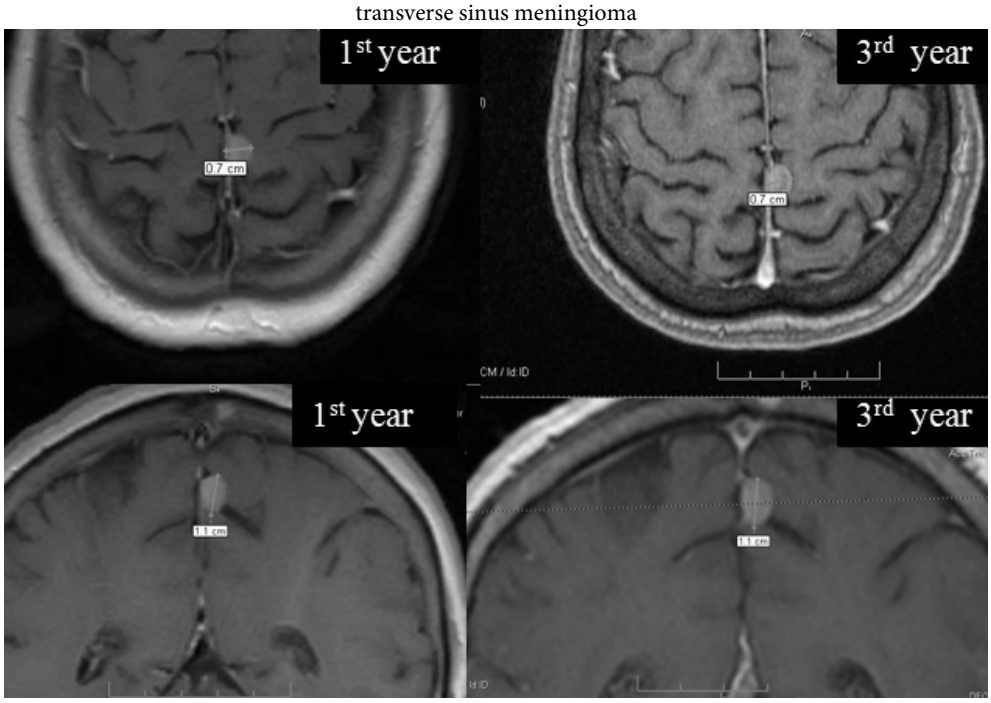

Figure 3 - (Case 2) Axial T1-weighted images with contrast showing a left parasagittal meningioma. No increase in size of meningioma was observed at 3 years of follow-up

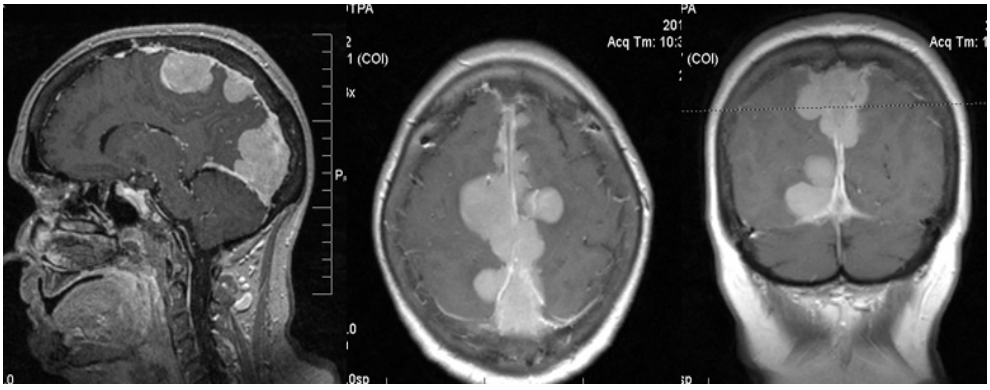

Figure 4 - (Case 3) T1-weighted images with contrast showing a superior sagittal sinus meningiomatosis

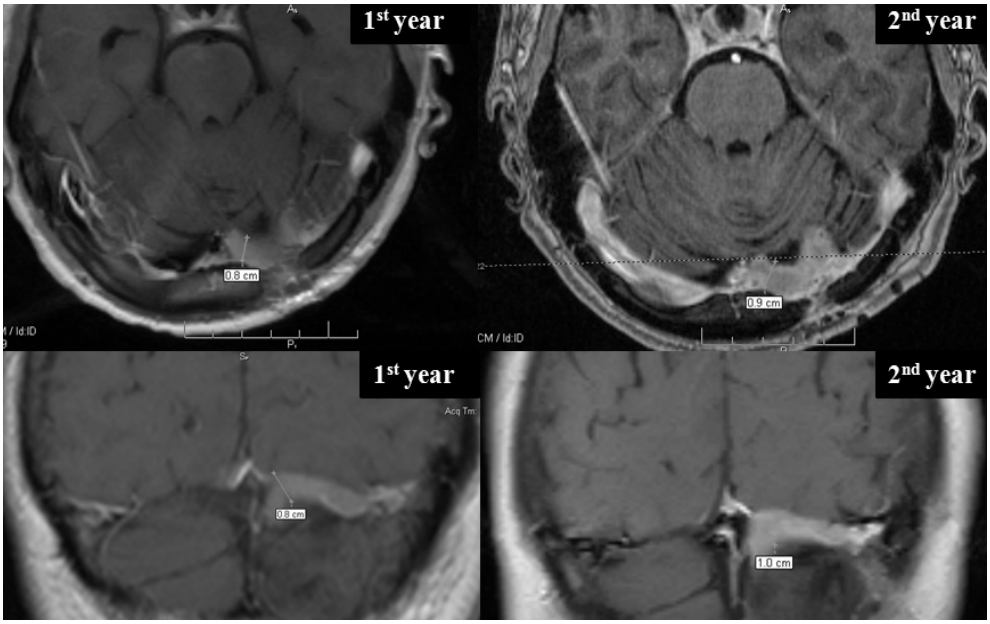

Figure 5 - (Case 2) T1-weighted images with contrast showing local recurrence of a left transverse sinus meningioma at 2 years follow-up

Symptomatology

The frequency of symptoms in MMs was proportional to the size of the tumours, the largest meningiomas being more asymptomatic, which was to be expected, since the mode of presentation of meningiomas is due to their mass effect. Skull base and midline meningiomas are more symptomatic than convexity meningiomas (33), and the most common location for meningiomas in asymptomatic patients has proven to be the convexity (22). In our case series, the symptoms were due to the mass effect on optic

chiasm and optic nerves (case 1), cerebellum (case 2) and motor cortex (case 3).

MMs distribution in the intracranial space. According to the literature, in MMs most patients have a major meningioma accompanied by one or several smaller meningiomas (12, 13), which was also true for two of our patients: the two large skull base meningiomas (the diaphragm sellae meningioma and the transverse sinus meningioma) were accompanied by convexity meningiomas (Figure 1. C and E) and parasagittal meningiomas (Figure 3). As concerns this association, in a study that included 39 patients with MMs, Huang et al. noted that in MMs a major meningioma is often accompanied by one or more smaller meningiomas (13). This was also reported by Domenicucci et al. that found that 11 of the 14 cases of MMs were composed of small and large meningiomas (12). Thus, Huang et al. argue that several different-sized tumours in the same MMs case would be an indication of the fact that meningiomas may develop at different times and that it is possible that an original major meningioma may disseminate to form multiple foci through the subarachnoid or subdural space (13).

In the same study, they noted that the main location of MMs is the cerebral convexity (12, 13). Huang et al. think that this predilection may be accounted for by the assumption that MMs develop from the major meningioma through the subarachnoid space, since disseminated meningioma cell tend to grow at the cerebral convexity by the circulation of the cerebrospinal fluid (13). This theory is also supported by the location of most of the MMs in the hemicranial space in some studies (4, 34).

Histopathology. In MMs, most meningiomas are benign (WHO grade I) and have uniform histology, the atypical or anaplastic subtypes being rare (15). Nevertheless, most meningiomas are benign on presentation. Thus, Turgot et al. removed 28 meningiomas from 8 patients, of which 14 were meningothelial (50%) (34). The predominance of the meningothelial subtype is also supported by Domenicucci et al.'s patient series (12). Other authors also reported predominantly benign histologies, yet different, like the fibrous and transitional subtypes (21) or the psammomatous type (27).

As concerns meningioma histology in the same patient, some studies have shown that the same patient may have meningiomas of different grade and different histological features (13, 19, 21). In a study that they recently published in 2017, Tsermoulas et al. also found that among patients who had more than 2 meningiomas removed, about 1 in 5 had tumours of different grades and most of them had different histological subtypes. From this point of view, some authors argue that these findings are evidence of the different origins of tumours from multiple foci and that their multiplicity is not the consequence of cell migration through the subarachnoid space (4, 19, 21). On the other hand, other authors have supported the theory of clonal spread from a single tumour (13, 16, 17, 24, 27, 30, 37). Some authors are of the opinion that both theories may apply in different cases and that further research on the genetics of MMs would clarify

the controversial standpoints on the histology and pathogenesis of these lesions (33).

Atypical meningiomas. As we have said before, most of the published series concluded that the vast majority of MMs cases described in literature have benign histology (27, 34), the atypical or anaplastic subtypes being rare (15). As far as the simultaneous occurrence of benign and atypical histological grades in sporadic MMs is concerned, Mocker et al. consider that this is extremely rare (19), as literature contains only few reports of benign histological types mixed with atypical types (4, 19, 23, 31).

Tumour recurrence is one of the main problems that have to be dealt with in AM management (8). Thus, Huang et al. found that four meningiomas in three patients were AM and all of these three patients had recurrence after the operation (13). In our three-patient series, only one AM exhibited tumour recurrence after 2 years (case 2). As concerns the other meningiomas, on which no surgery was performed, they did not grow in size during our 3 year follow-up (Figures 1 and 3). Our findings are in line with Wong et al., who did not note the tumour growth rates in patients with MMs to be higher than the growth rates of incidentally found solitary meningiomas (36).

Genetics of meningiomas. The most significant genetic abnormality in sporadic solitary meningiomas is the loss of heterozygosity on chromosome 22, which occurs in about 50% of patients. An early event of tumorigenesis in one third of these cases was found to be the somatic mutation of the NF2 gene (22q12.2) (5). On the other hand, familial MMs do not show mutation or loss of NF2 (28).

Some authors have described genetic alterations associated with meningioma progression and initiation, yet it is not yet possible to predict the rate of tumour growth or the probability of tumour recurrence (6). Thus, the genetics of tumour nodules for the appearance of MMs not yet fully known (19).

Management. Not all patients with MMs require treatment, and a challenge in the management of MMs may be the identification of the responsible tumour. In this algorithm, surgical removal remains the main form of treatment. Since the neurological deficits are usually caused by major tumours and peritumoral oedema, the size of the meningioma is an important factor in determining which of the meningiomas need to be removed (9, 13).

Radiosurgery seems to be an attractive and interesting option for MMs up to 3 cm in diameter or residual tumours, but further research is required to establish its effectiveness and determine whether it is safe or not (33). Therefore, the authors' opinions are controversial: some of them support the treatment of asymptomatic meningiomas with prophylactic radiosurgery, even without documented growth (14, 25), whereas others are more reserved on that point and they report a complication rate of radiosurgery of 10% (26). As far as MMs prognosis is concerned, it depends on the grade of the tumour, on the histological types and on the resection degree of the tumour (2, 8).

Conclusions

There has not been established any MMs management and therapy strategy so far. Our recommendation is to treat the symptomatic or the potentially symptomatic tumours and to avoid useless procedures and complications. The form of treatment is surgical removal, but radiotherapy may also be considered and may also play an important role, especially for AM. Nevertheless, even in MMs only some of the lesions require treatment, since most of them are small and asymptomatic and they only require clinical and imaging follow-up. Our philosophy is to treat symptomatic and accessible lesions or growing tumours and to apply the conservative approach, consisting of imaging follow-up for the asymptomatic lesions.

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