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Case Report

Paradoxical evolution of spheno-orbital meningioma after cessation of progestin treatment

Maximilien Steinmetz[1], Julie Lebeau[1], Olivier Bouchain[2], Martin Moïse[3], Elettra Bianchi[4], Cécile Andris[5], Anne-Catherine Chapelle[5], Axelle Pintiaux[6], Gilles Reuter[1]

Departments of [1]Neurosurgery, [2]Otorhinolaryngology, [3]Medical Imaging, [4]Anatomopathology, [5]Ophthalmology and [6]Gynecology, CHU Liège, Avenue de L'hôpital, Liège, Belgium.

E-mail: *Maximilien Steinmetz - msteinmetz@chuliege.be; Julie Lebeau - jlebeau@chuliege.be; Olivier Bouchain - o.bouchain@chuliege.be; Martin Moïse - martin.moise@chuliege.be; Elettra Bianchi - ebianchi@chuliege.be; Cécile Andris - cecile.andris@chuliege.be; Anne-Catherine Chapelle - ac.chapelle@chuliege.be; Axelle Pintiaux - axelle.pintiaux@chuliege.be; Gilles Reuter - gilles.reuter@chuliege.be

***Corresponding author:**
Maximilien Steinmetz,
Department of Neurosurgery,
CHU Liège, Avenue de
L'hôpital, Liège, Belgium.

msteinmetz@chuliege.be

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ABSTRACT

Background: Meningioma is the most frequent primary benign intracranial tumor, with a higher incidence in women. Treatment with progesterone acetates, including cyproterone, nomegestrol, chlormadinone, promegestone, medrogestone, and medroxyprogesterone acetate, has been identified as a risk factor of meningioma, particularly in the anterior and middle cranial fossae. Discontinuation of these treatments often leads to volume stabilization or regression of the tumor.

Case Description: A 42-year-old woman undergoing treatment with nomegestrol acetate (NA) presented with headaches and visual loss in her right eye. She was diagnosed with a large spheno-orbital meningioma invading the sphenoid and ethmoid sinuses, associated with hyperostosis of the sphenoid wing. An initial resection was performed using an extended endonasal approach. Immunohistochemistry confirmed a chondroid meningioma, Grade II, with progestin receptor in 100% of the tumor cell nuclei and a Ki-67 proliferation index of 3–5%. NA was immediately stopped on diagnosis. Despite the cessation of the NA, the intraosseous sphenoidal part of the tumor continued to grow, leading to optic nerve compression. A second surgery was performed using a right fronto-temporo-orbito-zygomatic approach. Examination of the dura of the middle fossa showed subtle tumoral infiltration, while the Ki-67% index was estimated at 1%. Examination of the sphenoid bone demonstrated reactive hyperostosis with minimal to no tumor infiltration.

Conclusion: This case illustrates that the proliferative activity of the progestin-associated meningioma does not account for intraosseous progression within the sphenoid bone following cessation of progestin therapy. Our observations suggest an upregulation of osteogenesis in infiltrated bone, even as the dural part of the meningioma regresses.

Keywords: Histopathological correlation, Hyperostosis, Meningioma, Paradoxical evolution, Progestin, Skull base

INTRODUCTION

Meningioma is the most frequent benign intracranial tumor, primarily affecting women and the elderly.[31] Its incidence in the general population is estimated to range between 0.9% and 3.0%,[29] with prevalence increasing with age.[5] Several risk factors have been established, including high-dose ionizing radiation exposure,[4] obesity,[19,22,23,28] Black race,[26] family

history of meningioma,[8] and certain genetic conditions such as neurofibromatosis and other genetic disorders (e.g., Neurofibromatosis 2 (NF2), Neurofibromatosis 1 (NF1), Protein patched homolog 1 (PTCH1), CREB binding protein (CREBBP), Von-Hippel-Lindau disease (VHL), Phosphatase and tensin homolog (PTEN), Cyclin dependent kinase Inhibitor 2A (CDKN2A), SWI/SNF-related matrix-associated actin-dependent regulator sub-family B(SMARCB1), SWI/SNF-related matrix-associated actin-dependent regulator sub-family E (SMARCE1)).[18] Due to the higher prevalence in women, the presence of sex hormone receptors within the tumor, progression during pregnancy, and regression after delivery,[9] the role of sex hormones in the disease's etiology has long been hypothesized and subsequently confirmed.[31] Cyproterone acetate, nomegestrol acetate (NA), chlormadinone acetate, promegestone acetate, medrogestone acetate, and medroxyprogesterone acetate have been associated with an increased risk of preexisting meningioma growth and the need for surgery.[16,27] Progestin-induced meningiomas typically have a predilection for the anterior and middle fossae.[7,10,16] Following progestin discontinuation, the tumor can exhibit a unique behavior: stabilization or reduction of the tumor volume.[15,20,30] However, paradoxical cases have been reported with continuous bony progression alongside intracranial regression after treatment cessation.[1] The pathophysiological underlying that phenomenon remains unknown. To address this contradictory evolution, we propose further clarification through immunohistopathological examination.

CASE REPORT

A 42-year-old woman presented with a 2-year history of headaches. She had no history of pregnancy and had been treated with NA (Lutenyl®) for the past 8 years for primary dysmenorrhea and menorrhagia. The patient reported right-sided exophthalmos, diplopia with limitation in elevation and abduction, and mild visual loss in the right eye (8/10). Fundoscopy revealed partial temporal atrophy. Visual field testing of the right eye showed diffuse alterations [Figure 1], while visual-evoked potentials demonstrated increased latency on the right side (P100 [ms]: 12': 120.4, 24': 126.2). Optical coherence tomography (OCT) of the ganglion cell complex (GCC) (ganglion cell layer + inner nuclear layer, [GCC]) indicated a superotemporal defect.

As illustrated in Figure 2 the magnetic resonance imaging (MRI) at diagnosis [Figures 2a, 2b and 2c] revealed a bulky, invasive spheno-orbital meningioma, intensely arterialized through the right sphenopalatine artery, measuring 5.3 × 5.0 × 3.4 cm. The tumor extended into the sphenoethmoidal sinuses with a right sphenocavernous intracranial involvement, invading the right superior orbital fissure and the right optic canal, accompanied by signs of compressive optic neuropathy. There was also stenosis of the right cavernous carotid artery and an extension in the right middle fossa floor. The tumor was further associated with hyperostosis of the right sphenoid wing and involvement of the clivus and the planum sphenoidale.

Due to the rapid visual decline, the patient was scheduled for a four-handed, bi-nostril extended endonasal resection of the tumor, along with orbital decompression. The procedure involved endonasal ethmoidectomy and sphenoidectomy, resection of the exophytic intrasinusal portion of the meningioma, opening the right lamina papyracea, and drilling of the right optic canal. A Simpson Grade III resection was successfully achieved. Postoperatively, the visual field defect and visual acuity improved, and diplopia resolved [Figure 1].

For histological examination, the tissue was fixed in 10% buffered formalin and embedded in paraffin. Sections of five-micron-thick were stained with hematoxylin and eosin. Immunohistochemistry was also performed using antibodies against epithelial membrane antigen (EMA) (Roche, Ventana, RTU), progesterone receptor (Roche, Ventana, RTU), and Ki-67 (Dako, 1:200).

As depicted in Figure 3, histological analysis confirmed a chordoid meningioma, Grade II, composed of cords and nests of epithelioid cells, often vacuolated and dispersed in a myxoid or fibrous matrix. The neoplastic cells exhibited round to oval nuclei and eosinophilic cytoplasm [Figure 3a].

Most neoplastic cells showed nuclear expression of the progesterone receptor and heterogeneous membrane positivity for EMA. Immunohistochemistry with the anti-Ki67 antibody revealed a proliferative activity of 3–5% [Figure 3b].

During follow-up, the intracranial portion of the meningioma showed regression, while the intraosseous meningioma continued to grow [Figures 2d, 2e and 2f]. The intradural volume decreased from 10.43 cm^3 to 9.49 cm^3, whereas the osseous part increased from 8.88 cm^3 to 17.53 cm^3 over 3 months. These volumes were calculated using the volumetric tool of the "syngo®.via" device by Siemens.

As optic nerve compression progressed, a right fronto-temporo-orbito-zigomatic approach was planned to remove the orbital bony component of the tumor. This procedure allowed an extensive resection of the roof and the lateral wall of the orbit, resection of the middle cranial fossa dura, and the placement of a 3D-printed poly methyl methacrylate acrylic (PMMA) orbital prosthesis (3D-Side, Mont-Saint-Guibert, Belgium) to prevent enophthalmos.

A consecutive altitudinal visual field defect was noted following this second surgery [Figure 1]. The OCT showed

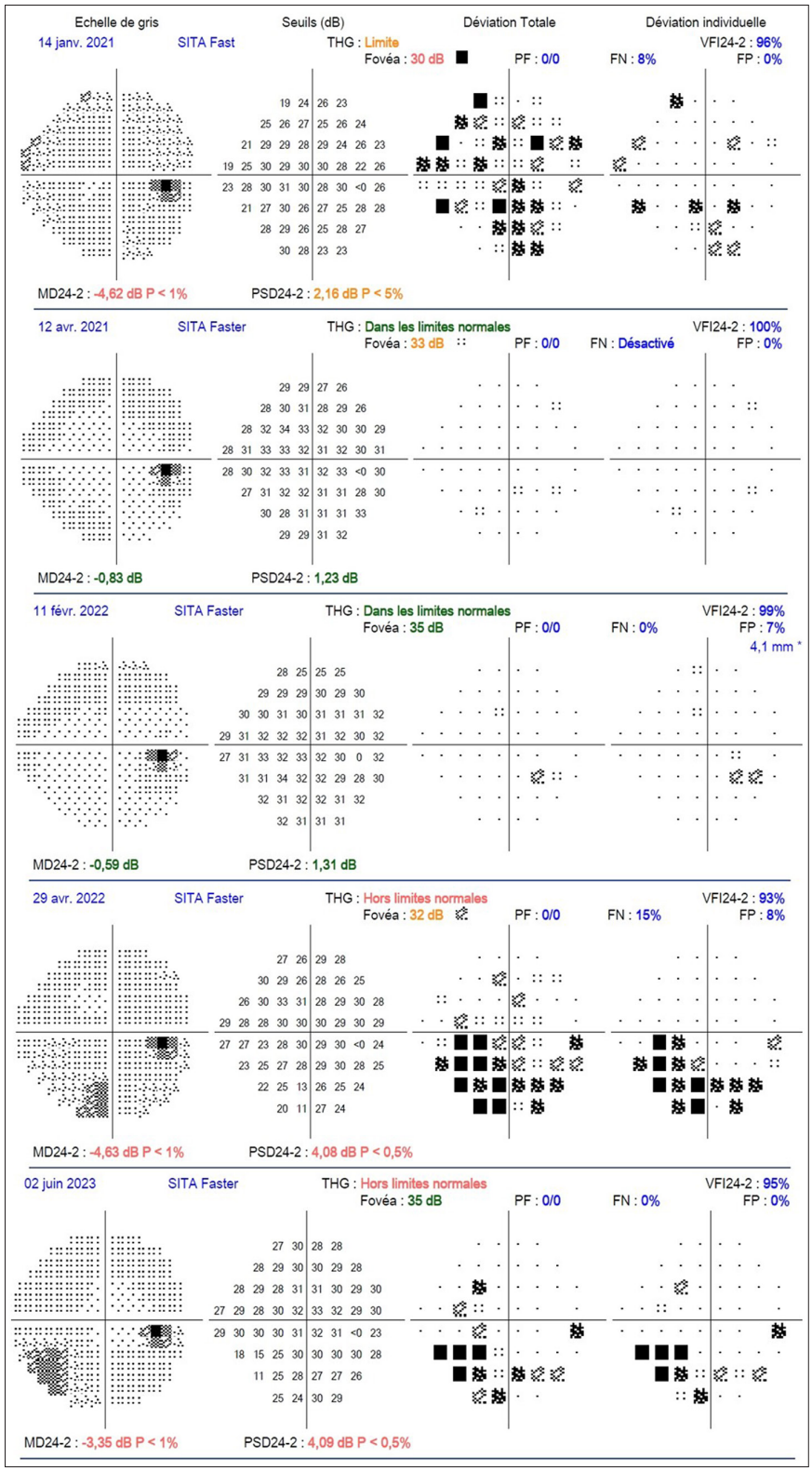

Figure 1: Visual field examination before and after surgical treatment. This figure shows the visual field examination of the right eye. Diffuse alteration of the visual field before the first resection (first line). One month after the endonasal resection, recovery of the visual field (second line). One year later, a novel decline in the visual acuity and visual field (third line). After fronto-temporo-orbito-zygomatic approach, iatrogenic altitudinal defect (fourth line). This defect improves over time (fifth line).

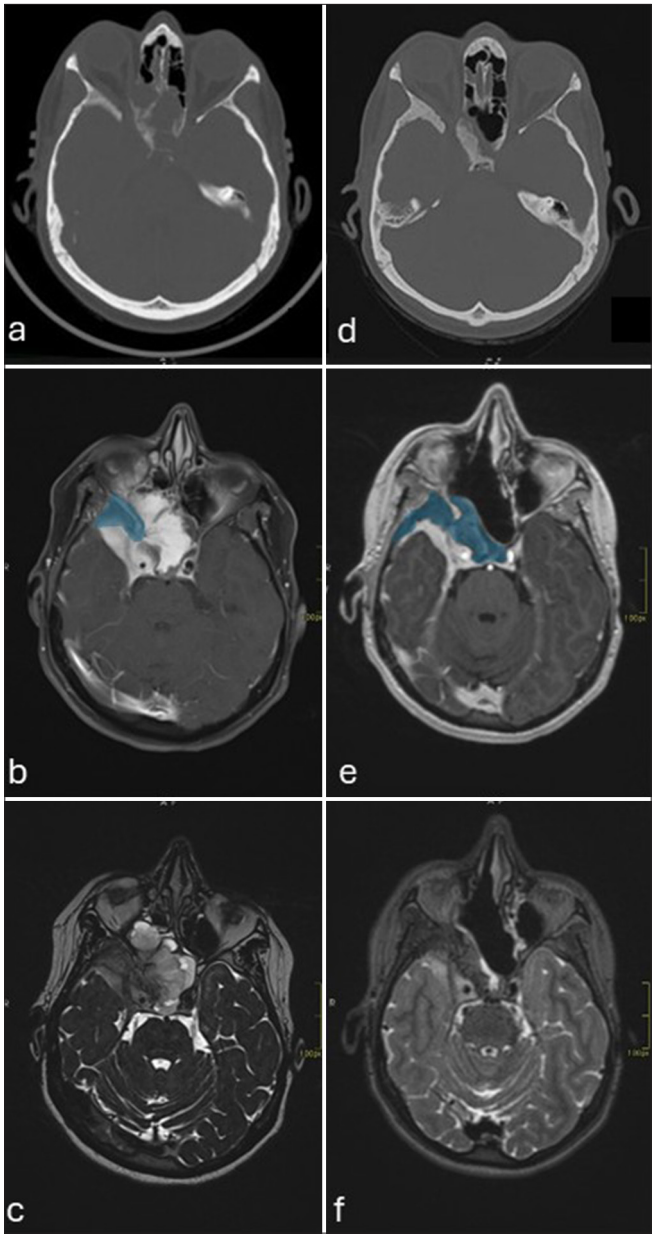

Figure 2: Radiological evaluation of the intra-osseous meningioma progression. (a and b) Bone computed tomography (CT) scan at presentation and 3 months after the first surgery. (c and d) T1 post gadolinium magnetic resonance imaging (MRI) at presentation and 3 months after the first surgery. (e and f) T2 MRI at presentation and 3 months after the first surgery. The blue areas correspond to the volumetry of the osseous part of the lesion before the first surgery (a) and 3 months after this treatment and cessation of Nomegestrol Acetate therapy (c). We realized the volumetry analysis by comparison between the CT scan at the MRI sequences. We demonstrated the bony progression with a growth from 8.88 cm^3 to 17.53 cm^3.

superotemporal atrophy of the retinal nerve fiber layer (RNFL), with significant thinning of GCC observed a few weeks later.

Following the second surgery, histological analysis, performed under the same conditions as previously described, showed sphenoid bone infiltration by meningioma, characterized by small clusters of poorly proliferating cells. The dura mater was also partially infiltrated [Figure 3c]. Meningiomatous cells were highlighted in the dural fibrous tissue by immunohistochemistry using EMA and progesterone receptor antibodies. Ki-67 immunohistochemistry performed on the dura mater confirmed the low mitotic activity of the tumor cells and was estimated at 1% [Figure 3d]. The growing bony portion of the meningioma harbored hyperostosis [Figure 3e].

Following the last surgery, the patient underwent radiation therapy (59.4 Gy in 33 fractions of 1.8 Gy).

At the 32-month follow-up, no signs of progression were noted on computed tomography (CT) or MRI, and the patient's visual status had partially improved [Figure 1].

DISCUSSION

Spontaneous regression of progestin-associated meningioma has been reported in several series.[6,24,30] However, recent reports have noted a paradoxical evolution in the intraosseous part of the meningioma.[1,13] These two case series report 42 meningiomas with an intraosseous portion that kept growing despite cessation of progesterone therapy. Eighteen of them are spheno-orbital tumors. Florea *et al.*[13] have reported the largest series of osteomeningiomas with a history of progesterone therapy with 39 tumors. About 81.3% of those lesions showed an increase in the osseous portion volume. Even though there is no statistical analysis about specific histological sub-type, 17 cases of spheno-orbital meningioma are described in this report. Only one showed bony regression. The other osseous tumors continued to grow after cessation of therapy, accounting for 94% of this population.

Moreover, spheno-orbital meningiomas under progesterone tend to present significant recurrence after surgical treatment. In their series, Apra *et al.* describe a recurrence of 26 tumors that needed new surgery from 124 spheno-orbital meningiomas previously operated on.[2] No information about the type of recurrence is noticed between osseous versus intracranial progression. According to the World Health Organization classification, meningothelial meningioma, Grade I is the most common histopathological subtype in these 21% of evolutive tumors. This observation must be discussed with the data given by Devalckeneer *et al.* In this series of nine surgical cases of Grade II progestin related meningioma, the authors pointed out that progestin related meningioma present less recurrence than the sporadic Grade II tumors after cessation of hormone therapy with no recurrence in this series after mean follow-up of 8.1 years.

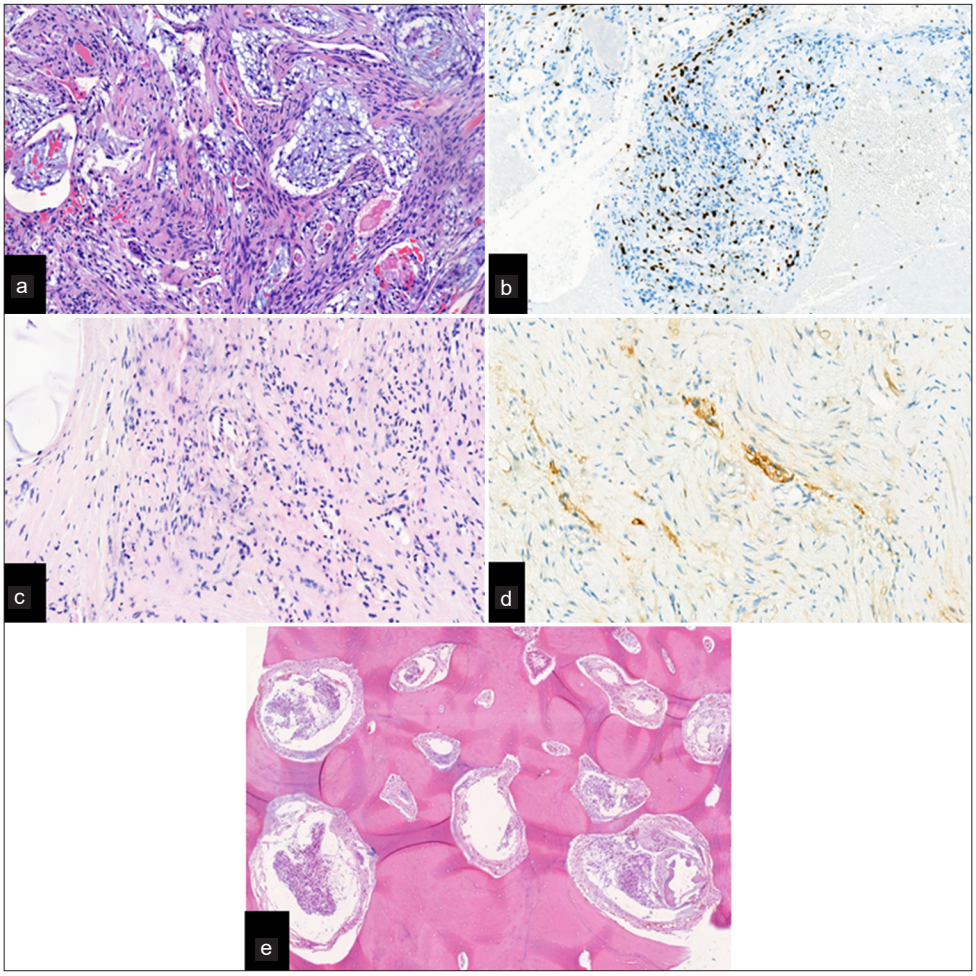

Figure 3: Histological examination of the various parts of the meningioma (a and b): Intranasal part of the meningioma (hematoxylin and eosin [H&E] and Ki67 [Dako 1:200], Magnification = 200× respectively) (c and d) Sphenoid wing dura (H&E and Ki67 [Dako 1:200] Magnification = 400× respectively) The high proliferative rate of the tumor with Ki67 between 3 and 5% before cessation of Nomegestrol in b drops to lower than 1% after cessation of Nomegestrol in d. (e) Sphenoid hyperostosis with a low tumor infiltration (H&E) Magnification = 100×.

Three cases of spheno-orbital meningiomas are mentioned. All of them presented a chordoid meningioma, a Grade II sub-type that expressed the progesterone receptor.[11]

Our case demonstrates that the tumor's proliferative rate significantly decreased after the cessation of the treatment, as evidenced by a drop in Ki-67 from 5% to 1%. This is the first time that this Ki-67 decline after progestin cessation is described in the literature. These findings align with the observations of volumetric regression of progestin-associated meningiomas.[20] With this novel information, this article excludes tumoral progression in bone as the sole explanation for the increase of the osseous portion and the paradoxical evolution of osteomeningioma. However, the reason behind the bony progression in progestin-associated meningiomas is still unknown.

Even if the influence of hormone steroids on bone metabolism is well known, with downregulation of osteoclast by estrogen/androgen and upregulation of osteoblast by progesterone leading to a positive bone turnover with bone deposition,[3,21] the physiopathology of hyperostosis due to meningioma seems to be independent of those elements. Some reports argue in favor of a change in the bone microenvironment due to tumor production of bone stimulating factors (osteoprotegerin, insulin-like growth factor 1, endothelin, and bone morphogenetic protein) and enzyme (matrix metalloproteinase).[12,25] Those mechanisms enable tumor invasion of the bone and produce a long-term dysregulation of the osteoclast-osteoblast equilibrium, producing hyperostosis. The meningiomas expressing receptors for both estrogen and progesterone seem to be potential candidates for developing those mechanisms.[25]

The osteoclast-osteoblast activity imbalance in meningioma has been under investigation [12], and further study is warranted. We believe that answering this question might

pave the way for novel research and therapeutic fields. Given that this incongruent tumoral behavior – bony progression and intracranial regression – appears unique to progestin-associated meningioma and is observed in selected cases, deciphering the mechanisms behind sustained hyperostosis may also explain why some women on progestin will develop meningiomas while other women do not, even when exposed to high doses for extended periods. As progestin-associated meningioma is an emerging public health issue, addressing this question is of paramount importance.

Despite stabilization or regression of meningioma after cessation of progestin therapy, 38.4% of all of them require surgical treatment.[20] In cases of spheno-orbital meningioma, surgery may be considered in cases of progressive hyperostosis with associated visual decline. Reconstructing the orbital roof can yield excellent cosmetic and functional results. Based on our experience, orbital reconstruction is indicated when more than 150 mm^2 of the orbital surface is decompressed, as this prevents enophthalmos and globe pulsations. As previously mentioned, operated spheno-orbital meningioma tends to recur in 21% of cases.[2]

In case of sustained progression or surgically inaccessible meningiomas, radiosurgery can be effective, offering high control rates.[17]

This case also highlights the importance of close follow-up for the osseous portion in progestin-associated sphenoid meningiomas and emphasizes the value of adding CT scans to MRI in these specific cases. While promising MRI alternatives are underway as surrogates for the CT scans, the spatial resolution of CT scans remains superior to conventional MRI at present.[14]

CONCLUSION

Progestin treatment can induce meningiomas, especially around the sphenoid bone. Tumor volume can stabilize or reduce on cessation of treatment. However, some meningiomas with an intraosseous component can continue to grow after progestin withdrawal, and this growth is not related to high tumor proliferation. Follow-up with CT scans, in addition to MRI, is recommended to monitor tumor evolution. In cases of symptomatic progression with visual impairment, surgical decompression, and adjuvant radiotherapy may be indicated.

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