Case Report

**Cavernous sinus syndrome as the first manifestation of metastatic breast disease**

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**Abstract**

**Background:** The cavernous sinus is a venous plexus crossed by vital neurovascular structures. Metastases to the region are uncommon and often associated with a headache, facial pain, or progressive neurological deficit in III, IV, and VI cranial nerves. The treatment options are surgery, including endoscopic approach, radiotherapy, radiosurgery, and chemotherapy.

**Case Description:** We report the case of a 26-year-old female with cavernous sinus syndrome due to breast cancer metastasis, who was subjected to chemotherapy with complete neurological recovery. A literature review was performed using the databases Bireme, Pubmed, Cochrane, Lilacs and Medline with the keywords: cavernous sinus/metastasis/surgery/radiosurgery for multiple management options review.

**Conclusion:** Cavernous sinus metastases are rare, and the cavernous sinus syndrome is rarely the first sign of cancer, especially in young patients. Because the syndrome has multiple causes, the history of rapid progression and atypical image findings can arise suggesting metastatic diseases. As in our case, the image was suggestive of meningioma, however, the clinical presentation and further investigations led us to suspect as a metastatic disease. The therapeutic decision considers clinical and functional status, the extent of primary and metastatic disease, radiological study, tumor histopathology, and biological behavior. Often associated with significant symptoms and disseminated systemic disease, nowadays radiosurgery is the first and less invasive strategy, offering low risk of new deficits, clinical improvement, and good local control. The prognosis depends on early treatment and disease staging because mortality is associated with progression of cancer.

**Key Words:** Breast, cavernous sinus, metastasis, radiosurgery, surgery

**INTRODUCTION**

The cavernous sinus is a venous plexus crossed by vital neurovascular structures. Metastases to the region are uncommon and often associated with a headache, facial pain, or a progressive neurological deficit in III, IV, and VI cranial nerves. Surgical intervention used to be the only option, however with the advance of technology, radiosurgery has become the first choice in such cases.

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Radiosurgery is a less invasive technique, offering good results.

CASE REPORT

A 26-year-old woman presented with 10 months of diplopia, 4 months of hemifacial hypoesthesia at the right side, and 2 months of frontal headache, which was also associated with a superior visual field deficit of the right eye, an ocular dry, and a convergent strabismus in the same eye. During neurosurgery clinical analysis, the patient presented hypoesthesia of maxillary (V2) division of trigeminal nerve (V), associated with partial III and complete VI nerve palsy, on the right side. Moreover, the patient had a scalp lesion, which had shown progressive growth during the last month, for which biopsy was done on the same day. Magnetic resonance imaging (MRI) showed an irregular contrast-enhanced lesion on the right cavernous sinus, causing a slight mass effect in the brainstem [Figure 1], with irregular borders, which the radiology assessment concluded as a meningioma. Immunohistochemistry suggested adenocarcinoma and possible breast or primary gynecologic tumor. The patient was referred to gynecology department, where breast examination revealed a mass in the left breast and palpable axillary lymph nodes. An invasive ductal carcinoma with positivity to estrogen and progesterone receptors was diagnosed [Figure 2]. After 3 months of the first neurosurgery examination, the patient reported worsening of hypoesthesia and strabismus. In addition, the patient had an III nerve palsy and a right mydriasis. At oncology follow-up, computed tomography (CT) and bone scan showed liver and bone metastases.

DISCUSSION

The cavernous sinus is a venous plexus crossed by vital neurovascular structures. Metastases to the region are uncommon, and the anatomical proximity described is responsible for different clinical manifestations, secondary to inflammatory, vascular, or neoplastic diseases. A headache, facial pain, or progressive neurological deficit associated with the III, IV, and VI cranial nerves are the signs and symptoms reported by most patients. A study of 42 patients presenting with cavernous sinus lesions showed headache in 88%, diplopia in 60%, and visual field defects in 55%.

Metastases to cavernous sinus occur in less than 1% of patients with cancer, and it is considered a late event when patients have disseminated disease. The most frequent primary tumors are lung and breast carcinoma followed by renal, thyroid, and gastric carcinoma. There is also the possibility of cavernous sinus invasion by contiguity of malignancies of the head and neck, which can be diagnosed by imaging studies.

The diagnosis of metastatic lesion considers the clinical condition and the radiological findings obtained on MRI. This investigation can detect hypointense signal on T1-weighted images and hyperintense on T2-weighted images. Moreover, it can demonstrate homogeneous or heterogeneous contrast enhancement. In several cases, the cavernous sinus metastasis can be mistaken as a meningioma, as occurred in our patient. Clinical and radiological correlation can exclude the differential diagnosis of metastasis, which includes other neoplastic, inflammatory, or infective diseases, as some presented in Table 1. Even though breast metastasis to the cavernous sinus is uncommon, we have to keep in mind other possible diagnoses as meningioma, pituitary adenoma, trigeminal schwannoma, chordoma, lymphoma, and aneurism.

Figure 1: MRI findings: irregular contrast enhanced lesion, localized at the cavernous sinus and extension to upper clivus, hypointense at T2, without restriction at the diffusion sequence, with no peripheral edema or brain tissue invasion

Figure 2: (a) Scalp histology: pleomorphic large cell neoplasia infiltrating subepithelial soft tissue (b) Scalp immunohistochemistry: epithelial neoplasia consistent with adenocarcinoma, breast or gynecological region are considered as possible primary sites - positive for estrogen receptors (c) Breast histology: invasive ductal carcinoma, Nottingham 2 (d) Breast immunohistochemistry: positivity for estrogen and progesterone receptors
### Table 1: Differential diagnosis cavernous sinus metastases: radiological analysis of MRI

| Pathology                  | T1-weighted      | T2-weighted      | Contrast-enhanced | Other features                          | Differential diagnosis                  |
|----------------------------|------------------|------------------|-------------------|-----------------------------------------|-----------------------------------------|
| Metastatic lesion          | Hypointense      | Hyperintense     | Homogeneous/      | Primary lesion                          | Inflammatory and infective diseases     |
| Meningioma                 | Isointense to grey matter | Isointense to grey matter | Homogeneous enhancement | Dural tail; internal carotid artery narrowing when encased | Schwanoma                               |
| Schwannoma                 | Iso-hypointense  | Hyperintense     | Homogeneous – small; large - heterogeneous | Dumbbelle shape; may be associated with neurofibromatosis | Meningioma                               |
| Internal carotid artery aneurysm | Flow void/ iso-hypointense if thrombosed | Flow void/ iso-hypointense if thrombosed | Luminal enhancement | MR angiography is useful; ghost artifact in phase encoding direction |                                      |

A study conducted by The Cleveland Clinic Foundation reported the use of 111 indium-octreotide brain scintigraphy (OBS) for noninvasive differentiation of meningiomas from other cranial dural-based pathology. The meningioma’s somatostatin receptors bind to octreotide after 6 hours from administration, and small meningiomas (volume <5 ml) should be evaluated after 24 hours. The OBS has 100% sensitivity, 50% specificity, and positive and negative predictor values of 75% and 100%, respectively. False positive results were found in 3 of the 50 patients studied (metastasis, chronic inflammation, and lymphoma). Despite this, OBS could exclude meningioma hypothesis for the case considered.

The low prevalence of metastasis to the cavernous sinus and the individual aspects of each case can perform different management strategies. Clinical and functional status, the extent of primary and metastatic disease, radiological study, tumor histopathology, and biological behavior, including response to prior therapy, are necessary for the therapeutic decision. Some tumors, as small cell lung cancer, breast cancer, and prostate cancer are sensitive to radiation and usually respond better to radiosurgery. On the other hand, melanoma, renal cell carcinoma, and sarcomas are frequently radioresistant, and surgery can be indicated in particular cases.

In cavernous sinus lesions, usually, complete resection is not achieved and can be related to several complications. A surgical analysis of Pamir et al. evaluated the results of nonmeningeal tumors of the cavernous sinus. It was possible to achieve complete resection in 21 (50%) patients, and gamma knife radiosurgery was used in 13 and fractionated radiotherapy in 3 of the incompletely resected cases. The surgical approaches used were pterional extradural (Dolenc), cranial-orbitozygomatic and combined crano-orbitozygomatic, and transfacial, 85.7%, 7.1%, and 4.8% of cases, and some were operated twice for tumor resection. Complications occurred in 12 (28.6%) patients, including cerebrospinal fluid fistula (4), hematoma in the surgical field (2), cerebral infarction (1), hydrocephalus (1), diabetes insipidus (1), and pulmonary embolus (1). The rate of cranial nerve morbidity was 26.1% for transient and 16.7% for new and permanent damage.

Endonasal access can also be used for anterior skull base lesions and can be indicated as a possible site for biopsy if no other local could be achieved. Zacharia et al. studied 749 patients of New York Presbyterian Hospital, 12 (1.6%) with metastatic disease, 1 (8%) of them to the cavernous sinus. The case had a thyroid carcinoma as the primary tumor, presenting left ptosis as the clinical manifestation of the metastasis. The surgical approach was transsphenoidal, transellar, and transcavernous. The surgery obtained subtotal resection (STR). Another analysis of endonasal surgery for skull base lesions revealed gross total resection (GTR) in 34–41.6% of cases. The median survival was 9.2–16 months, and better progression-free survival (PFS) was 18 months. All patients received adjuvant radiotherapy, and radiosurgery was performed in 2 (16.7%). New cranial nerve deficits were related to the III, temporary, and the VI, permanent, and the mortality was related to the systemic progression of pre-existing cancer. Despite considered an option, endonasal surgery could not be evaluated very precisely because the study sample was limited and there was interference of systemic disease and adjuvant therapy.

Radiosurgery, which began to be applied in the 1990s to patients who had failed in the previous radiotherapy, aims to preserve structures such as the optic nerve. Earlier treatment, within four months, is associated with better outcomes in cavernous sinus metastasis, since avoiding tumor progression and deterioration of nerve function. Furthermore, the effect is dose-dependent, and the dose must consider the lesion size (a volume of 6.3 cm³ was found in the study) and adjacent structures as optical apparatus. This relationship, previous radiotherapy, and larger tumor sizes were limiting factors of dose. Patients who received ≥15 Gy had better PFS, 22.9 months, compared to 9 months with lower margin dose. The PFS at one year was 89.7% and 55.9% for ≥15 Gy and <15 Gy, respectively. Although patients treated with the highest dose presented with lesion volume of 6.1 cm³, different of 11.7 cm³ of the lowest dose patients, the tumor size was not significantly associated with better...
PFS, which patients with cranial nerve deficits, 12 (35.3%) improved by approximately 1.7 months after treatment, associated with optic nerve (33.3%), oculomotor (33.3%), trochlear (40%), trigeminal (36.8%), and abducotent (40%) in addition to the improvement of facial palsy (10%). Of the four patients with hearing loss, none reported a change. Worsening of symptoms occurred in 8 patients, related to disease progression and not to radiosurgery. The remaining patients did not report clinical response to the treatment.[5]

Iwai et al. reported 47% improvement among 21 patients who underwent radiosurgery due to cranial nerve deficits secondary to metastasis to the cavernous sinus. Of these, 3 had complete success and 7 revealed good results related to the nerves – optic (2), oculomotor (2), trigeminal (4) and abducotent (4). No patient experienced nausea, vomiting, damage to cranial nerves, or radiographic and clinical evidence of radiation necrosis. The deaths were a result of tumor progression or bleeding in 2 cases, and 1 case had meningitis caused by the reduction of the tumor by radiosurgery.[6]

Chemotherapy is used for disseminated disease, however, can be limited due to the ability to cross the blood–brain barrier. Agent and concentration are directly associated with the brain penetration.[6]

Nowadays surgical resection for metastatic brain metastasis, even more for cavernous sinus, are not usually indicated. New chemotherapies and radiosurgery can achieve good local control with good neurological recovery without surgical risks.

CONCLUSION

Cavernous sinus metastases are often associated with prominent symptoms and disseminated systemic disease. We presented a case of a patient with a cavernous sinus lesion which was the first symptomatic lesion in a metastatic breast disease. The lesion was first radiologically diagnosed as a meningioma, nevertheless with further investigation and the clinical correlation, was rediscussed to be a cavernous sinus metastasis, that was referred to systemic chemotherapy and stereotactic radiosurgery for the lesion. After a month of chemotherapy, the patient had complete regression of the symptoms and the radiosurgery expected was no longer indicated.

Surgery can be indicated in metastases without a defined diagnosis, brain swelling, and manifestations due to its location, as brainstem compression,[4] which would not improve or respond to radiosurgery. Clinical and functional status, extent of primary and metastatic disease, radiological study, tumor histopathology, and biological behavior, including response to prior therapy, are considered for therapeutic decision.

The prognosis depends on the histologic type of the primary tumor, disease staging, and proximity to the optical apparatus, which defines the dose in radiosurgery. The use of ≥15 Gy showed better PFS,[3] compared to other treatments and patient survival is associated with systemic progression of cancer, the major contributor to mortality in the studied cases.[11]

Cavernous sinus metastases are a significant differential diagnose of the syndrome associated. In approximately 28% of cases the lesions can be the first sign of cancer,[2] the clinical progression and atypical radiological images require investigation of neoplastic disease.

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Conflicts of interest
There are no conflicts of interest.

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