

Clinical Study

Primary sphenoid sinus neoplasms: a report of four cases with common clinical presentation treated with transsphenoidal surgery and adjuvant therapies

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Summary

Background: Primary neoplasms of the sphenoid sinus are a rare occurrence, accounting for approximately 1–2% of all paranasal sinus tumors. Here we report a series of four such patients.

Methods: Four patients with sphenoid sinus neoplasms were identified (1%), all treated during the year 2003.

Results: The four patients included two women and two men (mean age 61 years, range 44–70 years). Two patients presented with unilateral abducens cranial nerve (CN) palsies; one had trigeminal facial numbness and dizziness; another had headache, epistaxis, and partial third and fourth CN palsies. MRIs in all patients demonstrated large sphenoid sinus masses with partial clival and sellar bone erosion but with clear visualization of the pituitary gland above the mass. Cavernous sinus invasion was present in all four cases, including one patient with tumor in the ethmoid sinus and intra-tumoral hemorrhage. No patients had endocrinopathy. All patients underwent subtotal tumor removal via an endonasal transsphenoidal route. Tumor histology included neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, mucoepidermoid carcinoma, and giant cell tumor. Post-operatively, all four patients had improved symptoms with complete resolution of diplopia in 3 of 3 patients. Metastatic work-ups were negative in all patients, and all received fractionated stereotactic radiotherapy; three received chemotherapy. One patient required a second endonasal tumor debulking 15 months after the first for new visual loss that then resolved. At a median follow-up of 21 months, all patients are alive and functional.

Conclusions: Intra-sphenoidal tumors are locally invasive tumors that include a wide pathological spectrum. In this small series, they presented with cavernous sinus symptoms and headache but not endocrinopathy. Recognizing their distinctive clinical presentation and MRI features is helpful in differentiating them from primary sellar tumors. Their aggressive nature warrants a multimodality treatment plan including surgical debulking, radiotherapy, and chemotherapy in some cases.

Introduction

Primary isolated malignancies of the sphenoid sinus are unusual. It is reported that neoplasms of the nasal cavity and paranasal sinuses account for 0.2–0.8% of all cancers and for 1–3% of head and neck carcinomas [1–4]. Typically, tumors in the sphenoid sinus arise by local tumor extension from surrounding structures such as the ethmoid sinus or rhinopharynx or from the sella turcica by growth of invasive pituitary macroadenomas. Primary sphenoid sinus masses are quite unusual, however, representing only 2–3% of paranasal sinus neoplasms. Given the relative rarity of these invasive and histolog-

ically variable tumors, their distinctive clinical presentation, and their need for aggressive adjuvant therapies, we summarize our recent experience with this entity. We describe four patients with primary sphenoid sinus neoplasms who all presented with symptoms and signs related to local mass effect on the cavernous sinus. All patients underwent initial tumor debulking through a direct endonasal surgical route with follow-up adjuvant therapies. Although various cranio-facial approaches have been described to remove sphenoid sinus cancers [5–7], complete resection is typically not possible given their locally invasive nature. Consequently, recent efforts have been aimed at less rhinologically destructive

approaches to these lesions [2, 8–10]. The direct endonasal approach used in our patients, recently described by Zada et al., represents a minimally invasive variation of the standardized sublabial transsphenoidal route [11].

Materials and methods

From the surgery database of the Pituitary Tumor and Neuroendocrine Program of the University of California Los Angeles (UCLA), we identified four patients with primary sphenoid sinus neoplasms operated upon by an endonasal transsphenoidal approach during the year 2003. Pituitary adenomas, clival chordomas, dermoids, esthesioneuroblastomas and other tumors not primarily arising from the sphenoid sinus were excluded from the present series. Patients' symptoms and signs, pre-operative diagnosis, magnetic resonance imaging (MRI) and in some cases computed tomography (CT) findings were noted (See Table 1). All patients had a pre-operative endocrine evaluation for possible hormonal deficiency or excess, especially hyperprolactinemia to rule out an invasive macroprolactinoma.

Patients were operated upon by means of a direct endonasal microsurgical approach for tumor removal, as recently described by Zada et al. [11] in one case (patient 3), the neurosurgical procedure was preceded by a right endoscopic middle turbinectomy performed by a

Head and Neck surgeon, with exposure of the ethmoid sinus and entrance into the sphenoid cavity. Intra-operative findings were described including tumor consistency and vascularity and estimated blood loss. Nasal packing was not used in any patients.

Post-operative status was defined in terms of neurological status and extent of tumor removal based on post-operative MRI or CT scans obtained within 2 days of surgery and then at 3 and 12 months or longer after surgery. The histological specimens were reviewed and re-examined with immunohistochemical analysis. All patients were discussed in a multi-specialty tumor board and appropriate adjuvant therapies were rendered based on this consensus conference.

Results

Clinical presentation

The four patients included two males and two females, with an age ranging from 44 to 70 years (mean age 61 years). At initial presentation, three patients complained of headache, and all four patients had symptoms and signs of cranial neuropathies, with a partial III cranial nerve (CN) palsy in one patient (case 4), CN VI palsy in two patients (cases 3 and 4), CN IV palsy in one patient (case 3), and trigeminal distribution facial

Table 1. Patient summaries

Case #	Age, sex	Tumor size	CT/MRI findings	Preop symptoms/signs	Surgery	Pathology	Adjuvant treatments	Status at follow-up
1	70, M	3 × 3 cm	Sphenoid mass with erosion of clivus and sella; elevation of pituitary gland.	Intermittent dizziness, left-sided facial numbness.	Subtotal removal. Soft in consistency.	Neuroendocrine carcinoma (High grade)	SRT, Chemotherapy	Stable local disease at 18 months since surgery
2	64, M	5 × 4 cm	Large sphenoid sinus mass with extension into posterior ethmoid sinus and anterior sella. Cavernous sinus invasion. Subacute hemorrhage.	Headache, epistaxis, sinus congestion, partial right III c.n. palsy.	Subtotal removal. Fibrous in consistency.	Sinonasal undifferentiated carcinoma (SNUC)	SRT, Chemotherapy	Reoperation 15 months after first surgery. Stable local disease at 24 months since first surgery
3	66, F	3 × 3 cm	Large sphenoid sinus mass with far lateral and inferior extension. Clival erosion and right cavernous sinus extension.	Headache, complete right VI c.n. palsy, right IV c.n. palsy.	Subtotal removal. Fibrous in consistency.	Mucoepidermoid carcinoma (High grade).	SRT, Chemotherapy	Stable local disease at 19 months since surgery
4	44, F	3 × 3.5 cm	Large sphenoid sinus mass with clival erosion and elevation of sella.	Headache, right VI c.n. palsy.	Subtotal removal. Soft in consistency.	Giant cell tumor	SRT	Residual tumor reduced in size after SRT at 23 months since surgery

SRT: Stereotactic radiotherapy; c.n.: cranial nerve

numbness in one patient (case 1). Hormonal evaluation revealed no pituitary hormone deficiencies or overproduction in any case.

All patients had pre-operative MRIs and two had CT scans. The site of the tumor was the sphenoid sinus in all cases, with complete or near complete filling of the sinus (Figure 1a, b). Extension beyond the sphenoid sinus was noted in all cases. Bony erosion over the cavernous sinuses was seen on MRI, CT or intra-operatively in all four cases and clival erosion was seen in three cases. An erosion of the sellar floor and extension into the sellar cavity, with associated compression and distortion of the pituitary gland, was evident in three cases (cases 1, 2, and 4). In particular, in one patient who had a history of sudden development of right CN III palsy and acute headache, the MR showed evidence of subacute hemorrhage into the tumor, with right cavernous sinus and dural infiltration, suggesting initially a pituitary macroadenoma with apoplexy. The MR and CT findings did not permit in any case a precise pre-operative diagnosis and the imaging characteristics were consistent with clival chordoma, invasive macroprolactinoma, carcinoma, other bony tumor or metastatic tumor. Two patients underwent preoperative transnasal biopsy of the sphenoid mass at an outside institution. These initial biopsies confirmed the diagnosis of mucoepidermoid carcinoma in one case (patient 3), and giant cell tumor in the other (patient 4).

Surgical treatment and initial outcome

A subtotal removal of the tumor was achieved in all four cases. In all cases the tumor was moderately to highly vascular, with a fibrous consistency in two cases (cases 2 and 3) and a soft consistency in two (cases 1 and 4). Intra-operative blood loss ranged from 100 cc to 1,500 cc. In all patients there was erosion of the surrounding bony structures and dural invasion into the sellar cavity, cavernous sinuses and into the clival dura, in various combinations. There were no intra-operative or post-operative CSF leaks or other surgical complications. Patients were discharged home on post-operative day 2 in two cases and on day 3 in two cases. At routine follow-up, in two patients there was a complete resolution of the pre-operative symptoms and neurological signs, while in two cases the symptoms improved after surgery. All patients had a metastatic work-up which was negative.

Tumor pathology

Histological analysis revealed four different tumor types in the four patients: sinonasal undifferentiated carcinoma, giant cell tumor of bone, mucoepidermoid carcinoma of intermediate grade, and neuroendocrine carcinoma (Figure 2 and Table 1). The pathological features of the tumors are summarized in Table 2.

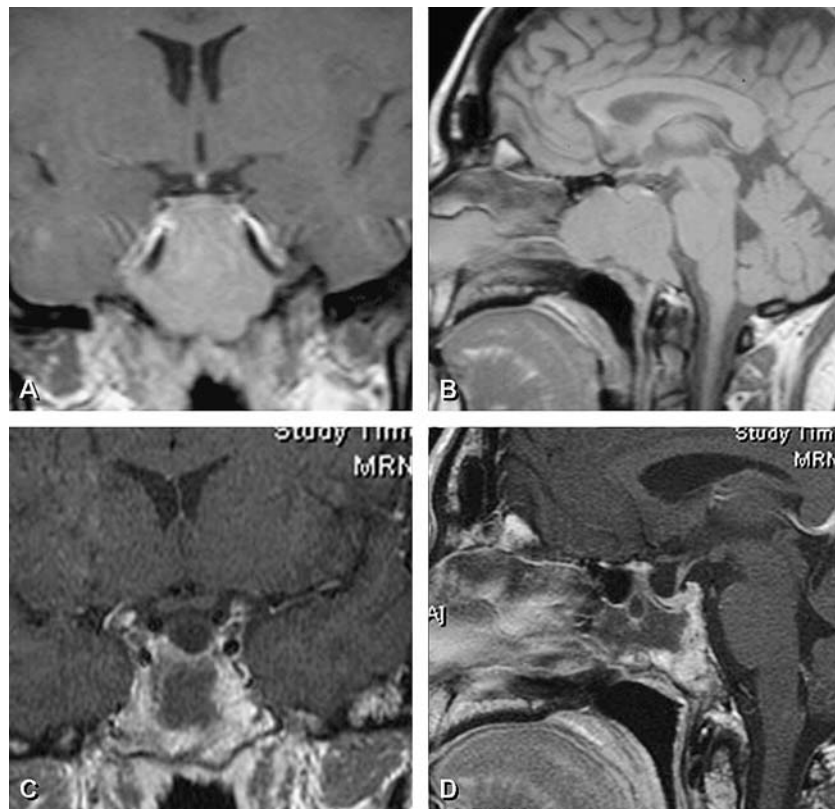


Figure 1. Sellar MRI, case #4. Pre-operative coronal (a) and sagittal (b) images after intravenous administration of gadolinium-DTPA: the lesion occupies the entire sphenoid cavity, erodes and extends into the clivus and both lateral walls of the sphenoid sinus. The sellar floor is eroded and the pituitary gland is pushed upward. Post-operative coronal (c) and sagittal (d) post-gadolinium images: small amounts of residual tumor are visible along the posterior and lateral walls of the sphenoid sinus, mostly in the clivus. The pituitary gland has descended into a more normal anatomical position.

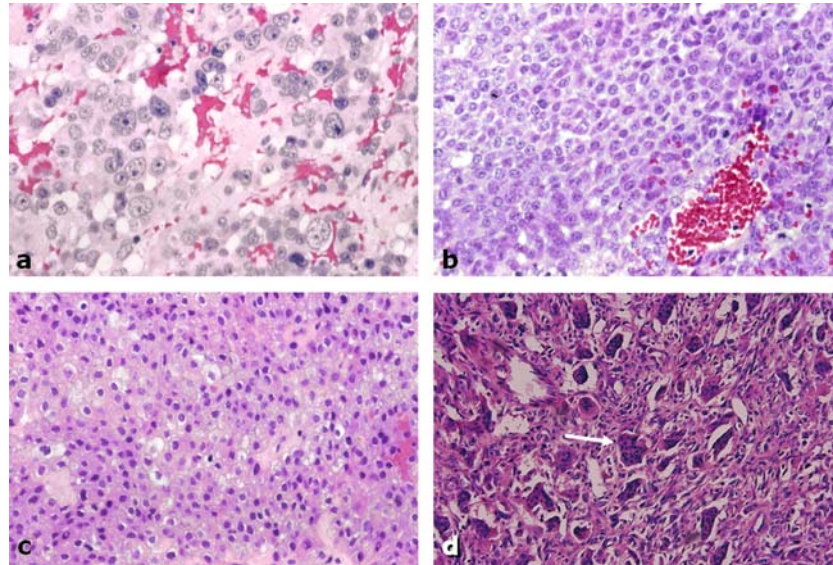


Figure 2. Panel A: High grade malignant neoplasm most c/w neuroendocrine carcinoma. Pleomorphic vesicular nuclei with variably prominent nucleoli, but a relative paucity of mitoses. Panel B: SNUC. Routine H&E stained section shows a neoplasm composed of moderately pleomorphic epithelioid cells with fairly distinct cytoplasm—an appearance very similar to that of pituitary adenoma. Panel C: Mucoepidermoid carcinoma with clear cell features. Tumor architecture includes sheets and nests of cells with relatively uniform epithelioid cytology. Many of the cells show clear cytoplasm; nuclei are relatively uniform, with either a ‘salt and pepper’ chromatin pattern and absence of nucleoli, or clear nuclei with pseudoinclusions. Panel D: Giant cell tumor of bone. Note multinucleated giant cells (e.g. arrow) scattered throughout a fibrous stroma.

Adjuvant therapy

All four patients underwent stereotactic radiotherapy (SRT, dose range 50–60 Gy) and three patients received chemotherapy in addition to the radiotherapy. In particular, patient #1 received fractionated radiation therapy in combination with chemotherapy (two cycles with cisplatin and VP-16); both patients #2 and #3 received a combination of hyperfractionated radiation treatment and chemotherapy (full doses of 5-fluoro-

uracile [5-FU] cisplatin); and patient #4 received fractionated radiation treatment only, given the fact that giant cell tumors rarely are malignant but they tend to recur (in our case, the Ki-67 labeling index was 2–5%).

Follow-up

Post-operative imaging (Figure 1 c, d) shows stable residual tumor in patient #1 at 12 months, and in patient #3 at 15 months. In patient #4 with giant cell

Table 2. Pathological features of the tumors of present series

Case #	Histology	Mitoses	Nucleoli	Immunostaining	Ki-67	Final diagnosis
1	Hypercellular tumor with bizarre pleomorphic large cells in sheets and vague nests. Ill-defined faintly eosinophilic to clear cytoplasm and large pleomorphic nuclei.	None	Eosinophilic macronucleoli	Pankeratin⊕ Chromogranin⊕ Synaptophysin⊕, CD45–, CK7–, CK20–, HMB45–, EMA–	4%	Neuroendocrine carcinoma of high grade
2	Sheets and lobules of epithelioid cells with well demarcated cytoplasmic borders and pale, eosinophilic cytoplasm	Rare	Prominent	Keratin⊕, EMA⊕, Pituitary Hormones	10–20%	Sinonasal undifferentiated carcinoma
3	Hypercellular tumor in sheets and infiltrating nests of round to oval epithelioid cells. Nuclei round to oval.	Rare	Inconspicuous	EMA⊕, Keratin 7⊕, Calponin–, CD10–, Keratin20–, Protein S-100–, Vimentin –	5–10%	Mucoepidermoid carcinoma with clear-cell features
4	Multinucleated giant cells (e.g. arrow) scattered throughout a fibrous stroma	None	Rare clear nucleoli with pseudoinclusions	CD68⊕	2–5%	Giant cell tumor of the bone

tumor, MRI at 14 months after surgery shows a 40% decrease in transverse tumor diameter. Patient #2 with sinonasal undifferentiated carcinoma, after receiving both stereotactic radiotherapy and chemotherapy, developed left eye visual loss 15 months after surgery secondary to another hemorrhagic tumor recurrence in the sphenoid sinus and left parasellar area, with extension into the posterior planum sphenoidale and left optic canal. He underwent a second endonasal tumor debulking after which his left eye vision returned to normal. He then underwent a second cycle of stereotactic radiotherapy and remains stable 9 months after his second operation. The clinical follow-up of all the patients ranges from 18 to 24 months (mean 21 months).

Discussion

Epidemiology

Primary sphenoid sinus neoplasms are distinctly unusual. Prior large series of paranasal sinus tumors report an incidence of primary sphenoid sinus cancers of only 2–3% of all paranasal sinus neoplasms [1–4, 10, 12–15]. The overall incidence in our series of all tumors in the sellar and parasellar regions is 1%. More often, lesions of the sphenoid sinus result from direct extension of neoplastic masses from the ethmoid sinus, the rhinopharynx and the clivus, or represent inflammatory disease, such as sphenoid mucocele [1, 12, 13, 16–19]. The most common histopathologic subtype of paranasal sinus tumor is squamous cell carcinoma, which accounts for 60–75% in most series, with most of the remaining cases comprised of undifferentiated tumors, adenoid cystic carcinoma, and adenocarcinoma [1, 10, 12, 14–16, 18, 20–24]. Other tumor types, including lymphomas, esthesioneuroblastomas, plasmacytomas, melanomas and sarcomas are rarely seen in the sphenoid sinus [25, 26]. However, involvement of the sphenoid sinus from large invasive macroprolactinomas is common in men. Therefore a prolactin level should always be performed with such lesions in the parasellar area. One should also be aware of the pitfall of the ‘high-dose hook effect’ in the chemiluminometric assay for determination of serum prolactin level. In very large macroprolactinomas, unless serum dilutions are performed an erroneously normal or slightly elevated prolactin level may lead to missing the diagnosis of a prolactinoma which could be treated with dopamine agonist therapy [27–31].

Pathology

Sphenoid sinus tumors can pose a significant diagnostic challenge at the time of frozen section (intraoperative consultation). The relatively bland cytologic and architectural features of many of these neoplasms (sheets and cords of epithelioid cells with relatively well demarcated cytoplasm, modest nuclear atypia) do not allow for their distinction from pituitary adenomas, in which virtually identical features may be present [32, 33]. As is the case with many endocrine tumors, pituitary adenomas may

show pronounced nuclear atypia and even mitoses, without the ominous prognostic implications of these findings when they are found in *non*-endocrine tumors; this makes the intraoperative differential even more problematic.

Clear communication between the neuropathologist and neurosurgeon (always recommended) becomes crucial in these cases [34] – e.g. knowing that the lesion is definitely distinct from pituitary gland makes the diagnosis of adenoma less likely, though not impossible. At the time of intraoperative consultation, the neuropathologist may issue a diagnosis using the terminology ‘consistent with...’, with the understanding that this will be refined after examination of the permanent sections. In three of the four cases presented, the intraoperative diagnoses at the time of initial resection were: ‘consistent with adenoma’, ‘malignant neoplasm, favor metastasis’, and ‘favor meningioma—cannot rule out metastatic tumor’. Paraffin sections are often more clearly diagnostic, e.g. in the neuroendocrine carcinoma, nuclear features were highly suggestive of a neuroendocrine tumor rather than adenoma. However, in the case of the SNUC, the distinction from a moderately pleomorphic pituitary adenoma was difficult even on high quality routine stained permanent sections.

Immunohistochemistry becomes extremely helpful, though even this type of evaluation may not be definitive. An important negative finding that frequently points to the diagnosis of *something other than* pituitary adenoma, is the complete *absence* of tumor immunoreactivity for any of the anterior pituitary hormones (prolactin, human growth hormone, etc). Synaptophysin immunoreactivity present strongly and diffusely throughout one of the tumors supported the diagnosis of neuroendocrine carcinoma, though patchy synaptophysin immunoreactivity can also be seen in pituitary adenomas. Strong, though focal, immunoreactivity for pankeratin and epithelial membrane antigen (EMA) supported the diagnosis of SNUC in one of the patients. Though cytokeratin immunoreactivity may be seen in pituitary adenomas, the combination of keratin and EMA staining is not [35]. CD68 is an excellent marker for macrophages and clearly highlighted the multinucleated giant cells in the giant cell tumor of bone .

Proliferating cell markers, detected immunohistochemically in tissue sections, are very helpful, though often not incorporated into current tumor classifications or grading because of the substantial inter-laboratory inconsistency in their application and quantification, and tremendous variability of staining even within a section showing apparently homogeneous neoplasm [35, 36]. In most laboratories, the ‘labelling index’ (LI) refers simply to a percentage of immunolabelled nuclei in a given section, since immunoreactivity implies an active stage of DNA synthesis, though not necessarily mitotic activity, i.e. mitotic activity is usually much lower than LI for a proliferating cell marker [36]. The most widely used marker for this is Ki-67, or MIB-1, which effectively and reproducibly labels the ‘*growth fraction*’ of tumor cells in paraffin sections. The Ki-67 can be rigorously quantified or estimated, as it was in our cases. In the case of SNUC in this series, the Ki-67 labeling index was strongly

suggestive of a neoplasm with aggressive growth characteristics, even though mitoses were relatively inconspicuous—the observed Ki-67 LI, estimated to be up to 20%, was far in excess of that seen in most pituitary adenomas, which usually show a LI of no more than 2–5% in the experience of one of the authors (HVV).

Clinical presentation

The most frequent symptoms of these four patients were headache and diplopia due to early involvement of the cavernous sinus dura and cranial nerves. Cavernous sinus involvement explains why tumors of the sphenoid sinus commonly cause symptoms such as headache, diplopia, and trigeminal sensory symptoms, whereas tumors of other paranasal cavities often present with epistaxis, nasal obstruction and discharge [2, 10, 12–15, 17, 21–24, 26, 37–40]. This typical presentation of oculomotor, abducens and trigeminal nerve palsies is not surprising given the immediate proximity of the cavernous sinus dura to the sphenoid sinus [2, 17, 21, 41, 42]. Cranial neuropathy in various combinations can occur with sphenoid cancers that erode the bony walls of the sinus. Harbinson et al. [21] identified three distinct groups of symptoms associated with sphenoid sinus cancers: all patients in our series are included in the so-called sphenocavernous syndrome, with early involvement of the cranial nerves of the cavernous sinus, rapidly evolving neuro-ophthalmological syndromes and facial pain or headache. Interestingly, one patient in our series who developed intense headache and a right partial 3 cranial nerve palsy 4 days prior to admission with subacute hemorrhage in his tumor had a clinical picture consistent with pituitary apoplexy [29, 43–47].

Imaging studies

Contrast-enhanced MRI and CT, although suggestive, particularly in retrospect, are generally not specific for a primary sphenoid cancer. While MRI is particularly useful in defining the intimate relationships between the tumor and the surrounding structures, thus allowing detection of dural invasion, and perineural and arterial encasement, CT scans, with multiplanar reconstructions, are superior in defining the degree and extent of bony erosion [2, 14, 29, 48]. In the present series, all the patients had a preoperative MR evaluation, while two also had CT. The only consistent imaging finding that indicated a non-pituitary tumor origin of these tumors was the upward displacement or non-involvement of the pituitary gland with sellar floor destruction, which thus favored a differential diagnosis of sphenoid sinus tumor, clival chordoma or other primary bony tumor or metastases. However, as mentioned, in one case the MRI features and clinical presentation favored pituitary apoplexy from a hemorrhagic macroadenoma. Two patients underwent transnasal biopsy which provided a definitive preoperative histological diagnosis that was confirmed with transsphenoidal tumor debulking.

Table 3. Expected survival rates for different tumor types in this series

Histologic type	Average survival rate (months)	5-year overall survival (%)
Neuroendocrine carcinoma	10	20 ± 3
Sinonasal undifferentiated carcinoma	51	40 ± 9
Mucoepidermoid carcinoma	52	50–80
Giant cell tumor	79	60 ± 5

See Refs. [2, 3, 7, 12, 13, 16, 19, 26, 38, 39, 49–51].

Surgical approach considerations

The natural history of malignant lesions of the sphenoid sinus is known to be relatively poor [3, 16, 20, 25, 39, 49–51]. However, some reports show a significant tumor-free survival after surgical resection with the best outcomes in patients with early diagnosis before onset of cranial neuropathies [2, 5, 21, 49], regardless of tumor pathology. In an effort to achieve gross tumor removal or *en bloc* resection, a number of craniofacial approaches for exposure of the sphenoid sinus have been proposed. These approaches facilitate maximal total tumor removal but may carry a higher rate of post-operative rhinological and cosmetic complications. Given that the tumors in these four patients were all localized to the sphenoid sinus, a direct endonasal microscopic approach to the sphenoid sinus was used in all cases. In one patient, a right endoscopic middle turbinectomy was also employed to gain greater access to the lateral sphenoid sinus. This direct endonasal approach is used routinely for all sellar lesions in our institution and requires minimal nasal mucosal dissection and generally allows a rapid recovery with few post-operative rhinological complications [11]. The major disadvantage of this approach is a more restricted exposure to the sphenoid sinus. However, all tumors exhibited extensive local invasion and two tumors were highly fibrous, rendering manipulations along dural planes more risky and hazardous. Complete tumor removal was thus not deemed possible in any patient. Consequently, even after knowing the definitive diagnosis in these patients, taking an additional more aggressive craniofacial approach to remove residual tumor was not recommended.

Adjuvant therapies and long-term prognosis

Because of the varied histological spectrum of sphenoid sinus neoplasms, there is a wide spectrum of prognosis among these neoplasms (Table 3) [1, 13–15, 25, 26, 37–39, 49–52]. At present, no universal standard treatment modality exists for such tumors, however there is considerable data regarding the effectiveness of radiation therapy [2, 3, 7, 13, 33, 39, 50, 51]. A dose between 50 and 60 Gy to the sphenoid sinus and surrounding tissues in a fractionated or hyperfractionated

stereotactic fashion appears optimal. However, mucoepidermoid carcinomas are known to have limited radiosensitivity. The role of chemotherapy is still unclear [2, 3, 20, 39]. Platinum-based regimens have been shown to have a response rate ranging from 36 to 84%. Neuroendocrine carcinomas appear to show a higher response with induction chemotherapy followed by radiotherapy [3]. All four of our patients received adjuvant stereotactic radiotherapy (SRT), and three also had chemotherapy. Longer follow-up is clearly needed in these patients to monitor for disease progression.

Conclusions

Primary sphenoid sinus tumors are rare neoplasms that commonly present with headache and cranial neuropathies attributable to cavernous sinus involvement. Recognition of these tumors and differentiating them from sellar masses is important in developing an appropriate multidisciplinary treatment plan that should include tumor debulking, postoperative radiotherapy and in some instances chemotherapy. Because of their invasive nature and often fibrous consistency, conservative transsphenoidal surgical debulking appears to be a reasonable approach.

References

- Alexander FW: Primary tumors of the sphenoid sinus. *Laryngoscope* 73: 537–546, 1963
- DeMonte F, Ginsberg LE, Clayman GL: Primary malignant tumors of the sphenoidal sinus. *Neurosurgery* 46: 1084–1091, 2000discussion 1091–1082, 2000
- Licitra L, Locati LD, Cavina R, Garassino I, Mattavelli F, Pizzi N, Quattrone P, Valagussa P, Gianni L, Bonadonna G, Solero CL, Cantu G: Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. *Ann Oncol* 14: 367–372, 2003
- Osguthorpe JD: Sinus neoplasia. *Arch Otolaryngol Head Neck Surg* 120: 19–25, 1994
- Al-Mefty O: Comment to the article: Liu JK, Decker D, Schaefer SD, Moscatello AL, Orlandi RR, Weiss MH, Couldwell WT: Zones of approach for craniofacial resection: minimizing facial incisions for resection of anterior cranial base and paranasal sinus tumors. *Neurosurgery* 53: 1136, 2003
- Liu JK, Decker D, Schaefer SD, Moscatello AL, Orlandi RR, Weiss MH, Couldwell WT: Zones of approach for craniofacial resection: minimizing facial incisions for resection of anterior cranial base and paranasal sinus tumors. *Neurosurgery* 53: 1126–1135, 2003 discussion 1135–1127, 2003
- Patel SG, Singh B, Polluri A, Bridger PG, Cantu G, Cheesman AD, deSa GM, Donald P, Fliss D, Gullane P, Janecka I, Kamata SE, Kowalski LP, Kraus DH, Levine PA, dos Santos LR, Pradhan S, Schramm V, Snyderman C, Wei WI, Shah JP: Craniofacial surgery for malignant skull base tumors: report of an international collaborative study. *Cancer* 98: 1179–1187, 2003
- de Divitiis E, Cappabianca P, Cavallo LM: Endoscopic transsphenoidal approach: adaptability of the procedure to different sellar lesions. *Neurosurgery* 51: 699–705, discussion 705–697, 2002
- de Divitiis E, Cappabianca P: Endoscopic Endonasal Transsphenoidal Surgery. Springer-Verlag, Wien, New York, 2003, p 198
- Donald PJ, Boggan J: Sphenoidal and cavernous sinus resection for tumor. *J Otolaryngol* 19: 122–129, 1990
- Zada G, Kelly DF, Cohan P, Wang C, Swerdloff R: Endonasal transsphenoidal approach for pituitary adenomas and other sellar lesions: an assessment of efficacy, safety, and patient impressions. *J Neurosurg* 98: 350–358, 2003
- Donald PJ, Boggan JE: Sphenoid sinus malignancies. *J Craniofac Surg* 6: 15–23, 1995
- Katz TS, Mendenhall WM, Morris CG, Amdur RJ, Hinerman RW, Villaret DB: Malignant tumors of the nasal cavity and paranasal sinuses. *Head Neck* 24: 821–829, 2002
- Lawson W, Reino AJ: Isolated sphenoid sinus disease: an analysis of 132 cases. *Laryngoscope* 107: 1590–1595, 1997
- Wyllie JW, Kern EB, Djalilian M: Isolated sphenoid sinus lesions. *Laryngoscope* 83: 1252–1265, 1973
- Bridger MW, Beale FA, Bryce DP: Carcinom of the paranasal sinuses – a review of 158 cases. *J Otolaryngol* 7: 379–388, 1978
- Levine H: The sphenoid sinus, the neglected nasal sinus. *Arch Otolaryngol* 104: 585–587, 1978
- Mickel RA, Zimmerman MC: The sphenoid sinus – a site for metastasis. *Otolaryngol Head Neck Surg* 102: 709–716, 1990
- Parsons JT, Mendenhall WM, Mancuso AA, Cassisi NJ, Million RR: Malignant tumors of the nasal cavity and ethmoid and sphenoid sinuses. *Int J Radiat Oncol Biol Phys* 14: 11–22, 1988
- Brasnu D, Laccourreye O, Bassot V, Laccourreye L, Naudo P, Roux FX: Cisplatin-based neoadjuvant chemotherapy and combined resection for ethmoid sinus adenocarcinoma reaching and/or invading the skull base. *Arch Otolaryngol Head Neck Surg* 122: 765–768, 1996
- Harbison JW, Lessell S, Selhorst JB: Neuro-ophthalmology of sphenoid sinus carcinoma. *Brain* 107((Pt 3): 855–870, 1984
- Lee KJ, Yanagisawa K: An obscure etiology for headache: sphenoid sinus disease. *Yonsei Med J* 29: 209–218, 1988
- Pearlman SJ, Lawson W, Biller HF, Friedman WH, Potter GD: Isolated sphenoid sinus disease. *Laryngoscope* 99: 716–720, 1989
- Rothfield RE, de Vries EJ, Rueger RG: Isolated sphenoid sinus disease. *Head Neck* 13: 208–212, 1991
- Waldron J, Witterick I: Paranasal sinus cancer: caveats and controversies. *World J Surg* 27: 849–855, 2003
- Weber AL, Stanton AC: Malignant tumors of the paranasal sinuses: radiologic, clinical, and histopathologic evaluation of 200 cases. *Head Neck Surg* 6: 761–776, 1984
- Barkan AL, Chandler WF: Giant pituitary prolactinoma with falsely low serum prolactin: the pitfall of the “high-dose hook effect”: case report. *Neurosurgery* 42: 913–915; discussion 915–916, 1998
- Cook RJ, Uttley D, Wilkins PR, Archer DJ, Bell BA: Prolactinomas in men masquerading as invasive skull base tumours. *Br J Neurosurg* 8: 51–55, 1994
- Majos C, Coll S, Aguilera C, Acebes JJ, Pons LC: Imaging of giant pituitary adenomas. *Neuroradiology* 40: 651–655, 1998
- Minniti G, Jaffrain-Rea ML, Lunardi P, Gulino A, Tamburrano G: 15-year-old boy with ocular palsy and headache. Invasive macroprolactinoma. *Eur J Pediatr* 155: 717–719, 1996
- Schoff C, Schoff-Siegert B, Karstens JH, Bremer M, Lenarz T, Cuarezma JS, Samii M, von zur Muhlen A, Brabant G: Falsely low serum prolactin in two cases of invasive macroprolactinoma. *Pituitary* 5: 261–265, 2002
- Asa SL: Tumors of the Pituitary Gland. Universities Associated for Research and Education in Pathology, Bethesda, 1997
- Firlik KS, Kondziolka D, Lunsford LD, Janecka IP, Flickinger JC: Radiosurgery for recurrent cranial base cancer arising from the head and neck. *Head Neck* 18: 160–165; discussion 166, 1996
- Vinters HV, Mischel PS, Ranchod M: Central nervous system. *Pathology (Phila)* 3: 513–534, 1996
- Ellison D, Love S, Chimelli L, Harding BN, Lowe J, Vinters HV: *Neuropathology A Reference Text of CNS Pathology*. 2Mosby, Edinburgh, London, 2004, p 717–728
- Prayson RA: Cell proliferation and tumors of the central nervous system, part II: radiolabeling, cytometric, and immunohistochemical techniques. *J Neuropathol Exp Neurol* 61: 663–672, 2002

37. Cakmak O, Ergin NT, Aydin MV: Isolated sphenoid sinus adenocarcinoma: a case report. *Eur Arch Otorhinolaryngol* 259: 266–268, 2002
38. Cheng VS, Wang CC: Carcinomas of the paranasal sinuses: a study of sixty-six cases. *Cancer* 40: 3038–3041, 1977
39. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T: Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 92: 3012–3029, 2001
40. Sjaastad O: Cluster headache: the possible significance of midline structures. *Cephalalgia* 8: 229–236, 1988
41. Cappabianca P, Alfieri A, de Divitiis E: Endoscopic endonasal transsphenoidal approach to the sella: towards functional endoscopic pituitary surgery (FEPs). *Minim Invasive Neurosurg* 41: 66–73, 1998
42. Sethi DS, Stanley RE, Pillay PK: Endoscopic anatomy of the sphenoid sinus and sella turcica. *J Laryngol Otol* 109: 951–955, 1995
43. Bills DC, Meyer FB, Laws ER Jr, Davis DH, Ebersold MJ, Scheithauer BW, Ilstrup DM, Abboud CF: A retrospective analysis of pituitary apoplexy. *Neurosurgery* 33: 602–608; discussion 608–609, 1993
44. da Motta LA, de Mello PA, de Lacerda CM, Neto AP, da Motta LD, Filho MF: Pituitary apoplexy Clinical course, endocrine evaluations and treatment analysis. *J Neurosurg Sci* 43: 25–36, 1999
45. Glendenning P, Pullan PT, Knuckey NW: Pituitary apoplexy: the importance of citing the differential diagnosis. *Med J Aust* 173: 548–549, 2000
46. Inamasu J, Hori S, Sekine K, Aikawa N: Pituitary apoplexy without ocular/visual symptoms. *Am J Emerg Med* 19: 88–90, 2001
47. Wakai S, Fukushima T, Teramoto A, Sano K: Pituitary apoplexy: its incidence and clinical significance. *J Neurosurg* 55: 187–193, 1981
48. Ginsberg LE: Neoplastic diseases affecting the central skull base: CT and MR imaging. *Am J Roentgenol* 159: 581–589, 1992
49. Alvarez I, Suarez C, Rodrigo JP, Nunez F, Caminero MJ: Prognostic factors in paranasal sinus cancer. *Am J Otolaryngol* 16: 109–114, 1995
50. Myers LL, Nussenbaum B, Bradford CR, Teknos TN, Esclamado RM, Wolf GT: Paranasal sinus malignancies: an 18-year single institution experience. *Laryngoscope* 112: 1964–1969, 2002
51. Rosenthal D, Barker JL, El-Naggar AK, Glisson BS, Kies MS, Diaz EM, Clayman GL, DeMonte F, Selek U, Morrison WM, Ang KK, Garden AS: Sinonasal carcinoma with neuroendocrine differentiation: patterns of failure according to histologic phenotype. *Int J Radiat Oncol Biol Phys* 57(Suppl 2): S248–S249, 2003
52. Jeng YM, Sung MT, Fang CL, Huang HY, Mao TL, Cheng W, Hsiao CH: Sinonasal undifferentiated carcinoma and nasopharyngeal-type undifferentiated carcinoma: two clinically, biologically, and histopathologically distinct entities. *Am J Surg Pathol* 26: 371–376, 2002

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