Head and Neck Pathol (2012) 6:75–100
DOI 10.1007/s12105-012-0336-9

NORTH AMERICAN SOCIETY OF HEAD AND NECK PATHOLOGY COMPANION MEETING, MARCH 18, 2012, VANCOUVER, BRITISH COLUMBIA

Ectopic Sphenoid Sinus Pituitary Adenoma (ESSPA) with Normal Anterior Pituitary Gland: A Clinicopathologic and Immunophenotypic Study of 32 Cases with a Comprehensive Review of the English Literature

Lester D. R. Thompson · Raja R. Seethala · Susan Müller

Received: 29 November 2011 / Accepted: 25 January 2012 / Published online: 20 March 2012

Abstract Ectopic sphenoid sinus pituitary adenoma (ESSPA) may arise from a remnant of Rathke's pouch. These tumors are frequently misdiagnosed as other neuroendocrine or epithelial neoplasms which may develop in this site (olfactory neuroblastoma, neuroendocrine carcinoma, sinonasal undifferentiated carcinoma, paraganglioma, melanoma). Thirty-two patients with ESSPA identified in patients with *normal* pituitary glands (intact sella turcica) were retrospectively retrieved from the consultation files of the authors' institutions. Clinical records were reviewed with follow-up obtained. An immunohistochemical panel was performed on available material. Sixteen males and 16 females, aged 2–84 years (mean, 57.1 years), presented with chronic sinusitis, headache, obstructive symptoms, and visual field defects, although several were asymptomatic (n = 6). By definition, the tumors were centered within the sphenoid sinus and demonstrated, by imaging studies or intraoperative examination, a normal sella turcica without a concurrent pituitary adenoma. A subset of tumors showed extension into the nasal cavity (n = 5) or nasopharynx (n = 9). Mean tumor size was 3.4 cm. The majority of tumors were beneath an intact respiratory epithelium (n = 22), arranged in many different patterns (solid, packets, organoid, pseudorosette-rosette, pseudopapillary, single file, glandular, trabecular, insular). Bone involvement was frequently seen (n = 21). Secretions were present (n = 16). Necrosis was noted in 8 tumors. The tumors showed a variable cellularity, with polygonal, plasmacytoid, granular, and oncocytic tumor cells. Severe pleomorphism was uncommon (n = 5). A delicate, salt-and-pepper chromatin distribution was seen. In addition, there were intranuclear cytoplasmic inclusions (n = 25) and multinucleated tumor cells (n = 18). Mitotic figures were infrequent, with a mean of 1 per 10 HPFs and a <1% proliferation index (Ki-67). There was a vascularized to sclerotic or calcified stroma. Immunohistochemistry highlighted the endocrine nature of the tumors, with synaptophysin (97%), CD56 (91%), NSE (76%) and chromogranin (71%); while pan-cytokeratin was positive in 79%, frequently with a dot-like Golgi accentuation (50%). Reactivity with pituitary hormones included 48% reactive for 2 or more hormones (plurihormonal), and 33% reactive for a single hormone, with prolactin seen most frequently (59%); 19% of cases were non-reactive. The principle differential diagnosis includes olfactory neuroblastoma, neuroendocrine carcinoma, melanoma, and meningioma. All patients were treated with surgery. No patients died from disease, although one patient died with persistent disease (0.8 months). Surgery is curative in the majority of cases, although recurrence/persistence was seen in 4 patients (13.8%). In conclusion, ESSPAs are rare, affecting middle aged patients with nonspecific symptoms, showing characteristic light microscopy and immunohistochemical features of their intrasellar counterparts. When encountering a tumor within the sphenoid sinus, ectopic pituitary adenoma must be considered, and pertinent imaging, clinical, and immunohistochemical evaluation undertaken to exclude tumors within the differential diagnosis. This will result in accurate classification,

L. D. R. Thompson (✉)
Woodland Hills Medical Center, Department of Pathology, Southern California Kaiser Permanente Group, 5601 De Soto Avenue, Woodland Hills, CA 91365, USA
e-mail: Lester.D.Thompson@kp.org

R. R. Seethala
Department of Pathology, University of Pittsburgh, Pittsburgh, PA, USA

S. Müller
Department of Pathology, Emory University, Atlanta, GA, USA

helping to prevent the potentially untoward side effects or complications of incorrect therapy.

Keywords Sphenoid sinus · Ectopic pituitary adenoma · Neuroectodermal tumor · Neuroendocrine tumor · Adenoma · Pituitary neoplasm · Nasal cavity · Pituitary hormones · Sphenoid sinus pathology · Immunohistochemistry · Prognosis · Survival · Imaging · Differential diagnosis

Introduction

Neuroectodermal and neuroendocrine tumors of the sinonasal tract encompass a selected tumor group, comprising <2% of all sinonasal tract tumors. These tumors include typical carcinoid (neuroendocrine tumor, grade 1), atypical carcinoid (neuroendocrine tumor, grade 2), small cell carcinoma (neuroendocrine tumor, grade 3), paraganglioma, Ewing sarcoma/primitive neuroectodermal tumor, olfactory neuroblastoma, melanotic neuroectodermal tumor of infancy, mucosal melanoma, and ectopic pituitary adenoma.

By definition of the World Health Organization, ectopic pituitary adenoma is a benign pituitary gland neoplasm occurring separate from, and without involvement of, the sella turcica (i.e., with normal anterior pituitary gland) [1]. The pituitary gland is housed within the sella just above the sphenoid sinuses. Immediately surrounding the pituitary gland are the paired, septated cavernous sinuses, which also envelop the internal carotid artery, and contain or surround branches of several cranial nerves. The vast majority of pituitary adenomas are within the sella. Thus, careful imaging evaluation of these structures is required, along with intraoperative assessment to make certain that the sella is intact. The relevant anatomy for imaging evaluation of the sphenoid sinus at the level of the nasopharynx is shown in Fig. 1.

The anterior pituitary primordium appears at about the 4th week of embryogenesis. During the 8th developmental week, the pituitary divides into sellar and pharyngeal parts. There is a supradiaphragmatic attachment to the pituitary stalk, while there is an infrasellar invagination referred to as Rathke's pouch. The craniopharyngeal canal allows for migration of the pituitary tissue into the sphenoid or nasopharynx. Therefore, it

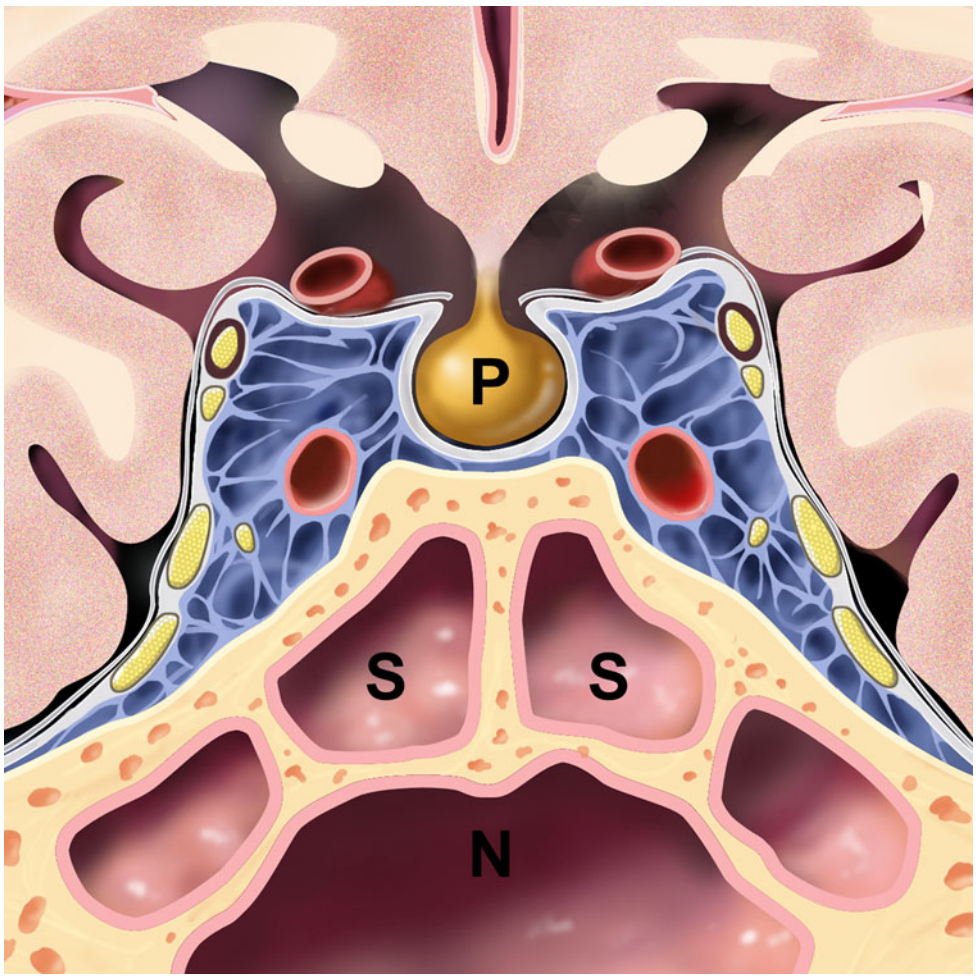

Fig. 1 A diagrammatic representation of the anatomy around the sphenoid sinus (*S*), immediately above the nasopharynx (*N*), and immediately below the sella turcica containing the pituitary gland (*P*). The cavernous sinus (*blue*), internal carotid arteries (*red*) and cranial nerve branches (*yellow*) all have an intimate relationship with the pituitary fossa and sphenoid sinus (Used by special permission of Amirsys, Inc., Salt Lake City, UT, USA)

is thought that "ectopic" pituitary adenomas are derived from these embryologic remnants along the path of migration of Rathke's pouch [2–4]. Nasopharyngeal and sphenoid sinus or sphenoid bone ectopic pituitary tissue can be fully functional, since pharyngeal pituitary tissue begins to produce hormones around the 17–18th week of gestation, about 8 weeks later than sellar pituitary function begins [5, 6]. Knowledge of pituitary embryonic development should result in the consideration of a pituitary adenoma in the assessment of a sphenoid sinus tumor.

Within the upper aerodigestive tract, ectopic pituitary adenomas are most frequent in the sphenoid sinus and the nasopharynx, although also identified in the nasal cavity, ethmoid sinus, temporal bone, and nasal bridge [7, 8]. Intracranial, extrasellar ectopic pituitary adenomas are also recognized (suprasellar, Meckel's cave, cavernous sinus, thalamus) [9], but these, along with tumors found exclusively in the nasopharynx and nasal cavity, are excluded from further consideration in this report.

Ectopic sphenoid sinus pituitary adenoma (ESSPA) *without* sella turcica involvement is rare, with few cases reported in the English literature [7, 10–41] (Table 1). The infrequency of these tumors may result in misclassification and subsequent inappropriate management. While there have been two series [20, 40] the information focused on imaging findings with only limited information about the histologic findings. Therefore, there is no large comprehensive evaluation of ESSPA when there is a normal sella turcica. This study focused on the clinical presentation, histologic features and immunohistochemical profiles of these tumors in relation to the differential diagnosis and patient management. It is important to state at the outset, however, that subclassification of these tumors by current methods, using pituitary transcription factors (Pit-1, T-pit, SF-1, ER-α, GATA-2, α-subunits) was not possible due to the consultative nature of the samples and lack of sufficient material. Nonetheless, this is not a treatise on primary pituitary tumors, but instead an exposition of paranasal sinus tumors.

Table 1 Clinicopathologic data on patients with ectopic sphenoid sinus pituitary adenomas from a review of the English literature [7, 10–41]

Characteristics	Sphenoid sinus pituitary adenoma total: n = 43
Gender	
Women	27
Men	16
Age (in years)	
Range	17–76
Mean	51.8
Women (mean)	50.1
Men (mean)	52.2
Symptom duration (in months)[a]	
Range	1–360
Mean	62.1
Women (mean)	68.0
Men (mean)	49.9
Symptoms at presentation[a, b]	
Obstruction, sinusitis, rhinorrhea, drainage, discharge	14
Headache or pain, nerve changes	13
Cushing symptoms (bruising, hypertension, acne, facial hair, weakness)	10
Acromegaly	8
Visual disturbances (diplopia, acuity loss, blurring)	8
Amenorrhea, galactorrhea or impotency	7
Epistaxis	3
Hormone production clinically[a]	
Cushing disease	12
Prolactin	12
Acromegaly	9
None	10
Size (in cm)[a]	
Range	0.5–7.5
Mean	2.5
Treatment	
Surgery alone	22
Surgery and medical therapy	9
Surgery and radiation	7
Other combinations	5

[a] Parameter was not stated in all cases

[b] Patients may have experienced more than one symptom

Materials and Methods

Thirty-two cases of pituitary adenoma involving the sphenoid sinuses were retrieved from the consultation files of the authors, supplemented by cases from the files of the Otorhinolaryngic-Head & Neck Tumor Registry of the Armed Forces Institute of Pathology, encompassing 1970 to 2010. An approximate incidence is suggested by the five ectopic pituitary adenomas identified from 201 primary sphenoid sinus lesions. During this same interval, 1,024 sphenoid sinus lesions identified compared to 1,024 pituitary adenomas diagnosed. This would suggest that approximately 0.48% (5/1024) of pituitary adenomas are ectopic; approximately 2.5% (5/201) of sphenoid sinus lesions are pituitary adenomas.

By definition, the sella turcica and pituitary fossa regions were required to be normal (i.e., unaffected by the neoplasm) for inclusion in this study. When available,

magnetic resonance imaging (MRI) is preferred for pituitary imaging, but computerized tomography (CT) was used in many cases.

Materials within the files were supplemented by a review of the patient demographics (gender, age, and race); symptoms and physical findings at presentation including chronic sinusitis, headache, obstructive symptoms, difficulty breathing, visual changes, mass, pain, nerve paralysis, changes in balance, and endocrinopathies; duration of symptoms; and past medical and surgical history. In addition, we reviewed imaging studies, surgical pathology and operative reports and obtained follow-up information by direct written or oral communication with the referring pathologist, patient's physician, oncology data services and tumor registries, or the patient (or patient's family member[s]). Follow-up data included information regarding presence of recurrent disease, treatment modalities used, and the current patient status. Patients who were found to have a primary pituitary adenoma within the sella turcica (during surgery; by preoperative imaging evaluation; or who developed a pituitary tumor within 12 months of surgery) were excluded from further consideration. Most cases were submitted as consultations to the authors, who conducted this study as a retrospective review. Submitted diagnoses by the primary pathologists included neuroendocrine carcinoma, olfactory neuroblastoma, sinonasal undifferentiated carcinoma, nasopharyngeal carcinoma, paraganglioma, melanoma, meningioma, and metastatic carcinoid. This clinical investigation was conducted in accordance and compliance with an Internal Review Board authorization (#5968) performed under the direction of Southern California Permanente Medical Group.

Specific information about the exact location, lateralization and tumor size (greatest dimension in cm) was documented. Hematoxylin and eosin-stained slides from all cases were reviewed to document specific histologic features, to include: respiratory epithelium (present or absent); tumor extension (bone(s), soft tissue: into the subepithelial stroma of the sinonasal tract); perineural invasion; lymph-vascular invasion; architectural pattern of growth (solid, single cell, organoid, trabecular, insular, papillary, glandular, cystic, rosettes); secretions or concretions present; necrosis (absent or present); tumor cellularity (low: at least the width of two nuclei between nuclei; moderate: nuclei adjacent to one another, but not crowded; high: nuclear overlapping and crowding); cell type (polygonal, plasmacytoid, spindled, cuboidal, oncocytic, granular); nuclear chromatin distribution; nuclear pleomorphism (mild: slight variation, with predominantly a monotonous population; moderate: intermediate variability with nuclei up to 2× the size of other nuclei, easily identified nucleoli, and chromatin distribution irregularities; or severe [anaplastic]: profound pleomorphism in aggregates or sheets of cells; high nuclear to cytoplasmic ratio, irregular nuclei and nuclear chromatin distribution, prominent and/or irregular nucleoli, indescribably bizarre nuclei); intranuclear cytoplasmic inclusions (present or absent); nucleoli (present: small or large; or absent); fibrous bodies; tumor cell multinucleation; mitotic figures (number of mitotic figures per 10 high power fields [magnification at 40× with a 10× objective lens using Olympus BX41 microscope]); atypical mitotic figures (present or absent, and defined by abnormal chromosome spread, tripolar or quadripolar forms, circular forms, or indescribably bizarre); background stroma; and the presence of other notable microscopic pathologic findings.

Immunophenotypic analysis was performed in cases with sufficient suitable material by a standardized Envision™ method employing 4 μm-thick, formalin fixed, paraffin embedded sections. Table 2 documents the pertinent, commercially available immunohistochemical antibody panel used. The analysis was performed on a single representative block for each primary tumor. However, the biopsies were often small, yielding a limited amount of tissue for additional examination. Epitope retrieval was performed, as required by the manufacturer's guidelines. Standard positive controls were used throughout, with serum used as the negative control. The antibody reactions were graded as absent to weak (0 to 1+), moderate (2+ to 3+) and strong (4+) staining, and the fraction of positive cells was determined by separating them into four groups: <10% (focal), 11–50% (patchy), 51–90% (majority), and >90% (diffuse); proliferation markers were separated into <2, 2–10, and >10%. Importantly, pituitary transcription factors were not tested due to the paucity of tumor material and the consultative nature of the samples obtained, many of which were without unstained slides or blocks available.

A review of the English literature based on a MEDLINE search from 1966 to 2011 was performed and all cases involving the sphenoid sinus specifically were included in the review (Table 1). However, cases were excluded if the lesion arose primarily in the nasopharynx, or involved the pituitary (sella turcica) at the time of presentation or at a later time [7, 42–44]. Clinical series were selected if critical information about sinonasal tract or sphenoid sinus lesions was included, but excluded if the information was too generalized [20, 40, 44]. Duplicate reports were excluded from further evaluation [45]. No foreign language articles were included.

Statistical evaluation was performed using a standard statistics software package (Daniel Soper) with categorical variables analyzed using Chi-square tests and Fisher's Exact tests to compare observed and expected frequency distributions. Comparison of means between groups were made with independent t-tests (including 1-tailed and 2-tailed tests with degrees of freedom) or one-way analysis of variance, depending on whether there were two groups or more than two groups, respectively. Confidence intervals

Table 2 Immunohistochemical panel

Antigen/antibody/clone	Type	Company	Dilution	Antigen recovery
Cytokeratin (AE1/AE3:M3515 and CAM5.2)	mm	Dako, Carpinteria, CA	1:40	CC1, 30 min
		Becton-Dickson, Franklin Lakes, NJ	1:8	
CK7 (OV-TL-12/30)	mm	Dako	1:200	CC1, 30 min
CK5/6 (D5/16 B4)	mm	Dako	1:25	E2, 20 min
CAM5.2 (CK8/18)	mm	Becton-Dickson	1:8	CC1, 30 min
Synaptophysin	rp	Ventana Medical Systems, Tucson, AZ	Neat	CC1, 30 min
CD56 (123C3.D5)	mm	Lab Vision/NeoMarkers, Fremont, CA	Neat	CC1, 30 min
NSE (BBS-NC-V1)	mm	Ventana Medical Systems	Neat	CC1
Chromogranin (LK2H10)	mm	Ventana Medical Systems	Neat	CC1, 8 min
CD99 (O13)	mm	Signet Laboratories, Dedham, MA	1:400	E2, 20 min
Ki-67 (MIB-1)	mm	Dako	1:100	CC1, 30 min
S100 protein	rp	Dako	1:2,000	CC1, 30 min
Prolactin (SPM108)	mm	Thermolife Scientific, Waltham, MA	1:1,500	Citrate buffer, 20 min
Follicle stimulating hormone (C10)	mm	Dako	1:50	None
Luteinizing hormone (C93)	mm	Dako	1:600	EDTH, 20 min
ACTH (02A3)	mm	Dako	1:4,000	None
Thyroid stimulating hormone (QB2/6)	mm	Leica Microsystems, Buffalo Grove, IL	1:400	EDTH, 20 min
Growth hormone (GH-45)	mm	Novus Biologicals, Littleton, CO	1:2,000	EDTH, 30 min
Calcitonin	rp	Fisher/Biomedical Inc., Venice, FL	1:8	EDTA, 20 min

mm mouse monoclonal; *rp* rabbit polyclonal

of 95% were generated for all positive findings. The alpha level was set at $p < 0.05$.

Results

Clinical

The patients included 16 women and 16 men (Table 3) who ranged in age from 2 to 84 years (mean, 57.1 years). There was no difference in the mean age at presentation between males and females. Tumors which involved more than the sphenoid sinus tended to present at a younger age: sphenoid sinus only: 61.0 years; sphenoid sinus and nasal cavity: 50.1 years; sphenoid sinus and nasopharynx: 52.8 years; although this did not reach statistical significance ($p = 0.095$). The majority of patients were white (n = 24), with six black patients. Six of the patients were asymptomatic (4 females; 2 males) and the tumors were identified during imaging evaluation for other reasons (such as a fall, work-up of epilepsy and cerebral palsy, work-up for metastatic tumor). The remaining patients presented with a variety of symptoms, and frequently with more than one symptom. Symptoms included: headache and/or pain (n = 10); chronic sinusitis (n = 9); obstructive symptoms (including difficulty breathing and nasal stuffiness; n = 7); visual disturbances (including double vision, blurred vision, increased lacrimation; n = 5); mass (n = 3); nerve changes (numbness or paresis; n = 2); balance alterations (n = 1); and hirsutism (n = 1). Symptoms were present from 1 month up to 360 months (average duration of 29.1 months). Female patients experienced symptoms longer (average of 58.4 months) compared to males (average 11.1 months). However, these differences were probably skewed by the single female patient with symptoms for 360 months. There was no difference ($p = 0.195$) in the average length of time with symptoms between sphenoid sinus only (8.3 months), and tumors that expanded into the nasal cavity (13.7 months) or nasopharynx (60.9 months). Seven patients had preoperatively elevated hormone levels tested as a result of finding a sphenoid sinus tumor, including three patients with prolactin (PRL) elevation (219–695 μg/L); two patients with adrenocorticotropic hormone (ACTH) elevation (115 and 192 pg/mL); one patient with elevated thyroid stimulating hormone (TSH); and one patient with elevated TSH, luteinizing hormone (LH), follicle stimulating hormone (FSH) and ACTH (plurihormonal elevation). It was only this latter patient, a 34-year-old woman, who had an endocrinopathy, specifically hirsutism (Cushing symptoms). Hormone elevation did not seem to correspond to outcome (mean survival: 15.4 years). Four patients had experienced separate additional primary tumors, unrelated to the sinonasal tract lesion: (1) a woman with endometrial carcinoma, with the sphenoid sinus tumor identified during imaging evaluation for metastases; (2) a man with a history of melanoma, who developed blurred vision; (3) a man with a

Table 3 Clinical characteristics

Clinical characteristics	Number: n = 32
Gender	
Females	16
Males	16
Race	
White	24
Black	6
Age (in years)	
Range	2–84
Mean	57.1
Women (mean)	57.7
Men (mean)	57.1
Sphenoid sinus only	61.0
Sphenoid and nasal cavity	50.1
Sphenoid and nasopharynx	52.8
Symptoms*	
Duration (range, in months)	1–360
Duration (mean, in months)	29.1
Females (mean duration of symptoms)	58.4
Males (mean duration of symptoms)	11.1
Asymptomatic	6
Headache and/or pain	10
Chronic sinusitis	9
Obstructive symptoms	7
Visual disturbances	5
Mass	3
Nerve changes	2
Balance or hirsutism	2
Anatomic site	
Sphenoid sinus alone	18
Sphenoid sinus and nasal cavity	5
Sphenoid sinus and nasopharynx	9
Laterality	
Right	13
Left	10
Bilateral	9
Size (cm)#	
Range	0.8–8.0
Mean	3.4
Female (mean)	3.2
Male (mean)	3.5
Sphenoid sinus alone (mean)	2.8
Sphenoid sinus and nasal cavity (mean)	3.6
Sphenoid sinus and nasopharynx (mean)	4.4

* More than one symptom may have been present

Parameter was not stated in all cases

history of nasopharyngeal carcinoma several years earlier (treated with radiation and chemotherapy), who was noted to have a sphenoid sinus mass during routine imaging follow-up; and (4) a man with a pulmonary small cell carcinoma, noted to have a sphenoid sinus mass during imaging evaluation for metastatic disease. Three of these patients died of disseminated disease related to their non-sphenoid tumor, while the patient with nasopharyngeal carcinoma was lost to long-term follow-up. None of the patients in this series had a syndrome or inherited genetic disorder (Multiple Endocrine Neoplasia type 1, Carney complex, McCune-Albright syndrome, Familial Isolated Pituitary Adenomas [46]).

Imaging Findings

The imaging studies demonstrated a mass within the sphenoid sinus, frequently associated with lateral wall erosion or destruction, expansion into the cavernous sinus, erosion of the anterior clivus, and/or expansion into the nasopharynx or roof of the nasal cavity (Fig. 2). Bone sclerosis or calcification at the advancing edge was noted, suggesting a tumor that had been present for some time. The pituitary fossa was intact without any pituitary defects detected. The floor of the sella turcica (infrasellar) was bowed upward in a few cases, but without breakthrough or expansion into the sella space. There was no central nervous system connection documented in any of the cases, either by imaging studies or during intraoperative assessment.

Pathologic Features

Macroscopic

The tumors involved the sphenoid sinus alone (n = 18), the sphenoid sinus with extension into the nasal cavity (n = 5), or the sphenoid sinus with nasopharynx extension (n = 9). Thirteen tumors affected the right side, 10 the left

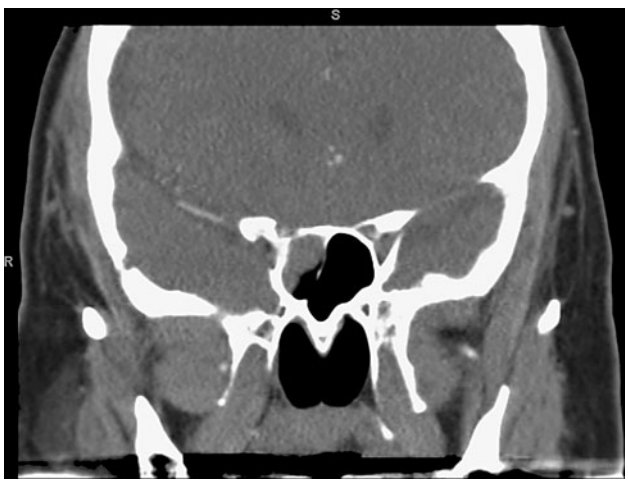

Fig. 2 A mass is noted within the right sphenoid sinus, showing intact wings of the sphenoid bone

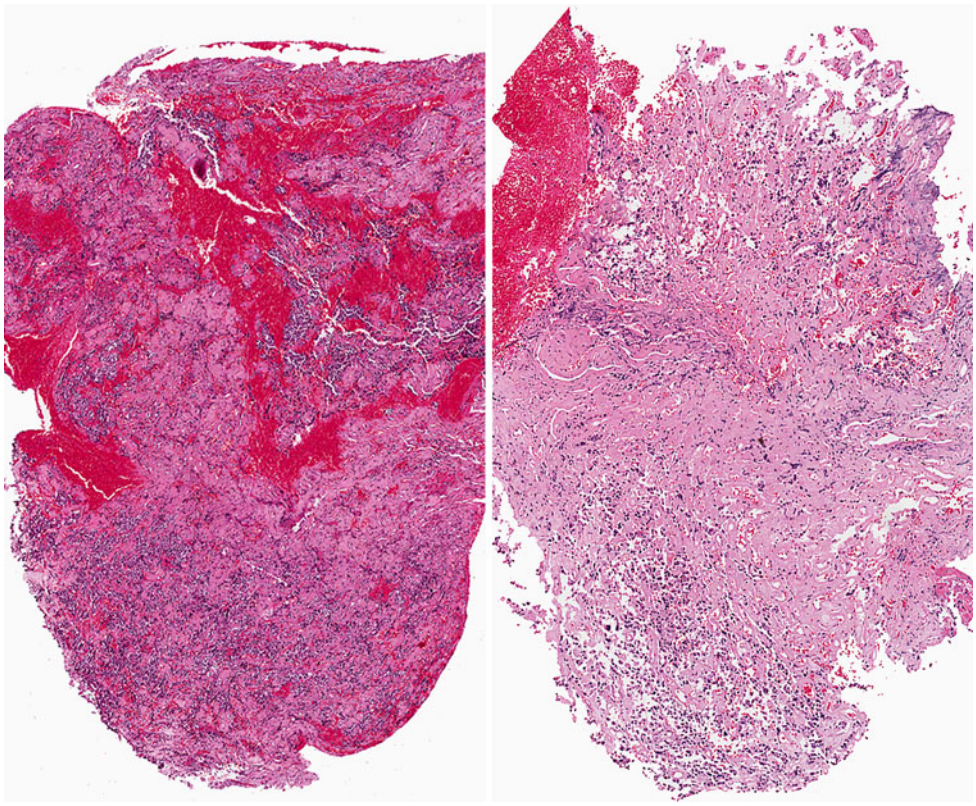

Fig. 3 Fragments of tissue may appear polypoid. *Left* Lesional hemorrhage and fibrosis surround the neoplastic cells. *Right* Heavy background stromal fibrosis nearly completely obscures the small cords of compressed tumor cells

side and nine were bilateral. The tumors ranged in size from 0.8 to 8.0 cm in greatest single dimension, with a mean size of 3.4 cm. There was no significant difference in mean size between females (3.2 cm) versus males (3.5 cm). The tumors were described as irregular, multiple fragments of pink-red to grey-white-tan tissue, usually removed in piece-meal fashion (Fig. 3). Fragments could be mucoid, gelatinous to vascular, soft to firm and occasionally polypoid. Cystic or degenerative changes were noted. Necrosis was not recorded.

Microscopic

The majority of tumors demonstrated overlying intact respiratory surface epithelium (n = 22) that was not affected by the neoplasm, showing a grenz zone of separation (Fig. 4). There were several cases (n = 10) in which there was no respiratory or metaplastic squamous mucosa within the sample (Table 4). The neoplastic cells were contained within fragments of tissue, as most samples were curetted rather than resected "en bloc". The neoplastic cells infiltrated into the stroma, which was usually richly-vascularized and associated with fibrosis. In several cases (n = 10) the background was heavily collagenized and sclerotic, "squashing" the tumor into poorly recognized cords or single cells (Fig. 4). The collagenized stroma was present in 3 *silent* lactotrophs; 1 lactotroph adenoma; 3 plurihormonal adenomas; and 3 unclassified adenomas. Two cases showed a heavily calcified stroma. Bone or cartilage invasion or involvement was present in 21 cases (Figs. 4 and 5), although bone was not included in several samples. The tumors were centered in the sphenoid sinus, but 14 cases expanded to involve the nasal cavity or nasopharynx. Therefore, bone destruction can be expected as the tumors expanded into the adjacent structures. Even though nerves were identified, perineural invasion was not present nor was lymph-vascular invasion.

The neoplastic cells were arranged in a multitude of different architectural patterns, with nearly all tumors showing more than one pattern within the same tumor. The majority of tumors were arranged in a solid configuration with nests and sheets of neoplastic cells separated by a delicate fibrovascular stroma (Fig. 6). There was often (n = 7) a background of hemorrhage, which would occasionally create a pseudopapillary to papillary architecture (Fig. 7). A packeted or organoid pattern (n = 12; Fig. 7) frequently blended with a glandular (n = 6), trabecular (n = 5) or insular (n = 2) pattern. The blending of organoid and trabecular or insular patterns created a festooned look. Rosettes and pseudorosettes (Fig. 7) were present (n = 10), although this was not identified as a single pattern. There was often a small vessel in the center, with the cells arranged around, but away from the lumen (pseudorosette). Single file infiltration (n = 9) was one of

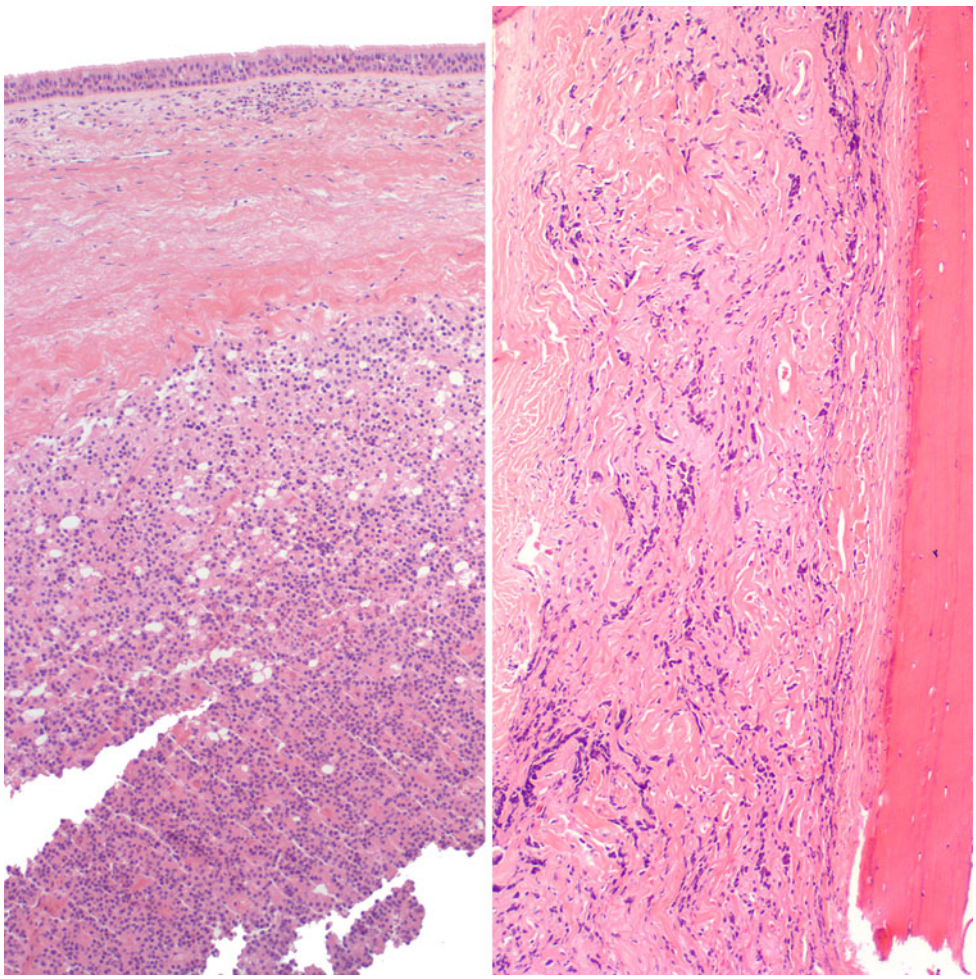

Fig. 4 *Left* An intact, uninvolved respiratory epithelium is subtended by a zone of fibrosis before the neoplastic proliferation is detected. *Right* Heavy stromal fibrosis compresses the neoplastic cells into small cords and individually infiltrating tumor cells. Note the bone (*right*)

the most difficult patterns to interpret, since the cells were squashed or compressed between bands of heavily collagenized stroma (Fig. 4). A predominantly cystic pattern was noted in a single case. An epithelioid appearance was most pronounced in the solid and glandular patterns, an important consideration when the differential diagnosis of sinonasal undifferentiated carcinoma or poorly differentiated carcinoma is considered. Secretions or concretions (Fig. 8) were identified within lumina or pseudolumina in 16 tumors. The material was eosinophilic and opaque, giving an appearance similar to "colloid" or "amyloid." Well-developed tumor necrosis (coagulative or comedonecrosis) was seen in 8 tumors (Fig. 8), although a number of additional tumors showed only apoptosis, a feature not considered within the spectrum of true tumor necrosis. The majority of tumors showed a low to moderate cellularity (n = 21), while 11 showed a high cellularity (Fig. 9). Based on the definition (see "Materials and Methods"), the high cellularity tumors were frequently those which were misinterpreted to represent an olfactory neuroblastoma or neuroendocrine carcinoma. In the tumors with a low cellularity, the cells had a low nuclear to cytoplasmic ratio or had abundant fibrovascular stroma that created more "space" in the lesion.

The neoplastic cells showed a variety of different appearances, to mirror the variation in patterns of growth. The dominant cell type was polygonal (n = 27), showing ample cytoplasm surrounding a round to regular nucleus. The cytoplasm ranged from amphophilic, eosinophilic, to granular or oncocytic (Fig. 10). A plasmacytoid appearance (n = 18) reflected nuclei eccentrically located within the cell that had abundant eosinophilic cytoplasm pulled off to one aspect. A "Golgi" space adjacent to the nucleus accentuated the plasmacytoid appearance (Fig. 10). Oncocytic cells, showing opacified, abundant, eosinophilic cytoplasm, were also common (n = 12). Spindled cells were uncommon (n = 1). The nuclear chromatin was delicate to hyperchromatic, arranged in a salt-and-pepper pattern, with heterochromatin distribution. Slightly open to vesicular nuclear chromatin was seen in several cases, a change which also highlighted nucleoli. Nuclear folds or grooves were present in a number of cases, resulting in nuclear contour irregularities. Nuclear pleomorphism was generally mild to moderate (n = 27), with severe

Table 4 Pathologic findings

Microscopic characteristics	Number: n = 32
Respiratory epithelium	
Present	22
Absent	10
Invasion	
Soft tissue invasion (subepithelial stroma)	30
Bone invasion on histology	21
Perineural invasion	0
Vascular invasion	0
Respiratory epithelium invasion/involvement	0
Pattern of growth*	
Solid	25
Organoid	12
Rosettes—pseudorosettes	10
Single file infiltration	9
Papillary—pseudopapillary	7
Glandular	6
Trabecular	5
Insular	2
Cystic	1
Secretions or concretions present	16
Necrosis	
Present	8
Absent	24
Tumor cellularity	
Low	14
Moderate	7
High	11
Cell type*	
Polygonal	27
Plasmacytoid	18
Granular	14
Oncocytic	12
Cuboidal	10
Spindled	1
Pleomorphism	
Mild	17
Moderate	10
Severe	5
Intranuclear cytoplasmic inclusions present	25
Multinucleated tumor cells	18
Nucleoli	
Present: small	17
Present: prominent, large	6
Absent	9
Mitotic figures	
Absent	14
Present	18
Range	0 – 3
Mean (per 10 HPFs)	1
Atypical figures (present)	0
Fibrous bodies	3
Background	
Sclerotic	10
Vascularized (fibrovascular), hemorrhagic	17
Calcified	2
Other	
Inflammatory sinonasal polyps	2
Mucinous or edematous change	2
Psammatoid calcifications	1

* Tumors showed more than one pattern of growth or cell type

pleomorphism present in only five cases (Fig. 11). All of the cases with severe pleomorphism also showed bone invasion, secretions, necrosis, high tumor cellularity, a solid pattern of growth, multinucleation, well developed nucleoli, and mitotic figures (mean, 1.8).

Intranuclear cytoplasmic inclusions were identified in most cases (n = 25), a finding which can be helpful in the differential diagnosis (Fig. 9). Well developed, membrane-lined inclusions were present within the nucleus, containing the same material as the adjacent cytoplasm (not nuclear bubble artifact or fixation clearing). Tumor cell multinucleation was present in 18 cases (Fig. 11). This was represented by multiple distinct nuclei within the cell, rather than multilobated nuclei or a single large, highly atypical nucleus (tumor giant cell). Nucleoli were not seen in the tumor nuclei in 9 cases, were present but small in 17 tumors, and large and eosinophilic in 6 tumors (Fig. 11).

Mitotic figures were overall difficult to identify in most cases. Fourteen tumors had no mitoses when 10 consecutive high-power fields were reviewed (and repeated). Eighteen tumors contained mitotic figures: 10 tumors with 1 mitosis/10 HPFs; 5 tumors with 2 mitoses/10 HPFs; and 3 tumors with 3 mitoses/10 HPFs. Mitotic figures did not seem to influence the risk of recurrence or persistent disease. Atypical mitotic figures were not identified. Concurrent inflammatory sinonasal tract polyps (n = 2), background edematous to mucinous degeneration (n = 2), and isolated psammoma bodies (n = 1) were noted. Squamous differentiation was not present and neither was melanin pigment.

Immunohistochemical Results

The immunohistochemistry studies performed (on available material), highlighted the epithelial and endocrine nature of the tumors, along with identifying specific

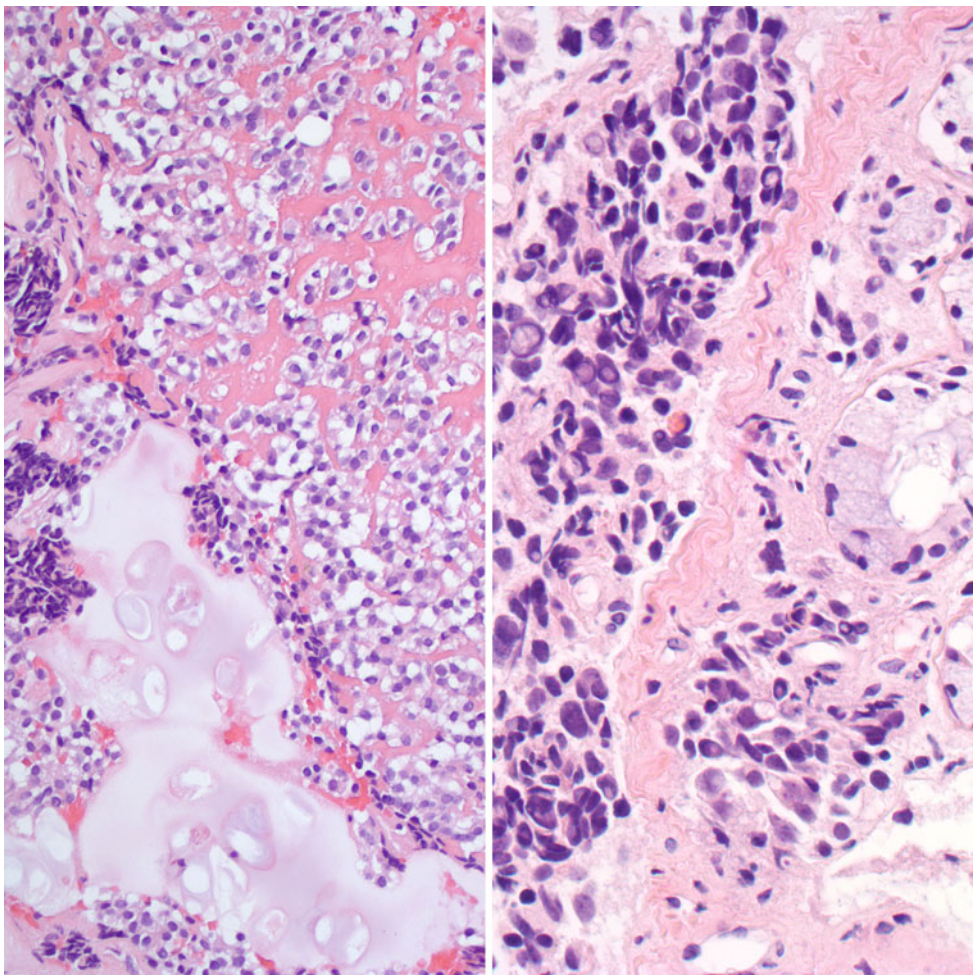

Fig. 5 *Left* Invasion into bone and cartilage was frequently detected. *Right* The neoplastic cells invade adjacent to minor mucoserous glands. Note the numerous intranuclear cytoplasmic inclusions

hormones in a number of cases (Table 5). The panel of immunohistochemistry antibodies was broader than may be inferred for a pituitary tumor based on the sinonasal tract location and differential diagnostic considerations. Specifically, 85.7% of cases were reactive with keratins, tested with pan-cytokeratin (CK-pan) and CAM5.2. CK-pan was more sensitive, detecting 79% of cases tested, while CAM5.2 was positive in only 61%. Therefore, CK-pan would be the more appropriate study to perform. There was a dot-like Golgi deposition in 10 (45.4%) cases (Fig. 12), although diffuse cytoplasmic reaction was more common. Synaptophysin (97%) and CD56 (91%) were more sensitive in detecting the neuroendocrine nature of the tumors than chromogranin (71%) or CD99 (40%). NSE was positive in 76% of cases, but was not as sensitive or specific a neuroendocrine marker as synaptophysin or CD56. There was a spectrum of reactivity patterns for the neuroendocrine markers, including diffuse cytoplasmic, diffuse granular, membranous, or dot-like (Figs. 13, 14).

A number of pituitary hormones were tested, with PRL (Fig. 15) the most frequently identified hormone (59%). Whenever tested, FSH, LH, GH, and TSH were never identified in isolation; this means that if one of these markers were positive, at least one other peptide was also positive at the same time: polypeptide positive. ACTH was identified in isolation in 3 cases (Fig. 15), although there was insufficient material available to test other peptides in an additional 2 cases. PRL was identified in isolation in 4 cases, with insufficient material available to test other peptides in an additional 4 cases. Therefore, these peptides may have been detected in isolation in a higher number of cases if material was available for testing. Based on the clinical symptoms, laboratory values and immunohistochemistry findings, the tumors were placed in the following general categories: *GH-PRL-TSH family*: Functioning lactotroph: n = 3; Nonfunctioning *silent* lactotroph: n = 7; *ACTH family*: Functioning corticotroph: n = 1; Nonfunctioning *silent* corticotroph: n = 3; *Gonadotropin family*: Nonfunctioning silent gonadotroph: n = 1; *Unclassified adenomas*: Plurihormonal adenomas: n = 8; Hormone *silent*: n = 4. However, these four hormone *silent* cases, and an additional five cases, were not classified as there was an insufficient number of antibodies performed to allow for an accurate classification. Calcitonin was positive

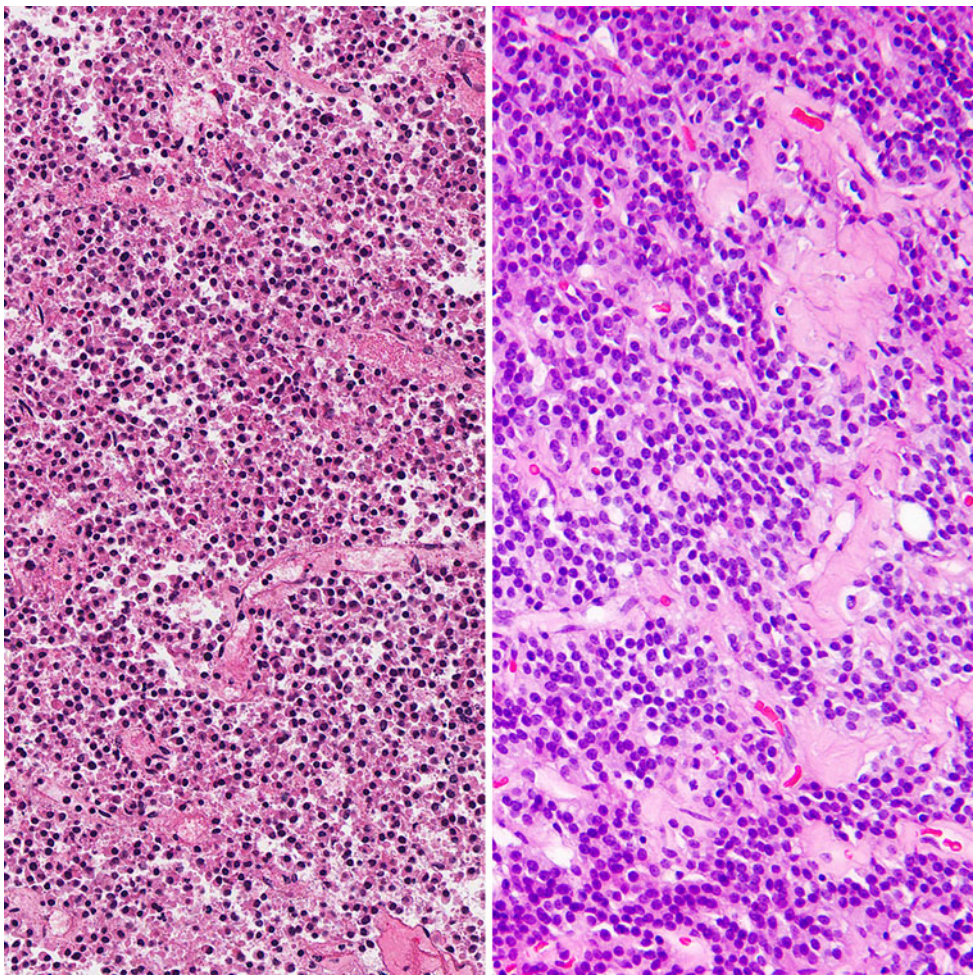

Fig. 6 *Left* A solid tumor pattern with delicate fibrovascular stroma. *Right* Fibrovascular stroma with greater collagen deposition. The tumor is moderately cellular with limited pleomorphism

in 20% of cases tested, suggesting aberrant hormone production can be seen (detected in patients without any other tumors). S100 protein was focally positive in one case, but not in a sustentacular distribution. Ki-67 showed a very low proliferation index, with 13 cases tested: 3 cases showed ~3% proliferation index; while 10 cases showed 1% or less. This finding correlates with the low mitotic count detected in H&E-stained material. Helpful in the differential diagnosis, CK7 and CK5/6 were non-reactive in all cases tested. Selected cases had additional immunohistochemistries performed during initial work-up by the primary pathologist, which were all *negative*: p63, TTF-1, myogenin, desmin, SMA, HMB-45, EBER, GFAP, and CD45RB.

Treatment and Follow-up

All patients were treated with either (A) surgery alone or with (B) surgery followed by post-operative radiation (n = 5) and chemotherapy (n = 1). However, radiation and chemotherapy were employed because of an incorrect diagnosis initially, while radiation was used to treat one patient with recurrence. Follow-up was available in 29 of 32 patients. The overall average follow-up was 10.2 years (Table 6). Four patients had recurrence or persistence of their tumors. One 76-year-old died with persistent disease 0.8 years after surgery, but the death was not related to the tumor (unclassified type). One 84-year-old had a pulmonary small cell carcinoma, with the sphenoid sinus tumor identified incidentally, and not treated after the initial core biopsy (plurihormonal tumor); one 24-year-old patient had persistent disease, managed with surgery and radiation, and is now free of tumor (3.5 years) (*silent* lactotroph); one 54-year-old patient developed a recurrence 2 years later and after surgery and radiation, is now free of disease (3 years) (unclassified type). The latter two patients had received the wrong diagnosis initially, resulting in incomplete surgery initially.

There was no statistically significant difference in outcome between patients based on gender, tumor size or specific anatomic site affected (Table 6). There were too few patients in each group who had died (with or without disease) to determine specific survival determinations.

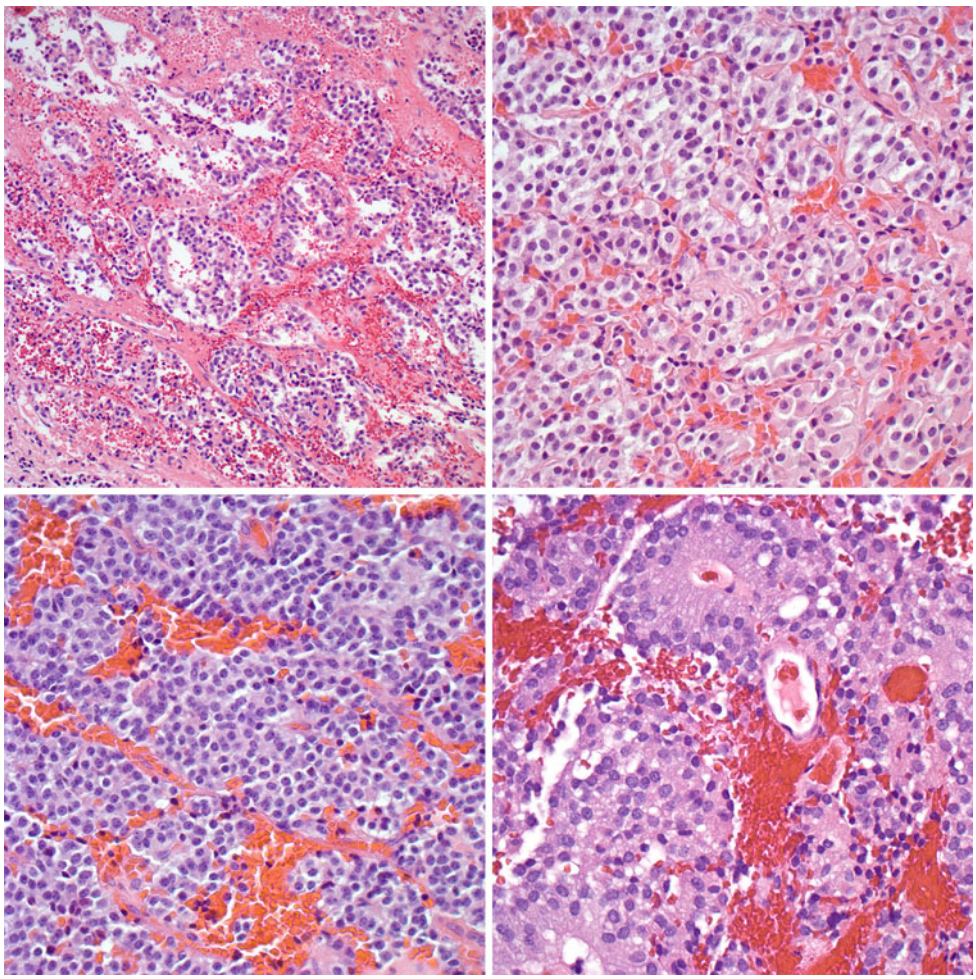

Fig. 7 Several different patterns of growth are highlighted. Pseudopapillary (*left upper*), organoid (*right upper*), trabecular to organoid (*left lower*) and pseudorosettes (*right lower*). Several different cytologic appearances are also seen

Discussion

Pituitary adenomas account for between 10 and 25% of all intracranial neoplasms [3, 47–49]. It is well known that primary pituitary adenomas can grow in any direction, and so extension into the sphenoid sinus is expected in about 2–3% of cases [2–4, 50, 51]. Extrasellar extensions are often larger than the intrasellar tumors [26]. At the time of neurosurgery, the hormone function, clinical setting, and imaging findings are known by the endocrinologist, and head and neck and neurosurgeons, respectively, which gives the pathologist an easy setting in which to make the appropriate diagnosis. However, when the pituitary gland is normal, the sella turcica uninvolved, and the patient is presenting clinically with non-specific sinonasal tract symptoms, and a "sphenoid sinus" mass by imaging studies, the clinicians and pathologist are faced with a more daunting task of diagnosis and management. When considering the incidence of ESSPA, based on all surgical pathology cases at one institution, about 0.48% of pituitary adenomas are ectopic; approximately 2.5% of sphenoid sinus lesions are pituitary adenomas; but overall, 0.0000014% of all surgical pathology cases reviewed were ESSPA.

As seen in this clinical series, only one patient presented with a hormonally active tumor: Cushing syndrome as a result of ACTH production. However, the other 97% of this clinical series did not present with hormone-related signs or symptoms. This is in contrast to the literature, where 58% of the patients presented clinically with abnormal hormone production resulting in Cushing syndrome, acromegaly or amenorrhea/galactorrhea. This is probably due to the single case report nature of these patients and reflects publication in primarily clinical and imaging journals, rather than pathology journals (only 11% of cases were reported in pathology journals [12, 16, 28, 32, 33]).

Retrospective analysis of a specific tumor is a difficult undertaking in modern medicine, and even more so when the entity is rare. However, clinical presentation, gender differences, anatomic site of distribution, size, histologic, and immunohistochemical features, and patient outcome have not been well-characterized by single case reports. The information in this study is combined with that gleaned

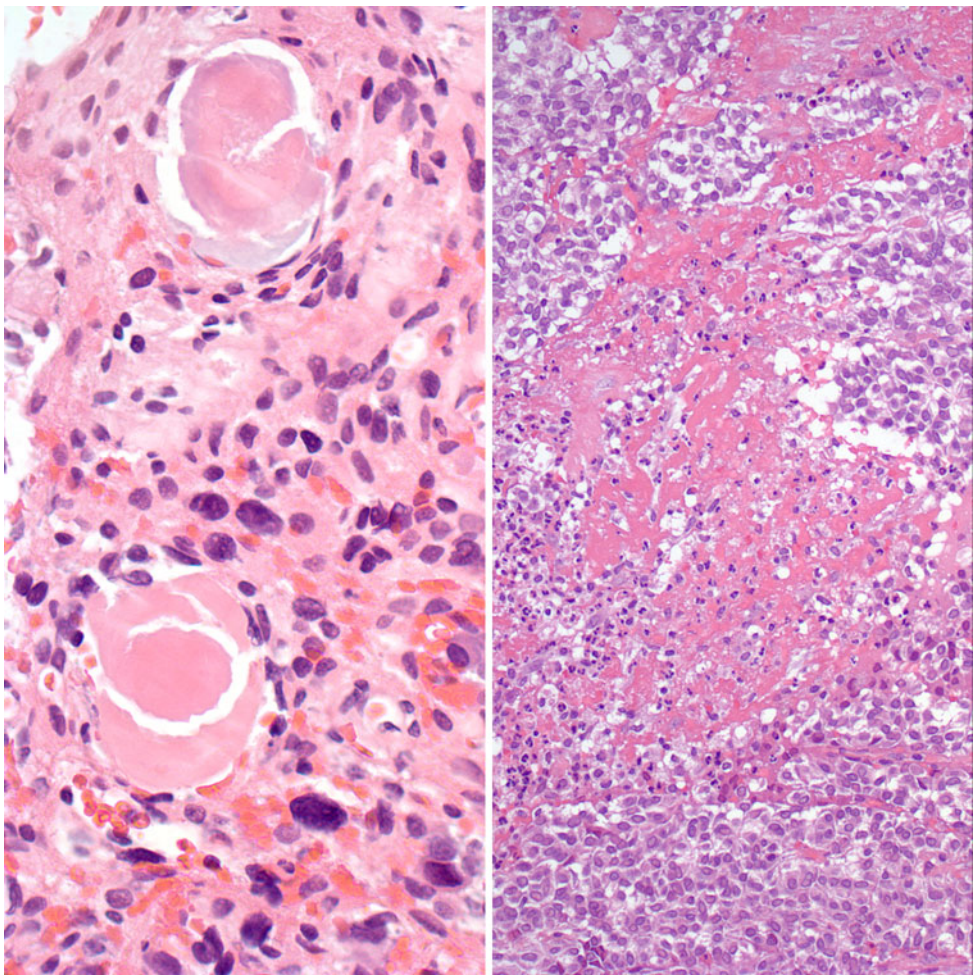

Fig. 8 *Left* Secretions or concretions are noted within the neoplastic proliferation. *Right* Tumor necrosis was infrequent, showing a comedonecrosis pattern in this tumor

from the literature (Table 7) in an attempt to more fully elucidate the nature of this uncommon tumor.

Clinical Information

There were 43 females and 32 males, suggesting a slight female predominance (1.3:1). A broad age range can be affected (2–84 years), but the majority of patients present in the 6th decade (mean, 53.8 years), without a gender difference. There is a trend towards patients presenting at a young age when tumors involve the sphenoid sinus and nasal cavity or nasopharynx, but this was not a statistically significant difference ($p = 0.095$). Although the cases reported in the literature tended to present with a symptom complex related to hormone production, the overwhelming majority of cases in this series did not have clinical symptoms related to hormone excess (97%). Overall, patients presented with symptoms which were present for 48.8 months. The majority of symptoms were non-specific and related to the sinonasal tract, including obstruction, sinusitis, rhinorrhea, discharge, drainage, headache, and pain. The symptoms related to visual disturbances (diplopia, visual acuity loss, blurring, proptosis), nerve changes (paresthesia, paresis), and alterations in balance were probably related to a sphenoid sinus tumor expanding into the cavernous sinus or clivus, thereby affecting the corresponding cranial nerves. The patients who presented with symptoms related to hormone excess, were still likely to have symptoms for some time, since hypertension, acne, facial coarsening, hand, foot, nose, jaw and/or forehead enlargement, voice deepening, fatigue, malaise, impotency and amenorrhea are also non-specific, frequently managed medically or symptomatically before additional evaluation is performed. It is also important to remember that ectopic pituitary hormones may also be secreted by bronchial and gastrointestinal neuroendocrine tumors, as well as pulmonary small cell carcinoma and ovarian small cell carcinoma, among other tumor types. Therefore, evaluation of patients with hormone production is not just limited to pituitary and midline sinonasal tract locations. Only three patients presented with epistaxis, but it was not in isolation, and was a symptom which brought the patients to clinical attention after many years of other non-specific symptoms. Finally, about 8% of all patients evaluated were

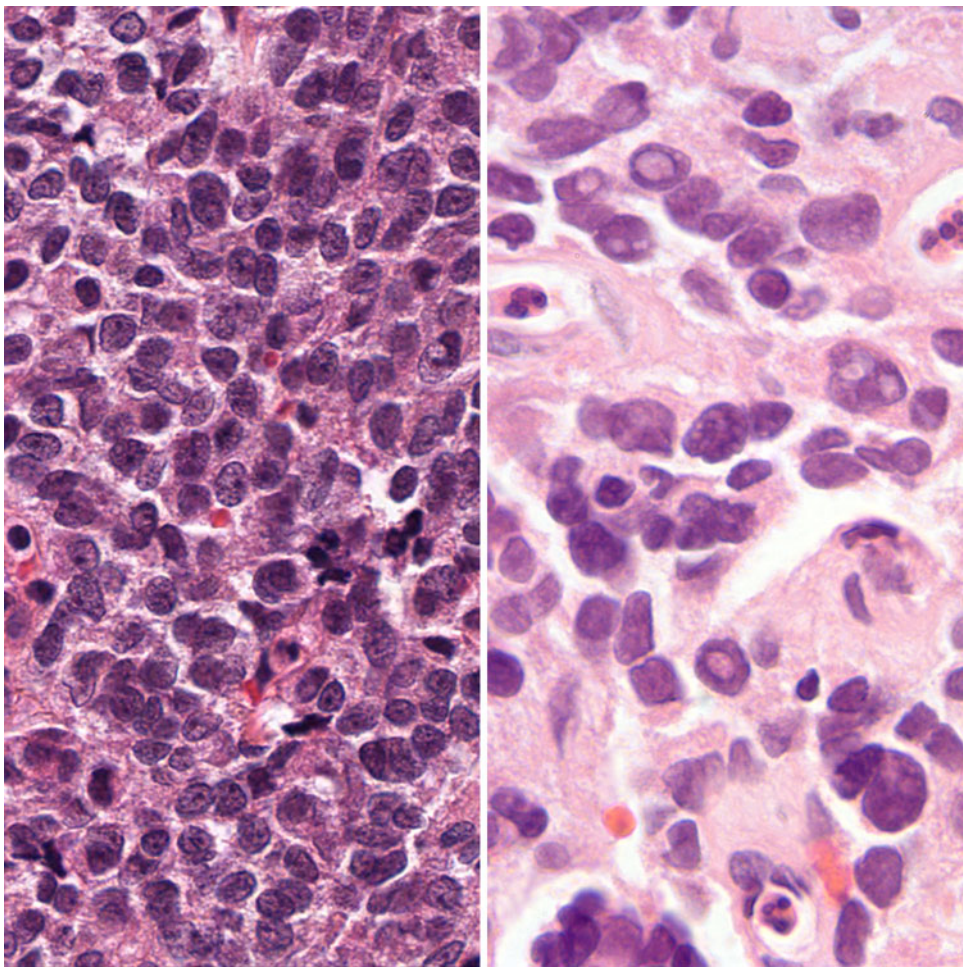

Fig. 9 *Left* High tumor cellularity could mimic other tumors of the upper aerodigestive tract. Note the delicate chromatin distribution, with grooves and small nucleoli. *Right* Intranuclear cytoplasmic inclusions were frequently seen, showing a well-formed membrane-lined inclusion

asymptomatic (19% of this clinical study). These tumors were incidentally discovered during evaluation for another reason, most commonly in the setting of metastatic work-up. It is in this latter clinical scenario that the pathologist must be even more vigilant, avoiding the trap of misdiagnosing the tumor as a metastatic neoplasm. Interestingly, in the asymptomatic patients who were being evaluated because of other malignancies, two presented with *silent* lactotroph adenomas; one with a functional lactotroph adenoma; and one unclassified, plurihormonal adenoma. This is different from patients with intrasellar tumors who also have another primary: in this latter group, the tumors are usually functional somatotroph adenomas (GH), with colonic primaries the most likely finding [48].

Laboratory investigation for elevated pituitary hormones, with and without stimulation or suppression testing, is recommended, as the current classification is based on functional status. Even though the patient may not yet have a symptom-complex related to hormone excess, it is important to document serologic elevation of hormones. The old pneumonic of "FLAG TOP" may help in performing the necessary evaluation, including FSH, LH, ACTH, GH, TSH and PRL. Oxytocin is produced by the posterior pituitary (neurohypophysis), which is embryologically distinct from the anterior pituitary, and therefore is not associated with sphenoid sinus tumor development. Axiomatic, the term "silent" adenoma should not really be used unless there is no evidence clinically or biochemically of an abnormality. This is often difficult to achieve by the pathologist, since an inadequate or incomplete clinical work-up should not be the reason to render the diagnosis of a "silent" adenoma. Therefore, in this series, where the exact clinical evaluation was not always known to the pathologist, it is possible that the term "silent" was used just to pigeon-hole the case instead of implying there was truly a silent lesion.

Imaging Studies

It is most important that appropriate imaging studies are performed as part of the evaluation of these ectopic tumors. Part of the definition for an ESSPA is that the sella turcica is uninvolved and that the pituitary gland is normal. Intraoperative assessment of the sella and pituitary can be

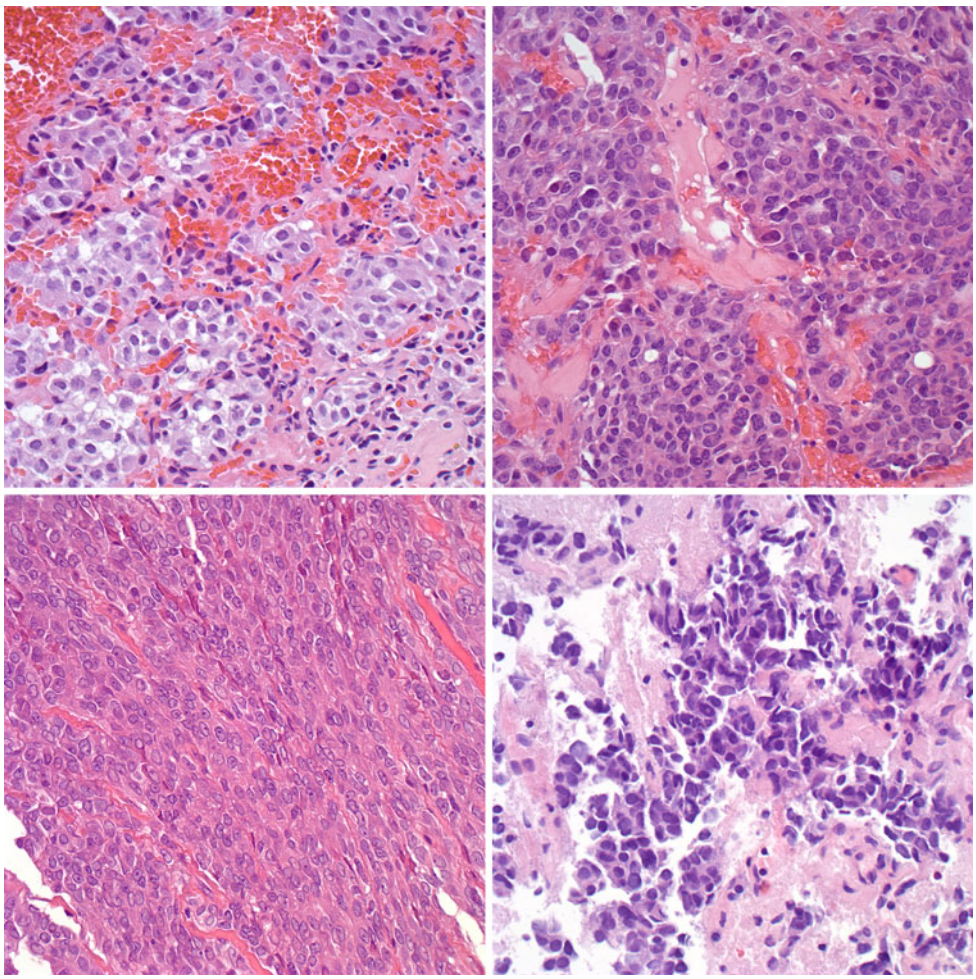

Fig. 10 A variety of cytologic appearances were seen, including plasmacytoid (*left upper*), polygonal (*right upper*), epithelioid to spindled (*left lower*) and small cell type (*right lower*)

performed, but pre-operative imaging evaluation will yield the most clinically useful information. Not only will imaging studies document a normal pituitary and sella turcica, but they will also highlight the size of the tumor, give information about the margins and extent of the tumor, and allow for appropriate surgical planning [19, 26, 40]. It is most important to exclude an invasive pituitary adenoma into the sphenoid sinus, a much more common finding than the ectopic pituitary adenoma. CT and MRI studies can detect abnormalities that are greater than 3 mm within the pituitary gland [48], with MRI reported to be more sensitive for pituitary gland evaluation and giving precise information about the relationship to the sphenoid sinus. Specifically, the imaging studies demonstrate a well-defined tumor margin, often with bony sclerosis, distinct and separate from the normal, uninvolved intrasellar pituitary gland. Bone destruction with expansion into the cavernous sinus was a frequent finding. MRI shows mild to moderate heterogenous contrast-enhancement, without a unique T1- or T2-weighted image intensity. Non-enhanced CT shows tumors that are iso- to hypo-dense to grey matter, showing modest enhancement in post-contrast studies [26, 40].

Pathology

Most tumors affected the sphenoid sinus alone, but it was not uncommon to have expansion into the adjacent nasopharynx or nasal cavity. Tumors were generally large for the anatomic site, with an average size of 2.9 cm for all cases evaluated. The tumors usually filled the sphenoid sinus. There was no difference in tumor size between males or females ($p = 0.312$). As expected, as the tumors expanded into adjacent structures, the average size increased, a finding which was statistically significant ($p = 0.015$). The macroscopic appearance of the tumors was non-specific and usually described as multiple fragments of tissue, ranging from firm to gelatinous and vascular.

An intact respiratory surface epithelium was present in most cases. Although absent in several, the surface epithelium was not destroyed or affected by the neoplasm. This may help in separating ESSPA from other neoplasms

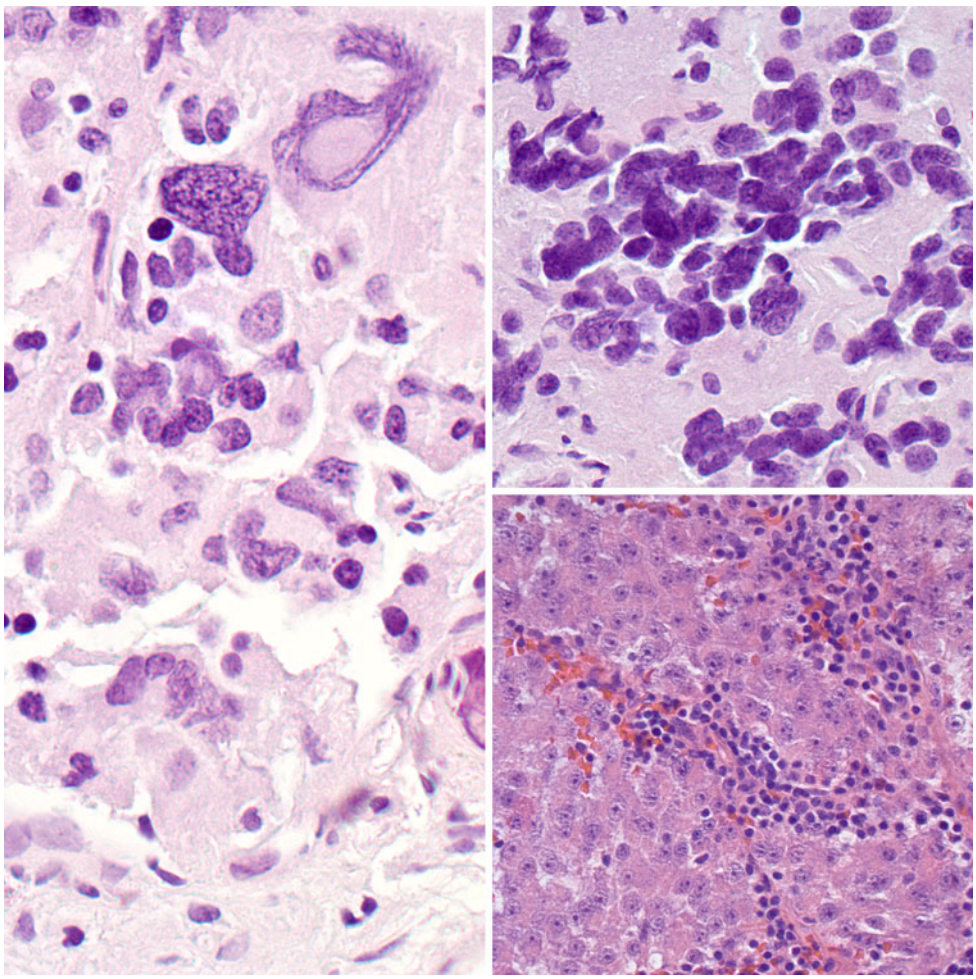

Fig. 11 *Left* Profound nuclear pleomorphism within this tumor. *Right upper* Tumor cell multinucleation was a common feature. *Right lower* Prominent nucleoli are seen in cells that have granular to eosinophilic cytoplasm and interspersed inflammatory cells

in the differential diagnosis, such as neuroendocrine carcinoma (NEC) and sinonasal undifferentiated carcinoma (SNUC), which frequently destroy the surface epithelium. Olfactory neuroblastoma is usually separate from the surface epithelium, but arises from the ethmoid sinus, associated with the cribriform plate. Melanoma may involve the surface epithelium with a "junctional" component, but more often than not, the surface epithelium is ulcerated and lost due to the neoplastic growth.

ESSPA are frequently associated with bone invasion or involvement, a function of their anatomic site rather than necessarily biologic aggression. Necrosis can also be seen in about 25% of cases. When present, other histologic features would need to be used to help separate the tumor from other lesions in the differential diagnosis. A richly-vascularized stroma is a common finding, separating the tumor nests into a variety of different patterns of growth. However, many cases show a heavily collagenized and sclerotic fibrosis. The neoplastic cells are often difficult to see in this pattern of growth. Therefore, when evaluating samples from the sphenoid sinus that seem to be "fibrosis only," careful high-power examination should be performed in order to make certain isolated neoplastic cells are not entrapped in the fibrosis. Invariably, small collections of neoplastic cells are present, but only discovered after diligent high-power review. Immunohistochemistry studies could be performed to highlight the cells, realizing that both a keratin and neuroendocrine marker would need to be performed to make certain the cells are captured. Perineural and lymph-vascular invasion were not identified in these tumors. This is a very helpful feature in the differential diagnosis, especially when one considers that significant lymph-vascular invasion and midline destruction can be caused by other tumors in the differential diagnosis.

Whenever there are many patterns of growth within a tumor, a neuroendocrine neoplasm should quickly rise to the top of the differential diagnostic considerations. While one pattern may dominate, there are usually several different patterns of growth in a pituitary adenoma. Even though described as "solid," there is still a very rich, albeit delicate fibrovascular stroma separating the tumor into smaller nests or islands. A true "lobular" pattern is not usually appreciated. Pseudorosettes, especially as they are

Table 5 Immunohistochemistry results

Antibody	Number of cases with positive reactions
Cytokeratin (Pan-keratin)	22/28 (79%)
CK7	0/8 (0%)
CK5/6	0/8 (0%)
CAM5.2	11/18 (61%)
Synaptophysin	29/30 (97%)
CD56	10/11 (91%)
NSE	13/17 (76%)
Chromogranin	17/24 (71%)
CD99	4/10 (40%)
Ki-67 (<3% proliferation)	13/13 (100%)
S100 protein	1/15 (6.7%)
Prolactin	13/22 (59%)
Follicle stimulating hormone	9/19 (47%)
Luteinizing hormone	7/19 (37%)
ACTH	6/18 (33%)
Thyroid stimulating hormone	5/17 (29%)
Growth hormone	5/19 (26%)
Calcitonin	2/10 (20%)
No polypeptide by hormone studies	*4/21 (19%)*
Single polypeptide	*7/21 (33%)*
Multiple polypeptides	*10/21 (48%)*

arranged around vessels in a palisaded appearance, are seen in about one-third of cases. The glandular architecture, with a lumen, can cause some diagnostic difficulty. Secretions or concretions may also be seen. However, this is usually an isolated finding, and not one that is dominant. In general, the tumors have a low to moderate cellularity. This means there is quite a bit of space between nuclei of the neoplastic cells: at least the width of two nuclei or at least the nuclei are approximating one another. When there is nuclear overlapping and crowding, then a high cellularity is identified (but this was not common among our cases). Again, in this setting, the differential diagnoses need to be carefully considered and excluded.

Most tumors contained small polygonal to plasmacytoid cells with a low nuclear to cytoplasmic ratio and ample cytoplasm surrounding the nuclei. The Golgi space adjacent to the nucleus was frequently easy to see, helping to suggest the neuroendocrine nature of the lesion. Although quite variable throughout a tumor, a delicate salt-and-pepper nuclear chromatin distribution was present. A delicate, even nuclear chromatin distribution with focally vesicular change was also noted. When the chromatin was open, nuclear grooves and folds became easier to detect. Nucleoli were usually inconspicuous to small. Large, irregular nucleoli were uncommon, and when present, suggested other tumors in the differential diagnosis. When the cells were smaller, a more hyperchromatic appearance was seen. Intranuclear cytoplasmic inclusions were identified in the majority of cases. This finding can also be seen in mucosal melanoma and meningioma, but in general the other histologic features are quite different and so the appearance of this feature can aid in correct diagnosis. Fibrous bodies in the cytoplasm were detected in three cases, but were not specifically correlated to a tumor type (prolactin; multiple hormones). Tumor multinucleation was also frequent. Tumor giant cell formation could be seen too (endocrine organ atypia), but the multinucleation of several small nuclei is different from several other tumors in the differential diagnosis. Finally, mitoses were usually inconspicuous, infrequent, and never atypical. Therefore, when evaluating a sphenoid sinus tumor, the lack of mitoses or identification of only isolated mitoses may help in making an accurate diagnosis.

There are approximately 14 recognized primary pituitary adenoma subtypes, with a very specific morphologic, immunohistochemical, ultrastructural and biologic classification scheme [47]. More recent classifications separate tumors based on symptoms and blood hormone levels, neuroimaging and intraoperative data, tumor size, histologic criteria, immunohistochemistry, and ultrastructure [49, 52]. Furthermore, many immunohistochemistry markers obviate the need for ultrastructural examination, except in the most unusual of circumstances [3]. Therefore, in general, tumors are separated into "functional" and "non-functional", with additional separation into specific families based on immunohistochemistry findings, while the terms "microadenoma" and "macroadenoma" are employed if the tumors are <1 or >1 cm, respectively. The non-functioning tumors are referred to as "silent" adenomas, and encompass all six hormones normally produced by the adenohypophysis (GH, TSH, PRL; ACTH; FSH, LH). Again, the term "silent" should only be accurately applied when a full work-up (clinically and biochemically) is negative—perhaps difficult for a pathologist to assess at the original diagnosis.

Given the wide variety of classifications employed, a modification is presented to categorize ESSPA (Table 8). Although a new classification scheme cannot possibly be suggested without pituitary transcription factor evaluation in addition to other ancillary studies, this model may be useful in future classifications of these tumors. In this system, tumors are classified as functional and nonfunctional. Functional tumors are defined by symptoms related to a specific hormone production, or evidence of serologic hormone elevation. Nonfunctional tumors are defined as not producing serologic hormone elevation, but producing immunohistochemical evidence of a specific hormone. Then the tumors are separated into specific families based on

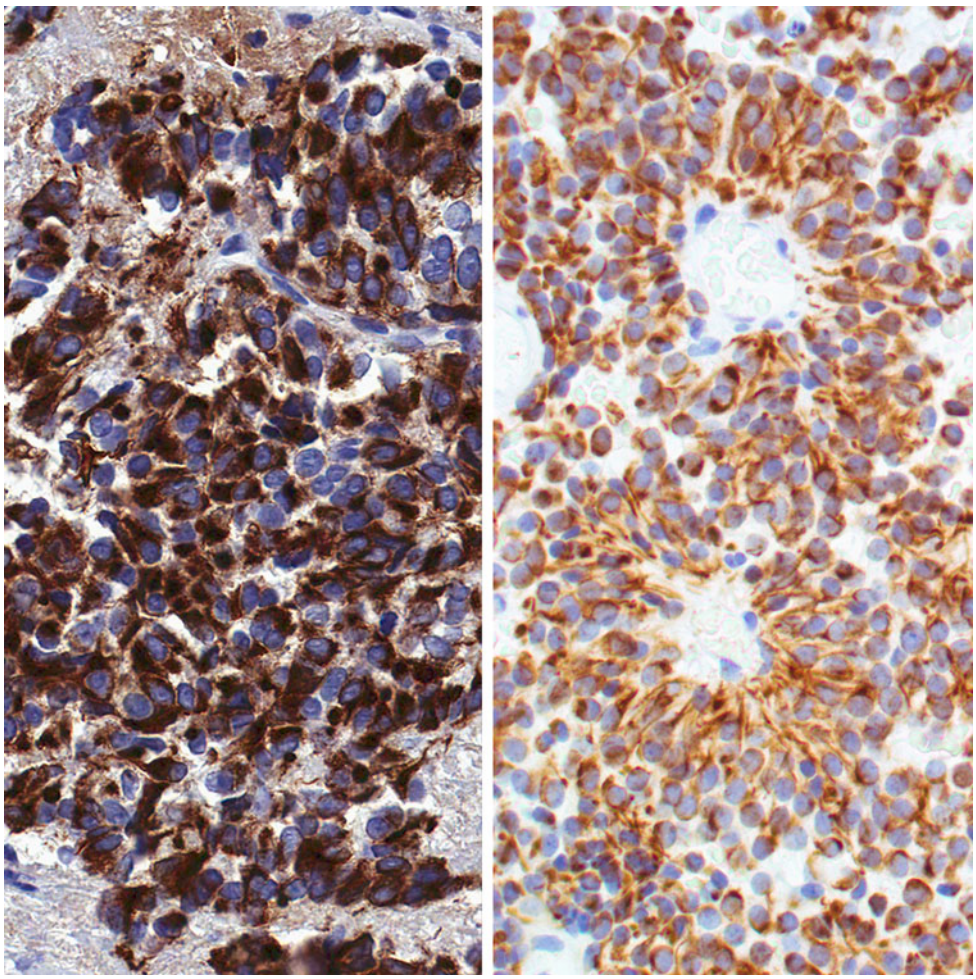

Fig. 12 Cytokeratin could be seen as a diffuse, cytoplasmic reaction of a "fibrous body" type (*left*) or producing a delicate "*dot-like*" perinuclear (Golgi) pattern (*right*)

similarities of histologic appearance, immunohistochemistry, or ultrastructural features. When more than one hormone is produced, excluding the combination of PRL and GH (which is given a specific designation based on laboratory findings), then the tumor is placed in the "unclassified, plurihormonal adenoma" category. For the combined PRL and GH producing adenomas, they are separated into nonfunctional and functional, with the latter further separated into lactotroph or mammosomatotroph group depending on which serologic value dominates clinically. Tumors which were tested for all six hormones and were negative were referred to as unclassified, silent adenomas. However, this is not a true "null-cell" category. It is well-known that current pituitary transcription factors can be employed in these cases to yield a specific subtype when other techniques have failed. However, in this retrospective review study with only limited material, definitive classification could not always be reached. As can be seen from the cases in this study combined with the literature, the majority of cases fell into the GH-Prolactin-TSH family of adenomas, with two-thirds functional and one-third clinically *silent*. The next largest group were the unclassified adenomas, with plurihormonal adenomas (n = 12) and *silent* adenomas (n = 13) comprising this group (see explanation above). Similar to intrasellar primaries, prolactinomas and unclassified silent adenomas are the most common subtypes [3, 48, 49]. Even though we only had a single child in the series, this ESSPA was a corticotrophinoma, known to be the most common pituitary tumor in pre-pubertal children [2, 48].

Immunohistochemical Studies

In general, the immunohistochemistry profile of ESSPA is identical in distribution and pattern to their intrasellar counterparts. It is most important to realize that the evaluation of ESSPAs is nearly always driven by the differential diagnosis with other tumors of this area. Therefore, a primary pituitary hormone panel, to include pituitary transcription factors, is not usually performed up-front. It is not the intention of this paper to suggest that a more thorough evaluation of these ectopic tumors not be undertaken by performing these additional studies. The thrust of this description is to make sure that a diagnosis of pituitary adenoma is rendered instead of the other

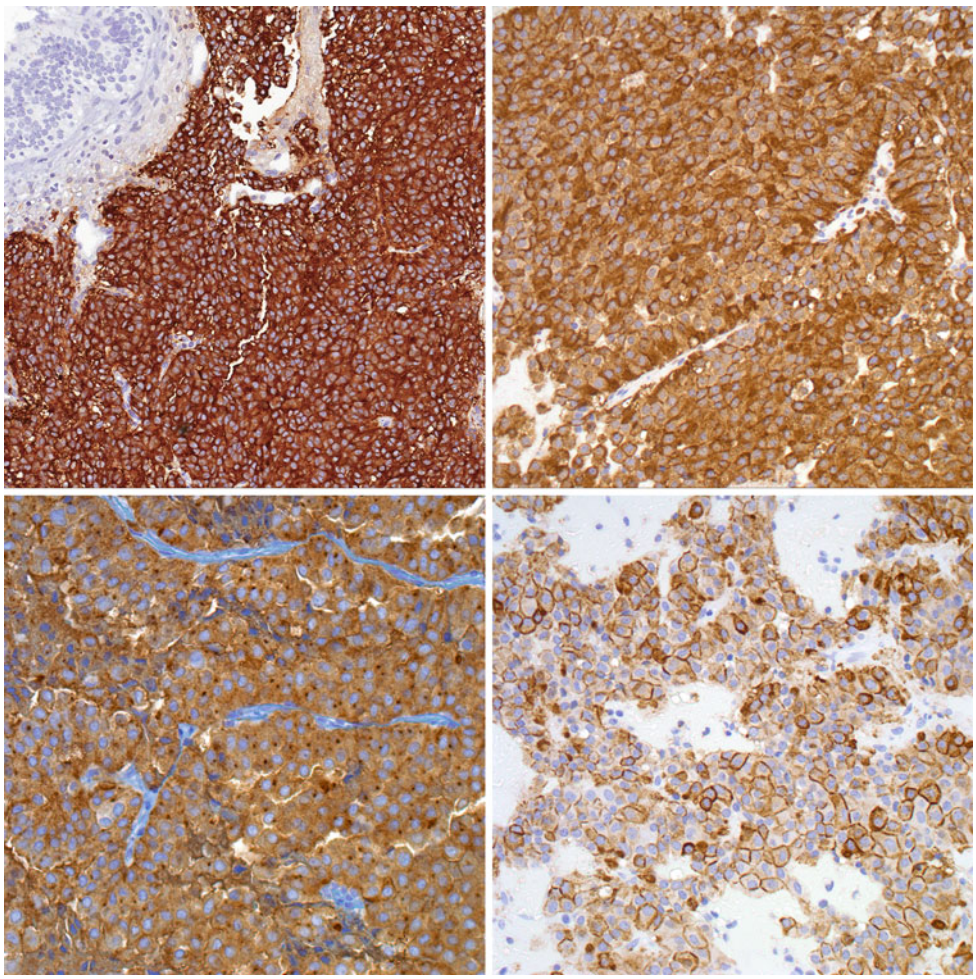

Fig. 13 Neuroendocrine markers were positive, showing a variety of different patterns: Strong diffuse cytoplasmic reaction with synaptophysin (note negative surface epithelium; *left upper*); a Golgi accentuation could also be seen (*left lower*); Chromogranin showing a granular strong to moderate cytoplasmic reaction (*right upper*) or a membranous accentuation (*right lower*)

diagnoses in the differential. A variety of neuroendocrine markers can be used, with synaptophysin and CD56 providing the most sensitive results. Chromogranin and NSE are positive in 70.8 and 76.5%, respectively. There was only 1 case in which NSE and chromogranin were reactive in which synaptophysin was negative (all hormones were also negative in this case); and there was 1 case that was negative with CD56, that was positive for synaptophysin and NSE, while negative for chromogranin and all hormone markers. Therefore, when evaluating a tumor which may represent an ESSPA, the neuroendocrine markers should include synaptophysin and CD56.

The tumors generally showed a keratin reaction, with pan-keratin reactive in 78.6%, increased to 85.8% if CAM5.2 was also performed. The presence of a Golgi dot-like pattern in 45% of cases was an additional helpful feature in the diagnosis, since most of the tumors in the differential diagnosis do not usually show this pattern of reaction. There is no reaction with CK5/6 or CK7, findings that are most helpful in the differential diagnosis. Likewise, S100 protein was negative in nearly all cases tested. There was neither sustentacular arrangement (as would be seen in olfactory neuroblastoma) nor a diffuse cytoplasmic reaction (as expected in mucosal melanoma).

It is difficult to specifically give guidance on the pituitary hormones to evaluate, since they should all be tested in an ideal setting to give a correct classification based on the proposed system in Table 8. Prolactin is the most frequently identified hormone, but GH, ACTH, LH, FSH, and TSH are all variably present. It is important to note that more dilute antibody titers may decrease the perceived plurihormonal results. By this we mean, if the concentration of the FSH and TSH were decreased (made more dilute), it is possible that the analyte would not be detected. Therefore, the monoclonal antibody used and dilution are critical in interpretation. If more than one hormone is identified when the six have been tested, then the classification system allows for a specific subclassification. In many cases, the patient symptoms or serologically elevated hormone levels dictated which immunohistochemistry to perform on the tumor. However, it is important to note that serologic elevation of a hormone may not be the only hormone identified in the tumor by IHC. Therefore, it is prudent to perform the battery of pituitary hormone studies

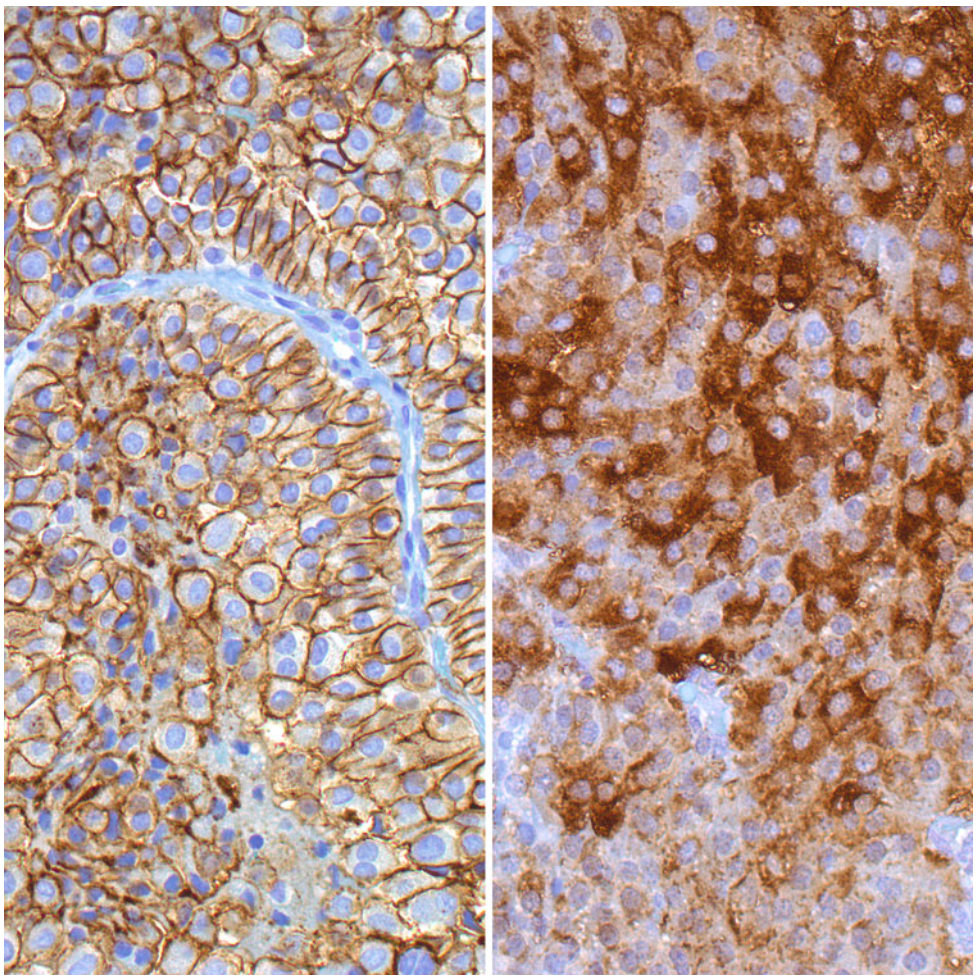

Fig. 14 *Left* CD56 usually produced a strong, diffuse, membranous reaction in the tumor cells. *Right* NSE showed a variable reaction, although it was usually a granular cytoplasmic reaction

for exact classification and potential management decisions. Specifically, pituitary transcription factors, such as Pit-1, T-pit, SF-1, ER-α, and GATA-2 can be performed to help yield a specific classification. Needless to say, since many of the cases in this series did not have sufficient material to perform these studies, there is, no doubt, a significant number which are placed in the "null-cell" or "silent" category that would otherwise have been placed into a specific classification were material available.

The finding of calcitonin is unique. Laryngeal neuroendocrine tumors are known to express calcitonin [53]. However, pituitary neoplasms are not known to produce calcitonin. A calcitonin gene-related peptide or m-CEA could not be performed to confirm this finding.

Differential Diagnosis

ESSPA is a very commonly misdiagnosed tumor. In 22 of 25 cases in which a diagnosis was postulated by the contributing pathologist, the diagnosis was incorrect. The most frequent misclassification was olfactory neuroblastoma, followed by neuroendocrine carcinoma (NEC), sinonasal undifferentiated carcinoma (SNUC), melanoma, meningioma, nasopharyngeal carcinoma, paraganglioma, metastatic "carcinoid" (submitted diagnosis), and lymphoma. The pattern of growth and immunohistochemistry findings would immediately eliminate lymphoma from further consideration.

Olfactory neuroblastoma (ONB) is a neuroectodermal-derived neoplasm, which is the most commonly misdiagnosed category for ESSPA. Clinically, nearly all of the tumors are hormonally silent, with non-specific clinical signs and symptoms. By imaging studies, the tumors are centered within the *ethmoid* sinus, nearly always involving the cribriform plate. The tumors show a significant intracranial expansion in many cases, giving a "dumb-bell" shaped tumor mass across the cribriform plate. The tumors are typically arranged in a lobular configuration (although a lobular and diffuse pattern can be seen), showing pseudorosettes or true rosettes in about 30% of all cases. There is often a neural matrix background. The lesional cells are usually small with scant cytoplasm. The nuclei may show a salt-and-pepper nuclear chromatin distribution. Nucleoli are inconspicuous and mitoses are rare in the low-grade tumors. While high-grade tumors may present a more

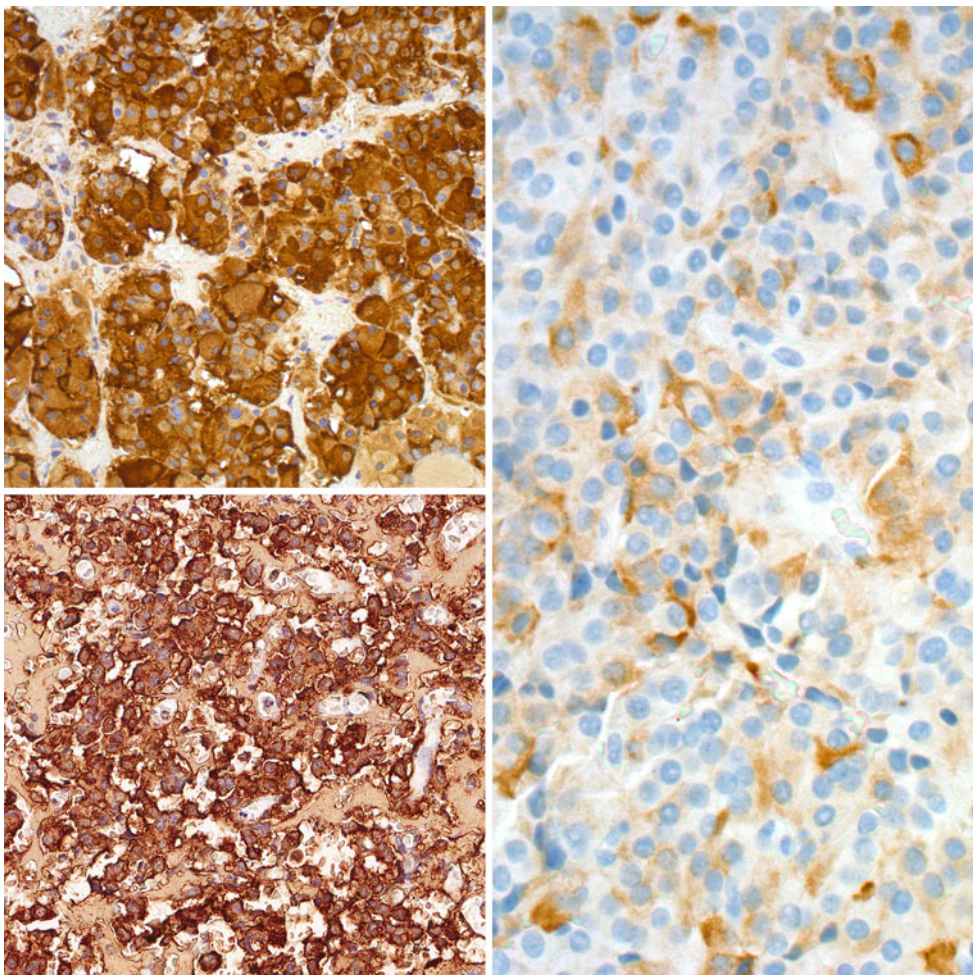

Fig. 15 *Left* Prolactin, when detected, usually yielded a strong reaction. *Right* Isolated tumor cells stained for specific peptides would look like this case of an ACTH reaction

difficult diagnosis, low-grade tumors are usually quite straight forward. The tumor cells are reactive with neuroendocrine markers, including synaptophysin, chromogranin, NSE, and CD56. However, there is a delicate S100 protein sustentacular supporting framework reactivity. It is known that pituitary adenoma within the sella can show a sustentacular reaction with S100 protein due to folliculostellate cells, which are modified glial cells [54]. However, this is an uncommon phenomenon. Keratins are negative in 95% of ONB cases. When keratin is reactive, it is limited to isolated cells and is not in a dot-like distribution. The specific anatomic site, lobular architecture, and unique immunohistochemical profile should allow for an accurate separation [55–58]. The distinction from ESSPA is important, since the management for ONB may involve major, destructive bi-craniofacial surgery (trephination) and possible additional potentially toxic radiotherapy and/or chemotherapy, with a very different prognosis. Endoscopic management is used in some cases, but surgery is still the main treatment.

As a group of tumors, neuroendocrine carcinoma (NEC) of the sinonasal tract are very poorly understood and classified. Without going into an extensive discussion of this group of lesions, small cell carcinoma, neuroendocrine type (SCCNET) and large cell undifferentiated neuroendocrine carcinoma (LCUNC) generally present in the upper nasal cavity with maxillary and ethmoid sinus involvement. Patients often present with epistaxis. There is generally a destructive pattern of growth. Histologically, either tumor usually has a very high grade appearance, showing nuclear molding, smudging and crush artifact. The appearance is similar to histologic counterparts in the lung. There are many mitoses, including atypical mitoses. There is no neurofibrillary matrix material. These tumors express keratin in a dot-like pattern, and have neuroendocrine marker reactivity; however, specific pituitary peptide markers are not present, with rare exceptions showing ACTH and antidiuretic hormone. While ESSPA may have pleomorphism, the pattern of growth and destruction is not the same as NECs. Furthermore, NEC will frequently have metastatic disease at presentation, with an associated high mortality rate. The separation is obviously important, as the patient management with combination radiation and chemotherapy, combined with their toxic side effects and

Table 6 Patient outcome

	All patients	A, NED	D, NED	D, D
All patients with follow-up (years)	29 (10.2)	16 (10.5)	12 (10.6)	1 (0.8)
Follow-up range (years)	0.8–32.7	0.9–26.5	0.9–32.7	0.8
Gender				
Males (mean, years)	15 (9.3)	7 (15.0)	7 (4.8)	1 (0.8)
Females (mean, years)	14 (11.1)	9 (6.9)	5 (18.6)	N/A
Size*	26 (11.0)	14 (11.3)	12 (10.6)	N/A
<4.0 cm	15 (10.1)	9 (13.1)	6 (5.7)	N/A
≥4.0 cm	11 (12.2)	5 (8.4)	6 (15.4)	N/A
Anatomic site				
Sphenoid sinus alone	16 (4.9)	8 (5.6)	7 (4.5)	1 (0.8)
Sphenoid and nasal cavity	4 (10.2)	2 (10.2)	2 (10.2)	N/A
Sphenoid and nasopharynx	9 (19.6)	6 (16.9)	3 (24.8)	N/A
Recurrence or persistence				
Present	4 (2.1)	2 (3.3)	1 (0.9)	1 (0.8)
Absent	25 (11.5)	14 (11.5)	11 (11.4)	N/A

A, *NED* alive, no evidence of disease; *D*, *NED* dead, no evidence of disease; *D*, *D* dead with persistent disease; *N/A* not applicable

* Size was not reported in all cases

dismal outcome is remarkably different [29, 58, 59]. Metastatic neuroendocrine tumors (previously used to include carcinoid) may be considered in the differential diagnosis, but in general, these tumors will have increased mitoses, a high proliferation index, a known history of a primary tumor elsewhere, and would probably not have pituitary hormone expression. We hasten to add, however, that inappropriate expression of selected pituitary hormones (ACTH, CRH, GHRH) can be seen in neuroendocrine tumors from other body sites, and so this differential may require additional clinical and imaging correlation. A variety of tumors in the sinonasal tract can co-express neuroendocrine markers, including sinonasal adenocarcinomas, sinonasal undifferentiated carcinoma, melanoma, and desmoplastic round cell tumor, among others. However, it is always important to realize that positive neuroendocrine markers in a tumor do not always confer upon the tumor a different diagnosis or a different diagnostic category. Melanomas are known to express neuroendocrine markers since melanocytes are of neural crest origin, while sinonasal undifferentiated carcinoma may also show immunophenotypic heterogeneity and plasticity along with lineage infidelity. Therefore, strict adherence to histologic criteria, focused immunohistochemical evaluation that may encompass several overlapping markers, with targeted molecular studies should help to keep categories more pure and reproducible.

Paraganglioma of the sinonasal tract is a vanishingly rare neoplasm, with only isolated cases reported. They would be keratin negative, similar to a few ESSPA cases. The zellballen architecture would be highlighted by an S100 protein reaction, a feature not seen in ESSPA. Furthermore, paraganglioma would be positive with tyrosine hydroxylase, while negative for both pituitary hormones and pituitary transcription factors [60–62].

Sinonasal undifferentiated carcinoma (SNUC) presents with a rapid clinical onset of obstruction, epistaxis, proptosis, facial pain and CN involvement. The imaging features demonstrate extensive infiltration of many different sites within the sinonasal tract, resulting in significant destruction. The tumors are not usually centered on the sphenoid sinus. The tumors are high grade neoplasms, perhaps showing surface dysplasia or carcinoma in situ. The cells are generally large, showing a high nuclear-to-cytoplasmic ratio and variable amounts of poorly-defined cytoplasm. The nuclei range from hyperchromatic to vesicular, with variably present nucleoli. Mitoses are greatly increased and include atypical forms. Confluent tumor necrosis is usually easily seen. Lymph-vascular and perineural invasion is seen in most cases. Rosettes and neurofibrillar matrix are absent, as are areas of squamous or glandular differentiation. These tumors are strongly positive with pan-cytokeratin and CK7, while non-reactive with CK5/6 and CK13. Occasional cases may show neuroendocrine markers (such as chromogranin, synaptophysin, CD56 or CD57), but reactivity is usually weak and limited. Pituitary hormone and transcription factors are negative [63–66]. Again, the management with multimodality therapy is very different from the management for ESSPA, with a very different prognosis and outcome.

Mucosal malignant melanoma (MMM), when it is non-pigmented, may present with a pattern of growth similar to

Table 7 Combination of current study patients with literature review cases

Characteristics	Ectopic pituitary adenoma total: n = 75[a]
Gender	
Women	43
Men	32
Age (in years)	
Range	2–84
Mean	53.8
Women (mean)	53.1
Men (mean)	54.7
Symptom duration (in months)[b]	
Range	1–360
Mean	48.8
Women (mean) ($p = 0.093$)	65.3
Men (mean)	28.0
Symptoms at presentation[b,c]	
Obstruction, sinusitis, rhinorrhea, discharge, drainage	26
Headache and pain	21
Visual disturbances (diplopia, acuity loss, blurring)	14
Cushing symptoms (bruising, hypertension, acne, facial hair, weakness)	11
Acromegaly	8
Asymptomatic	6
Impotency	4
Nerve changes	4
Amenorrhea and/or galactorrhea	3
Epistaxis	3
Mass	3
Balance	2
Size (in cm)[b]	
Range	0.5–8.0
Average	2.9
Males ($p = 0.312$)	3.2
Females	2.7
Hormone present by immunohistochemistry[b]	
Null type	13
Multiple hormones	12
Prolactin alone[d]	23
ACTH alone[d]	15
GH alone	7
All patients with follow-up (n = 52) (mean years of survival)[a]	
Follow-up range	0.03–32.7
Alive or dead, no evidence of disease (n = 45)	7.3
Alive or dead, with disease (n = 7)	0.7

[a] This table includes the current reported cases in combination with the literature

[b] Parameter was not stated in all cases

[c] Patients may have experienced more than one symptom

[d] All hormones were not tested in selected cases, so parameter may be overstated

pituitary adenoma. However, MMMs are usually large tumors centered within the nasal cavity or paranasal sinuses, usually not presenting with sphenoid sinus tumor only. The tumors are very cellular, show a remarkable variety of growth patterns and may have necrosis. The presence of intranuclear cytoplasmic inclusions, prominent nucleoli, plasmacytoid growth, and tumor cell multinucleation may give findings similar to an ESSPA. However, the application of the selected, pertinent immunohistochemistry panel would help with separation, as melanoma will show S100 protein, HMB-45 or Melan-A reactivity, while negative with keratins and pituitary hormones or transcription factors, and nearly always negative for neuroendocrine markers (chromogranin, synaptophysin, CD56) [58, 67].

A meningothelial pattern is not seen in ESSPA, but the presence of intranuclear cytoplasmic inclusions, a sheet-like to packeted growth, and isolated psammoma calcifications can raise the differential diagnosis of meningioma. However, meningioma is usually positive with EMA and CK7 (in a pre-psammoma body like pattern), while negative with neuroendocrine and pituitary hormone markers [68, 69].

Nasopharyngeal carcinoma (NPC) may be raised in the differential diagnosis of ESSPA with nasopharyngeal extension. The syncytial epithelial architecture, especially when the inflammatory element is prominent, is not a pattern seen in ESSPA. Occasionally, the epithelioid appearance with prominent nucleoli may result in incorrect diagnosis. However, NPC are strongly immunoreactive with pan-cytokeratin, CK5/6, p63, and nearly all cases are reactive with Epstein Barr virus-encoded RNA (EBER). There is a lack of neuroendocrine tumor markers as well as pituitary hormones [70].

In summary, the following considerations will greatly aid in the appropriate classification of ESSPA: (1) The anatomic site: Sphenoid sinus. As soon as the anatomic site is known, ectopic pituitary adenoma must be considered and actively excluded; (2) Imaging findings: The specific location and presence or absence of pituitary gland or sphenoid sinus involvement will help. Specifically, there is a lack of significant nasal cavity destruction; (3) The histologic appearance shows a variety of patterns of growth, nearly always associated with a very delicate fibrovascular stroma. Necrosis can be seen, and should not dissuade from the diagnosis. The presence of intranuclear cytoplasmic inclusions, tumor multinucleation, isolated pleomorphism, and a plasmacytoid appearance can considerably narrow the differential diagnosis; (4) The immunohistochemistry evaluation must include pan-keratin, a couple of neuroendocrine markers (synaptophysin and CD56), S100 protein, and then, depending on these results, a panel of pituitary hormone markers and/or transcription factors. Finally, in selected cases only where the tumor is a true "null-cell"

Table 8 Categorization of ectopic sphenoid sinus pituitary adenomas

Type	Nonfunctioning adenoma	Functioning adenoma	
GH-prolactin-TSH family (n = 31)	*Silent* lactotroph adenoma: n = 7	Adenomas causing hyperprolactinemia (n = 15)	Lactotroph adenoma (prolactin only): n = 14
			Lactotroph adenoma (prolactin and GH): n = 1
	Silent somatotroph adenoma: n = 1	Adenomas causing GH excess (n = 8)	Somatotroph adenoma (GH only): n = 5
			Mammosomatotroph adenoma (GH and prolactin): n = 3
	Silent thyrotroph adenoma: n = 0	Adenomas causing TSH excess	Thyrotroph adenoma (TSH)
ACTH family (n = 13)	*Silent* corticotroph: n = 4	Adenomas causing ACTH excess	Corticotroph adenoma (ACTH): n = 9
Gonadotropin family (n = 1)	*Silent* gonadotroph adenoma: n = 1	Adenomas causing gonadotropin excess	Gonadotroph (FSH or LH)
Unclassified adenomas (n = 25)	*Silent* (hormone negative) adenoma: n = 13*	Plurihormonal adenomas (multiple hormones): n = 12	

* This number represents cases from the literature and this study that have an insufficient number of ancillary studies performed to reach a definitive classification; no pituitary transcription factors nor electron microscopy were performed to further classify these

neoplasm, without hormone or transcription factors present, electron microscopy can be used to disclose the specific features seen in true silent pituitary adenomas, such as silent subtype III adenomas and acidophil stem cell adenomas.

Treatment and Prognosis

Surgical removal is the treatment of choice for ESSPA. Specifically, during surgery additional evaluation of the roof of the sinus and the sella turcica can be performed to help guide additional management. Margins are not usually assessed for these tumors, since they are usually removed in pieces. Various medical therapies have been employed, with bromocriptine (a dopamine agonist) used most frequently for PRL secreting tumors, effectively reducing their size [4]. However, medical management is not a cure, with drug effects identified only while medical therapy is ongoing. Therefore, when medication is stopped, the tumor may regrow. Therefore, if a dopamine agonist is employed, it should be continued for the patient's life [46]. There are potential benefits of initial medical therapy in an attempt to reduce the size of the tumor, but frequently the pre-operative diagnosis is not correct, limiting medical therapy to the post-operative setting.

Radiotherapy has been employed for these tumors in selected cases. Radiation was used in five patients in this series: 3 at the time of initial diagnosis, and 2 at the time of recurrence. There are well-known risks of radiation to this area, including macular ischemia, vasculopathy and even optic neuropathy. Furthermore, radiotherapy is not very effective in tumor control for tumors of the pituitary fossa [50], and so likewise, is probably not effective in ectopic foci either. Therefore, in selected cases, if the tumors are large or incompletely excised, post operative radiotherapy may be indicated for tumor control, although not cure [4].

Conclusion

ESSPA are exceedingly rare neoplasms. It is imperative in any tumor removed from the sphenoid sinus that careful consideration should be given to ectopic pituitary adenoma. Specifically, the exact anatomic site should be identified (not just "sinus"), the imaging findings reviewed, the clinical findings related to possible hormone excess identified, and selected but pertinent immunohistochemistry evaluation be performed to confirm the diagnosis. The tumors are benign without a metastatic potential. It is most important to render the correct diagnosis for this benign tumor in order to avoid the significant morbidity associated with treatments employed for several of the other tumors in the differential diagnosis.

Acknowledgment A special thanks to Ms. Hannah Herrera for her research assistance. Supported in part by Southern California Permanente Medical Group.

References

1. Luna MA, Cardesa A, Barnes L, et al. Benign epithelial tumours. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and genetics head and neck tumours. Lyon: IARC Press; 2005. p. 99–101.
2. Asa SL, Ezzat S. The pathogenesis of pituitary tumors. Annu Rev Pathol. 2009;4:97–126.
3. Asa SL. The pathology of pituitary tumors. Endocrinol Metab Clin North Am. 1999;28:13–vi.
4. Langford L, Batsakis JG. Pituitary gland involvement of the sinonasal tract. Ann Otol Rhinol Laryngol. 1995;104:167–9.

5. Hori A, Schmidt D, Rickels E. Pharyngeal pituitary: development, malformation, and tumorigenesis. Acta Neuropathol. 1999;98: 262–72.
6. Hori A, Schmidt D, Kuebber S. Immunohistochemical survey of migration of human anterior pituitary cells in developmental, pathological, and clinical aspects: a review. Microsc Res Tech. 1999;46:59–68.
7. Rasmussen P, Lindholm J. Ectopic pituitary adenomas. Clin Endocrinol (Oxf). 1979;11:69–74.
8. Wenig BM, Heffess CS, Adair CF, et al. Ectopic pituitary adenomas (EPA): a clinicopathologic study of 15 cases. Mod Pathol. 1995;8:56A.
9. Appel JG, Bergsneider M, Vinters H, Salamon N, Wang MB, Heaney AP. Acromegaly due to an ectopic pituitary adenoma in the clivus: case report and review of literature. Pituitary. 2011: PMID: 21960210.
10. Anand VK, Osborne CM, Harkey HL III. Infiltrative clival pituitary adenoma of ectopic origin. Otolaryngol Head Neck Surg. 1993;108:178–83.
11. Bethge H, Arlt W, Zimmermann U, Klingelhoffer G, Wittenberg G, Saeger W, et al. Cushing's syndrome due to an ectopic ACTH-secreting pituitary tumour mimicking occult paraneoplastic ectopic ACTH production. Clin Endocrinol (Oxf). 1999;51:809–14.
12. Borit A, Blanshard TP. Sphenoidal pituitary adenoma. Hum Pathol. 1979;10:93–6.
13. Burch WM, Kramer RS, Kenan PD, Hammond CB. Cushing's disease caused by an ectopic pituitary adenoma within the sphenoid sinus. N Engl J Med. 1985;312:587–8.
14. Chan MR, Ziebert M, Maas DL, Chan PS. "My rings won't fit anymore". Ectopic growth hormone-secreting tumor. Am Fam Physician. 2005;71:1766–7.
15. Chessin H, Urdaneta N, Smith H, Van Gilder J. Chromophobe adenoma manifesting as a nasopharyngeal mass. Arch Otolaryngol. 1976;102:631–3.
16. Coire CI, Horvath E, Kovacs K, Smyth HS, Ezzat S. Cushing's syndrome from an ectopic pituitary adenoma with peliosis: a histological, immunohistochemical, and ultrastructural study and review of the literature. Endocr Pathol. 1997;8:65–74.
17. Corenblum B, LeBlanc FE, Watanabe M. Acromegaly with an adenomatous pharyngeal pituitary. JAMA. 1980;243:1456–7.
18. Erdheim J. Uber einen hypophysintumor von Ungewohnlichen. Sitz Beitr Path Anat. 1909;46:233–40.
19. Gondim JA, Schops M, Ferreira E, Bulcao T, Mota JI, Silveira C. Acromegaly due to an ectopic pituitary adenoma in the sphenoid sinus. Acta Radiol. 2004;45:689–91.
20. Hattori N, Ishihara T, Saiwai S, Moridera K, Hino M, Ikekubo K, et al. Ectopic prolactinoma on MRI. J Comput Assist Tomogr. 1994;18:936–8.
21. Heitzmann A, Jan M, Lecomte P, Ruchoux MM, Lhuintre Y, Tillet Y. Ectopic prolactinoma within the sphenoid sinus. Neurosurgery. 1989;24:279–82.
22. Hori E, Akai T, Kurimoto M, Hirashima Y, Endo S. Growth hormone-secreting pituitary adenoma confined to the sphenoid sinus associated with a normal-sized empty sella. J Clin Neurosci. 2002;9:196–9.
23. Horiuchi T, Tanaka Y, Kobayashi S, Unoki T, Yokoh A. Rapidly-growing ectopic pituitary adenoma within the sphenoid sinus–case report. Neurol Med Chir (Tokyo). 1997;37:399–402.
24. Kammer H, George R. Cushing's disease in a patient with an ectopic pituitary adenoma. JAMA. 1981;246:2722–4.
25. Kepes JJ, Fritzlen TJ. Large invasive chromophobe adenoma with well-preserved pituitary gland. Neurology. 1964;14:537–41.
26. Kikuchi K, Kowada M, Sasaki J, Sageshima M. Large pituitary adenoma of the sphenoid sinus and the nasopharynx: report of a case with ultrastructural evaluations. Surg Neurol. 1994;42:330–4.
27. Kurowska M, Tarach JS, Zgliczynski W, Malicka J, Zielinski G, Janczarek M. Acromegaly in a patient with normal pituitary gland and somatotropic adenoma located in the sphenoid sinus. Endokrynol Pol. 2008;59:348–51.
28. Lloyd RV, Chandler WF, Kovacs K, Ryan N. Ectopic pituitary adenomas with normal anterior pituitary glands. Am J Surg Pathol. 1986;10:546–52.
29. Luk IS, Chan JK, Chow SM, Leung S. Pituitary adenoma presenting as sinonasal tumor: pitfalls in diagnosis. Hum Pathol. 1996;27:605–9.
30. Madonna D, Kendler A, Soliman AM. Ectopic growth hormone-secreting pituitary adenoma in the sphenoid sinus. Ann Otol Rhinol Laryngol. 2001;110:99–101.
31. Matsuno A, Katayama H, Okazaki R, Toriumi M, Tanaka H, Akashi M, et al. Ectopic pituitary adenoma in the sphenoid sinus causing acromegaly associated with empty sella. ANZ J Surg. 2001;71:495–8.
32. Matsushita H, Matsuya S, Endo Y, Hara M, Shishiba Y, Yamaguchi H, et al. A prolactin producing tumor originated in the sphenoid sinus. Acta Pathol Jpn. 1984;34:103–9.
33. Siegert B, vz Mühlen A, Brabant G, Saeger W, Vogt-Hohenlinde C. Ectopic nonfunctioning pituitary adenoma in the sphenoid sinus. J Clin Endocrinol Metab. 1996;81:430–1.
34. Slonim SM, Haykal HA, Cushing GW, Freidberg SR, Lee AK. MRI appearances of an ectopic pituitary adenoma: case report and review of the literature. Neuroradiology. 1993;35: 546–8.
35. Suzuki J, Otsuka F, Ogura T, Kishida M, Takeda M, Tamiya T, et al. An aberrant ACTH-producing ectopic pituitary adenoma in the sphenoid sinus. Endocr J. 2004;51:97–103.
36. Tovi F, Hirsch M, Sacks M, Leiberman A. Ectopic pituitary adenoma of the sphenoid sinus: report of a case and review of the literature. Head Neck. 1990;12:264–8.
37. Trulea M, Patey M, Chaufour-Higel B, Bouquigny F, Longuebray A, Rousseaux P, et al. An unusual case of ectopic adrenocorticotropin secretion. J Clin Endocrinol Metab. 2009;94:384–5.
38. Wang H, Yu W, Zhang Z, Xu W, Zhang F, Bao W. Ectopic pituitary adenoma in the spheno-orbital region. J Neuroophthalmol. 2010;30:135–7.
39. Warner BA, Santen RJ, Page RB. Growth of hormone and prolactin secretion by a tumor of the pharyngeal pituitary. Ann Intern Med. 1982;96:65–6.
40. Yang BT, Chong VF, Wang ZC, Xian JF, Chen QH. Sphenoid sinus ectopic pituitary adenomas: CT and MRI findings. Br J Radiol. 2010;83:218–24.
41. Zerikly RK, Eray E, Faiman C, Prayson R, Lorenz RR, Weil RJ, et al. Cyclic cushing syndrome due to an ectopic pituitary adenoma. Nat Clin Pract Endocrinol Metab. 2009;5:174–9.
42. Arita K, Uozumi T, Yano T, Sumida M, Muttaqin Z, Hibino H, et al. MRI visualization of complete bilateral optic nerve involvement by pituitary adenoma: a case report. Neuroradiology. 1993;35:549–50.
43. Esteban F, Ruiz-Avila I, Vilchez R, Gamero C, Gomez M, Mochon A. Ectopic pituitary adenoma in the sphenoid causing Nelson's syndrome. J Laryngol Otol. 1997;111:565–7.
44. Ali R, Noma U, Jansen M, Smyth D. Ectopic pituitary adenoma presenting as midline nasopharyngeal mass. Ir J Med Sci. 2010;179:593–5.
45. Shenker Y, Lloyd RV, Weatherbee L, Port FK, Grekin RJ, Barkan AL. Ectopic prolactinoma in a patient with hyperparathyroidism and abnormal sellar radiography. J Clin Endocrinol Metab. 1986;62:1065–9.
46. Daly AF, Tichomirowa MA, Beckers A. The epidemiology and genetics of pituitary adenomas. Best Pract Res Clin Endocrinol Metab. 2009;23:543–54.

47. Sanno N, Teramoto A, Osamura RY, Horvath E, Kovacs K, Lloyd RV et al. Pathology of pituitary tumors. Neurosurg Clin N Am. 2003;14:25–39, vi.
48. Clayton RN. Sporadic pituitary tumours: from epidemiology to use of databases. Baillieres Best Pract Res Clin Endocrinol Metab. 1999;13:451–60.
49. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. Cancer. 2004;101:613–9.
50. Oruckaptan HH, Senmevsim O, Ozcan OE, Ozgen T. Pituitary adenomas: results of 684 surgically treated patients and review of the literature. Surg Neurol. 2000;53:211–9.
51. van der Mey AG, van Seters AP, van Krieken JH, Vielvoye J, van DH, Hulshof JH. Large pituitary adenomas with extension into the nasopharynx. Report of three cases with a review of the literature. Ann Otol Rhinol Laryngol. 1989;98:618–624.
52. Kovacs K, Scheithauer BW, Horvath E, Lloyd RV. The World Health Organization classification of adenohypophysial neoplasms. A proposed five-tier scheme. Cancer. 1996;78:502–10.
53. El-Naggar AK, Batsakis JG, Vassilopoulou-Sellin R, Ordonez NG, Luna MA. Medullary (thyroid) carcinoma-like carcinoids of the larynx. J Laryngol Otol. 1991;105:683–6.
54. Yamashita M, Qian ZR, Sano T, Horvath E, Kovacs K. Immunohistochemical study on so-called follicular cells and folliculostellate cells in the human adenohypophysis. Pathol Int. 2005;55:244–7.
55. Thompson LDR. Olfactory neuroblastoma. Ear Nose Throat J. 2006;85:569–70.
56. Thompson LDR. Olfactory neuroblastoma. Head Neck Pathol. 2009;3:252–9.
57. Cohen ZR, Marmor E, Fuller GN, DeMonte F. Misdiagnosis of olfactory neuroblastoma. Neurosurg Focus. 2002;12:e3.
58. Devaney K, Wenig BM, Abbondanzo SL. Olfactory neuroblastoma and other round cell lesions of the sinonasal region. Mod Pathol. 1996;9:658–63.
59. Wick MR, Nappi O. Ectopic neural and neuroendocrine neoplasms. Semin Diagn Pathol. 2003;20:305–23.
60. Pellitteri PK, Rinaldo A, Myssiorek D, Gary JC, Bradley PJ, Devaney KO, et al. Paragangliomas of the head and neck. Oral Oncol. 2004;40:563–75.
61. Myssiorek D, Halaas Y, Silver C. Laryngeal and sinonasal paragangliomas. Otolaryngol Clin North Am. 2001;34:971–982, vii.
62. Iwase K, Nagasaka A, Nagatsu I, Kiuchi K, Nagatsu T, Funahashi H, et al. Tyrosine hydroxylase indicates cell differentiation of catecholamine biosynthesis in neuroendocrine tumors. J Endocrinol Invest. 1994;17:235–9.
63. Menon S, Pai P, Sengar M, Aggarwal JP, Kane SV. Sinonasal malignancies with neuroendocrine differentiation: case series and review of literature. Indian J Pathol Microbiol. 2010;53:28–34.
64. Cordes B, Williams MD, Tirado Y, Bell D, Rosenthal DI, Al-Dhahri SF, et al. Molecular and phenotypic analysis of poorly differentiated sinonasal neoplasms: an integrated approach for early diagnosis and classification. Hum Pathol. 2009;40:283–92.
65. Schmidt ER, Berry RL. Diagnosis and treatment of sinonasal undifferentiated carcinoma: report of a case and review of the literature. J Oral Maxillofac Surg. 2008;66:1505–10.
66. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. Adv Anat Pathol. 2005;12:134–43.
67. Thompson LDR, Wieneke JA, Miettinen M. Sinonasal tract and nasopharyngeal melanomas: a clinicopathologic study of 115 cases with a proposed staging system. Am J Surg Pathol. 2003;27:594–611.
68. Rushing EJ, Bouffard JP, McCall S, Olsen C, Mena H, Sandberg GD, et al. Primary extracranial meningiomas: an analysis of 146 cases. Head Neck Pathol. 2009;3:116–30.
69. Thompson LDR, Gyure KA. Extracranial sinonasal tract meningiomas: a clinicopathologic study of 30 cases with a review of the literature. Am J Surg Pathol. 2000;24:640–50.
70. Thompson LDR. Update on nasopharyngeal carcinoma. Head Neck Pathol. 2007;1:81–6.