



Ectopic Pituitary Neuroendocrine Tumors/Adenomas Around the Sella Turcica

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Functional or non-secretory ectopic pituitary neuroendocrine tumors (PitNET) can form around the sella turcica during the development of the adenohypophysis by differentiating and detaching from the pharyngeal roof. These tumors usually appear in the sphenoid sinus, clivus, cavernous sinus, infundibulum, and suprasellar cistern. Ectopic PitNETs typically display the characteristic magnetic resonance imaging findings of pituitary adenomas. However, preoperative diagnosis of PitNETs is usually challenging because of the variety of clinical and imaging presentations, locations, and sizes. Ectopic suprasellar PitNETs resemble

mass lesions in the pituitary stalk. Ectopic cavernous sinus of PitNETs are typically microadenomas in the medial wall. Ectopic sphenoclivar tumors are characterized by more aggressive tumor activity than the other ectopic PitNETs. Although ectopic PitNETs are exceedingly rare, they should be considered as a differential diagnosis for masses around the sella turcica. Treatment of the disease should be individualized and may include medical care, surgical resection, gamma-knife radiosurgery, and radiotherapy.

The pituitary gland is located at the base of the brain in the sella turcica. Pituitary adenomas, also known as pituitary neuroendocrine tumors (PitNETs), arise from the pituitary gland and frequently present as intrasellar tumors.¹ Although PitNET is the preferred nomenclature, pituitary adenoma is accepted. Ectopic PitNET, an extremely rare entity, is usually defined as an extrasellar PitNET without any connections to the intrasellar components.^{2,3} Ectopic PitNETs can be found in the nasopharynx, nasal cavity, ethmoid sinus, temporal bone, nasal bridge, and sphenoid sinus of the upper aerodigestive tract as well as the suprasellar cistern, Meckel's cave, cavernous sinus, thalamus, and cerebellopontine angle in the intracranial region.⁴⁻⁷ Because ectopic PitNETs are usually located close to the sella turcica, preoperative imaging diagnosis can be challenging.

Herein, we have reviewed data available on ectopic PitNETs located near the sella turcica with respect to their demography, clinical and laboratory manifestations, magnetic resonance imaging (MRI) features, differential diagnoses, and therapeutic options.

Anatomy

The sella turcica is a cup-shaped recession in the central basisphenoid bone, which encloses the inferior section of the infundibular stalk and the pituitary gland. The anterior wall of the sella turcica lies perpendicular to the posterior margin of the chiasmatic sulcus, and its superior edge is identified by a small elevation known as the tuberculum sellae. The middle clinoid processes are lateral extensions that occasionally protrude from the corners of the tuberculum sellae. The dorsum sellae is a broad ring of bone that extends forwards and upward to form the posterior wall of the sella turcica. Above this bony ridge, the lateral borders form curved projections known as the posterior clinoid processes, which serve as attachment points for the tentorium cerebelli. The diaphragma sellae, which divides the sella turcica from the suprasellar subarachnoid space, forms the superior border of the sella turcica. It is a dural reflection above the pituitary gland and has a narrow opening for the pituitary stalk. The suprasellar region, which is surrounded by the Willis circle, houses the optic nerves,

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chiasm, tuber cinereum, and superior part of the infundibular stalk. Situated above the infundibular stalk are the anterior recess of the third ventricle and the hypothalamus. A multiseptated venous canal called the cavernous sinus encircles the sella turcica on both sides. The cavernous sinus contains the internal carotid artery, cranial nerves III, IV, and VI, and the trigeminal nerve's ophthalmic (V_1) and maxillary (V_2) divisions.

Pituitary development

The embryology of the pituitary gland is well known because ectopic PitNETs are believed to be neoplastic growths of the pituitary gland during the course of its development. In contrast to the neurohypophysis, which originates from the neuroectoderm of the brain floor, the anterior pituitary gland is ectodermal in origin and is derived from the Rathke's pouch of the hard palate. The extracranial ectoderm of the primitive oral cavity forms a superiorly oriented invagination during the fourth week of pregnancy, resulting in the Rathke's pouch. During weeks 6 to 8, the ectoderm completely separates from the pouch and connects with the inferiorly oriented extension of the neuroectoderm. These two extensions form the pituitary gland in the sella turcica, which originates from the mesoderm.⁸⁻¹⁰

Magnetic resonance imaging

MRI is the best imaging modality for the evaluation of lesions in and around the sella turcica and should be performed using a 1.5- or 3-Tesla high-field scanner with a multichannel head coil. The standard protocol consists of sagittal and coronal T1- and T2-weighted (W) turbo spin echo sequences, a field of view of 13-18 cm, and slices of ≤ 3 mm thickness. An axial T2W sequence of the entire brain and nasopharynx should be included in the imaging

protocol because it can provide additional information in certain circumstances. It is also a common practice to obtain whole-brain imaging sequences such as diffusion-weighted, susceptibility-weighted, and FLAIR sequences when making a differential diagnosis.^{11,12} Coronal, gadolinium-enhanced, fat-suppressed, dynamic images are also required for evaluating sellar and parasellar lesions. Alternatively, one can use three-dimensional (3D) spoiled gradient-echo volume acquisition with a good signal-to-noise ratio that can be reconstructed in all three imaging planes.¹³ The infundibulum, which lies external to the blood-brain barrier, is enhanced early and intensely after intravenous contrast administration.¹⁴ MRI anatomy of the sellar and parasellar regions is shown in Figure 1.

In patients with pacemakers, ocular metallic foreign bodies, cochlear implants, or obesity that technically preclude the use of MRI, computed tomography (CT) can be performed for the primary diagnosis of ectopic PitNETs. Additionally, CT complements MRI for the diagnoses of other conditions such as meningiomas, craniopharyngiomas, and germinomas; it identifies calcifications or ossifications typical of these tumors. In addition to its application in surgical planning, CT is used to evaluate the bone integrity of the skull base.

Ectopic PitNETs

Ectopic PitNETs are benign tumors of the ectopic anterior pituitary gland cells that comprise secretory cells and produce pituitary hormones. These tumors are believed to originate from the neoplastic expansion of the pituitary during the embryological course of development. PitNETs were first described by Erdheim¹⁵ in 1909 and are predominantly described in case reports.

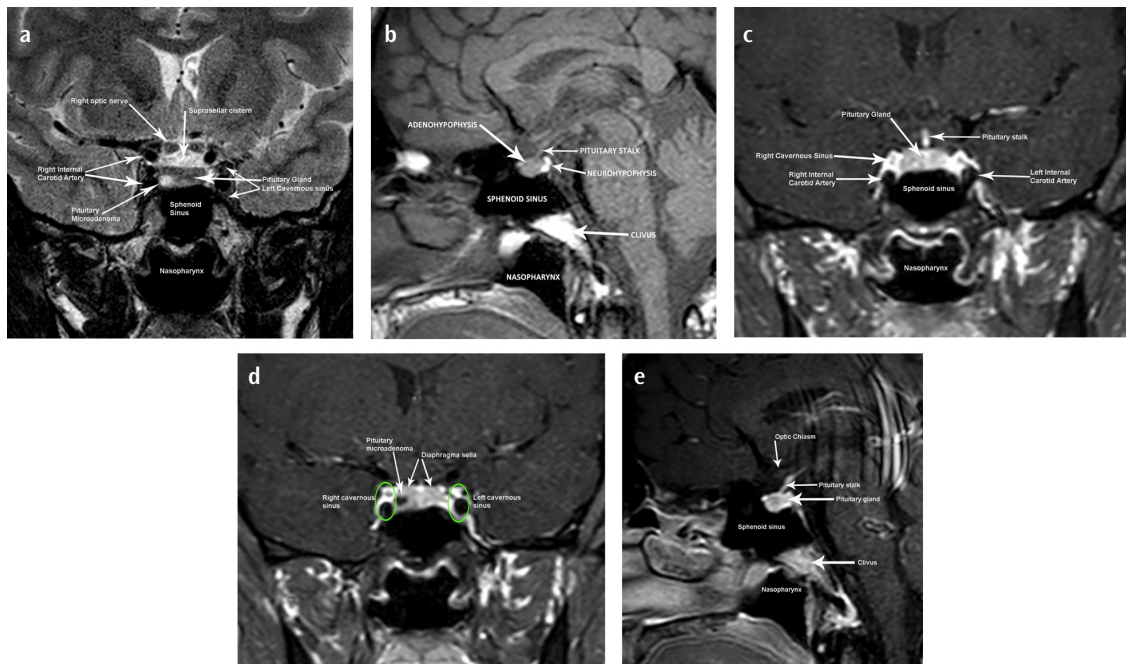


FIG. 1. Magnetic resonance imaging of the sellar and parasellar regions. (a) Coronal turbo spin echo T2-weighted (W), (b) sagittal spin echo T1-W, (c, d) coronal contrast-enhanced T1-W, and (e) sagittal contrast-enhanced T1-W images.

The change in the nomenclature of the tumor in the fifth edition of the World Health Organization (WHO) Classification 2021 and 2022 WHO Classification of Endocrine and Neuroendocrine Tumors can be attributed to its variable clinical and pathological features such as aggressive behavior, recurrence after treatment, and occasional metastasis.¹⁶⁻¹⁹ Additionally, neuroendocrine proteins such as chromogranin A, insulinoma-like protein 1, CD56, and synaptophysin are expressed by PitNETs, which are suggestive of neuroendocrine tumors.²⁰

Of the 176 patients with ectopic PitNETs analyzed in a study, 117 were female and 59 were male. These patients ranged in age from 6 to 82 years at diagnosis, with a mean age of 47.3 ± 17.9 years among the males and 44.6 ± 16.7 years among the females. The study revealed that most patients were in their 30-60s.³

Signs of excess hormone production, such as Cushing's syndrome, acromegaly, amenorrhea, lactation, decreased libido, hyperthyroidism, or hyperparathyroidism, are present in more than half of the patients with ectopic PitNET.²¹ Looking for an ectopic PitNET around the sella turcica or elsewhere becomes important if signs of excess hormonal production are evident without a PitNET in the sella turcica.²² However, non-functioning ectopic PitNETs are relatively more difficult to identify than functioning tumors; thus, they can be misdiagnosed as other pathologies. The typical sites for ectopic PitNETs include the sphenoid sinus, clivus, cavernous sinus, infundibulum, and suprasellar cistern (Figure 2).

Ectopic PitNETs can be categorized as either macroadenomas (≥ 10 mm) or microadenomas (< 10 mm) according to their size; masses > 40 mm in size are referred to as giant adenomas. The signal intensity of ectopic PitNETs on MRI varies because components such as water are not constant in these tumors and depend on the size and hormones they produce. PitNETs usually exhibit an isointense signal with gray matter on T1W MRI and demonstrate either heterogeneous or homogeneous enhancement in contrast-enhanced studies.²³ Degeneration of any form, hemorrhage, and infarction of ectopic PitNETs can cause variations in the T2 signaling. Furthermore, the sella may appear empty with ectopic PitNETs.

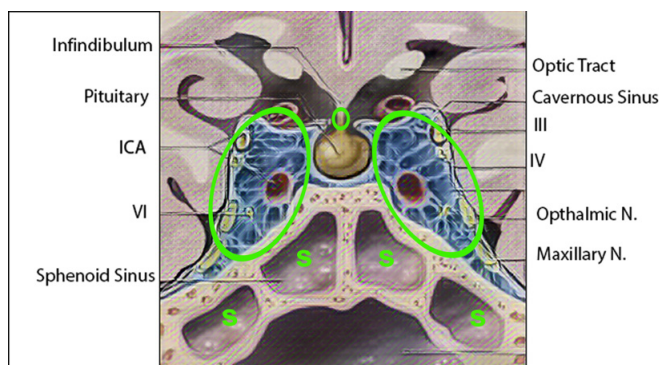


FIG. 2. Illustration of ectopic PitNETs around sella turcica. The small open green circle represents the pituitary stalk site. The large green circles represent the cavernous sinuses. The green "S"s represent the sphenoid sinus.

PitNETs, pituitary neuroendocrine tumors

Pituitary stalk PitNET and ectopic suprasellar PitNET

The suprasellar cistern is a common location for PitNET presentation. However, to characterize suprasellar PitNETs as ectopic, it is necessary to pay close attention to their anatomical relationships. According to anatomical studies, suprasellar PitNETs can be classified into three types depending on the surrounding tissue. Type 1 tumors arise from the pars distalis, the superior part of the anterior pituitary tissue, and they extend superiorly through the diaphragma sella. The more common type 2 suprasellar PitNETs originate from the pars tuberalis, which is an elevated portion of the anterior pituitary tissue that primarily makes up the pituitary stalk. Because of their attachment to an elevated region of the anterior pituitary tissue above the diaphragma sellae, these suprasellar forms are not regarded as "ectopic." A possible source of the type 3 suprasellar PitNETs is the arachnoid of the anterior pituitary cells in the perinfundibular area (Figure 3).^{22,24}

Table 1 summarizes the hormonal properties, symptoms, and typical MRI findings of ectopic PitNETs situated around the sella turcica.

The differential diagnoses of an abnormal nodular enhancement of the pituitary stalk on MRI include tumoral processes (germinoma, craniopharyngioma, hypothalamic glioma, lymphoma, pituitary tumor, granular cell tumor, pilocytic astrocytoma, metastasis, and hemangioblastoma), infections (tuberculosis and meningitis sequela), and cellular infiltrates (Langerhans cell histiocytosis, neurosarcoidosis and lymphocytic hypophysitis). Physicians should be aware of the main differential diagnoses and required diagnostic tests, perform a complete clinical examination, and obtain the full medical history. Although MRI is non-specific for pituitary stalk lesions, related cerebral characteristics can help restrict the number of differential diagnoses. In centers with access to a skilled neurosurgeon, a biopsy should be considered when a diagnosis is deemed necessary. The treatment of choice is based on the underlying cause of the illness and includes surgery, gamma-knife radiosurgery, radiotherapy, and medication.^{25,26}

Ectopic cavernous sinus PitNET

The occurrence of ectopic PitNETs in the cavernous sinus is extremely rare, and it usually presents as adrenocorticotrophic hormone-secreting microadenomas. Although ophthalmoplegia, ptosis, exophthalmos, chemosis, vision loss, Horner's syndrome, headache, and face pain are possible symptoms of a cavernous sinus mass, ectopic cavernous sinus PitNETs rarely present with any of these symptoms.²⁷ There are occasional reports of ectopic prolactin-secreting microadenomas in the cavernous sinus.²⁸ Elevated preoperative prolactin levels and characteristic imaging findings might be sufficient to diagnose ectopic tumors and initiate appropriate therapy without a biopsy because three-quarters of ectopic PitNETs are hormonally active. Most hormonally active ectopic PitNETs secrete adrenocorticotrophic hormone or prolactin (Figure 4).^{8,29} Ectopic adenomas are easier to identify with Ga-68 dotatate positron emission tomography/CT, a molecular imaging technique targeting the adrenocorticotrophin-releasing hormone receptor expressed within the corticotroph PitNETs.³⁰ Cushing's

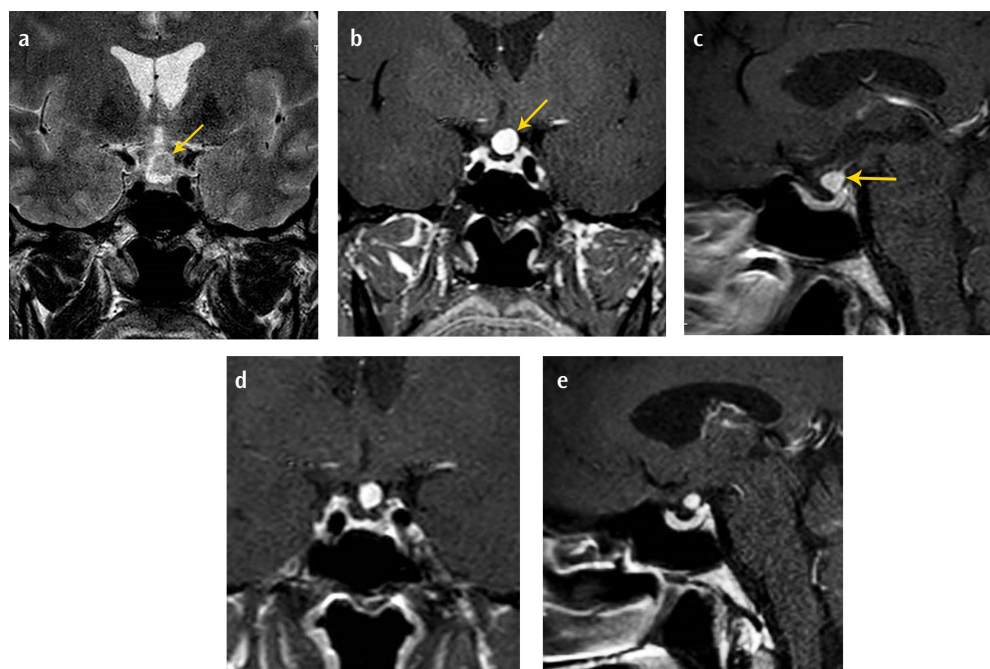


FIG. 3. Brain magnetic resonance imaging (MRI) of a 48-year-old woman with an ectopic suprasellar pituitary stalk PitNET and hyperprolactinemia. (a) Coronal T2-weighted (W) MRI showing a mass isointense to the cortical gray matter in the suprasellar region involving the pituitary stalk (arrow). (b, c) The mass demonstrates intense and homogeneous enhancement on coronal and sagittal T1-W sections of gadolinium-enhanced MRI (arrows). The pituitary gland is seen separate from the lesion. (d, e) Coronal and sagittal sections of gadolinium-enhanced MRI after 3 months of cabergoline administration demonstrate a reduction in the lesion size.

PitNETs, pituitary neuroendocrine tumors

TABLE 1. Ectopic PitNETs around the sella turcica.

Location	Hormonal properties	Types of symptoms (from most common to least common)	Typical MRI findings
Sphenoidal sinus	Non-functional (27.4%) Adrenocorticotrophic hormone-secreting (33.9%) Prolactin-secreting (24.2%) Growth hormone secreting (12.9%) (ref: 3)	Nasal obstruction, rhinorrhoea, headache, epistaxis, Cushing's syndrome, amenorrhoea, visual disturbance	A large solid mass with variable T1 and T2 signals May cause bone destruction May affect sphenoid sinus wall, sella floor, and nasal cavity, invade the cavernous sinus, and encase the adjacent internal cerebral artery
Cavernous sinus	Adrenocorticotrophic hormone-secreting (91.7%) Growth hormone-secreting (4.2%) Non-functional (4.2%) (ref: 3)	Cushing syndrome, amenorrhoea	Typically present as a microadenoma. Rarely internal cerebral artery encasement
Suprasellar/pituitary stalk	Adrenocorticotrophic hormone-secreting (43.5%) Non-functional (23.9%) Growth hormone-secreting (10.9%) Thyroid stimulating hormone-secreting (13%) Prolactin-secreting (8.7%) (ref: 3)	Visual disturbances, obstructive hydrocephalus, cranial nerve palsy, generalized seizures, Cushing syndrome	Enhancement of suprasellar solid mass involving the pituitary stalk with variable T1 and T2 signals No restricted diffusion on diffusion-weighted images No blooming artifact on SWI or T2 gradient-echo images
Clival	Non-functional (50%) Prolactin-secreting (25%) Growth hormone-secreting (21.4%) Adrenocorticotrophic hormone-secreting (3.6%) (ref: 3)	Headache, acromegaly, visual disturbances, menstrual symptoms, oculomotor dysfunction, Cushing's syndrome, nasal congestion	A large solid destructive osseous mass with variable T1 and T2 signals May be associated with sphenoid sinus, and sella floor, cavernous sinus involvement and ICA encasement

PitNETs, pituitary neuroendocrine tumors; MRI, magnetic resonance imaging.

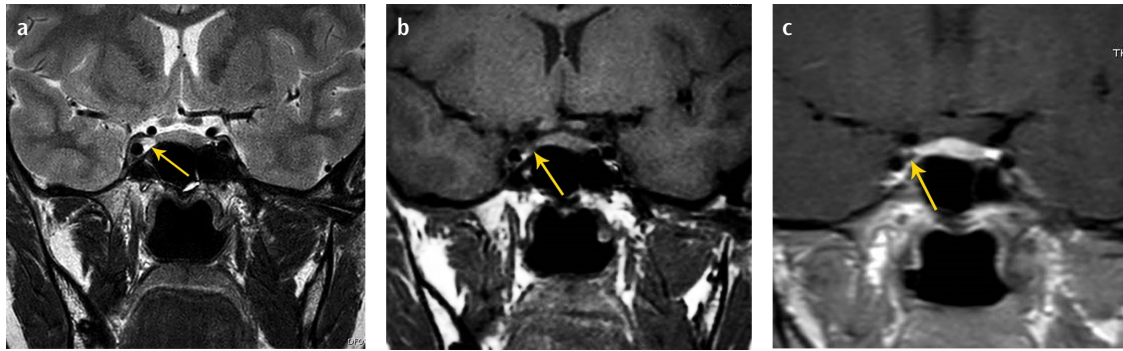


FIG. 4. Brain magnetic resonance imaging (MRI) of a 24-year-old female with an ectopic cavernous sinus PitNET and hyperprolactinemia. (a) Coronal T2-weighted (W) MRI showing a 1 cm hyperintense mass in the left cavernous sinus (arrow). (b) The lesion is hypointense on axial T1-W MRI (arrow). (c) The lesion is hypointense on contrast-enhanced axial T1-W MRI.

PitNETs, pituitary neuroendocrine tumors

disease recurrence or the source of an ectopic lesion in Cushing syndrome can be associated with a positive pituitary uptake of Ga-68 DOTA-TATE, indicating the presence of functioning pituitary tissue. The absence of pituitary uptake in patients with recurrent Cushing's disease also suggests an ectopic source of the adrenocorticotrophic hormone. In addition, radio-labeled somatostatin receptor analogs, such as Lu-177-DOTA-TATE, may be used to treat locally aggressive or metastatic pituitary cancers based on their Ga-68 DOTA-TATE uptake.³¹

Sampling of the inferior petrosal and cavernous sinuses can also be used for diagnosing pituitary or ectopic lesions; however, it is not more accurate than dynamic MRI.³² When MRI results are indicative of an adenoma, venous sinus sampling is less reliable. However, venous sinus sampling might have considerable significance when MRI results are negative, especially in the presence of microadenomas ≤ 6 mm in size.³³ More advanced MRI techniques are being developed to overcome this disadvantage. The use of 1-1.2 mm thin slices in postcontrast 3D spoiled gradient-echo T1-weighted sequences and thin-slice pituitary MRI with deep learning-based reconstruction might be useful in increasing the detection sensitivity of microadenomas.^{34,35} Furthermore, MRI is easy to perform and has no side effects. However, venous sampling is an invasive procedure that requires experience and is associated with complications.

The differential diagnoses for an ectopic cavernous sinus PitNET include meningioma, cavernoma, and schwannoma, even in the absence of clinical signs of endocrine dysfunction.²⁷

Ectopic sphenoid sinus and clivus PitNET

According to a systematic review, approximately 36.9% of ectopic PitNETs originate in the sphenoid sinus and 7.2% originate in the clivus. Furthermore, 30.9% of the tumors reportedly secrete corticotropin, 28.1% are prolactinomas, 27.4% are endocrine-inactive tumors, 6.8% are growth hormone-secreting tumors, and 3.4% are thyrotropin-positive tumors.³⁶ In another study, prolactin immunoreactivity was observed in 89% of patients with ectopic PitNETs.³⁷ Nasal obstruction, headache, decreased vision, cerebrospinal fluid leakage, cranial nerve palsy, and obvious

symptoms of endocrine disorders, such as decreased libido and fatigue, are the most common symptoms of ectopic PitNETs in the sphenoid sinus and clivus.^{36,37} Because these tumors may be larger and more invasive than those located in the cavernous sinus and suprasellar peri-infundibulum region, they could have different clinical presentations.

There are no distinguishing characteristics on an MRI that could aid the physician in taking these PitNETs into consideration before surgery. PitNETs of the clivus and sphenoid sinus usually appear as a heterogeneous, solid, expansile-enhancing mass with bone remodeling or erosion. These tumors may demonstrate calcification. Although sphenoid sinus PitNETs do not infiltrate the clivus, approximately 40% of clival tumors extend into the sphenoid sinus.³ The tumors may abut or destroy the sellar floor (Figure 5). Their growth path is selective; they involve the cavernous sinus and encase the adjacent internal carotid arteries.^{36,37}

Ectopic clival PitNETs can be highly aggressive, causing bone invasion.³⁶ Bone invasion almost always appears as areas of destruction on imaging. Tumoral seeding and malignant transformation can also occur.^{38,39} The reason for the aggressive behavior observed in some ectopic PitNETs remains unclear. In some cases, the invading muscles and encasing vessels identified can also be considered within the aggressiveness criteria.⁴⁰

Depending on the anatomical location and hormone secreted, ectopic PitNETs can have different clinical manifestations. The cavernous sinus and suprasellar region have a higher proportion of ACTH-secreting PitNETs than other locations. Because approximately 72% of ectopic PitNETs in the sphenoid sinus are secretory adenomas, presence of hormonal symptoms and evaluation of pituitary hormones can be diagnostic. Of the PitNETs with pituitary hormone reactivity, reportedly 48% are plurihormonal (reactive to two or more hormones) and 33% are reactive to a single hormone, with prolactin being the most common hormone (59%). Furthermore, 19% of PitNETs are non-reactive.⁴¹ Ectopic clival PitNETs can present with various hormonal properties, and endocrinopathy may rarely occur in some clival diseases because of the infiltration of the pituitary gland.^{3,42}

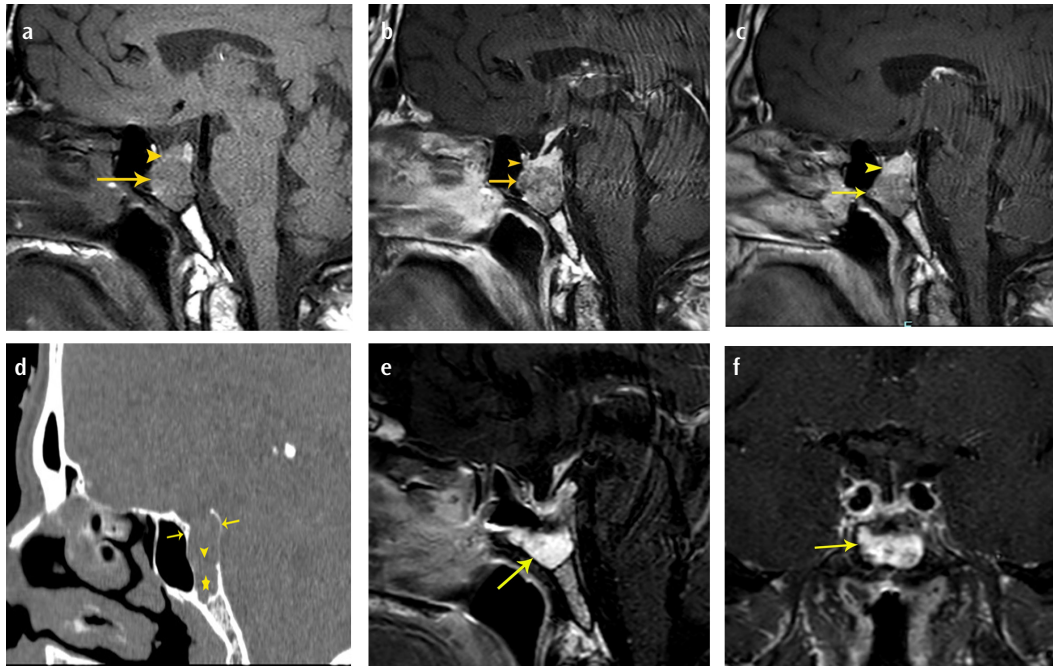


FIG. 5. Brain magnetic resonance imaging (MRI) of a 52-year-old male with ectopic sphenoclivus PitNET who presented with a headache. (a) Sagittal T1-weighted (W) MRI showing a sphenoclivus mass isointense to the cortical gray matter (arrow). Clivus and sellar floor are eroded. The pituitary gland adjacent to the superior edge of the tumor (arrowhead) appears normal. (b, c) The mass shows inhomogeneous enhancement on gadolinium-enhanced T1-W MRI (arrows). The pituitary gland shows homogeneous enhancement (arrowheads). (d) Sagittal reformatted computed tomography image in the bone window setting shows destruction of the clivus (star) and sellar floor (arrows), with an enlargement of the sellar cavity (arrows). (e, f) Posttreatment contrast-enhanced MRI demonstrates a marked decrease in tumor size (arrows). The pituitary gland appears normal.

PitNETs, pituitary neuroendocrine tumors

The differential diagnoses of ectopic sphenoid sinus and clivus PitNETs include other lesions in the central skull base region, such as chordoma, meningioma, chondrosarcoma, plasmacytoma, lymphoma, and metastasis. Despite their rarity, sphenoid sinus carcinoid tumors have been reported as the closest differential diagnosis for a corticotropin-secreting ectopic PitNET. The histopathological examination findings and neuroendocrine markers expressed in the two tumors might overlap. However, only ectopic PitNETs uniquely and exclusively express the pituitary-specific transcription factors T-PIT, PIT-1, and SF-1.⁴³ Given that the ectopic PitNETs of the clivus and sphenoid sinus primarily secrete hormones and that there could be a substantial window of opportunity for more conservative treatment, preoperative diagnosis is especially important for aggressive PitNETs of these sites. A multidisciplinary approach to treatment is typically required, involving radiotherapy, surgery, gamma-knife radiosurgery, and medical care.^{36,44}

There is clear heterogeneity of ectopic PitNETs around the sella in terms of clinical and MRI presentation as well as hormones secreted. These tumors demonstrate typical MRI characteristics of pituitary adenomas, which makes their diagnosis challenging given their size and location. Ectopic suprasellar PitNETs typically mimic pituitary stalk mass lesions. Ectopic cavernous sinus PitNETs are usually microadenomas located close to the medial wall. Ectopic clivosphenoidal tumors demonstrate more aggressive behavior than the other ectopic PitNETs. Although extremely rare, ectopic

PitNETs should be considered in the differential diagnosis of masses around the sella turcica.

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