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Surgical resection of granular cell tumor of the sellar region: three indications

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Abstract

Purpose This case series evaluates the surgical management of granular cell tumor (GCT) of the sellar region. This rare entity presents a unique diagnostic and surgical challenge.

Methods Institutional neuropathology databases at Brigham and Women's Hospital and Massachusetts General Hospital were searched for cases with a tissue diagnosis of GCT, and with a location in the sellar region. Patient, treatment, tumor, and follow-up data were extracted.

Results Three patients had a diagnosis of GCT of the sellar region occurring over an 18-year period. All three patients were followed postoperatively at our multidisciplinary pituitary center (median follow-up = 30 months; range 12–30 months). Hormonal disturbances, an incidental lesion requiring diagnosis, and neurological symptoms were indications for surgery in these patients. Two patients underwent a craniotomy and one underwent endoscopic transsphenoidal surgery. All three patients were free of tumor recurrence at last follow-up. In one case tested, positive thyroid transcription factor-1 (TTF-1) immunohistochemistry was observed.

Conclusion GCT is generally a benign tumor of the sellar region. Surgical resection is the standard treatment, more recently with transsphenoidal surgery when indicated. Surgical resection results in optimal outcome for patients.

Keywords Granular cell tumor · Transsphenoidal · Pituicytoma · Radiation

Introduction

The fourth edition of the World Health Organization Classification of Tumors of the Endocrine Organs (EN-WHO 2017), released in 2017, provided a revised definition of tumors of the neurohypophysis [1]. This updated schema defines four tumors of the neurohypophysis that are low-grade neoplasms derived from pituicytes, specialized astrocytes of the pituitary gland: granular cell tumor of the sellar region, pituicytoma, spindle cell oncocytoma, and sellar ependymoma [2]. Because of their common origin, these tumors often stain positively for the thyroid transcription factor-1 (TTF-1) [3–6].

Granular cell tumor of the sellar region (GCT) was first described by Boyce and Beadles in 1893 [7]. Sternberg classified this as a unique tumor entity in 1921 [8]. As with other pituicyte-derived neoplasms, GCT is uncommon, representing less than 0.5% of symptomatic lesions [9]. In a previous review, we analyzed 141 cases reported in the English-language literature, and national and institutional cancer

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databases combined [10]. GCT occurs more commonly in women and in middle to advanced age [5, 10]. The tumor's behavior is classified as WHO Grade I, with rarely reported progression and lack of invasive growth [11].

GCT can be encountered incidentally, or may present with an array of symptoms secondary to its location and mass effect, including partial or panhypopituitarism, hyperprolactinemia, and visual field deficits [5]. Approximately one-third of patients with pituicyte-derived tumors present with hypopituitarism [12]. It can be difficult to diagnose radiographically, and is often misdiagnosed as a pituitary adenoma or craniopharyngioma prior to surgical resection, the most common form of treatment [13]. Here, we review three cases of GCT treated at our institution, with particular focus on diagnosis, surgical management, and clinical outcomes.

Methods

Institutional Neuropathology databases at Brigham and Women's Hospital and Massachusetts General Hospital were searched for cases with a tissue diagnosis of granular cell tumor, and with a location in the sellar region. Patient data were extracted where available, including age, sex, symptoms, diagnostic studies, presumed diagnosis, histopathological analysis, surgical approach and result, use of radiation therapy, follow-up time and status at follow-up.

Pre-operative and post-operative radiographic studies were also reviewed, including the reports from neuroradiologists. Surgical pathology samples were prepared and analyzed with hematoxylin and eosin staining, periodic-acid Schiff staining, Ki-67/MIB-1 index of cellular proliferation, and TTF-1 staining when available.

Results

Three patients who remain under our care had a diagnosis of GCT of the sellar region occurring over an 18-year period. All three patients were followed postoperatively at our multidisciplinary pituitary center (median follow-up = 30 months; range 12–30 months).

Case 1

A 36-year-old woman presented with a 12-year history of infertility. Her breast and abdominal exams were unremarkable, and hysteroscopy was normal. Further evaluation revealed hyperprolactinemia (39 ng/mL; reference 2.7–26.7 ng/mL), with follicle stimulating hormone and estradiol levels within the reference range. The patient underwent an MRI for suspected prolactinoma. Imaging was suspicious for a 3-mm pituitary adenoma, and the patient was started on bromocriptine. Subsequently, she had a successful pregnancy and normal vaginal delivery. The patient was followed with serial MRIs to follow the growth of the presumed adenoma. Surgical options were withheld, as she never complained of galactorrhea, visual symptoms or headaches. For the next 16 years, she was followed with regular MRIs and endocrinology and neurosurgical consultations. Subsequently, imaging demonstrated slow but increasing growth of a suprasellar/hypothalamic/infundibular mass, with compression of the optic nerves and optic chiasm, suspicious for a pituicytoma, hypothalamic glioma, or craniopharyngioma. The patient continued to deny any related symptoms. Eventually, visual field testing revealed mild superior bitemporal field loss. The patient elected for surgical intervention. Pre-operative MRI revealed a $2.3 \times 2.0 \times 1.6$-cm enhancing lesion within the infrachiasmatic suprasellar cistern in close association to the infundibulum, with mass effect on the optic chiasm, optic nerves, and mammillary bodies (Fig. 1a).

The patient underwent a fronto-orbital craniotomy. The tumor was encapsulated, firm, and granular in nature. It was adherent to the chiasm, and there were some fragments of capsule remaining after tumor resection (Fig. 1b). Histologic analysis of the resected tumor was consistent with granular cell tumor, with positive Periodic acid-Schiff (PAS) staining, a low cellular proliferation index (MIB1 < 5%) and positive staining for S-100 (Fig. 2a). Post-operatively, she experienced a transient syndrome of inappropriate antidiuretic hormone secretion, and a low cortisol level (0.8 ug/dL; reference 2.3–19.4 ug/dL). MRI 2.5 years after surgery revealed a residual slowly recurring $9 \times 6 \times 5$-mm mass along the infundibulum. The patient continues to have hyperprolactinemia without symptoms. At the last follow-up, at age 56, she was noted to be doing well, without symptoms or complaints.

Case 2

A 60-year-old man with a history of resected esophageal carcinoma presented with a second episode of confusion within 2 weeks, prompting a brain MRI. He also complained of a mild, generalized headache, but had no complaints of fatigue or visual loss. He had normal and full visual fields to confrontation testing, a slender body habitus, and an unremarkable physical exam. Imaging revealed an irregular pituitary mass. It appeared to be arising directly from the pituitary stalk, extending into the sella and compressing the normal pituitary gland. There was no evidence of optic chiasm or optic nerve compression. This was suspicious for a primary tumor of the pituitary stalk or Rathke's cleft cyst, as opposed to an esophageal carcinoma metastasis. To determine the diagnosis, the patient elected for surgical intervention. Pre-operative MRI demonstrated a $1.0 \times 1.5 \times 1.5$-cm

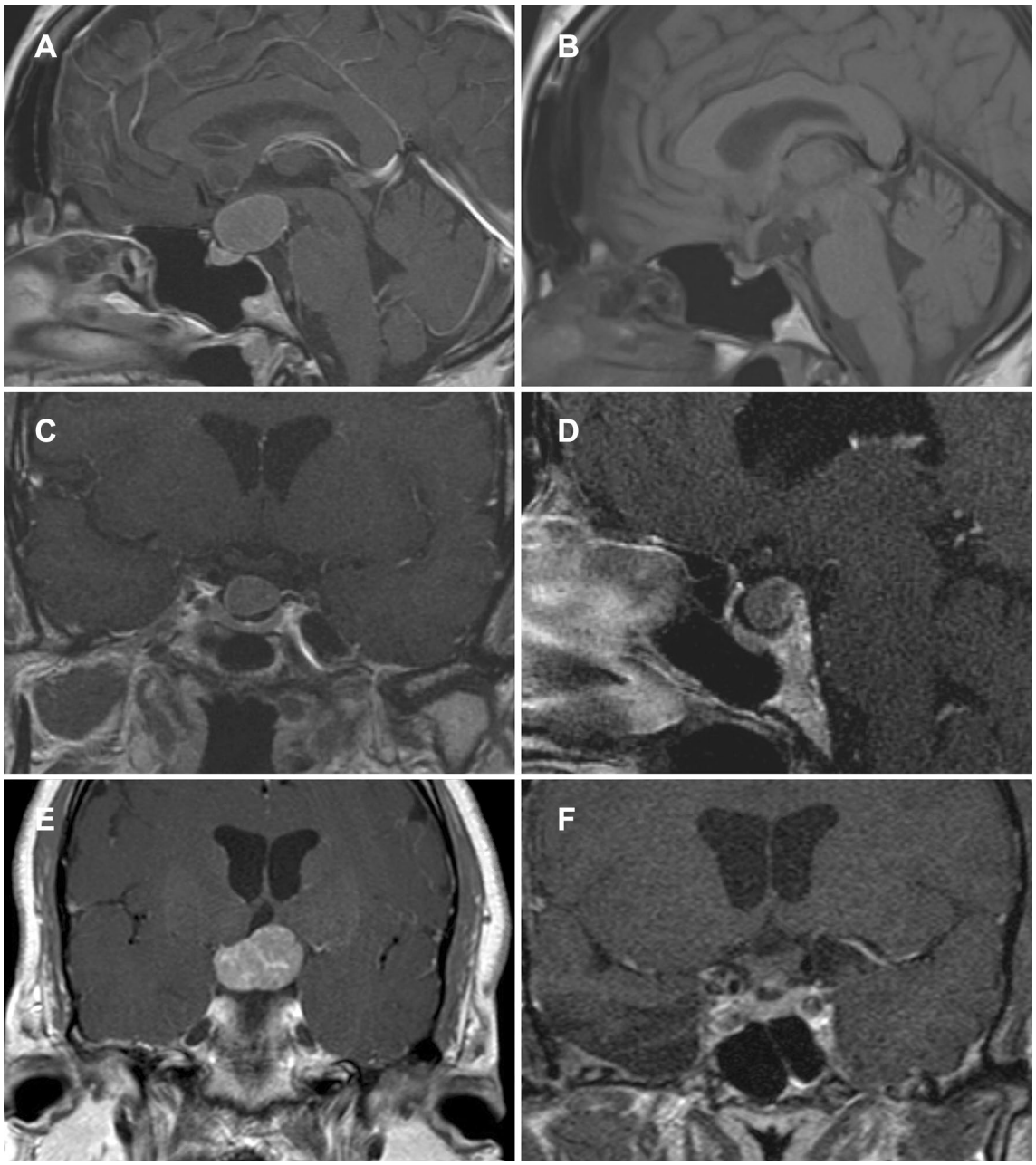

Fig. 1 **a**–**f** In case 1, T1-weighted, post-gadolinium MRI scans demonstrate an enhancing lesion in the infrachiasmatic suprasellar cistern abutting the infundibulum and exerting mass effect on the optic apparatus and mammillary bodies (**a**). After surgical resection, a fragment of capsule remained (**b**). In case 2, gadolinium-enhanced MRI demonstrated a nodular and lobulated homogeneously enhancing mass of the pituitary stalk/hypothalamus. In case 3, T1-weighted, post-gadolinium MRI scans revealed a homogeneously enhancing mass. It was associated with the infundibulum and caused splaying of the optic tracts (**e**). Post-operative scans revealed complete tumor resection (**f**)

nodular and lobulated homogeneously enhancing mass of the pituitary stalk/hypothalamus, suspicious for a craniopharyngioma (Fig. 1c, d).

The patient underwent an endoscopic transsphenoidal surgical resection, which revealed an intrasellar suprapituitary tumor originating from the pituitary stalk, with a cheesy-white appearance. Subtotal resection was achieved. Histologic examination showed large cells with abundant eosinophilic, granular cytoplasm, and positive PAS staining, consistent with a granular cell tumor (Fig. 2b, f). Cells stained positive for S100 and glial fibrillary acidic protein (GFAP). The patient experienced a transient syndrome of inappropriate antidiuretic hormone secretion post-operatively, which resolved. He required hormone replacement

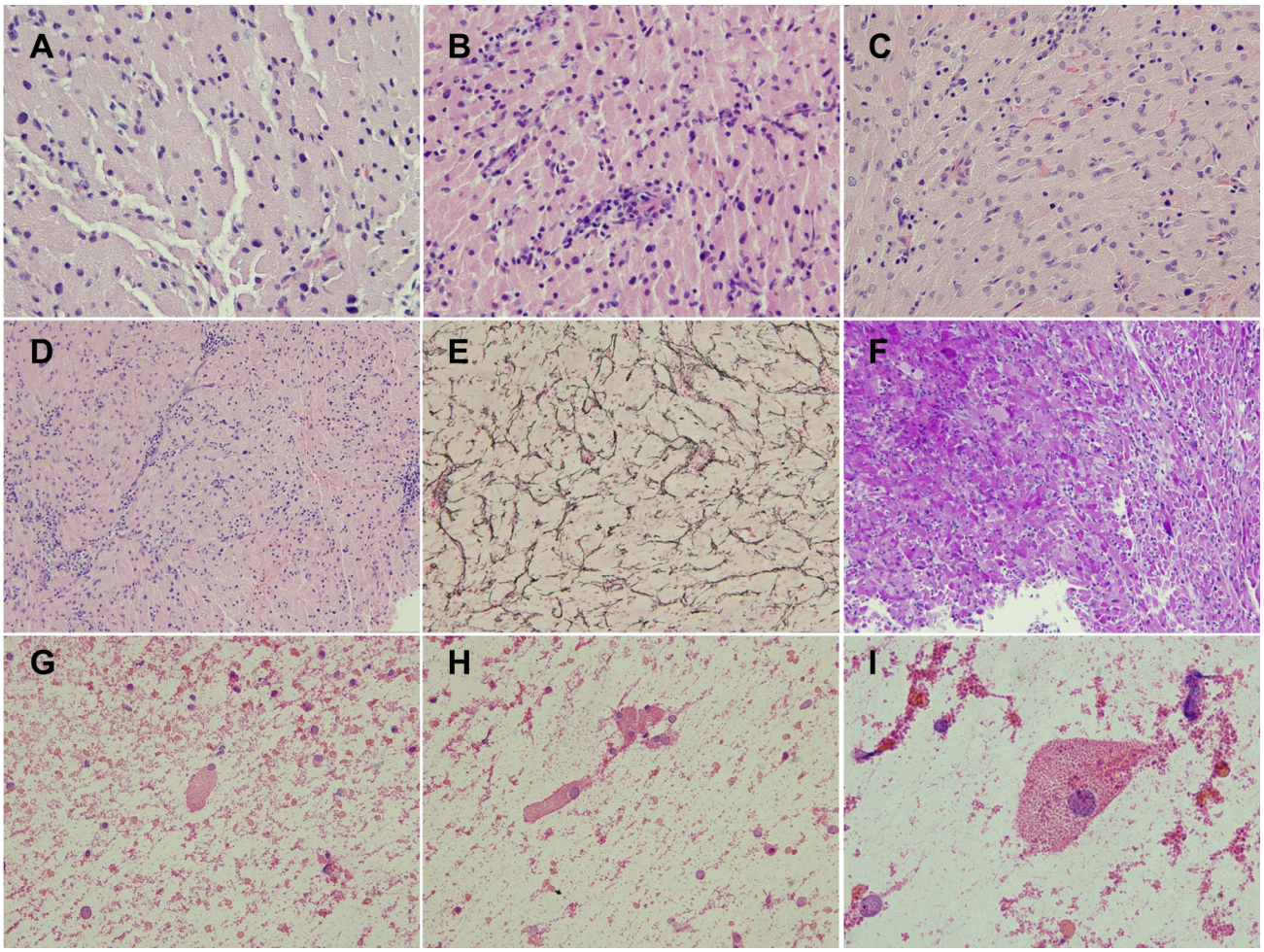

Fig. 2 **a–i** All three tumors demonstrated typical histology of granular cell tumors, consisting of dense proliferations of polygonal cells (**a** Case 1, **b** Case 2. **c** Case 3). The cells are arranged in a predominately nodular pattern, with perivascular infiltrates of lymphocytes commonly encountered (**d**, Case 3). Disruption of the normal acinar architecture of the pituitary is highlighted by a reticulin stain (**e**, Case 3). Cytoplasmic granules within tumor cells stain positively with Periodic acid-Schiff (PAS) stain, in a manner that is resistant to diastase digestion (**f**, Case 2). The prominent granularity of the tumor cells, resulting from the high density of phagolysosomes within the cytoplasm, is readily appreciated on cytologic smear preparation (**g–i**, Case 3)

therapy with hydrocortisone. He had full extraocular movements and his visual fields were intact to confrontation. He was followed for 2.5 years, during which time his imaging revealed no residual mass, and he remained free of new symptoms.

Case 3

A 49-year-old man with hypothyroidism was evaluated for low testosterone levels in the context of prednisone use for a spider bite. A brain MRI revealed a lobular, mildly enhancing mass in the region of the pituitary infundibulum, hypothalamus and optic chiasm. The patient did not complain of any visual loss. An ophthalmologic evaluation demonstrated full visual fields to confrontation. The patient was followed regularly with MRIs for six years. After that time, the patient complained of worsening vision in his left eye, and imaging was consistent with tumor enlargement. He was diagnosed with a left visual field deficit and the patient elected for surgical treatment. Pre-operative MRI revealed a homogeneously enhancing, lobulated $2.6 \times 2.5 \times 1.7$-cm mass that was separate from the pituitary gland. It was intimately associated with the infundibulum, and appeared to cause mass effect on the optic chiasm with splaying of the optic tracts (Fig. 1e).

The patient underwent a right frontotemporal craniotomy for resection. The tumor was beige in color and felt firm. Its capsule was adherent to the basilar artery, posterior cerebral artery, third cranial nerve bilaterally and internal carotid arteries bilaterally, the pituitary stalk, and the optic chiasm. Complete tumor resection was achieved (Fig. 1f). Histological analysis showed polygonal oncocytic cells with abundant

eosinophilic granular cytoplasm and focal areas of short fascicular architecture. The tumor was positive for TTF-1, S-100, and galectin-3, with a low MIB-1 index of cellular proliferation (<1%) (Fig. 2c–e, g–i). The final diagnosis was granular cell tumor. Post-operatively, the patient experienced a transient third cranial nerve palsy which resolved. One year after surgery, imaging showed no evidence of tumor persistence or recurrence.

Discussion

Granular cell tumor (GCT) of the sellar region is a rare clinical entity [9]. Here, we describe cases with three separate indications for surgical resection: hormonal disturbances, an incidental lesion requiring diagnosis, and neurological symptoms.

More than 140 cases of this entity have been reported in the literature [10, 13–16]. Systematic reviews and pooled analyses have provided basic information on this tumor's demographics, clinical presentation, histological features, treatment types and outcomes. GCT occurs more commonly in women, with a sex incidence rate ratio of 1.4–3:1, and most commonly presents in the late 4th and early 5th decade of life [10, 15, 16]. Common presenting symptoms and signs include bitemporal hemianopia or diplopia, headache, cranial nerve palsies, particularly of the nerves traversing the cavernous sinus, and decreased libido, as was seen in two of the cases presented here [10, 16]. An endocrine evaluation can reveal a variety of hormonal perturbations. Hyperprolactinemia is the most common positive finding, likely secondary to pituitary stalk compression and lack of dopamine inhibition, as in Case 1 [17–22]. GCTs also present with partial or panhypopituitarism [16].

Systematic reviews of the MRI features of GCT have revealed several consistent findings. The tumor tends to be suprasellar, with intimate association with the infundibulum and separation from the pituitary gland, as was seen in all three cases [5, 10, 16]. It is often isointense to gray matter on T1-weighted imaging, and hypo/isointense on T2-weighted imaging. Contrast enhanced T1-weighted imaging demonstrate enhancement in most cases, most commonly with heterogenous enhancement [13, 15]. In the cases reported here, the tumors were isointense on T1 and T2-weighted imaging, and two were homogenously enhancing. On average, tumors are 2.9 cm in radiographic size, on their longest axis [10]. Size in these three cases ranged from 1.5 to 2.6 cm.

Accurate radiographic assessment is critical not only to inform the neurosurgeon on tumor size and anatomy, but also to suggest pre-operative diagnosis [23]. Pre-operative differential diagnoses for this tumor have included pituitary adenoma, craniopharyngioma, Rathke's cleft cyst, meningioma, glioma, germinoma, hamartoma, and others [10, 15, 16]. Specific CT and MRI findings characteristic of these other lesions can assist in differentiation.

Most patients are treated with surgical resection, as in our cases. Surgical approaches include frontal craniotomy, frontotemporal craniotomy, pterional craniotomy, and more commonly in recent decades, transsphenoidal resection [9, 10, 16]. Transphenoidal resection is being used for an increasing diversity of sellar, suprasellar, and anterior skull base masses [24].

With appropriate patient selection, based on tumor size, intimacy with neurovascular structures, nasal, and skull base anatomy, the transsphenoidal approach can yield complete resection of GCT as in Case 2, and previously reported cases [11, 20, 22, 23, 25–28]. Transcranial approaches may be indicated when tumors compromise neurovascular structures, or demonstrate suprasellar and parasellar extension, as seen in Case 3. GCT tends to be a vascular and firm fibrous tumor which should be considered when developing a surgical plan, as heavy bleeding can occur [13, 17, 20]. If surgical pathology demonstrates GCT, converting to an enlarged expanded transsphenoidal approach has been suggested [20]. Recurrence has been reported in 14% of tumors, and complete resection may increase overall survival [9, 10].

GCT can be diagnosed by several histological features after surgical resection. It is comprised of densely packed sheets and spindles of polygonal granular cells (Fig. 2a–c) [5]. Cytoplasmic granules stain positively with periodic-acid Schiff stain, which tends to be diastase resistant (Fig. 2f). The cytoplasm is eosinophilic and granular (Fig. 2g–i). Perivascular lymphocytic infiltrates are commonly noted. GCTs are immunopositive for TTF-1, like most pituicyte derivative neoplasms, and for S-100 protein [29, 30]. Unlike pituicytoma, GCTs stain positive only occasionally for GFAP [5]. MIB-1 (Ki-67) index of cellular proliferation is usually low (< 5%).

Patients with GCT have occasionally been treated with post-operative radiation therapy, although none of the patients in this series was so treated. In one case, up-front gamma-knife radiation therapy resulted in transient progression-free survival, however, subsequent surgical resection was indicated [31]. In another case, post-biopsy gamma-knife radiation therapy resulted in nine years of progression-free survival [25]. In a systematic review of pituicyte-derived tumors, radiation therapy was noted to be used in 25% of patients with persisted or recurred tumor [12].

Conclusion

GCT of the sellar region is a unique subtype of pituicyte-derived neoplasm that is a rare and distinct clinical entity. The three cases presented here add to the growing clinical, radiographic, and pathologic literature on this tumor.

GCT is generally a benign tumor that presents with visual or other neurological disturbances, hormonal perturbances, or is found incidentally. Surgical resection is the standard treatment, more recently with transsphenoidal surgery when indicated. Surgical resection results in optimal outcome for patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Lloyd RV, Osamura RY, Kloppel G, Rosai J (2017) WHO classification of tumours of the endocrine organs, 4th edn. International Agency for Research on Cancer, Lyon
2. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131(6):803–820
3. El Hussein S, Vincentelli C (2017) Pituicytoma: review of commonalities and distinguishing features among TTF-1 positive tumors of the central nervous system. Ann Diagn Pathol 29:57–61
4. Giantini Larsen AM, Cote DJ, Zaidi HA, Bi WL, Schmitt PJ, Iorgulescu JB, Miller MB, Smith TR, Lopes MB, Jane JA, Laws ER (2018) Spindle cell oncocytoma of the pituitary gland. J Neurosurg 131(2):517–525
5. Shibuya M (2018) Welcoming the new WHO classification of pituitary tumors 2017: revolution in TTF-1-positive posterior pituitary tumors. Brain Tumor Pathol 35(2):62–70
6. Viaene AN, Lee EB, Rosenbaum JN, Nasrallah IM, Nasrallah MP (2019) Histologic, immunohistochemical, and molecular features of pituicytomas and atypical pituicytomas. Acta Neuropathol Commun 7(1):69
7. Boyce R, Beadles CF (1893) A further contribution to the study of the pathology of the hypophysis cerebri. J Pathol Bacteriol 1(3):359–383
8. Sternberg C (1921) Ein choristom der neurohypophyse bei ausgebre-iteten oedemen. Ebl Alleg Path Anat 31:585–589
9. Zada G, Lopes MBS, Mukundan S, Laws E (2016) Granular cell tumors. In: Zada G, Lopes MBS, Mukundan S, Laws ER (eds) Atlas of sellar and parasellar lesions: clinical, radiologic, and pathologic correlations. Springer, Cham, pp 311–315
10. Ahmed AK, Dawood HY, Penn DL, Smith TR (2017) Extent of surgical resection and tumor size predicts prognosis in granular cell tumor of the sellar region. Acta Neurochir (Wien) 159(11):2209–2216
11. Cohen-Gadol AA, Pichelmann MA, Link MJ, Scheithauer BW, Krecke KN, Young WF Jr, Hardy J, Giannini C (2003) Granular cell tumor of the sellar and suprasellar region: clinicopathologic study of 11 cases and literature review. Mayo Clin Proc 78(5):567–573
12. Guerrero-Perez F, Marengo AP, Vidal N, Iglesias P, Villabona C (2019) Primary tumors of the posterior pituitary: a systematic review. Rev Endocr Metab Disord 20(2):219–238
13. Covington MF, Chin SS, Osborn AG (2011) Pituicytoma, spindle cell oncocytoma, and granular cell tumor: clarification and meta-analysis of the World Literature since 1893. Am J Neuroradiol 32(11):2067–2072
14. Guerrero-Perez F, Vidal N, Marengo AP, Pozo CD, Blanco C, Rivero-Celada D, Diez JJ, Iglesias P, Pico A, Villabona C (2019) Posterior pituitary tumours: the spectrum of a unique entity. A clinical and histological study of a large case series. Endocrine 63(1), 36–43
15. Polasek JB, Laviv Y, Nigim F, Rojas R, Anderson M, Varma H, Kasper EM (2018) Granular cell tumor of the infundibulum: a systematic review of MR-radiography, pathology, and clinical findings. J Neurooncol 140(2):181–198
16. Zhang Y, Teng Y, Zhu H, Lu L, Deng K, Pan H, Yao Y (2018) Granular cell tumor of the neurohypophysis: 3 cases and a systematic literature review of 98 cases. World Neurosurg 118:e621–e630
17. Aquilina K, Kamel M, Kalimuthu SG, Marks JC, Keohane C (2006) Granular cell tumour of the neurohypophysis: a rare sellar tumour with specific radiological and operative features. Br J Neurosurg 20(1):51–54
18. Cummings TJ, Bentley RC, McLendon RE (2001) Pathologic quiz case: pituitary mass in a 48-year-old woman. Arch Pathol Lab Med 125(2):299–300
19. Cusick JF, Ho K-C, Hagen TC, Kun LE (1982) Granular-cell pituicytoma associated with multiple endocrine neoplasia type 2. J Neurosurg 56(4):594–596
20. Gagliardi F, Spina A, Barzaghi LR, Bailo M, Losa M, Terreni MR, Mortini P (2016) Suprasellar granular cell tumor of the neurohypophysis: surgical outcome of a very rare tumor. Pituitary 19(3):277–285
21. Ogata S, Shimazaki H, Aida S, Miyazawa T, Tamai S (2001) Giant intracranial granular-cell tumor arising from the abducens. Pathol Int 51(6):481–486
22. Piccirilli M, Maiola V, Salvati M, D'Elia A, Di Paolo A, Campagna D, Santoro A, Delfini R (2014) Granular cell tumor of the neurohypophysis: a single-institution experience. Tumori J 100(4):160e–164e
23. Iglesias A, Arias M, Brasa J, Páramo C, Conde C, Fernandez R (2000) MR imaging findings in granular cell tumor of the neurohypophysis: a difficult preoperative diagnosis. Eur Radiol 10(12):1871–1873
24. Cote DJ, Wiemann R, Smith TR, Dunn IF, Al-Mefty O, Laws ER (2015) The expanding spectrum of disease treated by the transnasal, transsphenoidal microscopic and endoscopic anterior skull base approach: a single-center experience 2008–2015. World Neurosurg 84(4):899–905
25. Koutourousiou M, Gardner PA, Kofler JK, Fernandez-Miranda JC, Snyderman CH, Lunsford LD (2013) Rare infundibular tumors: clinical presentation, imaging findings, and the role of endoscopic endonasal surgery in their management. J Neurol Surg B Skull Base 74(1):1–11
26. Mumert ML, Walsh MT, Chin SS, Couldwell WT (2011) Cystic granular cell tumor mimicking Rathke cleft cyst: case report. J Neurosurg 114(2):325–328
27. Popovic V, Pekic S, Skender-Gazibara M, Salehi F, Kovacs K (2007) A large sellar granular cell tumor in a 21-year-old woman. Endocr Pathol 18(2):91–94
28. Schlachter LB, Tindall GT, Pearl GS (1980) Granular cell tumor of the pituitary gland associated with diabetes insipidus. Neurosurgery 6(4):418–421

29. Hagel C, Buslei R, Buchfelder M, Fahlbusch R, Bergmann M, Giese A, Flitsch J, Ludecke DK, Glatzel M, Saeger W (2017) Immunoprofiling of glial tumours of the neurohypophysis suggests a common pituicytic origin of neoplastic cells. Pituitary 20(2):211–217
30. Lopes MBS (2017) The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. Acta Neuropathol 134(4):521–535
31. Faramand A, Kano H, Flickinger JC, Gardner P, Lunsford LD (2018) A case of symptomatic granular cell tumor of the pituitary treated with stereotactic radiosurgery. Stereotact Funct Neurosurg 96(3):197–203