Calcified Prolactinoma of the Pituitary Gland: Illustrative Case Reports Highlighting Medical versus Surgical Intervention

Sherwin Tavakol¹ Asma Hasan² Michelle A. Wedemeyer¹ Joshua Bakhsheshian¹ Chia-Shang J. Liu³
Mark S. Shiroishi³ Anna Mathew⁴ John D. Carmichael² Gabriel Zada¹

¹Department of Neurological Surgery, University of Southern California Keck School of Medicine, Los Angeles, California, United States

²Division of Endocrinology and Diabetes, University of Southern California Keck School of Medicine, Los Angeles, California, United States

³Division of Neuroradiology, Department of Radiology, University of Southern California Keck School of Medicine, Los Angeles, California, United States

⁴Department of Pathology, University of Southern California Keck School of Medicine, Los Angeles, California, United States

Address for correspondence: Gabriel Zada, MD, MS, FAANS, FACS, 1200 N State Street, Suite 3300, Los Angeles, CA 90033, United States (e-mail: Gabriel.Zada@med.usc.edu).

J Neurol Surg B 2020;81:22–29.

Abstract

Keywords

- calcified prolactinoma
- pituitary adenoma
- amyloid
- Rathke's
- prolactin
- sella
- turcica

The presence of calcification is uncommon in pituitary adenomas, and often lends support to other diagnoses including craniopharyngioma. The majority of calcified pituitary adenomas are prolactin-secreting tumors. We report two patients with calcified macroprolactinomas, one that was treated medically with a biochemical response and partial tumor response, and one that was treated successfully via an endoscopic endonasal transsphenoidal approach. Suspected calcified prolactinomas can be initially managed medically as per standard treatment for typical prolactinomas; however, the presence of diffuse calcification may hinder tumor shrinkage. Tumors that are refractory to medical treatment can be safely managed with surgery.

Introduction

Though calcifications are commonly observed in various sellar region masses such as craniopharyngiomas, meningiomas, and aneurysms, calcification of pituitary adenomas is a rare occurrence with a prevalence of < 7%.¹ Calcification of pituitary adenomas usually takes two distinct forms: (1) an “egg-shell” appearance, in which a pituitary adenoma is surrounded by a thin layer of calcification that may represent an expanded sella or calcified pseudocapsule, or (2) multiple small nodules of calcification within the adenoma. A “pituitary stone,” however, is a more specific and classical description of a large, dense deposit of calcium within a pituitary adenoma originally

described on roentgenogram.^{2,3} Pituitary stones can be further divided into two types depending on the mechanism of formation. Type 1 pituitary stones (16 reports in the literature) have primary calcification as their source, while type 2 pituitary stones (2 reports in the literature) arise from osteoid metaplasia.⁴ Four (25%) of the type 1 pituitary stones reported in the literature and both (100%) of the type 2 pituitary stones were prolactin (PRL)-secreting.^{2,3,5,6}

Despite several older case reports of pituitary stones, recent reports pertaining to the management and histopathological findings of densely calcified prolactinomas remain sparse. In this report, we present two very different cases underscoring the spectrum of varying strategies for calcified prolactinomas,

received

July 19, 2018

accepted after revision

December 15, 2018

published online

February 5, 2019

© 2020 Georg Thieme Verlag KG
Stuttgart · New York

DOI <https://doi.org/10.1055/s-0039-1677678>.
ISSN 2193-6331.

ranging from traditional medical management with dopamine agonist (DA) medications to surgical resection. In addition, the literature was reviewed to identify studies relating to management of calcified pituitary adenomas, focusing on prolactinomas and response rates to medical and surgical intervention.

Patient 1

Case Presentation

A 35-year-old man initially presented with a 1-week history of worsening tooth pain. Detailed history revealed progressive headache, double vision, and decreased libido with a 50-pound weight gain, worsening hypertension, and increased thirst. Formal ophthalmologic examination revealed bitemporal visual field loss, worse in the right than the left eye, with evidence of atrophy of the bilateral retinal nerve fiber layers.

Investigation

Biochemical testing revealed FT4 0.8 ng/mL (n [normal] 0.8–1.8 ng/mL), thyroid-stimulating hormone (TSH) 1.42 mIU/L (n 0.4–4.5 mIU/L), total testosterone 138 ng/dL (n 250–1100 ng/dL), and total cortisol of 13.8 µg/dL (4–22.0 µg/dL). The serum PRL was >1,000 ng/mL (n 2–18 ng/mL), without serial dilution testing. Noncontrast-enhanced computed tomography (CT) of the head showed a large, calcified sellar and parasellar mass (►Fig. 1). Contrast-enhanced magnetic resonance imaging (MRI) with and without gadolinium contrast revealed a large mass with portions of T1- and T2-hypointensity measuring $2.8 \times 4.5 \times 3.9$ cm with suprasellar extension and mass effect on the optic chiasm, brain stem, hypothalamus, and third ventricle (►Fig. 1). These regions

of T1- and T2-hypointensity were confirmed to represent calcifications on CT.

Video 1

Surgical video demonstrating the main steps of the operation. The video starts with the sphenoid sinus exposure and identification of sella, followed by exposure of the sellar dura. Then the micro-Doppler was used to confirm location of the carotid arteries prior to performing an X-shaped incision in the sellar dura. At this point, the densely calcified pituitary mass was exposed. The tumor was then internally debulked, and after maximal safe tumor resection was completed, cerebrospinal fluid leak was noted from the posterior suprasellar arachnoid. Therefore, a complex closure was completed with both a fascia lata and pedicled nasal septal flap. Online content including video sequences viewable at: www.thieme-connect.com/products/ejournals/html/10.1055/s-0039-1677678.

Treatment

PRL levels were most consistent with a macroprolactinoma and less likely to be pituitary stalk effect from a nonsecreting tumor, such as a craniopharyngioma. The patient was started on medical therapy with a dopamine agonist (cabergoline 0.5 mg per os [PO] twice a week, and then increased to 1 mg twice a week a month later). He continued to take cabergoline with frequent clinic visits, laboratory checks, and imaging done at 3 to 6 months intervals.

Fig. 1 Patient 1. (A) Coronal noncontrast T2-weighted magnetic resonance image showing scattered hypointensity consistent with calcifications, as seen on computed tomography (CT) imaging. Noncontrast sagittal T1-weighted images (B) show a large sellar and suprasellar mass with scattered components of T1 hypointensity internally. Coronal (C) and sagittal (D) T1 postcontrast images show a Knosp stage IV heterogeneously enhancing mass with extension into left cavernous sinus and mass effect upon the midbrain, hypothalamus, and third ventricle. After 3 months of cabergoline, the patient demonstrated decrease in size and enhancement of mass on coronal (G) and sagittal (H) T1-weighted postcontrast images with decreased mass effect most notable around the brain stem. However, mass effect on adjacent structures persisted. Calcifications and mass effect seen on coronal (I) and sagittal (J) CT were stable to slightly improved after >2 years of dopamine agonist therapy when compared with findings on coronal (E) and sagittal (F) CT at start of treatment.

Outcome and Follow-Up

PRL levels decreased to 5.3 ng/mL after 3 months of dopamine agonist therapy. A 3-month interval MRI revealed interval decrease in tumor size from $4.7 \times 3.1 \times 3.2$ cm to $3.9 \times 2.8 \times 3.1$ cm, with decreasing mass effect particularly of the brain stem, supporting the diagnosis of a prolactinoma (**Fig. 2**). The patient reported improvement in his headaches and visual deficits. Despite demonstrating a biochemical response, a significant mass effect was still observed on the optic chiasm. The prominent calcifications with invasion into the cavernous sinus and diencephalon placed the patient at greater risks of surgical complications. To this end, given a biochemical and clinical response to medical therapy was observed, the patient preferred to continue medical management. Imaging obtained after 6 and 30 months of dopamine agonist therapy showed continued decrease and stabilization of the size of the mass, respectively, with persistent calcification. Concurrent laboratory tests demonstrated PRL levels

within the normal range. Cabergoline dose was escalated to 1.5 mg PO twice a week to promote further tumor shrinkage. However, the patient developed behavior problems that may have been attributed to cabergoline. Therefore, the dose was, therefore, subsequently decreased to 1 mg PO twice a week. Throughout this time period, he also had significant pain due to headaches requiring narcotic use and follow-up with a pain management specialist. The patient was followed with serial CT scans, as it was thought this would better visualize the calcifications. At 30-month follow-up, the patient also complained of decreased libido and raised concerns about fertility. Testosterone levels were found to be low and he was started on testosterone replacement. He was also started on treatment for central hypothyroidism with levothyroxine. At his final follow-up (39 months), he no longer had visual symptoms (formal ophthalmologic testing was not available), while imaging demonstrated a stable mass showing no evidence of progression.

Fig. 2 Patient 1. Postcontrast sagittal (A) T1-weighted images demonstrate enhancement of the large sellar and suprasellar mass, with mass effect on the midbrain and pons as well as the adjacent brain parenchyma. Contrast-enhanced sagittal (B) computed tomography (CT) reformations demonstrate a heavily calcified mass, with portions of nonenhancement on the sagittal magnetic resonance imaging (MRI), particularly the anterior aspect of the mass, corresponding to coarse calcifications as seen on CT. After a course of cabergoline, there is interval decrease in size of the calcified sellar and suprasellar mass as seen on MRI (C) and CT (D), with decreased mass effect on the midbrain and pons.

Patient 2

Case Presentation

A 31-year-old man with no significant past medical history presented with fatigue and diminished libido. He denied any history of headaches or visual changes and physical examination was unremarkable.

Investigation

Initial laboratories revealed a low testosterone level (99 ng/dL, n 348–1197 ng/dL), luteinizing hormone (LH) 3.5 mIU/mL (n 1.7–8.6 mIU/mL), follicle-stimulating hormone (FSH) 3.6 mIU/mL (n 1.5–12.4 mIU/mL), and elevated PRL level (168.9 ng/mL, n 4–15.2 ng/mL). MRI revealed a T1 and T2 hypointense mass with possible internal hemorrhage or calcification in the pituitary gland measuring $1.0 \times 1.4 \times 1.0$ cm without suprasellar extension or mass effect on optic chiasm. Calcification was confirmed on CT imaging from an outside hospital (not available for inclusion in this article).

Treatment

At initial presentation, the mass was presumed to be a Rathke's cleft cyst or an intrasellar craniopharyngioma due to hypointensity on T1 and T2 imaging (►Fig. 3). Given the size (>1cm) and evidence of hypopituitarism, he underwent endoscopic endonasal transsphenoidal resection of the mass (►Video 1). During the surgery, a very dense calcified pituitary mass was removed with preservation of the normal pituitary gland; however, the patient developed

a complex intraoperative cerebrospinal fluid leak requiring fat and fascial graft for repair. Pathology was consistent with a prolactinoma. The tumor showed disruption of the reticulin fiber network, foci of calcifications, and deposits of amyloid. Congo red stain showed apple green birefringence of amyloid with polarized light (►Fig. 4). Immunohistochemical stains of the tumor showed strong immunoreactivity for PRL with Golgi-type staining (sparsely granulated subtype). The tumor was negative for all other pituitary hormones (adrenocorticotrophic hormone [ACTH], FSH, LH, growth hormone [GH], TSH), α subunit, and p53; Ki-67 proliferation index was negligible.

Outcome and Follow-Up

During postoperative admission, the patient had an episode of transient diabetes insipidus requiring one dose of desmopressin. The 2-week postoperative serum PRL level was 0.6 ng/mL. The patient tolerated the surgery well without complications and was discharged without need for any medical therapy. At 6-month follow-up, MRI revealed gross total resection of the previously noted sellar mass (►Fig. 2). There was no definite residual T1 or T2 hypointensity to suggest the presence of residual tumor. Since surgery, symptoms of fatigue have resolved. The patient reported improvement in sexual libido and noticed increased growth of hair on his chest and legs. No clinical signs consistent with hormone deficiencies are present. The most recent PRL level was normal (5.3 ng/mL, n 4–15.2 ng/mL), as was the testosterone level (558 ng/dL, n 348–1197 ng/dL).

Fig. 3 Patient 2. Coronal noncontrast T1 (A) and T2 (B)-weighted images demonstrate a round T1/T2 hypointense sellar mass surrounded by a rim of T1/T2 isointense tissue, with postcontrast T1-weighted coronal (C) and sagittal (D) images demonstrating minimal central enhancement in the round sellar mass; imaging characteristics suggest presence of mineralization and/or hemorrhage. Surgical excision revealed a very dense mass presumed to be due to significant calcification. Postoperative MRI showed gross total resection of mass with complete resection of the T1 (E) and T2 (F) hypointense lesion on coronal noncontrast images (D) and postsurgical changes on coronal (G) and sagittal (H) postcontrast T1-weighted images.

Fig. 4 Patient 2. (A) Hematoxylin and eosin (H&E) stain: Monotonous sheets of cells with speckled chromatin and prominent nucleoli consistent with pituitary adenoma, (B) H&E: Sheets of pituitary adenoma and deposits of amyloid, (C) H&E: Focus of calcification, (D) Prolactin immunohistochemical stain: Tumor demonstrating immunoreactivity for prolactin with juxtanuclear dot-like positivity in some tumor cells, (E) Reticulin stain: Loss of reticulin fiber network in pituitary adenoma, (F) Congo red stain: Apple green birefringence of amyloid with polarized light.

Discussion

Calcification in the sellar and suprasellar region may be associated with a variety of pathological entities, including craniopharyngioma, meningiomas, chordomas/chondrosarcomas, and occasionally pituitary adenomas. However, calcified macroprolactinomas remain a very rare diagnosis. CT imaging plays an important role in the diagnosis and measuring the degree of calcification. Classically, craniopharyngiomas are solid and/or cystic masses arising from the infundibulum, and are often associated with calcifications. Rathke's cleft cysts appear as cystic masses often arising from the pars intermedia or suprasellar region, but may be noted to have internal calcification. Meningiomas may also be calcified and are often homogeneously enhancing masses arising from the tuberculum sellae or diaphragm sellae, often with a dural tail. Chordomas and chondrosarcomas are noted to be hyperintense masses on T2 imaging with less avid enhancement patterns, and often arise from the clivus or petroclival region. Calcified pituitary macroadenomas, on the other hand, are often associated with expansion of the sella turcica and displacement of the normal pituitary gland.⁷ ▶Table 1 provides a more in-depth description of imaging characteristics for these sellar and suprasellar lesions.

Calcification is rarely found in pituitary prolactinomas. Although the literature varies regarding the prevalence of calcified pituitary adenomas, large independent case series obtained from radiograph analysis of the sellar region show the frequency to be around 7% (▶Table 2).^{8–11} In this report, we present two widely varied, yet successful, intervention strategies for calcified prolactinomas, including medical

treatment resulting in reduction in size and improvement in clinical symptoms in one patient, and complete surgical resection with improved endocrine status in another. Since Landolt and Rothenbühler suggested in 1977 that “local factors” and certain hormonal secretions play a significant role in the calcification of pituitary adenomas, many authors have found paralleled evidence in their reports.⁹ As shown in ▶Table 2, consistency between neuroimaging and histological findings regarding the prevalence of calcification seem to differ among reported series.

CT remains to be the gold standard imaging technique in diagnosing calcification.¹² On both T1- and T2-weighted MRI, calcification can present with varying signal intensities based on the interaction of the surrounding water molecules with the calcium compounds.¹³ Typically, more coarse calcifications demonstrate T1- and T2-hypointensity, whereas peripheral calcification is more isointense and fine calcification present as foci of hyperintensity on T1-weighted imaging, underscoring the need to differentiate this from other commonly hyperintense lesions of the sellar region, such as blood, protein, fat, or paramagnetic substances like manganese or melanin.¹⁴ With CT, the Hounsfield units of calcification are much higher than that of blood, protein, or fat, allowing for easier characterization of calcium from the other substances. Thus, suspected areas of calcification seen on MRI should always be confirmed using CT imaging for definitive diagnosis and coordination of calcification location.^{15,16} When hypointense areas are discerned on T2-weighted images, amyloid deposits should also be included in the differential diagnosis.¹⁷ As exhibited by the radiological and histological analyses of patient 2

Table 1 Imaging characteristics for various sellar and suprasellar lesions

Sellar/suprasellar lesion	Imaging characteristics
Pituitary macroadenoma ³⁸	MRI—usually isointense to gray matter on T1- and T2-weighted imaging, larger tumors can appear heterogeneous and contain regions of necrosis/cystic change/hemorrhage, demonstrate moderate to prominent contrast enhancement CT—calcifications rare
Craniopharyngioma (adamantinomatous-type) ³⁹	MRI—solid and cystic appearing; iso- to hyperintense to brain on T1-weighted imaging, variable but usually partially hyperintense on T2-weighted imaging, prominent contrast enhancement in solid portions CT—calcifications seen in 90% of cases
Rathke's cleft cyst ^{38,40}	MRI—hypo/hyperintense on T1-weighted imaging, variable signal intensity on T2-weighted imaging, non-enhancing T1 hyperintense/T2 hypointense nodule virtually pathognomonic, no central contrast enhancement, thin peripheral enhancement may represent compressed pituitary gland CT—calcifications uncommon, can appear curvilinear in wall if present
Meningioma ^{41,42}	MRI—can be variable but typically isointense to gray matter on T1- and T2-weighted imaging, prominent homogeneous contrast enhancement, dural tail commonly seen but not pathognomonic CT—often hyperdense, calcifications common, hyperostosis sometimes present
Aneurysm ^{43,44}	MRI—patent aneurysms show flow voids on T1- and T2-weighted imaging, laminated heterogeneous signal can be present in thrombosed aneurysms, pulsation artifacts may be seen in phase-encoding direction CT—calcification can be seen wall

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

Note: This table describes various pathology of the sellar and suprasellar region and imaging characteristics that can aid in differentiating them.

Table 2 Four large case series of calcified PA

Author(s)	Total PA	PA w/ calcification			
		No. of cases (% of total PA)	Visible on roentgenogram (% of calcified PA cases)	Visible on microscopy (% of calcified PA cases)	Calcified prolactinomas (% of total PA)
Deery (1929) ⁸	285	19 (6.7%)	19 (100%)	0 (0%)	n/a
Landolt and Rothenbühler (1977) ⁹	137	9 (6.6%)	4 (44.4%)	2 (22.2%)	n/a
Riliet et al (1981) ¹⁰	755	51 (6.8%)	13 (25.5%)	51 (100%)	38 (5.0%)
Müller and Hoffmann (1967) ¹¹	408	30 (7.4%)	1 (3.3%)	30 (100%)	n/a

Abbreviation: PA, pituitary adenomas.

Note: This table shows the frequency of calcification within PA, as well as the visibility of calcification on imaging/microscopy, for the four large case series referenced in this article.

(► **Fig. 4**), occurrence of amyloid within pituitary adenomas is reported to be as high as 71% and most frequently in prolactinomas.^{18–20}

Tumor mass and relative shrinkage were determined using MRI. These studies were performed on clinical 1T scanners in the sagittal and coronal planes using T1-weighted gradient recalled-echo. Post-DA treatment maximal tumor diameter was compared with baseline tumor size to ascertain tumor shrinkage. A semiquantitative four-point scale was utilized to measure reduction in tumor diameter as previously published: < 10% as absent, 10 to 20% as mild, 20 to 30% as moderate, and > 30% as remarkable.²¹ Comparison of pre- and post-treatment imaging for patient 1 indicated an 18% reduction in maximal tumor diameter, illustrating the

efficacy of medical management of calcified macroprolactinomas in certain clinical settings (► **Fig. 2**). These changes were stable on multiple repeat follow-up imaging studies.

Hormone-secreting tumors represent a significant portion of calcified pituitary adenomas. In Riliet's series of 755 total pituitary adenomas, nearly 75% of those with calcification were prolactinomas, 30 of 38 of which were found in males. Additionally, no ACTH-secreting or TSH-secreting tumors were found to have calcification in this series and none were identified in our institutional pituitary outcomes database of >1700 pituitary surgeries. Pituitary stones individually secreting PRL, GH, TSH, and ACTH have been reported. Interestingly, a pituitary adenoma that was positive for PRL, TSH, and GH has been reported.⁴ Serum PRL

levels can vary widely between patients with calcified prolactinomas. Various cases report PRL elevation ranging from only slightly above normal to 2,000 mg/dL.^{2,22–24} PRL levels tend to correlate with tumor size, which may explain why patient 1 had a higher elevation in serum PRL. In all cases, hyperprolactinemia from a prolactinoma must be differentiated from pituitary stalk effect caused by another tumor type.

The vast majority of calcified prolactinoma cases in the literature were initially treated with transsphenoidal adenectomy, which differs from current standard practice. Initial treatment of symptomatic micro- and macroprolactinomas typically involves use of a dopamine agonist since nearly 90% of tumors will respond with normalization of PRL levels.^{25–27} Asymptomatic microprolactinomas are typically not treated because they rarely grow.^{27,28} When treatment is indicated, cabergoline is usually preferred, given it is better tolerated by patients and has greater effectiveness than bromocriptine.²⁹ There are no large case series looking at medical treatment of calcified pituitary masses, but previous cases have shown response to bromocriptine.²⁴ For symptomatic patients treated with standard doses of dopamine agonist therapy who do not attain normalization of PRL levels or experience significant tumor shrinkage, DA dose should be escalated to the highest amount tolerated.^{26,27,30,31} Tumors that do not respond to DA therapy entirely are usually large and invasive, but review of literature has not mentioned calcifications as a possible cause of resistance. While this is true, even invasive giant prolactinomas can be extremely responsive to medical treatment and should be managed first with DA therapy.^{21,32,33} A surgical approach can be used for patients with DA resistant tumors or for those who cannot tolerate high doses of DA therapy.^{34,35} Medical therapy should also still be initially attempted for calcified tumors unless there is a compelling reason to pursue surgery first, such as an unclear diagnosis of the tumor, which was the case with patient 2. The calcified nature of these masses may make surgery more difficult than for noncalcified pituitary adenomas. In the calcified prolactinoma case reported by Inoue et al, strong adherence of the highly hemorrhagic tumor to surrounding structures prevented any resection.²⁴ Months of postoperative external radiation therapy did not show a reduction in tumor size on CT imaging and PRL levels remained basally elevated. Subsequent initiation of bromocriptine therapy, however, resulted in sudden drastic decrease in PRL levels and eventual tumor shrinkage as evidenced by CT studies.

In general, rates of intraoperative CSF leakage are higher in craniopharyngiomas than pituitary adenomas, possibly due to the higher rates of calcification and adherence found in craniopharyngiomas.³⁶ While there is no discussion in the literature of rates of intraoperative CSF leaks or other complications during resection of calcified prolactinomas, increased pituitary adenoma size and density have been shown to correlate with increased rates of intraoperative CSF leakage.³⁷ Firm tumor adherence to surrounding structures can also contribute to intraoperative CSF leaks during resection. Additionally, tumor extension, particularly into

the anterior cranial fossa, has also been associated with increased likelihood of intraoperative CSF leakage.³⁷

Conclusion

The presence of calcifications in a sellar region mass can be found with several pathological entities. Although craniopharyngiomas are the most common entity to show dense calcification in this region, a differential for Rathke's cleft cysts, meningiomas, chordomas, and occasional pituitary adenomas should be considered. Pituitary endocrine laboratories can help differentiate functional PAs from many of the above entities. In particular, PRL levels can help differentiate a prolactinoma. Densely calcified lesions pose numerous surgical obstacles due to adherence to surrounding structures while carrying elevated risks for postoperative CSF leakage. Calcified prolactinomas can still be managed first with medical therapy, reserving surgical intervention for refractory cases or other specific scenarios.

Author Contributions and Acknowledgments

ST, AH, JB, and MAW contributed to the generation and editing of the manuscript. AM provided pathology images and interpretation. CJL and MS provided radiology images, interpretation, and editing of the manuscript. JC provided interpretation of biochemical measures in addition to editing of the manuscript. GZ provided surgical expertise in addition to editing of the manuscript.

Funding Statement

No funding sources to declare.

Declaration of Interest

The authors have no conflicts of interest to declare.

References

- Schiffer D, Sibour F, Vesco C. Les calcifications dans les tumeurs cérébrales. Considérations pathogénétiques. *World Neurol* 1961; 2:1069–1082
- Carapella CM, Pompei P, Mastrostefano R, Occhipinti E, Rocco A, Falaschi P. Calcified pituitary adenoma associated with severe hyperprolactinemia. Case report. *J Neurosurg* 1983;59(05):871–874
- Rasmussen C, Larsson SG, Bergh T. The occurrence of macroscopic pituitary calcifications in prolactinomas. *Neuroradiology* 1990;31(06):507–511
- Tanriover N, Kucukyuruk B, Hatipoglu E, Comunoglu N. Pituitary stone: a case report and review of the literature. *Turk Neurosurg* 2014;24(06):967–973
- Ke C, Deng Z, Lei T, et al. Pituitary prolactin producing adenoma with ossification: a rare histological variant and review of literature. *Neuropathology* 2010;30(02):165–169
- Mukada K, Ohta M, Uozumi T, Arita K, Kurisu K, Inai K. Ossified prolactinoma: case report. *Neurosurgery* 1987;20(03):473–475
- Zada G, Lopes MBS, Mukundan S Jr, Laws ER Jr. Atlas of Sellar and Parasellar Lesions: Clinical, Radiologic, and Pathologic Correlations. New York, NY: Springer Publishing Co; 2016: 11–22, 109–195, 197–226
- Deery EM. Note on calcification in pituitary adenomas. *Endocrinology* 1929;13:455–458
- Landolt AM, Rothenbühler V. Pituitary adenoma calcification. *Arch Pathol Lab Med* 1977;101(01):22–27

- 10 Rilliet B, Mohr G, Robert F, Hardy J. Calcifications in pituitary adenomas. *Surg Neurol* 1981;15(04):249–255
- 11 Müeller W, Hoffmann H. Über Verkalkungen in Hypophysenadenomen. *Zentralbl Neurochir* 1967;28:287–290
- 12 Wu Z, Mittal S, Kish K, Yu Y, Hu J, Haacke EM. Identification of calcification with MRI using susceptibility-weighted imaging: a case study. *J Magn Reson Imaging* 2009;29(01):177–182
- 13 Wehrli FW. Magnetic resonance of calcified tissues. *J Magn Reson* 2013;229:35–48
- 14 Bonneville F, Cattin F, Marsot-Dupuch K, Dormont D, Bonneville JF, Chiras J. T1 signal hyperintensity in the sellar region: spectrum of findings. *Radiographics* 2006;26(01):93–113
- 15 Avrahami E, Cohn DF, Feibel M, Tadmor R. MRI demonstration and CT correlation of the brain in patients with idiopathic intracerebral calcification. *J Neurol* 1994;241(06):381–384
- 16 Tsuchiya K, Makita K, Furui S, Nitta K. MRI appearances of calcified regions within intracranial tumours. *Neuroradiology* 1993;35(05):341–344
- 17 Kitamura K, Nakayama T, Ohata K, Wakasa K, Miki Y. Computed tomography and magnetic resonance imaging appearance of prolactinoma with spheroid-type amyloid deposition. *J Comput Assist Tomogr* 2011;35(02):313–315
- 18 Saitoh Y, Mori H, Matsumoto K, et al. Accumulation of amyloid in pituitary adenomas. *Acta Neuropathol* 1985;68(02):87–92
- 19 Martin SW, Lefton DR, Pinto RS, Rosenblum M, Elowitz E. MR imaging characteristics of amyloid deposits in pituitary adenoma. *AJNR Am J Neuroradiol* 2002;23(03):368–370
- 20 Kim SH, Kim SH, Lee SK, Kim TS. Squash smear findings of spherical amyloid in pituitary prolactinoma. A case report. *Acta Cytol* 2004;48(03):447–450
- 21 Wu ZB, Yu CJ, Su ZP, Zhuge QC, Wu JS, Zheng WM. Bromocriptine treatment of invasive giant prolactinomas involving the cavernous sinus: results of a long-term follow up. *J Neurosurg* 2006;104(01):54–61
- 22 Phansey S, Powers JM, Sagel J, Hungerford GD, Rawe SE, Williamson HO. Calcified pituitary prolactinoma. *Obstet Gynecol* 1981;57(6, Suppl):62S–66S
- 23 Horiuchi T, Tanaka Y, Kobayashi S, Yokoh A, Unoki T. Total capsular calcification in a prolactinoma—case report. *Neurol Med Chir (Tokyo)* 1996;36(10):729–732
- 24 Inoue H, Kazuno T, Suzuki M, et al. Effective bromocriptine therapy for large, calcified prolactinoma—pathogenesis of calcifications. *Neurol Med Chir (Tokyo)* 1986;26(01):26–29
- 25 Colao A, Savastano S. Medical treatment of prolactinomas. *Nat Rev Endocrinol* 2011;7(05):267–278
- 26 Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. *Endocr Rev* 2006;27(05):485–534
- 27 Melmed S, Casanueva FF, Hoffman AR, et al; Endocrine Society. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011;96(02):273–288
- 28 Schlechte J, Dolan K, Sherman B, Chapler F, Luciano A. The natural history of untreated hyperprolactinemia: a prospective analysis. *J Clin Endocrinol Metab* 1989;68(02):412–418
- 29 Di Sarno A, Landi ML, Cappabianca P, et al. Resistance to cabergoline as compared with bromocriptine in hyperprolactinemia: prevalence, clinical definition, and therapeutic strategy. *J Clin Endocrinol Metab* 2001;86(11):5256–5261
- 30 Molitch ME. Pharmacologic resistance in prolactinoma patients. *Pituitary* 2005;8(01):43–52
- 31 Molitch ME. Dopamine resistance of prolactinomas. *Pituitary* 2003;6(01):19–27
- 32 Wu ZR, Zhang Y, Cai L, et al. Long-term clinical outcomes of invasive giant prolactinomas after a mean ten-year followup. *Int J Endocrinol* 2016;2016:8580750
- 33 Shrivastava RK, Arginteanu MS, King WA, Post KD. Giant prolactinomas: clinical management and long-term follow up. *J Neurosurg* 2002;97(02):299–306
- 34 Oh MC, Aghi MK. Dopamine agonist-resistant prolactinomas. *J Neurosurg* 2011;114(05):1369–1379
- 35 Pellegrini I, Rasolonjanahary R, Gunz G, et al. Resistance to bromocriptine in prolactinomas. *J Clin Endocrinol Metab* 1989;69(03):500–509
- 36 Karnezis TT, Baker AB, Soler ZM, et al. Factors impacting cerebrospinal fluid leak rates in endoscopic sellar surgery. *Int Forum Allergy Rhinol* 2016;6(11):1117–1125
- 37 Zhou Q, Yang Z, Wang X, et al. Risk factors and management of intraoperative cerebrospinal fluid leaks in endoscopic treatment of pituitary adenoma: analysis of 492 patients. *World Neurosurg* 2017;101:390–395
- 38 Pisaneschi M, Kapoor G. Imaging the sella and parasellar region. *Neuroimaging Clin N Am* 2005;15(01):203–219
- 39 Sartoretti-Schefer S, Wichmann W, Aguzzi A, Valavanis A. MR differentiation of adamantinous and squamous-papillary craniopharyngiomas. *AJNR Am J Neuroradiol* 1997;18(01):77–87
- 40 Crenshaw WB, Chew FS. Rathke's cleft cyst. *AJR Am J Roentgenol* 1992;158(06):1312
- 41 Greenberg H, Chandler WF, Sandler HM. Brain tumors. New York, NY: Oxford University Press; 1999
- 42 Lee JH. Meningiomas. London, UK: Springer-Verlag; 2008
- 43 Takahashi S. Neurovascular Imaging, MRI & Microangiography. London, UK: Springer-Verlag; 2010
- 44 Wiebers DO, Whisnant JP, Huston J III, et al; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* 2003;362(9378):103–110