Rathke Cleft Cyst with Entirely Ossified Cyst Wall and Partially Solid Cyst Content: A Case Report and Literature Review

Case Report

Rathke cleft cyst with entirely ossified cyst wall and partially solid cyst content: a case report and literature review

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A running head; Ossified rathke cleft cyst with solid content

Key words; ossification, rathke cleft cyst, inflammation, metaplasia, nodule

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Abstract

BACKGROUND: In Rathke cleft cysts (RCCs), the inflammation arising from the cyst contents occasionally spreads to the surrounding structures. Calcification, which is believed to be a consequence of chronic inflammation of the cyst wall, may be found in RCCs and ossification is extremely rare.

CLINICAL PRESENTATION: A 60-year-old woman presented with headaches, fatigue, and weight loss due to panhypopituitarism. Magnetic Resonance imaging revealed a mass lesion in the sellar region, which comprised two different parts, with anterior hypointensity and posterior hyperintensity on T1-weighted image (WI), and the rim was significantly hypointense exclusively on T2-WI. During the transsphenoidal surgery, the rigidity of the cyst wall was rendered challenging its slicing and removal. The cyst contained mucinous fluid with both old and new hemorrhages, and a yellowish, elastic -hard, solid nodule. The postoperative histological analysis led to a diagnosis of RCC with unusual lymphocyte infiltration, massive granulation, and mature bone formation. Six months later, the fluid in the cyst re-accumulated and the patient presented with headaches. Removal of the entire cyst wall was performed to collapse the cyst cavity in

order to prevent a further recurrence. Postoperatively, the panhypopituitarism was unchanged and the symptoms were treated with hormonal replacement. The cyst did not recur for 2 years after the second surgery.

CONCLUSIONS: Persistent, long-term inflammation induced by the RCC content, the mucin-containing fluid, and several phases of hemorrhage may have been responsible for the formation of a mature bone on both the cyst wall and the elastic, solid nodule within the cyst.

BACKGROUND

Rathke cleft cysts (RCCs) are non-neoplastic epithelial-lined cysts located in the sellar and suprasellar regions. These cysts are derived from the remnants of the Rathke pouch generated at 3 to 4 weeks of gestation.[1-3] RCCs are diagnosed on the basis of histological verification of a single layer of cuboidal or columnar epithelium, including cilia and goblet cells, which secrete mucus into the cyst cavity.[2,4] RCCs are usually asymptomatic and can be found in 13–22% of unselected autopsy studies.[1,2,5] The inflammation spread by the cyst content and the compressive action of the cyst on the surrounding structures rarely induce headaches, endocrinological insufficiency, and visual function disturbance.[6-8]

Calcification of the cyst wall in RCC is rare and ossification occurs even less frequent. To our knowledge, only four cases have been reported so far.[4,9-11] Because calcification is commonly found in craniopharyngioma, the presence of calcium deposition plays an important role in distinguishing the two disorders.[12,13] Although, it is believed that calcification may result from chronic inflammation of the cyst wall, the detailed mechanism of ossification in RCC remains unknown. In the present case, the

developmental mechanism of an extremely rare case of ossified RCC was explored with an immunohistochemistry (IHC) study.

CASE REPORT

A 60-year-old woman complaining of headaches, fatigue, and weight loss consulted the local hospital in May 2013. Computed tomography (CT) showed a round cyst in the sellar region and calcification on the cyst wall (Figure 1A). Magnetic resonance imaging (MRI) revealed an oval mass in the sellar region with suprasellar extension. The mass had two different parts of anterior hypointensity with heterogeneous contrast enhancement and of homogeneous posterior hyperintensity on T1-weighted image (WI) (Figure 1B,C), and the rim with significant hypointensity on T2-WI (Figure 1D). Hyperintensity of the posterior lobe of the pituitary gland was not found on T1-WI.

The endocrinological analysis revealed that all the hormonal secretions from the anterior lobe were significantly lower than the control values of a healthy menopausal woman: free triiodothyronine (T3: 1.53 pg/mL, normal range: 2.2–4.3), free thyroxin (T4: 0.63 ng/mL, 0.8–1.8), thyroid stimulating hormone (TSH: <0.01 μIU/mL, 0.27–4.65), luteinizing hormone (LH: <0.1 mIU/mL, 5.7–64.3), follicle-stimulating hormone (FSH: 1.1 mIU/mL, <0.5), prolactin (PRL: 3.96 ng/mL, <25.6), growth hormone (GH: 0.17 ng/mL, <2.1), insulin-like growth factor-1 (IGF-1: 36 ng/mL, 70-201 for a 60-year-old

woman), cortisol (1.7μg/mL, 6.2–19.7), adrenocorticotropic hormone (ACTH: <5.0 pg/mL, <46). Polyuria occurred as soon as the cortisol and levothyroxine replacement was administered. The low levels of urine osmolality (259 mOsm/L, 440–1096) with a lack of increase by hypertonic saline loading, the urine specific gravity (1.001–1.003, 1.005–1.025), and the daily urine volume of over 3,000 mL, resulted in the diagnosis of masked diabetes insipidus (DI).

Endoscopic endonasal transsphenoidal surgery (TSS) was performed with a preoperative diagnosis of RCC or cystic craniopharyngioma. After the sellar floor was removed, the extremely rigid wall of the mass was exposed (Figure 2A); the Kerrison Rongeurs were required for performing a partial removal. This procedure released white, turbid, mucinous fluid with hemorrhage out of the mass (Figure 2B). After aspiration of the fluid from the cyst, we found a yellowish, elastic-solid nodule, which was firmly adherent to the thick cyst wall. The nodule was dissected carefully and completely removed from the wall (Figure 2C). The rest of the cyst wall was not removed and the plasty of the sella floor was not performed. The histological examination of the cyst wall showed single columnar ciliated epithelium, consistent with a diagnosis of RCC (Figure

3A). In the epithelium, the staining for β-catenin was negative in the nuclear, but positive in the cytoplasm, which led to the rejections of the craniopharyngioma diagnosis (data not shown). The normal pituitary gland tissue structure was distorted (Figure 3B), infiltration of aggregative lymphocytes and plasma cells, massive granulation (Figure 3C), and cholesterol clefts were found (Figure 3D). The vascular proliferation in the cyst wall was confirmed by IHC using an antibody against CD34 (Figure 3E). A significant invasion of macrophages was confirmed by positive staining for CD68 (Figure 3G). Mature bone formation (Figure 3E) was also observed and a positive staining for bone morphogenetic protein 2 (BMP2) was found in all the pituitary gland affected by the infiltration of many inflammatory cells (Figure 3H,I). The solid part of the cyst was an aggregation of connective tissue and amorphous tissue.

Postoperative MRI revealed the remaining cyst cavity in the sella turcica. Six months later, MRI detected the re-expansion of the cyst with the recurrence of chronic headaches. We hypothesized that the rigidity of the cyst wall prevented the collapse of the cyst cavity, thereby urging the total removal of total cyst wall. Endoscopic endonasal TSS was performed to remove the entire cyst wall and aspirate the cyst content. At the

time of procedure, the sellar floor had regenerated as firm as the one observed during the first operation; therefore, it was removed widely with the Kerrison Rongeurs. The cyst contained thick, yellow, and mucinous fluid. After complete aspiration of the cyst contents, the entire cyst wall was found to be firmly attached to the dura mater at the sella and the diaphragma sellae. The cyst wall was completely dissected. No nodule was found in the cyst cavity. Neither the anterior nor the posterior lobes of the pituitary gland were identified in the sella. The diaphragma sellae did not descend into the sella. Intraoperative cerebrospinal fluid leakage was identified during the dissection of the posterior wall of the cyst; therefore, we sealed the torn arachnoid membrane performing a sellar floor plasty using the autologous fascia, a bone graft from the nasal septum and the mucosal pedicle flap.

The ordinary postoperative clinical course comprised hormonal replacement thereby of 15 mg of cortisol and 50 μg of levothyroxine per day. DI was controlled with 0.025 mL of 1-deamino-8-D-arginine vasopressin daily. The RCC was absent on postoperative MRI (Figure 4), and has not recurred for 2 years after surgery.

Discussion

Although the ossification of the sellar lesion is usually found in craniopharyngioma, this ossification is extremely rare in RCC and, to our knowledge, only four cases have been reported so far. [4,9-11] In craniopharyngioma, the ossification might be caused by a metaplasia due to the chronic inflammation. Sato and Kubota proposed the following mechanism of ossification; the mesenchymal cells in the connective tissue adjacent to the keratinized nest differentiate into osteoblastic cells; subsequently, the keratinized nest promotes the ossification process which may require more time than the calcification process.[13,14]

In some cases, the clinical and pathological differentiation of RCCs and cystic craniopharyngiomas is challenging. However, the differentiation is critical because the prognoses of these condition are quite different.[1,15] Several neuropathologists have reported that the challenging differentiation of RCC from craniopharyngioma may be owing to the fact that RCCs with significant squamous and/or stratified epithelium might be transitional forms of craniopharyngioma, although this has rarely been described.[16,17] Therefore, it has been reported that the nuclear β-catenin accumulation is a reliable

marker for craniopharyngioma useful differentiating RCCs.[17,18] In the present case, the IHC analyses resulted in a negative nuclear staining and the diagnosis of RCC was confirmed.

It is well known that the mucin in RCCs is a strong mediator of inflammation.[6,19] In the symptomatic RCCs, mucus, hemorrhage from the cyst wall result in chronic inflammations of the adjacent hypophysis leading to irreversible changes.[1,2,7] In our patient, preoperative panhypopituitarism was thought to be caused by irreversible changes to the hypophysis. Levels of all hormones secreted from the anterior lobe were significantly lower, and the DI was apparent after hormonal replacement. The endocrinological status did not improve postoperatively and the DI became permanent. Both the preoperative and postoperative MRI revealed a decrease in hyperintensity in the posterior lobe.

Ossification due to mucin-induced inflammation can be observed in the pathological conditions of various organs and tissues, such as colorectum[20], testis and paratestis[21], orbita[22], lung[23], breast[24], nerve sheath[25], heart,[26] pancreas[27], soft tissue,[28] choroid plexus,[29] and ovary.[30] In agreement with other histological observations, cancer cells

with large quantity of mucin in the cytoplasm, capillary proliferation, scattered necrosis, and mesenchymal cells were found around the ossification.[20] In other case reports, mature bone and fibrous stroma with cholesterol clefts, multinucleated giant cells, infiltration of lymphocytes, and foamy, vacuolated macrophages were observed.[21,23,24]

BMPs production by tumor cells is one of the putative mechanisms of ossification in the process of metaplasia due to inflammation. BMPs are low-molecular-weight glycoproteins acting as cytokines which typically target immature, multipotent cells and cause the stimulation of mesenchymal differentiation into osteoblasts.[31,32] In our case, the BMP2 IHC results were positive, indicating the participation of BMP2 in the process of ossification in RCCs. Moreover, another report suggested that fibrosis could be a precursor of diffuse pulmonary ossification and was often associated with BMP2 expression in tumor cells.[33] In our study, positive staining for BMP2 was present in the pituitary gland affected by the inflammation. Therefore, the compromised pituitary gland may have secreted the BMP2, which in turn, induced the metaplastic ossification.

To our knowledge, four cases of ossified RCCs have been reported[4,9-11] In one case, a solid portion in the cyst was identified, in analogy with the case reported here.[34] The

average age of the patients in aforementioned studies was 32.8 (21-45) years old; one of these patients was male and 3 were female. The patient in our case was a 60-year-old woman, i.e., elder than the patients in the previous reports, suggesting the presence of a longer period of inflammation. The previously reported patients showed visual function disturbances in three cases and amenorrhea and headaches in 2. Histological examination revealed fibrosis, granulation with significant lymphocyte and macrophage invasion, and hemorrhage. These conditions further confirm the hypothesis of a long-term persistent inflammation, as shown by ossification in mucin-producing tumors (Table 1). To our knowledge, the present study is the first one reporting the results of IHC analyses in an extremely rare case of ossified RCC with hypopituitarism. These results will further our understanding of the mechanisms underlying this condition.

Surgical procedures should be focused on preventing the recurrence of these entirely ossified RCCs. In 3 out of the 4 cases reported in the literature, the total removal of the cyst wall was performed and recurrence was not encountered. However, in the other case (e.g., case-1) and the present case, only a small part

of the cyst wall was removed during the first surgery. In our case, the total removal of the cyst wall was performed after the recurrence, while in case-1, a part of the capsule was removed during the second surgery (Table 1). Therefore, the surgical removal of the majority of the cyst wall (or the total removal whenever possible) is strongly recommended.

CONCLUSION

Long-term of chronic inflammation induced by RCC's content may promote the formation of both a mature bone and an elastic-solid nodule, while old and new phases of hemorrhage may induce granulation tissue. This metaplastic ossification of the wall strongly suggested the presence of an unusual, extreme, and complex process of persistent inflammation. Whenever possible, the total removal of the ossified cyst wall is recommended for preventing RCC recurrences.

Conflict of Interest Disclosure

The authors declare that they have no conflict of interest.

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Figure Legends

Figure 1.

(A) Preoperative plain CT scan of the head shows crescent-like calcification in the cyst wall. (B) T1-weighted MR image shows an oval mass in the sellar region with suprasellar extension on the coronal section. (C) The mass consists of two different parts with anteriorly hypointensity area characterized by a heterogeneous contrast enhancement with gadolinium and a posterior homogeneous hyperintensity area on the sagittal section. (D) T2-weighted MR image showing the rim of the mass with significant hypointensity.

Figure 2

(A) Endoscopic endonasal transsphenoidal surgery was performed and after the removal of the sellar floor, the rigid wall of the mass was exposed (arrows). (B) Immediately after the partial removal of the rigid wall, turbid mucinous fluid mixed with blood flowed out of the cyst (arrow). (C) A yellowish, elastic, hard, solid lesion appeared (arrow) after the complete aspiration of the fluid in the cyst.

Figure 3

Results of the histological examination of the cyst wall

(A) The single columnar ciliated epithelium was consistent with a diagnosis of RCC. (B) The normal structure of the pituitary gland was severely altered, and (C) unusual lymphocyte and plasma cell infiltration, massive granulation on the cyst wall, and (D) cholesterol clefts were observed. (E) Mature bone formation on the cyst wall has been observed (A-E: Hematoxylin-eosin staining, magnification X200). (F) IHC showed vascular proliferation in the cyst wall, which was confirmed with antibody staining against CD34. (G) Significant invasion of macrophages was confirmed with antibody staining against CD68. (H) Staining with antibody BMP2 was diffuse, strongly positive and evenly distributed in the cytoplasm of the pituitary cells invaded by inflammatory cells (magnification: F-H X 200, I X 400).

Figure 4

Postoperative coronal and sagittal MR images sections reveal that RCC has not recurred for 2 years after the second TSS.

Table Legend

Table 1. Characteristics of previously reported ossified RCCs and the present case

Figure 1

Yasuhiko Hayashi

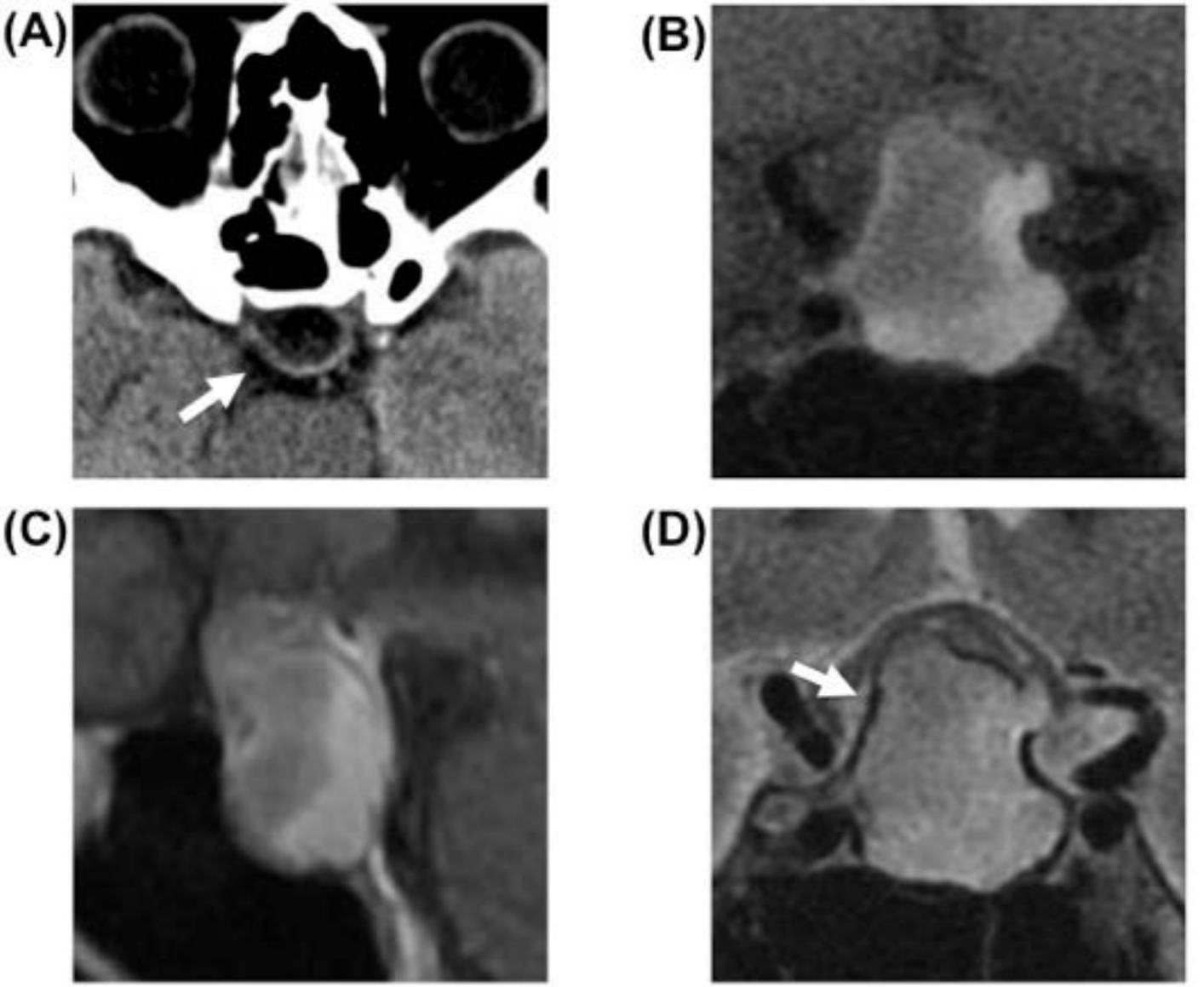

Figure 2

Yasuhiko Hayashi

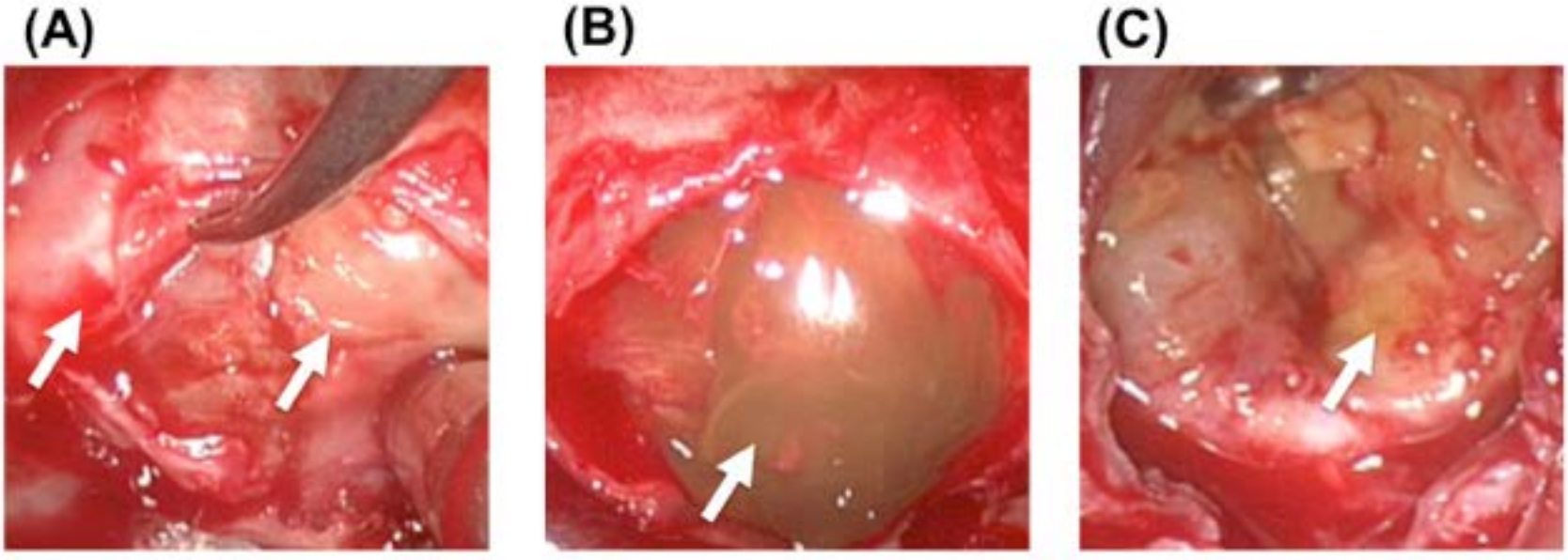

Figure 3

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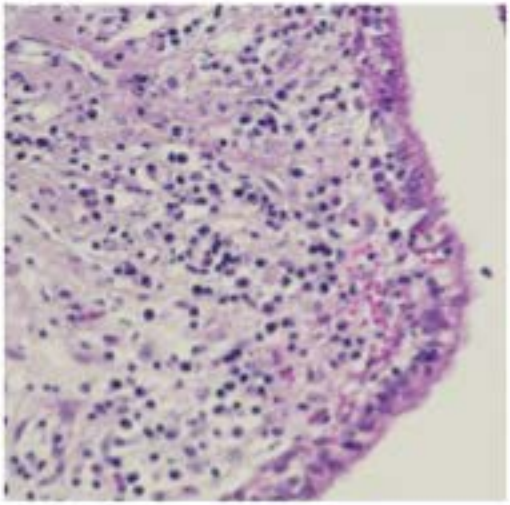
(A)



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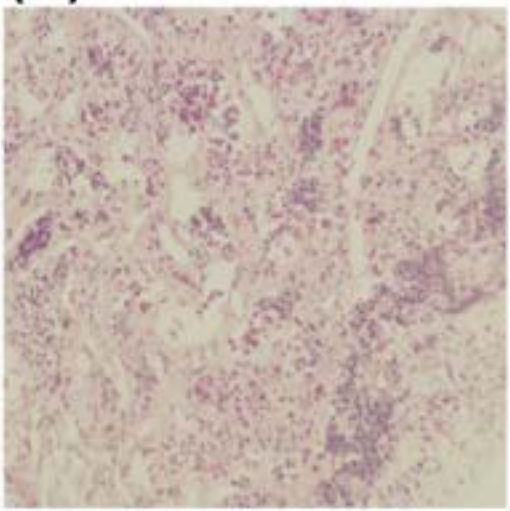

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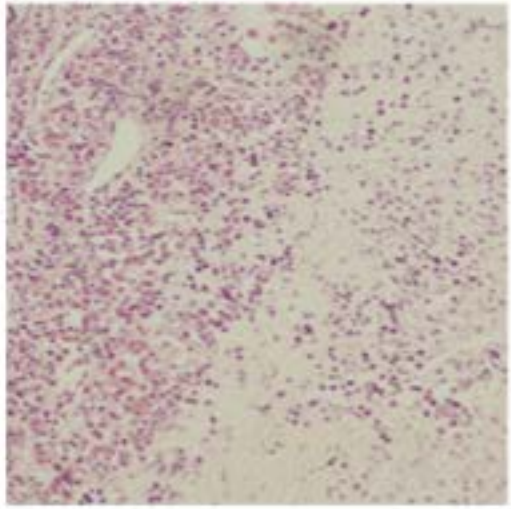

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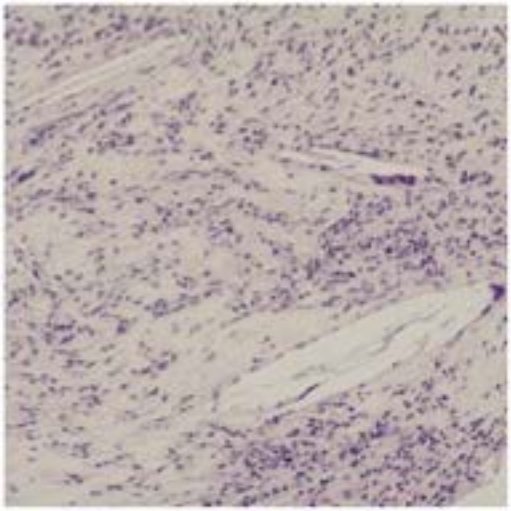

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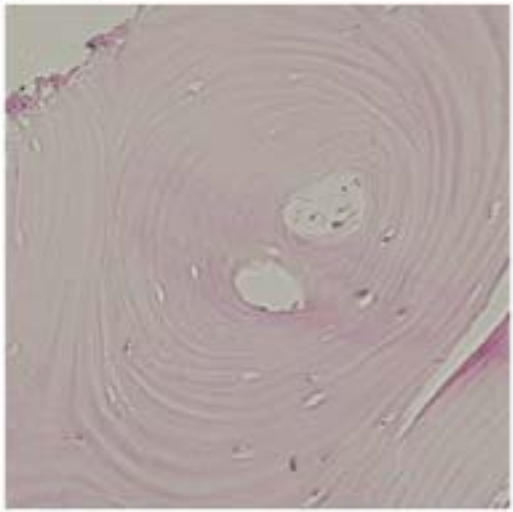
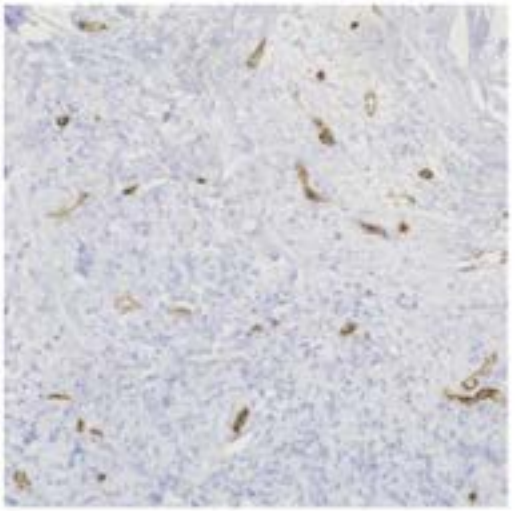


Figure 3

Yasuhiko Hayashi

(F)



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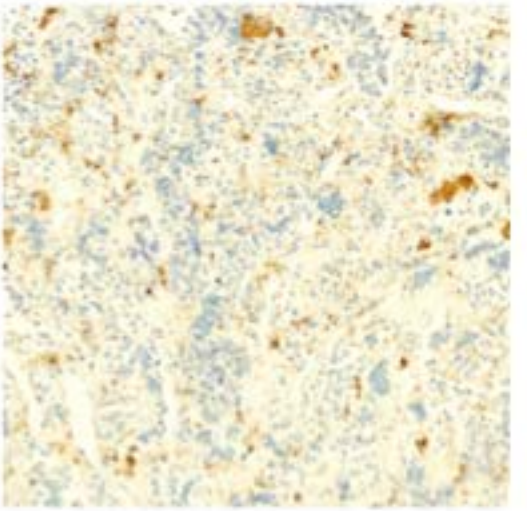


(H)

(I)

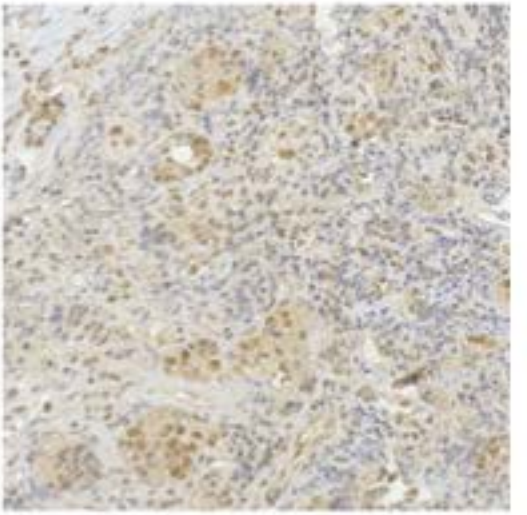
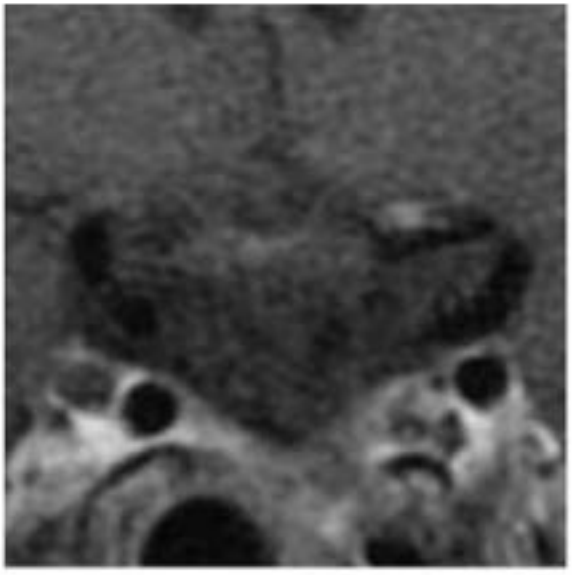


Figure 4

Yasuhiko Hayashi

(A)



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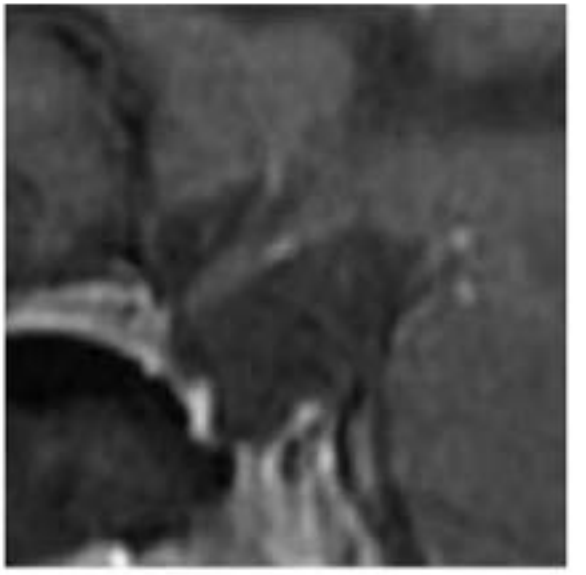

Table 1. Characteristics of previously reported ossified RCCs and present case

		Sex / Age	Symptoms	MRI	Endocrinological insufficiency	Operation	Procedure	Histological Findings	Recurrence
				T1 / T2				(except fot mature bone formation)	
1	Nakasu Y (1999) [3]	23 / F	ED	Hyper / Hyper	LH	TSS / TSS	IR, PR	fibrosis, inflammatory cells	+
2	Lee CH (2008) [4]	42 / M	HA	Mixed / Mixed	-	TCS	CR	fibrous stroma, blood clot	-
3	Ogawa Y (2010) [1]	21 / F	HA, VD	Mixed / Mixed	not mentioned	TSS	CR	fibrosis, macrophage invasion, CC	-
4	Vijayasaradhi M (2012) [5]	45 / F	ED, HA, VD	Iso / Hyper	FSH, LH	TCS	CR	pancytokeratin positive	-
5	Present Case (2016)	60 / F	ED, HA	Mixed / Mixed	Panhypopitutiarism	TSS / TSS	IR, PR → CR	fibrosis, macrophage invasion, CC	+

CC: cholesterin cleft, CR: complete removal, ED: endoscrinological disturbance, FSH: follicle stimulating hormone, HA: headache, IR: irrigation, LH: lutenizing hormone, PR: partial removal, VD: visual disturbance