

Clinicopathological features of sellar region xanthogranuloma: correlation with Rathke's cleft cyst

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Abstract Xanthogranuloma of the sellar region is a rare clinical observation. Although it was included in the World Health Organization (WHO) brain tumor classification in 2000, its clinical features and pathogenesis remain uncertain. We report herein seven cases of xanthogranuloma of the sellar region who underwent transsphenoidal surgery at Tokyo Women's Medical University between 2005 and 2011, and discuss the clinical characteristics of this tumor. Six out of these 7 patients (86 %) presented with endocrinological dysfunction, six (86 %) had headaches, five (71 %) had visual field disturbances, and three (43 %) had diplopia including two with unilateral ptosis. Pathological findings revealed cholesterol clefts, hemosiderin deposits, chronic inflammatory infiltrates, multinucleated giant cells, macrophages, and fibrous proliferation. Of these seven cases, components of Rathke's cleft cyst were observed for six. Xanthogranuloma in the sellar region is suspected of being a terminal stage resulting from a secondary reaction caused by repeated inflammatory change, hemorrhage, and degeneration of a Rathke's cleft cyst.

Keywords Xanthogranuloma of the sellar region · Transsphenoidal surgery · Inflammatory change · Hemorrhage · Rathke's cleft cyst

Abbreviations

RCC Rathke's cleft cyst
MRI Magnetic resonance imaging
T1 T1 weighted image
T2 T2 weighted image
Gd Gadolinium enhancement
TSS Transsphenoidal surgery

Introduction

Xanthogranulomas (XG), known as cholesterol granulomas, which have the histologic characteristics of both granuloma and xanthoma, develop in a variety of locations, for example in the abdomen, skin, and central nervous system [1–6]. Intracranial XG, especially in the sellar region is very rare and had been regarded as a variant of adamantinomatous craniopharyngioma. Paulus et al. [7] in 1999 reported 37 XGs in the sellar region that differ from classical craniopharyngioma (CP). As a result of this report, XG of the sellar region was added to the World Health Organization (WHO) brain tumor classification in 2000 [8]. However, its natural history is still unknown. We report seven cases of XG of the sellar region and discuss their clinical, endocrinological, and pathological characteristics and possible histogenesis in relation to Rathke's cleft cyst (RCC).

Patients and methods

Seven patients undergoing transsphenoidal surgery for XG of the sellar region at Tokyo Women's Medical University

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between 2005 and 2011 were reviewed. These seven cases with xanthogranulomatous changes without typical CP and ciliated RCC were taken from our series consisting, at the moment, of 123 RCCs and 51 CPs. Surgery was performed on 4 males and 3 females. The age of the patients ranged from 12 to 68 years (average 46.6). Postoperatively the minimum and average follow-up periods for inclusion in the study were 12 and 40.3 months, respectively (Tables 1, 2). CT and MRI results were available for all patients, and anterior pituitary lobe stimulation tests were performed before and after surgery. Pituitary function was investigated by use of standardized basal and dynamic stimulation tests and was evaluated in accordance with currently accepted criteria. Visual fields were examined pre and postoperatively by use of Goldmann or Humphrey perimetry methods for patients whose optic chiasm was compressed by the mass on MRI.

All patients underwent endonasal transsphenoidal surgery. The intent of surgery was cyst decompression and removal of a specimen of its wall and adjacent fibrous tissue. Pathological investigation was also performed intraoperatively to distinguish the xanthogranuloma from CP and make a decision how much we should remove. The surgical material was fixed in 10 % buffered formalin, embedded in paraffin, and sectioned. For light microscopy, the tissues were stained with hematoxylin–eosin and Masson-trichrome stain. Immunostaining for keratin and cytokeratin was also performed in all cases.

Results

Pre-operative clinical presentation is shown in Table 1 and post-operative status in Table 2. Six of these 7 patients (86 %) presented with endocrinological dysfunction. There were effects on multiple axes (2–6 axes, average 4.3 axes) with three cases having diabetes insipidus. After surgery, one case (case 2) improved, four cases remained unchanged, except that the affected prolactin inhibiting factor-related hyper-prolactinemia normalized, and one case (case 6) deteriorated. Six patients (86 %) presented with headache; for all patients this disappeared after surgery. Five patients (71 %) had visual field disturbance, subjectively for three and objectively for two. All improved after surgery. Three patients (43 %) presented with diplopia including two cases with unilateral ptosis; all recovered after surgery. The duration of these symptoms ranged between 4 months and 11 years.

Preoperative radiological findings are shown in Table 1 and Figs. 1, 2, 3, 4, 5, 6, 7. On MRI, a wide range of signal-intensity patterns was observed for the cyst and one case was a solid mass without cyst. Tumor size was defined as the maximum preoperative tumor diameter recorded; this

Table 1 Preoperative symptoms and radiological findings for seven patients with xanthogranuloma of sellar region

Case	Age/ gender	Headache	Visual field dysfunction	Diplopia	Endocrinological dysfunction	Duration of symptom (months)	MRI findings maximum diameter (mm), T1, T2, Gd	Location	Calcification on Ct
1	20/M	(+)	(-)	(-)	GH, Gn, Ad, Th, DI, hP	17	12, high, iso-high, rim enhance	Intra-supra sella	(-)
2	64/M	(+)	(-)	(+) with ptosis	GH, Gn, Th	4	18, iso-high, low-high, rim enhance	Intra-supra sella	(-)
3	12/M	(+)	(+)	(-)	GH, Gn, Th, DI, hP	18	20, high, low-iso, -	Intra-supra sella	(-)
4	40/F	(+)	(+)	(-)	GH, Gn, Ad, Th, hP	60	32, high, low-high, rim enhance	Intra-supra sella	(+)
5	59/F	(-)	(+)	(+) with ptosis	Normal	18	11, high, low-high, rim enhance	Supra sella	(-)
6	63/F	(+)	(+)	(+)	Gn, hP	6	18, high, low-high, -	Supra sella	(+)
7	68/M	(+)	(+)	(-)	GH, Gn, Ad, Th, DI	132	23, low-high, low-high, rim enhance	Intra-supra sella	(+)

GH growth hormone, Gn gonadal axis, Ad adrenal axis, Th thyroid axis, DI diabetes insipidus, hP hyper prolactinemia

Table 2 Intra-operative findings and postoperative symptom for seven patients with xanthogranuloma of sellar region

Case	Age/ gender	Cyst content	Extent of removal of cyst wall and solid mass	Headache	Visual field disturbance	Diplopia	Endocrinological dysfunction	Recurrence or regrowth	Follow up (months)
1	20/M	Xanthochromic fluid	Partial	Cure			GH, Gn, Ad, Th, DI	(–)	84
2	64/M	Xanthochromic fluid	Partial	Cure		Cure	GH, Gn	(–)	63
3	12/M	Yellow-brown mucus	Total	Cure	Cure		GH, Gn, Th, DI	(–)	45
4	40/F	Yellow-brown mucus with motor oil like liquid	Sub-total	Cure	Improvement		GH, Gn, Ad, Th	(–)	31
5	59/F	Yellow-brown mucus	Total		Cure	Cure	Normal	(–)	25
6	63/F	Yellow-brown mucus with motor oil like liquid	Total	Cure	Cure	Cure	GH, Gn, Ad, Th	(–)	22
7	68/M	Nothing	Sub-total	Cure	Improvement		GH, Gn, Ad, Th, DI	(–)	12

GH growth hormone, Gn gonadal axis, Ad adrenal axis, Th thyroid axis, DI diabetes insipidus, hP hyper prolactinemia

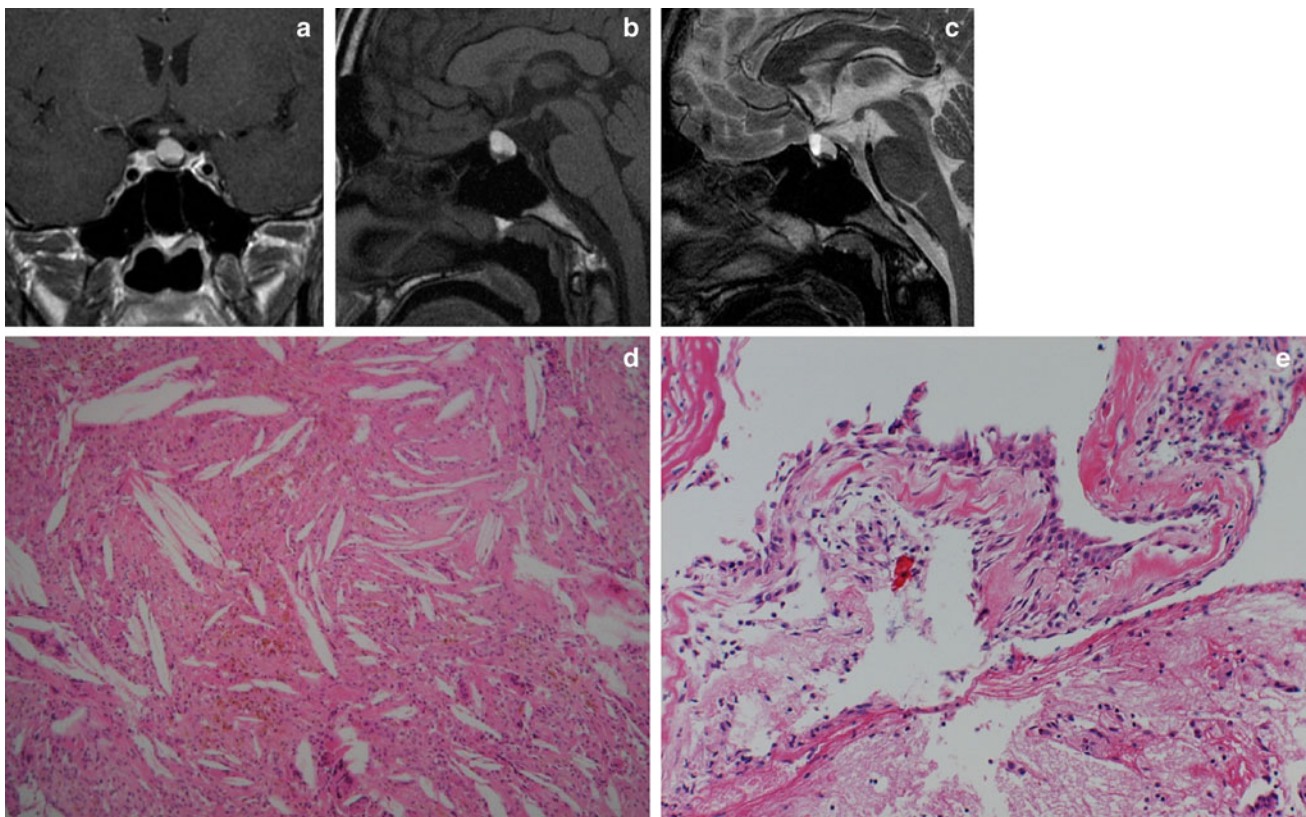


Fig. 1 Case 1. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery; (b) sagittal T1; (c) sagittal T2. (d) Photomicrograph of surgical specimen revealing granomatous tissue with cholesterol cleft, hemosiderin

deposits, multinucleated giant cells, and chronic inflammatory infiltrates (H&E staining $\times 100$). (e) Photomicrograph of a fragment of columnar epithelium (H&E staining $\times 200$)

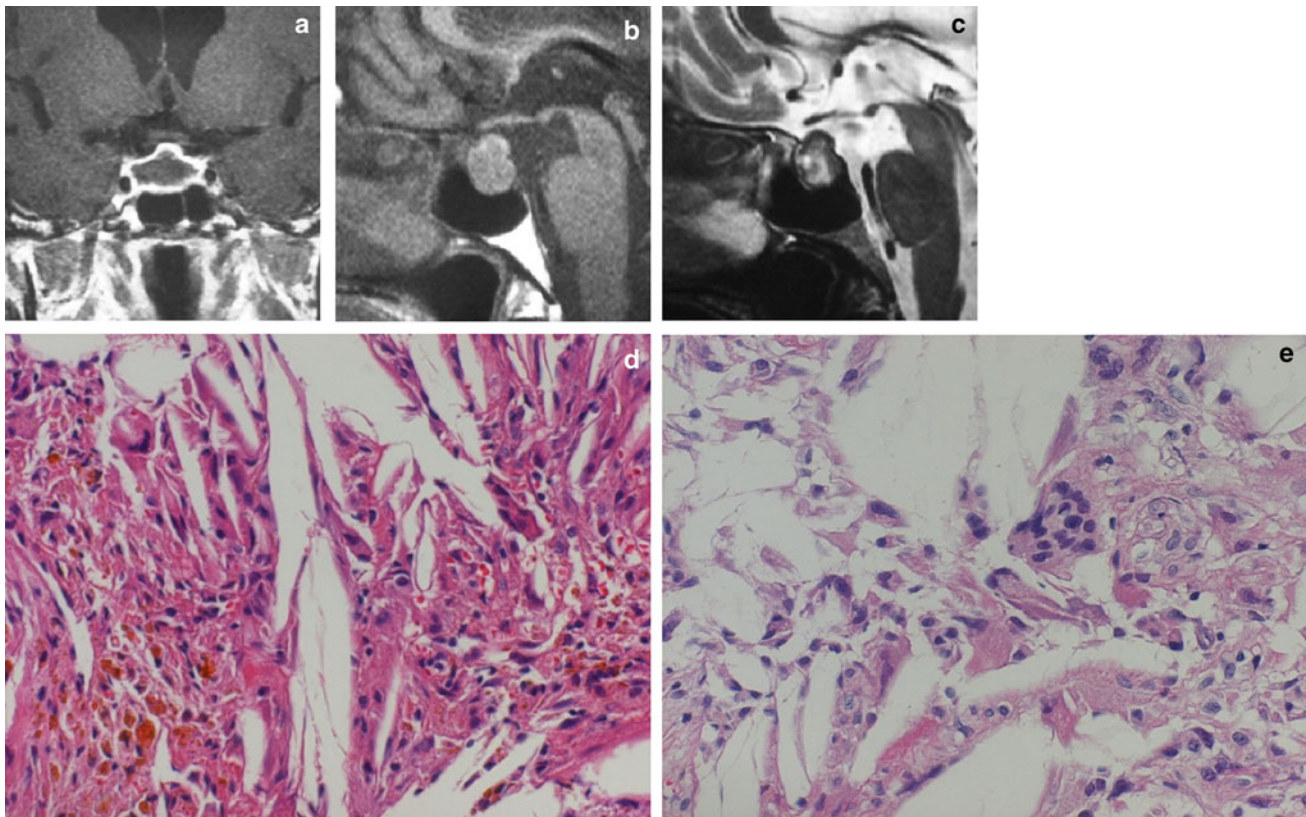


Fig. 2 Case 2. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery; (b) sagittal T1; (c) sagittal T2. (d) Photomicrograph of surgical specimen revealing granulomatous tissue with cholesterol cleft, hemosiderin

deposits, multinucleated giant cells, and chronic inflammatory infiltrates (H&E staining $\times 200$). (e) Photomicrograph showing columnar epithelium is not visible (H&E staining $\times 200$)

ranged from 12 to 32 (mean 19.1) mm. CT revealed calcification for three patients.

All patients underwent transsphenoidal surgery. Cysts contained xanthochromic fluid in two, yellow-brown mucus in two, and yellow-brown mucus with motor oil-like liquid in two. After drainage and irrigation of the cyst, cyst wall, fibrous tissue, and any solid mass were removed partially for two patients, sub-totally for two, and totally for three (Table 2).

Histopathological findings are listed in Table 3 and shown in Figs. 1, 2, 3, 4, 5, 6, 7. They revealed cholesterol clefts, hemosiderin deposits, chronic inflammatory infiltrates, multinucleated giant cells, macrophages, and fibrous proliferation. Of these seven cases, calcification was observed for five and components of RCC were observed for six.

Discussion

Xanthogranulomas in the sellar region are very rare. As a result of the scarcity of XG in the sellar region, their natural history, pathogenesis, and clinical presentation remain

unclear. Paulus et al. [7] first described XG in the sellar region as a different entity from classical CP, focusing on age, radiological findings, anatomical localization, size, symptoms (marked endocrinological deficits and visual disturbances), outcome, and pathological features. Consequently, XG of the sellar region was added to the World Health Organization (WHO) brain tumor classification in 2000 as a new entity [8]. Since then we have found ten reports of XG in the sellar region [9–18], but it is still difficult to distinguish among XG in the sellar region, CP, and RCC pre-operatively and even, occasionally, post-operatively [19–22]. The reason is the overlap of features and, in some cases, transitional status.

Our seven cases of XG in the sellar region are characterized by their radiological findings, endocrinological dysfunction, pathological findings, and good outcomes. MRI findings revealed a variety of T1 and T2 intensities. They derived from the different degree of intra-cystic inflammation and amount of hemorrhage. Severe multi-axis endocrinological dysfunction was observed for six of the seven cases. This might be a consequence of inflammatory changes, similarly to RCC. One case (case 5) had normal pituitary function. The most probable reason for the

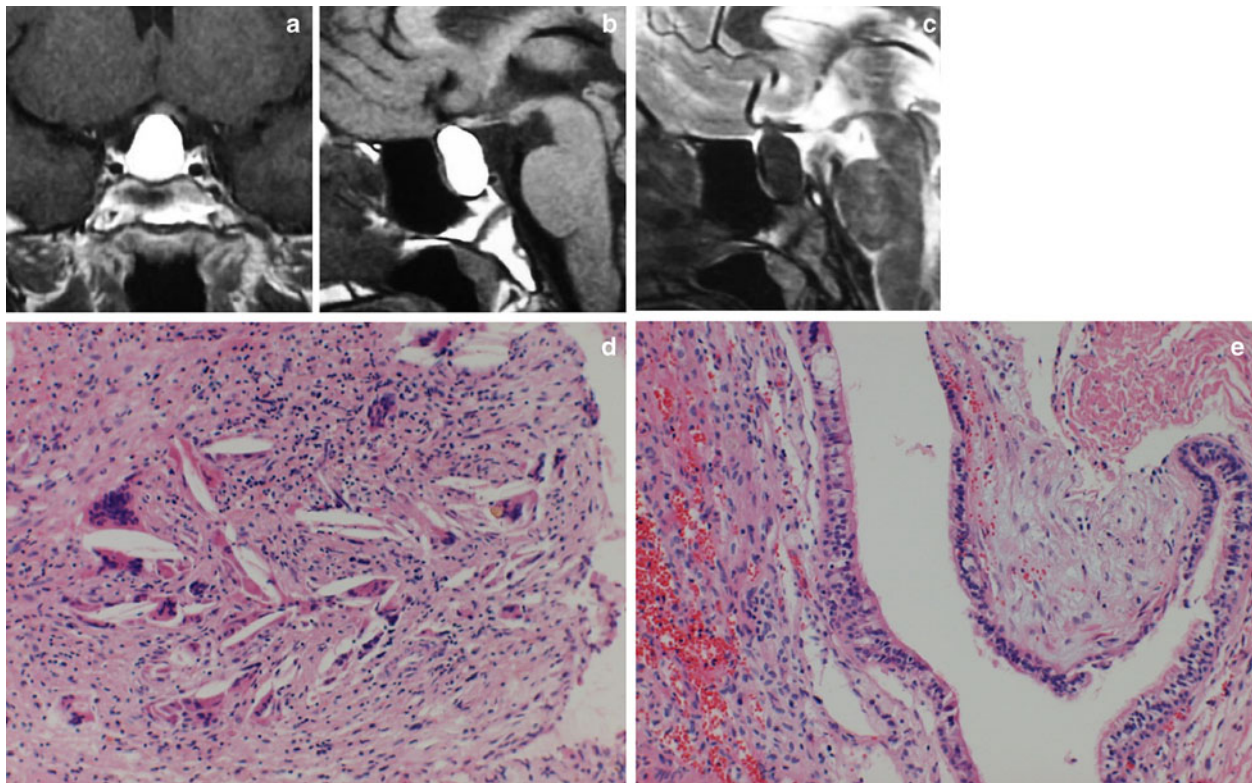


Fig. 3 Case 3. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery; (b) sagittal T1; (c) sagittal T2. (d) Photomicrograph of surgical specimen revealing granulomatous tissue with cholesterol cleft, hemosiderin

deposits, multinucleated giant cells, and chronic inflammatory infiltrates (H&E staining $\times 200$). (e) Photomicrograph of fragment of columnar epithelium (H&E staining $\times 200$)

absence of endocrinological dysfunction was its entirely supra sellar location, so inflammation could probably not spread to the normal gland. Histopathological studies revealed cholesterol clefts, hemosiderin deposits, chronic inflammatory infiltrates, multinucleated giant cells, macrophages, and fibrous proliferation. But a single important characteristic was that six of these seven cases had components of RCC. Six cases with headache and three cases with diplopia of these seven cases were all relieved after surgery. These symptoms may be attributed to the inflammation.

On the other hand, the incidence of RCC has increased with the widespread availability of, and advances in, MRI [23, 24]. An estimated 13–22 % of the population has incidental asymptomatic RCC at autopsy [25]. Some RCCs remain unchanged in size for long periods of time or even regress, whereas others can become sufficiently large, undergo inflammatory changes, associate with pituitary apoplexy, produce calcifications or ossify, and cause visual impairment, hypothalamic-pituitary dysfunction, and headaches. As just described, RCC has the potential to present a variety of clinicopathological features [26–41]. Although inflammation of RCC differs in degree, it is not only its severity that induces xanthogranulomatous changes. We

might speculate that the RCC becomes inflamed, then bleeds, and subsequently degenerates. These interactions occur repeatedly and induce the xanthogranulomatous change.

Whether we can find the RCC's component or not depends on the extent of surgical removal of the lesion and how RCC's components were modified by inflammation and hemorrhage. Of these seven cases, we removed cyst wall, fibrous tissue, and any solid mass partially in two, sub-totally in two, and totally in three. There is a possibility that small components of CP might have existed in the residual lesion, and only total resection can guarantee proof of tumor origin from RCC. However, total resection may result in deterioration of pituitary function. Furthermore most of RCCs and XGs have good prognosis that does not require total removal.

In some cases, when the RCC's components were more distinctive, diagnosis was RCC with xanthomatous change, whereas in the absence of RCC's components, diagnosis was XG of the sellar region [7, 41]. There have, furthermore, been reports of hypophysitis and pituitary adenomas with xanthogranulomatous reaction [42–45]. Pituitary adenoma and hypophysitis sometimes coexist with RCC [46]. It is possible that the RCC's components disappeared as a consequence of the severe inflammation and

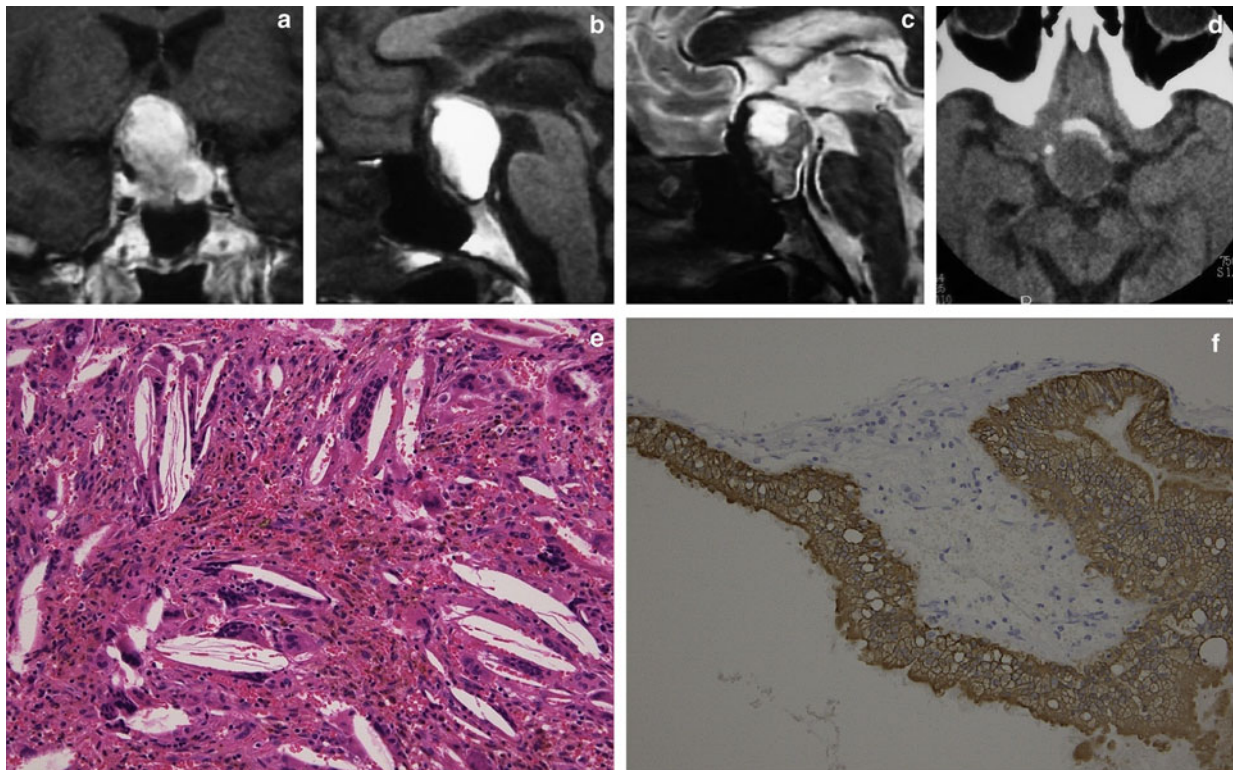


Fig. 4 Case 4. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery; (b) sagittal T1; (c) sagittal T2. (d) Computed tomography showing calcification. (e) Photomicrograph of surgical specimen revealing granulomatous

tissue with cholesterol cleft, hemosiderin deposits, multinucleated giant cells, and chronic inflammatory infiltrates (H&E staining $\times 200$). (f) Photomicrograph of fragment of columnar epithelium (AE1/AE3 staining $\times 200$)

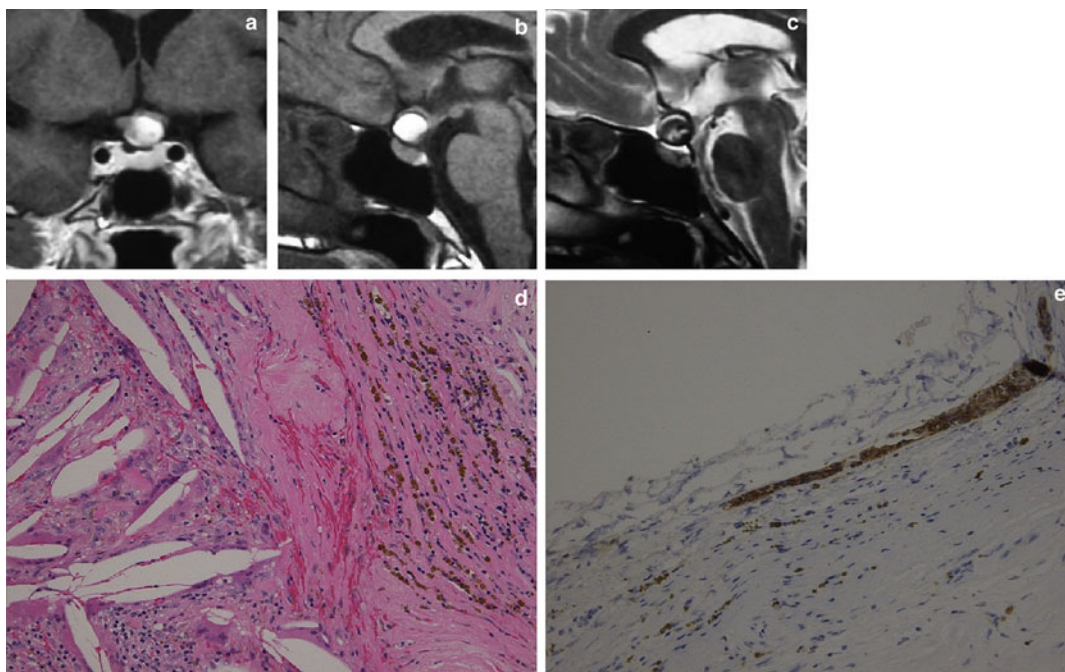


Fig. 5 Case 5. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery; (b) sagittal T1; (c) sagittal T2. (d) Photomicrograph of surgical specimen revealing granulomatous tissue with cholesterol cleft, hemosiderin

deposits, multinucleated giant cells, macrophage, and chronic inflammatory infiltrates (H&E staining $\times 200$). (e) Photomicrograph of fragment of columnar epithelium (AE1/AE3 staining $\times 200$)

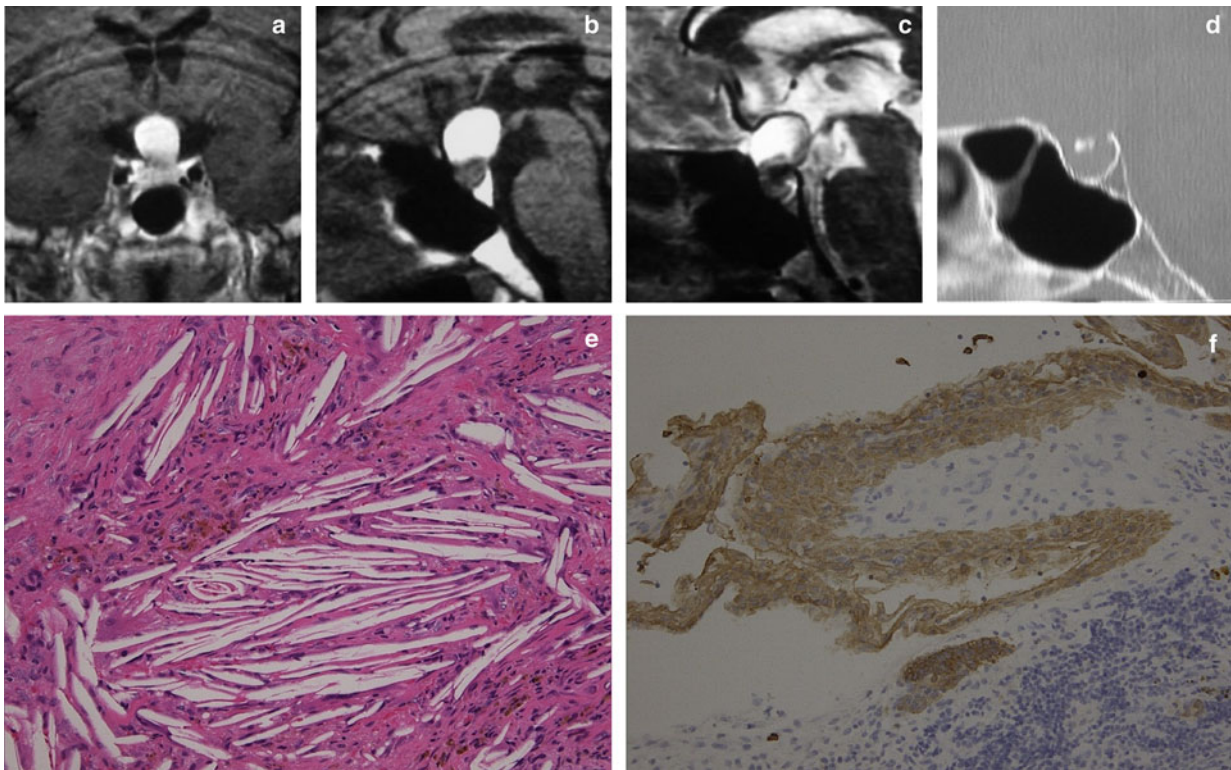


Fig. 6 Case 6. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery, revealing a strongly enhanced mass lesion with cyst; (b) sagittal T1; (c) sagittal T2. (d) Computed tomography showing intra sellar calcification. (e) Photomicrograph of surgical specimen revealing granulomatous

tissue with cholesterol cleft, hemosiderin deposits, multinucleated giant cells, and chronic inflammatory infiltrates (H&E staining $\times 200$). (f) Photomicrograph of fragment of columnar epithelium (AE1/AE3 staining $\times 200$)

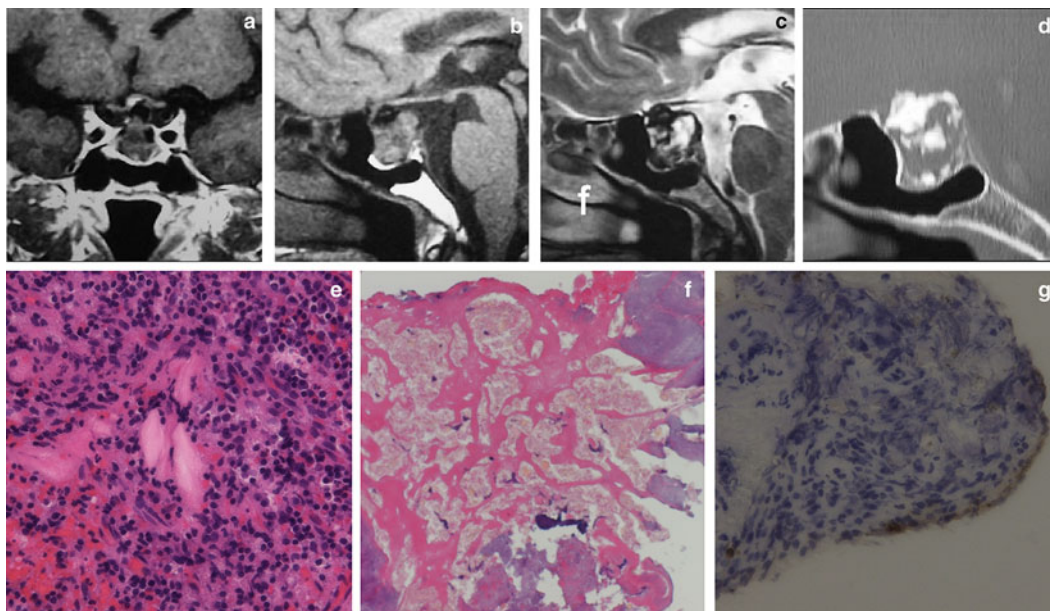


Fig. 7 Case 7. Coronal T1-weighted magnetic resonance (MR) images with gadolinium: (a) obtained before surgery, revealing a strongly enhanced mass lesion with cyst; (b) sagittal T1; (c) sagittal T2. (d) Computed tomography showing intra-supra sellar calcifications. (e) Photomicrograph of surgical specimen revealing granulomatous

tissue with cholesterol cleft, and chronic inflammatory infiltrates (H&E staining $\times 200$). (f) Photomicrograph of ossification, mature bone formation, and hemosiderin deposits (H&E staining $\times 200$). (g) Photomicrograph of fragment of columnar epithelium (AE1/AE3 staining $\times 200$)

Table 3 Histopathological findings for seven patients with xanthogranuloma of the sellar region

Case	Age/ gender	Cholesterol-cleft granulomas	Hemosiderin deposits	Chronic inflammation infiltrates	Multinucleated giant cells	Calcification	Component of Rathke's cleft cyst
1	20/M	(+)	(+)	(+)	(+)	(-)	(+)
2	64/M	(+)	(+)	(+)	(+)	(+)	(-)
3	12/M	(+)	(+)	(+)	(+)	(+)	(+)
4	40/F	(+)	(+)	(+)	(+)	(+)	(+)
5	59/F	(+)	(+)	(+)	(+)	(-)	(+)
6	63/F	(+)	(+)	(+)	(+)	(+)	(+)
7	68/M	(+)	(+)	(+)	(-)	(+)	(+)

hemorrhage or were not included in the resected specimen at surgery. In fact, in three of our six cases the RCC's components were found on a subsequent review of the specimens.

Rathke's cleft cyst is basically a cystic mass, but many XGs without cyst have been reported, including by Paulus et al. One of our 7 cases was a solid mass without cyst. In the solid case (case 7), the solid lesion became completely ossified and SONOPET was needed to remove the ossified mass. In cases with cysts it is quite likely that the original cyst-lining epithelial lesion, presumably RCCs in most cases, had induced the xanthogranulomatous change. On the other hand, the cause of XG is ambiguous in solid cases without cysts. It was suspected that cyst content became absorbed in the prolonged course or was pressed by the granulation and disappeared. When no component of an epithelial lesion responsible for the reaction could be detected, despite radical resection, it should be termed "xanthogranuloma of the sellar lesion".

Xanthogranulomas may occur at different intracranial and skull base sites, other than the parasellar lesion, for example petrous apex, other skull base locations, and choroid plexus [1–6]. It is unreasonable to consider that XGs associated with other lesions are also related to RCCs. There might be other primary histological structures, except RCC, as a background for inflammatory changes.

Therefore, we might speculate that a XG in the sellar region, RCC with xanthogranulomatous change, hypophysitis with xanthogranulomatous reaction, and to some extent also pituitary adenoma with xanthogranulomatous reaction have the pathological characteristics of an entity originating from RCC, with the final status resulting from the secondary changes: repeated inflammation, hemorrhage, and degeneration.

Conclusions

Xanthogranuloma of the sellar region can be differentiated from adamantinomatous CP, and its characteristics are very

similar to those of Rathke's cleft cyst with inflammatory changes. Xanthogranuloma of the sellar region is suspected to be a final stage resulting from secondary reactions caused by repeated inflammation, hemorrhage, and degeneration of Rathke's cleft cyst.

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Conflict of interest The authors report no conflict of interest concerning the materials or methods in this study or the findings reported in this paper.

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