# Sellar Xanthogranuloma: A Quest Based on Nine Cases Assessed with an Anterior Pituitary Provocation Test

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■ BACKGROUND: **Xanthogranuloma is a chronic inflammatory mass characterized by cholesterol crystal deposition, which is rarely seen in the sellar region. The objective of this study is to identify the clinical features and cause of sellar xanthogranulomas.**

■ METHODS: **We retrospectively analyzed manifestation, radiographic, and endocrinologic presentation in 9 patients (7 women and 2 men) whom we had previously treated.**

■ RESULTS: **The patients were between 26 and 73 years of age (median, 56 years). The chief symptoms were visual symptoms in 3, polyuria in 3, headache in 4, and tiredness in 4 patients. Perimetry found visual field deficit in 6 patients. Anterior pituitary provocation tests disclosed impairment of ≥1 hormone in all patients: growth hormone in 8 patients and adrenocorticotropic hormone—cortisol axis in 8 patients. The lesions were suprasellar in 2 patients, intrasellar in 2 patients, and intrasuprasellar region in 5 patients. Three of the lesions were solid and 6 were single cystic to multicystic. Very low intensity area on T2-weighted magnetic resonance imaging was observed in 4 lesions. Postcontrast study performed in 7 lesions showed enhancement in solid parts or cyst walls. Surgical decompression improved visual disturbance in half of the patients but rarely improved hormonal deficits. Follow-up (median, 47 months) found no recurrence of the lesion. In addition to these 9 cases, we found 2 xanthogranulomatous lesions pathologically associated with ciliated epithelia, which also presented with severe hypopituitarism.**

■ CONCLUSIONS: **Xanthogranuloma seems to be the last stage of the chronic inflammation affecting Rathke cleft cyst or craniopharyngioma presenting with severe anterior pituitary insufficiency.**

## INTRODUCTION

Xanthogranulomas are pathologically composed of features of chronic granulomatous inflammation including cholesterol cleft, multinucleated giant cells, foamy macrophage, lymphocytes, hemosiderin deposition, and necrotic debris.[1,2] These lesions are commonly seen in the skin of young children and are occasionally accompanied by an eye or lung lesion. However, they are very rarely seen in the sellar region.[3] A pure xanthogranuloma in the sellar region without features of neoplasm or epithelial cyst was first described in 1988.[4] It has been considered to be an independent clinical entity from other sellar neoplastic lesions.[2,5] Because of the paucity of reported case series, its origin, neuroimaging characters, symptomatic presentation, effect on pituitary function, and prognosis are not well known. Specifically, there is no systemic assessment of the pituitary function in xanthogranuloma and no comparison with other sellar disease. Of the 540 hypothalamopituitary tumors that

**Key words**
- Cholesterol crystal
- Chronic inflammation
- Hypopituitarism
- Rathke cleft cyst
- Xanthogranuloma

**Abbreviations and Acronyms**
**ACTH**: Adrenocorticotropic hormone
**CT**: Computed tomography
**GH**: Growth hormone
**MRI**: Magnetic resonance imaging
**SD**: Standard deviation
**T1WI**: T1-weighted imaging
**T2WI**: T2-weighted imaging
**TSS**: Transsphenoidal surgery

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we have treated during the last 12 years, we have found 9 (1.7%) sellar xanthogranulomas.

Herein, we retrospectively review these 9 cases to explore the characteristics of such lesions, focusing on the anterior pituitary function, which was evaluated by provocation tests.

## METHODS

### Patients

The study included 9 patients (7 women and 2 men). The age ranged from 26 to 73 years (median, 56 years; mean, 52.4 ± 16.2 standard deviation [SD]). The diagnosis of xanthogranuloma was pathologically made based on the presence of cholesterol clefts, lymphocytic infiltration, multinucleated foreign body giant cells, foamy macrophages, and fibrous tissue proliferation tainted by hemosiderin deposits. In this series, the absence of neoplastic components such as pituitary adenoma and craniopharyngioma or ciliated epithelium indicating Rathke cleft cyst was mandated for the diagnosis. Length of postoperative follow-up ranged from 11 to 143 months (median, 47 months).

### Anterior Pituitary Function

We assessed the anterior pituitary hormonal function using a triple provocation test in all 9 patients preoperatively and in 8 at the 6-month postoperative period, as one of the routine examinations conducted in our institute for patients with hypothalamic pituitary diseases. The test was carried out by administering bolus injection of insulin, 0.12 U/kg; luteinizing hormone-releasing hormone, 100 μg; and thyrotropin-releasing hormone, 500 μg. Melmed and Kleinberg criteria were used to determine intactness of pituitary hormone secretion.[6] The peak growth hormone (GH) level was set at >3 ng/mL. Regarding adrenocorticotropic hormone (ACTH)-cortisol, the peak cortisol level was >18 μg/dL or an increase of 7 μg/dL above the basal level. For thyroid-stimulating hormone, the peak value was >2.5-fold the basal level or >6 mU/L. The peak prolactin value was set at greater than twice the basal level. The peak luteinizing hormone value was >3-fold the basal level or a 10 IU/L increase from the basal level. For follicle-stimulating hormone, the peak value was >2-fold the basal level or a 2-IU/L increase from the basal level.

### Statistical Analysis

A Mann-Whitney U test was used for the statistical comparison between the 2 nonpaired groups. $P < 0.05$ was defined as showing statistical significance.

### Ethical Consideration

This noninterventional and retrospective study was endorsed by the medical ethics committee of Kagoshima University Hospital (reference number 180039, epidemiology research). We certify that this study involving human patients was conducted in accordance with the Helsinki Declaration of 1975 as revised in 2000 and with the Ethical Guidelines for Epidemiological Research (effective on 1 July, 2002) by the Ministry of Education, Culture, Sports, Science and Technology, Japan. Informed consent for the treatment and for the use of their data in general research on hypothalamopituitary disease was obtained from all patients. Study-specific informed consent was waived because of the retrospective and noninvasive nature of our study. An opt-out approach was offered to all patients. To protect patient privacy, all data were collected and analyzed and anonymity was maintained.

## RESULTS

### Clinical Features

The size of the lesion was 16–35 mm (median, 22; mean, 24.7 ± 9.3 SD) (Table 1). The chief symptom (multiple count was allowed) was headache in 4 patients, general fatigue in 4, visual disturbance in 3, and polyuria in 3. Preoperative examinations found diabetes insipidus in 6 patients, visual impairment in 6, and pituitary insufficiency (≥1 axis) in all patients.

### Radiologic Findings

Lesions were detected in the suprasellar region in 2 patients (22.2%), in the intrasellar region in 2 patients (22.2%), and in the intrasuprasellar space in 5 patients (55.6%) (Table 2). The sella turcica was enlarged in 5 patients. The lesions were solid in 3 patients and single cystic to multicystic in 6 patients. Calcification on computed tomography (CT) was seen in 1 patient. The lesion was hyperintense in 3 patients and isointense in 6 patients on T1-weighted imaging (T1WI) magnetic resonance imaging (MRI). The lesion was hyperintense in 4 patients, isointense in 3, and hypointense in 2 on T2-weighted imaging (T2WI) MRI. An extremely hypointense area was seen in 4 lesions on T2WI MRI. A gadolinium enhancement study was conducted for 7 patients who had no renal failure. The postgadolinium MRI showed heterogeneous enhancement effects in all 3 solid lesions. The cyst walls were strongly enhanced in all 4 cystic lesions for which the contrast medium was administered.

**Table 1.** Summary of Cases and Manifestations

| | |
|---|---|
| Sex, male/female (n) | 2:7 |
| Age (years), range (median, mean ± standard deviation) | 26–73 (56, 52.4 ± 4.2) |
| Size (mm), range (median, mean ± standard deviation) | 16–35 (22, 24.7 ± 9.3) |
| Manifestations | |
| Chief symptoms (multiple count is allowed), n (%) | |
| Headache | 4 (44) |
| General fatigue | 4 (44) |
| Visual disturbance | 3 (33) |
| Polyuria | 3 (33) |
| Findings (on examination), n (%) | |
| Visual impairment | 6 (67) |
| Diabetes insipidus | 6 (67) |
| Pituitary insufficiency (in ≥1 axis) | 9 (100) |

**Table 2.** Summary of Radiologic Findings

| Imaging | Findings | N (%) |
|---|---|---|
| Computed tomography | Calcification | 1 (11) |
| | Solid | 3 (33) |
| | Cystic | 6 (67) |
| T1-weighted MRI | Hyperintense | 3 (33) |
| | Isointense | 6 (67) |
| | Hypointense | 0 |
| T2-weighted MRI | Hyperintense | 4 (44) |
| | Isointense | 3 (33) |
| | Hypointense | 2 (22) |
| | Partly very hypointense | 4 (44) |
| Postcontrast MRI (7 cases) | Enhancement of solid part | 3/3 (100) |
| | Enhancement of cyst wall | 4/4 (100) |

MRI, magnetic resonance imaging.

## Treatment

A solid lesion, which was solely located in the suprasellar space, was completely removed by an interhemispheric approach. Transsphenoidal surgery (TSS) was performed for the other 8 lesions. Among these 8 lesions, the lesion including cyst wall was subtotally removed in 5 patients. The cystic contents were drained and its walls were partially removed in 2 patients. One suprasellar solid lesion was biopsied through the transsphenoidal approach. Symptomatic recurrence of the lesion was not seen during the 47-month (median) follow-up period.

## Visual Function

Perimetry found bitemporal hemianopia in 3 patients and a monocular defect in 3 patients. Impaired visual acuity was shown in 3 patients (Table 3). Postoperative improvement of the visual function was observed in 3 of these 6 patients with preoperative visual impairments. In 1 patient, the bilateral visual acuity was newly compromised (from 1.5 to 0.9 in the right eye and 1.2 to 0.6 in the left eye) after the attempt to completely remove the lesion strongly attached to optic chiasm.

## Pituitary Function

The preoperative pituitary provocation test showed that ≥1 pituitary hormonal axis was impaired in all 9 patients (Table 4). GH deficiency was seen in 8 patients and ACTH-cortisol axis deficiency was seen also in 8 of 9 patients. Hyperprolactinemia was seen in 7 patients and diabetes insipidus was seen in 6 patients.

To gauge the seriousness of the pituitary dysfunction resulting from xanthogranuloma and its causative factors, we compared the peak GH and cortisol level during the triple provocation test between the xanthogranulomas in all 9 cases, Rathke cleft cysts (35 cases), and nonfunctioning pituitary adenomas (102 cases) that we have treated for the last 12 years.

The size of the xanthogranulomas was not remarkably different from Rathke cysts ($P = 0.6620$, Mann-Whitney $U$ test) but significantly smaller than nonfunctioning pituitary adenomas ($P = 0.0207$) (Figure 1). However, the peak GH level in the xanthogranulomas was significantly lower than that of Rathke cysts ($P = 0.0049$) and nonfunctioning pituitary adenomas ($P = 0.0043$) (Figure 2). The peak cortisol level in the xanthogranulomas was also significantly lower than that of Rathke cysts ($P = 0.0029$) and nonfunctioning pituitary adenomas ($P < 0.0001$) (Figure 3).

Postoperatively, the pituitary function rarely recovered; the impairment ratio of each hormonal axis was essentially similar to the preoperative one.

## Representative Cases

***Case 1.*** A 73-year-old woman presented with left visual field deficit (Figure 4). CT showed sellar enlargement and isodense intrasellar lesion with slight suprasellar extension. Dense calcification was

**Table 3.** Visual Function

| | Before Surgery | | After Surgery | |
|---|---|---|---|---|
| Case, Age/Sex | Visual Field | Visual Acuity | Visual Field | Visual Acuity |
| Case 1, 73/F | Monocular defect | Normal | No change | Normal |
| Case 2, 26/M | Bitemporal hemianopia | Normal | No change | Normal |
| Case 3, 58/M | Bitemporal hemianopia | Left 0.4 | Improved | No change |
| Case 4, 58/F | Monocular defect | Normal | Worsened | Worsened |
| Case 5, 67/F | Normal | Normal | Normal | Normal |
| Case 6, 56/F | Bitemporal hemianopia | Left 0.4 | Improved | No change |
| Case 7, 54/F | Monocular defect | Right 0.01 | Improved | Improved |
| Case 8, 54/F | Normal | Normal | Normal | Normal |
| Case 9, 26/F | Normal | Normal | Normal | Normal |

M, male; F, female.

**Table 4.** Impairment of Pituitary Hormone

| | Before Surgery, n (%) | After Surgery, n (%) |
|---|---|---|
| Growth hormone deficiency | 8/9 (89) | 5/7 (71) |
| Adrenocorticotropic hormone (cortisol) deficiency | 8/9 (89) | 6/8 (75) |
| Thyroid-stimulating hormone deficiency | 4/9 (44) | 6/8 (75) |
| Hyperprolactin | 7/9 (78) | 6/8 (75) |
| Luteinizing hormone deficiency | 5/9 (56) | 3/8 (38) |
| Follicle-stimulating hormone deficiency | 3/9 (33) | 3/8 (38) |
| Diabetes insipidus | 6/9 (67) | 5/9 (56) |

seen in the periphery of the lesion. MRI showed hyperintensity of the lesion on T1WI and T2WI. An extremely low intensity rim was seen on T2WI. Because of the panhypopituitarism identified using the triple-bolus test, thyroxin and hydrocortisone treatment was started. Endoscopic TSS showed xanthochromic and serous fluid containing a whitish pulpy substance in the cyst. The thick and fibrous lining of the capsule was peeled away from the dura mater and the dead space was filled with adipose tissue. The visual field deficit remained despite sufficient decompression of the optic apparatus. Pathologically, the removed tissue was composed of

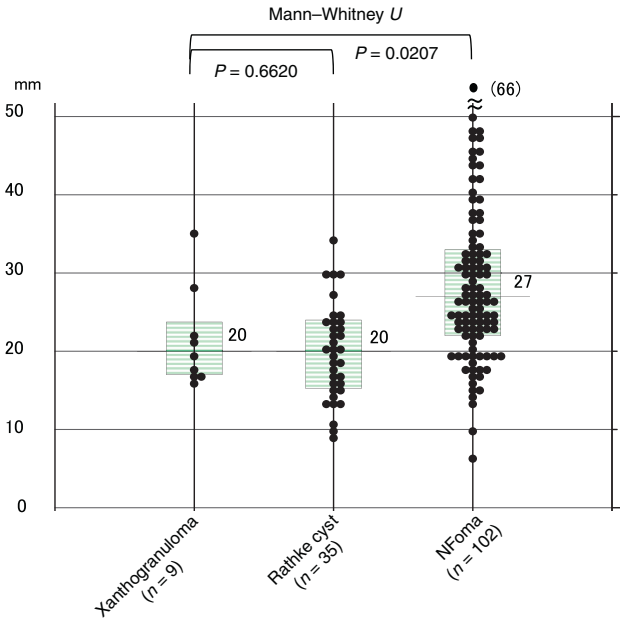


**Figure 1.** Comparison of sizes of xanthogranulomas, Rathke cleft cysts, and nonfunctioning pituitary adenomas (NFomas). The sizes of xanthogranulomas resembled those of Rathke cysts but are significantly smaller than those of nonfunctioning pituitary adenomas ($P = 0.0207$).

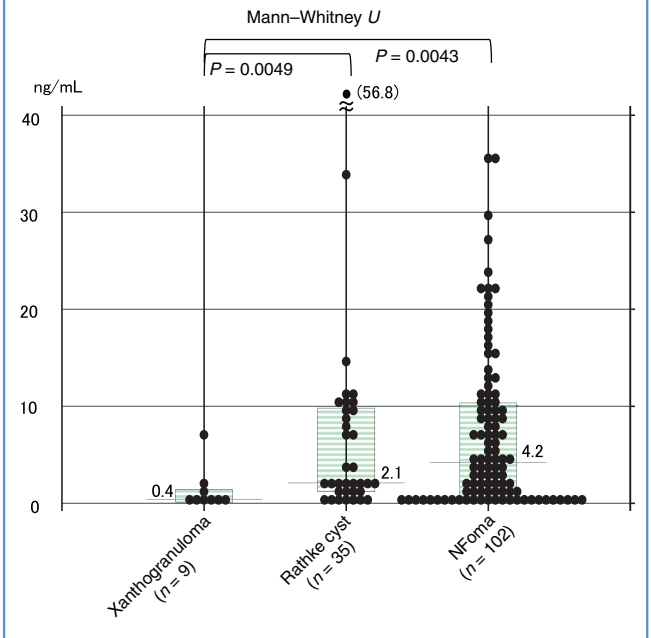


**Figure 2.** Comparison of peak growth hormone level during triple-bolus test in xanthogranulomas, Rathke cleft cysts, and nonfunctioning pituitary adenomas (NFomas). Peak growth hormone levels in xanthogranulomas are significantly lower than those in Rathke cysts and nonfunctioning pituitary adenomas ($P = 0.0049$ and $P = 0.0043$, respectively).

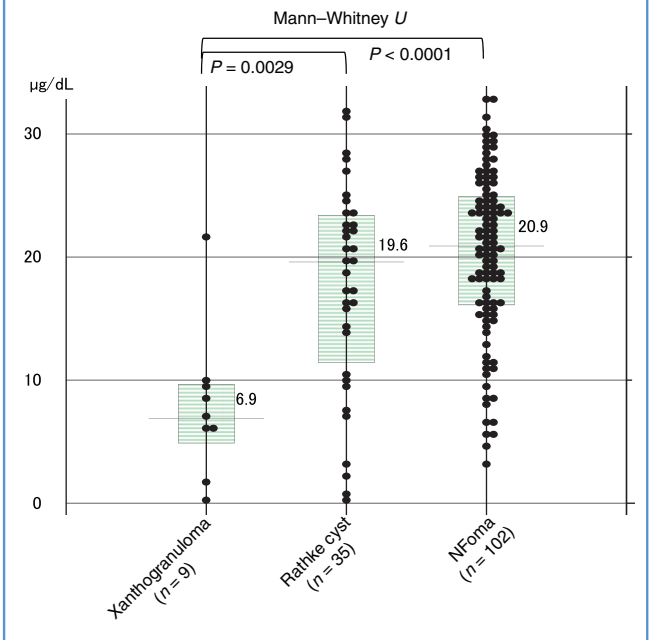


**Figure 3.** Comparison of peak cortisol level during triple-bolus test in xanthogranulomas, Rathke cleft cysts, and nonfunctioning pituitary adenomas (NFomas). Peak cortisol levels in xanthogranulomas are significantly lower than those in Rathke cysts and nonfunctioning pituitary adenomas ($P = 0.0029$ and $P < 0.0001$, respectively).

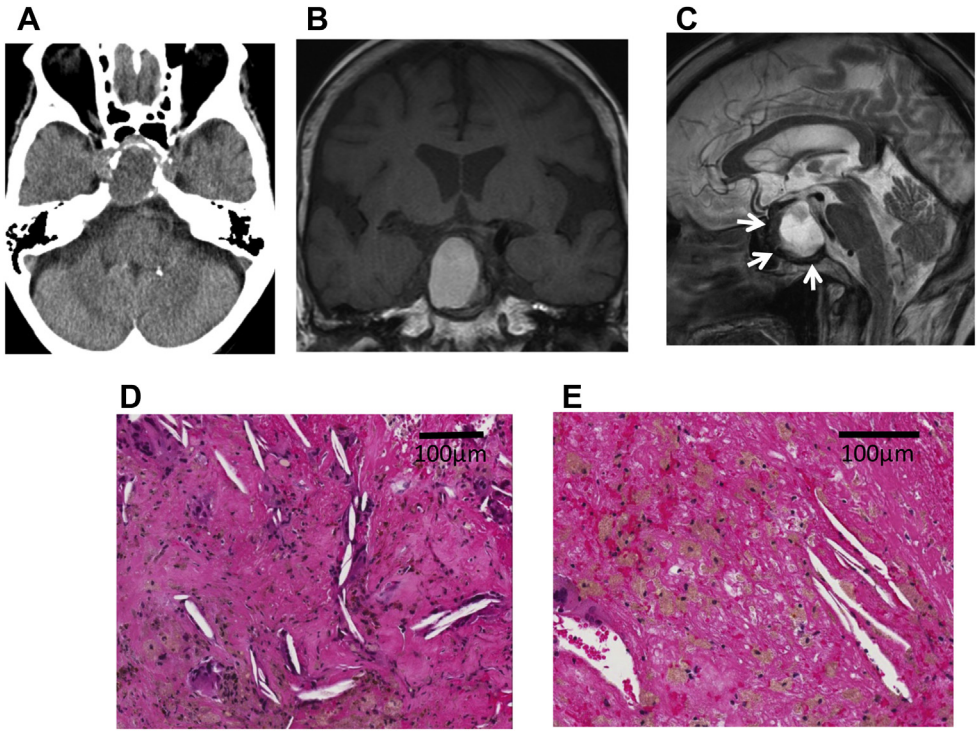


**Figure 4.** A 73-year-old woman presented with left visual field deficit. Computed tomography (CT) showed an enlarged sella turcica containing isodense cystic content and partial calcification in the periphery of the lesion (**A**). The cystic content was hyperintense on both (**B**) T1-weighted and (**C**) T2-weighted magnetic resonance imaging. Extremely low intensity rim was observed on T2-weighted magnetic resonance imaging (*arrows*). Pathologically, the cyst wall was composed of thick collagenous tissue containing cholesterol clefts, giant cells, and hemosiderin (**D, E**).

thick and hemosiderin-laden collagenous tissue containing cholesterol clefts, histiocytes, foamy macrophages, and giant cells.

***Case 2.*** A previously reported 26-year-old man presented with general fatigue, bitemporal hemianopia, and polyuria (Figure 5).[7] Endocrinologic examination showed severe hypopituitarism. MRI showed a clearly defined suprasellar mass, which was heterogeneously enhanced by gadolinium. The mass was extremely hypointense on T2WI. Under the preoperative diagnosis of craniopharyngioma, total surgical removal was achieved. Histologically, the tumor was composed of fibrous tissue including multinucleated giant cells and hemosiderin deposits. Abundant cholesterol clefts were seen in the fibrous tissue. No epithelial cells were identified.

***Case 3.*** A 58-year-old man presented with bitemporal hemianopia and general fatigue (Figure 6). Hormonal examination found diabetes insipidus and panhypopituitarism. CT showed isodense intrasellar to suprasellar lesion. The intrasellar part was hyperintense on T1WI and T2WI, whereas the suprasellar part was hypointense on T2WI. Pituitary tissue removed by endoscopic TSS was found infiltrated by lymphocytes and macrophages, which were surrounded by thick fibrous tissue including many cholesterol clefts. The surgery led to an improvement in his visual field but not in pituitary function.

### Two Cases of Xanthomatous Granulation with Ciliated Epithelia

We experienced 2 other patients presenting with predominant xanthomatous granulation accompanied with ciliated epithelia suggesting Rathke cleft cyst (Figure 7). Both were cystic lesions, hyperintense on T1WI MRI and isointense to hyperintense on T2WI MRI. GH deficiency and hyperprolactinemia were found in both patients. In addition, ACTH deficiency and thyroid-stimulating hormone deficiency were also found in 1 patient.

## DISCUSSION

We report 9 cases of sellar xanthogranuloma presenting with widely varied symptoms but commonly showing severe hypopituitarism.

### Definition and Origin of Sellar Xanthogranuloma

In 1988, Shirataki et al.[4] first reported sellar xanthogranulomas in the Japanese literature, in which they described 4 lesions "composed of pure cholesterol xanthomatous reaction" among the 15 sellar tumors presenting with a xanthomatous reaction. Paulus et al.,[5] in 1999, described sellar xanthogranuloma as an independent entity that is pathologically and clinically different from craniopharyngioma. These investigators found 37 tumors that had a predominately xanthogranulomatous component among 110 craniopharyngiomas, of which 3 showed histologic

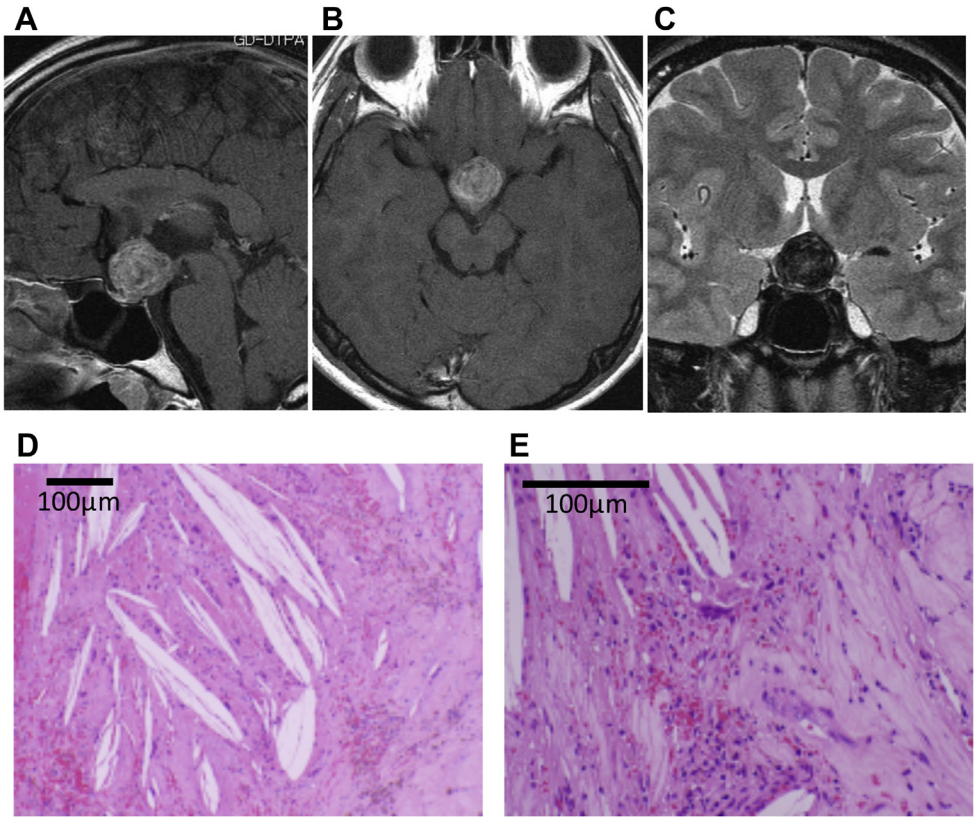


**Figure 5.** A 26-year-old man presented with bitemporal hemianopsia and panhypopituitarism. Postcontrast T1-weighted magnetic resonance imaging showed a heterogeneously enhanced suprasellar round mass (**A, B**), which was markedly hypointense on T2-weighted imaging (**C**). The lesion consisted of fibrous tissue intermingled with cholesterol clefts and hemosiderin deposits (**D**) surrounded by multinucleated giant cells (**E**).

features of adamantinomatous craniopharyngioma and 13 of which showed a nonadamantinomatous epithelium. Paulus et al. suggested that these lesions may form a part of the spectrum of craniopharyngioma. Other investigators also considered the presence of squamous epithelium in xanthogranulomas and rare calcifications indicated that they arise from adamantinomatous craniopharyngiomas.[3,8] Two of our 9 xanthogranulomas were solely contained in the suprasellar region, without intrasellar component, strongly suggesting that the lesion arose from a suprasellar craniopharyngioma.

Le et al.[9] reported that xanthomatous change was frequently observed (46%) in 28 Rathke cleft cysts and suggested that the changes showed a secondary inflammation in Rathke cleft cysts. Amano et al.[10] studied 7 sellar lesions with predominant xanthogranulomatous inflammation among 123 Rathke cleft cysts and 51 craniopharyngiomas. These investigators found components of Rathke cyst in 6 of 7 sellar xanthogranulomas. In Rahmani et al.'s[3] review of the literature, 29 of the 72 cases of xanthogranulomatous lesions in the parasellar region had some form of epithelium consistent with Rathke cleft cyst. Duan et al.[11] found the pathologic evidence of the ruptured Rathke cyst in 6 of their 7 patients with xanthomatous hypophysitis. Recently, a giant sellar xanthogranuloma, which developed from a Rathke cleft cyst partially removed 2 years previously, was reported.[12] The 2 lesions of predominant xanthogranulomatous chronic inflammation accompanied with ciliated epithelia presented here seem to be on a spectrum from subacute inflammation in Rathke cleft cyst to xanthogranuloma. Rathke cleft cyst often shows acute or chronic inflammation, which is supposed to be triggered by the leakage of cystic content or hemorrhage.[13-18] Therefore, the evidence strongly suggests that most sellar xanthogranulomas arise secondarily from an inflammatory reaction in Rathke cleft cyst.[1,3,9,11]

Nishioka et al. histologically found a reaction in 5 patients (2.2%) with 231 consecutive pituitary adenomas treated surgically. These investigators suggested that a xanthogranulomatous reaction could develop as a reaction to a hemorrhagic event in pituitary macroadenomas.[19]

Thus, xanthogranuloma is the last stage of chronic and repeated inflammation, which has overwhelmed the original disease, such as Rathke cyst or craniopharyngioma,[1] and possibly the pituitary adenoma.[19]

Here, we apply the term sellar xanthogranuloma only to the lesions without an epithelial component to identify the clinical

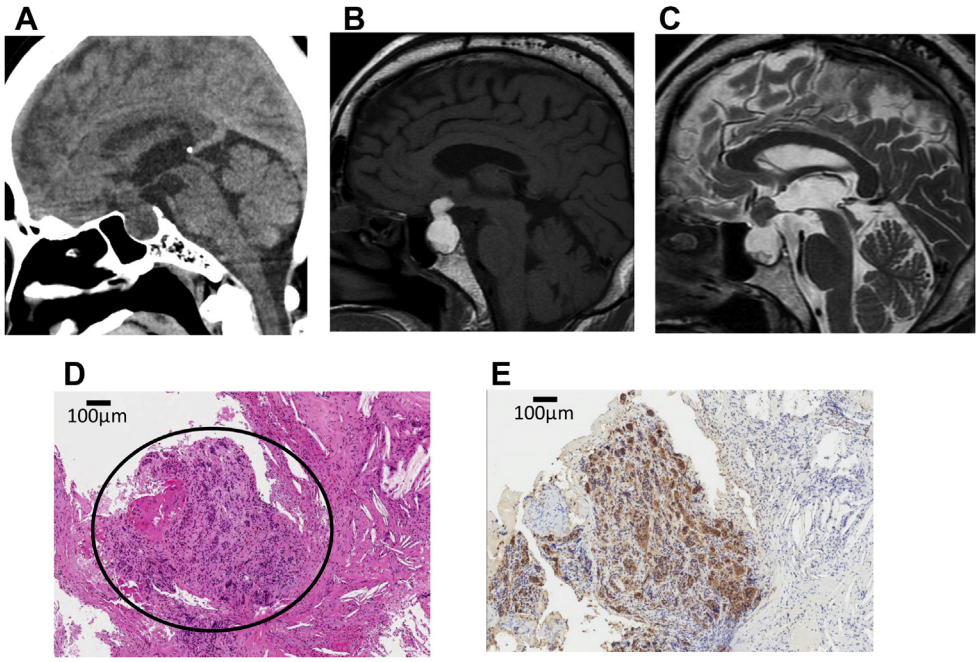


**Figure 6.** A 58-year-old man presented with bitemporal hemianopia and general fatigue. Computed tomography showed isodense intrasellar to suprasellar lesion (**A**). The intrasellar part was hyperintense on T1-weighted and T2-weighted imaging (**B, C**), whereas the suprasellar part was hypointense on T2-weighted imaging (**C**). Pituitary tissue encircled in (**D**), positive for growth hormone (**E**), and infiltrated by lymphocytes and macrophages was surrounded by thick fibrous tissue including numerous cholesterol clefts (**D**).

features of this extreme stage of chronic inflammation. Therefore, the additional 2 cases we presented must be classified as Rathke cleft cyst with severe inflammation caused by the presence of ciliated epithelia, which seems to be in the final process to xanthogranuloma.

## Epidemiology

The reported incidence of sellar xanthogranuloma varied from 0.6% to 3%,[3,12,20-23] in agreement with our series (i.e., 1.7%). Reported female preponderance was also consistent with our data (7:2).[20,22] In a literature review of 27 sellar xanthogranulomas, the mean age was 36.6 years[20]; however, it may affect any generation,[3,19] because the mean ± SD was 52.4 ± 16.2 in our series. Considering that a sellar xanthogranuloma is a transformation of the Rathke cleft cyst, it is reasonable to assume that its mean age is essentially similar to that of Rathke cleft cyst in our series (50.1 ± 16.8 SD; $n = 35$).

## Clinical Presentation

Common presenting features of sellar xanthogranuloma included headache, visual disturbance, diabetes insipidus, and anterior pituitary dysfunction. It may present with oculomotor paresis,[10] but unique signs and symptoms for the entity have not been reported.[3,20,22,23]

The visual symptoms usually improved postoperatively in the reported series.[3,20,21,23] Improvement of the visual function was observed in 3 patients (50%) in our series. The postoperative improvement ratio of visual field was 83% and visual acuity was 64% in 124 nonfunctioning pituitary adenomas with preoperative visual impairment (data not published). The relatively low improvement ratio in sellar xanthogranuloma may be caused by irreversible inflammatory damage on optic nerve and chiasm and severe inflammatory adhesion between the lesion and the surrounding neurovascular structures.[12,23]

## Pituitary Function

Symptoms of endocrinologic deficit are common in sellar xanthogranuloma. Hernández-Estrada et al.[20] reported that panhypopituitarism was found in 74% of patients in their review. Amano et al.[10] reported that 86% of patients with sellar xanthogranuloma presented with anterior pituitary deficiency involving 2–6 axes. Its persistence after surgical decompression has also been reported previously.[22]

The advantage of this study is that we preoperatively and postoperatively performed triple-bolus provocation tests in all patients, which has not commonly been conducted in previous studies, to identify the exact degree of anterior pituitary dysfunction. We also compared the results of the tests with those in Rathke cleft cysts and nonfunctioning pituitary adenomas to elucidate the magnitude and mechanism of pituitary insufficiency in xanthogranulomas.

The pituitary provocation test showed impairment of ≥1 hormonal axis in all 9 patients, with the impairment ratio of GH and ACTH-cortisol being as high as 89%. Considering the significantly

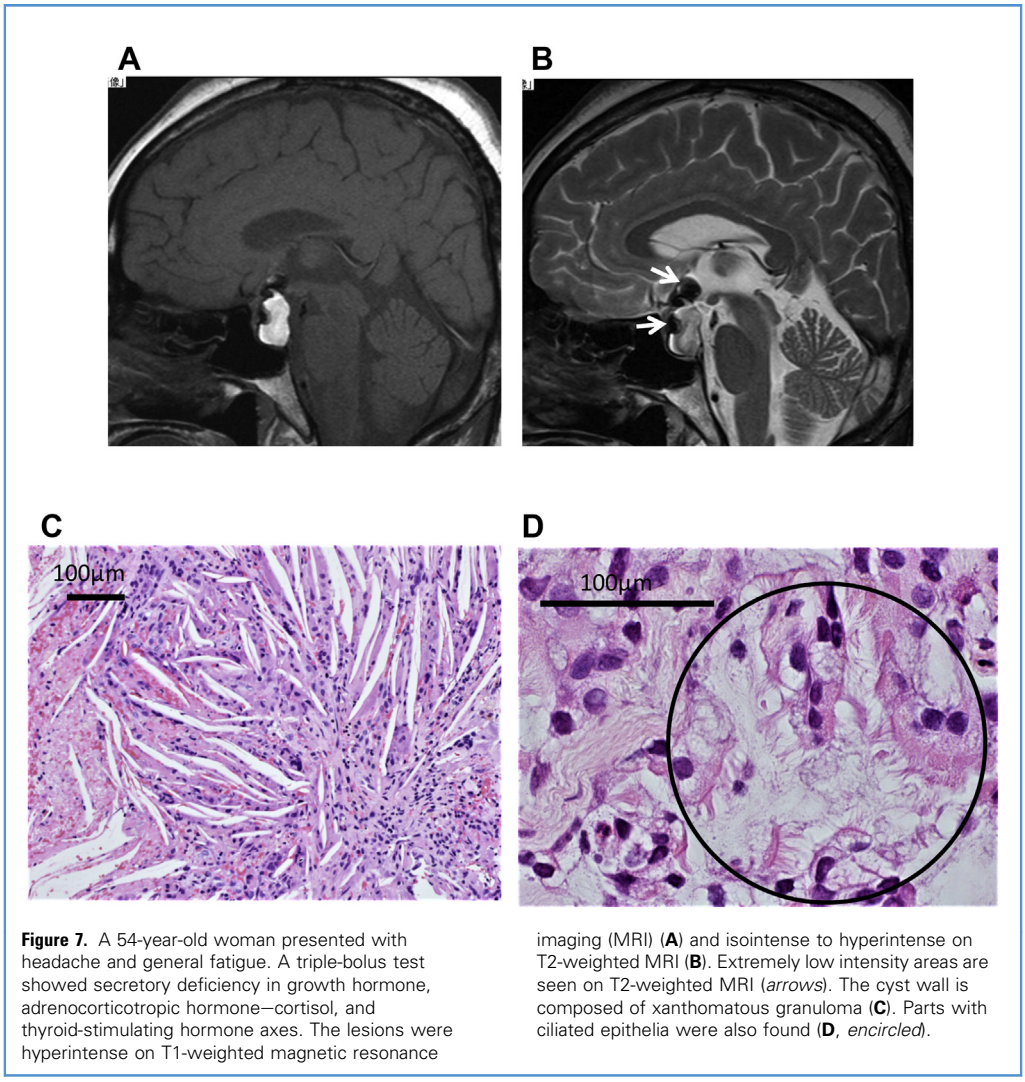


**Figure 7.** A 54-year-old woman presented with headache and general fatigue. A triple-bolus test showed secretory deficiency in growth hormone, adrenocorticotropic hormone—cortisol, and thyroid-stimulating hormone axes. The lesions were hyperintense on T1-weighted magnetic resonance imaging (MRI) (**A**) and isointense to hyperintense on T2-weighted MRI (**B**). Extremely low intensity areas are seen on T2-weighted MRI (*arrows*). The cyst wall is composed of xanthomatous granuloma (**C**). Parts with ciliated epithelia were also found (**D**, *encircled*).

small size and severe impairment of GH and cortisol responses to a triple-bolus test compared with nonfunctioning pituitary adenoma, the impairment of pituitary function by xanthogranuloma does not seem to be caused by the compression by the lesion but by hypophyseal inflammation. Compared with Rathke cleft cyst, which is similar in size, xanthogranuloma still showed a significantly lower response of GH and cortisol to the triple-bolus test. Thus, severe hypopituitarism in a small lesion may hint at xanthogranuloma rather than at cystic pituitary adenoma or Rathke cleft cyst.

Diabetes insipidus is also a common clinical symptom, seen in 67% of patients in our series, which is rarely presented in pituitary adenoma and Rathke cleft cyst. This situation could be result from severe inflammatory destruction of the posterior pituitary.

## Preoperative Diagnosis

Location of the lesion was purely intrasellar in 3 patients (11%), suprasellar in 6 (22%), and both intrasellar and suprasellar in 18 (67%) according to a previous review,[20] which is comparable to our results (22.2%, 22.2%, and 55.6%, respectively).

Neuroimaging evidence to differentiate xanthogranuloma from other cystic sellar lesion is desirable but difficult to obtain, because it falls in the spectrum of chronic inflammations of the Rathke cleft cyst and other neoplasms.[20] T1 hyperintensity, reflection of cholesterol component,[24,25] was frequently seen in previously reported series as well as in ours (33%).[10,20,22,26] Extremely low intensity on T2WI and T1WI, which may correspond to hemosiderin, dense fibrous tissue, and paramagnetic free radical—laden macrophages,[22,25,27] was seen in our 4 cases. Enhancement of cyst wall is common in xanthogranuloma[10,22,23] and is rarely and partially present in Rathke cleft cyst unaccompanied with inflammation.[24,28,29]

Although there was no pathognomonic neuroimaging appearance, presence of hyperintense cystic content on T1WI, very low intense area on T2WI, cyst wall enhancement, and profound impairment of pituitary function inconsistent with the

size of the lesion may lead to the preoperative diagnosis of sellar xanthogranuloma.

### Treatment

Even although gross total resection was achieved in only 64% of 27 patients in Hernández- Estrada et al.'s review,[20] recurrence was seen in only 1 case, suggesting that the lesion is essentially indolent. In our series, recurrence was not observed during 47 months (median) follow-up after subtotal or partial removal, excepting 1 total removal. Considering that xanthogranuloma is the last stage of chronic and repeated inflammation and endocrinopathy was caused by the hypophysitis but not mass effect, the primary aim of surgery should be decompression of the optic apparatus. Decompression of the pituitary stalk may lead to improvement of pituitary function in some cases.

In addition, as we suggested in a previous report,[14] if endocrinologic examination indicates the presence of hypophysitis in a patient with asymptomatic Rathke cleft cyst, early intervention could be justified to prevent further progression of inflammation resulting in a total xanthogranulomatous change.

## CONCLUSIONS

Xanthogranuloma is supposed to be the last stage of chronic inflammation affecting Rathke cleft cyst in most instances and craniopharyngioma in some cases, which may have overwhelmed the entire lesion. Postsurgical recurrence is rare, but reversal of the pituitary hormonal dysfunction was rarely observed. We hope that future prospective studies will elucidate the significance of early surgical intervention for asymptomatic Rathke cleft cyst with anterior pituitary dysfunction.

## REFERENCES

1. Kleinschmidt-DeMasters BK, Lillehei KO, Hankinson TC. Review of xanthomatous lesions of the sella. *Brain Pathol*. 2017;27:377-395.
2. Buslei R, Rushing EJ, Giangaspero F, Paulus W, Burger PC. Craniopharyngioma. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. *IARC WHO Classification of Tumours*. 4th ed. New York, NY: IARC; 2007:324-328.
3. Rahmani R, Sukumaran M, Donaldson AM, Akselrod O, Lavi E, Schwartz TH. Parasellar xanthogranulomas. *J Neurosurg*. 2015;122:812-817.
4. Shirataki K, Okada S, Matsumoto S. Histopathological study of the "cholesterol granuloma reaction" in the sellar and juxta-sellar tumors. *No To Shinkei*. 1988;40:133-139.
5. Paulus W, Honegger J, Keyvani K, Fahlbusch R. Xanthogranuloma of the sellar region: a clinicopathological entity different from adamantinomatous craniopharyngioma. *Acta Neuropathol*. 1999;97:377-382.
6. Melmed S, Kleinberg D. Anterior pituitary. In: Melmed S, Polonsky K, Larseneds PR, eds. *Williams Textbook of Endocrinology*. 11th ed. Philadelphia, PA: Saunders; 2008:241.
7. Sugata S, Hirano H, Yatsushiro K, Yunoue S, Nakamura K, Arita K. Xanthogranuloma in the suprasellar region. *Neurol Med Chir (Tokyo)*. 2009;49:124-127.
8. Burger PC, Scheithaeur BW, Vogel FS. *Surgical Pathology of the Nervous System and Its Coverings*. 3rd ed. New York, NY: Churchill Livingstone; 1991:537-545.
9. Le BH, Towfighi J, Kapadia SB, Lopes MB. Comparative immunohistochemical assessment of craniopharyngioma and related lesions. *Endocr Pathol*. 2007;18:23-30.
10. Amano K, Kubo O, Komori T, et al. Clinicopathological features of sellar region xanthogranuloma: correlation with Rathke's cleft cyst. *Brain Tumor Pathol*. 2013;30:233-241.
11. Duan K, Asa SL, Winer D, Gelareh Z, Gentili F, Mete O. Xanthomatous hypophysitis is associated with ruptured Rathke's cleft cyst. *Endocr Pathol*. 2017;28:83-90.
12. Cho SM, Cho HR, Park YS, Chang HG. Giant sellar xanthogranuloma after surgical treatment of symptomatic Rathke's cleft cyst. *Brain Tumor Res Treat*. 2018;6:82-85.
13. Hama S, Arita K, Tominaga A, et al. Symptomatic Rathke's cleft cyst coexisting with central diabetes insipidus and hypophysitis: case report. *Endocr J*. 1999;46:187-192.
14. Hama S, Arita K, Nishisaka T, et al. Changes in the epithelium of Rathke cleft cyst associated with inflammation. *J Neurosurg*. 2002;96:209-216.
15. Komatsu F, Tsugu H, Komatsu M, et al. Clinicopathological characteristics in patients presenting with acute onset of symptoms caused by Rathke's cleft cysts. *Acta Neurochir (Wien)*. 2010;152:1673-1678.
16. Macaulay RJ. Ruptured Rathke's cleft cyst: a possible cause of Tolosa-Hunt syndrome. *Clin Neuropathol*. 1997;16:98-102.
17. Roncaroli F, Bacci A, Frank G, Calbucci F. Granulomatous hypophysitis caused by a ruptured intrasellar Rathke's cleft cyst: report of a case and review of the literature. *Neurosurgery*. 1998;43:146-149.
18. Wearne MJ, Barber PC, Johnson AP. Symptomatic Rathke's cleft cyst with hypophysitis. *Br J Neurosurg*. 1995;9:799-803.
19. Nishioka H, Shibuya M, Ohtsuka K, Ikeda Y, Haraoka J. Endocrinological and MRI features of pituitary adenomas with marked xanthogranulomatous reaction. *Neuroradiology*. 2010;52:997-1002.
20. Hernández-Estrada RA, Kshettry VR, Vogel AN, Curtis MT, Evans JJ. Cholesterol granulomas presenting as sellar masses: a similar, but clinically distinct entity from craniopharyngioma and Rathke's cleft cyst. *Pituitary*. 2017;20:325-332.
21. Petrakakis I, Pirayesh A, Krauss JK, Raab P, Hartmann C, Nakamura M. The sellar and suprasellar region: a "hideaway" of rare lesions. Clinical aspects, imaging findings, surgical outcome and comparative analysis. *Clin Neurol Neurosurg*. 2016;149:154-165.
22. Ved R, Logier N, Leach P, Davies JS, Hayhurst C. Pituitary xanthogranulomas: clinical features, radiological appearances and post-operative outcomes. *Pituitary*. 2018;21:256-265.
23. Yang B, Yang C, Fang J, et al. Clinicoradiologic features and surgical outcomes of sellar xanthogranulomas: a single-center 10-year experience. *World Neurosurg*. 2017;99:439-447.
24. Kunii N, Abe T, Kawamo M, Tanioka D, Izumiyama H, Moritani T. Rathke's cleft cysts: differentiation from other cystic lesions in the pituitary fossa by use of single-shot fast spin-echo diffusion-weighted MR imaging. *Acta Neurochir (Wien)*. 2007;149:759-769.
25. Nishiuchi T, Murao K, Imachi H, et al. Xanthogranuloma of the intrasellar region presenting in pituitary dysfunction: a case report. *J Med Case Rep*. 2012;29:119.
26. Burt MG, Morey AL, Turner JJ, Pell M, Sheehy JP, Ho KK. Xanthomatous pituitary lesions: a report of two cases and review of the literature. *Pituitary*. 2003;6:161-168.
27. Schwartz KM, Erickson BJ, Lucchinetti C. Pattern of T2 hypointensity associated with ring-enhancing brain lesions can help to differentiate pathology. *Neuroradiology*. 2006;48:143-149.
28. Nishioka H, Haraoka J, Izawa H, Ikeda Y. Magnetic resonance imaging, clinical manifestations, and management of Rathke's cleft cyst. *Clin Endocrinol (Oxf)*. 2006;64:184-188.
29. Sumida M, Uozumi T, Mukada K, Arita K, Kurisu K, Eguchi K. Rathke cleft cysts: correlation

of enhanced MR and surgical findings. AJNR Am J Neuroradiol. 1994;15:525-532.

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