Original Article

Two Children with Xanthogranuloma of the Sellar Region

Toshihiro Tajima¹, Yutaka Sawamura², Katsura Ishizu¹ and Jyunko Tsubaki¹

¹Department of Pediatrics, Hokkaido University School of Medicine, Sapporo, Japan
²Department of Neurosurgery, Hokkaido University School of Medicine, Sapporo, Japan

Abstracts. We report the cases of two Japanese children with cystic pituitary enlargement on magnetic resonance imaging (MRI) causing central diabetes insipidus (DI). In the first patient, endocrinological examination demonstrated slightly impaired growth hormone and thyroid stimulating hormone secretions, but normal responses of other anterior pituitary hormones. The second patient had normal basal levels of anterior pituitary hormones. Transsphenoidal resection of the tumors was performed in both patients. Histological analysis of the tumor sections demonstrated granulomatous tissue with cholesterol clefts, foamy macrophages, multinucleated giant cells and no epithelial component. Thus, these tumors were pathologically diagnosed as xanthogranuloma of the sellar region, different from adamantinomatous craniopharyngioma. Post-operatively, the two patients continue to have DI, however other hormone replacement therapy after one year of follow-up has not been required. Currently, it is not clear whether xanthogranuloma is a distinct entity from adamantinomatous craniopharyngioma. Although, to our knowledge, a clinical report of xanthogranuloma of the sellar region has not been reported at pediatric age, it would be included in the differential diagnosis of the sellar region.

Key words: xanthogranuloma, craniopharyngioma, pituitary

Introduction

Pituitary insufficiency in childhood is often secondary to pituitary or hypothalamic space-occupying lesions. The differential diagnosis in etiologies of a mass in the sella is broad in spectrum, including Rathke’s cyst, tumor, autoimmune diseases, primary or metastatic neoplasms, and granulomatous inflammation. Among them, xanthomatous pituitary diseases are rare in childhood. These conditions include xanthomatous hypophysitis, xanthogranulomatous hypophysitis and xanthogranuloma of the sellar region (1–5). Xanthogranuloma of the sellar region is characterized by a granulomatous lesion containing cholesterol clefts, macrophages, chronic inflammatory infiltrates, and hemosiderin deposit (6). This condition has been traditionally regarded as a hallmark of the adamantinomatous craniopharyngioma even in the absence of epithelium (6). However, Paulus et al. (7) suggested that xanthogranuloma is likely to constitute a different entity from the classical adamantinomatous craniopharyngioma clinically and pathologically. After their original report, several patients with xanthogranuloma of the
sellar region have been described (8, 9). However, to our knowledge, there is no detailed clinical report of xanthogranuloma of the sellar region in cases of pediatric age. Here, we report the cases of two children with xanthogranuloma of the sellar region, presenting central diabetes insipidus (DI).

**Case Reports**

**Case 1**

A 9-yr-old Japanese boy was referred to our clinic because of a 6-mo history of polyuria and polydipsia. He had no headache, vomiting or fever. On admission, his height was 135.3 cm (+0.7 SD) and body weight 29.9 kg. Physical examination was unremarkable. Ophthalmologic evaluation revealed no visual field disturbance. Daily urine output was 4000–5000 ml. Endocrine findings are shown in the Table. The growth hormone (GH) releasing hormone (GHRH) and the thyroid stimulating hormone releasing hormone (TRH) tolerance tests showed subnormal responses of GH and TSH, respectively (Table 1). The corticotropin releasing hormone (CRH) tolerance test showed normal responses

**Table 1**  Endocrinological findings of Cases 1 and 2

|                     | Case 1 |          | Case 2 |          | Normal range |
|---------------------|--------|----------|--------|----------|--------------|
|                     | before | after*   | before | after**  |              |
| free T4 (ng/dl)     | 0.77   | 1.25     | 1.27   | 1.61     | 1.24–1.78    |
| free T3 (pg/ml)     | 2.67   | 3.12     | 4.06   | 3.24     | 2.16–3.67    |
| TSH (µU/ml)         |        |          |        |          |              |
|         Basal       | 1.62   | 1.14     | 1.24   | 3.13     | 0.34–3.78    |
|         TRH-stimulated | 6.66  | 10.77    | ND     | 9.85     | >10          |
| IGF-1 (ng/ml)       | 187.8  | 164.3    | 136.9  | 145.0    | 64–203 (age 5 to 7) |
|                     |        |          |        |          | 50–356 (age 7 to 9) |
| GH (ng/ml)          |        |          |        |          |              |
|         Basal       | 2.81   | 0.36     | 0.11   | ND       | 0.5 0.61     |
|         GHRH-stimulated | 10.2  | 19.2     | ND     | 42.9     | >15 (peak value) |
|         Arginine tolerance | 9.8   | ND       | 18.4   |          | >10 (peak value) |
| LH (mIU/ml)         |        |          |        |          |              |
|         Basal       | <2.0   | <2.0     | ND     | <2.0     | <2.0         |
|         GnRH-stimulated | <2.0  | <2.0     | ND     | <2.0     | <2.0 (prepubertal stage) |
| FSH (mIU/ml)        |        |          |        |          |              |
|         Basal       | 1.6    | 1.2      | ND     | 1.2      | 0.3–4.0      |
|         GnRH-stimulated | 9.0   | 4.9      | ND     | 6.1      | 4.3–9.4 (prepubertal stage) |
| ACTH (pg/ml)        |        |          |        |          |              |
|         Basal       | 40.82  | 33.2     | 78.3   | 33.2     | 9.2–25.3     |
|         CRH-stimulated | 194.1 | 89.21    | ND     | 86.4     | 17.5–135.1   |
| Cortisol (µg/dl)    |        |          |        |          |              |
|         Basal       | 21.1   | 11.2     | 12.3   | 12.1     | 6.2–18.2     |
|         CRH-stimulated | 45.2  | 25.5     | ND     | 24.1     | 13.1–35.6    |

*, Endocrinological evaluation was performed two months after surgery. **, Endocrinological evaluation was performed one month after surgery. ND, Not determined.
of ACTH and serum cortisol (Table 1). Magnetic resonance imaging (MRI) revealed an intrasellar mass with well-defined borders (Fig. 1). The mass was hyperintense on the T1-weighted (Fig. 1A) and T2-weighted images (Fig. 1B). The posterior pituitary bright signal was absent in the T1-weighted images. Gadolinium administration caused no enhancement of the mass. The pituitary stalk deviated to the frontal direction and the anterior pituitary gland was compressed by the tumor. There was no calcification of the mass detected by computed tomographic (CT) scan. Rathke’s cyst was suspected preoperatively by the MRI findings, however a definite diagnosis could not be made. The tumor was resected by transsphenoidal surgery. The capsule of the tumor had tightly adhered to the dura of the sellar floor. A tense cystic lesion contained yellow fluid. Histological examination of the tumor showed fibrous tissue with cholesterol clefts, macrophages, multinucleated giant cells, and lymphocyte infiltration (Fig. 2). There was no epithelial tissue. Thus, the pathological findings fit the category of xanthogranuloma. Postoperatively, DI remains and has been treated with desmopressin acetate (DDAVP). Two months after surgery, GH and TSH responses after stimulation tests recovered (Table 1). An 8-mo postoperative MRI was normal. After one-year follow-up, the patient continues to have DI, but his basal levels of IGF-1, fT3, fT4 and TSH are within normal ranges.

Case 2

A 6-yr-old Japanese boy was admitted to our
hospital for evaluation of polyuria and polydipsia of 6-mo duration. He showed no other manifestations such as headache, vomiting or growth failure. Neurological and visual examinations revealed no abnormalities. His height was 113.2 cm (–0.8 SD) and body weight was 18.8 kg. Endocrine findings are shown in the Table. Brain MRI showed an intrasellar mass, which was high on the T1-weighted (Fig. 3A) and hypointense on the T2-weighted images (Fig. 3B). The posterior pituitary bright signal was diminished in the T1-weighted images. Gadolinium administration did not enhance the mass. The pituitary stalk deviated to the right side. A compressed anterior pituitary gland was detected under the tumor. CT scan did not detect calcification of the mass. Transsphenoidal surgery was performed. A brownish partially fibrous and partially cystic thick-walled mass was found. The intrasellar tumor was completely removed. Histological analysis revealed cholesterol clefts and macrophages, and lymphocyte infiltration (Fig. 4 A, B). Thus, the pathological diagnosis of xanthogranuloma was made. GHRH, TRH, and CRH tolerance tests showed normal responses one month after surgery (Table 1). The patient is currently well only on DDAVP medication, 12 mo after surgery. He does not need any other pituitary hormone replacement.

Discussion

We report the cases of two children with xanthogranuloma in the pituitary region with DI. Xanthogranuloma in the sellar region has been traditionally considered to be a variant of adamantinomatous craniopharyngioma despite the lack of epithelium (6). However, Paulus et al. (7) reviewed histological sections of 110 patients diagnosed with craniopharyngioma and found sections from 37 patients were exclusively or predominantly composed of xanthogranulomatous tissue. According to their study, pathological findings were characterized by cholesterol clefts (100%), macrophages infiltrates, lympho-plasmacellular infiltrates (100%), marked hemosiderin deposits (97%), fibrosis (87%), and foreign-body giant cells around cholesterol clefts (86%). Only sections
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Fig. 3 Radiological appearance on MRI. The mass had a high appearance on the T1-weighted images (A). T2-weighted image showed a hypointense mass (B). Gadolinium administration caused no enhancement of the mass.

Fig. 4 Histological findings of the tumor in Case 2. (A) Cholesterol clefts (arrows) were observed. (B) Macrophages (black arrowheads) were observed. × 200.
from 3 of these patients had small adamantinomatous components (corresponding to calcifying odontogenic cyst), which are histological features of adamantinomatous craniopharyngioma. Based on these findings, Paulus et al. suggested that xanthogranuloma of the sellar region is pathologically distinct from adamantinomatous craniopharyngioma. In our two patients, histological findings of cholesterol clefts, macrophages including cholesterol droplets, multinucleated giant cells, lymphocytes, and the absence of adamantinomatous components are consistent with those previously reported by Paulus et al. (7).

Clinically, xanthogranuloma in the sellar region has been reported to cause severe endocrinological deficits (7). Yonezawa et al. (9) also described one adult Japanese patient with xanthogranuloma in the pituitary showing panhypopituitarism. By contrast, our patients did not have severe defects of anterior pituitary hormones and showed only central DI. In the first report, xanthogranuloma of the pituitary in children was reported, but the frequency in children, and the clinical and endocrinological findings were not mentioned (7). To answer whether clinical manifestations of xanthogranuloma in children are different from those of adults, more patients with xanthogranuloma of pediatric age must be studied.

If xanthogranuloma is different form adamantinomatous craniopharyngioma, what is the origin of xanthogranuloma in the sellar region? Xanthogranulomatous inflammation (also known as cholesterol granuloma) has been reported in various tissues such as the middle ear, mastoid, and choroid plexus. Xanthogranuloma of the choroid plexus has been related to hemorrhage (10). Also the obstruction of the gall flow has been considered to cause inflammation, eventually developing to xanthogranulomatous cholecystitis (11). In addition, it is suggested that Rathke's cyst and neuroepithelial cyst may undergo xanthogranulomatous changes (12, 13). Taken together, xanthogranuloma of the sellar region is likely to represent a non-specific tissue reaction to hemorrhage or degenerative changes originating from heterogeneous etiologies. It may be plausible that xanthogranulomas of our patients were responses to ruptured cysts, however, no confirmation of pre-existing cysts has been identified. Any attempt to characterize this entity based on our cases would be speculative.

Xanthogranuloma is difficult to differentiate from craniopharyngioma and Rathke's cyst by MRI findings. MRI findings of craniopharyngioma demonstrate significant variability. Cystic and solid lesions may have any pattern of signal intensity on the T1 and T2-weighted images, although most often they are hypointense to isointense on the T1-weighted images and hyperintense on the T2-weighted images. Cystic lesions tend to be brighter on the T2-weighted images than solid lesions. On CT, craniopharyngiomas typically appear as moderate-to-large, partially calcified mass. Rathke's cysts are present as intrasellar masses. As with craniopharyngiomas, the signal characteristics are variable on the T1 and T2-weighted images due to the variable quality of the cyst fluid. In our two patients, xanthogranuloma showed hyperintense on the T1-weighted images of MRI. Previously, two reports have also described xanthogranuloma as hyperintense on T1-weighted images (8, 9). In addition, there was no calcification of masses in our patients, as well as in previous reports (8, 9). These points may be helpful in considering xanthogranuloma of the pituitary region. However, there is no reliable way to distinguish xanthogranuloma from craniopharyngioma and Rathke's cyst without histological examination.

In conclusion, we report the cases of two children with xanthogranuloma in the sellar region. Currently, whether this condition is a
true distinct entity or merely a different manifestation of adamantinomatous craniopharyngioma is unclear. To clarify the natural history, pathogenesis and prognosis in childhood, further accumulation of well-characterized pediatric cases with xanthogranuloma will be necessary.

References

1. Shirataki K, Okada S, Matsumoto H. Histopathological study of the cholesterol granuloma reaction in the sellar and juxtasellar tumors. No to Shinkei 1988;40:133–9 (in Japanese).
2. Folkerth RD, Price DL, Schwartz M, Black PM, De Girolami U. Xanthomatous hypophysitis. Am J Surg Pathol 1998;22:736–41.
3. Cheung CC, Ezzat S, Smith HS, Asa SL. The spectrum and significance of primary hypophysitis. J Clin Endocrinol Metab 2001;86:1048–53.
4. Reithmeier T, Trost HA, Wolf S, Stolzle A, Feiden W, Lumenta CB. Xanthogranuloma of the Erdheim-Chester type within the sellar region: a case report. Clin Neuropathol 2002;21:24–8.
5. 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;6:161–8.
6. Burger PC, Scheithauer BW, Vorgel FS. Surgical pathology of the nervous system and its coverings. 3rd ed. New York; Churchill Livingstone, 1991.
7. Paulus W, Honegger J, Keyvani K, Fahlbusch R. Xanthogranuloma of the sellar region: a clinicopathological entity different from adamantinomatous craniopharyngioma. Acta Neuropathol (Berl) 1999;97:377–82.
8. Vaitai I, Kopniczky Z, Buza Z, Kovacs J, Kovacs Z, Varga Z, et al. Cholesterol granuloma at the sellar region: a new method of the differential diagnosis of craniopharyngioma. Orv Hetil 2001;142:451–7.
9. Yonezawa K, Shirataki K, Sakagami Y, Kohmura E. Panhypopituitarism induced by cholesterol granuloma in the sellar region-case report. Neurol Med Chir (Tokyo) 2003;43:259–62.
10. Muenchau A, Laas R. Xanthogranuloma and xanthoma of the choroid plexus: evidence for different etiology and pathogenesis. Clin Neuropathol 1997;16:72–6.
11. Ladefoged C, Lorentzen M. Xanthogranulomatous cholecystitis. A clinicopathological study of 20 cases and review of the literature. APMIS 1993;101:869–75.
12. Hadfield MG, Ghatak NR, Wanger GP. Xanthogranulomatous colloid cyst of the third ventricle. Acta Neuropathol (Berl) 1985;66:343–6.
13. Schwartz AM, Jensen ME, Saks DA, Ghatak NR. Epithelial cyst in cerebellopontine angle with xanthogranulomatous changes simulating cholesterol granuloma. Surg Neurol 1989;31:451–8.