Adolescent Physiological Pituitary Gland Hypertrophy Transformed into a Prolactin-secreting Macroadenoma in Early Adulthood

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The concept of physiological pituitary gland hypertrophy is well recognized in settings of increased physiological needs, such as pregnancy and puberty. However, it is very uncommon for it to transform into a neoplastic pituitary lesion in the form of a functioning or non-functioning pituitary adenoma. In this case report, we present a 24-year-old woman with an initial diagnosis in adolescence of physiological pituitary hypertrophy following neuroradiological evaluation of her persistent headache, who developed a neoplastic symptomatic prolactinoma 9 years later. She underwent endoscopic endonasal tumor excision, which was uneventful with no intraoperative complications. The present case study revealed the possibility that adolescent physiological pituitary gland hypertrophy can develop into prolactinoma. Hence, patients with symptomatic physiological pituitary gland enlargement should have long-term follow-up using clinical, laboratory, and neuroradiology evaluations. *Shinshu Med J 70 : 101—106, 2022*

(Received for publication September 28, 2021 ; accepted in revised form November 11, 2021)

Key words : adolescent, physiologic pituitary hypertrophy, prolactinoma, pituitary adenoma, endoscopic endonasal approach

Abbreviations : MRI, Magnetic Resonance Imaging ; CT, Computed Tomography ; PHPG, Physiologic Hypertrophy of Pituitary Gland

I Introduction

The concept of physiological hypertrophy of the pituitary gland (PHPG) is well recognized, and is defined as an absolute increase in the number of one or more adenohypophysis cell subtypes, manifesting radiologically as pituitary enlargement beyond the normal range[1)-3)]. This is a common finding in pregnancy and in adolescent girls during puberty due to the increased physiological needs of pituitary hormones during these periods of human development[4)].

Although PHPG is common, its transformation into neoplastic pituitary lesions in the form of functioning or non-functioning pituitary adenoma is uncommon based on a review of the relevant literature. Most previous observational studies on pituitary tumorigenesis could not link PHPG to the eventual development of pituitary adenoma[2)4)5)]. Hence, most physicians reassure patients with PHPG without proper long-term follow-up.

Here, we report a female adolescent with PHPG that transformed into a prolactin-secreting macroadenoma in early adulthood.

II Case Presentation

Here, we report a 24-year-old woman who initially presented 9 years previously as an adolescent with

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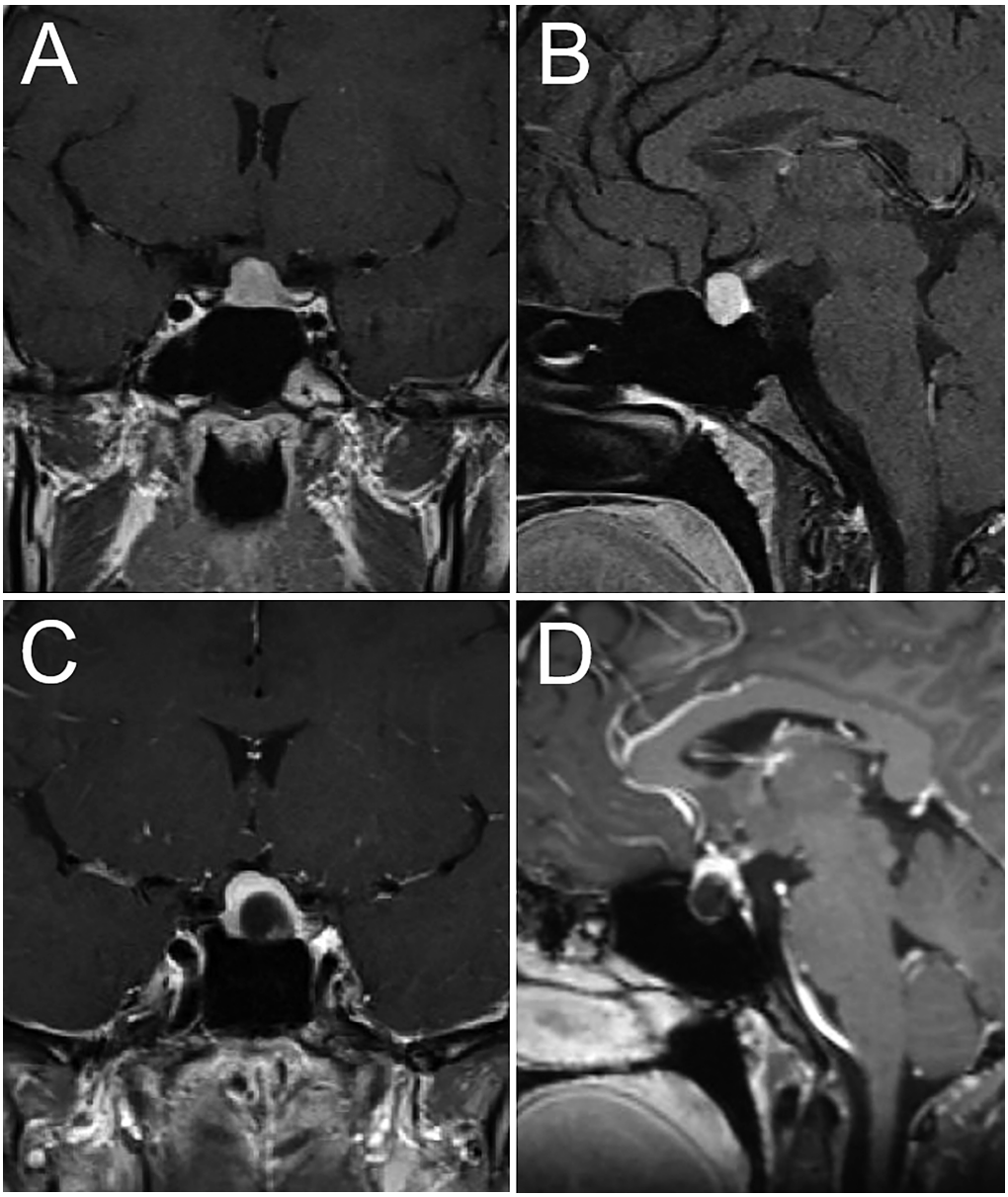

Fig. 1 MRI showing homogenous pituitary gland enhancement which is in keeping with physiologic enlargement with 11 mm in pituitary hight (A and B). Current MRI images after nine years from the initial scan, which revealed a less enhanced sellar mass that is consistent with pituitary adenoma compressing the pituitary gland upward (C, D).

persistent bilateral dull headache and underwent brain magnetic resonance imaging (MRI) and hormonal evaluations **(Fig. 1A, B)**. Anterior pituitary hormone levels including prolactin (7.5 ng/ml) and thyroid stimulating hormone (0.977μIU/ml) were all within the normal limits, and primary hypothyroidism was clinically excluded (fT4 : 1.32 ng/dl) **(Table. 1)**. Thus, the neuroimaging and hormonal assessments revealed features consistent with PHPG, and she was then managed as a case of benign headache with good response and complete disappearance of symptoms. About 9 years later, she developed menstrual disturbance and worsening of disabling headache pain. Laboratory evaluation revealed hyperprolactinemia (111.0 ng/ml) and MRI identified a de novo less-enhanced pituitary tumor with optic nerve and pituitary stalk compression **(Fig. 1C, D)**. However, she was neurologically intact on clinical examination. Apart from the increase in prolactin level, other pituitary hormones were within the normal limits.

The pituitary tumor might have been a de-novo non-functioning pituitary adenoma as well as prolactinoma, because the prolactin level was not so high as prolactinoma, and there was a possibility of hyperprolactinemia due to the stalk effect associated with a non-functioning pituitary. With sufficient informed consent, she preferred to undergoing endoscopic endonasal tumor resection for decompression of the optic nerve and making a definitive diagnosis, rather than medical treatment including dopamine agonists. Intraoperative findings revealed a cystic tumor with clear serous liquid and a thin solid component, which was whitish, soft, and hemorrhagic **(Fig. 2A, B)**. Gross total tumor removal was accomplished. Surgery was uneventful with no intraoperative complications.

Postoperative neuroimaging revealed satisfactory findings, without any signs of ischemia, hemorrhage, or residual tumor **(Fig. 3A, B)**. The patient showed good clinical recovery with no postoperative neurological deficit. Prolactin level normalized immediately

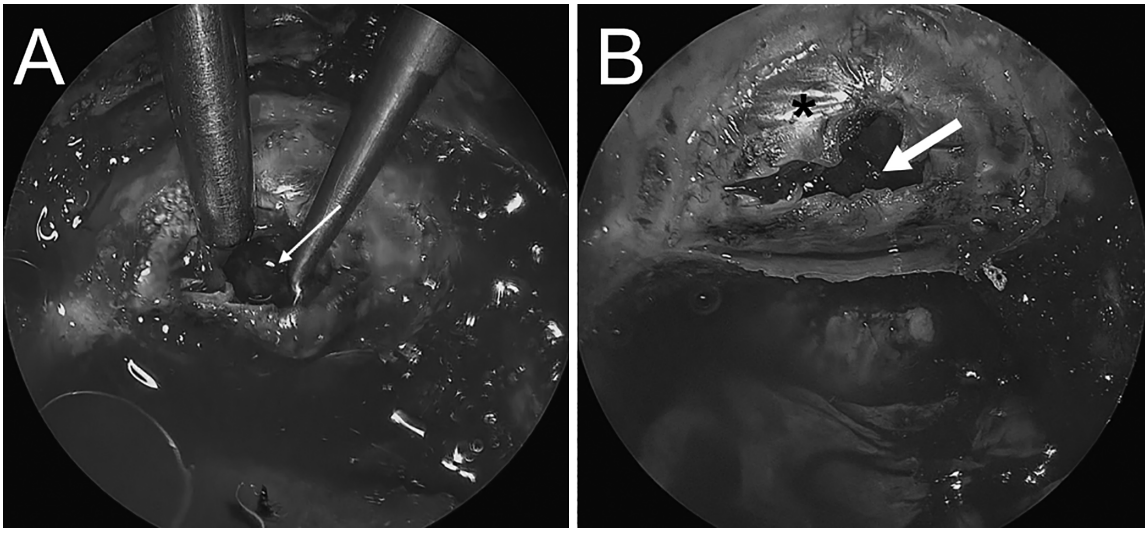

Fig. 2 Intraoperative endoscopic view : (A) A tumor with a thin solid component, which was whitish, soft, and hemorrhagic (thin arrow). (B) Normal pituitary grand and excision cavity (thick arrow) after gross total resection of the tumor. asterisk, dura mater

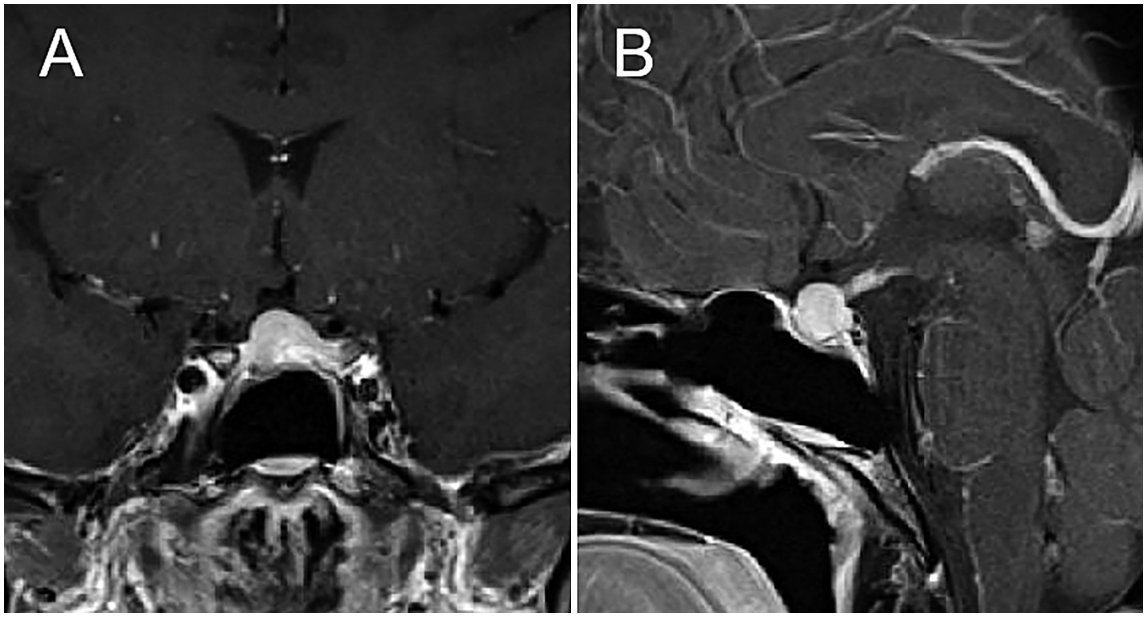

Fig. 3 Postoperative MRI showing complete tumor extirpation (A, B).

Table 1　Preoperative and postoperative day 7 endocrinological data

Hormone level (normal range)	preope.	postope.
fT3 (2.3–4.0 pg/ml)	3.05	2.76
fT4 (0.9–1.7 ng/dl)	1.52	1.49
TSH (0.50–5.00 μIU/ml)	1.51	1.09
GH (0.13–9.88 ng/ml)	0.1	0.3
FSH (1.47–16.60 mIU/ml)	6.5	4.6
LH (1.3–88.33 mIU/ml)	19.6	15.1
PRL (4.0–30.0 ng/ml)	111	14.8
Cortisol (1.0–15.0 μg/dl)	13.2	8.1
ACTH (7.2–63.3 pg/ml)	26.3	32.7

fT3, free T3 ; fT4, free T4 ; TSH, thyroid stimulating hormone ; GH, growth hormone ; FSH, follicle stimulating hormone ; LH, luteinizing hormone ; PRL, prolactin ; ACTH, adrenocorticotropic hormone

after surgery and other pituitary hormones were within the normal limits **(Table. 1)**. A tissue sample obtained during the surgical procedure was subjected to histological analysis. Histological examination showed diffusely growing adenoma cells with eosinophilic cytoplasm **(Fig. 4A)**. Immunohistochemical studies for hormones showed that the tumor was positive for prolactin **(Fig. 4B)**, and negative for growth hormone **(Fig. 4C)**. This tumor was composed of uniform medium-sized cells with pale eosinophilic cytoplasm, which was positive with Cytokeratin CAM5.2, and central nuclei **(Fig. 4D)**. These pathological findings suggested that it was a sparsely granulated lactotroph adenoma. There were no indications for further oncological treatment and the patient is currently on regular neuroradiological follow-up.

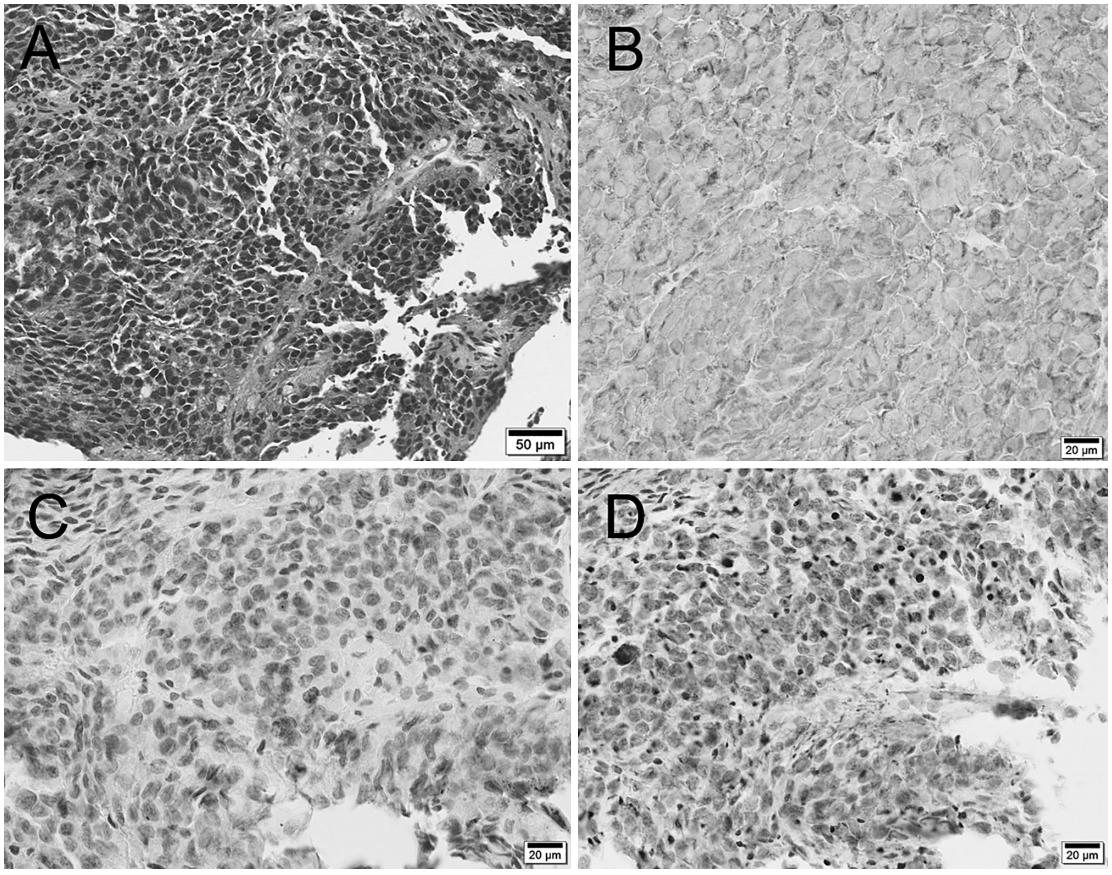

Fig. 4　An H&E-stained section revealing the typical diffuse pattern of a pituitary adenoma, which consisted of uniform medium-sized cells with pale eosinophilic cytoplasm and central nuclei (A). Immunohistochemistry showing positive staining for prolactin (B), negative staining for growth hormone (C) and positive with Cytokeratin CAM5.2 (D).

Ⅲ Discussion

Adolescents, particularly girls, tend to have pituitary gland enlargement, which can be explained by hypertrophy secondary to physiological-endocrinological events associated with increased need for sex hormones, such as follicle stimulating hormone, luteinizing hormone, estradiol, and estrone, around puberty[1]. This enlargement may cause a mass effect as patients predominantly present with headache and rarely with visual disturbance[1)3)6)]. The diagnosis of PHPG is largely clinico-hormono-radiological. Thus, pituitary enlargement (pituitary height≥9 mm, or greater than that predicted by age, gender, and ethnicity) with normal hormonal assessment and gland homogeneity on plain and contrast-enhanced MRI with a conspicuous posterior pituitary bright spot is considered as PHPG to avoid therapeutic errors[3)4)7)]. Therefore, proper evaluation of patients on initial presentation is the key to differentiating PHPG from adenoma. However, the duration over which peripubertal pituitary gland hypertrophy persists is still unknown, and few data are available on the epidemiology, diagnosis, and treatment of PHPG. These issues must be addressed by further research on pituitary gland pathologies.

In the present case study, it was especially noteworthy that PHPG diagnosed in adolescence later developed into a prolactin-secreting pituitary macroadenoma after a period of 9 years. The transformation of PHPG into a neoplastic lesion in the form of functioning or non-functioning pituitary adenoma has not been reported previously. We believe that this is a consequence of some hormonal factors involved in the pathogenesis of pituitary tumors, which has not been previously implicated. Studies in several animal models have shown that hormonal effects, such as hypothalamic trophic or inhibitory hormones, or abnormal feedback regulation mechanism from peripheral hormones, could lead to pituitary adenoma[5)8)]. However, previous studies could not provide evidence for this in humans[5)]. Meanwhile, the preponderance of prolactinomas in females may be linked to the influence of estradiol on the pituitary gland, and factors involved in the physiological regulation of the pituitary gland, such as somatostatin analogs and dopamine agonists, are utilized therapeutically as analogs of inhibitory hypothalamic factors in the treatment of functioning pituitary adenomas, including prolactinomas and non-functioning pituitary adenomas[5)9)-11)]. A literature search identified some individual case reports of corticotroph adenoma in patients with Addison's disease after treatment with corticosteroids[5)9)12)]. Although these observations point to the potential roles of hormonal factors in pituitary tumorigenesis, the correlation between PHPG and pituitary adenoma formation remains unclear.

Another possibility is that the patient had an adenoma in situ misdiagnosed as PHPG at the initial presentation in adolescence, which later increased in size and then acquired secreting potential, because she had no prior histological confirmation of PHPG as her initial diagnosis was largely based on clinico-hormono-radiological evaluations. Conversely, previous attempts at surgery for biopsy or decompression for PHPG resulted in therapeutic mishaps as histopathological results did not add diagnostic value to the clinical diagnosis, yet the patients have to bear the morbidity associated with the surgery[4)7)]. Data available in the literature recommend only clinico-hormono-radiological evaluation for diagnosis of physiological hypertrophy of the pituitary gland[3)4)].

This present case was diagnosed with symptomatic PHPG in adolescence 9 years before this recent presentation of functioning pituitary adenoma, but she had no long-term follow-up care because of the belief that physiological pituitary enlargement is benign and has no risk of neoplastic transformation. Therefore, this case presentation suggests the need for an appropriate regimen of long-term follow-up in patients with symptomatic physiological pituitary hypertrophy. Finally, the significant issue of this case report was that the transformation from PHPG to prolactinoma has not been clarified histologically, molecular biologically and clinically, and further studies of this issue are warranted.

Ⅳ Conclusions

This case presented is an unusual example of pituitary adenoma that revealed the possibility of adolescent physiologic pituitary gland hypertrophy undergoing transformation into a prolactinoma. Hence, patients with symptomatic physiological pituitary gland enlargement should have long-term follow-up with clinical, laboratory, and neuroradiology evaluations. This case report will improve knowledge on pituitary tumorigenesis.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the participant included in the study.

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(2021. 9. 28 received ; 2021. 11. 11 accepted)