

Case Report

Pituitary adenoma with rich folliculo-stellate cells and mucin-producing epithelia arising in a 2-year-old girlHye Sook Min,¹ Seung June Lee,² Seung-Ki Kim² and Sung-Hye Park¹*Departments of ¹Pathology and ²Pediatric Neurosurgery, Seoul National University College of Medicine, Seoul, Korea*

Pituitary adenoma is a rare neoplasm in childhood, with prolactin and adrenocorticotrophic hormone (ACTH)-secreting adenomas predominating in this age group. Herein is reported a case of an ACTH-producing macroadenoma with an unusual histology that occurred in a 2-year-old girl. Because of the patient's age and the macroadenoma's suprasellar location and large size (up to 4 cm in diameter), radical surgery was performed under the suspicion of craniopharyngioma or germ-cell tumor. Pathologically, it was a unique pituitary adenoma composed of monotonous ACTH-producing cells, smaller folliculo-stellate cells (FSC), and mucin-producing cells. The FSC, non-hormone-secreting pituitary cells of uncertain function, were confirmed by their S-100 protein, glial fibrillary acidic protein and cytokeratin expression immunoprofiles. The abrupt transition between the prominent gland-forming mucin-producing epithelia and the FSC component suggested that the mucin-producing epithelia might be derived from the FSC. This association might represent so-called 'retrodifferentiation' of adenoma cells to the FSC and the precursor cells of Rathke's pouch.

Key words: folliculo-stellate cell, mucin-producing epithelium, pituitary adenoma, Rathke's pouch, retrodifferentiation

Pituitary adenoma is a rare neoplasm among children. It comprises approximately only 3.5–6% of all surgically treated pituitary adenomas at all ages, and only 2.7% of all supratentorial tumors in childhood.^{1,2} The majority of pediatric pituitary adenomas are functioning adenomas; prolactinomas and adrenocorticotrophic hormone (ACTH)-cell adenomas predominating among them.³ Therefore, the most common

symptom in children with pituitary adenomas is endocrinopathy, and visual deterioration and headache are also common symptoms.³ Because of an overall good surgical outcome, trans-sphenoidal tumor removal should be considered to be the primary treatment modality.

Several series of adenomatous and non-tumorous pituitaries have shown that folliculo-stellate cells (FSC) are found in various proportions in pituitary adenomas, particularly in growth hormone (GH)- and prolactin-producing types.^{4–7} In some previous reports, 4–19% of pituitary adenomas contained relatively abundant FSC,^{4,5} but the number of FSC among adenoma cells did not depend on sex, age, and prognosis. Some authors insisted that adenoma cells can retrodifferentiate into FSC,⁸ while others believed that FSC can be subdivided according to their positivity for S-100, glial fibrillary acidic protein (GFAP), or cytokeratin (CK).^{5,8,9}

Although the precise role of FSC remains poorly understood, there are several hypotheses on their nature and origin in adenohypophysis. The first is that they are an analog of sustentacular cells in other endocrine organs, based on their stellate morphology and their scattered distribution among normal glandular cells.^{8,10} Secondly, it is suggested that they are non-hormone-secreting cells associated with hormonal regulation and phagocytosis, in that they often contain cell debris and lysosomes ultrastructurally.⁸ In contrast, it is assumed that they are a modified form of glial cell originated from neuroectoderm, considering their S-100 immunoprofile as well as their GFAP and CK expression.¹ Lastly, they would be one type of adult stem cell that is capable of differentiating to Rathke's pouch epithelia.⁸

As mentioned above, we are reporting a case that occurred in a 2-year-old girl of a histologically unusual pituitary adenoma composed of three cell components: ACTH-producing adenoma cells, FSC, and mucin-secreting epithelial cells. The last two components formed minute follicular or larger glandular structures. The present case might represent the 'retrodifferentiation' of adenoma cells to Rathke's-pouch-origin precursor cells.⁸

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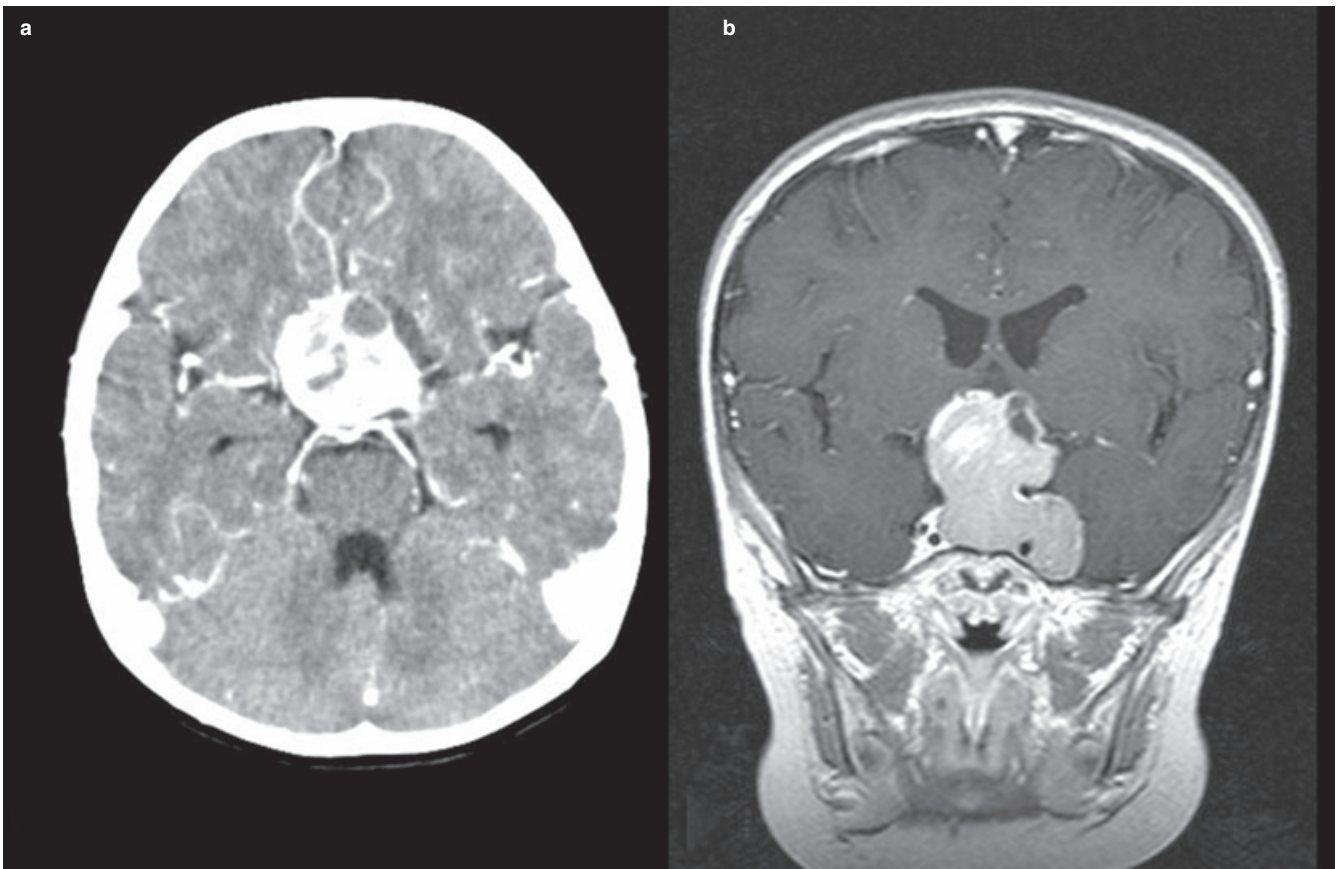


Figure 1 (a) Preoperative brain CT and (b) T2-weighted magnetic resonance imaging show a 4 cm suprasellar mass with extension to the left cavernous sinus and the petrous bone.

CASE REPORT

A 2-year-old girl was admitted to Seoul National University Children's Hospital with a strabismus and 2-months' decreased visual acuity of the right eye. She had been diagnosed with amblyopia and received 1 month's occlusion therapy at another hospital but, showing no improvement, she was referred to Seoul National University Children's Hospital for further evaluation. The findings of a physical examination were within normal limits, except for the patient's short stature (<10th percentile for age). A neurological examination indicated a loss of light reflex with mild medial gaze palsy of the right eye suggesting right 3rd nerve palsy, as well as a sluggish light reflex of the left eye. Visual acuity could not be checked owing to the poor cooperation of the patient, but a test for visual evoked potential showed no response in either eye. In a blood test, the ACTH level was elevated to 106 pg/mL (0–60 pg/mL), but the patient did not show any features of Cushing's disease. The other hormones and tumor markers were within normal limits. CT showed a well-enhancing suprasellar mass containing internal calcification and a cystic portion (Fig. 1a), and magnetic resonance imaging (MRI) showed a 4 cm suprasellar mass extending

into the left cavernous sinus and the petrous bone (Fig. 1b). Craniopharyngioma or germ-cell tumor was suspected, and the patient underwent radical interhemispheric subfrontal surgery. However, the suprasellar mass could not be completely excised, a portion of it remained. During a 5 month postoperative follow-up period the light reflex visual acuity reappeared and became prompt in both eyes, and the patient had adequately recovered to read a picture book with a normal level of ACTH. Adjuvant therapy was postponed considering the patient's age and there was no progression of the residual suprasellar mass, as shown on a follow-up MRI.

PATHOLOGICAL FINDINGS

The mass was generally well-encapsulated, pinkish and friable in consistency. On microscopic examination the mass was found to contain two distinct cell populations (Fig. 2a). The majority was a diffuse sheet of uniform round cells with a delicate capillary network. The nuclei of these cells were round to oval in shape, centrally located and had a characteristic salt and pepper chromatin pattern. The cytoplasm was abundant granular and basophilic or amphophilic. All of

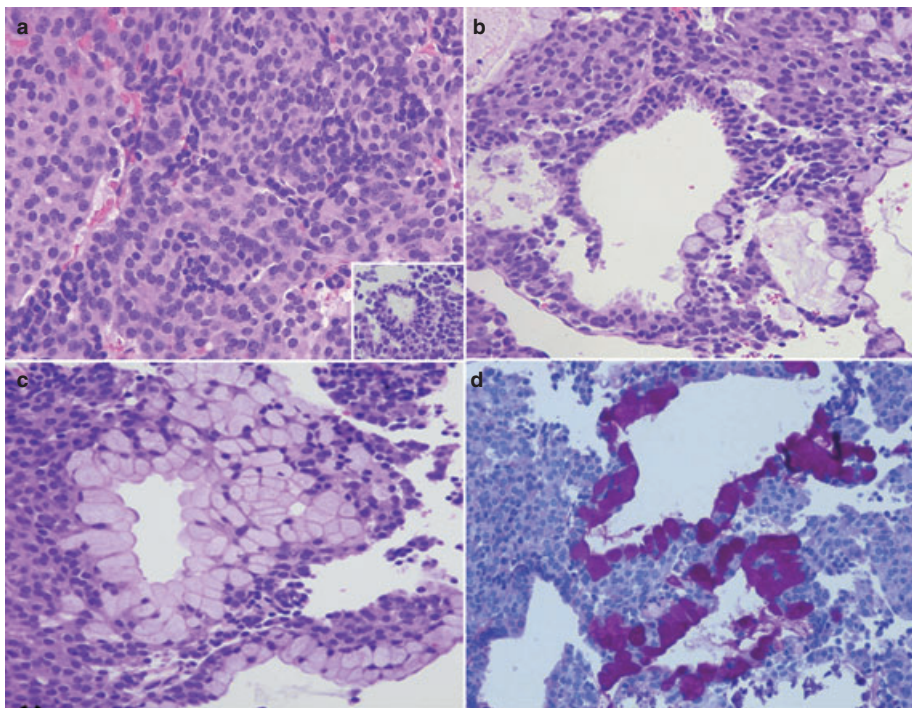


Figure 2 Two distinct cell populations consist of uniform round adenoma cells and smaller round to stellate cells. (a) The latter subset shows a variable pattern including the luminal follicle (inset). (b) Between them, the abrupt transition to the mucinous glandular epithelium is observed, and (c) these cells include copious mucin-resembling goblet cells, which are (d) intensely positive for periodic-acid Schiff (PAS).

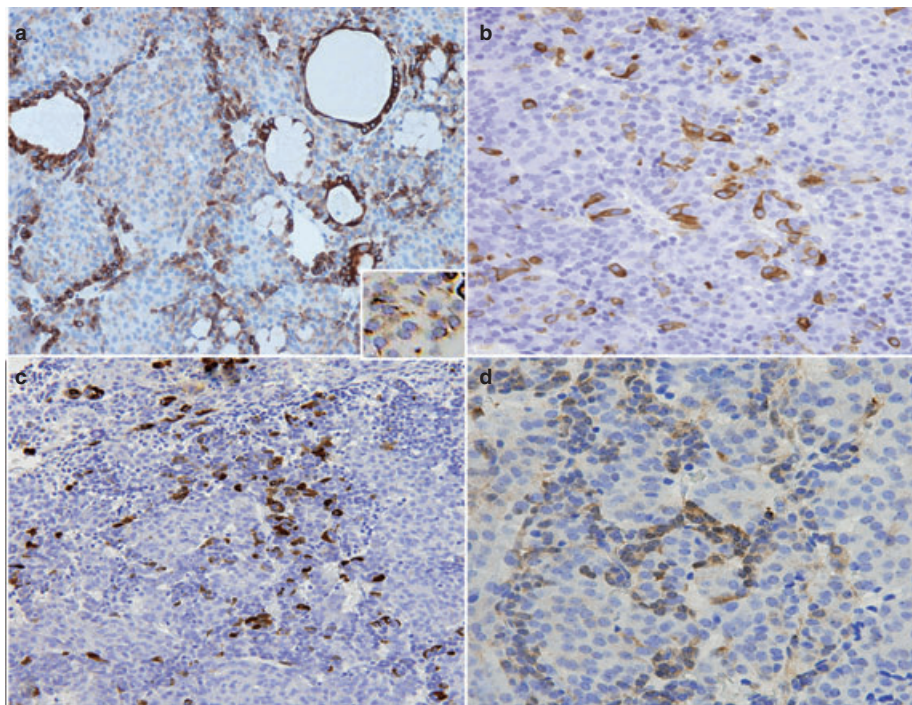


Figure 3 Strong positive immunoreactivity for (a) cytokeratin (CK) is scattered mainly in the folliculo-stellate cells (FSC), but there is weak reactivity in the adenoma cells (inset). (b) The adenoma cells are focally but robustly positive for adrenocorticotropic hormone. (c) Focal positivity for S-100 is observed in the FSC, which are scattered randomly among the adenoma cells. But (d) the glial fibrillary acidic protein (+) areas are not overlapped with the S-100 (+) area.

these features were compatible with pituitary adenoma cells. The second subset was smaller than the adenoma cells and had a round to stellate shape, having more hyperchromatic nuclei and relatively scanty cytoplasm, which were compatible with FSC morphologically. These cells were intermingled with the former cell group forming irregular nests, cord-like arrangements or follicular structures, and characteristically

they showed an abrupt or continuous transition into the adenoma cells. Additionally, glandular structures lined by epithelia resembling goblet cells were observed, which had a strong positivity for PAS and mucicarmine (Fig. 2b–d). In these areas the abrupt transitional pattern from the FSC to the mucinous epithelium was also observed (Fig. 2b). Immunohistochemically, the adenoma cells of the major subset

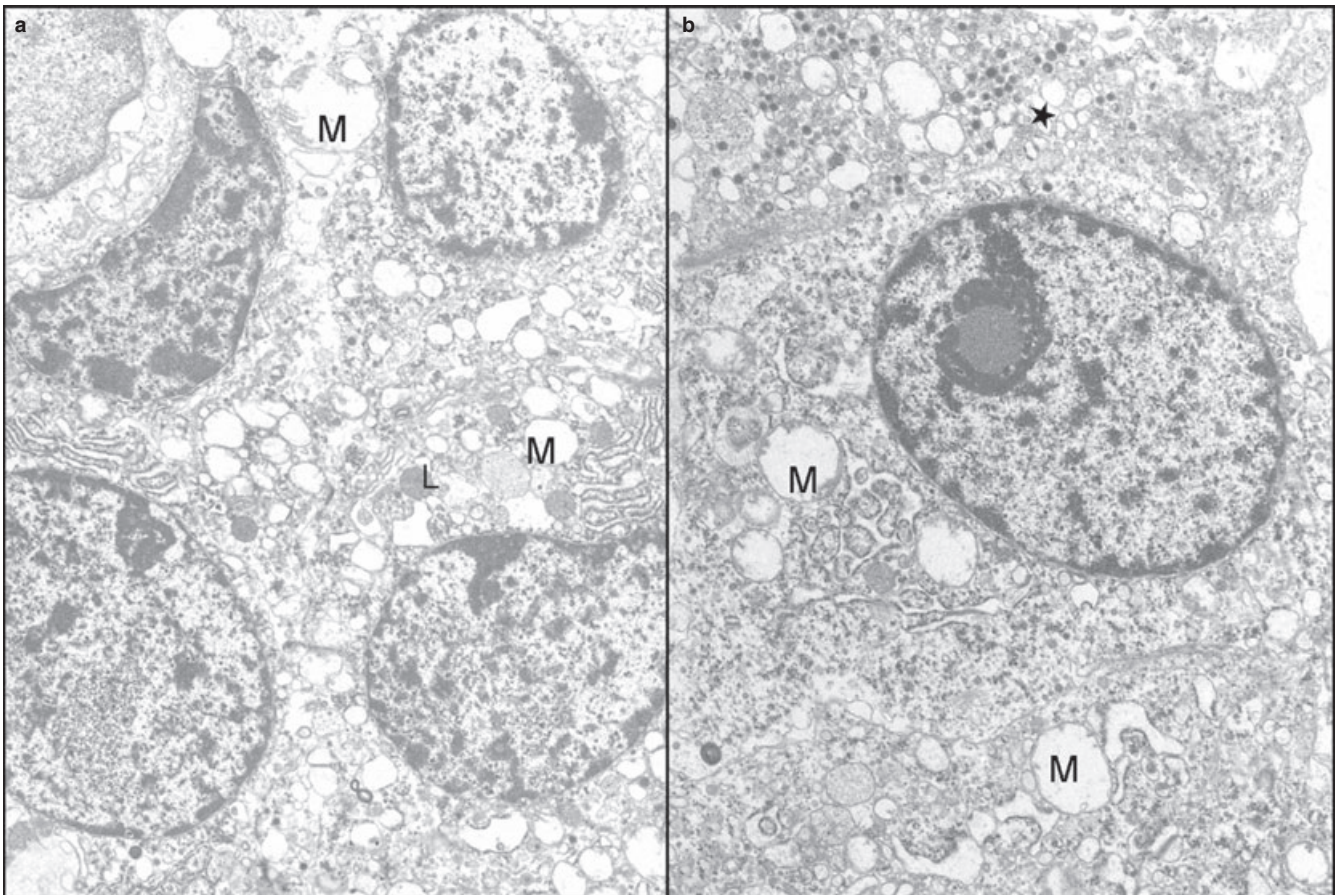


Figure 4 The nests of folliculo-stellate cells (a) have a relatively small amount of cytoplasm, which have stacks of rough endoplasmic reticula, a fair number of swollen mitochondria (M), several lysosomes (L), but few electron-dense core neurosecretory granules, in contrast with the adenoma cells (b) that have abundant neurosecretory granules (star). (b) The nucleus of the folliculo-stellate cell has a smoothly contoured oval shape with heterochromatic chromatin and a small nucleolus. In the intercellular borders, no desmosomal junction is present, and nuclear inclusion was not found in the present case. (a,b, uranyl acetate and lead citrate stain).

were diffusely positive for synaptophysin, and positive for pan-CK in cytoplasmic dots (Fig. 3a, inlet), and focally positive for ACTH (Fig. 3b), but negative for other hormonal markers including prolactin, GH, follicle-stimulating hormone, luteinizing hormone, and thyroid-stimulating hormone. The FSC were also negative for all of the hormonal markers, but showed a diffuse positivity for pan-CK (Fig. 3a), and a heterogeneous positivity for S-100 (Fig. 3c) and GFAP (Fig. 3d). The positive populations of GFAP and S-100 were overlapped with the CK (+) cells, whereas the S-100 (+) and GFAP (+) areas were not overlapped. The CK immunostaining showed a stronger intensity in the follicle-forming FSC than in the scattered or the nested FSC; but S-100 and GFAP were negative for these follicular cells. The mucinous epithelium expressed CK intensely, but did not express other markers. Ultrastructurally, the major tumor cells were adenoma cells that contained dilated rough endoplasmic reticulum (RER) and a fair number of variable-sized membrane-bound electron-dense core secretory granules in the cytoplasm (Fig. 4). There were nests or clusters of

smaller FSC among the adenoma cells, which could be easily distinguished from adenoma cells due to the few membrane-bound electron-dense core secretory granules. Individual FSC had heterochromatic rounded nucleus with peripherally located small nucleolus. Their cytoplasm contained stacks of RER, swollen mitochondria, small Golgi apparatus and ribosomes (Fig. 4a). Desmosomal junctions or nuclear inclusions were not found in the present case, which have been described in previous reports.⁸

DISCUSSION

FSC are non-hormone-secreting pituitary cells of unknown function that are found in both normal and neoplastic pituitaries. They are morphologically characterized by oval-to-stellate-shaped small cells with dark nuclei and scanty cytoplasm, and have variable expression of CK, S-100 protein and GFAP immunohistochemically.^{4-8,10} Because of their GFAP and S-100 protein expression immunoprofiles,

these cells have been considered to be of glial in nature and/or neuroectodermal in origin,¹¹ but other investigators have suggested that FSC could be an analog of sustentacular cells in other endocrine organs^{8,10} or one type of pituitary stem cells that is capable of differentiating into precursor cells of Rathke's pouch,⁸ as aforesaid. In the developmental period, GFAP and S-100 protein-expressing cells are found in the pars intermedia mainly, but only in a certain fetal developmental phase, that is, around the 13th gestational week.¹¹ As fetal development advances these cells move to the pars distalis and come to express CK, which suggests the acquisition of an epithelial nature by these cells.¹¹

In the present case the FSC expressed CK more diffusely and strongly, and GFAP and S-100 protein (+) FSC were overlapped with these CK (+) FSC. This finding is slightly different from those of previous reports that the CK (+) FSC and GFAP (+) FSC are mutually exclusive.⁴ However, the present finding is consistent with another report in that the GFAP (+) and S-100 protein (+) populations were not overlapped with each other.⁸ Moreover, the intense positivity for CK but negativity for both GFAP and S-100 in the more differentiated follicle-forming FSC support the possibility of the gain of CK expression and the loss of both S-100 protein and GFAP expression in the transformation stage.⁸

Follicle or microcyst formation by FSC has been described in pituitary adenoma,¹ and FSC have been observed to directly join the surrounding adenoma cells by adherent junction ultrastructurally.¹² Some mucin granules, in several cases, have been found forming microcysts in FSC, which is a similar feature to that of Rathke's cyst-lining cells.^{8,13} The present case is very unique in that there were rich FSC and an abrupt transition between the FSC and the mucin-producing glandular epithelia, resembling goblet cells. The presence of FSC in adenoma can be explained from three different viewpoints: they might be entrapped normal cells, or reactive hyperplastic cells, or neoplastic cells.¹⁴ We agree with the hypothesis of the neoplastic nature of the FSC because there were transitional arrangements between the adenoma cells, the FSC, and the mucinous epithelial cells. The glandular structures lined by copious mucin-producing epithelia, seen in the present case, are reminiscent of Rathke's cyst-lining cells. It suggests that the mucin-producing epithelia are formed through 'retrodifferentiation' of adenoma cells to FSC and the Rathke's pouch precursor of the mucin-producing type, according to Horvath and Kovacs.⁸

The present case had sparsely granulated ACTH-producing adenoma pathologically, but some investigations have reported that the plurihormonal,⁸ prolactin^{6,8} or GH-producing type,^{6,7} or non-functioning adenomas⁴ related to abundant FSC or to follicle formation of FSC. Because of the rarity of large-series studies on pituitary adenoma, the bias of the relatively few studied cases might contribute to

this discordance, but the hormonal subtypes appear not to be associated with the amount of FSC in adenoma.^{4-6,8,10}

Clinically, the present patient did not have any evidence of Cushing's disease, which implicated the diagnosis of silent corticotroph cell adenoma. A recent study addressed the possibility that they may be derived from a subpopulation of pars intermedia distinct from ACTH-producing anterior lobe corticotrophs.¹⁵ Furthermore, compared with the adenomas of Cushing's disease, high frequency of the large size and radiographic invasion was reported in silent corticotroph cell adenomas.¹⁶ The present case also showed a similar aggressive manner, including relatively large size (4 cm) and invasion to the left cavernous sinus and the petrous bone radiologically. Some authors described subtypes I and II in this group according to their differentiation and morphological findings.¹⁶ In the present case the negativity for PAS, focal positivity for ACTH and only sparse granulation in its ultrastructure in adenoma cells suggested that this tumor could be included in type II silent corticotroph cell adenoma, the less differentiated type.

In summary we have described the case of a 2-year-old girl presenting with silent ACTH-producing macroadenoma, which, uniquely, contained abundant FSC with mucin-producing epithelia. The morphological and immunophenotypic findings suggested the transition of the adenoma cells to FSC and mucin-producing Rathke's pouch-originated precursor cells. The environmental and intrinsic factors causing this transformation and its clinical implications should be evaluated in a larger case study.

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REFERENCES

- 1 Gold FB. Epidemiology of pituitary adenomas. *Epidemiol Rev* 1981; **3**: 163–83.
- 2 Hoffman HJ. Pituitary adenomas. In: American Association of Neurological Surgeons, eds. *Pediatric Neurosurgery: Surgery of the Developing Nervous System*. New York: Grune & Stratton, 1982; 493–9.
- 3 Pandey P, Ojha BK, Mahapatra AK. Pediatric pituitary adenoma: A series of 42 patients. *J Clin Neurosci* 2005; **12**: 124–7.
- 4 Tachibana O, Yamashima T. Immunohistochemical study of folliculo-stellate cells in human pituitary adenomas. *Acta Neuropathol (Berl)* 1988; **76**: 458–64.
- 5 Voit D, Saeger W, Ludecke DK. Folliculo-stellate cells in pituitary adenomas of patients with acromegaly. *Pathol Res Pract* 1999; **195**: 143–7.

- 6 Iwaki T, Kondo A, Takeshita I, Nakagaki H, Kitamura K, Tateishi J. Proliferating potential of folliculo-stellate cells in human pituitary adenomas. Immunohistochemical and electron microscopic analysis. *Acta Neuropathol (Berl)* 1986; **71**: 233–42.
- 7 Lauriola L, Cocchia D, Sentinelli S, Maggiano N, Maira G, Michetti F. Immunohistochemical detection of folliculo-stellate cells in human pituitary adenomas. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1984; **47**: 189–97.
- 8 Horvath E, Kovacs K. Folliculo-stellate cells of the human pituitary: A type of adult stem cell? *Ultrastruct Pathol* 2002; **26**: 219–28.
- 9 Yamashita M, Qian ZR, Sano T, Horvath E, Kovacs K. Immunohistochemical study on so-called follicular cells and folliculo-stellate cells in the human adenohypophysis. *Pathol Int* 2005; **55**: 244–7.
- 10 Burger PC, Scheithauer BW, Vogel FS. *Surgical Pathology of the Nervous System and its Coverings*. Philadelphia, PA: Churchill Livingstone, 2002.
- 11 Coates PJ, Doniach I. Development of folliculo-stellate cells in the human pituitary. *Acta Endocrinol (Copenh)* 1988; **119**: 16–20.
- 12 Sbarbati A, Fakhreddine A, Zancanaro C, Bontempini L, Cinti S. Ultrastructural morphology of folliculo-stellate cells in human pituitary adenomas. *Ultrastruct Pathol* 1991; **15**: 241–8.
- 13 Cinti S, Sbarbati A, Balercia G, Cigolini M. An ultrastructural study on muciparous microcysts of the human adenohypophysis. *Acta Anat* 1985; **121**: 94–8.
- 14 Miyazaki H, Toya S, Otani M, Kameya T, Wada C. [Folliculo-stellate cells in normal human adenohypophyses and in pituitary adenomas]. *No Shinkei Geka* 1988; **16**: 713–19.
- 15 Horvath E, Kovacs K, Lloyd R. Pars intermedia of the human pituitary revisited: Morphologic aspects and frequency of hyperplasia of POMC peptide immunoreactive cells. *Endocr Pathol* 1999; **10**: 55–64.
- 16 Scheithauer BW, Jaap AJ, Horvath E *et al*. Clinically silent corticotroph tumors of the pituitary gland. *Neurosurgery* 2000; **47**: 723–9.