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Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with the McCune-Albright syndrome

A histologic, immunocytologic and ultrastructural study of the surgically-removed adenohypophysis

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Summary. An 11-year-old girl, with the McCune-Albright syndrome, exhibited fibrous dysplasia of several bones, skin pigmentation, precocious puberty, growth hormone hypersecretion, acromegaly and hyperprolactinemia. Histologic, immunocytologic and ultrastructural investigation of the surgically-removed pituitary showed massive mammosomatotroph hyperplasia. Since no adenoma was found, the abundance of these bihormonal cells, capable of producing both growth hormone and prolactin, was implicated in the causation of growth hormone and prolactin excess. Somatoliberin overproduction and/or somatostatin and dopamine deficiency could not account for the hypophysial abnormality, since changes in secretory rates of these hypothalamic hormones would lead to proliferation of mature somatotrophs and lactotrophs, rather than mammosomatotrophs. In our patient, a congenital hypothalamic malfunction might have been accompanied by hypersecretion of an unidentified releasing factor, resulting in pathologic differentiation of the pituitary and mammosomatotroph hyperplasia. Alternatively, mammosomatotroph hyperplasia may have been due to an inherent genetic or embryonic defect affecting primarily the pituitary. According to this interpretation, the pituitary lesion represented yet another developmental error in the setting of the McCune-Albright syndrome.

Key words: Acromegaly – hyperprolactinemia – McCune-Albright syndrome – pathology – Pituitary – Ultrastructure

The McCune-Albright syndrome, described by McCune in 1936 and Albright et al. in 1937, is a rare disease of unknown etiology. The principal

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disorder is polyostotic fibrous dysplasia which may be associated with pigmentation of the skin and a variety of endocrine abnormalities, including precocious puberty, hyperthyroidism and hypercorticism (Lichtenstein and Jaffe 1942; Sternberg and Joseph 1942; Benedict 1962; Hall and Warrick 1972; Warrick 1973; MacMahon 1975). The occurrence of acromegaly or gigantism and/or hyperprolactinemia has been rarely noted and only a few well documented cases have been described (Scurry et al. 1964; Lightner et al. 1975; Joishy and Morrow 1976; Powell 1976; Carr et al. 1979; Albin and Wu 1981; Lipson and Hsu 1981; Polychronakos et al. 1982; Chung et al. 1983).

We report here a patient with the McCune-Albright syndrome with unusual endocrinologic manifestations and a heretofore undescribed pituitary abnormality. This 11-year-old girl exhibited the characteristic osseous lesions, skin pigmentation, precocious puberty and acromegaly with elevated serum growth hormone levels and hyperprolactinemia. The unique feature of the case is that the patient underwent intracranial surgery to correct facial deformities, as well as intermittent diplopia. Non-adenomatous anterior pituitary tissue was removed for detailed morphologic studies, including immunocytology and electron microscopy. The investigations established the presence of mammosomatotroph hyperplasia of the pituitary, which, since no adenoma was found, could account for acromegaly, elevated serum growth hormone and prolactin concentrations.

Report of case

Clinical findings. The $4^{2}/_{12}$-year-old girl presented with breast development and a 1-week history of vaginal bleeding. Her early growth and development were entirely normal. On physical examination, height and weight were above the 97th percentile. Cafe-au-lait pigmentation with irregular borders was noted on the left chest, upper arm and neck. Multiple bone lesions of fibrous dysplasia were noted. The breasts and uterus were of pubertal size. The bone age was $4^{2}/_{12}$ years. Serum and urine gonadotropins were within the prepubertal range. Therapy with medroxyprogesterone acetate to suppress menses was begun.

At $6^{0}/_{12}$ years, rotatory nystagmus and bilateral, easily expressible galactorrhea were noted. X-rays showed a normal sella turcica, but the base of the skull was markedly increased in density. The serum growth hormone (GH) and prolactin levels were 18.4 ng/ml (normal < 5 ng/ml) and greater than 200 ng/ml (normal < 25 ng/ml), respectively. The GH concentration did not suppress fully after glucose loading confirming the diagnosis of childhood acromegaly.

Over the next several years, occasional vaginal bleeding episodes occurred and she continued to grow at an accelerated rate. Basal GH values continued to more than 30 ng/ml, and the prolactin levels remained elevated in the 100–150 ng/ml range. A single somatomedin C concentration (courtesy of Dr. William H. Daughaday) was elevated.

Therapy with bromocriptine, 2.5 mg 4 times a day, for childhood acromegaly and hyperprolactinemia was begun. Prolactin levels were brought to within the low normal range (approximately 5 ng/ml), but there was little or no suppression of GH concentrations. The dose of bromocriptine was increased to 20 mg per day without obvious effect on the growth rate, and only a small decrement in the mean GH levels (16 ng/ml) versus 26 ng/ml previously).

Increasing facial deformity of polyostotic fibrous dysplasia was noted on high resolution computed tomographic scan. The sella was of normal size, and no mass was seen either before or following intravenous injection of contrast. Craniofacial surgery was undertaken (December, 1982) for the facial deformities. In the course of intracranial surgery, hypophysectomy was performed (bromocriptine therapy was continued until the night prior to surgery). Pre-operatively, the serum somatomedin C concentrations were elevated (6.0–12.0 U/ml), but

returned to the normal range 3 days post-operatively. Several months post-operatively, she has had less sweating and is otherwise asymptomatic with normal serum electrolytes. She receives cortisol, 25 mg per day and dDAVP 5–10 μg per day.

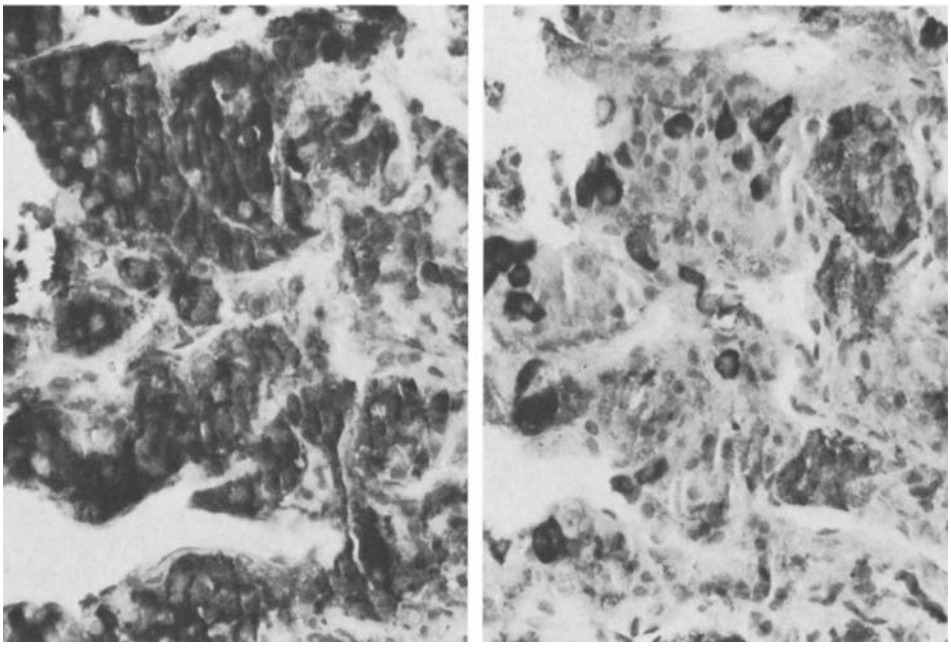
Morphologic investigation

Methods. For light microscopy, pituitary tissue was fixed in 10% buffered formalin and embedded in paraffin. Sections of 4–6 μm thickness were stained with hematoxylin-eosin, PAS and lead hematoxylin methods. The reticulin fibers were examined by the Gordon-Sweet silver procedure. For the demonstration of adenohypophysial hormones, the immunoperoxidase technique was used, as described in detail elsewhere (Kovacs et al. 1981). The following antibodies were tested: anti-growth hormone (1:1000 dilution, donated by the Pituitary Hormone Distribution Program, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, Bethesda, Maryland, USA); anti-prolactin (1:2000 dilution; donated by Dr. H. Friesen, Department of Physiology, University of Manitoba, Winnipeg, Manitoba, Canada); anti-ACTH (1:1000 dilution; donated by Pituitary Hormone Distribution Program, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, Bethesda, Maryland, USA); anti TSH (1:5000 dilution; donated by Bio-Rad, Richmond, California, USA); FSH and LH (1:1000 dilution; donated by the Pituitary Hormone Distribution Program, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, Bethesda, Maryland, USA).

For electron microscopy, pituitary tissue was fixed in 2.5% glutaraldehyde, in Sorensen's buffer, postfixed in 1% osmium tetroxide in Millonig's buffer, dehydrated in graded ethanol, processed through propylene oxide and embedded in Araldite. Ultrathin sections were stained with uranyl acetate and lead citrate and investigated with a Philips 300 electron microscope.

Light microscopic findings. Approximately two-thirds of the specimen was taken from the lateral wing of the pars distalis. The most prominent finding was the formation of large, confluent acini delineated by fine reticulin fibers and populated by relatively small, fairly well-granulated acidophilic cells. These areas, interpreted as multifocal hyperplasia, were uniformly positive for immunoreactive growth hormone and also contained immunoreactive prolactin as shown by immunoperoxidase technique (Figs. 1 and 2). Investigation of consecutive sections showed the presence of growth hormone and prolactin in the same general areas. Positive immunostaining for growth hormone or prolactin was also demonstrated in cells occurring singly or in small groups, as seen in the normal adenohypophysis. In one part of the specimen, many cells stained for immunoreactive TSH, FSH or LH. Only one isolated area contained a few groups of corticotrophs. The reticulin fiber network was distorted but preserved. No adenoma was identified.

Electron microscopic findings. The hyperplastic areas were occupied by a syncytium like aggregate of cells (Fig. 3). The nuclei were irregular, often



Figs. 1, 2. Immunocytochemistry demontrates fairly uniform positivity for growth hormone. On consecutive sections, immunoreactive prolactin is present in the same areas. A few scattered large cells, showing intense staining, are conspicuous. Immunoperoxidase technique for growth hormone and prolactin, $\times 250$

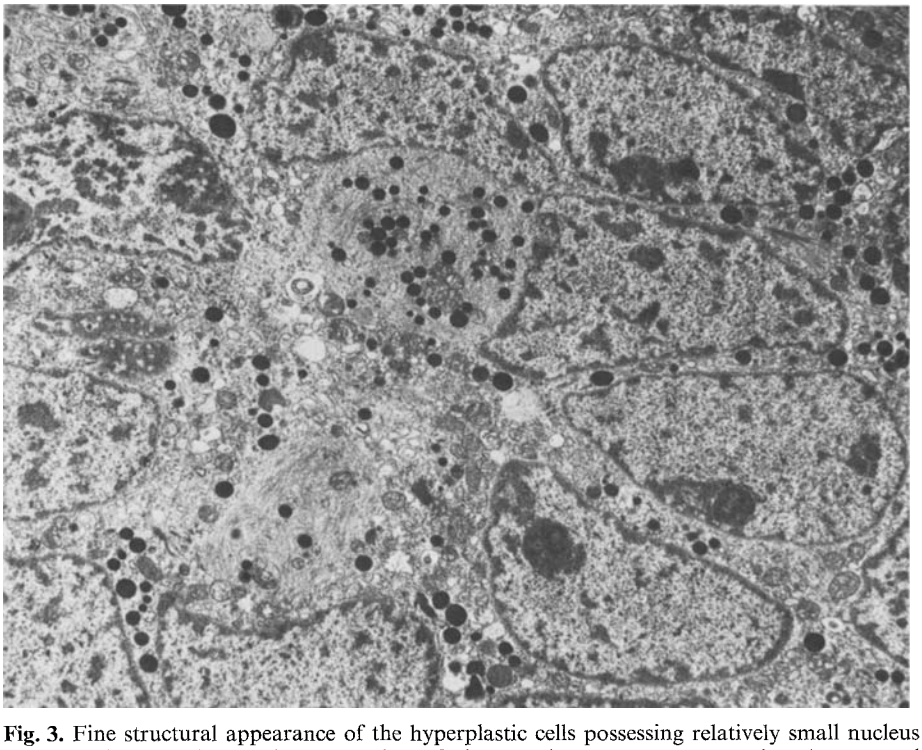


Fig. 3. Fine structural appearance of the hyperplastic cells possessing relatively small nucleus and cytoplasm, and a moderate number of electron dense secretory granules. An unusual feature is the presence of fibrous bodies. $\times 6{,}100$

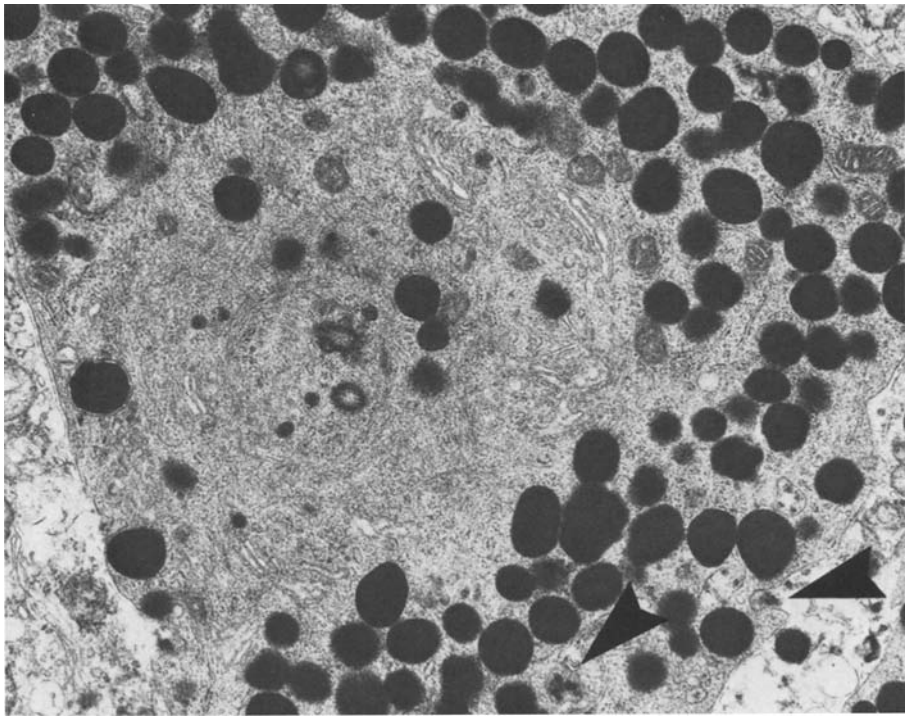


Fig. 4. A mammosomatotroph cell is shown with prominent Golgi apparatus and large secretory granules. Note some granules with mottled appearance (*arrowhead*) and granule extrusions (*arrowhead*) characteristic of this cell type. ×15,700

flattened, with large nucleoli. The cytoplasm appeared to be smaller than that of normal somatotrophs. The rough-surfaced endoplasmic reticulum and Golgi complexes were well developed. A moderate number of dense, spherical or ovoid secretory granules, with diameters of 100–500 nm, were present; the majority measured approximately 400 nm. In the Golgi areas, small but distinct filamentous aggregates representing fibrous bodies, often containing 1–5 centrioles, were commonly encountered. On the pericapillary aspect of cells, granule extrusions were noted. Based on their ultrastructural features, these cells were regarded as mammosomatotrophs.

Outside the hyperplastic areas, somatotrophs showed regular features, except for the prominence of Golgi complex. An unusual finding was the abundance of mammosomatotrophs (Fig. 4), an uncommon cell type in the normal adenohypophysis. The fine structural appearance of these cells was similar to that of mature, densely granulated somatotrophs which also may contain very large secretory granules. In addition, however, mammosomatotrophs possessed large, irregularly shaped secretory granules with a mottled core and, in contrast to normal somatotrophs, they exhibited exocytosis. In the present case, several mammosomatotrophs contained fibrous bodies in the vicinity of the prominent Golgi complex. Well differentiated

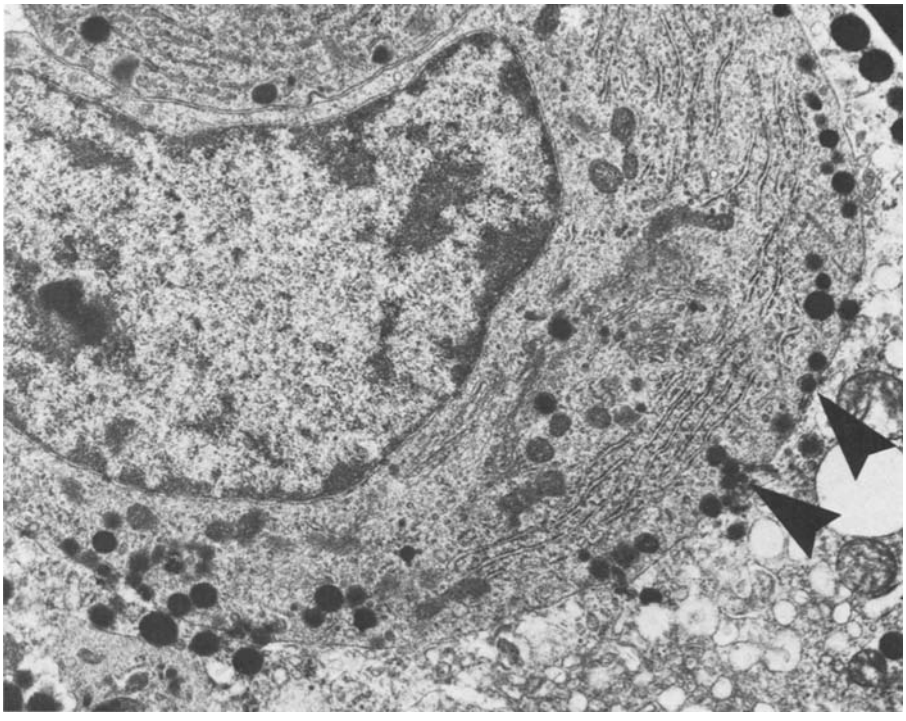


Fig. 5. Lactotroph showing signs of active secretion: well developed RER and Golgi complex, as well as several granule extrusion sites (*arrowheads*). ×12,700

lactotrophs were not more numerous than in normal glands. They displayed all the fine structural signs of stimulation such as abundant rough-surfaced endoplasmic reticulum, conspicuous Golgi apparatus and often granule extrusions as well (Fig. 5).

Corticotrophs occurred in clusters; thyrotrophs showed no major abnormalities. Gonadotrophs were small and appeared to be unstimulated. The capillaries showed normal features. No adenoma cells were identified in the electron microscopic specimens.

Discussion

The morphologic changes in the adenohypophyses of subjects with the McCune-Albright syndrome have been insufficiently examined. The few reported histologic studies describe either chromophobic adenoma (Joishy and Morrow, 1976), basophilic cell hyperplasia (Sternberg and Joseph 1942; MacMahon 1975), or no structural abnormalities (Jervis and Schein 1951; Wiggins 1955; Albin and Wu 1981). In our case, which represents the first surgically-removed adenohypophysial tissue investigated not only by conventional histologic methods, but also by immunocytology and electron microscopy, a massive hyperplasia of a bihormonal cell type, capable of

producing both growth hormone and prolactin was demonstrated. Since no adenoma was found, the abundance of such mammosomatotrophs, conclusively shown by electron microscopy, may provide an explanation for the observed development of acromegaly, high serum growth hormone levels and hyperprolactinemia. The ultrastructural analysis, by indicating that the mammosomatotrophs were in a phase of active secretion, lent further support to the view that mammosomatotroph hyperplasia can be implicated in the causation of growth hormone and prolactin excess.

The presence of mammosomatotrophs in the normal human pituitary was long a point of conjecture. It had generally been assumed that two distinct monohormonal cell types – somatotrophs and lactotrophs – were responsible for growth hormone and prolactin production (Halmi et al. 1975; Kovacs et al. 1977). Recently, however, mammosomatotrophs have been identified in the human pituitary (Horvath et al. 1983). These bihormonal cells containing both growth hormone and prolactin, are uncommon in the nontumorous human adenohypophysis. A rare form of pituitary adenoma, consisting of mammosomatotrophs, has also been reported (Halmi 1982; Horvath et al. 1983). Such mammosomatotroph adenomas are associated with acromegaly, high serum growth hormone levels, and occasionally hyperprolactinemia; they show immunopositivity for growth hormone and prolactin, and possess characteristic fine structural features which permit their identification by electron microscopy. The present case provides conclusive evidence that mammosomatotrophs exist in the nontumorous human pituitary, and that their hyperplasia may bring about significant endocrinologic abnormalities, including acromegaly, elevated serum growth hormone levels and hyperprolactinemia.

Bromocriptine is known to decrease serum prolactin levels, cause regression of prolactin-producing adenomas (Thorner et al., 1980) and induce characteristic fine structural changes in adenomatous lactotrophs, such as reduction of nuclear volume, condensation of nuclear chromatin, decrease of nucleolar size and involution of the cytoplasm with diminished volume densities of rough endoplasmic reticulum and Golgi apparatus (Tindall et al. 1982). Although in our patient serum prolactin levels fell substantially following bromocriptine therapy, ultrastructural alterations attributable to the dopaminergic agonist drug were noted neither in mammosomatotrophs nor in lactotrophs. The cause accounting for the lack of morphologic response is not clear. The bromocriptine-induced involution of adenomatous lactotrophs is reversible (Thorner et al. 1981) and no morphologic change can be detected a few weeks after withdrawal of medication (Tindall et al. 1982). Since in our patient bromocriptine was given up to the surgery and serum prolactin levels were lowered, the possibility that the lactotrophs were not exposed to dopaminergic suppression could be excluded. We have also studied somatotroph adenomas removed from bromocriptine-treated patients showing a decrease in serum growth hormone concentrations, but no evidence of cellular response. Hence, it appears that various pituitary cell types may react differently to bromocriptine; whereas, adenomatous lactotrophs exhibit involution, adenomatous somatotrophs, hyperplastic mammosomatotrophs and nontumorous lactotrophs may not be altered morphologically.

The pathogenesis of mammosomatotroph hyperplasia in association with the McCune-Albright syndrome is obscure. It has been suggested that overgrowth of bone at the base of the skull might exert pressure on the hypothalamus, thus producing changes in the secretion rate of hypothalamic hormones (Lichtenstein and Jaffe 1942; Thannhauser 1944). This interpretation may be discarded in that abnormal pituitary function has been noted in several patients with no osseous deformities of the sellar regions (Hall and Warrick 1972; Warrick 1973). According to several workers, pituitary overactivity in patients with the McCune-Albright syndrome may be due to a congenital hypothalamic abnormality causing hypersecretion of hypothalamic releasing hormones (Hall and Warrick 1972; Warrick 1973; Lightner et al. 1975; Albin and Wu 1981). Although stimulation of preexisting mammosomatotrophs by humoral agents is an intriguing possibility, it is difficult to understand why somatoliberin excess and/or somatostatin and dopamine deficiency would selectively affect mammosomatotrophs and result in their proliferation, rather than inducing hyperplasia of mature somatotrophs and lactotrophs. Alternatively, it may be that secondary to a congenital defect of the hypothalamus, an abnormal hypothalamic factor is produced which stimulates preexisting dormant mammosomatotrophs and elicits their proliferation. Yet another cause of mammosomatotroph hyperplasia could be a somatoliberin secreting extrapituitary tumor (Frohman et al. 1980; Thorner et al. 1981). These uncommon neoplasms are accompanied by acromegaly and, in at least one such case, proliferation of mammosomatotrophs was demonstrated in the pituitary (unpublished observation). This hypothesis, however, cannot be supported in this case, since no extrapituitary tumor was demonstrated. Explanations based on the theory of increased pituitary sensitivity to hypothalamic stimulating factors or decreased sensitivity to hypothalamic suppression are also unlikely, since they are not supported by laboratory data indicating lack of exaggerated response to hypothalamic-releasing hormones.

A viable alternate explanation for the presence of mammosomatotroph hyperplasia is that it represents an associated inherent genetic or embryonal defect, resulting in an abnormal differentiation of the pituitary with the emergence and proliferation of bihormonal cells, which in turn secrete excessive quantities of growth hormone and prolactin and cause the clinical manifestations of acromegaly and hyperprolactinemia. It may well be that the pituitary lesion represents a primary autonomous disorder which develops unrelated to the hypothalamus, i.e. a complex congenital, multiple error of development may be the principal defect in the McCune-Albright syndrome (Albright et al. 1937; Jervis and Schein 1951; Benedict 1962) which involves to varying degrees many types of tissues, primarily the bones and endocrine system with no direct relation to the hypothalamus.

The question of whether mammosomatotroph hyperplasia can undergo neoplastic transformation remains an unproven but attractive hypothesis. Interestingly, in one reported patient with the McCune-Albright syndrome, the manifestations of acromegaly were noted to precede the development of adenoma (Chung et al. 1983), thus suggesting that the adenoma may

have arisen in the setting of preexisting hyperplasia. Whether, in our patient, the observed mammosomatotroph hyperplasia represented a preneoplastic condition remains unresolved.

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