PITUITARY CYST OF RATHKE'S CLEFT ORIGIN WITH HYPOPITUITARISM

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Pituitary adenoma most frequently is the cause of hypopituitarism occurring in adult life. However, a pituitary cyst, with certain distinctive histologic features pointing to an origin from Rathke's cleft, may be the pathologic cause. The rarity of this condition is evidenced by the paucity of published reports.6–8,12,14 Some of the patients, in the reported cases, had signs of hypopituitarism, others had a predominance of effects of pressure on nearby structures.

The incidental finding, post mortem, of such a cyst, in an elderly man who clinically had presented signs of myocardial infarction and hypopituitarism, warranted this report. It deals with the embryologic and morphologic aspects of the cyst together with the clinical and laboratory findings.

CLINICAL ABSTRACT

A 72-year-old negro male was first hospitalized at the Southern Division of Albert Einstein Medical Center, Philadelphia, on Sept. 11, 1957 with precordial pain and dyspnea of 11 years' duration, and vague abdominal pain of 3 years' duration, associated with slight nausea and vomiting. Food and alkali relieved the gastrointestinal dyspnea. He preferred hot weather. There was loss of pubic hair in the past 4 years. He wore glasses, but did not suffer from headaches or visual disturbances.

The main findings, on physical examination, were the total absence of beard, pubic and axillary hair; female configuration of the trunk; a pale, smooth and glassy-looking skin; a dry scaling over the dorsum of the right foot; and a finely nodular cirrhosis of the liver. The height was 5 feet 8 inches and weighed 165 pounds. Hemogram, blood electrolytes and urinalyses were within normal limits. The upper and lower gastrointestinal series were negative except for narrowing of the pyloric antrum. Gastric analysis revealed normal acidity. Electrocardiography showed right bundle-branch block with ischemia of the anterior wall of the left ventricle. Radiographic of the skull revealed destruction of the dorsum sellae and posterior clinoids, more towards the left. No tumor was seen in the pituitary fossa. The pituitary gland was not found, but the sella contained loose fibrous tissue. There were erosion and destruction of the posterior clinoids and dorsum sellae.

The thyroid gland weighed 10 gm. and was small, firm, gray-yellow and fleshy. Both adrenals weighed together 11.5 gm. and had thinned cortices. The testes had a combined weight of 21 gm. and were firm. The rest of the autopsy disclosed the following: extensive healing myocardial infarctions of the anterior wall of the left ventricle and interventricular septum, associated with marked atheromatous narrowing of the descending branch of the left coronary artery; bilateral pleural effusion; and a finely nodular cirrhosis of the liver.

Microscopic findings. Sections of the pituitary cyst showed the walls to be thrown into papillary folds and lined, for the most part, by tall columnar ciliated epithelium with interspersed goblet cells. A layer of small conical basal cells was present between the columnar cells and the well-formed basement membrane. The ciliated cells were present in the region of the sella (Fig. 1). The cerebrospinal fluid showed no abnormalities. Endocrinological studies on urine and blood done during both admissions are listed in Tables 1, 2 and 3. A 24-hour urine examined for gonadotropin in September 1957 was 5 rat units (our normal, 10 to 24 rat units/day). While in the hospital, the patient was treated for a presumed gastric ulcer, and given, in addition, Acthar gel 40 units, twice daily.

Course. He was re-admitted on Sept. 9, 1959 with an acute exacerbation of the precordial pain with definite radiation to the right arm. Electrocardiography confirmed the clinical suspicion of acute myocardial infarction. He had no symptoms referable to the pituitary lesion. The blood count and serum electrolytes were within normal limits. The physical signs of pituitary insufficiency and the cranial findings were unchanged. Despite vigorous treatment for congestive heart failure, his condition deteriorated and he expired 17 days after hospitalization. The clinical diagnoses were acute myocardial infarction and hypopituitarism secondary to a pituitary adenoma.

Pathological Examination. Autopsy was performed 3 hours after death. Gross findings. The external features were those seen clinically.

Attached to the brain in the region of the pituitary stalk was the wall of a collapsed cyst, measuring 1.5 cm. in diameter, the fluid content of which was lost during removal of the brain. The mammillary bodies and adjacent structures at the base of the brain were distorted and displaced in an upward and posterior direction, and more towards the left. No tumor was seen in the pituitary fossa. The pituitary gland was not found, but the sella contained loose fibrous tissue. There were erosion and destruction of the posterior clinoids and dorsum sellae.

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TABLE 1

Endocrine studies

<table>
<thead>
<tr>
<th>Date</th>
<th>Test</th>
<th>Normal Values</th>
<th>Patient's Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>9/23/57</td>
<td>Protein-bound iodine</td>
<td>3.4–6.7 μg. %</td>
<td>5.4 μg. %</td>
</tr>
<tr>
<td>9/23/57</td>
<td>Non-protein-bound iodine</td>
<td>1–3 μg. %</td>
<td>1.9 μg. %</td>
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<tr>
<td>9/30/57</td>
<td>Blood cholesterol</td>
<td>130–230 mg. %</td>
<td>325 mg. %</td>
</tr>
<tr>
<td>9/30/57</td>
<td>24-hour I-131 thyroid</td>
<td>10%–45%</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>I-131 conversion ratio at 24 hours</td>
<td>Up to 33%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Fro. 1. There is enlargement of the sella with destruction of the dorsum sellae and posterior clinoid processes.

cytoplasm of the ciliated columnar cells was vacuolated, and the nuclei were situated mostly in the center of the cells. Goblet cells occurred in groups of two or more, a picture suggesting intestinal epithelium or mucous-secreting salivary gland. The contents of the goblet cells gave positive reactions with periodic acid Schiff and mucicarmine stains. The columnar ciliated cells gave way, in many areas, to many-layered cells, also lined luminally by cilia. In still other but rare zones, the lining consisted of a single layer of cuboidal cells devoid of cilia (Figs. 2 and 3).

The stroma immediately adjacent to the lining epithelium was loose and edematous and showed few fibroblasts. Further away, the stroma was collagenous, and in these areas there were surviving foci of anterior pituitary cells with adjacent pars nervosa. These anterior pituitary cells were mainly amphophilic, showing minimal granularity by the periodic acid Schiff stain (Fig. 4).

There were multiple foci of calcification in the stroma and in the walls of the large arteries. There was no evidence of neoplasm. Sections of brain, particularly those from the hypothalamus, disclosed no abnormalities.

The testes showed complete testicular atrophy with absence of Leydig cells (Fig. 5). The thyroid was replaced extensively by lymphoid tissue with definite formation of follicles and germinal centers. Scattered islands of small thyroid follicles with flattened epithelium containing pale to pink-staining colloid were present (Fig. 6). The adrenal cortices were markedly thinned (Fig. 7). The gross impressions of healing and healed myocardial infarctions and inactive nutritional-type of cirrhosis of the liver were confirmed.

Our final diagnoses were: Pituitary cyst; old and healing myocardial infarctions with advanced occlusive coronary arteriosclerosis; bilateral pleural effusion; Laennec’s cirrhosis of liver; atrophy of testes; moderate atrophy of thyroid; and clinical hypopituitarism.

DISCUSSION

An unusual feature in this cyst is the presence of columnar ciliated epithelium in its lining. A better understanding of the origin of such a cyst probably can be obtained after the development of the hypophysis cerebri has been reviewed.

Embryologically, the hypophysis arises from two anlage. The pars buccalis develops from an evagination of the buccal mucosa known as Rathke’s pouch. This begins in the 3 mm. human embryo and grows upward toward the ventral surface of the neural tube. Various claims as to the ectodermal or entodermal origin of the hy-

TABLE 2

Glucose tolerance test

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose</th>
</tr>
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<tbody>
<tr>
<td>Fasting</td>
<td>88 mg. %</td>
</tr>
<tr>
<td>1/2 hour</td>
<td>120 mg. %</td>
</tr>
<tr>
<td>1 hour</td>
<td>165 mg. %</td>
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<tr>
<td>2 hours</td>
<td>102 mg. %</td>
</tr>
<tr>
<td>3 hours</td>
<td>48 mg. %</td>
</tr>
<tr>
<td>4 hours</td>
<td>52 mg. %</td>
</tr>
<tr>
<td>5 hours</td>
<td>72 mg. %</td>
</tr>
</tbody>
</table>

(NO glucose in urine at any time)
pophysis have been made. After studying the smallest human embryo available to him, that measuring 4.68 mm., Atwell stated categorically that there was no means of determining where entoderm ceases and ectoderm of the mouth begins.

The anterior surface of the upper part of the pouch develops into the pars anterior, the posterior surface into the pars intermedia, while the cavity of the evagination persists as the hypophyseal cleft between the pars anterior and the pars intermedia. In most animals, this cleft persists throughout life. In man, it remains until about the 16th year when it is either obliterated or becomes loculated by trabeculae of cuboidal epithelium, the loculi being filled by colloid.

Bailey believes that the hypophyseal cleft is either completely obliterated or persists as isolated cystic cavities which may be distinguished from other cavities in this region by their lining of ciliated epithelium. He further stated that the cells of Rathke’s pouch should have the ability to differentiate into all the structures formed from the stomodeum, i.e., mucous membrane, squamous epithelium, teeth, and salivary glands.

In an excellent study, Rasmussen discussed the incidence and significance of ciliated epithelium and mucous-secreting cells in the residual cleft of the human hypophysis. He found tall columnar ciliated cells in only 2 out of 200 hy-

**Fig. 2.** Lining of cyst composed of loose fibrous tissue with papillary infoldings and mixed type of epithelial lining (×100).

**Fig. 3.** Higher magnification of lining of cyst, showing specifically goblet cells and ciliated epithelium (×970).
The ciliated cells were distributed irregularly and were found mostly on the side of the residual cleft next to the anterior lobe. The description of the columnar epithelium, cilia, goblet cells and mucin reaction generally resembles that of our own case. Gillman, in a more recent study of the pituitaries of the normal adult Bantu, found ciliated epithelium and mucous cells in 16 out of 80 such pituitaries in the residual clefts and in vesicles lying in the adjacent pituitary tissue. The residual clefts and cysts measured from 0.2 to 1 mm. in diameter and occurred in persons of ages 3 to 53 years. In the pituitary of a 5-month Bantu fetus, 2–4 ciliated cells were observed in a small alveolus 25 μ in diameter, situated in the substance of the anterior lobe but not connected with the residual cleft. A few of the cells lining this alveolus contained mucin. Shanklin reported an incidence of 13 cysts in 100 pituitaries examined. Most of the cysts were lined with ciliated epithelium but mucous cells were seen in a few only. The cysts measured from 1.1 × 1.5 mm. to 2 × 3.02 mm. The ages ranged from 3½ years to 83 years. There was an 18.9 per cent incidence of ciliated cysts in the age-group 40 to 86 years as compared with 25
per cent in the age-group 20–39 years and 4.3 per cent in the age-group “newborn” to 19 years.

An analogy can be made between the appearance of the cells in the different parts of the present cyst, and those of the nasal and paranasal sinuses, and intestinal epithelium or mucus-secreting salivary glands. This analogy is made because all the structures are derived from the same primitive tissue. The areas of the cyst that resemble the mucus-secreting glandular epithelium show an absence of cilia, thus pointing to increased specialization of the cells. Our cyst shows histologic features that suggest the incorporation of endodermal or nasopharyngeal elements, as suggested by Rasmussen.

On the basis of the above histology and on the evidence submitted by Rasmussen, Gillman and Shanklin, the present cyst is designated a cyst of Rathke’s cleft. This is a true cyst, not to be confused with cystic hypophyseal duct tumors or craniopharyngiomas, which have in the past been referred to interchangeably as Rathke’s cleft cyst. No adamantinomatous or squamous epithelial remnants are seen in our sections.

How long had the cyst been growing? On the basis of the evidence presented by the above-
mentioned investigators, particularly the finding by Gillman of a ciliated alveolus in the anterior lobe of a 5-month fetus, it is possible that the cyst in our patient had been present since birth, and grew and expanded over many years. However, since the greatest incidence of asymptomatic tiny pituitary clefts and cysts with ciliated and mucous epithelium is found at autopsy in persons over the age of 20, it is also possible that the cyst had originated later in life via a process of embryonic metaephelial reversal of pituitary precursor cells. This issue cannot be settled since there is no way of pin-pointing the time of origin or inception of the cyst. It may have taken months or more probably many years for the cyst to expand and destroy enough pituitary gland to result in clinical and laboratory manifestations of hypopituitarism.

Laboratory support for hypopituitarism was seen in depressed adrenocortical functions and gonadal function (Tables 1 and 2). The latter, as measured by one urinary gonadotropin in September 1957, was 5 rat units (normal 10-24 rat units/day). The complete absence of Leydig cells with complete tubular atrophy in the testes corroborated this low activity. Thyroid function, on the other hand, was within normal limits (Table 3). This was surprising, in view of the generalized atrophy and lymphoid-tissue infiltration of the thyroid parenchyma. It would appear that the few remaining intact thyroid follicles were able to maintain a satisfactory functioning state. These results are in direct contrast to those of previous clinical observations that gonadal failure was chronologically the first to appear in hypopituitarism, followed by thyroid insufficiency and, lastly, by adrenocortical insufficiency.

From the above and from the autopsy findings, it appeared that the cyst expanded anteriorly and destroyed approximately 90 per cent of the anterior pituitary lobe, leaving a few scattered islands of amphiophilic pituitary cells which maintained minimal activity of the target organs. In view of this it is surprising that no symptoms or signs referable to pressure on the optic chiasma were produced. In addition, the cyst expanded in an upward and posterior direction, distorting the mammillary bodies of the hypothalamus and destroying the posterior clinoids and dorsal sellae. Despite the location and pressure of the cyst on the regional structures of the hypothalamus, there were no clinical findings to suggest diabetes insipidus.

**SUMMARY**

A pituitary cyst of Rathke's cleft origin in a 72-year-old negro male has been presented. This cyst had destroyed most of the anterior pituitary lobe leaving only a rare island of amphiophilic anterior pituitary cells. Hypopituitarism was manifest clinically and as reflected in tests of endocrinological function, particularly adrenocortical functions. Histologically the cyst was lined by columnar ciliated and mucous-secreting epithelium. A brief survey of pituitary embryology and the frequency of finding residual columnar ciliated epithelium in human hypophyses has been presented.

**REFERENCES**


