Symptomatic Rathke's cleft cyst with amyloid stroma

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SYNOPSIS A patient with panhypopituitarism and visual field defects due to a Rathke's cleft cyst is presented. These cysts are commonly found in random pituitaries examined at necropsy, but rarely produce symptoms. Subtle endocrine deficiencies, however, may now be uncovered more frequently with modern diagnostic techniques. An unusual and unreported feature of this cyst was an apudamyloid stroma. This would imply that cells derived from the neural crest participate in the formation of the cyst. Recognition of these cysts at the time of operation is important in avoiding confusion with pituitary adenomas and unnecessarily aggressive treatment.

Small cysts of Rathke's cleft which are asymptomatic are common (Bayouini, 1948; Shanklin, 1951). Occasionally, however, they may produce both neurological and endocrinological symptoms (Frazier and Alpers, 1934; Berry and Schlezinger, 1959; Fager and Carter, 1966; Giuffre and Gagliardi, 1968; Shuangshoti *et al.*, 1970; Ringel and Bailey, 1972), when they may be mistaken clinically for chromophobe adenomas. This can lead to unnecessarily aggressive treatment.

Reported is a Rathke's cleft cyst associated with hypopituitarism and chiasmal compression. Histological studies of the cyst unexpectedly revealed an amyloid stroma, the implications of which are discussed.

CASE HISTORY

A 53 year old black male steelworker was admitted to a community hospital in August 1971, complaining of lethargy and loss of libido.

At examination he had the clinical features of hypothyroidism and hypogonadism without visual impairment. Skull radiography revealed a large sella with depression of the floor and thinning of the dorsum. No treatment was ordered and he was lost to follow up.

In May 1972, he was admitted to the Loch Raven VA Hospital again with features of hypothyroidism and hypogonadism but no polyuria, headaches, or visual disturbance. The main findings on examination were as follows: height 172.7 cm (68 in.), weight 100 kg (220 lb). He was well oriented, somnolent but easily roused. His pulse was 55/min regular; blood pressure was 140/90 mmHg. His skin was cool and dry; the thyroid was not palpable. Ankle jerk relaxation was delayed. Beard, axillary and pubic hair were sparse. The prostate was not palpable, testes were 2.5 × 1.5 cm soft. Visual ability was (R) 20/25 (L) 20/25; fields were full on tangent screen examination.

ENDOCRINE STUDIES² (1) *Thyroid* Serum thyroxine (T4) level was 30.9 nmol/l (2.4 µg/dl) (Murphy-Pattee, N. 5-13.7 µg/dl); I¹³¹ uptake at 24 hours was 5%, after 10 u TSH intramuscularly it was 36%; basal serum TSH (radioimmunoassay) was not detected, in response to TRH 50 µg intravenously, it was not detected up to 20 minutes, reaching a peak of 12.4 µU/ml at 60 minutes. (2) *Adrenal* 24 hour urinary free cortisol was 276 nmol (10 µg). (N. 16-71 µg/24 hrs), with 40 units ACTH infused over eight hours it rose to 1167.5 nmol/24 hrs (42.3 µg/hr); plasma cortisol at 8 a.m. was 24.8 nmol/l (0.9 µg/dl) (N. 9-20 µg/dl), after 25 units ACTH infused over five hours it rose to 690.0 nmol/l (25.0 µg/dl); 24

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² Abbreviations: T4—total thyroxine. TSH—thyroid stimulating hormone. RAI—radioiodine. TRH—thyrotrophin releasing hormone. ACTH—adrenocorticotrophic hormone. Compound S—11-deoxy cortisol. LH—luteinizing hormone.

FIG. 1 Preoperative visual fields.

hours urinary tetra-hydro compound S (on the day of and the day after oral metyrapone 750 mg four hourly for six doses) was 2.0 and 1.3 mg/24 hr respectively. (3) *Gonads* Serum testosterone concentration was 150 ng/ml (radioligand assay), basal

serum LH (radioimmunoassay) <4 mIU/ml; after oral clomiphene citrate 200 mg/day for six days, LH was still <4 mIU/ml. (4) *Growth hormone (GH)* Basal serum GH (radioimmunoassay) 1 pg/ml, after intravenous, regular (soluble) insulin 0.1 U/kg body wt, blood glucose fell to 1.7 mmol/l (31 mg/dl); GH did not rise above 1 pg/ml. (5) *Posterior pituitary* Average output of urine was 1.5–2.0 l/24 hr; serum sodium 138–141 mmol/l; without fluids overnight, at 8 a.m. the serum osmolality was 288 mmol/kg, urine osmolality 700 mmol/kg.

Radiology of the skull showed an enlarged sella (20 mm long, 15 mm deep). Bilateral carotid angiograms were normal.

The patient was discharged on hormone replacement with oral L-thyroxine and cortisone acetate, and intramuscular testosterone. By August 1973 outpatient follow-up revealed a left visual field defect for

FIG. 2 Preoperative neuroradiology:
A. Lateral skull showing enlarged sella.
B. Pneumoencephalogram with questionable suprasellar extension of tumour.
C and D Normal carotid arteriogram.

FIG. 3 Convoluted cyst replacing one-third of the hypophysis. *H and E stain, $\times 48$.*

FIG. 4 Cyst lined by ciliated columnar cells. *H and E stain, $\times 300$.*

the first time (Fig. 1) with no additional signs. The sella now measured 24 mm long by 19 mm deep, the EEG was normal, and the pneumoencephalogram showed normal ventricles with no air in the sella but questionable suprasellar extension of a tumour mass (Fig. 2). Right frontal craniotomy was performed with the presumptive diagnosis of a pituitary adenoma. At operation a large encapsulated and apparently solid intrasellar tumour was found compressing both optic nerves. This was removed completely.

Postoperatively the patient developed partial diabetes insipidus with 24 hour urine volumes of 4–5

litres. The maximal urinary osmolality after dehydration was 350 m osmol/kg, promptly rising to 512 m osmol/kg with aqueous pitressin injected subcutaneously. This polyuria was initially well controlled with a combination of chlorpropamide and clofibrate, but cleared spontaneously after about nine months. The preoperative visual field defect was only partially corrected.

PATHOLOGY The specimen consisted of multiple pieces of soft tissue weighing approximately 0.5 g. No gross cyst was identified.

Microscopically, one-third of the hypophysis was replaced by a convoluted cyst (Fig. 3). This was lined by simple cuboidal epithelium with occasional patches of ciliated columnar cells (Fig. 4). PAS positive, diastase resistant, and mucicarmine positive material was present intracellularly and in the cystic cavity which appeared distended and occasionally ruptured into a fibrous stroma. This fibrous stroma showed areas of homogeneous acidophilic material that stained positively for amyloid with Congo Red, by bright and polarized light. Thioflavine S staining was also positive (Fig. 5). Histochemical staining for tryptophan and tyrosine (Pearse, 1972) was negative.

A rim of compressed but entirely normal anterior lobe of the gland and some remnants of the posterior lobe were identified. The exact relations of the cyst to the stalk could not be determined. The gross impression of solid tumour was probably caused by the prominent fibrous stroma.

DISCUSSION

Cysts of Rathke's cleft are found in 13–22% of randomly examined pituitary glands (Bayouini, 1948; Shanklin, 1951); clinically detectable cysts,

FIG. 5 Positive fluorescence of stroma. *Thioflavine S, $\times 64$.*

however, are rare with only 30 odd cases reported and only 18 of these removed surgically. These cases produced asymptomatic enlargement of the sella turcica, or suprasellar symptoms such as headache and visual field defect, and endocrine dysfunction (Berry and Schlezinger, 1959).

This patient had sellar enlargement, visual field defects, and endocrine abnormalities which had remained quiescent for a period of years and then deteriorated, possibly due to cyst enlargement. Detailed endocrine studies are not available in the literature largely because the reported cases were studied before modern diagnostic techniques were available. Subtle partial hypopituitarism, therefore, may be more common with these cysts than is realized. The clinical impression of hypogonadism and hypothyroidism in our case was confirmed by the low serum testosterone and T4 and the low RAI uptake at 24 hours. A pituitary lesion was implicated as the cause by the low baseline LH which failed to rise with clomiphene stimulation (Bardin *et al.*, 1967), and by the undetectable basal TSH levels which rose subnormally after TRH (Fleischer *et al.*, 1970), while the RAI uptake did respond briskly to exogenous TSH. Along with these lesions, the presence of growth hormone deficiency indicated by the lack of response to insulin hypoglycaemia (Rabkin and Frantz, 1966) was expected. There were no clinical signs, however, of the secondary hypo-adrenalism, demonstrated by the low baseline steroids which rose with exogenous ACTH, and the subnormal tetrahydro compound S response to metyrapone (Liddle *et al.*, 1959). Pre-operatively water metabolism was normal, but the patient developed partial diabetes insipidus immediately after operation, achieving on deliberate dehydration a maximum urinary osmolality of 512 m osmol/kg (Miller *et al.*, 1970). This was presumably due to pituitary stalk damage at the time of operation, and had disappeared after nine months.

The prognosis for Rathke's cleft cysts is in general excellent. Characteristically, the disease progresses slowly and may remain stable for long periods of time (as in this case). The current therapy advocated is drainage with liberal opening of the wall (Fager and Carter, 1966) and only two recurrences have been reported (Ringel and Bailey, 1972). Therefore, before complete removal of any pituitary tumour is performed

initial biopsy and examination of a frozen section is advocated to exclude this benign condition.

Histopathologically, the presence of ciliated columnar epithelium, forming cyst-like spaces with mucin material intracellularly and in the contents of the cyst, is diagnostic of so-called Rathke's cleft cysts (Berry and Schlezinger, 1959).

The embryological origin is controversial. The most commonly held view is that the cysts derive from Rathke's pouch epithelium (Frazier and Alpers, 1934; Shanklin, 1951; Berry and Schlezinger, 1959; Fager and Carter, 1966; Giuffre and Gagliardi, 1968; Ringel and Bailey, 1972), but the possibility that some may take origin from neuroepithelium cannot be easily rejected (Shuangshoti *et al.*, 1970).

An unexpected finding in the present case was amyloid deposition in relation to the cyst. This is apparently rare. A solitary previous case report was found where amyloid was described in a chromophobe adenoma following radiation therapy in a dosage of 4,500 rads (Barr and Lampert, 1972). Amyloid may also occur in the pituitary in primary familial amyloidosis with polyneuropathy (Portuguese type) (Lampert, 1968). There was no evidence of this condition in our patient.

The amyloid we describe stained negatively for tryptophan and tyrosine. This is a feature of 'apudamyloid' distinguishing it from the more common 'immunamyloid' (Pearse, 1972) associated with abnormal immunoglobulin production. Apudamyloid is known to occur in a select group of endocrine tumours including medullary carcinoma of the thyroid, islet cell tumours of the pancreas, pheochromocytoma, foregut carcinoids, and carotid body tumours (Lampert, 1968; Pearse, 1969, 1974). These tumours have similar staining properties, histochemistry and histology. Furthermore, they have the potential for peptide hormone production and apudamyloid may represent fragments of these peptides (Pearse, 1972). There is now strong evidence that these close relationships are explained by a common origin of the cells involved from the primitive neural crest (Weichert, 1970).

Our findings therefore suggest that neural crest cells may participate in the development of Rathke's cleft cysts. Alternatively the apudamyloid may represent retained peptide hormone

products from the compressed adjacent anterior pituitary. Here the 'c' and 'm' cells producing ACTH/MSH could be implicated since they are also considered to be neural crest derivatives (Pearse, 1974).

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