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Ectopic anterior pituitary corticotropic tumour in a six-year-old boy

Histological, ultrastructural and immunocytochemical study

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Summary. The report documents a silent, oncocytic, ACTH-producing ectopic anterior pituitary tumour in a 6-year-old boy. The invasive intrahemispheric neoplasm had no connection with the pituitary gland, the sella turcica or the sphenoid sinuses. The apparent similarities existing between this tumour, some choroid plexus carcinomas and steroid-producing neoplasms are discussed.

Key words: Corticotropic adenoma – Ultrastructure – Pituitary oncocytoma – Choroid Plexus carcinoma – Mitochondrial morphology

Introduction

Ectopic anterior pituitary tumours with normal anterior pituitary glands are exceptional in children. In the literature, we only found two cases in which this diagnosis could be made. Both patients were 15 years old. In the first case, the tumour was completely parasellar, extending into the superior orbital fissure and had no attachment to the sellar region (Ortiz-Suarez and Erickson 1975). Although radiologically, mottling of the sella turcica was seen, at surgery a normal pituitary gland was visualized and post-operatively the patient required no hormonal replacement. In the second case, the sphenoid bones and the sella were not affected (Rothman et al. 1976). The tumour involved the hypothalamus and the floor of the third ventricle and had no connection with the sellar region. However, after surgical removal, clinical evidence of hypopituitarism developed. In both cases the tumours which were only studied histologically, were diagnosed as chromophobe adenomas.

The purpose of the present report is to document a large ectopic anterior pituitary tumour affecting the left hemisphere of a 6-year-old boy. Histological evaluation of the tumour was completed by ultrastructural and immunocytochemical studies which showed it to be a non-functional oncocytic corticotropic cell neoplasm.

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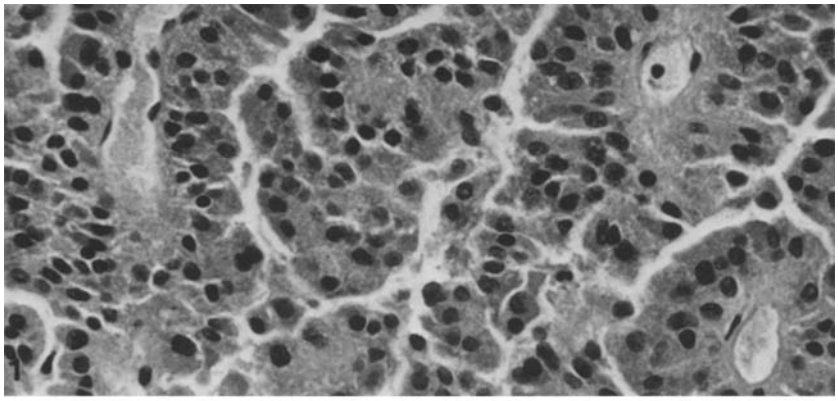
Case history

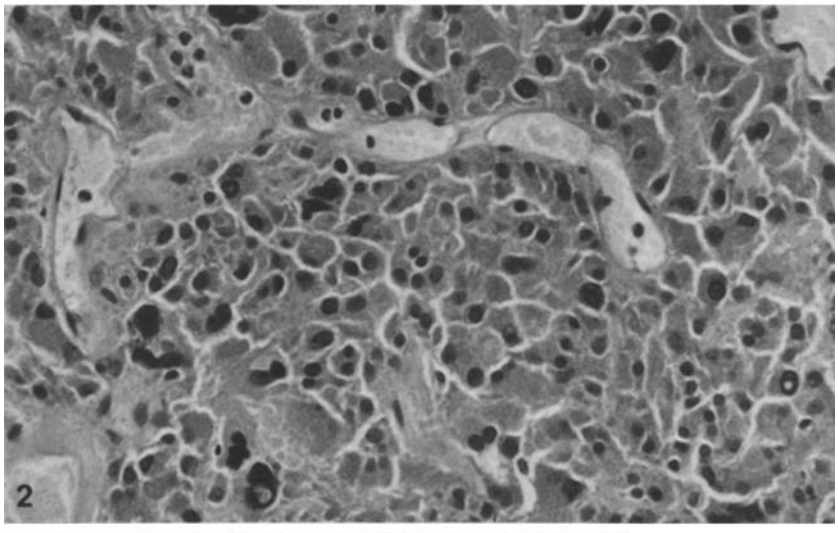
A 6-year-old male presented with somnolence, vomiting, and occipital headache. Physical examination revealed papilloedema, and skull x-rays showed signs consistent with chronically raised intracranial pressure. Computerized tomography (CT) demonstrated a large left hemispheric mass extending from the temporal pole to the centrum semi-ovale. The sphenoid bones and the sella turcica were normal. The tumour was partially resected. Subsequent investigations, including chest x-ray, excretory urogram, skeletal survey, and liver-spleen scan were negative. Radiotherapy (4500 rads) and chemotherapy (Vincristine and CCNU) were administered over the ensuing months. The residual mass persisted. The patient deteriorated rapidly, and was unable to walk or talk and became blind. When the diagnosis of ectopic anterior pituitary tumour was established further investigation was not judged justifiable as the patient had never shown evidence of endocrine dysfunction. Endocrinological studies were not performed. The patient is now 15 years old and severely handicapped, but did not develop metastatic lesions.

Materials and methods

For histological studies, formalin fixation was used and, in addition to stains employed for routine evaluation of neuroglial tumours, the following stains were performed: Hematoxylin-Phloxine-Saffron (HPS), Periodic Acid-Schiff (PAS) with and without diastase treatment, PAS-Orange-G, Slidder's orange-fuchsin-green and, mucicarmine.

For electron microscopy, routine methods were used. Immunocytochemical studies were performed on formalin-





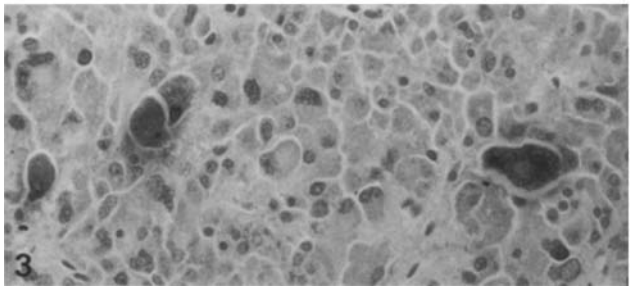


Fig. 1. Representative histological field: epithelial organization centered, in places, around blood vessels. The cells are granular and eosinophilic (*HPS*)

Fig. 2. Marked cytoplasmic and nuclear pleomorphism, with many giant hyperchromatic forms. (*HPS*)

Fig. 3. Immunoreactive ACTH demonstrated in cells scattered throughout the tumour. (*PAP technique*)

fixed, paraffin-embedded samples. An attempt at demonstration of glial fibrillary acidic protein (GFAP) and neuron-specific enolase (NSE) was made using the peroxidase-antiperoxidase (PAP) technique and the immunohistology kits obtained from Miles Scientific, Naperville, IL. The same technique was employed for demonstration of immunoreactive adrenocorticotrophic hormone (ACTH), Growth Hormone and Prolactin. The kits were obtained from Immunon-Lipshaw, Detroit, MI. For neurofilament-protein (NFP), the indirect peroxidase-labelled antibody technique and the kit produced by Euro-diagnostics (Apeldoorm, Holland) for monoclonal antibodies were used. S-100 protein demonstration was attempted with the PAP technique using lyophilized rabbit S-100 protein antiserum obtained from the Hospital for Sick Children Research Development Corporation (Toronto, Ontario, Canada). Sections of normal brain, astrocytoma, ependymoma, normal pediatric and adult pituitary glands were used as positive and negative controls. In each instance, the supplier's instructions were followed.

Results

Histological sections revealed a well-vascularized, non mucin-producing neoplasm composed, in some fields, of columnar cells, with basally-oriented nuclei, growing around blood vessels, and occasionally forming sinusoids and papillary projections (Fig. 1). Cellular, and particularly nuclear, pleomorphism was prominent in other fields where many large and multinucleated cells were seen (Fig. 2). Prominent nucleoli were also present. Mitoses were extremely rare. Generally, the cytoplasm was abundant, eosinophilic, and very granular. Intranuclear cytoplasmic invaginations were commonly seen in the multinucleated cells.

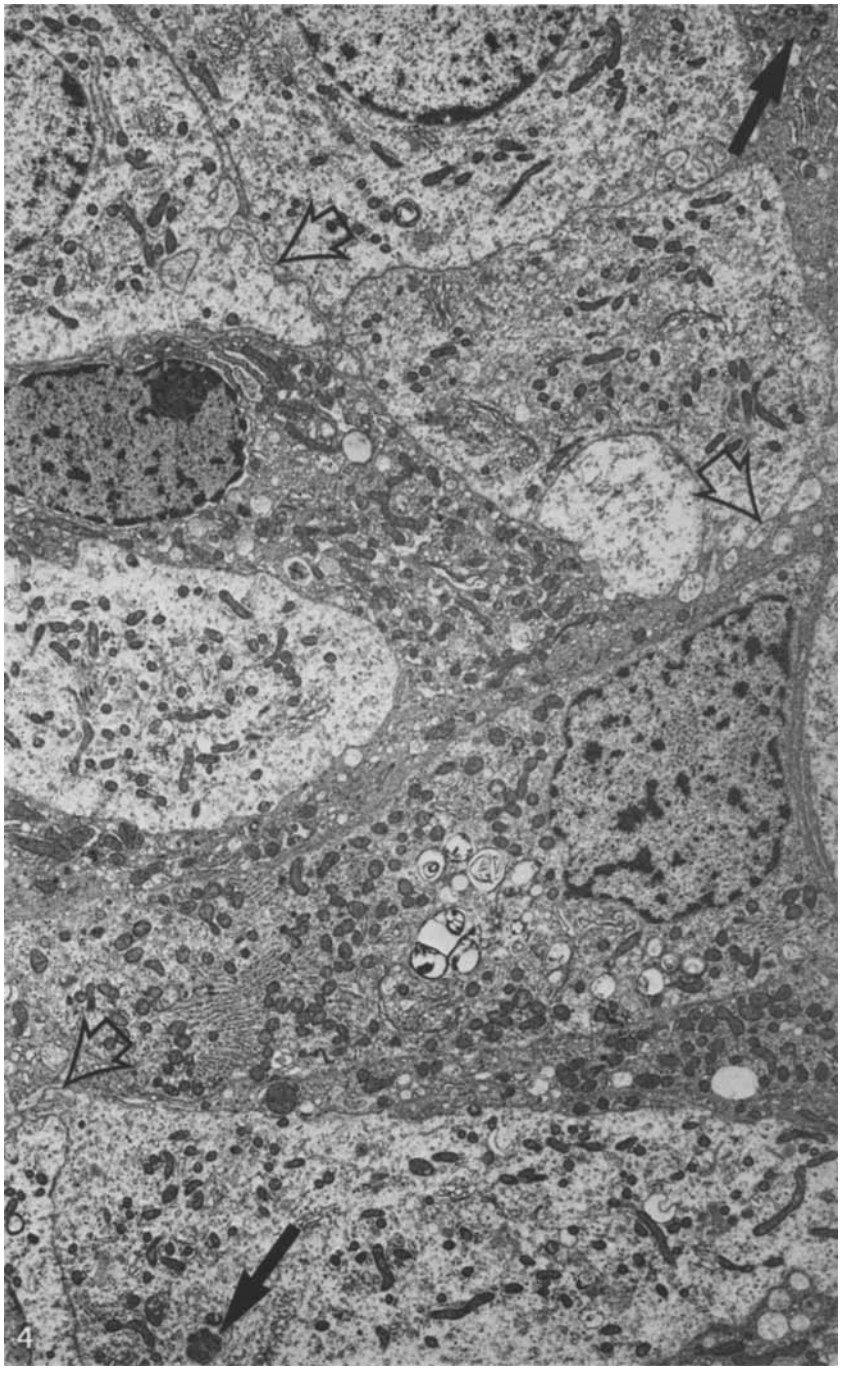


Fig. 4. Low-power electron micrograph of the tumour: clear and dark cells closely apposed, joined by complex interdigitations (*open arrows*). Variable amounts of mitochondria and smooth and rough endoplasmic reticulum are present. Each cell contains multiple Golgi complexes. Some contain (*black arrows*) numerous centrioles (see Fig. 8) and aggregates of ciliary bodies (see Fig. 9). (× 5000)

Moderate to strong positive staining for NSE was seen throughout. The reaction for ACTH was strong in many diffusely scattered cells. However, most were negative or weakly positive (Fig. 3). Immunoreactivity for Prolactin, Growth Hormone, GFAP, S-100 protein, and neurofilaments was not demonstrable.

Ultrastructurally, the solid parts of the tumour appeared to be composed of closely apposed pale and dark cells with round nuclei and occasional prominent nucleoli (Fig. 4). In many cells the cytoplasm was almost completely filled with mitochondria. In addition, some cells showed an abundance of smooth-walled vesicles resembling smooth endoplasmic reticulum (SER). The mitochondria in some cells, were very large and bizarrely shaped (Fig. 5) and often contained large matrical homogeneous osmophilic inclusions measuring up to

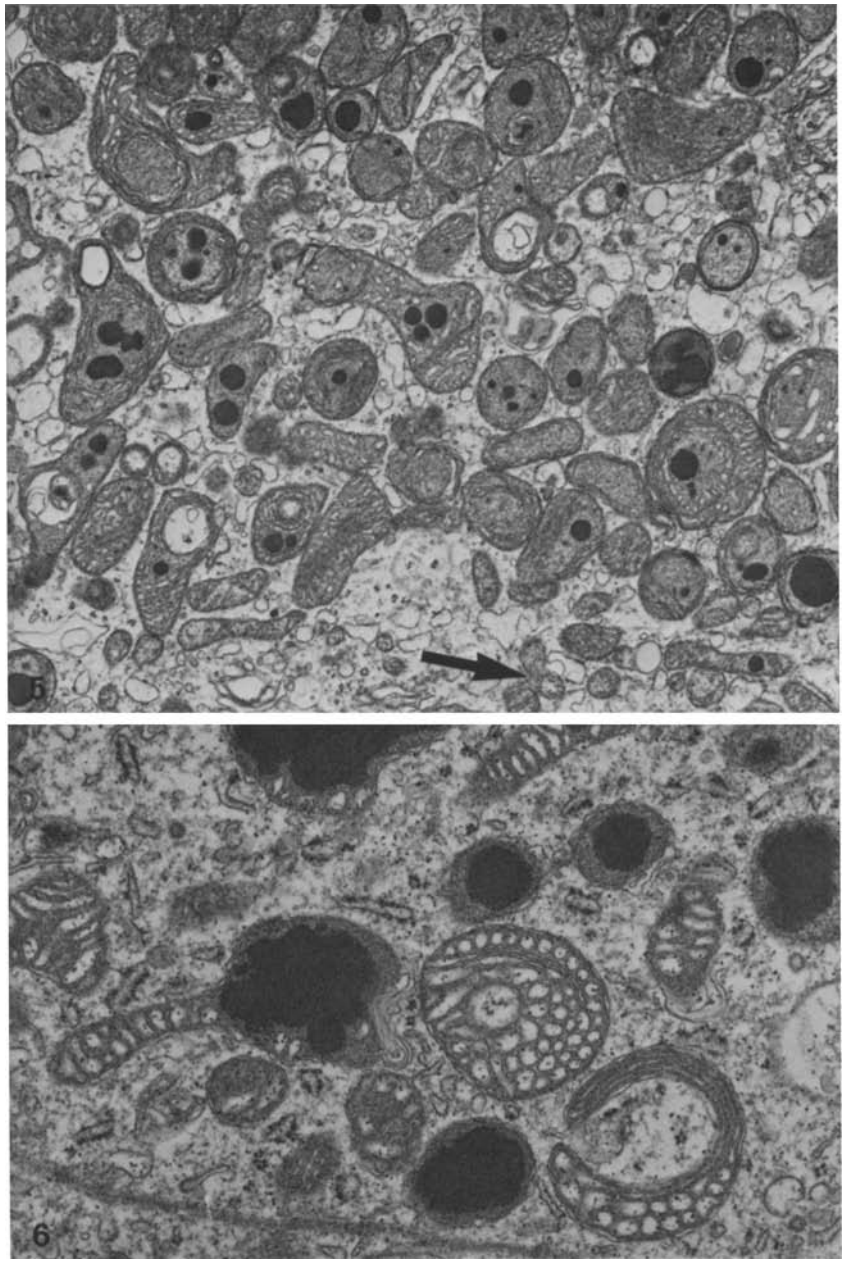
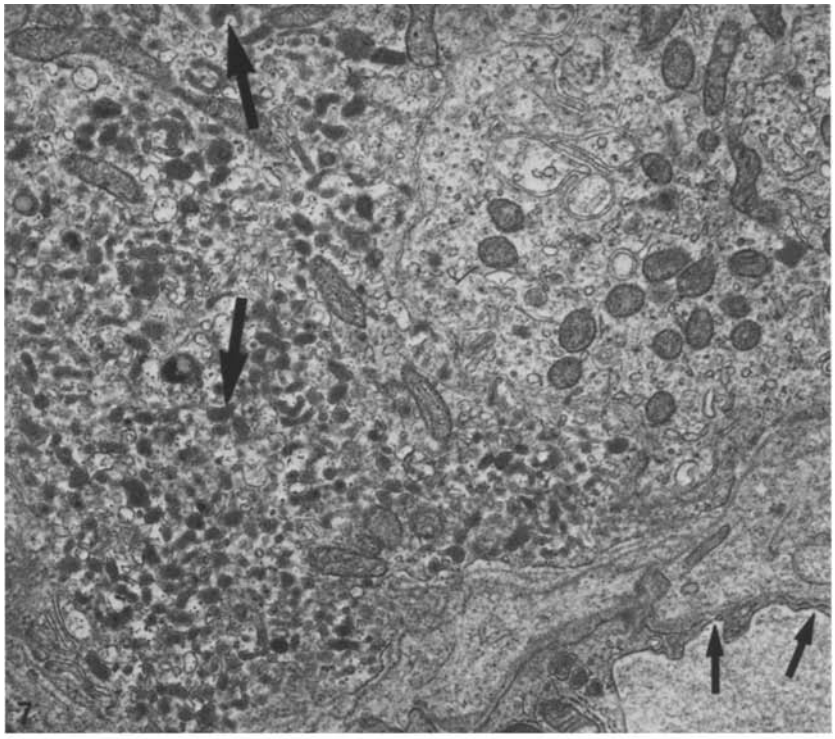


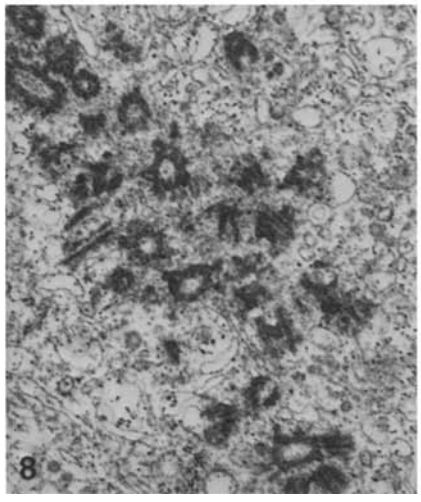
Fig. 5. Oncocytic change with abnormally-shaped large mitochondria and large matrical electron-dense inclusions. For comparison, the arrow indicates mitochondria of normal size. In the cytoplasm, a background rich in smooth endoplasmic reticulum can be seen. (×11250)

Fig. 6. Ultrastructural detail of the abnormal mitochondria, clearly showing lamellar cristae separated by swollen and empty-looking matrix. (×21375)

500 nm. They also had complex lamellar cristae separated by markedly swollen and electron-lucent inter-cristal spaces which imparted to the organelles a superficial resemblance to mitochondria with tubular cristae (Fig. 6). Scattered cells, in which the number and size of mitochondria approached normality, contained electron-dense membrane-bound granules in the cytoplasm. Such cells were usually adjacent to vessels in which segments of fenestrated endothelium could be seen (Fig. 7). Their granules measured 150 nm to 300 nm and many had a "tear drop" shape. Extensive complex interdigitating cytoplasmic folds and, in places, numerous well-developed tight junctions were present between adjacent cells. Prominent Golgi zones, rough endoplasmic reticulum, free ribosomes and some lysosomes were seen in many cells. Rare annulate lamellae were also present. Some cells contained numerous centrioles (Fig. 4 and 8). Aggregates of ciliary bodies were also noted (Fig. 4 and 9). In some areas, there was evidence of basal lamina deposition between the neoplastic cells. However, clear cellular polarization in relation to basal laminae could not be found in the blocks examined.

At the completion of these studies, the neo-





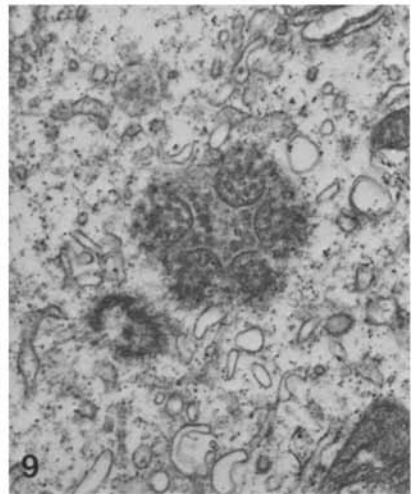


Fig. 7. Electron micrograph of a perivascular area. Fenestration of the endothelium is indicated by the small arrows. Overlying the basal lamina, is a secretory granule-rich cell. Many granules have the "tear drop" shape characteristic of ACTH granules (*big arrow*). (×11250)

Fig. 8. Aggregate of centrioles. (×17500)

Fig. 9. Rudimentary cilia bordering a small luminal space. (×25000)

plasm was diagnosed as silent and invasive anterior pituitary corticotropic cell tumour with oncocytic change.

Discussion

The subject of ectopic anterior pituitary adenomas with a normal intrasellar gland has been recently reviewed (Lloyd et al. 1986). In adults, those rare tumours usually involve the sphenoid sinus.

In the young pituitary adenomas are very rare (Challa et al. 1985; Farwell et al. 1977; Schoenberg et al. 1976). This explains why, when an ectopic intrahemispheric anterior pituitary tumour (APT) develops in a child whose sella turcica and sphenoid bones are normal and who shows no evidence of endocrine dysfunction, the cell of origin of the neoplasm may be difficult to recognize.

In the present case, the leading working diagnosis was originally that of choroid plexus carcinoma (CPC). CPC is seen in children and may invade the ventricular system and the hemispheres, and exhibit histological patterns and cytological features similar to those seen in this case (Dohrmann and Collias 1975; Nakashima et al. 1982). Occasionally, choroid plexus tumours (papillomas) may

even be oncocytic (Stefanko and Vezevski 1985). However, save for melanin and globules of mucin, secretory products have not been shown to be present in CPC cells and those demonstrated ultrastructurally in the present case (Fig. 7) have never been shown in choroid plexus tumours to our knowledge (Boesel and Suhan 1979; Coffin et al. 1986). However, they are consistent with the size and shape of the secretory granules seen in ACTH-producing cells. This finding was pivotal in raising the possibility of an ectopic APT, which was later confirmed by the demonstration of intracytoplasmic immunoreactive ACTH. The biological behaviour of the tumour after a follow-up of 9 years also supports this interpretation. As for the remaining ultrastructural features observed, they are consistent with both choroid plexus and anterior pituitary origin. In both, ciliary bodies, annulate lammelae, and increased numbers of mitochondria within the cytoplasm of closely apposed clear and dark cells joined by interdigitating folds and tight junctions have been reported. In both, the endothelium of the supporting stroma may be fenestrated (Boesel and Suhan 1979; Challa et al. 1985; Horvath et al. 1980; Kovacs et al. 1984; Moss 1983; Nakashima et al. 1983). The negative immunocytochemistry results obtained for GFAP, NF, and S-100 protein are also consistent with both diagnoses, although positivity for S-100 protein has been demonstrated within normal choroid plexus cells and some papillomas and carcinomas. Focal GFAP positivity has been detected, on occasion, in choroid plexus papillomas. NSE has been demonstrated in both anterior pituitary and, choroid epithelium cells (Coffin et al. 1986; Kimura et al. 1986; Rubinstein and Brucher 1981; Taylor 1986).

Non-functional pituitary tumours containing hormone-producing cells have been called "silent". Such tumours may contain ACTH-producing cells, be invasive and have been shown to display oncocytic change and ultrastructural features similar to those seen in the present case (Challa et al. 1985; Horvath et al. 1980; Kovacs et al. 1983; Scheithauer 1984). Our failure to detect perinuclear filaments and "enigmatic bodies" could be reflecting the state of hypoactivity and nonresponsiveness of the tumour to the normal feedback mechanism regulating ACTH production (Challa et al. 1985; Scheithauer 1984; Horvath et al. 1977). Other features observed in this case were unusual and are potentially misleading. They have been reported in pituitary oncocytic tumours: the presence of abnormal mitochondria containing large matrical osmophilic inclusions, in association with a smooth endoplasmic reticulum. This could impart to the cells a morphology reminiscent of the steroid-producing cells (Silva et al. 1982). This is particularly true when the mitochondrial cristae are tubular (Gjerris et al. 1978). However, the resemblance is probably coincidental, reflecting a non cell-specific phenomenon: SER has been seen in pituitary oncocytic tumours (Horvath et al. 1980) and the large matrical inclusions within the mitochondria have been illustrated in various non-neoplastic and neoplastic tissues undergoing oncocytic change (Ghadially 1985; Tandler et al. 1970). They have even been seen in non-neoplastic oncocytes of the choroid plexus epithelium (Kepes 1983). Their observation within the same cell, therefore, is a possibility which could be anticipated. As for the cristae, in this case at least, they were lamellar and not tubular. The potentially confusing appearance suggesting a tubular cristal configuration was due to the marked swelling and electronlucency of the matrix.

Oncocytic change in pituitary tumours, while rare in children, is not linked to an age group or a cell type (Gjerris et al. 1978; Horoupian 1980; Kalyanaraman et al. 1980). Based on currently prevailing definitions, the degree of oncocytic change was insufficient to call the tumour an oncocytoma. It could be also debated whether it should be called adenoma or carcinoma. In the absence of metastases, neoplasms with similar behaviour have been referred to as invasive adenomas (Kovacs et al. 1984; Scheithauer 1984).

The pharyngeal pituitary, the intra-sphenoidal portion of the obliterated pharyngeal duct, and the pars tuberalis have been proposed as possible origin of extrasellar anterior pituitary tumours (Lloyd et al. 1986; Rothman et al. 1976; Scheithauer 1984). Cushing (1930) also suggested that ectopic APT could arise from the stalk, above the membranous diaphragm, or could escape through the diaphragm, without expanding the sella. One can only speculate as to whether, if any, of those mechanisms was operative in the present case.

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