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Cytomegalic Adrenal Hypoplasia with Pituitary Cytomegaly

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Summary. A case of cytomegalic congenital adrenal hypoplasia (C.C.A.H.) is reported with similar cytomegalic changes in the hypophysis. In this case the pituitary gland was small as were the thyroid and testes. The various groups of patients with C.A.H. are presented. Associated pituitary cytomegaly does not appear to have been previously described, and this association between the adrenal and pituitary changes is discussed. It is suggested that the adrenal cytomegaly is the result of overstimulation by the pituitary and the similar change in the latter may be the result of overstimulation of a hypoplastic organ.

Key words: Adrenal gland hypoplasia – Adrenal cytomegaly – Pituitary gland hypoplasia – Pituitary cytomegaly.

Introduction

Congenital adrenal hypoplasia (C.A.H.) has been classified as primary or cytomegalic and secondary, which is usually associated with anencephaly, by Kerenyi (1961). At the present time four groups of patients with C.A.H. may be recognised: – 1. C.A.H. of adult miniature type with normal pituitary (Winquist, 1961). 2. Cytomegalic C.A.H. with normal pituitary (Harlem and Myhre, 1957). 3. C.A.H. of adult type with pituitary hypoplasia and anencephaly (Angevine, 1938). 4. C.A.H. of adult type without anencephaly but with hypopituitarism (Mosier, 1956) or absent pituitary (Blizzard and Alberts, 1956). The cytomegalic type is inherited as an x-linked recessive condition (Weiss and Mellinger, 1970). From a review of the literature it would appear that similar cytomegalic changes have not been found in the cells of the adenohypophysis.

The present report concerns an infant in whom cytomegaly of the cells of the anterior pituitary was found in addition to similar changes in the adrenal cortex.

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Case Report

The mother is a 26 years old caucasian, 0 positive, W.R. negative. In 1973 she gave birth to a healthy full-term female infant. In June, 1975 she had a D. and C. following a hydatidiform mole pregnancy with uneventful follow-up. Her subsequent conception could be accurately estimated and at 33 weeks an X-ray showed a single normal fetus with bone maturity of 30 weeks. Three subsequent estimations of 24 h urinary oestriol excretion proved to be very low. Due to the poor fetal growth and low oestriol levels an early Caesarean Section was carried out. A live male infant was delivered, weighing 1,200 g, which is below the second centile. Head circumference was 27 cm, on the 10th centile for 33 weeks. He had abnormal genitalia with a hooded prepuce and moderate hypospadias in addition to a hypoplastic scrotum and undescended testes. At five weeks of age he had slight peripheral oedema and gradually became anaemic. Chromosome investigations showed normal complement (46 XY). No positive viral cultures were obtained from urine, nose or throat. Viral antibody titres for cytomegalovirus, on two occasions, were not compatible with the diagnosis of this infection. Bone age estimation at 8 weeks of age was equivalent to 35 weeks maturity. The child was discharged nine weeks after birth, weighing 2.26 kg, haemoglobin 9 g/dl and heart rate 160/min. During the period of follow-up the infant was found to have seborrhoea of face and scalp. He was gaining weight very slowly and suffering from repeated episodes of vomiting. Three weeks prior to death he was treated for an upper respiratory tract infection and loose motions but expired at the age of $6^1/_2$ months. The death was unexpected and the case was included in a "cot-death" survey.

Post Mortem Findings

The body was that of a poorly nourished infant, 46 cm in length, weight 4.104 kg. There was hypospadias with hypoplastic scrotum and the testes were not palpable. The thymus and thyroid glands were small in size and the adrenals were triangular in shape, each weighing 1 g. The testes were at the internal inguinal rings and were regarded as being small. The pituitary was also considered to be diminished in size.

On microscopy, significant findings were limited to the endocrine glands. The adrenals had well-formed medulla and cells of fetal cortical type with no recognisable permanent cortex. The cells were enlarged and eosinophilic with giant nuclei sometimes having a bizarre appearance (Fig. 1). A prominent feature was the presence of chromatin rings which enclosed granular acidophilic cytoplasm. (Fig. 2). No actual cytoplasmic invaginations were seen at the light microscope level. Using the O.F.G. stain (Slidders, 1961), the pituitary showed diminution of acidophilic cells in the anterior lobe. The majority of cells appeared to be undifferentiated although some clearly defined basophilic and chromophobic cells were seen. Cytomegaly with intranuclear cytoplasmic inclusions similar to those seen in the adrenal cortex were present in undifferentiated cells (Fig. 3). Only occasional giant cells were noted in the pituitary whereas the majority of adrenal cortical cells had this appearance.

The pancreas had prominent islet tissue but the latter was regarded as being within normal limits. The thyroid had moderate amounts of colloid with follicles showing cuboidal epithelium. The parathyroids were made up of cells with clear cytoplasm. The testes had tubules with numerous spermatogonia and there were groups of up to eight Leydig cells which had swollen vacuolated cytoplasm (Fig. 4).

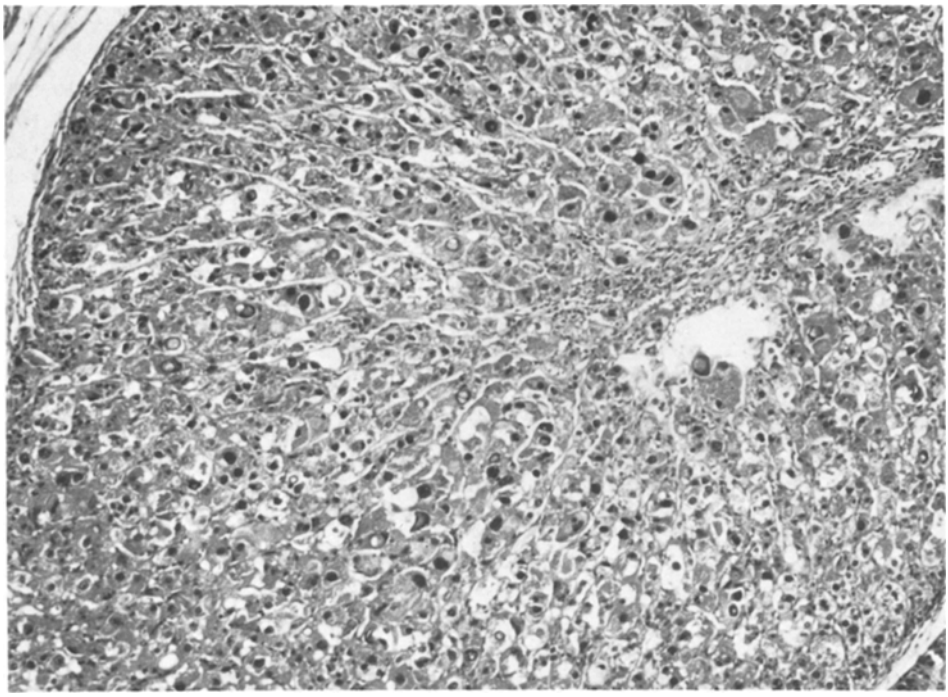

Fig. 1. Photomicrograph of adrenal showing large cells with some resemblance to fetal adrenal cortex. H & E $\times 50$

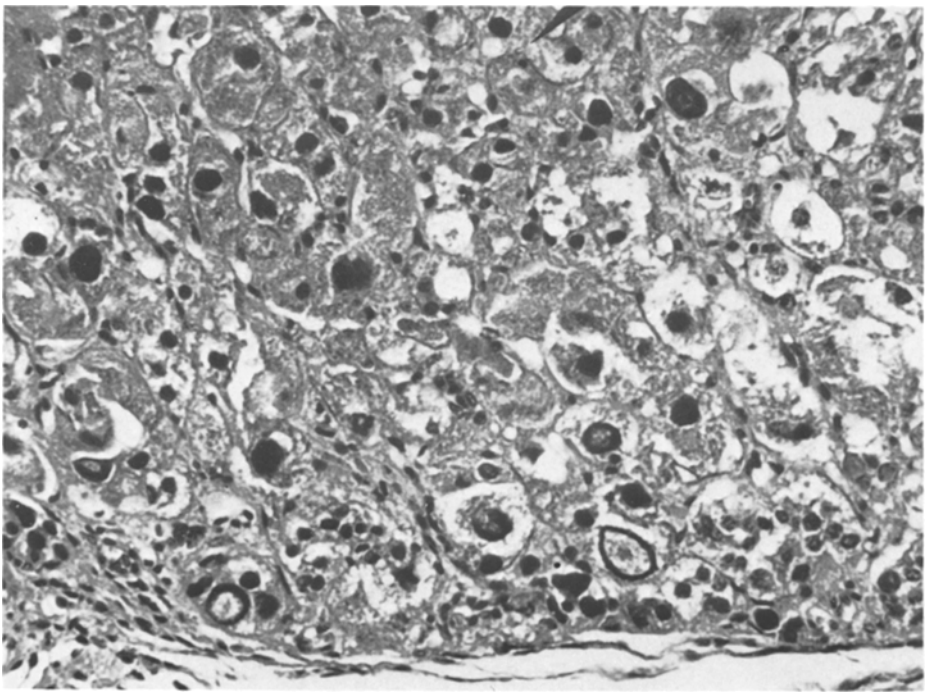

Fig. 2. Detail of adrenal showing bizarre nuclei, cytoplasmic vacuolization and intranuclear cytoplasmic masses. H & E $\times 250$

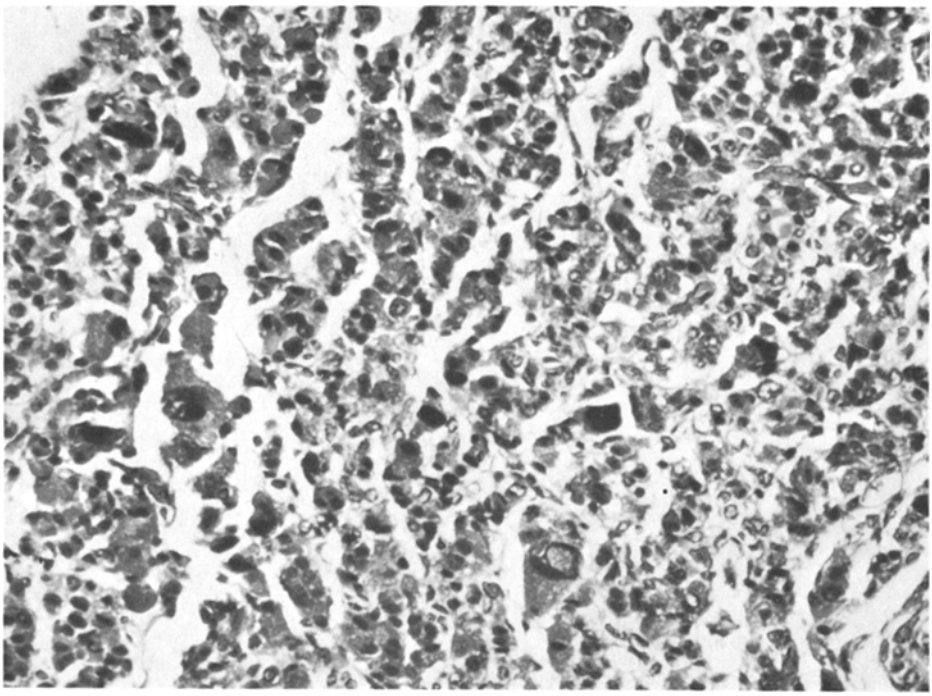

Fig. 3. Photomicrograph of the pituitary with occasional large cells. Some of the latter have bizarre nuclei and an intranuclear cytoplasmic invagination is clearly shown. H & E ×125

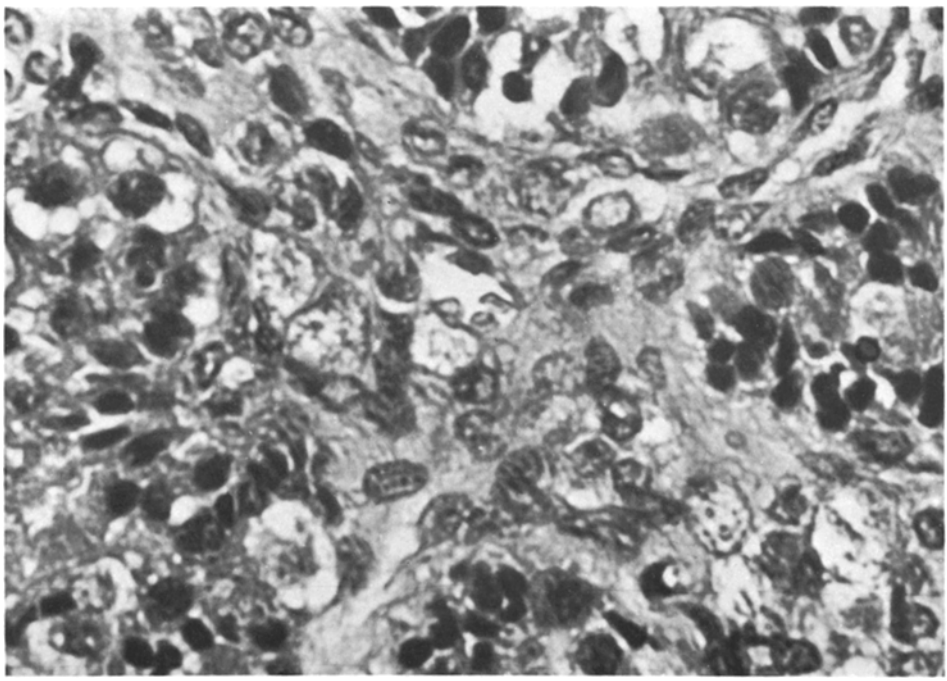

Fig. 4. Photomicrograph of the testis showing a group of swollen, vacuolated interstitial cells. H & E ×500

Discussion

The normal fetal adrenal cortex consists of a broad zone of large eosinophilic cells which disappears after birth. There is, in addition, a narrow rim of smaller cells which develops into the permanent adrenal cortex. The cells in the adrenal gland of cytomegalic C.A.H. have been considered to be of fetal cortical origin and in this condition there appears to be lack of development of the permanent adrenal cortex.

The adrenal cells in cytomegalic C.A.H. are larger than normal fetal adrenocortical cells and show nuclear changes. Apart from enlargement of nuclei, cytoplasmic masses may be seen in the nuclei themselves. These have the appearance of Cowdry's Type B nuclear inclusions (Cowdry, 1924). These inclusions were originally thought to be of viral origin but electronmicroscopic studies have shown that this is not the case in cytomegalic C.A.H. (Sobel et al., 1969; Oppenheimer, 1970). Borit and Kosek (1969) showed that the cytoplasmic masses are invaginations although the point of invagination into the nucleus may not be readily visible at the light microscope level. Sobel et al. (1969) suggest that there is cytoplasmic swelling with extension of the swollen cytoplasm into the nucleus, a process which may be aided by frequent or atypical mitoses with trapping of cytoplasmic material in the nucleus (Bloom, 1967). The changes in the cytomegalic cell may be regarded as the result of hyperactivity. Degenerative changes in the invaginated cytoplasm seen at the ultrastructural level have been considered to be the result of exhaustion, possibly following hyperactivity (Borit and Kosek, 1969).

Cytomegalic changes do not appear to have been previously described in the pituitary gland in association with cytomegalic hypoplasia of the adrenal. Cases of combined adrenal and pituitary hypoplasia have been reported (Mosier, 1956) and in this case cytomegaly is not a feature of either organ. Cytoplasmic nuclear inclusions in the human pituitary gland have been found in a variety of hyperfunctional states which are listed by Serber (1961). This author showed such inclusions in the pituitary of the hamster in association with gonadectomy, atrophy of the testis and senility.

The presence of cytomegalic pituitary changes in the present case of cytomegalic C.A.H., which is not a feature of previous reports, may be due to the following reasons:—

1. No mention of the pituitary is made in some reports (MacMahon et al., 1957; Deamer and Silver, 1950; Oppenheimer, 1970). In the paper by Kerenyi (1961) the pituitary is listed as normal in the case of Deamer and Silver and also of MacMahon et al. It is particularly difficult to explain this assessment in the latter case when permission to examine the head at autopsy was not, in fact, given.

2. The cytomegalic changes may be a temporary phenomenon as found by Serber (1961) in her study on gonadectomised hamsters.

3. The pituitary changes may be minimal and therefore missed in occasional sections. Serber (1961) found an average of three inclusions per thousand cells in the first three months after gonadectomy.

4. The pituitary in the present case is hypoplastic and would be subject

to greater stimulation per cell than the normal-sized gland. In the case of cytomegalic C.A.H. reported by Harlem and Myhre (1957) the pituitary was found to be normal.

5. There is hypoplasia of the thyroid and testis in the present case. The finding of hyperplastic vacuolated Leydig cells is consistent with increased gonadotrophic activity. The hypoplasia of three endocrine organs might give rise to greater pituitary stimulation and resultant cytomegaly in the hypophysis.

Hay (1977) suggests that cytomegalic C.A.H. is regularly associated with gonadotrophin deficiency. In the present case there is evidence of gonadotrophic activity although it is possible that the hypoplastic pituitary might have been inadequate at puberty. However, it should be kept in mind that cytomegalic C.A.H. may not be a primary or single organ defect.

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