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VIRILIZATION CAUSED BY A LIPOID-CELL TUMOUR OF THE OVARY

H. C. SEFTEL, B.Sc., M.B., B.Ch., DIP. MED. (RAND), *Department of Medicine, Baragwanath Hospital;* D. ROSENZWEIG, M.B., B.Ch. (RAND), *Department of Medicine, Baragwanath Hospital;* and C. ISAACSON, M.B., B.Ch. (RAND), D.C.P. (LOND.), DIP. PATH. (R.C.P. AND S.), *South African Institute for Medical Research and Baragwanath Hospital, Johannesburg*

The ovarian lesions associated with virilization may be either neoplastic or hyperplastic in nature. Hyperplastic conditions include hyperthecosis and hyperplasia of the hilus or ovarian Leydig cells, while the neoplasms include the arrhenoblastomas and the lipoid-cell tumours. The term 'lipoid-cell tumour' is one used by Morris and Scully[1] to designate a group of ovarian tumours composed of cells that resemble in general cells of the adrenal cortex, hilus cells and granulosa or theca-lutein cells. In the past this group of tumours has been given a variety of names, such as 'adrenal-rest tumour', 'adrenal-like tumour', 'hypernephroma', 'Leydig-cell tumour', 'luteoma', 'masculinovoblastoma' and 'androblastoma diffusum'. None of these terms, however, is appropriate to the group as a whole. While in some cases the tumour morphology is sufficiently distinctive to warrant a term such as adrenal-rest or Leydig-cell tumour, in others it may be impossible to establish the identity of the cell of origin. Nor are these tumours always associated with virilization, as implied by the term 'masculinovoblastoma'. In some cases the tumour may be non-functioning or associated with hormonal disturbances other than virilization. For these reasons Morris and Scully employ the non-committal term 'lipoid-cell tumour', based on the morphological characteristic common to all the tumours in this group — their cellular lipoid content. Here we report a lipoid-cell tumour which produced gross virilization before puberty.

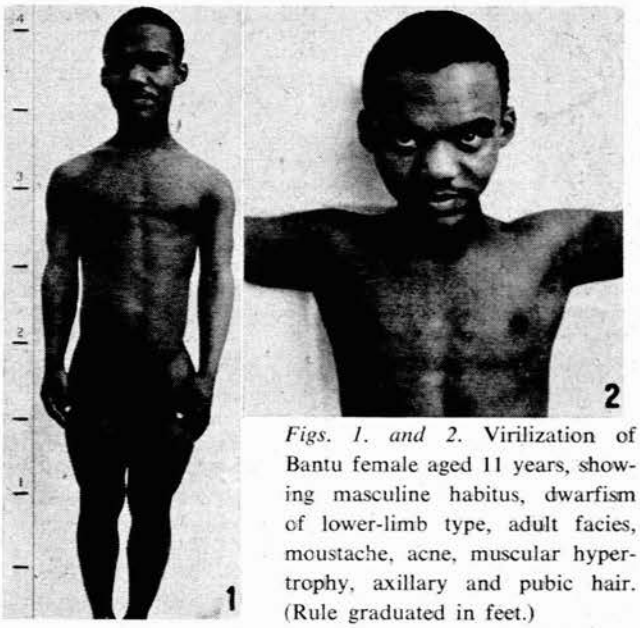
CASE REPORT

The patient, an 11-year-old Bantu female, was admitted to Baragwanath Hospital in September 1959. One week earlier she had been examined by a district surgeon following an allegation of rape. No objective evidence of this was found, but it was obvious that the child's physical development was grossly abnormal. This had never been investigated and she was therefore referred to Baragwanath Hospital.

The following history was obtained from the patient's parents. Until the age of 3 years the patient's appearance and development were those of a normal female. At that time she began to show facial hirsuties and a degree of muscular development which was quite clearly excessive for her age. This coincided with the beginning of a period of rapid growth which lasted for 4 - 5 years, during which the patient was definitely taller than normal. Thereafter growth ceased, with the result that she was now shorter than children of her own age. Muscle growth, however, had been continuous, and she now possessed the strength of an adult male. The facial hirsuties also continued to increase, and from about the age of 4 years axillary and pubic hair was noted. At the age of 5 years her voice began to deepen and enlargement of the clitoris was first observed. Both these features had become steadily more prominent. Psychologically the patient was shy and withdrawn and kept largely to herself. The rest of the history was negative.

Clinical Examination

On examination the patient presented the picture of marked virilization with dwarfism of the lower-limb type (Figs. 1 and 2). Her height was 50½ inches, span 50 inches, crown - pubis 29 inches, and pubis - heels 21½ inches. Her entire musculature



Figs. 1. and 2. Virilization of Bantu female aged 11 years, showing masculine habitus, dwarfism of lower-limb type, adult facies, moustache, acne, muscular hypertrophy, axillary and pubic hair. (Rule graduated in feet.)

was markedly hypertrophied and muscle power was correspondingly increased. The patient's facial appearance resembled that of an adult male, with acne, beard and a well-developed moustache. The voice was deep and gruff and clearly masculine in character. Axillary and pubic hair was abundant,

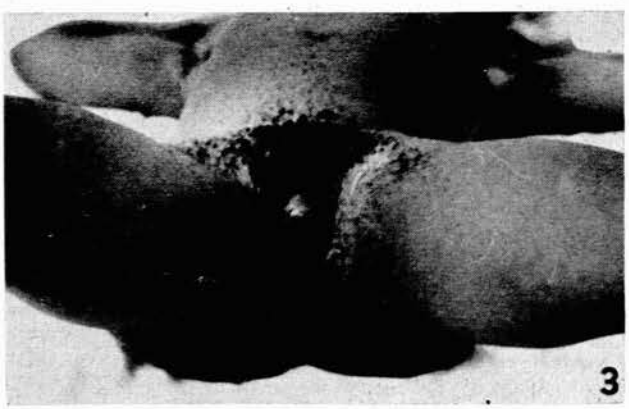


Fig. 3. Enlarged clitoris and male distribution of pubic hair.

the pubic hair showing a male distribution. The clitoris was markedly enlarged (Fig. 3). The patient was a virgo intacta, and rectal examination performed by a gynaecologist revealed no abnormalities. The blood pressure was 120/80 mm.Hg, and the remainder of the physical examination was negative.

Investigations

Urinalysis, haemoglobin level, white-cell count, and serum-protein, serum-cholesterol, serum-alkaline-phosphatase and serum-calcium levels were all within normal limits.

X-ray examination of the chest, skull and pituitary fossa was normal. The patient's bone age was between 18 and 25 years.

The 24-hour urinary excretion of 17-ketosteroids was markedly elevated, being 35 mg. The average normal excretion of 17-ketosteroids for children aged 7 - 12 years is 4·0 mg.[2] A repeat estimation of the 17-ketosteroid excretion yielded a value of 33·8 mg. The 24-hour urinary excretion of 17-hydroxycorticosteroids was normal, being 7·3 mg.

Our diagnosis at this stage was that of acquired virilization of either adrenal or ovarian origin. If of adrenal origin, the diagnosis lay between adrenal hyperplasia and adenoma, since carcinoma was virtually excluded by the duration of the history. To distinguish between these possibilities the cortisone-suppression test was performed. The 24-hour urinary excretion of 17-ketosteroids was again estimated and was found to be 39·0 mg. Cortisone acetate, 100 mg. daily for 7 days, was then administered by intramuscular injection. Following this, the 17-ketosteroid estimation was repeated and found to be 25 mg. This value, while definitely less than the basal level of 39·0 mg., still represented a marked elevation of 17-ketosteroid excretion and suggested that, if our patient's virilization was of adrenal origin, we were dealing with an adenoma rather than hyperplasia. The possibility of a virilizing tumour of the ovary was not excluded by the result of the test.

An attempt was then made to demonstrate a possible adrenal adenoma by combined retroperitoneal pneumography and intravenous pyelography. This showed no abnormality of the adrenal glands. Aortography was similarly negative.

A laparotomy was then performed. This revealed a tumour involving the whole of the left ovary, which was removed. No evidence of malignancy was found. The right ovary, uterus and tubes, and both adrenal glands were normal.

Pathological Report of the Ovarian Tumour

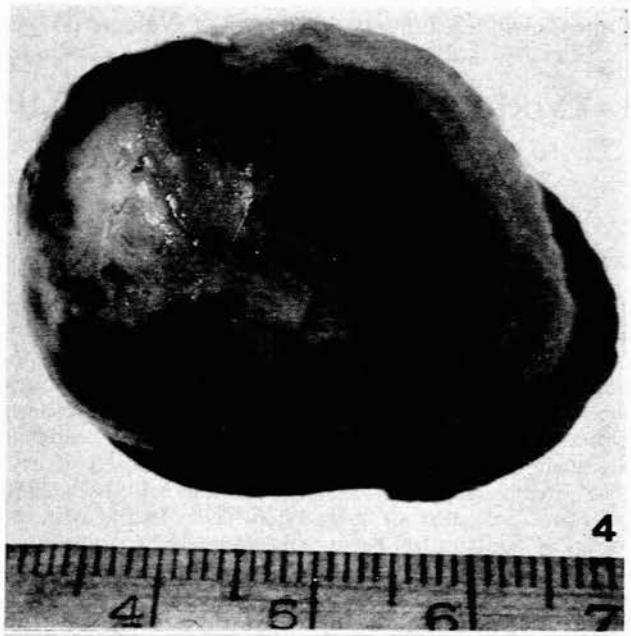
The specimen consisted of a rounded regular mass 3·5 cm. in its widest diameter (Fig. 4). The surface was smooth and presented a mottled yellowish-brown colour over one half, the other half being uniformly light yellow. The cut surface was dark-brown in colour and soft in consistency except for occasional small foci of calcification (Fig. 5). The tumour was well encapsulated and weighed 15·5 G.

Microscopic examination showed that tumour tissue had almost entirely replaced the ovary and a thin segment of ovarian tissue was present at one pole only. This tissue contained numerous primordial follicles. The tumour was composed of rounded, oval or polyhedral cells which varied considerably in size, some giant forms being present. The cells were arranged as diffuse sheets, large nests of cells being separated by a scanty connective-tissue stroma. The cytoplasm of the tumour cells was generally foamy and rather pale with eosinophilic or brownish granules. The nuclei were large, vesicular, and round, and often contained nucleoli (Figs. 6 and 7). Reinke crystalloids were not observed. The stromal collagen contained foci of calcification. The cytoplasm of many of the tumour cells showed intense sudanophilia, and silver impregnation showed reticulin fibres in abundance, surrounding nests of cells, and individual cells (Fig. 8). Many of the brownish cytoplasmic granules were periodic-acid-Schiff positive and remained so after diastase digestion.

A portion of the tumour was submitted for hormone assay, and was found to contain 0·5 mg. of 17-ketosteroids per gram.

Postoperative Course

The patient made an uneventful recovery and was discharged from hospital one month after the operation. Two estimates of 24-hour urinary 17-ketosteroids 9 and 16 days after operation were found to be normal — 5 mg. and 4·5 mg. respectively.



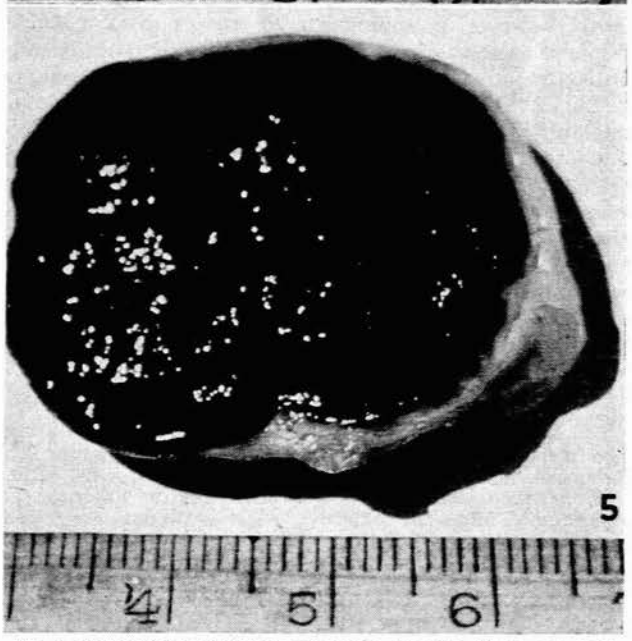


Fig. 4. Macroscopic appearance of ovarian tumour. (Rule graduated in cm.)
Fig. 5. Cut surface of the tumour. (Rule graduated in cm.)

When the patient was seen again 2 months after the operation, breast development was commencing, facial hair and acne were less in evidence, and the patient had just had her first menstrual period. Psychologically she was much less shy and withdrawn, and mixed with other girls of her age. Six months later there was good breast development, facial hair and acne had disappeared (Fig. 9), the pubic hair now showed a female distribution and she was menstruating regularly. Twenty months after operation the remaining abnormalities were dwarfism (which was to be expected in view of the advanced bone age), a deep voice, an enlarged clitoris and hypertrophied musculature. All these features, except the dwarfism, were beginning to show signs of regression.

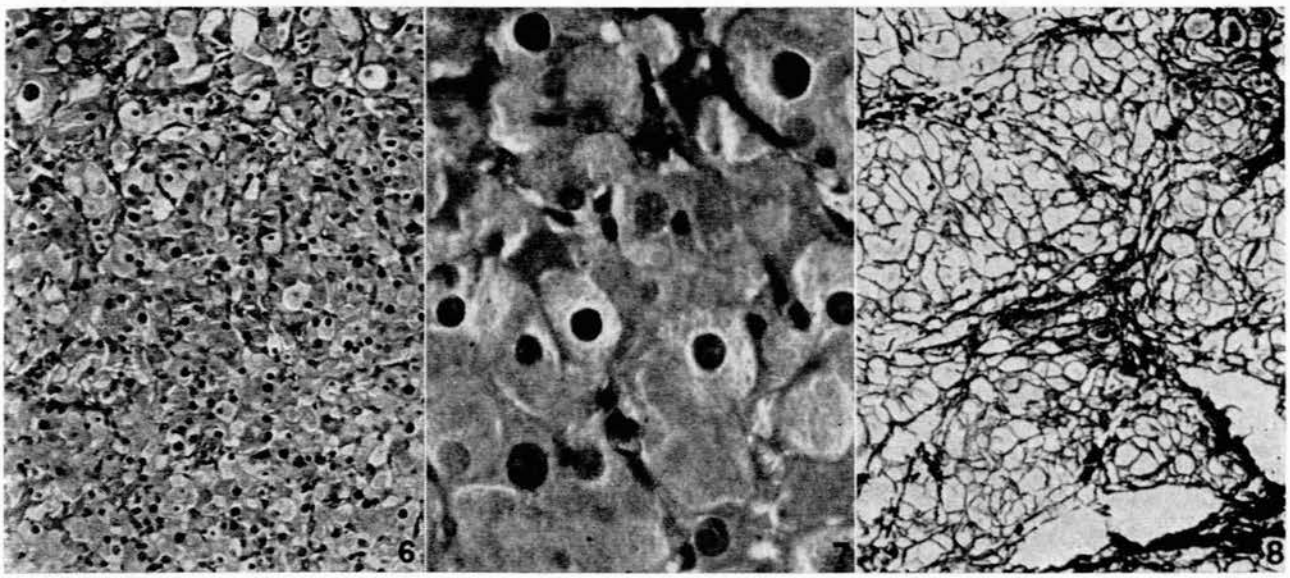


Fig. 6. Section of the tumour showing cells arranged in diffuse sheets (haematoxylin and eosin × 120).
Fig. 7. High-power view showing large cells with vacuolated or granular cytoplasm (haematoxylin and eosin × 480).
Fig. 8. Reticulin network surrounding tumour cells (Gordon and Sweet's silver impregnation × 120).

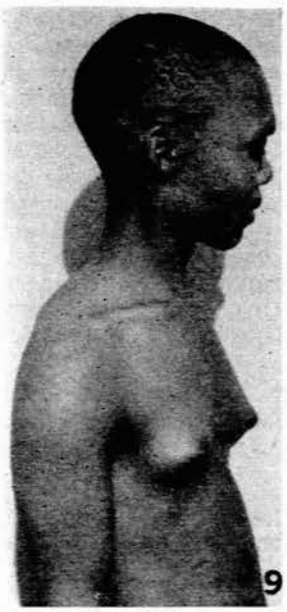


Fig. 9. Breast development and disappearance of moustache after removal of tumour.

DISCUSSION

The clinical and pathological features of the lipoid-cell tumours have been comprehensively reviewed by Morris and Scully.[1] The true incidence is difficult to establish, but there can be little doubt that these tumours are rare, less than 100 having been reported in the literature. The age incidence ranges from 3½ to 86 years. The majority present after puberty, with premenopausal cases twice as common as postmenopausal.

Endocrinologically, the majority of lipoid-cell tumours have been associated with defeminization and with masculinization. In some cases there have been manifestations suggesting Cushing's syndrome — polycythaemia, obesity, hypertension and disturbances of carbohydrate metabolism — but there has apparently been no case with a fully developed Cushing's syndrome. In a few cases menstrual abnormalities were the principal feature and, in some, progestational endometrial changes have been recorded. A number of tumours have been functionless.

Numerous endocrine assays have shown that the most consistent abnormal finding is an elevation in the urinary excretion of 17-ketosteroids, values as high as 270 mg. per l. of urine having been recorded. On fractionation, the 17-ketosteroids have been found to be mainly of the alpha type. The high 17-ketosteroid excretion differentiates the lipoid-cell tumours from other virilizing conditions of the ovary, such as the arrhenoblastomas and hyperthecosis, in both of which the 17-ketosteroid excretion is usually normal or only slightly raised. Occasionally patients with lipoid-cell tumours have had raised urinary pregnanediol levels.

Characteristically, the lipoid-cell tumours are generally rounded yellowish-brown masses, not more than a few centimetres in diameter, although the rare malignant varieties may reach 20 cm. in diameter. Microscopically, the cells are arranged in nests and columns surrounded by reticulin. The cells are usually large and the cytoplasm is either vacuolated or eosinophilic and granular. Lipochrome granules are also frequently seen, and characteristically there is cellular lipoid. In some cases the tumour morphology strongly suggests an origin from adrenal cells (presumably from adrenal nests in the ovary), ovarian Leydig or hilus cells, or luteinized granulosa or theca cells, but in others the cell type defies identification. A number of the tumours, both functioning and non-functioning, have proved to be malignant with metastases in pelvis, bowel, liver and bone.

Our own case of lipoid-cell tumour is of interest for 2 reasons. Firstly, there is apparently only one other report of virilization caused by a lipoid-cell tumour in a prepubertal female;[2] this occurred in a patient who presented at the age of 4 years, and developed a deep voice, male pubic and axillary hair, clitoral enlargement and increased stature. The tumour cells were described as resembling Leydig cells, and the increased excretion of 17-ketosteroids consisted chiefly of androsterone. The other recorded examples of lipoid-cell tumours in the prepubertal female, 5 in all, were all described as consisting of cells resembling those of the adrenal cortex, and were all associated with the development of precocious puberty without any evidence of virilization.[4-8]

The second point worthy of note is the rapidity with which normal female sexual development ensued following removal of the tumour. Within 2 months breast development and menstruation had commenced. The reason for this rapid development is not clear, but it may be related to the fact that the tumour was removed when the patient was 11 years old, i.e. when she was at or close to the age when puberty is normally expected. Similarly it has been noted that, when patients with virilization resulting from adrenal hyperplasia are treated with cortisone at about the time of puberty, female sexual development may occur with unusual rapidity.[9]

SUMMARY

A case is reported of virilization caused by a lipoid-cell tumour of the ovary in a Bantu prepubertal female. Removal of the tumour was followed by regression of the virilization and unusually rapid development of female sex characteristics.

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