
From the Department of Medicine, University Clinic, Bergen, Norway. (Professor H. Rasmussen, M.D.)

FEMINIZING ADRENO-CORTICAL CARCINOMA AND CARCINOMA OF THE PROSTATE

BY

JON MYHRE

The adrenogenital syndrome nearly always appears as a masculinization of women or as a precocious puberty of a masculine type in children of both sexes. Characteristics of the Cushing syndrome are often seen in these cases.

But the adrenal glands may also induce feminization. This is, however, considerably rarer than an effect in the masculine direction. A definite feminization of males as the result of an adrenal cortical tumour has previously been described in at least 15 cases, including two patients of respectively 15 and 5 years of age. The possibility that feminization may be due to hyperplasia of the adrenal cortex has been suggested (Broster & Vines, 1938, Glass & Bergman, 1938), though it does not seem to have been generally accepted.

Among the 15 patients with cortical tumour there were 13 cases of carcinoma, 1 patient had an anaplastic tumour called »sarcomatous dysembryoplasia with adrenocortical differentiation« (Staffieri et al., 1949), and only in the case of the 5 year old boy was an adenoma found.

Below is recorded still another case of a feminizing adrenocortical carcinoma, in which some hormone estimations of the urine and a post-mortem examination were performed.
The patient was born in 1912. He was married and had 3 children, of whom the youngest one was born in 1944. From 1942 he had noticed diminishing libido, gradually increasing impotencia coeundi, and swelling and tenderness of both breasts. He had previously always been in good health.

In 1946 he was admitted to hospital. A considerable symmetrical swelling of both breasts was found, but no fluid could be pressed out. On palpation of the abdomen nothing abnormal was found. The Friedman test was negative and quantitative estimation of gonadotrophin showed <33 mouse units per litre. The excretion of androgens amounted to 1 rat unit per litre. The comments of the laboratory read: "Titration of gonadotrophin shows normal low values. The quantity of androgens is below the average but within the normal limits." Further hormone estimations were not performed at that time. X-ray examination of the abdomen for adrenal tumour gave negative results. Pneumoradiography was not tried. A number of tests not related to the adrenal glands also gave normal results and the patient was discharged with a diagnosis of gynecomastia of unknown etiology.

During the following years the condition remained unchanged, except for the external genitals which possibly decreased slightly in size.

In 1948 the patient developed a feeling of fulness in the epigastrium, at times even oppressive pains. A large firm tumour was detected under the left costal margin and with a diagnosis of splenomegaly he was again sent to hospital. On examination he was found to be a fairly well nourished male. The blood pressure was 135/95 mm. Hg., the pulse regular, 64 per minute. The temperature was normal. The distribution of body hair was of the virile type with plenty of hair on the thorax and in the genital region. The breasts from which no fluid could be expressed were quite large and symmetrically developed. (Fig. 1).

From under the left costal margin a large mass with uneven surface, reaching down as far as the navel, could be palpated in the abdomen. The testicles were soft and somewhat small. The penis seemed normal. The routine urine tests revealed nothing abnormal. The blood sedimentation rate was 55 mm.hr., the haemoglobin content 12.3 gm. per cent. Excretion urography showed nothing abnormal on the right side. On the left side no kidney contours could be seen, but over the whole of the left upper part of the abdomen there was a shadow with a convex lower contour off the 3rd lumbar disc. There was no excretion of the contrast medium on this side. X-ray examination of the lungs revealed numerous, evenly spread densities of a size varying from quite small to the size of...
an almond. The Friedman test and the frog test for urinary gonadotrophin were negative. But the excretion of 17-ketosteroids was greatly increased — 256 mg. per 24 hrs.

As surgical therapy was not indicated, the patient was discharged with a diagnosis of adrenal cortical carcinoma with metastases. Before leaving he got an intramuscular implantation of 300 mg. testosterone propionate, simply ut aliquid fiat.

Fig. 1.
Appearance of patient in December 1948.

In March 1949 he was readmitted to hospital for a few days. He had up to then done light work for some hours daily. He had occasionally had slight pains in the thorax and on the left side of the abdomen, and on exertion quickly became breathless. The gynecomastia and impotence were unchanged. The abdominal mass now reached down past the iliac crest. X-ray examination revealed some increase of the infiltrations in the lungs. The urinary excretion of 17-ketosteroids was 262 mg. per 24 hrs. 300 mg. testosterone propionate were implanted intramuscularly at this time.

The patient died in May 1949. Autopsy was carried out 24 hours after death (Gade Institute, Department of Pathology). The main findings were:

Throughout both lungs there were numerous firm, elastic, greyish to yellow nodules, varying in size from that of a pea to that of a tomato. Similar nodules were also found in the liver. The right adrenal gland weighed 8 gm. and appeared normal. The left adrenal gland weighed 2090 gm. It was surrounded by a thin vascularized capsule. The consistence was for the most part elastic, but in some
places softer. The cut surface was greyish-white with some areas of dirty brown colour. The left kidney was displaced downwards. On gross inspection the prostate and the testicles appeared normal.

Microscopic examinations: The neoplastic tissue from the left adrenal gland (Fig. 2) consisted of closely packed cells with dark eosinophilic cytoplasm and relatively large, dark nuclei. The nucleoli were distinct and there were numerous mitoses. The cells formed solid strands and columns with scanty interstitial tissue. Several areas showed degeneration, necrosis and calcification.

The nodules in the lungs and the liver had the same microscopic characteristics as the adrenal tumour.

The testicles showed atrophy of the germinative epithelium, mostly without any sign of spermatogenesis. The interstitial tissue was somewhat increased and showed a tendency towards hyalinization.

In one section of the prostate the picture was completely normal, but sections from another block showed atypical epithelial cells infiltrating the connective tissue in irregular strands and alveoli (Fig. 3). The appearance of these anaplastic cells and their mode of

---

Fig. 2.
Microscopic appearance of adrenal carcinoma (×180).
Fig. 3.
Microscopic appearance of prostatic carcinoma (× 50).

growth differed completely from the picture found in the adrenal tumour.

In the breasts small atrophic ducts were found, more numerous than normal. There were no acini, and there was an increased amount of hyalinized connective tissue.

Autopsy diagnosis: Carcinoma of the adrenal cortex with metastases to the lungs and the liver. Carcinoma of the prostate.

On admission to hospital in 1946 the chief features were impotence and gynecomastia. Impotence is such a common complaint that it is of little diagnostic value except as part of more extensive syndromes. Gynecomastia is also far from being a diagnostically specific phenomenon. It has been noted in diseases and injuries of the testicles, in lesions of the spinal cord, in cirrhosis of the liver, and as a result of starvation and vitamin deficiency states. Furthermore it has been seen during the administration of oestrogens, androgens and desoxycorticico-
sterone. Sometimes gynecomastia is found as a stationary, inexplicable phenomenon in men who are otherwise normal in every respect, even sexually, and in such cases it has often commenced during puberty.

For the differential diagnosis of gynecomastia, hormonal estimations are of great interest and some observations in cases of feminizing adrenal tumour shall be mentioned.

The excretion of oestrogens was not examined in our case, but has been investigated in 4 of the earlier reported cases. Two of these patients had quite exceptionally large quantities of urinary oestrogens > 3000 mouse units per litre (Simpson & Joll, 1939) and approximately 5000 mouse units per 24 hrs. respectively (Roholm & Teilum, 1942). Among the two others, one had urine with an oestrogen activity corresponding to 5.3 μg oestradiolbenzoate per 24 hrs. (Wilkins, 1948) and the second had a 24 hrs. excretion amounting to 5 rat units (Wilkins, 1948). The last value refers to the 5 years old patient with adenoma.

Androgen excretion has been investigated only in the two patients with a great excess of oestrogens in the urine. One of them excreted between 50 and 100 capon-comb units per 24 hrs. and the other between 50 and 80 capon-comb units per litre. It is not possible to compare these findings with the value for androgen excretion in our patient, who was only examined once, and by another and less exact method.

As to urinary gonadotrophins information is available from 3 of the previously reported cases. Two of them had, like our patient, no increased excretion, (Roholm & Teilum, 1942, Simpson & Joll, 1939), but in the third case the Friedman test was positive (Mc Fadzean, 1946). Quantitative estimation was not performed. It is remarkable that the reaction was found negative 20 days after the operative removal of the tumour. Adrenal cortical tumours are generally supposed not to influence the excretion of gonadotrophin. In a case of gynecomastia and left-sided abdominal tumour, 800 to 1000 mouse units of urinary gonadotrophin per 24 hrs. were found, the presence of an intra-abdominal chorionepithelioma was therefore assumed, and
later verified by autopsy (Heiberg & Hamburger, 1941). Recently still another case of adrenal cortical carcinoma with abnormally large excretion of gonadotrophins in the urine (though without gynecomastia) has been reported (Chambers, 1949).

The excretion of 17-ketosteroids was not estimated during our patients’ first stay in hospital, as it was not possible to have this examination performed in Norway in 1946. The large increase in excretion of 17-ketosteroids found during the periods in hospital in 1948 and 1949 agree with the general experience in cases of adrenal cortical carcinoma. No differentiation in α- and β-fraction was tried in our case. At the first admission to hospital the disease had already progressed so far that an estimation of 17-ketosteroids in the urine at that time would probably have been of great diagnostic value.

The excretion of 17-ketosteroids in the urine has been investigated in 4 of the previously published cases of feminizing adrenocortical tumour. In one of them the excretion was considerably increased. Even at the first examination 190 mg. per 24 hrs. were found (Wilkins, 1948). Another patient in spite of definite gynecomastia, palpable abdominal mass and dislocation of the corresponding kidney, did not excrete more than 34 mg. per 24 hrs., but 4 months later this value had increased to 108 mg. (Armstrong & Simpson, 1948). In the patient with »sarcomatous dysembryoplasia« the excretion was below, if near, the normal upper limit, being 24 mg. per 24 hrs. In the fourth patient, the boy with adenoma, the excretion was also normal, amounting to 5 mg. per 24 hrs.

While the masculinizing form of the adrenogenital syndrome is quite often combined with a more or less complete Cushing syndrome this is not so in cases of feminization. But the patient with »sarcomatous dysembryoplasia« had serious disturbances of the carbohydrate metabolism. In this case hypoglycæmic crises were the chief feature, and the blood sugar tolerance test was definitely abnormal. The fasting blood sugar level and the results of the tolerance test (ingestion of 1 gm. glucose per kilogr. body weight as 10 per cent solution) were quite normal.
in our patient, as in the other cases in which the blood sugar values have been examined in the fasting state and after ingestion of sugar.

Another important aspect of feminizing adrenocortical tumour, especially from a therapeutic point of view, is the duration of the disease and the results of operative treatment.

According to the statements made by our patient, the breasts commenced to swell and libido to diminish 7 years before his death in 1949. It is certain that when he first came to hospital he had well-developed gynecomastia. Similar cases of several years duration are on record. One of the untreated carcinoma patients lived for 5 years after the first manifestations of his illness (Roholm & Theilum, 1942). In other patients the disease seems to have run a much shorter course, lasting only a few months.

The mortality in feminizing adreno-cortical tumour has been heavy. The boy with adenoma was operated on and 4 years later was apparently quite well. The patient with »sarcomatous dysembryoplasia« also underwent a successful operation and was well 5 months later. Operation was tried on 6 of the patients with carcinoma. In 2 of them the tumour on laparotomy was found to be inoperable, but in the other 4 cases it was removed. About one of these patients nothing is stated concerning the duration of the disease before laparotomy or of his condition afterwards, except that he died of metastases. About the 3 others it is stated that laparotomy was done approximately 17, 20 and 24 months after the first manifestations of the illness, after which the patients quickly regained sexual potency, the breasts at least in 2 cases diminishing in size. The patient operated on after 24 months again became impotent about 10 months later and at the same time his breasts once more began to swell (Simpson & Joll, 1939). He died of metastases 2 or 3 years after the operation. Of the remaining 2 patients one was still improving 6 weeks after the operation (Mc Fadzean, 1946), and the other was quite well 12 months after the tumour had been removed (Holl, 1930). The possibility of a complete cure therefore seems to exist but depends
greatly on early diagnosis. The importance of examining the urinary excretion of oestrogens and 17-ketosteroids in all patients developing gynecomastia can scarcely be doubted, and surgical exploration of the adrenal glands should be performed in all cases of gynecomastia of unknown etiology but with increased excretion of these substances, even if the increase is only moderate.

In the previously reported post-mortems of cases of feminizing carcinoma of the adrenal cortex, the prostate seems to have been normal. The surprising discovery of a prostatic carcinoma in our case can scarcely be considered of importance in the development of the patients symptoms and signs. The tumour of the prostate can not be regarded as a metastasis from the adrenal tumor or vice versa. The histological appearances of the two tumours according to the pathologist leaves no room for doubt as to their origins. Neither can any doubt be raised as to the adreno-cortical origin of the secondary growths in the lungs and the liver. No metastases from the prostatic carcinoma were found. Even if the two tumours are distinctly different, it is tempting not to look upon the appearence of the prostatic carcinoma as a pure coincidence. The age of the patient may, amongst other things, make it permissible to suggest the influence of hormonal disturbances, but any attempt at a closer explanation must be purely speculative. Oestrogens usually have a retarding effect on carcinomas of the prostate, whereas androgens have the opposite effect. The testosterone propionate administered therapeutically can scarcely have been of importance in this connection.

SUMMARY

A case of feminizing carcinoma of the adrenal cortex in a male, 35 years old, is reported. The untreated condition lasted for approximately 7 years. The chief features were gynecomastia and impotence and later on a large abdominal tumour. Metastases appeared chiefly in the lungs and the liver. The
weight of the adrenal tumour at autopsy was 2090 gm. While
the gross appearance of the prostate was normal, the micro-
scopic examination revealed a carcinoma of this organ too.
Some hormonal changes are discussed. The excessive excre-
tion of 17-ketosteroids in our case is stressed.
The often very slow development of the disease is of major
prognostic importance, leaving a chance for effective therapy
if hormonal estimations and exploratory laparotomy are used
as aids for an early diagnosis.

REFERENCES
Heiberg, B. & Hamburger, C.: Nord. med. 9, 141, 1941.
Kooyman, J. C.: Nederl. tijdschr. v. geneesk. 84, 4688, 1940.
1949.