GYNAECOMASTIA AND DISEASES OF THE THYROID

By

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ABSTRACT

Coexistent gynaecomastia was observed in 2 patients with thyrotoxicosis and in 1 with an active malignant thyroid adenoma. During treatment of the thyrotoxicosis the gynaecomastia disappeared completely in 1 of the patients. Mastectomy was performed on the other 2 patients.

The pathogenesis of gynaecomastia is discussed on the basis of the findings made in a fairly extensive endocrine study of 2 of the patients, and the possible aetiological factors are discussed.

Gynaecomastia has been associated with both hypo- and hyperfunction of the thyroid gland. As far as we know, it has not been observed to be coexistent with malignant diseases of the thyroid. Marine (1939) has stated that "impotence, loss of libido, testicular atrophy and gynaecomastia are common in myxoedema", but according to Hall (1959), gynaecomastia is not common in myxoedema, and the reported cases are not supported by accurate clinical and laboratory data.

In those cases in which the gynaecomastia appears at roughly the same time as, or soon after, symptoms of thyrotoxicosis and in which it regresses during treatment of the thyrotoxicosis, it appears reasonable to assume a causal relationship. Only relatively few cases have been described. Thus, in 1959, Hall was only able to trace in the literature 26 cases of gynaecomastia associated with thyrotoxicosis. Only 17 of his cases satisfied the above criteria for a causal relationship. Gynaecomastia is, however, probably more common in this connection than is suggested by these figures. Thus, within a period of 18 months Berson & Schreiber (1953) found gynaecomastia in 4 of 45 patients with thyrotoxicosis.
Only in a few of the cases on record were examinations performed that might help to explain the mechanism of development of gynaecomastia.

*Rosenthal & Lees* (1958) described 2 patients with increased excretion of 17-ketogenic steroids in the urine. In both cases the gynaecomastia disappeared during treatment with carbimazole.

*Albright* (1954) found that the urinary gonadotrophin was increased in 1 of his 2 cases. In this patient libido was reduced, the testes were small, and biopsy showed azoospermia. The urinary excretion of the 17-ketosteroids was normal. One month after subtotal thyroidectomy, gynaecomastia disappeared, libido returned, and the testes grew to normal size.

*Hall* (1959) described a 56-year old man with simultaneous development of bilateral gynaecomastia and thyrotoxicosis. The urinary 17-ketosteroid and gonadotrophin levels were normal, while the excretion of oestrogens was increased (oestrone 15, oestradiol 2 and oestriol 31.5 micrograms per 24 hours). Biopsy of the testes and liver function tests revealed nothing of note. The gynaecomastia disappeared during treatment with propylthiouracil.

*Stokes* (1962) described a case in which the excretion of 17-ketosteroids as well as of oestrone was normal. The gynaecomastia disappeared after treatment with carbimazole and 131I.

**OWN OBSERVATIONS**

During the last year we had the opportunity of seeing 3 cases of gynaecomastia in association with thyroid disease.

**Case 1.** The patient was a man, aged 64, in whom symptoms of thyrotoxicosis were promptly followed by swelling of the left breast. A malignant neoplasm was suspected and mastectomy was performed. The histological picture showed typical gynaecomastia. The thyrotoxicosis was treated with radioactive iodine and no change in the right breast has since been observed.

**Case 2.** The patient was a forester, aged 36, who for some years had a swelling of the right thyroid lobe, which had assumed the size of a golf ball. In the course of a few months palpitation, a feeling of increased warmth and diarrhoea developed. At the same time he noticed a tender swelling of the right breast, for which he sought medical advice. He felt somewhat nervous, libido and potency were preserved. At the time of examination he had lost weight. The testes were of normal size. The basal metabolic rate was +5°/o, blood cholesterol 233 mg/100 ml, and 24 hours after administration of a tracer dose of 131I, 32 °/o had been taken up by the thyroid and 50 °/o had been excreted in the urine. The major part of the 131I was recorded over the area of the thyroid adenoma. Roentgen examination of the sella, kidneys and lungs revealed no abnormalities. Repeated liver function tests gave normal values. The urinary excretion of 17-ketosteroids, 17-hydroxysteroids, total gonadotrophins and oestrogens (biological determination) were within the normal range. The serum electrolytes were normal. The sperm was found to be normal and sex chromatin was absent.

Subtotal thyroidectomy was done. Histological examination of the operative specimen showed the picture of an active malignant adenoma. No signs of metastases were
found. After the operation the patient was given 80 mc 131I and substitution therapy was started. After the operation he was clinically euthyroid and remained so. During the following 2 months rightsided gynaecomastia increased and the left breast also began to swell. This swelling was accompanied by decreased libido. Repeated hormone analysis still showed normal excretion of oestrogens, while the excretion of 17-ketosteroids was low, 3.2–5.4 mg/24 hour (normal value 7.5–24 mg/24 hours). Substitution therapy with thyroid hormone was withdrawn for 2 months, during which a slight regression of the gynaecomastia was noticed. At re-examination the excretion of 17-ketosteroids was again normal. In view of the thyroid cancer, thyroid substitution therapy was resumed (gland. thyr. succ. stand. 100 mg/24 hours, «Thyranon», Pharmacia). The gynaecomastia then persisted unchanged and since the patient was inconvenience by his gynaecomastia, bilateral mastectomy was done 2 months later. The operative specimen from the right side weighed 55 g, that from the left 11 g. Histological examination showed signs of typical bilateral gynaecomastia without any signs of malignancy.

Case 3. A man, aged 42, who had previously felt well, was troubled in December 1961 by intense sweating, palpitation and increased nervousness. Libido decreased, he became impotent and noticed a tender swelling of both breasts. He was admitted for investigation of the gynaecomastia in January 1962: he then had symptoms of thyrotoxicosis with finger tremor and warm skin. He weighed 59 kg. Hairgrowth was normal and the testicles were somewhat small. Typical gynaecomastia was palpated. The thyroid was moderately and diffusely enlarged.

Roentgen examination of sella, lungs and kidneys showed no signs of a pathological condition. Films taken after retroperitoneal insufflation of air showed adrenals of normal size. Examination of liver function including the bromsulphalein test and the galactose tolerance, SGO-T and SGP-T, gave normal values both before and one month after the operation. Both fields of vision were normal.

Examination of thyroid function showed basal metabolic rate + 33 %, PBI 7.1 mg/100 ml, increased according to lab. standard, Jacobsson & Widström (1962), cholesterol 170 mg/100 ml, and the 24-hour uptake of 131I over the thyroid was 68 % with a urinary excretion of 11 %. The patient was subjected to subtotal thyroidectomy. Histological examination of the operative specimens showed toxic goitre. Biopsy of the two breasts showed typical gynaecomastia.

Even during the preoperative treatment with iodine the breasts became softer. One month after the operation, no glandular parenchyma could be palpated, the patient was euthyroid, and he had gained 3 kg in weight. Libido and potency had again become normal.

A series of hormone analyses had been performed both before and after the operation. The 17-hydroxysteroids varied between 5.7–14.4 mg/24 hours, the 17-ketosteroids between 6.7–13.8 mg/24 hours, i.e. within the normal laboratory range. No significant change was noted in the values found after operation. The total number of eosinophils in the peripheral blood was normal. No electrolyte disturbances were demonstrable. The immune biological pregnancy test according to Wide & Gemzell (1960) was negative. In one urine sample collected before the operation the total gonadotrophin was more than 53 MU per sample, the animals died with higher doses. At re-examination the values lay between 13–53 MU and were thus normal. A series of oestrogen determinations were made which showed an increase in the oestrogen excretion before, but normal values 4 weeks after the operation (Table 1).

Thus in case 2, the excretion of 17-ketosteroids decreased during progression of the gynaecomastia. In case 3, the secretion of oestrogens clearly increased during the
Table 1.
Analysis performed at Hormone Lab., Department of Gynaecology and Obstetrics, Karolinska sjukhuset, Stockholm (E. Diczfalussy)

<table>
<thead>
<tr>
<th></th>
<th>Oestrone (3–8 µg/d)</th>
<th>Oestradiol (0–2 µg/d)</th>
<th>Oestriol (1–8 µg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>14.4</td>
<td>7.2</td>
<td>2.1</td>
</tr>
<tr>
<td>4 weeks after operation</td>
<td>4.9</td>
<td>0</td>
<td>3.5</td>
</tr>
</tbody>
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Normal ranges given in brackets.

The thyrotoxic phase and returned to normal after the operation at the same time as the gynaecomastia disappeared.

DISCUSSION

The observations made in thyrotoxicosis with gynaecomastia are insufficient to allow of any certain conclusions. Different factors may be operative in different cases. It is well known that relative liver insufficiency may occur in thyrotoxicosis. Such insufficiency may also contribute to the development of gynaecomastia. In the present cases, however, no impairment of liver function could be demonstrated. No direct mammatrophic effect of the thyroid hormone has ever been observed (Pitt-Rivers & Tata 1959).

In published cases of thyrotoxicosis with gynaecomastia increases have been noted in the urinary excretion of 17-ketogenic steroids (Rosenthal & Lees 1958), of gonadotrophins (Albright 1954), and of oestrogens (Hall 1959, our case 3).

Rosenthal & Lees (1958) believe, that increased 17-ketogenic steroid excretion in their cases can be ascribed to a direct effect of the thyroid hormone on the adrenal cortex. Hypertrophy and signs of increased activity of the zona fasciculata of the adrenal cortex have been demonstrated in dogs (Deane & Greep 1947), guinea pigs (Levin & Daughaday 1955), rats (Krüsskemper 1961) and humans (Jacobson 1958; Brown et al. 1958; Felber et al. 1959).

Hall (1959) also believes, that the increased oestrogen excretion, which he observed, may be due to increased stimulation of the adrenal cortex. It may be regarded as established that oestrogenic substances can be formed in the adrenal cortex under different conditions (see Diczfalussy & Lauritzen 1961).

Albright (1954) found gynaecomastia, azoospermia, small testes and increased gonadotrophin in the urine in one of his two cases. Testis biopsy also
showed signs compatible with Klinefelter's syndrome, but all the changes disappeared after thyroideotomy. Evans & Simpson (1930) found that removal of the thyroid gland of young female rats was followed by a decrease in the gonadotrophin production by the hypophysis, while administration of thyroid tissue to normal rats resulted in an increased formation of the hormone. It is not known whether such measures produce corresponding effects in man. The clinical course in Albright's case suggests that the changes were secondary to the thyroid disease.

Disturbances of the cortisol, testosterone and oestradiol metabolism have been described in thyrotoxicosis as well as following administration of triiodothyronine (Hellman et al. 1959, 1961; Fishman et al. 1962). Hydrocortisone metabolism tends to be accelerated by way of biologically less active 11-ketone metabolites; this leads to a secondary increased ACTH stimulation resulting in adrenocortical hypertrophy. In addition, the androsterone/aetiocholanolone ratio in the urine is reduced, while a greater proportion of the oestradiol is metabolised to 2-methoxyoestrone than to the biologically less active oestriol. Brown & Strong (1962) arrived at a similar conclusion about the oestrogen metabolism in thyrotoxicosis.

It would thus appear that the gynaeomastia, reduced libido and testicular atrophy in some cases of thyrotoxicosis may be ascribed to the thyroid hormone interfering directly or indirectly with the equilibrium between biologically active metabolites and thereby disturbing the androgen/oestrogen balance.

REFERENCES


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