Case report

Gynecomastia, obesity and underdeveloped testis and penis: suspected hypophysitis successfully cured with low dose of cyclosporine A

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Keywords: gynecomastia; pituitary; inflammation; biopsy; cyclosporine A

Gynecomastia, characterized by the growth of breast glandular tissue in boys, is occasionally seen in clinics. This growth can manifest at any age, but 40% of cases present in adolescent boys. Even though gynecomastia is a benign condition, patients are often emotionally burdened by this condition. The pathophysiological process of gynecomastia is mainly due to the imbalance between testosterone and free estrogen effects on the breast tissue, and hormone therapy.1-3 The disease is characterized by declined testosterone and slightly elevated estrogen. In general, the impaired synthesis of testosterone results in an increased release of gonadotropin, such as luteinising hormone (LH) and follicle-stimulating hormone (FSH) if the pituitary gland continues to secrete a sufficient amount of hormone. However, an inflammation in the pituitary gland, such as lymphocytic hypophysitis, can lead to pituitary cell destruction and eventually to hypopituitarism. Under such circumstances, LH and FSH would not be sufficiently released to meet the requirement for the testis to be stimulated correspondingly.4,5 One case of gynecomastia, with obesity and underdeveloped testis and penis as simultaneous characteristics, was successfully cured after a low dose of cyclosporine A (CsA) was administered to the patient, who had been suspected of having hypophysitis, which was indirectly detected by muscular biopsy.

CASE REPORT

A 19-year-old man presented with gynecomastia, spano-beard, excessive shyness, depression and frequent fatigue at the endocrinology clinic. The patient noted a progressive bilateral breast enlargement since he was 7 years old and complained of an intermittent discomfort or pain of the chest wall. These symptoms were progressive, affecting his life and bothering him. He was full-term normally delivered and was able to raise his head, sit, and walk like other babies when he was about 1 year old. His medical history was significant as he developed “mumps” at the age of 4, and he is without testitis. He denied any history of trauma to his testis, surgery, and the use of any drugs known to induce breast enlargement. His voice became rough at the age of 16, and his facial and pubic hairs showed up, but was sparse, at the age of 18. Hitherto showing up to our clinic, his penis could not erect normally and nocturnal emission occurred occasionally.

A physical examination indicated that the patient had a male somatotype without signs of feminization. His height was 174 cm while his body weight was 90 kg. He was normally developed and well nourished. There was some acne on his face. The olfactory sensation was normal. The neck had no resistance without goiter. The breasts had symmetrically enlarged to Tanner stage III with the two nipples retracted. There was no galactorrhea. Rubbery tissue that was concentric with the nipple-areolar complex could be felt, and tenderness was found on the palpation. The facial and pubic hairs were sparse, without axillary hairs. His penis was underdeveloped. The size of his testicle was slightly smaller than that of a normal boy of the same age. Hormone studies revealed that testosterone in the serum was 217 ng/dl (male: 241–827 ng/dl), which is extremely low, while FSH was 6.6 U/L (male: 1.4–18.0 U/L), LH was 5.9 U/L (male: 1.5–34.6 U/L), prolactin was 6.75 ng/ml (male: 2.1–17.7 ng/ml), estradiol was 46.99 pg/ml (male: 0–52.00 pg/ml), adrenocorticotropic hormone (ACTH) was 55.9 pg/ml (0–46.0 pg/ml), Cor was 16.6 µg/dl (5.0–25.0 µg/dl), FT3 was 6.15 pmol/L (3.5–6.5 pmol/L), FT4 was 21.2 pmol/L (11.5–23.5 pmol/L), and thyroid stimulating hormone (TSH) was 1.36 µU/L (0.3–5.0 µU/L). All of the hormones were within the normal range, except the low testosterone and slightly elevated ACTH. Blood and urine routine tests, and hepatic and kidney function tests were all normal. No occupying lesion was found near the pituitary area by MRI scanning. The karyotype was 46, XY. Muscular biopsy was carried out on his triangular muscle on the left side. Application of the immunofluorescence technique showed that there were many immunoglobulins and immunocomplexes being deposited on the surface of the muscular cells, such as IgA’, IgG3’, IgM’, C3’, C1q’ and FRA2’ (Figure 1).

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Table. The variation of the gonadal hormone before and after treatment with CsA for 7 months

<table>
<thead>
<tr>
<th>Variables</th>
<th>FSH (1.4–18.0 U/L)</th>
<th>LH (1.5–34.6 U/L)</th>
<th>Prolactin (2.10–17.70 ng/ml)</th>
<th>Estradiol (0–52.00 pg/ml)</th>
<th>Testosterone (241–827 ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before the treatment</td>
<td>6.6</td>
<td>5.9</td>
<td>6.75</td>
<td>46.99</td>
<td>217</td>
</tr>
<tr>
<td>After the treatment for 7 months</td>
<td>4.7</td>
<td>4.7</td>
<td>8.33</td>
<td>24.60</td>
<td>9350</td>
</tr>
</tbody>
</table>

According to the symptoms, endocrine investigations, and the immunofluorescence test result, the patient might have an autoimmune injury on both muscular cells and the pituitary gland, and possibly other organs that partially lead to hypophysitis and hypopituitarism. A dose of CsA, as low as 25 mg, was given to the patient as a treatment aiming to remove the immunological injury and to recover pituitary function. The therapeutic efficacy was amazing; by the end of the second month of the treatment, the bilateral breast became smaller, and the pain was completely relieved. The beard and moustache became thicker, and the axillary hairs began to grow. Laboratory tests showed that testosterone skyrocketed from 217 ng/dl to 509 ng/dl and eventually more than 900 ng/dl. After seven months of treatment, he became much stronger than before. The enlargement of the symmetrical breasts reduced to Tanner stage II, and the two nipples protruded without tenderness. The axillary hairs became thicker. His height increased from 174 cm to 181 cm within 7 months while his body weight reduced from 90 kg to 84 kg. The patient became aggressive, optimistic, energetic, and spirited. However, he did complain of penile erection every morning and had a strong sexual desire. After seven months of the treatment, his testosterone increased to 935 ng/dl while his estradiol decreased to 24.6 pg/ml, the FSH was 4.7 U/L and the LH was 4.7 U/L (Table and Figure 2). After 18 months of the treatment, the gynecomastia was completely cured (Figure 3).

DISCUSSION

Physiological, pathological, and idiopathic factors are the three main causes of gynecomastia. There are three main reasons for pathological gynecomastia: testosterone deficiency, estrogen overproduction, and drug-induction. Gynecomastia commonly occurs during mid-to-late puberty, during which relatively more estrogen may be produced by the testes and peripheral tissues before adulthood. Another reason is that the testes secrete too little testosterone to normally develop the testes, leading to either primary or secondary hypogonadism. Testosterone has two different effects on the body: anabolic effects which promote growth and muscle building, and androgenic effects which develop the male sex organs and secondary sex characteristics, such as the...
deepening of the voice and growth of facial hair. A patient with low testosterone might feel reduced sexual desire, and the penis may fail to erect. Also, the patient might feel fatigue and faint.\(^7\)\(^8\)

For this patient, because the serum level of testosterone was very low, he gradually developed gynecomastia, spano-beard, depression, and fatigue. If the function of his pituitary gland was normal, the gonadotropic hormones, such as FSH and LH, would be significantly elevated. In contrast, his FSH and LH still remained within the normal range. Thus, we realized that there might be a relative deficiency in the gonadotropic hormones in the pituitary gland due to hypopituitarism, which leads to hypogonadotropic hypogonadism as gynaecomastia might be the first clinical manifestation of the hypopituitarism. Apart from traumatic brain injuries and pituitary tumors, the third reason is the hypophysitis, which is supposed to exist. The results were encouraging, while studying the response from the pituitary gland, which is well known to be a dangerous procedure and almost impossible to be executed in routine clinical practice. This paper introduces the idea of muscular biopsy, which is safe, convenient, and still quite suggestive. The finding from our muscular biopsy, even though it is not direct evidence for the diagnosis of autoimmune hypophysitis, is quite suggestive from a humoral immunological point of view. Based on the findings, the deposition of either immunoglobulins or complements, we would have an opportunity to attempt the treatment of the muscular tissues while studying the response from the pituitary gland, which is supposed to exist. The results were encouraging, the patient's testosterone in the serum was elevated very rapidly while his second sex characteristics developed, suggesting that our theory worked at least in this case. It also indicates that autoimmune injuries can attack multiple organs, rather than any specific organs, including the pituitary and muscular tissues.

Our study pilots a clinical investigation different from the traditional way of thinking about the disease. The patient would have to receive the replacement therapy his entire life while the disease would be still developing if the patient was treated in the traditional way. For gynaecomastia, an estrogen antagonist, such as tamoxifen, is often used for resolution. However, it is only effective for a recent-onset disorder while nausea and epigastric discomfort may appear. Regardless, the results were relatively satisfactory without any side effects observed. This new idea may pave a way for other diseases to be treated. Unfortunately, the gynaecomastia still exists, and possibly will do so for many years because the tissue fibrosis did not disappear even though a high level of testosterone was retrieved. We are sure that his gynaecomastia will continue to be improved if our treatment continues to be carried out.

CsA is one of the immunosuppressants. It is mainly used for organ transplantation; however, it is also used for many other autoimmune disorders. It has been described to have many side effects on human beings. When a very low dose of cyclosporine is used, the side effects can be ignored. In our patient, there were no side effects found. It seemed to be safe and very effective.

Finally, it could be concluded that in this case, by treating the patient with a low dose of CsA, the supposed hypophysitis due to autoimmune injuries could be partially relieved. We believe that muscular biopsy is not only a powerful technique to provide new information, but also a completely new way to think about the disease. The pathological and immunohistochemical analysis may provide new evidence in studies of diseases with unknown reasons.

REFERENCES


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