Painful gynecomastia in a patient with malignant thymoma

Malign timomalı bir hastada ağrılı jinekomastı

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Gynecomastia is an abnormal increase in the volume of the male breast. This pathological change may occur unilaterally or bilaterally and is generally considered to be due to an increased estrogen/androgen ratio. Gynecomastia is more common in pubertal ages and in older men. Chemotherapy may injure gonadal and hormonal functions and is associated with development of gynecomastia. In this case, a 36-year-old man who had bilateral acute painful gynecomastia associated with malignant thymoma is presented together with a review of the literature. Tamoxifen 20 mg daily was started. Twenty days later, tamoxifen resulted in complete regression of gynecomastia. After an extensive literature search, we found that gynecomastia had not been previously documented in malignant thymoma.

**Key words:** Malignant thymoma; painful gynecomastia; tamoxifen.


**Anahtar sözcükler:** Ağrılı jinekomastı; malign timoma; tamoksifen.

**CASE REPORT**

A 36-year-old man with an anterior mediastinal mass and respiratory failure was admitted to our hospital 9 months ago. Debulking surgery was performed via median sternotomy. Histopathological diagnosis had revealed unresectable thymic cancer, and induction chemotherapy was administered (cyclophosphamide 500 mg/m², epirubicin 75 mg/m², and cisplatin 75 mg/m² on day 1; and prednisone 100 mg/per day on days 1-5). This cycle was repeated four times at three-week intervals. Surgery was not possible because of extensive vasc-
cular invasion. He was treated with radiotherapy (total dose 6000 Gy in 30 fractions in six weeks). One month later, the patient presented with bilateral acute painful gynecomastia. Physical examination showed slightly enlarged breasts (Fig. 1).

The patient presented with bilateral acute painful gynecomastia. On physical examination, he appeared well, and his vital signs were normal. The lungs were clear, heart sounds were normal, and the abdomen was soft, with no masses or tenderness. The results of a complete blood count and the levels of electrolytes, calcium, creatinine, urea nitrogen, protein, albumin, globulin, and bilirubin were normal. There was no adenopathy, and testicular examination was normal. Abdominal ultrasonography (USG), testicular USG, and magnetic resonance imaging of the sella turcica were normal. Follicle-stimulating hormone (FSH) 26.18 (1.4-18 mIU/ml) and luteinizing hormone (LH) 16.83 (1.5-9.3 mIU/ml) were high. Beta-human chorionic gonadotropin, testosterone, prolactin, dehydroepiandrosterone sulfate, alpha-fetoprotein, insulin-like growth factor 1, thyroid function tests and cortisol level were normal. In view of progression in this patient, ifosfamide was given as second-line chemotherapy. Tamoxifen (TAM) 20 mg daily was started. Twenty days later, TAM resulted in complete regression of gynecomastia and there has been no recurrence in follow-up physical examinations.

**DISCUSSION**

Gynecomastia is common, present in 30% to 50% of healthy men. Conditions associated with gynecomastia are shown in Table 1. Men with recent-onset gynecomastia or mastodynia need a more detailed evaluation, including selected laboratory tests, to search for an underlying cause. Treatment depends on the cause and may include observation, withdrawal of an offending drug, therapy of an underlying disease, administration of androgen or antiestrogen drugs, or plastic surgery. Most cases of gynecomastia result from an imbalance between esterogenic (stimulatory) and androgenic (inhibitory) effects on the breast. Drug-induced gynecomastia accounts for 20% to 25% of cases. Some drugs can cause gynecomastia through multiple mechanisms. For example, drugs mimicking or having estrogenic or antiandrogenic effects may also be associated with development of gynecomastia. Even with detailed evaluation, there is no identifiable cause.
in about 25% of cases. Causes may include excessive local production of estrogen due to increased aromatase activity, decreased estrogen degradation, or changes in androgen or estrogen receptors.

Primary hypogonadism due to Leydig cell damage from any cause (e.g., mumps orchitis, trauma, cytotoxic chemotherapy, alkylating agents, vincristine, nitrosoureas, methotrexate) is commonly associated with gynecomastia. First, levels of total and free testosterone decrease. Second, the resulting increase in serum LH stimulates the aromatase enzyme in testicular Leydig cells to produce more estrogen. In addition, peripheral aromatization of the adrenal androgen androstenedione to estrogen remains unaffected.

Preliminary efficacy data from a retrospective chart review of patients with gynecomastia indicated that TAM was associated with reductions in breast size and decreased pain. TAM, in an uncontrolled study, resulted in complete regression of gynecomastia in 70% of cases.

### Causes of gynecomastia

**Physiological**
- Neonatal
- Pubertal
- Aging

**Pathological**
- Idiopathic
- Drug-induced

#### Increased serum estrogen
- Increased aromatization (peripherally or glandular)
  - Sertoli cell tumors
  - Sex cord tumors
  - Testicular germ cell tumors
  - Leydig cell tumors
  - Adrenocortical tumors
  - Hermaphroditism
  - Obesity
  - Hyperthyroidism
  - Liver disease
  - Testicular feminization
  - Refeeding after starvation
  - Primary aromatase excess
  - Displacement of estrogen from SHBG
    - Spironolactone
    - Ketoconazole

#### Decreased estrogen metabolism
- Cirrhosis (?)

#### Exogenous sources
- Topical estrogen creams and lotions
- Ectopic hCG production
  - Lung carcinoma
  - Choriocarcinoma
  - Liver carcinoma
  - Kidney carcinoma
  - Gastric carcinoma

#### Decreased testosterone synthesis
- Primary gonadal failure, congenital
  - Anorchia
  - Klinefelter syndrome
  - Hermaphroditism
  - Hereditary defects in testosterone synthesis
- Primary gonadal failure, acquired
  - Viral orchitis
  - Castration
  - Granulomatous disease (including leprosy)
- Testicular failure due to hypothalamic and/or pituitary disease
- Androgen resistance due to androgen receptor defects

**Other**
- Chronic renal failure
- Chronic illness
- HIV
- Enhanced breast tissue sensitivity

**Table 1**
Causes of gynecomastia

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<thead>
<tr>
<th>Physiological</th>
<th>Pathological</th>
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<td>Drug-induced</td>
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| Cirrhosis (?)                        |                                                   |

| Exogenous sources                    |                                                   |
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| Ectopic hCG production               |                                                   |
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| Kidney carcinoma                     |                                                   |
| Gastric carcinoma                    |                                                   |

SHBG: Sex hormone-binding globulin; HIV: Human immunodeficiency virus.
LH and FSH are secreted by adenocarcinoma and large cell carcinoma. However, to our knowledge, there is no case in the literature describing paraneoplastic gynecomastia with malignant thymoma. It can be speculated that LH and FSH are secreted in malignant thymoma and that gynecomastia developed as a paraneoplastic entity.

REFERENCES