Digoxin Induced Gynecomastia: Case Report

Digoksinin Neden Olduğu Jinekomasti

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ABSTRACT Gynecomastia is defined as the development of prominent breast tissue in male. Once gynecomastia has been confirmed on history and physical examination, the clinician must determine whether the underlying cause is physiologic or pathologic. Many systemic illnesses, tumors and side effects of various drugs may possibly be underlying causes of gynecomastia. Treating the underlying cause may lead to improvement in the condition. We report a case of a 57-year-old male diagnosed to have several etiologies for gynecomastia, including non-small cell lung cancer, hyperthyroidism, use of an angiotensin-converting enzyme inhibitor and a positive inotropic agent for congestive heart failure, and a history of treatment with chemotherapeutic drugs. The likelihood of a causal connection between the etiologic factor and gynecomastia was assessed using the Naranjo probability scale.

Key Words: Gynecomastia; digoxin

ÖZET Jinekomasti erkek meme dokusunun belirgin büyümesi olarak tanımlanır. Öykü ve fizik muayene ile jinekomasti tanısı doğrulandığında klinisyen altta yatan sebebin fizyolojik mi patolojik mi olduğunu saptamalıdır. Birçok sistemik hastalık, tümör ve çeşitli ilaçların yan etkileri jinekomastinin altta yatan muhtemel sebepleri olabilir. Allta yatan sebebin tedavi edilmesi jinekomastinin düzelmesine neden olabilir. Küçük hücreli olmayan akciğer kanseri, hipertiroidi, konjestif kalp yetmezliği tanısıyla anjiyotensin dönüştürücü enzim inhibitörü ve pozitif inotropik ajan kullanımı ve kemoterapötik ilaçlar ile tedavi öyküsü gibi jinekomastiye neden olabilen birbirinden farklı etiyolojik faktörlere sahip olduğu teşhis edilen 57 yaşında bir erkek hasta olgusunu sunuyoruz. Etiyolojik faktörler ve jinekomasti arasındaki nedensel ilişki olasılığı Naranjo olasılık çizelgesi kullanılarak değerlendirildi.

Anahtar Kelimeler: Jinekomasti; digoksin

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Gynecomastia is a relatively common finding on physical examination and may raise serious cosmetic concerns. Although gynecomastia can be physiologic, it may also be a sign of underlying disease or an undesirable drug side effect.[1] The clinician should consider whether the cause of gynecomastia is physiologic or pathologic. The combination of a careful history and physical examination and a few diagnostic tests can result in the identification of the cause of gynecomastia in the majority of patients. We present the clinical course of a male with several potential pathologic causes of gynecomastia.

CASE REPORT

We present a case of a 57-year-old white male with gynecomastia who was diagnosed to have a metastatic large cell lung carcinoma, hyperthyroidism and congestive heart failure (CHF).

He had a history of Stage IIIB non-small cell lung cancer (NSCLC) with supraclavicular node involvement. Pathological examination of the resected node was diagnosed histologically as metastatic large cell carcinoma. He was managed by combined modality therapy, chemotherapy plus radiation therapy, and is now in clinical remission having survived for more than 3.5 years after the initial diagnosis.

He had symptoms suggesting CHF and the diagnosis was confirmed by physical examination, chest X ray, electrocardiogram and echocardiogram. Echocardiogram revealed mildly depressed ejection fraction (EF of approximately 40-45%) and that not all parts of the heart wall were contributing equally to the heart's pumping activity. Therapy with enalapril, furosemide, carvedilol, acetylsalicylic acid and digoxin was prescribed earlier by his physician to control symptoms.

He was admitted with bilateral breast tenderness and symmetrical enlargement, occurring two months before the present hospital admission. He did not recall any similar episode in the past. Physical examination of his breasts was consistent with the diagnosis of bilateral gynecomastia. On examination, there was no ulceration, nipple retraction, skin dimpling and discharge was not expressed from the nipple. Imaging by ultrasound of his breasts revealed proliferation of the glandular component. The size of the glandular tissue was 6.3 mm on the right, and 5 mm on the left. Routine biochemical tests, including kidney, liver function tests, levels of serum testosterone, estradiol, LH, FSH and prolactin, and tumor markers such as hCG and PSA were within normal limits. Thyroid function tests showed the patient to have mild degree of hyperthyroidism. Ultrasound images displayed enlargement and multinodularity of the both thyroid lobes with a 20 x 13 cm solid mass in the left lobe with diffuse heterogeneous echotexture and multiple, smaller, izoechoic nodules scattered throughout the gland. Radioisotope scanning (with technetium-99m) was performed for identifying the nature of the mass. Thyroid scintigraphy demonstrated multiple, non-functioning cold nodules in the left thyroid lobe. For cytological diagnosis fine-needle aspiration biopsy (FNAB) was done. The findings from the thyroid nodule FNAB sample were reported as a cystic degenerated nodule. Low dose propylthiouracil (PTU) was used for the treatment of hyperthyroidism for 6 months. When he became euthyroid the drug was discontinued and the patient was followed-up without anthytiroid medication.

After he was asked to avoid taking digoxin his breast pain abated after several weeks and gynecomastia did not persist.

DISCUSSION

Various medications and conditions are associated with gynecomastia.[2]

Medications, including antiandrogens (cyproterone acetate, flutamide, finasteride), antibiotics (ethionamide, isoniazid, ketoconazole, metronidazole), antiulcer drugs (cimetidine, ranitidine, omeprazole) cancer chemotherapeutic drugs (alkylating agents, methotrexate, vinca alkaloids, combination chemotherapy, imatinib), cardiovascular drugs (amiodarone, captopril, digitalis, diltiazem, enalapril, methyldopa, nifedipine, reserpine, spironolactone, verapamil), drugs of abuse (alcohol, amphetamines, heroin, marijuana, methadone), hormones (androgens, anabolic steroids, chorionic gonadotropin, estrogens, growth hormone), psychoactive drugs (diazepam, haloperidol, phenothiazines, tricyclic antidepressants), have all been identified as possible causative agents.

Gynecomastia may be also seen in systemic conditions such as cirrhosis, chronic renal failure and dialysis, hyperthyroidism, and starvation. Primary and secondary hypogonadism, testicular neoplasm (germ-cell, leydig-cell, or sertoli-cell), feminizing adrenocortical tumors, ectopic production of human chorionic gonadotropin (large cell carcinoma of the lung, gastric carcinoma, renal cell

carcinoma and occasionally hepatoma), true hermaphroditism, androgen insensitivity syndromes, excessive extraglandular aromatase activity may also be associated with gynecomastia.

Paraneoplastic syndromes are common in lung cancer. Some of these syndromes are more specifically associated with particular cancer histology. Gynecomastia has most often been described in association with large cell carcinoma of the lung, which may produce human chorionic gonadotropin (hCG) or related hormones.[3] After chemotherapy and radiation therapy, the patient presented clear PET activity with no abnormal clinical or radiologic findings. Furthermore, complete remission of disease was confirmed by a follow-up PET scan at admission. Therefore, malignancy was considered unlikely as a possible underlying cause of gynecomastia in the present case.

Gynecomastia has been reported in 10% to 40% of men with hyperthyroidism. SHBG is often increased in hyperthyroidism, resulting in high normal or elevated total serum testosterone and decreased free testosterone levels. Peripheral conversion of androgens to estrogens by aromatase may also be enhanced in hyperthyroidism.[4] Breast enlargement usually resolves after the euthyroid state is restored. In our case antithyroid medication was adjusted to normalize serum thyroid hormone levels, given for 6 months and stopped after the patient had become biochemically euthyroid. However, gynecomastia in the present case resolved completely before that time, suggesting another underlying cause.

Prolonged use of chemotherapy drugs, especially alkylating agents and enalapril, as present in the case reported herein, may also cause gynecomastia. If the gynecomastia is drug-induced, the regression of the breast enlargement usually occurs within one month after discontinuation of the offending drug. However, if the gynecomastia is of long duration (more than one year), it is unlikely to regress spontaneously because of the presence of fibrosis.[5] Improvement in gynecomastia after withdrawal of digoxin strongly suggested that digoxin was responsible. Digoxin induced gynecomastia is probably due to its estrogen like action.[6] Using the Naranjo probability scale, gynecomastia was rated as possibly being a result of the therapy with digoxin. The Naranjo scale has proved to be useful for assessing the causality of the likelihood that a medication resulted in the adverse reaction.[7]

In conclusion, no causal factors other than digoxin could be identified in the present case. Digoxin is one of the most commonly used drugs in medicine and although is rarely responsible for new-onset gynecomastia, should always be in mind as a possible cause.

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