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Gynecomatia in a Renal Transplanted Patient

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Abstract: Gynecomastia is a benign enlargement of the glandular tissue of the male breast, being present in 30% to 50% of healthy men. We describe the case of a male kidney transplant recipient who presented a gynecomastia after immunosuppressive therapy.

Keywords: Gynecomastia, kidney transplantation, cyclosporine

INTRODUCTION

Gynecomastia is a benign enlargement of the glandular tissue of the male breast, being present in 30% to 50% of healthy men [1]. In two case series, palpable breast tissue was detected on physical examination in 36% of healthy younger adult men, 57% of healthy older men, and more than 70% of hospitalized elderly men. In autopsy studies, its prevalence was as high as 55% [2].

Most cases of gynecomastia result from an imbalance between estrogenic (stimulatory) and androgenic (inhibitory) effect on the breast. The etiology may be physiological (during puberty), pharmacological (drug-induced gynecomastia), pathological (primary or secondary hypogonadism, Klinefelter syndrome…) or even idiopathic. Iatrogenic gynecomastia occurs in about one in five cases [3].

We describe the case of a male kidney transplant recipient who presented a gynecomastia after immunosuppressive therapy.

CASE REPORT

Our patient is 24 years old; he was followed for renal failure on chronic glomerulonephritis and hypertension. Hemodialysis was started in March 2011. He was also treated by calcium channel blocker (CCB): Amlodipine 10 mg per day, and beta blocker: Carvédilol 25 mg per day. He was transplanted on January 2012 by the kidney from a related living donor (his twin brother). The patient received induction therapy based on basiliximab at days 1 and 4. Immunosuppression was based on cyclosporine (CsA) 150 mg twice daily, mycophenolate mofetil (MMF) 1000 mg twice daily and prednisolone tapered progressively. He was also receiving CCB to control his high blood pressure. The postoperative outcome was without complications and renal function was normal in day 6 after transplantation.

One month later, the patient presented a bilateral gynecomastia and breast pain without any clinical signs of malignancy: there was no palpable mass, no skin dimpling, no nipple retraction or discharge, and no axillary lymphadenopathy. Routine blood tests were within normal range. Breast ultrasound showed an enlarged bilateral glandular tissue nodule without any malignant signs. A hormone profile showed normal values: follicle-stimulating hormone (FSH): 4.09 IU / l, luteinizing hormone (LH): 4.89 IU / l, estradiol 10 ng / l, testosterone 11.89 nmol /l and prolactin 12µg / l. Residual concentration of CsA (C_0) was in the targeted immunosuppression range in the early post kidney transplant.

After these tests we were able to eliminate any secondary cause of gynecomastia. The drug cause was retained. Two molecules were suspected to be implicated: CsA and CCB. Since the donor and recipient were twins, we proceeded to a gradually reduction of the CsA dose to a complete stop and kept the patient under MMF. We also replaced the CCB by another anti-hypertensive class. The evolution was marked by the regression of the gynecomastia. Mastodynia disappeared after 4 months.

Table-1: Drugs that can cause gynecomastia [5, 6]

Hormones and antihormones
- Estrogens - Androgens and anabolic steroids - Chorionic gonadotropins - Antiandrogens: cyproterone acetate, flutamide, nilutamide ...
antibiotics
- Isoniazid - Ketoconazole
chemotherapy
– Alkylating agents, vincristine, nitrosoureas, methotrexate
Antiulcer
- Cinétidine, omeprazole, ranitidine
Anti-retroviral
Cardiovascular drugs
- Digitoxin, amiodarone, captopril, enalapril, methyldopa, nifedipine, verapamil, reserpine, spironolactone …
Psychoactive drugs
- Neuroleptics - phenothiazines - Tricyclic Antidepressants - Amphetamines
Toxic drugs
- Alcohol - Canabis - Heroin

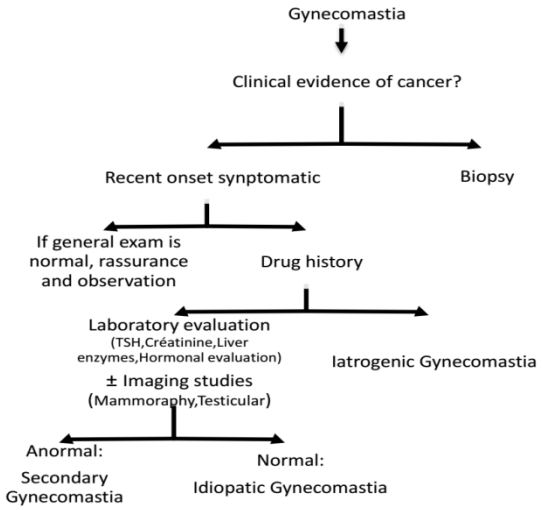

Fig-1: Diagnostic approach to the evaluation of male breast enlargement

DISCUSSION

Drug-induced gynecomastia is common and may account for 20% to 25% of cases [4]. Mechanisms that have been reported include increased direct estrogen activity, increased secretion of estrogens, decreased testosterone synthesis, decreased androgen sensitivity, increased metabolic conversion of exogenous androgens into estrogenic compounds, among others. Some drugs can cause gynecomastia through multiple mechanisms. To date, many substances have been associated with gynecomastia (table 1), such as anti-androgens, antibiotics, antiulcer drugs, cytotoxic agents, cardiovascular drugs, hormones (androgens, anabolic steroids, chorionic gonadotrophin, oestrogens, growth hormone), antiretroviral and psychoactive medications, allopurinol, drugs abuse (alcohol, amphetamines, heroin, methadone, marijuana) and herbal supplements (lavender oil, tea tree oil) [5,6].

The breasts should be examined in detail, looking for signs of malignancy. Ultrasonography or mammography may be helpful in evaluating at high risk men [2].

Men with recent-onset breast enlargement or who present with breast pain and tenderness require a more detailed evaluation to search for a possible

underlying cause. Laboratory screening should include measurements of:

- Thyroid function
- Liver enzymes
- Serum creatinine
- Serum total and free or bioavailable testosterone, estradiol, LH, follicle-stimulating hormone (FSH), and prolactin
- Serum beta-HCG

Imaging tests should not be ordered unless clinical signs or laboratory results dictate them. Imaging tests may include testicular sonography or thermography, computed tomography of the adrenal glands, magnetic resonance imaging of the sella turcica, and mammography (figure 1).

In our case, CsA oral doses and blood levels were within normal ranges, and estradiol levels were normal. We may only speculate that CsA acted through a direct mechanism which is induced by the action of amlodipine. Since the symptoms were not present when our patient was receiving amlodipine prior to transplantation, this argues against that the CCB is solely responsible. Regression of the gynecomastia and mastodynia after interruption of CsA treatment confirms the putative role and the reversible nature of its hormonal side effects.

Indeed, CsA is known to induce hormonal disorders as side effects of its long-term use. This may cause gynecomastia in male transplant recipients. Most of the currently available evidence on CsA induced hormonal changes refers to kidney transplant recipients, leading to speculation about a dose-dependent relation [7].

The exact mechanisms underlying CsA-related gynecomastia are not fully understood, but CsA reduction or discontinuation has been reported to be of value in restoring pre transplant conditions and hormonal status. A dose-dependent drug effect might also be speculated due to the fact that CsA-induced gynecomastia has been mainly reported among pediatric liver transplant recipients and kidney graft patients, usually under higher immunosuppressive regimens [8].

An interaction between cyclosporine (CsA) and felodipine has previously been reported to cause massive breast enlargement needing reduction mammoplasty in a renal transplant recipient [9]. It has also been shown that CsA may elevate serum prolactin levels by displacing prolactin from peripheral binding sites and down regulating its receptors. In our case report, prolactin level was in the normal range. Concomitant administration of CsA with CCB has been reported to increase incidence of CsA-related hormonal changes. *Jacobs and al.* have reported hypergalactinaemia, mastadenoma, and gynecomastia resulting from combined CsA and CCB therapy that normalised after removal of the calcium channel antagonist [10, 11].

In conclusion it appears that an interaction between CsA and amlodipine may lead to gynecomastia and mastodynia. An awareness of this potential interaction may avoid expensive and elaborate laboratory investigation in renal transplant recipients.

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