Irreversible Unilateral Gynecomastia in a Cadaveric Kidney Transplant Recipient

Kadaverik Böbrek Transplant Alıcısında Geriye Dönüşümsüz Tek Taraflı Jinekomasti

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ABSTRACT

Gynecomastia (GM) is a benign condition characterized by enlargement of the male breast, which is attributed to proliferation of the glandular tissue and local fat deposition. We present here a case with unilateral GM that gradually developed after cadaveric renal transplantation.

A 37-year-old man who underwent renal transplantation in 2010 was admitted to our center with complaints of unilateral right-sided GM. There was no nipple discharge, pain or redness in the affected breast. His graft was functioning well. His medications consisted of Cyclosporine (CsA) at a dose of 200 mg/d, mycophenolic acid at a dose of 2000 mg/d, prednisolone at a dose of 5 mg/d, doxazosin 8 mg/d, and metoprolol 50 mg/d. CsA-induced GM was considered, and CsA was switched to sirolimus. After two months, GM regression was not observed. Fine needle aspiration of a right breast mass revealed a benign condition. Estrogen and progesterone receptor was strongly positive on microscopic examination of the tissue.

GM is a rare condition that is generally caused by CsA treatment. However, GM may persist after the discontinuation of CsA.

KEY WORDS: Cyclosporine A, Gynecomastia, Renal transplantation

ÖZ

Jinekomasti, bölgesel yağ birikimi ve glanduler dokunun proliferasyonunu ile olan, erkek memesinin büyümesi ile karakterize benign bir durumdur. Biz burada, kadaverik böbrek transplantasyonu sonrası gelişen tek taraflı jinekomasti olgusunu sunduk.

2010 yılında böbrek transplantasyonu olan 37 yaşında bir erkek hasta, merkezimize tek-sağ taraflı jinekomasti bulgusu ile kabul edildi. Etkilenen memede ağrı, kızarıklık, akıntı yoktu. Greft fonksiyonu iyiydi. İlaçları siklosporin 200 mg/gün, mikofenolik asit 2000 mg/gün, prednizolon 5 mg/gün, doksazosin 8 mg/gün, metoprolol 50 mg/gün idi. Siklosporine bağlı jinekomasti düşünüldü ve siklosporin sirolimus ile değiştirildi. 2 ay sonra jinekomastide gerileme gözlenmedi. Sağ memeden yapılan ince iğne aspirasyon biopsisi benign sonuç geldi. Dokuların mikroskobik tetkikinde; östrojen ve progesteron reseptörleri güçlü pozitif geldi.

Kalsinörin tedavisi ile meydana gelen jinekomasti nadir bir durumdur. Fakat jinekomasti kalsinörin kesildikten sonra kalıcı olabilir.

ANAHTAR SÖZCÜKLER: Siklosporin A, Jinekomasti, Böbrek nakli

INTRODUCTION

Gynecomastia (GM) is a benign condition characterized by enlargement of the male breast, which is attributable to proliferation of the glandular tissue and local fat deposition. Male breast tissue proliferation can occur at all ages, particularly in adolescents, and may be unilateral or bilateral. However, only a few reports have described the new onset of GM after solid organ transplantation (1).

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There are many causes that have been associated with development of GM (2). Drugs including cimetidine, ranitidine, omeprazole, growth hormones, cyclosporine (CsA), calcium channel blockers have also been reported to cause the phenomenon. Drugs are estimated to cause about 10-25% of all cases of GM (3). Although the mechanisms by which many medications induce GM are not yet understood, some mechanisms are clear (4). We present here a case with unilateral GM that gradually developed after cadaveric renal transplantation.

CASE REPORT

A 37-year-old man who had undergone cadaveric renal transplantation in December 2010 was admitted to our center with complaints of gradually developed (about six months) of unilateral right-sided GM (Figure 1). There was no nipple discharge, pain or redness in the affected breast. His graft was functioning well. His medications consisted of CsA at a dose of 200 mg/d, mycophenolic acid 2000 mg/d, prednisolone 5 mg/d, doxazosin 8 mg/d, and metoprolol 50 mg/d. His serum CsA level was maintained at an appropriate therapeutic level after transplantation. On physical examination, there was no abnormality except for GM. Body mass index was 28 kg/m^2. No testicular abnormality was found.

Laboratory findings on admission (Table I) were as follows: complete blood count normal; serum creatinine 1.0 mg/dl (normal range 0.5–0.9 mg/dl); serum albumin 4.1 g/dl; proteinuria 230 mg/d; low density lipoprotein (LDL) 120 mg/dl; and erythrocyte sedimentation rate 22 mm/h. Liver enzymes, international normalized ratio (INR), fasting blood glucose, C-reactive protein, and urinalysis were all normal. Hepatitis B surface antigen, anti-HCV antibody, and human immunodeficiency virus (HIV) antibody were all negative.

Figure 1: *Right-sided gynecomastia on admission.*

Serum levels of progesterone, prolactin, gonadotropins (FSH, LH), and estradiol were slightly elevated on admission.

The drugs associated with GM including antipsychotics, spironolactone, cocaine, heroin, and calcium channel blockers were ruled out. Nonetheless, after ruling out the presence of concomitant endocrine diseases or disorders and pituitary dysfunction, CsA-induced GM was considered. GM often regresses after stopping CsA so we switched CsA to sirolimus, and observed the patient for two months. GM regression was not observed after two months, while the hormone levels returned to normal ranges (Figure 2). Breast magnetic resonance findings were compatible with GM (Figure 3). Chest X-ray and echocardiogram showed no abnormalities. We performed fine needle aspiration of a right breast mass. Histopathological

Table I: Hormone levels on admission and after discontinuation of CsA.

Hormone	At the time of gynecomastia	Two months after the drug switch	Normal values for males
Free thyroxine, pmol/L	14.62	NC	12-22
TSH, μIU/mL	1.2	NC	0.27-4.2
Progesterone, ng/mL	3.2	0.9	0.2-1.4
Prolactin, ng/mL	96	9.62	4.1-18.4
FSH, IU/L	37.3	9.7	1.5-12.4
Estradiol pg/mL	63.8	32.6	13.5-59.5
Testosterone, ng/mL	5.8	4.2	0.28-8
LH, IU/L	38.6	6.4	1.7-8.6
Beta HCG, mIU/mL	<0.01	NC	0-6

TSH: Thyroid-stimulating hormone, **FSH:** Follicle-stimulating hormone, **LH:** Luteinizing hormone, **HCG:** Human chorionic gonadotropin, **NC:** Not controlled.

Figure 2: *Irreversible gynecomastia after 9 months of follow up after discontinuation of CsA.*

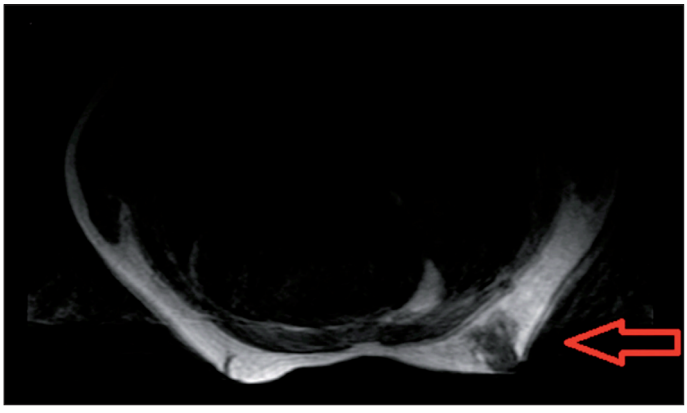

Figure 3: *Contrast-enhanced fat-saturated T1-weighted axial images demonstrate subareolar asymmetric fibroglandular tissue proliferation in the right breast. The enhancement is slow, persistent and non-mass like. This finding is consistent with unilateral gynecomastia.*

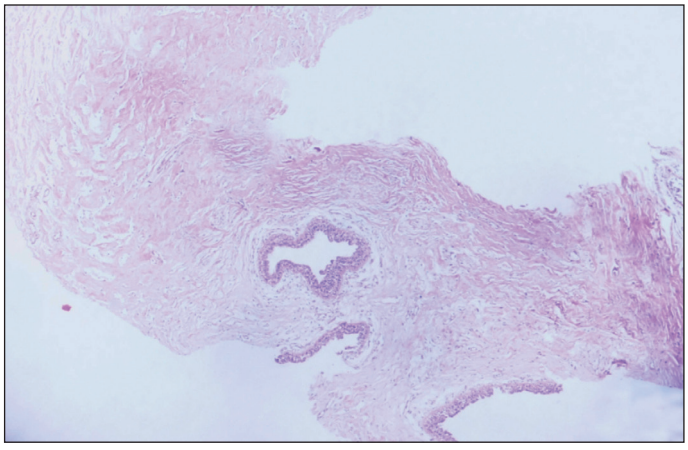

Figure 4: *Ducts sections with halos of edema on a fibrohyalinisated background is shown (H&E, original magnification ×40).*

investigation revealed GM findings (Figure 4) with estrogen and progesterone receptor positivity (Figure 5). Tamoxifen was administered at a dose of 20 mg/d for three months. The GM did not regress. Surgical treatment was recommended but the patient refused.

DISCUSSION

GM, a benign proliferation of the glandular tissue of the male breast, is common in adolescence and in middle-aged to elderly men. Fat deposition without glandular proliferation is termed pseudo GM and is often seen in obese men.

GM occurs in about 50 percent of patients treated with maintenance hemodialysis. However, it may occur following renal transplantation as gonadal function improves (re-feeding GM) and/or because of the use of some medications including calcium channel blockers (CCBs) and CsA. Immunosuppressant drugs often cause different types of cancer to develop in renal transplant patients and GM must be differentiated from breast carcinoma. Breast carcinoma is much less common, generally unilateral as in our patient, eccentric in location rather than symmetrical to the nipple, hard or firm, and may be associated with skin dimpling, nipple retraction or discharge, and axillary lymphadenopathy. In a study of 36 male patients who underwent subcutaneous mastectomy for a unilateral breast mass, 30 (83%) had GM, 4 (11%) had lipoma, and 2 had breast cancer (5). Our patient did not demonstrate a malignant appearance on physical examination except for the unilateral mass.

A few cases of benign breast lesions have been reported among transplant patients treated with CsA therapy (6). These benign breast lesions can be focal or generalized. Focal changes commonly occur in the form of fibroadenoma, which may be single, multiple, unilateral or bilateral. A diffuse pattern usually occurs in the multiple nodular form, fibrocystic disease in men with GM (7).

There does not appear to be any difference in the responsiveness of the male or female breast glandular tissue to hormonal stimulation. Concomitant administration of CsA with CCBs has been to increase the incidence of CsA-related hormonal changes, either through an increase in CsA and/or CsA metabolites blood levels or a direct action at a molecular level (8). It has been suggested that CsA may have an effect on the hypothalamic-pituitary axis (9). It has also been demonstrated that CsA increases estrogen levels in human beings (10) while estrogens induce ductal epithelial hyperplasia and ductal branching, and an increase in vascularity. The histological picture is similar in the male and female breast tissue after exposure to estrogen. Furthermore, CsA may increase serum prolactin levels as in our patient, with concurrent down-regulation of prolactin receptors. This could have consequential effects on hypothalamic regulation of prolactin secretion. CsA administration also increases the circulation of prolactin by dislocating prolactin from peripheral binding sites (11). Serum

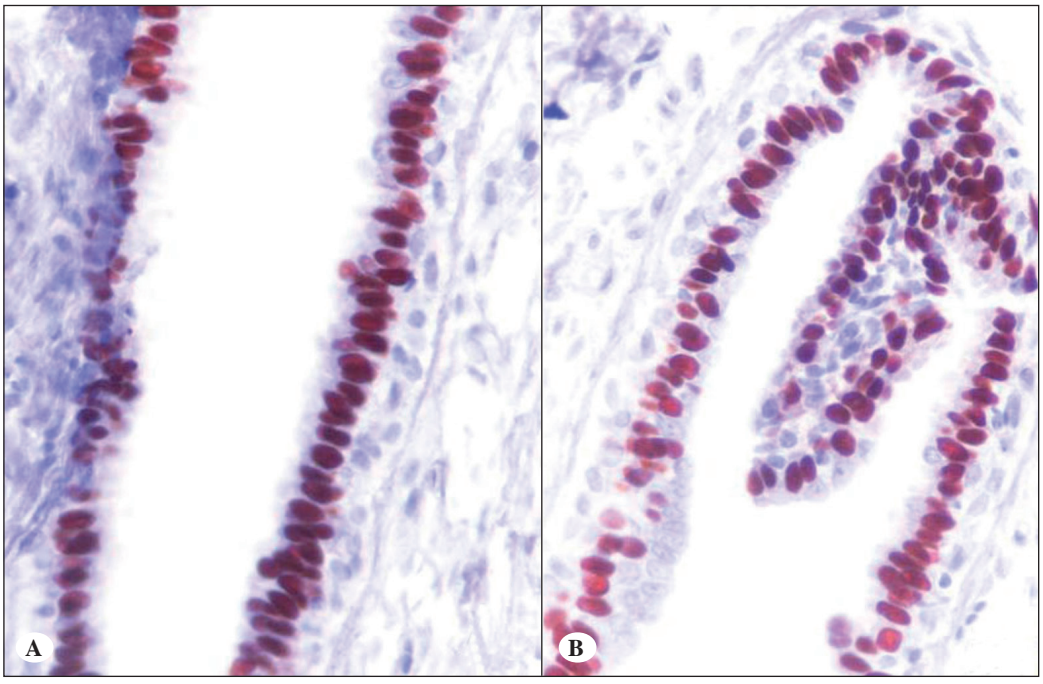

Figure 5:A) *Strong nuclear Estrogen and* ***B)*** *Progesterone receptor positivity (Immunohistochemistry, original magnification ×200).*

levels of estradiol, prolactin and gonadotropins were slightly elevated in our patient. After a careful differential diagnosis, we considered CsA-induced GM. Serum levels of estradiol, prolactin, and gonadotropins returned to normal ranges after CsA discontinuation in the patient but interestingly we did not observe a reduction in the breast mass.

Only a few reports have described the new onset of GM after solid organ transplantation (1). Recently, Iaria et al. reported a patient with GM in a liver transplant recipient associated with CsA treatment (12). They successfully treated GM by switching from CsA to tacrolimus. Kumar et al. reported CsA as a cause of unilateral GM in a renal transplant recipient. Their patient had undergone surgical excision for multiple bilateral breast and axillary fibroadenomas (13). Discontinuing the CsA may induce some improvement in early cases, but the breast may not return to its former size due to breast fibrosis, as in our patient (14).

CONCLUSIONS

The screening of breasts in male renal transplant recipients who receive CsA should be performed routinely. We conclude that early detection and discontinuation of CsA is important for the reversibility of GM.

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