Table 1. Data of test on admission

Venous blood	
Glucose	79mg/dl
Urea	367mg/dl
Creatinine	4.49mg/dl
Na	138mEq/l
K	4.2mEq/l
Cl	97mEq/l
GOT	40mEq/l
GPT	20U/l
Total bilirubin	1.17mg/dl
CRP	25.1mg/l
pH	7.42
pCO2	32.8mmHg
Bicarbonate	21.2mmol/l
Leukocytes	6720/ul
Neutrophils	86%
Eosinophils	0.3%
Haemoglobin	5g/dl
Haematocrit	16%
Platelets	184,000/ul
Quick	17%
INR	4.55
Prothrombin time	21.2s
Thrombin time	>120s
Urine sediment	
Leukocytes	100-200/C
Bacteria	Abundant on direct vision

GOT: glutamate-oxaloacetate transaminase, GPT: glutamate pyruvate transaminase, INR: International normalized ratio; CRP: C reactive protein.

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Painful gynaecomastia secondary to cyclosporine A and tacrolimus in a patient with focal segmental glomerulosclerosis

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To the Editor:

Mammary gland hypertrophy is frequently observed as a side effect of medications such as calcium channel blockers, angiotensin II receptor antagonists, omeprazole or some immunosuppressants such as cyclosporine A.[1-3] In women with a kidney transplant on treatment with calcineurin inhibitors, mammary gland growth of varying intensity has been described, usually after more than one year. The patient may not always return after the drug is withdrawn and sometimes corrective mammoplasty is required to reduce the large volumes. However, we have not found this adverse effect reported in patients with glomerulonephritis on treatment with cyclosporin A.

CASE STUDY

Our patient is a 48-year-old male who had been referred 9 months previously due to proteinuria. He had high blood pressure for 2 years and had been on treatment with amlodipine, atenolol and irbesartan for several years. The general test displayed: proteinuria of 1200mg/day, 448 red blood cells/µl in sediment, creatinine of 1.05mg/dl and negative immunology. The renal biopsy showed: 5-10 glomeruli without remarkable cellularity, without exudation, 2-4 glomeruli with complete sclerosis, discrete chronic interstitial lymphocyte-monocyte infiltrates, without vascular involvement and without tubular atrophy. In the immunofluorescence: IgM immunoglobulin deposits of focal and segmental distribution in 10 glomeruli, with + and + + intensity in the mesangial region. It was treated as focal segmental glomerulosclerosis with 2.5-5mg/day of ramipril being administered, and proteinuria decreased to <400mg/day. Three years ago, the patient had an increase in proteinuria of 1.6g/day, albuminuria of 895mg/day and 250 red blood cells/µl with normoalbuminaemia and oedemas. We treated him with prednisone and cyclophosphamide, with a decrease in proteinuria being observed after 7 months of treatment to 1.1g/day, but with proximal muscle weakness, which was interpreted as a myopathy due to steroids. Prednisone was discontinued and replaced by 1g/day mycophenolate mofetil and we withdrew amlodipine due to its potential influence on oedema, with 12.5mg of hydrochlorothiazide being administered due to poor blood pressure control. After 2 months we

suspended mycophenolate because the patient expressed experiencing significant fatigue, which he attributed to this drug. Cyclosporine A was then administered at a dose of 150mg/day (1.9mg/kg/day) with good initial tolerance (67.8ng/ml). After 2 months, the patient presented with pain in left breast accompanied by a retroareolar nodule sensitive to touch, which was the size of a chestnut. Cyclosporine A was discontinued and a mammography and ultrasound were performed. We found glandular increase with no evidence of malignancy, and therefore it was interpreted as medication-related glandular hyperplasia. Eight months later we introduced tacrolimus (6mg/day with subsequent reduction to 4-5mg/day with levels <8ng/ml). Two months later, the patient presented again with left breast pain, and as such tacrolimus was discontinued upon finding proteinuria of <250mg/day. In the last review 5 months later, proteinuria had increased to 650mg/day and glandular growth had stopped. The patient was subsequently treated with doxazosin, atenolol, irbesartan and ramipril.

DISCUSSION

Cyclosporine is occasionally associated with uni- or bilateral breast growth in women, accompanied by variable local inflammatory signs, with significant erythema and considerable pain.[2] The histology usually shows mild to intense mammary glandular epithelial hyperplasia which may even raise suspicion of malignancy, although it is not atypical. In addition to glandular growth, variable growth of the surrounding fibrous tissue is normally observed, which is comparable with the histology of fibroadenomas that may reach a large size and be non-reversible, depending on the degree of fibrosis.[2] This histological profile is similar to that of cyclosporine A-induced gingival hypertrophy, although an association between the two profiles has not been observed and no relationship has been found with drug levels.[4]

It is unknown what stimulates glandular growth, although it is considered that TGF-beta is involved. Sometimes it occurs with an increase in estradiol and a decrease in the FSH (follicle stimulating hormone)[4] and in one case increased prolactin levels were found and associated with lactation, although in most cases prolactin is normal. In 2 male liver transplant recipients there was an increase in the LH (luteinizing hormone) coinciding with the administration of cyclosporin A, and a decrease in these levels on replacing the immunosuppressive drug with tacrolimus.[3] Cyclosporin A and tacrolimus are able to effectively inhibit estradiol degradation, which would explain the increased levels of estradiol, a mechanism also suggested for spironolactone.[5]

Some of the antihypertensive drugs taken by the patient have been associated with the appearance of gynaecomastia.[1] However, there was a clear temporal relationship between the introduction and discontinuation of cyclosporine A and subsequently tacrolimus, and the occurrence of painful breast growth, which stopped when calcineurin inhibitors were introduced, which means that they were most likely the cause of breast growth. The time on treatment it takes for gynaecomastia to appear varies in the literature. In our case, it occurred at an early stage. It is uncommon to observe it in males and most fibroadenomas of the breast described occur in solid organ transplant recipients,[3] unlike with our patient, in whom it was established during treatment for chronic glomerulonephritis.

The progression of this breast hyperplasia was benign and growth stopped when cyclosporine A was discontinued. In transplant patients in whom it is replaced with tacrolimus, clinical improvement may occur in up to a third of patients, although it is frequently necessary to replace it with another immunosuppressive drug.[6] We changed the patient to tacrolimus after 8 months without cyclosporine A and he displayed the same symptoms again quickly. As such, we discontinued medication definitively. In cases in which growth is not reversible and causes discomfort, lumpectomy or breast reduction may be considered.[7]

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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