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SHORT COMMUNICATION

Sirolimus-induced Inflammatory Lymphoedema of the Breast Resolved After Switching to Cyclosporine

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The main causes of acquired unilateral inflammatory breast oedema are infection, neoplasia (inflammatory breast cancer, angiosarcoma) and inflammatory mastitis. More rarely, it can be the consequence of impaired venous drainage in patients with congestive cardiac failure or with renal failure treated by haemodialysis. Unilateral lymphoedema of the breast can also occur as a consequence of lymphoedema secondary to the treatment of breast cancer (1). Unilateral lymphoedema of the breast has been reported in a few patients with no history of breast cancer but treated with mammalian target of rapamycin (mTor) inhibitors (2). Moreover, unilateral lymphoedema of the breast has been reported with lymphoedema located on homolateral or both limbs in 6 other patients treated with mTor inhibitors (3).

We report a new case of unilateral inflammatory lymphoedema of the breast which had appeared after beginning treatment with sirolimus (also called rapamycin), and which disappeared after switching from sirolimus to cyclosporine.

CASE REPORT

A 56-year-old woman, with no history of breast cancer, consulted her gynaecologist for pain and unilateral swelling of her left breast that had appeared 6 weeks earlier (Fig. 1a). She had no fever. Palpation showed tender erythema and swelling of the left breast. Blood cell count and C-reactive protein levels were within normal ranges. Mammography and ultrasound examination revealed no glandular abnormality, but a doubling of dermal thickness compared to the healthy side, due to dermal oedema (Fig. 2). Two skin biopsies were performed one month apart that showed mild dermal oedema and mild mixed perivascular infiltrate (Fig. S1[1]).

The patient had received a kidney transplant in 2004 after end-stage renal failure related to polycystic kidney disease. Immunosuppressive therapy with cyclosporine and mycophenolate mofetil had been changed to sirolimus and mycophenolate mofetil in July 2011, after the occurrence of *in situ* cervical carcinoma and *in situ* squamous cell carcinoma of the skin.

Inflammatory lymphoedema related to sirolumus was suspected. The first-step of decreasing the dose of sirolimus was associated with a decrease in plasma level of sirolimus from 14.7 to 6 ng /ml but there had been no reduction of oedema after 3 months. Sirolimus was then replaced with cyclosporine and the dose of mycophenolate mofetil was unchanged. Oedema and erythema of the breast gradually disappeared within 4 months with no recurrence after 15 months (Fig. 1b). However, ultrasound examination showed persistent dermal oedema.

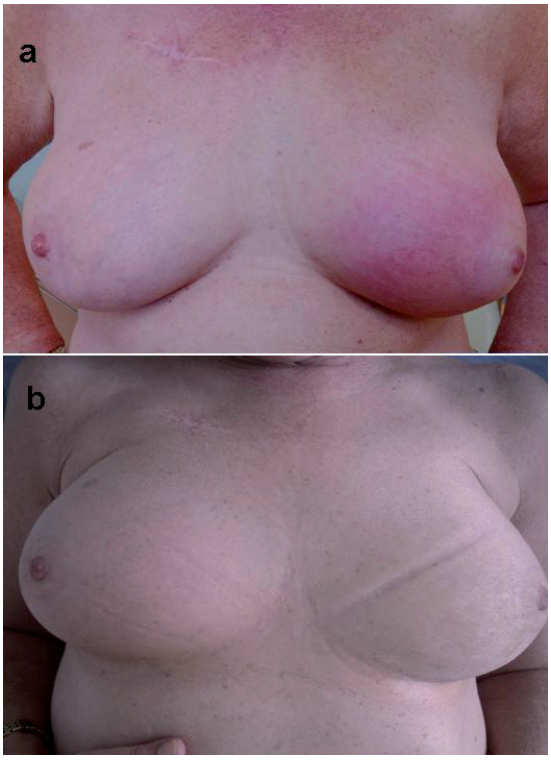

Fig. 1. Unilateral inflammatory oedema of the left breast (a) and (b) clinical appearance 15 months after withdrawing sirolimus.

DISCUSSION

We report here a new case of isolated, unilateral breast lymphoedema that had appeared 10 months after starting sirolimus. The diagnosis of unilateral lymphoedema was established on clinical and ultrasound examination that showed a marked homogenous increase in dermal thickness (4). The lymphoedema disappeared within 6 months of ceasing treatment with sirolimus in this kidney-grafted patient. The temporal causal relationship with the drug is therefore probable.

Peripheral bilateral oedema is frequent, occurring in up to half of the patients treated with mTor inhibitors (5). Such oedema is multifactorial and is usually controlled with low doses of furosemide and with reduction of the daily dose of mTor. However, withdrawal of the mTor inhibitor was necessary in 28% of cases (5). True acquired lymphoedema has rarely been reported. A series of 8 cases of acquired lymphoedema confirmed by lymphoscintigraphy was reported in patients treated

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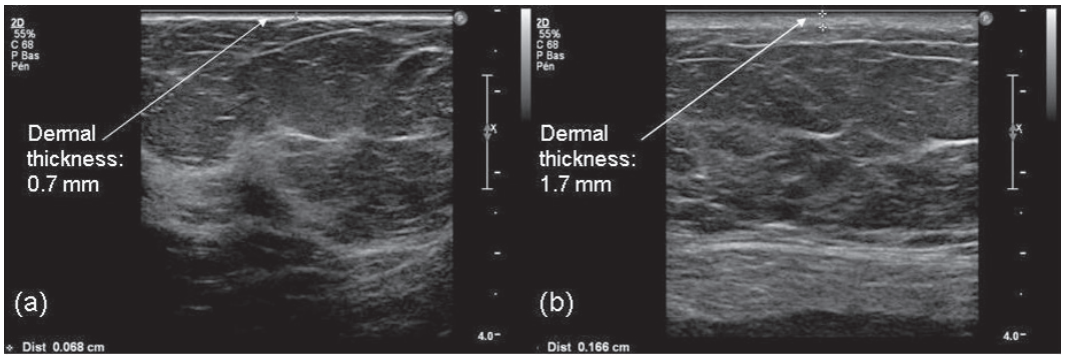

Fig. 2. Ultrasound examination: (a) normal appearance of unaffected side contrasting (b) with oedema located within the dermis and hypodermis of affected side.

with sirolimus in 2009 (3). About 15 other isolated cases have been published (3, 6, 7) mainly affecting the lower or upper limbs. These cases were generally unilateral (3), but occasionally bilateral (6, 7). Moreover, a series of 5 patients with lymphoedema restricted to the breast was reported in 2012 (2). Four patients were treated with everolimus, and one with sirolimus, that begun 2–14 months before the occurrence of lymphoedema. The mTor inhibitor was withdrawn in 3 cases (everolimus in 2 cases, sirolimus in 1 case), resulting in regression of erythema and partial regression of oedema in all 3 cases, as in the case presented here.

The pathophysiology of sirolimus-induced lymphoedema is probably related to changed lymphatic angiogenesis. Most of the proteins that are encoded by the genes mutated in primary lymphoedema seem to act in a single functional pathway involving VEGFR3 signalling (8). Sirolimus was found to inhibit the protein expression of VEGF receptor 3 (VEGFR-3) by inhibiting protein synthesis and promoting protein degradation of VEGFR-3 in an *in vitro* model of lymphangiogenesis (9). VEGF-D is a major player in promoting lymphatic vascular growth both during development and in pathological conditions by activating VEGFR3. VEGF-D is increased in patients with lymphangioleiomyomatosis and is significantly decreased by sirolimus. It was found to be associated with pulmonary improvement in a randomised study (10).

In conclusion, mTOR inhibitors are increasingly used to prevent graft rejection and also in the treatment of cancer. mTor inhibitors display anti-lymphangiogenic properties *in vitro*, which in part explains the antitumoural activity. *In vivo*, they can provoke lymphoedema and we believe that cases are probably under-recognised. It is very important to suspect lymphoedema clinically and to confirm this with lymphoscintigraphy or ultrasound, because it usually decreases with the substitution of an mTor inhibitor of another therapeutic class. The risk/benefit ratio of switching has to be weighed as the antitumoural properties of mTor inhibitors are valuable in secondary prevention of squamous cell carcinoma in graft recipients treated with cyclosporine (11), particularly in patients with polycystic kidney disease, as this is an independent risk factor for non-melanoma skin cancer following kidney transplantation (12).

The authors declare no conflict of interest.

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