

## Refractory Subacute Cutaneous Lupus Erythematosus Treated With Rituximab<sup>☆</sup>

### Lupus eritematoso cutáneo subagudo refractario tratado con rituximab

To the Editor:

Subacute cutaneous lupus erythematosus (SCLE) is a variant of photosensitive cutaneous lupus erythematosus that is often associated with anti-Ro antibodies.<sup>1</sup>

We present 3 cases of treatment-refractory SCLE that resolved satisfactorily with rituximab.

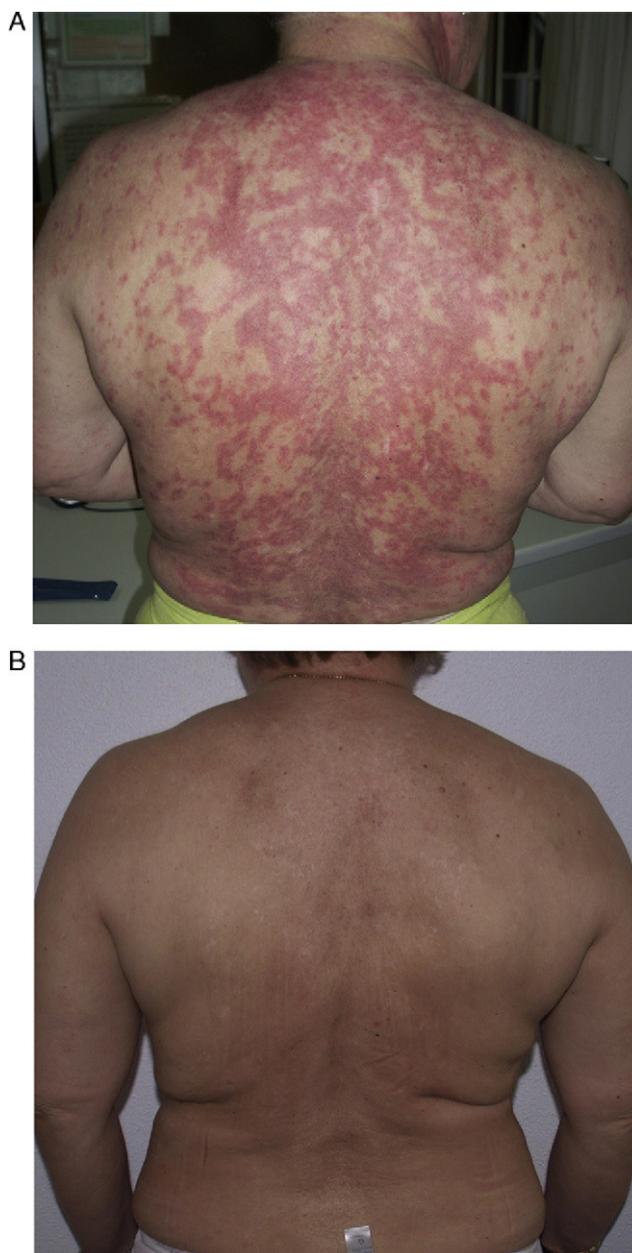
Patient 1 was a 54-year-old woman (smoker) diagnosed with SCLE. She had annular lesions on her back (Fig. 1 A), upper chest, and arms. Testing for antinuclear antibody (ANA) was positive (titer, 1/640), with a homogeneous pattern; the results for other antibodies were negative.

The patient received high-dose prednisone (50 mg/d), antimalarial agents (chloroquine 250 mg/d and hydroxychloroquine 400 mg/d) for 3 years, thalidomide 50-150 mg/d for 16 months, cyclophosphamide 100 mg/d, mycophenolate 500 mg/d, etanercept (50 mg, 2 doses per week), and intravenous immunoglobulins (2 g/kg). Improvement was partial, and the patient experienced the following side effects: blurred vision (antimalarial agents), sensory axonal polyneuropathy (thalidomide), and leukopenia (cyclophosphamide).

In view of the lack of response, rituximab was started at a weekly dose of 375 mg/m<sup>2</sup> (4 doses) combined with prednisone 5-10 mg/d. Remission was complete after 2 months. The same regimen was repeated annually (1 g/15 d, 2 doses) for 4 years because of the appearance of new outbreaks, and control of the cutaneous lesions was excellent (Fig. 1 B).

Patient 2 was a 37-year-old woman (smoker) with epilepsy, for which she was receiving carbamazepine but later switched to valproic acid. She had been diagnosed with SCLE at age 34 years and had annular lesions on her upper chest, back, and arms. Her ANA pattern was homogeneous (titer, 1/640), anti-La was positive, and testing for the remaining antibodies, including antihistone antibodies, was negative.

She had responded well to prednisone 50 mg/d, hydroxychloroquine 400 mg/d (18 months), and azathioprine 100 mg/d, which was discontinued because of drug-induced leukopenia. Her skin lesions worsened considerably when azathioprine was stopped (Fig. 2 A); therefore, rituximab was started at a weekly dose of 375 mg/m<sup>2</sup> (4 doses) combined with low-dose prednisone (10 mg/d) and antimalarial agents. The patient progressed favorably, with no active lesions after 3 months. The regimen was repeated 1 year later (1 g/15 d, 2 doses), and the patient remained free of active lesions during the 8 months following the last infusion of rituximab (Fig. 2 B). Control of the disease was maintained with hydroxychloroquine 200-400 mg/d.



**Figure 1** A, Patient with extensive subacute cutaneous lupus erythematosus lesions before starting therapy with rituximab. B, The patient is lesion-free 8 months after her fourth cycle of rituximab.

Patient 3 was a 28-year-old woman who consulted with malar rash, asthenia, arthritis, low-grade fever, and annular lesions on the upper chest, back, and arms. Skin biopsy confirmed a clinical diagnosis of SCLE. A blood workup revealed reduced C3 and C4 levels, ANA (titer, 1/320) with a homogeneous pattern, and positive results for double-strand anti-DNA, anti-Ro, antiribonucleoprotein, and anti-Sm antibodies. The patient was diagnosed with systemic lupus erythematosus (SLE) and started treatment with prednisone 40 mg/d combined with hydroxychloroquine 400 mg/d for 6 months. The response was good, although her condition

<sup>☆</sup> Please cite this article as: D.E. Cieza-Díaz, J.A. Avilés-Izquierdo, C. Ceballos-Rodríguez, R. Suárez-Fernández. Lupus eritematoso cutáneo subagudo refractario tratado con rituximab. *Actas Dermosifiliogr.* 2012;103:555-557.



**Figure 2** A, Patient with extensive crusted subacute cutaneous lupus erythematosus lesions before starting therapy with rituximab. B, The patient is lesion-free 8 months after her second cycle of rituximab.

deteriorated when the dose of corticosteroid was reduced. Given our previous experience, we started treatment with rituximab at a weekly dose of  $375 \text{ mg/m}^2$  (4 doses). Two months later, the patient's skin and clinical symptoms had improved considerably, although the malar rash persisted on the center of her face. Positive results were found for ANA, anti-DNA, and anti-Ro antibodies; the results for the remaining antibodies were negative. She is currently receiving prednisone at  $10\text{-}20 \text{ mg/d}$  in combination with oral anti-malarial agents.

Treatment of SCLÉ is based on strict photoprotection and administration of antimalarial agents as the first-line systemic approach. These drugs enable the disease to be controlled in up to 75% of cases.<sup>1,2</sup> However, the remaining 25% require other types of systemic immunomodulatory or immunosuppressive therapy, which have variable efficacy and are not free of side effects.<sup>1,2</sup>

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen, which is expressed in pre-B cells, mature B cells, and memory cells, and leads to depletion of B lymphocytes.<sup>3</sup> It is indicated mainly for B-cell lymphoproliferative disorders involving expression of CD20 (chronic lymphocytic leukemia and non-Hodgkin lymphoma),<sup>4</sup> as well as in rheumatoid arthritis.<sup>5</sup> Case series show its efficacy in pemphigus vulgaris, paraneoplastic pemphigus, cutaneous B-cell lymphoma, chronic graft-versus-host disease, and dermatomyositis.<sup>6</sup>

In SLE, depletion of B cells could lead to diminished production and expansion of autoreactive antibody-forming cells and to loss of the costimulatory signals delivered by B cells to T cells (CD40-CD40L interaction), thus blocking the antibody-dependent and antibody-independent tissue damage that occurs in lupus.<sup>3</sup> Furthermore, the clinical efficacy and safety of rituximab has been reported in case series and open-label trials in patients with SLE. The duration of the drug's effectiveness varies, and it usually lasts from at least 5 months to around 14 months.<sup>3,7</sup> However, few case reports show successful management of refractory cutaneous lupus with rituximab.

Risselada and Kallenberg<sup>8</sup> reported the first 2 cases of refractory cutaneous lupus treated with rituximab in patients with SLE ( $2 \times 1000 \text{ mg/m}^2$ ). The improvement in skin lesions was both marked and persistent. Uthman et al<sup>9</sup> reported the case of a patient with SLE and extensive recalcitrant SCLÉ lesions that had been treated with rituximab ( $1 \text{ g/wk}$ , 2 doses) and improved considerably.<sup>9</sup> Kieu et al<sup>10</sup> presented the first case of SCLÉ that did not fulfill the criteria for SLE and was refractory to antimalarial agents and immunosuppressants. Treatment was with rituximab at a weekly dose of  $375 \text{ mg/m}^2$  (4 doses). The same dose was administered a year later because the lesions recurred. The patient remained lesion-free for 2 years with maintenance therapy ( $375 \text{ mg/m}^2$  every 8 weeks).

We present 3 cases of refractory SCLÉ treated successfully with rituximab, which was well tolerated. Limited published experience and our findings in the present manuscript allow us to propose rituximab as an alternative for treatment of SCLÉ refractory to the usual approaches. However, larger-scale studies will enable us to set limits for this indication and establish the safety profile in this group of patients.

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## Angiosarcoma of the Skin After Breast Cancer Radiotherapy<sup>☆</sup>

### Angiosarcoma cutáneo tras radioterapia por cáncer de mama

To the Editor:

In recent years, there has been a trend towards conservative management of breast cancer, which involves the use of adjuvant radiotherapy. This approach carries a risk of radiation-induced secondary malignancy.

We present the case of a 70-year-old woman who underwent quadrantectomy combined with adjuvant radiotherapy to treat invasive ductal carcinoma in her right breast in 2007. She was referred to our center 3 years later with a 1-month history of skin lesions. Examination revealed several red-violaceous nodules and papules, with multifocal involvement of the treated breast (Fig. 1).

Histopathology of 1 of the nodules revealed a poorly defined dermal tumor infiltrating the subcutaneous layer, which was formed by a proliferation of vascular structures alternating with undifferentiated solid areas (Fig. 2). The vascular structures were covered by endothelial cells with atypia, whereas the solid areas contained highly proliferative pleomorphic epithelioid cells (6 mitoses per 10 high-power fields) and interstitial hemorrhaging. The tumor cells proved to be immunoreactive to vascular markers (CD31 and CD34) and negative to epithelial markers (epithelial membrane antigen and pancytokeratin). Immunostaining for herpes simplex virus type 8 was negative.

<sup>☆</sup> Please cite this article as: M. Armengot-Carbó, M.J. Roca-Estellés, E. Quecedo-Estébanez, E. Gimeno-Carpio. Angiosarcoma cutáneo tras radioterapia por cáncer de mama. *Actas Dermosifiliogr*. 2012;103:557-9.

These findings confirmed the diagnosis of angiosarcoma, and the patient underwent simple mastectomy. Pathological examination of the surgical specimen showed the presence of several dermal nodules (the largest measuring 4 × 3 cm) and foci in the breast parenchyma (2–5 mm). Histopathology confirmed the diagnosis of high-grade angiosarcoma, with disease-free margins. The results of the staging study (computed tomography of the thorax, abdomen, and pelvis and positron emission tomography) were negative. After a 9-month follow-up period, the patient remains disease-free.

Angiosarcoma is a very uncommon endothelial cell tumor.<sup>1</sup> It accounts for less than 1% of cases of sarcoma and most frequently affects the skin.<sup>2,3</sup> Cutaneous angiosarcoma can be divided into 3 main types: the classic or idiopathic type, the chronic lymphedema-associated type, and the radiation-induced type. Classic idiopathic angiosarcoma affects the skin of the head and neck in elderly patients<sup>3,4</sup> and is the most frequent variety (50%–60%).<sup>5</sup> Chronic lymphedema-associated angiosarcoma



**Figure 1** Multiple erythematous-violaceous nodules and papules on the irradiated breast.