To the Editor:

We report the case of a 27-year-old woman with a 10-year history of tuberous sclerosis. Her first visit to the dermatologist revealed several of the cutaneous manifestations characteristic of the disease, namely, disseminated facial angiofibromas (Fig. 1), multiple periungual Koenen tumors on both feet, hypopigmented macules on the trunk, and a shagreen plaque on the back. The patient also had epilepsy and mental retardation. She had no known internal hamartomatous lesions.

A number of treatments—multiple shave excisions, pulsed-dye laser, electrodessication, and 0.1% topical tacrolimus ointment—had been applied in order to improve her facial appearance and reduce the number of angiofibromas. The response to treatment had been poor, with no appreciable reduction in the number of lesions and persistence of erythema. At that time, pharmacy-prepared topical rapamycin, 1 mg/mL, was applied twice daily on the affected areas of both cheeks. A clear clinical improvement was observed after 3 months’ treatment, with a reduction in the number of lesions and in the underlying erythema (Fig. 2).

Tuberous sclerosis is an autosomal-dominant genodermatosis characterized by hamartomas affecting various organs, including the skin and central nervous system. Its pathogenesis is based on abnormalities of the proteins hamartin and tuberin, which are coded on the loci 9p34 and 16p13.3, respectively. Symptoms comprise the classic triad of multiple angiofibromas, epilepsy, and mental retardation, although this combination is only seen in 26% of patients.

Despite its wide clinical variability and variable penetrance, facial angiofibromas are found in 83–90% of cases. These lesions are considered pathognomonic and develop mainly on the nasolabial folds, cheeks, chin, scalp, forehead, and ears. They usually appear during the first decade of life, stabilize during adolescence, and are lifelong. They are not malignant, although their appearance constitutes a very frequent presenting complaint in these patients.

Treatment can take several forms, including simple excision, cryosurgery, curettage, dermabrasion, carbon dioxide laser, and photodynamic therapy. No single treatment has proven sufficiently effective to control their onset or prevent recurrence.

Rapamycin (sirolimus) is an oral immunosuppressive agent used mainly in kidney transplantation. Its mechanism of action has not been clearly defined, although it is known to interfere with the mTOR protein pathway, which is responsible for cell proliferation and inhibition of apoptosis in patients with tuberous sclerosis. The proteins hamartin and tuberin also suppress mTOR pathway activity. These proteins are modified in tuberous sclerosis in such a way that their altered function causes permanent activation of the mTOR pathway, thus leading to the onset of hamartomatous tumors in various regions. It has been suggested that the mechanisms by which rapamycin reduces the number and size of tumors in tuberous sclerosis are inhibition of angiogenesis and of aberrant growth factors, although these phenomena have only been verified in extracutaneous hamartomatous lesions (brain, kidney, and lung).

After the failure of the therapeutic approaches adopted to control the facial angiofibromas in our patient, we decided to try topical treatment with rapamycin, an alternative that has been described in 2 previous publications. Ours is the fourth reported case in which this therapy was administered to control facial angiofibromas. A clear improvement was observed in all 4 patients, with a marked reduction or complete disappearance of the lesions. Facial erythema also improved after only a few months’ treatment. Of the 3 cases reported previously, 2 were treated with rapamycin solution (1 mg/mL) and the remaining patient with 0.1% rapamycin ointment. Treatment was adminis-
tered in 1 or 2 applications per day and, as in our patient, seemed to be well tolerated, with no local or systemic adverse events. The pharmacological basis for the efficacy of rapamycin in treating facial angiofibromas in patients with tuberous sclerosis should be clarified in future studies.

No commercial preparations of topical rapamycin are currently available in the United States or Europe; therefore, the formulation has to be prepared in the pharmacy. In theory, topical administration should be safer than oral medication, although longer follow-up is necessary before these observations can be confirmed. Given the small number of cases described to date, the most suitable presentation of the product has not yet been determined.

In conclusion, we report a new case of multiple facial angiofibromas treated with topical rapamycin in a patient with tuberous sclerosis. This drug could be a valid alternative in this setting, although more cases must be reported in order to verify the long-term safety and efficacy profile of the medication.

References


P. Valerón-Almazán, a M. Vitiello, a A. Abuchar, b F.A. Kerdel a

a Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain
b Florida Academic Dermatology Center, University of Miami Hospital, Miami, FL, United States

Corresponding author.
E-mail address: dr.kerdel@fadcenter.com (F.A. Kerdel).
Dear Editor:

First described by Kossard\(^1\) in 1994, frontal fibrosing alopecia is a type of cicatricial alopecia that is clinically characterized by progressive and symmetrical recession of the frontotemporal hairline. It is accompanied by partial alopecia of the eyebrows in most cases\(^2\) and loss of body hair in a variable number of patients.\(^3\) It is more frequent in postmenopausal women, although there have been reports of cases in men and premenopausal women.\(^2,4\) Histopathology shows it to be a variant of lichen planopilaris, which is characterized by a reduced number of hair follicles, a perifollicular lymphocytic inflammatory infiltrate, and fibrosis.\(^5\) Few published studies describe the dermoscopic features of frontal fibrosing alopecia.\(^6,7\)

We report the case of a 51-year-old woman who consulted with a 12-month history of hair loss at the frontal hairline. No other symptoms or associated diseases were present. Physical examination revealed a bald patch in the form of a band that delimited the hairline of the frontal region (Fig. 1). She also had partial alopecia of the eyebrows. The remaining findings were normal. The patient had previously taken high-potency topical corticosteroids and 2% minoxidil with no signs of improvement.

Dermoscopy (Dermlite 00 multispectral) highlighted a marked reduction in the number of follicular ostia in the central area and erythema, perifollicular desquamation, and perifollicular blue-gray dots at the border of the patch (Fig. 2). A biopsy specimen was taken, and histopathology revealed a marked reduction in the density of the pilosebaceous units, as well as laminar fibrosis and a perifollicular lymphocytic inflammatory infiltrate around the isthmus and infundibulum (Fig. 3). The clinical, dermoscopic, and histopathologic findings confirmed a diagnosis of frontal fibrosing alopecia.

Since it was first described in 1994, just under 200 cases of frontal fibrosing alopecia have been reported throughout the world.\(^1,2,4\) Although initially considered an uncommon entity, this condition is believed to be a much more common cause of cicatricial alopecia than previously thought.\(^2\) There are few published reports of dermoscopic findings in patients with this condition. Several dermoscopic findings are characteristic of frontal fibrosing alopecia, whereas others also appear in other types of cicatricial alopecia, such as discoid lupus erythematosus or lichen planopilaris. Inui et al.\(^6\) reported 3 dermoscopic findings in 4 patients with frontal fibrosing alopecia, namely, reduced follicular ostia, erythema, and perifollicular scale, which were also found in the case we report. Other dermoscopic findings also reported in patients with this condition include ramified capillaries, honeycomb-like pigment network, white patches, white dots, and vellus hair.\(^7\) In the present case, we also identified blue-gray dots around some follicles, a finding that has previously been reported in discoid lupus erythematosus, but not in frontal fibrosing alopecia.\(^7\) Although no studies have established a correlation between dermoscopic findings and histopathologic findings in cicatricial alopecia, it has been suggested that the white patches correspond to fibrosis and that they are more commonly found in longstanding bald patches.\(^7\) The blue-gray dots correspond to melanophages in the papillary dermis and the white dots to pigment incontinence;\(^1\) the honeycomb pattern is the result of exposure of the bald patches to sunlight.\(^8\) Erythema and hyperkeratosis are the results of inflammation in the follicle and the hyperkeratosis that develops in lichen planopilaris and frontal fibrosing alopecia.\(^8\)

Dermoscopic criteria are proving useful in the diagnosis of alopecia.\(^9\) In the present case, dermoscopic findings enabled us to rule out other causes of alopecia, such as alopecia areata. The correlation between clinical findings, dermoscopic findings, and histopathologic findings enabled us to establish a diagnosis of frontal fibrosing alopecia.