Granuloma Faciale Effectively Treated with Topical Pimecrolimus

Granuloma faciale (GF) is a rare skin disorder with a chronic-relapsing course. Cutaneous lesions affect predominantly the face of middle-aged Caucasian men with characteristic reddish papules, nodules, or plaques; however, various atypical cases with unusual morphology or extra facial involvement have been reported (1-3). Despite many treatment options, both surgical and medical, GF remains therapeutically resistant and even if effective treatment is achieved, the condition often recurs.

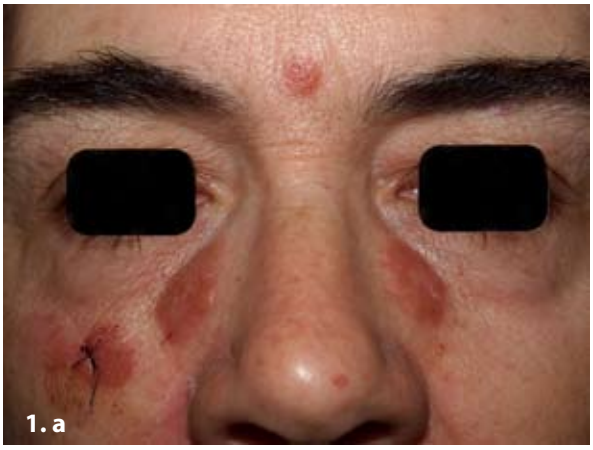
A 60-year-old woman was referred to our department with skin lesions that appeared in spring of 2008 and were resistant to topical antibiotic and corticosteroid treatment. There were no other subjective complains except for aggravation from sun exposure. Clinical examination revealed four erythematous plaques localized symmetrically on both sides of the nose, on the right cheek, and between the eyebrows (Fig. 1a). A wide range of differential diagnoses were taken into consideration, including: cutaneous lupus erythematosus, sarcoidosis, polymorphic light eruption, Jessner-Kanof lymphocytic infiltration, and erythema fixum. Hematological and biochemical blood investigations were within normal ranges, and the serology for *Treponema (T.) pallidum* and *Borrelia (B.) burgdorferi* and the ANA test were negative. The histologic evaluation revealed diffuse hyperkeratosis, acanthosis, and a dense perivascular inflammatory infiltrate in the upper dermis, demarcated from the epidermis by a highly demonstrative Grenz zone. Polymorphous infiltrate of lymphocyte, neutrophils, eosinophils, and plasma cells was seen around the small- and middle-sized vessels in the papillary dermis (Fig. 1b). The patient was treated with chloroquine 250 mg po bid. and topical betamethasone valerate cream for three months. The lack of significant therapeutic response led us to switch treatment to topical 1% pimecrolimus cream, applied twice daily for a period of three months. A follow-up visit after six months showed visual improvement of highly satisfying cosmetic outcome (Fig. 2).

Granuloma faciale is a rare skin disease of unknown etiology. The first case was reported by Wigley in 1945 as "eosinophilic granuloma", and was later named granuloma faciale by Pincus (4). A spectrum of exogenic and endogenic factors such as actinic exposure, trauma, allergy (1), an Arthus-like reaction, or light irradiation (5) have been suspected to trigger the disease. GF has been typically described in middle-aged white men, though it can occur in any gender, race, or age group. Our case features GF changes in a middle-aged woman, which is a relatively rare phenomenon.

GF clinical presentation is characterized with variously colored papules, nodules, or plaques, commonly elevated and soft. These lesions have a well-defined border and may vary in size from a few millimeters to several centimeters, as in our patient. Lesions are situated almost exclusively on the face (2,3), but may rarely appear on the trunk, scalp, and extremities which has been termed extrafacial GF (1). GF lesions are generally symptomless but some patients may complain of tender itching, stinging, or burning sensations.

Histological findings play a crucial role in confirming the clinical diagnosis. A Grenz zone of uninvolved dermis located beneath the epidermis and a polymorphous infiltrate of lymphocytes, neutrophils, eosinophils, and occasionally mast cells are the most characteristic indications. Sometimes, leukocytoclastic vasculitis can be observed, although this is often referred to as an epiphenomenon. With the chronification of the process lesions may show considerable storiform fibrosis (7).

Even the pathophysiology of GF is unknown; more recent theories suggested that a proliferation of unknown T-cell lymphocytes cause IL-5 production and eosinophil hemotaxis to the lesional skin (6). Recently, Cesinaro *at al.* reported a significant number of GF cases associated with an abnormal content of IgG4 plasma cells, proposing that GF might represent a localized form of IgG4-related sclerosing diseases.



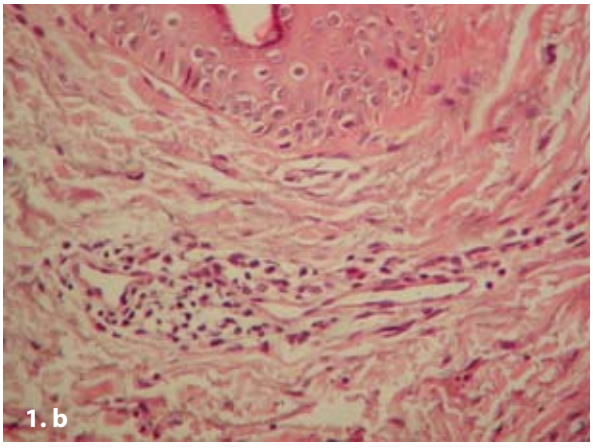


Figure 1a. Erythematous plaques on both sides of the nose, on the right cheek, and between the eyebrows in a 60 year-old patient with granuloma faciale.

Figure 1b. Acanthotic epidermis, demarcated with a Grenz zone from a polymorphous perivascular infiltrate (hematoxylin and eosin, ×400).

This is supported by the obliterative vascular inflammation and storiform sclerosis which are seen in all chronic GF cases (7).

GF is resistant to treatment and many different medical strategies have been tried, both conservative or surgical. The surgical or destructive methods include: a simple excision, dermabrasion, electrosurgery, cryotherapy, argon, CO_2, or 585-nm pulsed dye lasers. Scarring may occur with many of these therapeutic modalities. The pulsed-dye laser often leads to resolution without scarring, and is claimed to be the preferred surgical method (8). The medical therapeutic options that have been tried and are reported to be effective include topical or intralesional corticosteroids, antimalarials as in our case, isoniazid, calciferol, topical PUVA, and radiation therapy. Dapsone is the oral medication most frequently reported to be somewhat effective. Topical tacrolimus has been reported to have a beneficial effect in at least 9 patients (2,3,9).

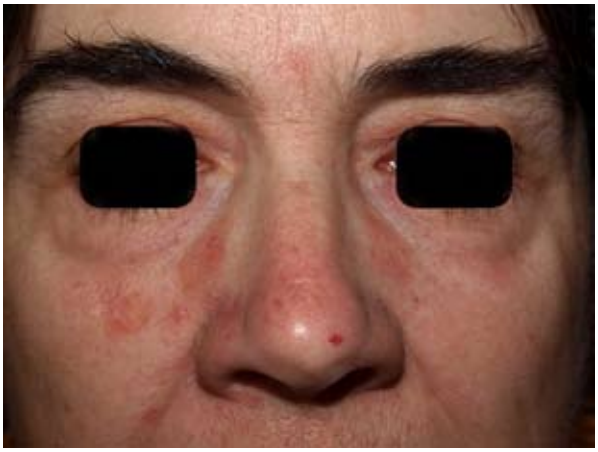


Figure 2. The same patient on follow-up visit in six months.

Pimecrolimus, which was our therapeutic choice, belongs to the ascomycin class of macrolactam immunosuppressives. These immunosuppressive drugs inhibit the calcineurin pathway T-cell activation by suppression of the release of numerous inflammatory cytokines, thus interrupting the immuno-inflammatory cascade. A thorough literature review shows only one previous publication of GF treatment with topical 1% pimecrolimus cream (10), applied twice a day for two months. Herein, we confirm the beneficial effect of this therapeutic approach, which may suggest pimecrolimus as an additional topical modality to treat GF.

In conclusion, we reported on a woman with clinically and histologically verified GF, who was effectively treated with 1% pimecrolimus cream. The follow-up observations showed an excellent cosmetic result. Despite the unpredictable long-term outcome, we believe that pimecrolimus can be considered an effective therapeutic modality for non-invasive treatment of GF.

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