HYDROXYCHLOROQUINE AND OTHER TREATMENTS IN GRANULOMA FACIALE

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ABSTRACT
Granuloma Faciale (GF) is a rare chronic skin condition of unknown aetiology, characterized clinically by single or multiple brownish-reddish plaques, papules and nodules that mostly present on the face. Histopathological examination assists in ruling out the common differential diagnosis considered. Multiple therapies have been reported with varying degrees of success. GF is usually resistant to treatment. We share our experience in treating a 75 year old lady with a biopsy proven GF with hydroxychloroquine.

INTRODUCTION
Granuloma Faciale (GF) is a rare chronic skin condition of unknown aetiology, initially described by Wigley as Eosinophilic Granuloma of the skin in 1944 (1). Later on in 1952 Pincus named it Granuloma faciale (2). GF is characterized clinically by single or multiple brownish-reddish plaques, papules and nodules that mostly present on the face with 38% on the forehead, 30% on the cheeks, 27.5% on the nose, 10.5% on the eyelid, 1% on the lips and rarely might present on extrafacial sites such as scalp, trunk, upper and lower limbs (3). GF is more common in men with a median age of 53 years old at diagnosis (4).

Management
There are many topical, systemic, physical treatment options available that have been reported in case reports in management of Granuloma Faciale, although there has been variable degree of clinical response to each and in some cases GF might be resistant to treatment with frequent recurrence. Commonly reported treatment options include topical Tacrolimus, Dapsone, topical and intralosomal steroids, laser therapy and cryotherapy (5).

Topical Tacrolimus 0.1 % was used for 2 months to treat a solitary asymptomatic GF lesion, on the face of a 40 year old woman which led to complete resolution of the lesion (6). Similarly topical Tacrolimus 0.1 % was used twice daily for 8 weeks to treat GF lesions on the forehead of a 33 year old women which lead to the lesions significantly resolving with no relapse after 6 months follow up (7). Caldarola et al. reported a 72 year old man who presented with a 3 month history of three violaceous nodules located on his left cheek and forehead, after the diagnosis of GF was confirmed by a skin biopsy, the patient was treated with topical Tacrolimus 0.1 % twice daily. He was reviewed bimonthly for duration of 1 year, two lesions on the forehead completely resolved and the lesion on the left cheek became less infiltrated (8).Topical Pimecrolimus 1% cream was used twice daily for 3 months to treat a 60 year old women who presented with four GF lesions that were previously resistant to treatment with topical antibiotic and corticosteroid, six months follow up showed significant cosmetic improvement in all lesions (9). Dapsone 100 mg daily was used to treat a 25 year old female who presented with GF lesions localized to the forehead and around her mouth which lead to resolution of her lesions, she was previously treated with oral prednisolone with good response but had recurrence of the lesions after the treatment was stopped and she also had...
incomplete response to topical Tacrolimus applied twice daily for 2 months(10). Colchicine 1mg/day for 16 months was used to treat a 63 year old women who had a solitary GF lesion on her left cheek, which lead to complete resolution of the lesion (11). In some cases combination treatment has been used, intralesional Triamcinolone acetonide and topical Tacrolimus ointment 0.03 % twice daily for 2 months was used to treat a 40 year old women who had a history of GF lesion on the right cheek for 1 year, the combination has led to complete resolution of the lesion (12). Surgical therapy includes excisions, cryotherapy, electrocautery and 595-nm pulsed dye laser which has led to complete resolution without recurrence after 6 months of follow up (13).

In our experience we treated a 75 year old female patient, who presented to our department with a 12 month history of erythematous plaques on both left and right maxilla, causing her a burning sensation (Figure 1). Examination revealed the erythematous plaque was more pronounced on the left maxilla than the right maxilla. We organized a series of investigations including blood tests and performed a 3mm punch biopsy from the left maxilla. The clinical impression was that of Granuloma Faciale, with differential diagnosis including discoid lupus erythematosus and sarcoidosis. The biopsy confirmed characteristic histological features of Granuloma Faciale. The patient was started on Hydrocortisone butyrate 0.1% twice daily; after 3 months of treatment there was no improvement so the Hydrocortisone butyrate 0.1% was stopped. The patient was then started on Hydroxychloroquine 200 mg once daily and was followed in the clinic every 2-3 months with repeat blood tests over a period of 4 years. Her Granuloma Faciale improved significantly.

**Histopathology**

Histopathological examination of the left maxilla punch biopsy showed a normal epidermis and Grenz zone overlying a dense, vaguely nodular mixed inflammatory infiltrate of eosinophils, lymphocytes, histiocytes, and neutrophils in the mid and superficial dermis (Figure 2A and 2b). The blood vessels showed focal leukocytolysis and perivascular fibrin deposition with associated extravasation of red blood cells (Figure 2C).

![Figure 1A – Right maxilla](image1.png)

![Figure 1B – Left maxilla](image2.png)

![Figure 2A](image3.png) Low power view of nodular mixed inflammatory infiltrate of superficial and mid dermis with overlying Grenz zone (arrowed) and normal dermis

![Figure 2b](image4.png) Mixed inflammatory infiltrate with prominent eosinophils

![Figure 2c](image5.png) Leukocytolysis (arrowed) around vessel
The histological findings were most in keeping with a diagnosis of Granuloma faciale with no features to suggest the differential diagnoses of sarcoidosis or discoid lupus erythematosus. Characteristic histological findings in GF are those of a leukocytoclastic small vessel vasculitis, associated with a polymorphous inflammatory cell infiltrate as identified in this biopsy (14). Extravasated red blood cells and haemosiderin results in the clinical appearance of “red/brown” discoulouration. In longstanding lesions, concentric fibrosis may be identified around dermal capillaries.

DISCUSSION
Granuloma Faciale is considered a misnomer since there has been reported cases of extrafacial involvement and granulomas are not detected histologically but refers to the clinical appearance of “granules” (15).

Although the pathogenesis of Granuloma Faciale is unknown multiple mechanisms have been suggested resulting in vascular injury (14). Analysis of the cellular infiltrate and cytokine production revealed predominance of CD4+ T-helper cells which produce interferon (IFN-γ), chemotaxis of eosinophils to the lesion is thought to be due to the production on interleukin 5 (IL-5) by clonal T cells (16). Interferon gamma helps express ICAM molecules on keratinocytes and chemotaxis of lymphocytes, but in GF basal keratinocytes do not express ICAM and so this results in the Grenz zone seen histologically (14). Differential diagnosis of GF include: sarcoidosis, discoid lupus erythematosus, lupus vulgaris, mycobacterioses and fungal infection (17). If GF presents in extrafacial sites, then Erythema Elevatum Diutinum (EED) is another important differential diagnosis to consider, EED presents as multiple lesions affecting the extensor aspect of joints, while GF presents mainly as isolated lesion affecting the face in majority of the cases (14). The most frequently seen dermoscopic patterns in Granuloma Faciale lesions are dilated follicular openings, perifollicular whitish halo and linear vessels (18). Less frequently seen dermoscopic features have been reported, and include amorphous yellow or yellow-brown areas, which corresponds to haemosiderin deposition (19).

CONCLUSION
Most of the information we have about GF are from case reports and retrospective analysis. GF is an uncommon condition, presents frequently with facial involvement and rarely may involve extrafacial sites. Lesions are typically resistant to treatment. Multiple therapies have been reported with varying degrees of success. Histopathological examination assists in ruling out the common differential diagnosis considered. The pathogenesis of GF is still poorly understood with different mechanisms suggested. The overall prognosis of GF is good.

References