

Granuloma Faciale With Subglottic Eosinophilic Angiocentric Fibrosis: Case Report and Review of the Literature

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Granuloma faciale (GF) is an uncommon inflammatory dermatosis that usually presents on the face as reddish brown or violaceous papules and nodules that may coalesce into plaques. Eosinophilic angiocentric fibrosis (EAF) is a rare fibrosing condition that shares many histologic characteristics with GF and is regarded by some authors as a mucosal counterpart of GF. We present a case of GF with concurrent EAF in a subglottic location with excellent response to an intralesional corticosteroid on the GF lesion, CO₂ laser on the EAF lesion, and oral dapsone treatment.

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Granuloma faciale (GF) was first reported as sarcoid of Boeck by Wigley¹ in 1945. However, Pinkus² first suggested the term *granuloma faciale* a few years later. Granuloma faciale is an uncommon inflammatory disorder of the skin that manifests as soft or moderately firm, elevated, and well-circumscribed red-brown or purple papules and nodules that sometimes become confluent and form large plaques. There often is follicular accentuation and superficial telangiectasia. Because of the

occasional depression of their centers, some plaques have an annular appearance. As indicated by its name, these lesions usually appear on the face, but there are a few reports of extrafacial locations.³⁻⁷ The sites of predilection of GF are sun-exposed areas such as the sides and tip of the nose, the preauricular area, the cheeks, the forehead, and the helix. The lesions typically are asymptomatic, though some patients report pruritus, burning, or tenderness. The disease can be seen in both sexes at any age but usually affects middle-aged white men.⁸⁻¹⁰

Granuloma faciale is a delightful misnomer, reflecting a clinical appearance sometimes suggestive of granules but usually not accompanied histologically by granulomatous inflammation.¹¹ Histologic examination usually demonstrates a dense infiltrate that consists mostly of eosinophils in combination with fibroblasts, neutrophils, histiocytes, lymphocytes, and mononuclear cells in the upper two-thirds of the dermis, which often is separated from the epidermis by a narrow zone deprived of cells, known as the grenz zone. Leukocytoclastic vasculitis with fibrinoid degeneration within and around the microvessels sometimes is seen. The changes that make GF more distinctive emerge with time as fibrosis supervenes, often with a concentric orientation around small vessels.¹⁰⁻¹²

Eosinophilic angiocentric fibrosis (EAF) is a rare fibroinflammatory condition first described by Roberts and McCann¹³ in 1985. Many pathologists consider EAF to be the mucosal counterpart of GF.¹⁴ In fact, the conditions share many histopathologic characteristics and at least one-third of the reported cases occurred in patients with concurrent GF. Likewise, both present in an early phase with a narrow grenz zone and a dense inflammatory infiltrate comprised of mainly neutrophils and eosinophils affecting the upper portion of the dermis, often

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The authors report no conflict of interest.

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with leukocytoclasia. A continuum of changes from endothelial swelling to frank fibrinoid necrosis of small vessels with red blood cell extravasation and hemosiderin deposition may be seen, which varies with the age of the lesion. Although older lesions of GF can present with extensive fibrosis, they usually lack the characteristic perivascular, obliterative,

onionskin-whorled pattern of EAF.¹⁵ The Table lists the main characteristics of these 2 conditions.

Twenty-two cases of EAF have been reported in the literature, most of them within the nasal cavity but rarely in the subglottis; 8 of these cases were associated with GF.¹⁶ More than 40 cases recently were reported by Sunde et al.¹⁷

Granuloma Faciale and Eosinophilic Angiocentric Fibrosis

Clinical Entity	Granuloma Faciale	Eosinophilic Angiocentric Fibrosis
Name	A misnomer based on the clinical appearance and not reflecting the histologic findings	A designation reflecting the histologic pattern of perivascular, obliterative, onionskin-whorled fibrosis
Location	Most frequent: face (nose, preauricular area, cheeks, forehead, helix); some reports of extrafacial locations, mainly on the trunk, neck, and upper limbs	Most frequent: nose (septum and/or lateral wall); 2 reports of subglottic location and 1 report of gingival location
Cause	Unknown; postulated: actinic damage, localized Arthus-like reaction	Unknown; postulated: allergy, trauma
Pathogenesis	Begins as a variant of small vessel vasculitis with a polymorphous infiltrate rich in eosinophils and neutrophils that progresses to fibrosis, often concentric around blood vessels	Begins as an eosinophil-predominant vasculitis, progressing to perivascular fibrosis with a concentric onionskin-whorled pattern
Clinical diagnosis	Violaceous plaque with dilated follicular ostia in a suggestive location	Progressive nasal swelling leading to obstruction, epistaxis, or pain; shortness of breath
Treatment	Not established; the first option seems to be intralesional corticosteroids; also some reports on the efficacy of topical calcineurin inhibitors and PUVA, oral dapsone, chloroquine, clofazimine, and isoniazid; cryosurgery and laser therapy may provide satisfactory results	Not established; surgical excision appears to be the most effective; marginal effect of oral and intralesional corticosteroids; reports on oral immunosuppressants and dapsone with variable success
Prognosis	Variable response to treatment; slowly progressive lesions with frequent recurrences; spontaneous resolution is rare	Variable response to treatment; slowly progressive disease with frequent recurrences

Abbreviation: PUVA, psoralen plus UVA.

Case Report

A 68-year-old previously healthy man presented with a gradually enlarging violaceous plaque involving his entire nose of 3 years' duration (Figure 1A). Recently a similar but much smaller lesion had appeared on the right angle of the mandible. He had previously undergone several cutaneous biopsies that were not conclusive. Blood investigations revealed relative eosinophilia (6.7% [reference range, 2.7%]; $0.44 \times 10^9/L$ [reference range, $0-0.45 \times 10^9/L$]) and a slightly increased erythrocyte sedimentation rate. Immunologic study including antineutrophil cytoplasmic antibodies and total IgE levels were normal.

The thoracic radiograph revealed no abnormalities. The progressive growth of the lesion caused nasal obstruction, which was confirmed on computed tomography; therefore, we decided to perform a deeper and larger biopsy that revealed a dense polymorphous infiltrate involving the dermis in a diffuse way with fibroblastic proliferation with a concentric perivascular orientation and eosinophilic vasculitis without fibrinoid necrosis. A narrow grenz zone between the dermal infiltrate and epidermis was consistently observed, which allowed the diagnosis of GF (Figure 2). Meanwhile the patient reported hoarseness and dyspnea, and his lung function tests revealed

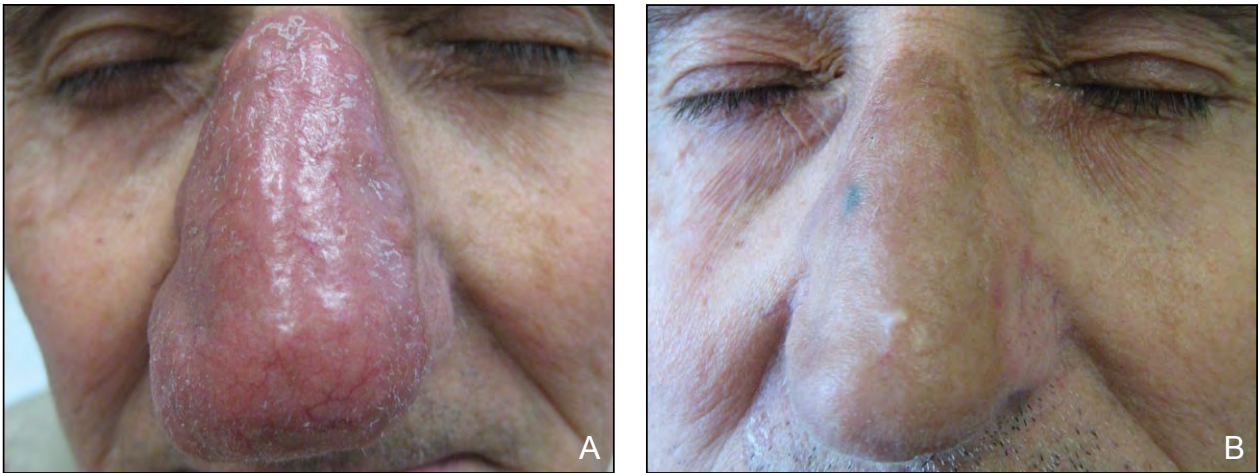


Figure 1. A violaceous plaque involving practically the entire nose with telangiectases and dilated follicular openings (A). After 3 months of treatment, the nose plaque resolved with only residual hyperpigmentation (B).

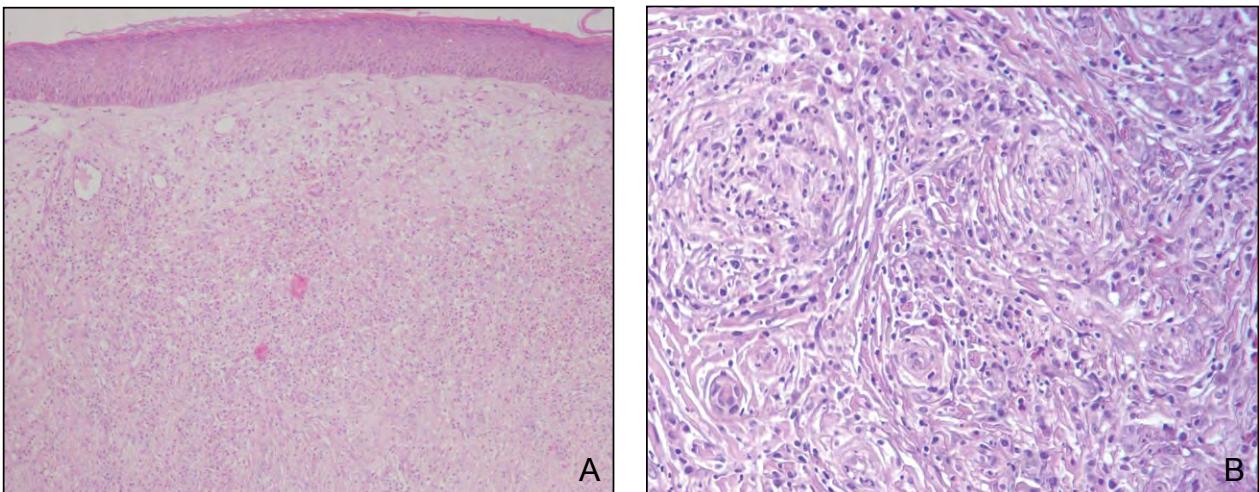


Figure 2. Granuloma faciale was diagnosed based on a biopsy from the nose, which showed an uninvolved grenz zone and a dense polymorphous infiltrate in the dermis (A)(H&E, original magnification $\times 10$). A dense polymorphous perivascular inflammatory infiltrate was present as well as fibrosis distributed concentrically around blood vessels (B)(H&E, original magnification $\times 40$).

extrathoracic obstruction. He was referred to the otolaryngology department, and a subglottic indurated stenosis was seen both on contrast computed tomography (Figure 3) and on laryngoscopy. A biopsy was taken and the lesion was destroyed with CO₂ laser. The histology showed fibrosis distributed concentrically around blood vessels and a polymorphous inflammatory infiltrate rich in eosinophils, which are characteristic of EAF (Figure 4). He started monthly intralesional injections of methylprednisolone on the nose and oral dapsone (100 mg daily for 4 months), which resulted in resolution of the nose plaque after 3 months with only residual hyperpigmentation (Figure 1B). The patient's hoarseness and dyspnea also improved. He did a control bronchofibroscope, which only revealed a slight cicatricial irregularity of the mucosa on the upper third of the trachea.

Comment

Granuloma faciale is an uncommon disorder that often is clinically and histologically misdiagnosed; therefore, a great degree of suspicion is necessary. This disease usually is not associated with internal involvement, but the possibility of coexistent EAF should be kept in mind, especially in patients who have sinus or pulmonary signs or symptoms.¹⁸

Granuloma faciale is considered a chronic form of histologic rather than clinical cutaneous vasculitis that might be caused by a localized persistent allergic hypersensitivity reaction to retained antigens or by a localized persistent immune complex disease. Supporting this idea, there have been some descriptions of immunoglobulin and complement surrounding blood vessels.¹⁹ Recently, the production of IL-5 by the clonal T-cell population has been implicated in the attraction of eosinophils to the lesions.²⁰ The etiology of GF is unclear, though actinic exposure has been advanced. It also has been suggested that it may be a form of vasculitis mediated by a localized Arthus-like reaction.¹⁸

In the clinical differential diagnosis, sarcoidosis, lupus vulgaris, fungal infections, discoid lupus erythematosus, pseudolymphoma, leukemic infiltrations, and angiolymphoid hyperplasia with eosinophilia should be considered. Dilated follicular ostia may help to distinguish GF from sarcoidosis, basal cell carcinoma, and cutaneous lymphoma, which do not show this feature.⁹ When GF occurs in extrafacial locations, the major differential diagnosis is erythema elevatum diutinum; because of their clinical and histologic similarities, some authors even suggest the conditions are related. However, the latter usually presents symmetrically on the distal and extensor parts of the extremities, and the histology shows fewer eosinophils, absence of grenz

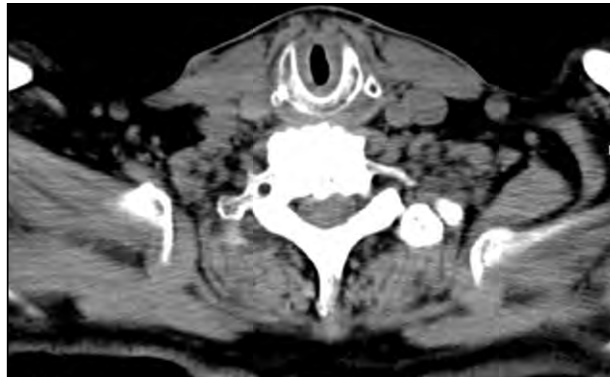


Figure 3. Computed tomography of larynx showed concentric subglottic fibrosis.

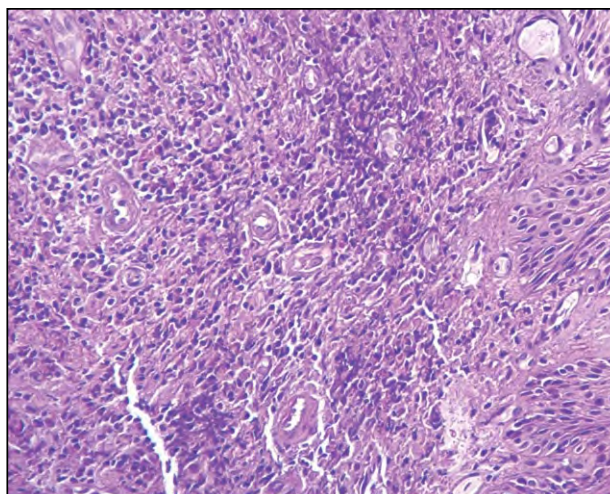


Figure 4. Subglottic eosinophilic angiocentric fibrosis was diagnosed based on findings of focal concentric fibrosis around blood vessels and a polymorphous inflammatory infiltrate rich in eosinophils (H&E, original magnification ×40).

zone, and an inflammatory infiltrate with predominantly neutrophils rather than eosinophils.¹¹

Eosinophilic angiocentric fibrosis is an exceedingly rare fibrosing disease that affects mainly the sinonasal tract of young to middle-aged patients, causing progressive obstruction of the upper airways. It also may cause epistaxis and pain.²¹ The cause of this disease also remains unclear, but the eosinophilic infiltrate in the lesions and a clinical history of allergy reported in several patients may support an allergic etiology.¹⁶ Trauma also has been claimed as an eliciting factor because some patients have undergone ear, nose, or throat surgical procedures before the diagnosis; however, given that no histopathologic studies were performed prior to surgery in these cases, this conclusion cannot be accurately drawn. Moreover, EAF generally does not seem to be a reaction to trauma.²²

The differential diagnosis for EAF includes inflammatory conditions such as Churg-Strauss syndrome, Wegener granulomatosis, infectious granulomatous diseases, sarcoidosis, angiolymphoid hyperplasia with eosinophilia, and erythema elevatum diutinum. Also, benign and malignant neoplasms must be considered. Most of these entities feature distinctive clinical, laboratory, and histologic characteristics.^{22,23}

Because both GF and EAF are rare situations without established pathogenesis, their management is a challenge. Indeed, the available literature on this matter lacks etiologic treatments, guidelines, or controlled studies.

Although GF is not a lethal disease, the lesions tend to persist, and as the face is most commonly involved, it can be quite disfiguring. Many treatment options have been described with variable success, not to mention the possibility of spontaneous resolution.¹⁰ For classifying purposes, they can be divided in 2 groups: destructive techniques and the use of anti-inflammatory and antiproliferating agents. Destructive techniques comprise surgical excision, radiation therapy, electrodesiccation, curettage, dermabrasion, and cryosurgery. The first 2 are considered inadequate because recurrence is the rule. Electrodesiccation, curettage, and dermabrasion have been used with various results. Cryosurgery appears to be more effective, with various favorable reports in the literature and satisfactory cosmetic results but with occasional resultant hypopigmentation.¹⁰ More recently, argon laser, CO₂ laser, pulsed dye laser, and KTP laser have been used with promising results.^{8,24}

The second group (anti-inflammatory and antiproliferating agents) consists basically on a medical approach. In this regard, gold injections have been used in the past with variable results; topical steroids also are frequently tried with poor outcome, but the efficacy is heightened when they are administered intralesionally. Because there is a lack of scarring with corticosteroids, it might be a good first-line therapy, as highlighted by our case.¹⁰

There are a few reports on the efficacy of dapsone 100 to 200 mg daily.^{21,25-27} This drug has beneficial effects on neutrophil-mediated disorders, as it interferes with neutrophil chemotactic migration and suppresses local production of toxic products, including oxygen-derived radicals. Furthermore, dapsone blocks the inflammatory cascade by reducing the release of the arachidonic acid derivatives such as prostaglandins and leukotrienes.^{21,27} In our patient, this drug had an excellent adjunctive effect on both lesions of GF and EAF. Although each type of lesion was additionally treated individually (intralesional corticosteroid [methylprednisolone] and CO₂ laser, respectively), we believe that the parallel response

of both lesions to dapsone therapy further supports the hypothesis that GF and EAF are the same disease process in a cutaneous and mucosal location.

There also are some reports on the usefulness of chloroquine; clofazimine; isoniazid; topical psoralen plus UVA; and topical calcineurin inhibitors, such as tacrolimus and pimecrolimus.⁸⁻¹⁰ Curiously, in the only case of GF associated with neoplasia, namely prostate adenocarcinoma, a regression of the disease was observed with antiandrogen therapy (cyproterone acetate 300 mg intramuscularly every 2 weeks and leuprolide acetate 375 mg once monthly).²⁸

The natural history of EAF appears to be similar to that of a benign but potentially progressive disorder.²¹ Symptoms usually present for years with relentless worsening over time, but malignant degeneration has not been reported to date. The treatment approaches have been multiple but generally have been unsuccessful. The approach that has been used mostly comprises surgical resection along with adjuvant therapy with oral or intralesional corticosteroids, oral immunosuppressants, or dapsone with variable success and frequent recurrences.¹⁶ Curiously, 2 cases of subglottic EAF have been addressed with wide local excision of the lesion followed by a laryngotracheoplasty with complete resolution of the lesions.²¹ In our patient, after 8 months of follow-up there had not been a recurrence after the treatment with CO₂ laser and adjunctive dapsone therapy. In contrast, the GF lesion relapsed in a small area at the tip of the nose but resolved with an intralesional corticosteroid. The patient was lost to follow-up for a year, but there has been no further relapse.

Conclusion

Eosinophilic angiocentric fibrosis is a rare condition that may be underreported because, in the absence of adequate clinical information, many pathologists may otherwise find similar biopsy samples to be nonspecific chronic inflammation and fibrosis. Its common occurrence with the also rare GF, which has a similar histologic pattern, seems much more than a mere coincidence and points toward a common etiology. Whether they are no more than the same disease in different locations is still a debate.

According to a PubMed search of articles indexed for MEDLINE using the terms *eosinophilic angiocentric fibrosis* and *granuloma faciale*, our patient represents the third reported case of EAF affecting the subglottis and the first in this location with concurrent GF. Most of the cases of EAF have been reported in the ear, nose, and throat literature,^{14,21,29} but a greater awareness of this condition is necessary for dermatologists because GF can give the diagnostic clue for EAF as a cause for obstructive nasal or pulmonary symptoms.

REFERENCES

1. Wigley JE. Eosinophilic granuloma? sarcoid of Boeck. *Proc R Soc Med.* 1945;38:125-126.
2. Pinkus H. Granuloma faciale. *Dermatologica.* 1952;105: 85-99. Cited by: Radin D, Mehregan D. Granuloma faciale: distribution of the lesions and review of the literature. *Cutis.* 2003;72:213-219.
3. Cecchi R, Paoli S, Giomi A. Granuloma faciale with extrafacial lesions. *Eur J Dermatol.* 2002;12:438.
4. Inanir I, Alvur Y. Granuloma faciale with extrafacial lesions. *Br J Dermatol.* 2001;145:360-362.
5. Zargari O. Disseminated granuloma faciale. *Int J Dermatol.* 2004;43:210-212.
6. Castellano-Howard L, Fairbee SI, Hogan DJ, et al. Extra-facial granuloma faciale: report of a case and response to treatment. *Cutis.* 2001;67:413-415.
7. Rossiello L, Palla M, Aiello FS, et al. Granuloma faciale with extrafacial lesions. *Skinmed.* 2007;6:150-151.
8. Ludwig E, Allam JP, Bieber T, et al. New treatment modalities for granuloma faciale. *Br J Dermatol.* 2003;149:634-637.
9. Ertam I, Ertekin B, Unal I, et al. Granuloma faciale: is it a new indication for pimecrolimus? a case report. *J Dermatolog Treat.* 2006;17:238-240.
10. Panagiotopoulos A, Anyfantakis V, Rallis E, et al. Assessment of the efficacy of cryosurgery in the treatment of granuloma faciale. *Br J Dermatol.* 2006;154:357-360.
11. LeBoit PE. Granuloma faciale: a diagnosis deserving of dignity. *Am J Dermatopathol.* 2002;24:440-443.
12. Ortonne N, Wechsler J, Bagot M, et al. Granuloma faciale: a clinicopathologic study of 66 patients. *J Am Acad Dermatol.* 2005;53:1002-1009.
13. Roberts PF, McCann BG. Eosinophilic angiocentric fibrosis of the upper respiratory tract: a mucosal variant of granuloma faciale? a report of three cases. *Histopathology.* 1985;9:1217-1225.
14. Burns BV, Roberts PF, De Carpentier J, et al. Eosinophilic angiocentric fibrosis affecting the nasal cavity. a mucosal variant of the skin lesion granuloma faciale. *J Laryngol Otol.* 2001;115:223-226.
15. Yung A, Wachsmuth R, Ramnath R, et al. Eosinophilic angiocentric fibrosis—a rare mucosal variant of granuloma faciale which may present to the dermatologist. *Br J Dermatol.* 2005;52:574-576.
16. Nigar E, Dhillon R, Carr E, et al. Eosinophilic angiocentric fibrosis and extrafacial granuloma faciale. *Histopathology.* 2007;51:729-731.
17. Sunde J, Alexander KA, Reddy VV, et al. Intranasal eosinophilic angiocentric fibrosis: a case report and review. *Head Neck Pathol.* 2010;4:246-248.
18. Marcoval J, Moreno A, Peyr J. Granuloma faciale: a clinicopathological study of 11 cases. *J Am Acad Dermatol.* 2004;51:269-273.
19. Barnadas MA, Curell R, Alomar A. Direct immunofluorescence in granuloma faciale: a case report and review of the literature. *J Cutan Pathol.* 2006;33: 508-511.
20. Gauger A, Ronet C, Schnopp C, et al. High local interleukin 5 production in granuloma faciale (eosinophilicum): role of clonally expanded skin-specific CD4⁺ cells. *Br J Dermatol.* 2005;153:440-446.
21. Tabaei A, Zadeh MH, Proytcheva M, et al. Eosinophilic angiocentric fibrosis. *J Laryngol Otol.* 2003;117:410-413.
22. Chinelli PA, Kawashita MY, Sotto MN, et al. Granuloma faciale associated with sinonasal eosinophilic angiocentric fibrosis. *Acta Derm Venereol.* 2004;84:486-487.
23. Thompson LD, Heffner DK. Sinonasal tract eosinophilic angiocentric fibrosis. a report of three cases. *Am J Clin Pathol.* 2001;115:243-248.
24. Cheung ST, Lanigan SW. Granuloma faciale treated with the pulsed-dye laser: a case series. *Clin Exp Dermatol.* 2005;30:373-375.
25. van de Kerkhof PC. On the efficacy of dapsone in granuloma faciale. *Acta Derm Venereol.* 1994;74:61-62.
26. Guill MA, Aton JK. Facial granuloma responsive to dapsone therapy. *Arch Dermatol.* 1982;118:332-335.
27. Zhu YI, Stiller MJ. Dapsones and sulfones in dermatology: overview and update. *J Am Acad Dermatol.* 2001;45: 420-434.
28. Roussaki-Schulze A, Klimi E, Zafiriou E, et al. Granuloma faciale associated with adenocarcinoma of the prostate. *Int J Dermatol.* 2002;41:901-903.
29. Narayan J, Douglas-Jones AG. Eosinophilic angiocentric fibrosis and granuloma faciale: analysis of cellular infiltrate and review of the literature. *Ann Otol Rhinol Laryngol.* 2005;114:35-42.



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