

Granuloma faciale as a diagnostic and therapeutic challenge

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ABSTRACT

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Introduction: Granuloma faciale is a rare dermatosis classified within the group of eosinophilic dermatoses, which presents a persistent challenge in both diagnosis and treatment.

Objective: Presentation a case of granuloma faciale along with a comprehensive discussion of the pathophysiology, clinical presentation, and treatment of the disease.

Case report: A 68-year-old man presented to a dermatologist with nodular and plaque-like lesions on his face that had been present for 6 months. Initially, based on histopathological findings, fixed drug eruption was diagnosed, and the patient was instructed to discontinue the medications he had been taking, including acetylsalicylic acid and non-steroidal anti-inflammatory drugs. Nevertheless, the skin lesions persisted. Following extended differential diagnosis (including dermoscopy and repeated histopathological examination), the diagnosis of granuloma faciale was established and, consequently, cryotherapy with liquid nitrogen was administered, resulting in a significant improvement in the patient's skin condition.

Conclusions: Despite being typically located in the specific areas, granuloma faciale poses diagnostic challenges. Cryotherapy seems to be an effective and safe therapeutic approach in patients who fail to respond to topical medications.

Key words: granuloma faciale, eosinophil, eosinophilic dermatoses, differential diagnosis, cryotherapy.

INTRODUCTION

Granuloma faciale (GF) is an extremely rare dermatosis usually presenting clinically as a solitary nodule or multiple nodules located on the facial skin. The condition was first described in 1945 by John Edwin Mackonochie Wigley (1892–1962) as eosinophilic granuloma (the name is now reserved for a variant of Langerhans cell histiocytosis). In 1952, Hermann Karl Benno Pinkus (1905–1985), one of the most emi-

nent dermatopathologists, gave the disease its current name [1–3].

OBJECTIVE

The study presents the case of a patient with multiple granuloma faciale lesions, successfully treated with cryotherapy. Special emphasis is placed on the differential diagnosis of the condition, highlighting

the crucial role of histopathological examination in determining the final diagnosis.

CASE REPORT

A 68-year-old Caucasian man sought consultation at the Dermatology Outpatient Clinic due to red-brown nodular lesions on the facial skin, persisting for the past 6 months. The lesions were located on the nasal alae, forehead, and cheek on the right side. The patient was treated topically with clobetasol propionate ointment for a month, resulting in a partial remission of the cheek lesion, with no impact on the remaining skin lesions. During a subsequent visit, a skin biopsy was taken from the residual lesion on the cheek for histopathological examination. The following result was obtained: "the characteristics may be consistent with fixed drug eruption". Considering the fact that the patient had been taking acetylsalicylic acid at 75 mg/24 hours for the previous

5 years (history of thrombosis of his left eye), it was advised, following consultation with an ophthalmologist, to discontinue the medication and monitor for changes. In addition, the patient intermittently took tranexamic acid because of angioedema of unknown origin and nonsteroidal anti-inflammatory drugs due to herniated nucleus pulposus in the lumbar spine. The six-month withdrawal period of the drugs did not affect the morphology of the skin lesions. Over the subsequent months, the patient regularly referred to dermatological consultations and used topical steroid ointments (mometasone furoate, methylprednisolone aceponate) and tacrolimus 0.1%, without clinical improvement. After several years the patient was consulted by the authors of this paper. Clinical and dermatoscopic examinations revealed a 1.5 × 1.5 cm nodule, brown-red in color, on the right nasal ala (P), with isolated telangiectasias and prominent follicular openings (fig. 1). In addition, a brown, flat-topped plaque, 4 × 2.5 cm in diameter, was identified on the



Figure 1. Reddish-brown nodule on the nasal ala. Prominent follicular openings and telangiectasias are visible



Figure 2. Brown plaque on the forehead (visible scar after biopsy)

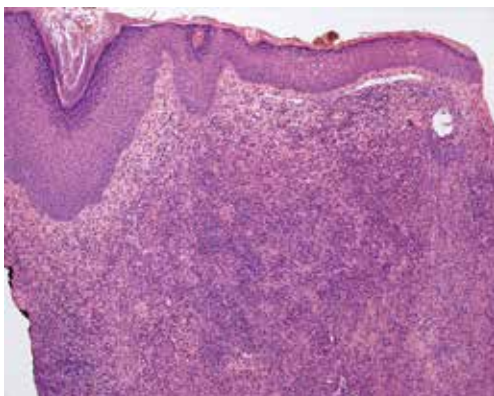


Figure 3. Skin biopsy. Low-power view – dense, mainly perivascular infiltrate within the dermis. The infiltrate spares the upper dermis, creating a prominent grenz zone (magnification 100×)

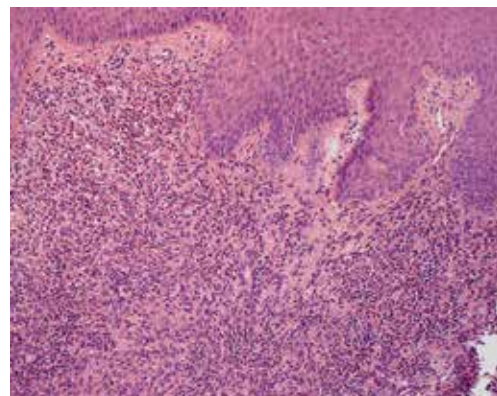


Figure 4. Higher power view – grenz zone (papillary dermis) with the dense mixed type inflammation below (magnification 200×)

right side of the forehead (fig. 2). No pathological eruptions were identified on the right cheek, except for a small biopsy scar. Another biopsy specimen was obtained from the lesion on the forehead for histopathological examination, revealing no pathological changes in the epidermis and papillary dermis (figs. 3, 4). Within the dermis, a dense inflammatory infiltrate comprised of lymphocytes, neutrophils and isolated eosinophils arranged around blood vessels

was observed (fig. 5). There were also signs of leukocytoclasia and mild edema of endothelial cells (fig. 6). Based on the correlation between the clinical presentation and histopathological findings, the diagnosis of granuloma faciale was established. Additional examinations, including CBC, liver enzyme tests, creatinine, general urine analysis, and pulmonary and abdominal imaging, revealed no abnormalities. The patient was informed of the available therapeutic op-

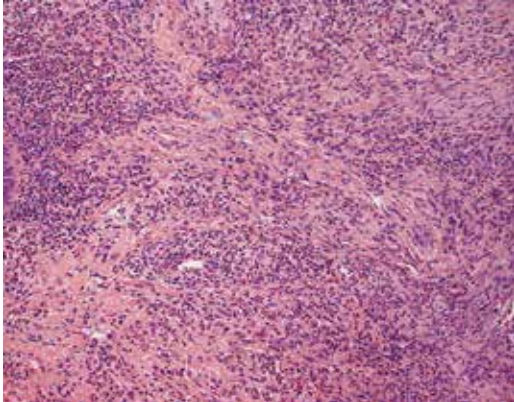


Figure 5. Skin biopsy revealed lymphocytes, eosinophils, and neutrophils within the infiltrate. Pronounced fibrosis between dense collection of inflammatory cells (magnification 200x)

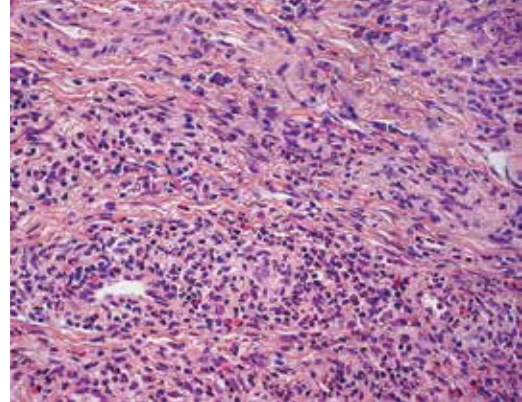


Figure 6. Mixed inflammatory cell infiltrate surrounding a blood vessel is visible with endothelial cell edema. Leukocytoclasia is present (magnification 400x)



Figure 7. Patient's skin condition after a course of cryotherapy – nose



Figure 8. Patient's skin condition after a course of cryotherapy – forehead

tions: topical glucocorticosteroid injections or liquid nitrogen cryotherapy, systemic dapsone or antimalarial drugs. The patient consented only to cryotherapy. After a course of 20 sessions (contact cryotherapy), there was a significant improvement in the skin condition, which the patient deemed completely satisfactory (figs. 7, 8).

DISCUSSION

The reported case is particularly interesting in the context of clinical practice. The disease course and clinical manifestations were non-specific, and the patient remained undiagnosed for over 3 years despite multiple dermatological consultations. It is important to highlight that the final diagnosis required a biopsy obtained from an untreated skin lesion. The initial biopsy, taken from a resolving lesion treated with topical glucocorticosteroids, was inconclusive and pointed towards the diagnosis of fixed drug eruption.

Granuloma faciale is a chronic condition confined to the skin, classified within the group of eosinophilic dermatoses. It is characterized by a mixed inflammatory infiltrate of acidophilic granulocytes (eosinophils) which are frequently degranulated within the skin lesions. A typical, though non-specific, sign of eosinophilic infiltration in the skin is the presence of the so-called flame figures in histological examination, associated with the accumulation of eosinophil cationic protein (ECP) and major basic protein (MBP), with subsequent collagen denaturation [4, 5]. Moreover, GF may involve eosinophilia in peripheral blood.

Table 1 presents the widely accepted classification of eosinophilic dermatoses into classic types, frequently of varied unknown etiology (unrelated to parasitic infection or hypersensitivity reactions), and non-classic types associated with tissue eosinophilia (of allergic or infectious origin) [4–7].

Eosinophils make up to 5% of total leukocytes in peripheral blood, and when their count exceeds 6%

Table 1. Classification of eosinophilic dermatoses (based on [4–7])

Classic eosinophilic dermatoses	Dermatoses with (secondary) eosinophilic infiltration
Eosinophilic cellulitis (Wells' syndrome)	Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)
Eosinophilic fasciitis (Shulman's syndrome)	Atopic dermatitis
Granuloma faciale	Bullous pemphigoid
Eosinophilic pustular folliculitis (Ofuji's disease)	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Recurrent cutaneous eosinophilic vasculitis (RCEV)	Contact dermatitis
	Prurigo nodularis
	Reaction to insect bite
	Parasitic infections
	Dermatitis herpetiformis
	Urticaria

Table 2. Selected characteristics of eosinophilic cells [8–10, 12–16]

Histological features	12–17 μm in diameter, bilobed nucleus, large acidophilic granules (up to 1 μm) in the cytoplasm
Acidophilic granules	MBP, ECP, EDN, EPO, CLC/Gal-10
Reactive oxygen species	O^- , H_2O_2 , BrO^- , ClO^- , HOSCN^- , NO
Surface markers	CD9, CD11b, CD15, CD35, CD62L, IL-5Ra (CD125), CD123, CCR3(CD193), Siglec-8
Released cytokines	IL-1 β , IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, TNF- α , IFN- γ , TGF- β , GM-CSF
Mediators derived from arachidonic acid	LTC $_4$, LTD $_4$, LTE $_4$, PGE2
Main target organs	Digestive tract, uterus, ovaries, mammary gland, thymus, spleen, lymph nodes
Conditions associated with eosinophil dysfunction	Type I allergies (e.g. allergic bronchial asthma), eosinophilic granulomatous vasculitis, eosinophilic dermatoses
Body organs physiologically devoid of eosinophils	Lungs, esophagus, skin

MBP – major basic protein, ECP – eosinophil cationic protein, EDN – eosinophil-derived neurotoxin, EPO – eosinophil peroxidase CLC/Gal-10 – Charcot-Leyden crystal galectin, CD – cluster of differentiation, IL – interleukin, IL-5Ra – interleukin 5 receptor alpha subunit, CCR3 – c-c chemokine receptor type 3, Siglec-8 – sialic acid-binding Ig-like lectin 8, TNF- α – tumor necrosis factor α , IFN- γ – interferon γ , TGF- β – transforming growth factor β , GM-CSF – granulocyte-macrophage colony-stimulating factor, LTC $_4$ – leukotriene, PGE2 – prostaglandin E2, Gal-10 – galectin-10, O^- – superoxide anion, H_2O_2 – hydrogen peroxide, BrO^- – hypobromite, ClO^- – hypochlorite, HOSCN^- – hypothiocyanite, NO – nitric oxide.

(> 500/mm³), the condition is classified as eosinophilia. Hypereosinophilia is a clinical condition characterized by an elevation in blood eosinophil count above 1,500/mm³ and/or the presence of eosinophilic infiltrates in body tissues. The ratio of blood/tissue eosinophils in humans is 1 : 100. In patients with GF, eosinophilia is transient and usually mild [8–11]. The immunophenotype of mature eosinophils is characterized by the expression of adhesion molecules including CD11b, CD62L, Siglec-8 lectin, complement receptor 1 (CD35), chemokine CCR3 receptor (CD193), and interleukin 5 receptor α subunit (CD125). Currently, their differentiation from other granulocytes primarily relies on the analysis of forward scatter channel (FSC) and side scatter channel (SSC) in flow cytometry [8–10, 12, 13]. A brief description of eosinophils is presented in table 2. Eosinophils differentiate from CD34⁺ stem cells in the bone marrow. The process is mainly stimulated by granulocyte-macrophage colony-stimulating factor (GM-CSF), and further influenced by interleukins (IL) IL-3 and IL-5. Following their release from the bone marrow, eosinophils typically remain in the blood for 8 to 18 hours. Subsequently, they migrate to the tissues without re-entering the circulation. The survival of eosinophils is known to vary from 2 to 5 days, depending on the tissue studied. However, *in vitro* studies have demonstrated that their survival can be extended up to 14 days following cytokine stimulation. The dominant population of eosinophils comprises gastrointestinal eosinophils residing in the lamina propria in all segments of the gastrointestinal tract below the esophagus [12–15]. The primary function of eosinophils is protection against multicellular parasites, which is achieved through the presence of specific acidophilic granules in the cytoplasm comprising, among others, MBP, ECP, eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN). In addition, eosinophils exhibit moderate phagocytic activity and the capacity to present antigens to T cells. When activated, they can produce large amounts of free oxygen radicals [15]. Eosinophils can also potentially contribute to antiviral immunity, especially against RNA viruses (e.g. RSV), while granule proteins (e.g. ECP and EDN) display ribonuclease activity by degrading single-stranded RNA viruses. In broad terms, the role of eosinophils in the immune system can be characterized as that of an activator (or amplifier) of the immune response. MBP stimulates the degranulation of basophils and mast cells, triggering the rapid release of substantial amounts of inflammatory mediators in the tissue. Moreover, eosinophils produce cytokines that impact the immune polarization of T cells, targeting the inflammatory response depending on the etiology of inflammation [15].

The key role in the pathophysiology of eosinophilic dermatoses is attributed to the process of eosinophil migration to the skin occurring in response to a gradient of specific chemokines or other mediators that affect membrane receptors. The central role is played by eotaxin 3 (CCL11), with additional involvement from the complement component C5a, platelet-activating factor (PAF), leukotrienes B4 and C4, prostaglandin D2, and the chemokine RANTES (CCL5; regulated on activation, normal T cell expressed and secreted) [5]. Another important factor in eosinophil chemotaxis is the capacity for diapedesis. Constitutive expression of intercellular adhesion molecule-1 (ICAM-1) molecules on endothelial cells prevents a greater number of these cells from leaving the circulation due to their low affinity to these adhesion molecules. The phenomenon prevents the infiltration of healthy tissues by eosinophils. The secretion of IL-4 and IL-13 at the site of inflammation stimulates the expression of vascular cell adhesion molecule-1 (VCAM-1) molecules on the endothelium, which show a predilection for eosinophils. The interaction between α 4 β 1 and α 4 β 7 integrins with VCAM-1 molecules on endothelial cell surfaces leads to a partially selective, cytokine concentration-dependent migration of eosinophils into tissues. From the viewpoint of eosinophil physiology, a particularly important cytokine is IL-5. It stimulates eosinophil functions and viability, and it is also responsible for stimulating bone marrow stem cells to produce eosinophils [5, 16–18].

The precise pathophysiology of GF remains unclear due to the rarity of the condition, which underscores the need for further research, including studies in animal models [19, 20]. The condition appears to be associated with the mechanism of eosinophilic leukocytoclastic vasculitis. The inflammatory process

Table 3. Differential diagnosis of granuloma faciale [26–28, 38, 39]

Non-cancerous conditions	Cancers
Rosacea (granulomatous variant)	Skin lymphomas
Erythema elevatum et diutinum	Basal cell carcinoma
Discoid lupus erythematosus	Melanoma
Jessner lymphocytic infiltration	Hemangioma
Sarcoidosis	Kaposi's sarcoma
Seborrheic keratosis	
Kimura's disease	
Histiocytosis	
Foreign body cutaneous granuloma (FBCG)	
Cutaneous tuberculosis	
Follicular mucinosis	
Keloid	

Table 4. Characteristics of the most common dermatoses differentiated with GF [27, 28, 40–42]

Disease	Predominant clinical features
Rosacea	Erythema (transient or persistent) of facial skin (especially cheeks, forehead, and chin), dilation of small superficial vessels, often accompanied by papules and pustules (or hypertrophic lesions).
Sarcoidosis	Particularly lupus pernio with infiltrative foci, blue-violet or red in color, located primarily on the nose, cheeks, earlobes, lips or forehead. The skin lesions persist for an extended period and typically leave behind scars and telangiectasias.
Cutaneous lymphoma	Non-specific onset of lesions (erythema, dry, frequently itchy patches or slightly crusted plaques). More specific lesions include nodules or tumors which often become ulcerated. Also, the adjacent lymph nodes should be monitored for potential enlargement. OBLIGATORY skin lesion biopsy.
Erythema elevatum et diutinum	Red, purple or brown plaques or papules appearing bilaterally with a predilection for the dorsal aspects of the joints. Histologically, the findings are very similar to GF.

Table 5. GF treatment methods [43–46]

Topical treatment	Systemic treatment	Invasive therapies
Topical tacrolimus	Dapsone	Contact cryotherapy (liquid nitrogen)
Topical glucocorticosteroids	Clofazimine	Cryotherapy with fractional Er:YAG and CO ₂ laser
Topical tofacitinib	Psoralen with UV-A therapy	Excision of skin lesion
	TNF- α antagonists	Glucocorticosteroids in topical injections

Er:YAG – erbium-doped yttrium aluminum garnet laser, UV-A – ultraviolet A.

is confined to the skin (single-organ cutaneous small-vessel vasculitis), and this positioning of GF is widely accepted [1, 21]. On direct immunofluorescence, deposits of IgG, IgA, IgM, C3c, and C1q antibodies suggest that vasculitis during the course of GF involves classical activation of the complement pathway [22]. Higher counts of IgG4-positive plasma cells have also been noted within GF eruptions. This observation may imply that the dermatosis represents a local manifestation of an IgG4-dependent disease, though it remains unclear whether the finding is specific [23–25].

As the name of the disorder suggests, skin lesions in GF affect the face and they are multifocal in approximately 30% of cases. Ortonne *et al.* [26], in their retrospective study encompassing the largest group of GF patients to date (66 individuals, mean age: 53 years), found the most commonly affected sites to include the forehead (38%), cheeks (30%), nose (27.5%), and eyelid (10.5%). Facial involvement in GF may be attributed to the heating of tissues in this body region which may occur in certain occupations (e.g. in welders) or exposure to UV radiation [27, 28]. Extrafacial involvement is infrequent (only 5/66 patients in the study by Ortonne *et al.*) and represents a particularly demanding diagnostic challenge. Lesions may be located on the trunk, limbs, and even in the genital area [6, 26, 28, 29]. GF manifests as smooth, soft nodules/tumors, papules or plaques, brown-red, violaceous or blue in color, accompanied by telangiectasias and prominent follicular openings. The mean size of the skin lesions is approximately 2 cm in diameter. Notably, the lesions never ulcerate. The condition is typi-

cally asymptomatic, though moderate pruritus may be present in some patients [26, 30].

GF affects primarily middle-aged to elderly Caucasian men. However, reliable epidemiological data is lacking due to the rarity of this dermatosis [31].

Clinical suspicion of GF can also be verified by dermoscopy, which typically reveals features including parallel dilated blood vessels, brown dots and globules, and prominent dilated follicular openings [32]. The usefulness of this diagnostic method has been highlighted in recent studies [33, 34].

The conclusive diagnosis of GF should be based on histopathological findings. GF is characterized by the presence of a grenz zone, perivascular mixed inflammatory infiltrate (neutrophils, lymphocytes, plasma cells and eosinophils) with nuclear dust, vascular leakage and even fibrinoid necrosis. All these elements contribute to a typical picture of leukocytoclastic vasculitis [1, 27]. Grenz zone is a band of normal-appearing collagen within the superficial papillary layer of the dermis, which separates the inflammatory infiltrate from the epidermis and hair follicles [35]. Despite the name of the condition, histopathological examination of GF lesions reveals no features of granuloma [36, 37]. Oliveira *et al.* in their study [27] showed a significant prevalence of T cells (CD3+; CD8+>CD4+) over B cells (CD20+) in the inflammatory infiltrate.

GF needs to be differentiated from various dermatoses (table 3 [26–28, 38, 39]) that are known to affect facial skin and present similar symptoms.

It appears to be particularly important to differentiate GF from rosacea (granulomatous variant), sarcoidosis,

cutaneous lymphoma, and erythema elevatum et diutinum (EED) for accurate diagnosis (table 4) [27, 28, 40–42].

Therapeutic management of patients diagnosed with granuloma faciale is a complex issue. As yet, there are no widely accepted therapeutic recommendations for GF in the existing literature (table 5) [25, 43–45].

Treatment of patients with GF is regarded as challenging and relies on experience in different medical centers. Initial treatment is usually based on topical medications, and if these prove ineffective, systemic drugs and/or invasive procedures may be considered [44]. Recent reports have highlighted the therapeutic efficacy of topical treatment with 2% tofacitinib, a janus kinase (JAK) inhibitor. It is important to note that topical JAK inhibitors carry a lower risk of complications and can be used in the treatment of patients with immunosuppression and multimorbidity [45].

The patient reported on here consented only to cryotherapy as a treatment option. The choice of this therapeutic modality was motivated by the patient's

additional general comorbidities and low risk of complications. The application and efficacy of cryotherapy in the management of GF are confirmed by the existing studies [46]. Recent publications also provide evidence for the benefits of combined cryo- and laser therapy in GF (Er: YAG fractional laser; CO₂ laser), particularly in patients with drug-refractory GF [46, 47].

CONCLUSIONS

The case reported here is similar to the cases of GF documented in the existing literature. Nevertheless, given the rarity of the disease, reporting new cases is important to prevent diagnostic errors and improve the efficacy of therapies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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