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Granuloma faciale – a difficult diagnosis? – A case report

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VERSITA

Abstract

Granuloma faciale is an uncommon inflammatory skin disorder clinically characterized by single or multiple, reddish-brown nodules or plaques primarily occurring on the face of middle-aged men. Occasionally, extra-facial involvement has been reported, usually on sun-exposed areas. Although the etiology is somewhat unclear, granuloma faciale is considered a localized form of chronic leukocytoclastic vasculitis with a prominent eosinophilic infiltrate and fibrosis in the later stages of the disease. Histological examination of lesions reveals a dense polymorphous inflammatory infiltrate that consists mainly of eosinophils and neutrophils separated from the epidermis by a narrow band zone with normal collagen, deprived of cells. Leukocytoclastic vasculitis is often seen. Clinical diagnosis is suspected in few cases, so definite diagnosis of granuloma faciale requires a biopsy. The disease is notoriously resistant to many therapies and often tends to relapse after treatment is discontinued.

We present a female patient with granuloma faciale on the back and on the tip of the nose, misdiagnosed clinically as basall cell carcinoma and granuloma annulare. Her original histological diagnosis, made by a pathologist, was pyogenic granuloma. After revision of histologic findings of the biopsy specimens, granuloma faciale was diagnosed by a dermatopathologist. The treatment with cryotherapy and topical steroids was unsuccessful. Improvement of lesions was observed after use of tacrolimus 0.1% ointment, but lesion recurred after discontinuation of treatment.

Key words

Granuloma + diagnosis; Skin Neoplasms; Cryosurgery; Tacrolimus; Administration, Topical; Histology

Granuloma faciale (GF) or *granuloma faciale eosinophilicum* is a rare chronic inflammatory disease clinically characterized by asymptomatic cutaneous reddish brown to violaceous nodules and plaques occurring primarily on the face, with occasional extrafacial involvement. The term granuloma faciale was originally described by Wigley in 1945 (1) as eosinophilic granuloma of the skin, and was defined more precisely by Lever and Leeper (2), whereas Pinkus recommended the present term in 1952 (3). Although the etiology is somewhat unclear, GF is considered a localized form of chronic leukocytoclastic vasculitis with a prominent eosinophilic infiltrate and fibrosis in the later stages of the disease. Granuloma faciale is limited to the skin, without any systemic manifestations. The disease is found in both sexes, at any age, but it usually affects middle-aged men (4). Clinically, GF presents with reddish-brown to violaceous plaques on the face, often with follicular accentuation and superficial telangiectasia. The sites of predilection are sun-exposed areas such as the sides and tip of the nose, the preauricular area, the cheeks, forehead and the helix of the ear. Definite diagnosis of GF requires clinically consistent lesions and a confirming biopsy. Histological examination of the lesions reveals a dense polymorphous inflammatory infiltrate that consists of eosinophils, neutrophils, lymphocytes, histiocytes, plasma cells, fibroblasts in the upper two-thirds of the dermis or even to subcutis, which is separated from the epidermis and pilosebaceous units by a narrow zone deprived of cells (Grenz zone) (5). Leukocytoclastic vasculitis

with fibrinoid degeneration within and around the microvessels is often seen. GF follows a chronic course with intermittent acute flares. It is often refractory to treatment and tends to relapse when treatment is discontinued. As a result, a wide variety of treatment modalities, both surgical and medical, have been used to treat this condition.

We present a patient with GF on the nose, misdiagnosed clinically as basal cell carcinoma and pyogenic granuloma on histopathology examination and treated as granuloma annulare.

Case report

A 65-year-old woman was admitted to our Department with a 5-month history of gradually enlarging, asymptomatic, infiltrated lesions on her nose. Four months before, a clinical suspicion of basal cell carcinoma was made by a plastic surgeon and an excisional biopsy from the middle of the infiltrated plaque on the back of the nose was performed. Histological examination of the biopsy specimen revealed a dense inflammatory infiltrate that consisted of eosinophils in combination with neutrophils, histiocytes and lymphocytes. Numerous dilated blood vessels with edematous walls were found. Her original histological diagnosis, made by a pathologist, was pyogenic granuloma. Beside these findings, skin lesions were identified as granuloma annulare, and treated with open-spray cryotherapy by a dermatologist. Cryotherapy with liquid nitrogen caused no improvement of the lesion, with peripheral enlargement, so the patient asked for second opinion.

Physical examination revealed a sharply bordered (3 x 2.5 cm), erythemolivid plaque, over the back and the tip of the nose. In the center of the lesion an atrophic cicatrix was seen on the site of the biopsy. The infiltrated plaque showed orange-peel surface markings with prominent telangiectasia (Figure 1a-c). The patient was otherwise healthy and all laboratory tests were normal. Peripheral blood eosinophils were within a normal range.

Revision of the biopsy specimen, performed by a dermatopathologist at our Clinic, revealed a normal-appearing epidermis and a dense, mixed, inflammatory infiltrate in the upper and mid dermis. The infiltrate was composed of numerous eosinophils and neutrophils, lymphocytes, histiocytes, and plasma cells. A band of normal collagen referred to as a "Grenz' zone" typically separated the inflammatory infiltrate from the epidermis and pilosebaceous appendages. In addition, vasculitis, with fibrinoid deposits near and within the vessel walls, and extravasation of erythrocytes around the capillares were also evident. A mild fibrosis area was also found. These findings were in agreement with the diagnosis of GF (Figures 2,3,4).

Several treatments with mid-to high-potency topical corticosteroids showed only minimal and transient improvements during drug administration,

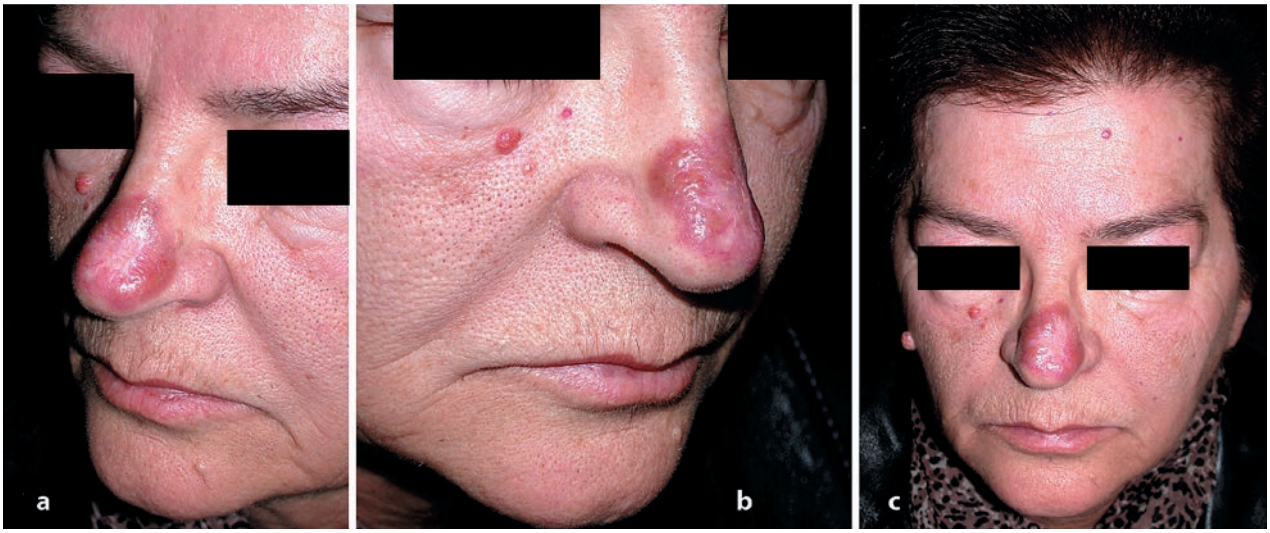

Figure 1. Granuloma faciale: a) sharply bordered (3 x 2.5 cm), erythemolivid plaque over the back and the tip of the nose; b) orange-peel surface markings and prominent telangiectasia; c) in the center of the lesion there is an atrophic cicatrix on the site of the biopsy

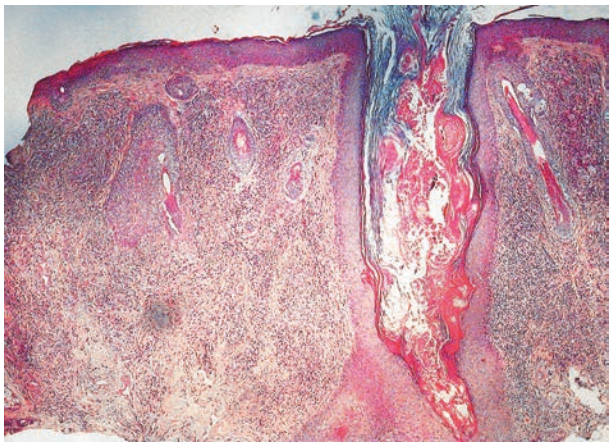

Figure 2. Histopathological presentation of granuloma faciale: normal-appearing epidermis and a band of normal collagen referred to as a 'Grenz' zone, typically separated the inflammatory infiltrate from the epidermis and pilosebaceous appendages (H&E, x50)

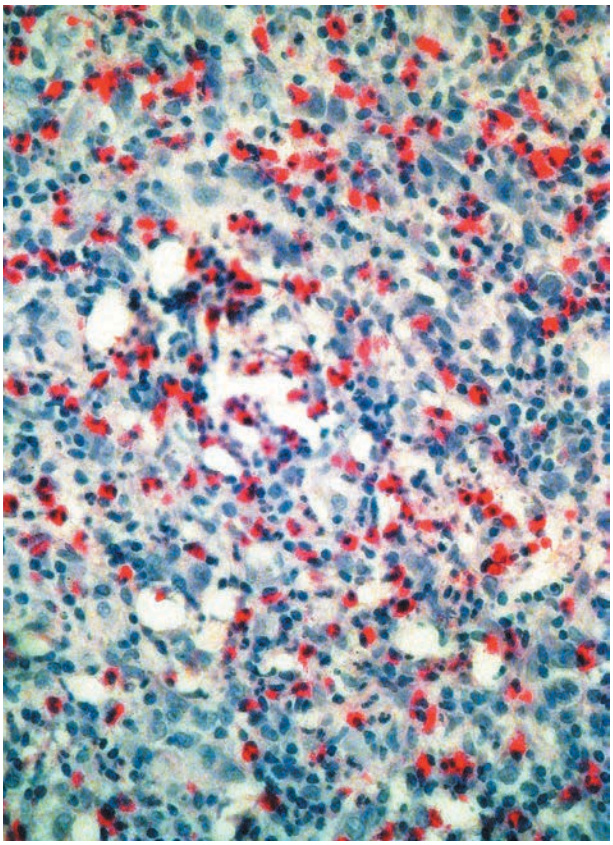

Figure 3. Histopathological presentation of granuloma faciale: dense, mixed inflammatory infiltrate composed of numerous eosinophils, neutrophils, lymphocytes, hystiocites, and plasma cells. (H&E, x100)

followed by rapid recurrences after their discontinuation. Treatment with tacrolimus 0.1% ointment, twice a day, for 2 months was introduced, and then reduced to once a day for 2 months. The lesion appeared very much improved after 4 months of topical application, but the peripheral margin remained slightly infiltrated and pigmented. The patient discontinued the treatment and experienced new peripheral nodules one month after discontinuing tacrolimus 0.1% ointment. As the lesion was not a great cosmetic concern for our patient, she refused any further treatment.

Discussion

GF is considered to be a histological variant of chronic leukocytoclastic vasculitis with a prominent eosinophilic infiltrte (6). Imunohistochemically, the lymphocytes are CD4+ producing IL-5, a powerful eosinophil chemoattractant (7). GF is characterized by asymptomatic, well circumscribed, soft reddish-brown or violaceous papules, plaques or nodules. GF typically presents on the face, often as a solitary plaque or nodule or in oligolesional (limitted number of lesions) fashion. Extrafacial lesions have been reported both in conjunction with facial lesions, or as isolated findings. Twenty-seven cases of extrafacial GF have been described in the English and Spanish literature as reviewed by Ziemer et al (8). Plaques have smooth surface with dilated follicular ostia and

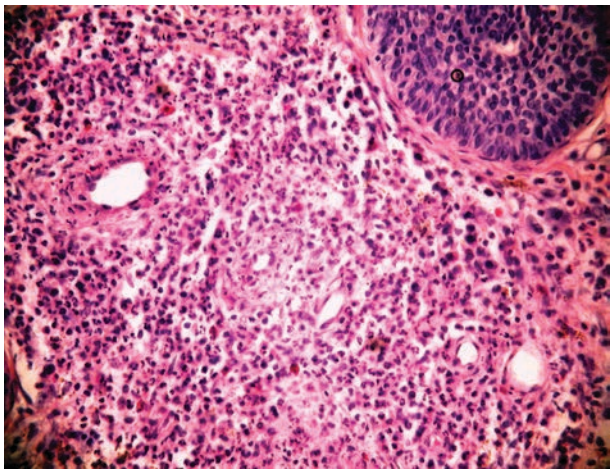

Figure. 4. Histopathological presentation of granuloma faciale: vasculitis with extravasation of erythrocytes and pigment in the upper dermis. (H&E, x100)

telangiectasia. The diagnose is based on clinical and histopathological findings. GF is also characterized by a mixed inflammatory infiltrates with a predominance of eosinophils and neutrophils, separated from the normal appearing epidermis and pilosebaceous structures by a band of normal collagen without cells. Granuloma faciale is an uncommon condition. The first thorough review of GF was published by Pedace and Perry in 1966 (9). They reported on 21 patients (13 males and 8 females), 7 of whom (33%) had a single lesion. Extrafacial lesions were found in two patients. A Grenz zone was usually present, and tissue eosinophilia was considered to be necessary for microscopic diagnosis of GF.

In 2004, Marcoval et al. published findings on 11 patients (9 males and 2 females) with GF (10). All of them had facial lesions. Histopathologically, all cases showed a Grenz zone, a dense infiltrate with eosinophils and neutrophils, extravasated erythrocytes and nuclear dust.

The largest clinicopathological study of 66 patients (41 males and 25 females) with GF was performed by Ortonne et al. (5). Five patients presented with extrafacial lesions, while forty patients (62%) showed single lesions. The most frequent histopathological findings included presence of lymphocytes (100%), neutrophils (93%), teleangiectasia (74%), a Grenz zone (74%), hemosiderin (70%) and leukocytoclasis (66%). In contrast to previous studies, eosinophils were found only in 57.5% of cases and extravasated erythrocytes only in 19%. Dermal fibrosis was present in 45%. Clinical diagnosis of GF was made in only 10 cases; sarcoidosis, lupus, lymphoma and basal cell carcinoma were the main differential diagnoses.

The disease mimics many other dermatoses and may be confused with other conditions, such as sarcoidosis, granuloma annulare, lymphocytic infiltrate of Jessner, basal cell carcinoma, angiolymphoid hyperplasia with eosinophilia, discoid lupus erythematosus, mycosis fungoides or erythema elevatum diutinum, when extrafacial localization occurs. Our patient was clinically misdiagnosed as basal cell carcinoma, because the lesion was solitary, localized on the back and the tip of the nose, with prominent telangiectasia, and raised border of coalescent nodules.

The most likely pathologic differential diagnosis of GF is erythema elevatum diutinum (EED). The histopathology of GF and EED is very similar and overlapping due to identical sequential inflammatory changes. First, there are neutrophils accompanied by nuclear dust, which are followed by eosinophils, lymphocytes, plasma cells and finally macrophages (11).

Criteria for histopathological distinction of GF from EED in classical dermatology books include sparing of the epidermis and papillary dermis, presence of many eosinophils within the infiltrate and less fibroplasia. In their retrospective study, Ziemer M. et al. reviewed in a blinded manner, 9 cases of EED and 41 cases of GF (8). High density of the infiltrate was noted in 97% of cases with GF, but only in 56% of cases with EED. Eosinophils were the predominant cell type in 59% of cases with GF, but in none of the cases with EED. Plasma cells were more frequent in GF (64%) than in EED (22%), and granulomas were not found in GF, but in 22% of EED. A zone of perijunctional sparing (Grenz zone) was observed in about three quarters of cases in both groups. They concluded that presence of a Grenz zone and patterned fibrosis does not distinguish the two diseases. It remains controversial whether EED and GF are separate entities or different names for the same condition at different anatomic sites taking into account that GF is predominantly located on the head, and EED involves extremities or trunk.

Histological interpretation of the biopsy specimen from the infiltrated plaque on the nose was misinterpreted as granuloma pyogenicum. Although lobular proliferation of small blood vessels, which erupt through a breach in the epidermis, to produce a globular pedunculated tumour was missing, the proliferating vessels surrounded by a mixed cell population of fibroblasts, mast cells, lymphocytes, plasma cells and polymorphonuclear leukocytes initiated the diagnosis of granuloma pyogenicum.

Due to the prominent location of GF on the face, treatment is often desired. The pathogenesis of the disease is unknown, and no etiological treatment exists. Its therapy remains a challenge, but spontaneous resolutions have also been reported. Therefore, different destructive and antiinflammmatory and antiproliferating agents have been used, but none of them has been consistently satisfactory. Surgical excision of the lesion, which was already used in the past (12) seems to be ineffective,

as it is followed by recurrence; the same applies for radiation therapy. Electrodessication (12), curettage (12) and dermabrasion (13) have also been used with various results. Cryosurgery with liquid nitrogen seems to be more efficient (14), especially when used with intralesional corticosteroids (15). Our patient did not respond well to treatment using open spray technique with liquid nitrogen. This failure to treatment was previously reported by Goldner et al. (16). Topical, intralesional and systemic corticosteroids, dapsone (17), clofazimine (18) and PUVA therapy (19) have been applied with different responses. Lately, different lasers such as argon laser, CO_2 laser (20), pulsed dye laser (21, 22), 532 nm laser (23) and 595 nm PDL (24) have been used with good results in the treatment of GF. Finally, successful treatment of GF with tacrolimus ointment 0.1% (25, 26) and topical pimecrolimus 1% (27) was recently reported. Pimecrolimus and tacrolimus are effective and safe calcineurin inhibitors that can be used in the treatment of inflammatory skin diseases. They inhibit T-cell activation by the blockage of signal transfer into T-cells, and inhibition of inflammatory cytokine synthesis. These medications shown no risk of scarring or pigmentation compared to destructive procedures. In our patient we started treatment with tacrolimus ointment 0.1% and good results were established after 2 months.

Conclusion

Granuloma faciale is not easy to diagnose, neither clinically, nor histologically. Clinically it is often misdiagnosed. On the other hand, its spectrum is broad, so it is easily histologically misdiagnosed as well. We believe it is important to remind clinicians of this rare condition with facial and extrafacial distribution, the need of performing biopsy and correct histopathological interpretation by dermatopathologists. After the diagnosis is established, different treatment options are available, especially if it is a great cosmetic concern for patients.

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Abbreviations:

GF – Granuloma faciale
EED – Erythema elevatum diutinum
IL – Interleukin
PUVA - Photochemotherapy (psoralen +UVA)
$C0_2$ – Carbon dioxide
PDL – Pulsed dye laser

Facijalni granulom – da li ga je teško dijagnostikovati? – Prikaz slučaja

Sažetak

Uvod: Granuloma faciale ili granuloma faciale eosinophilicum je retka, hronična inflamatorna dermatoza koja se klinički manifestuje asimptomatskim crvenkasto-braon ili lividnim nodulima ili plakovima, koje su primarno lokalizovane na licu, a retko mogu da se jave i ekstrafacijalno. Bolest se javlja kod oba pola, ali se češće sreće kod muškaraca srednje dobi. I pored toga što je etiopatogeneza bolesti nedovoljno razjašnjena, granuloma faciale pretstavlja lokalizovanu varijantu hroničnog leukocitoklastičnog vaskulitisa sa izrazitim eozinofilnim infiltratom. U prilog tome da je granuloma faciale imuno-kompleks medirani vaskulitis govori nalaz IgG depozita unutar i oko dermalne vasculature. Imunohistohemijskim markiranjem detektuju se CD4+ limfociti koji sintetizuju IL-5, moćni eozinofilni hemoatraktant. Histopatološkim pregledom može se utvrditi prisustvo gustog polimorfnog inflamatornog infiltrata koji se sastoji pretežno od eozinofila i neutrofila. Karakteristično je da je infiltrat odvojen od intaktnog epidermisa i pilosebacealnih jedinica sa uskom zonom normalnog kolagena, siromašnom ćelijama tzv. Grenz zona. Može se naći leukocitoklastični vaskulit, a u kasnijim fazama bolesti, prisutna je fibroza. Dijagnoza se potavlja na osnovu kliničke slike, facijalne lokalizacije dobro ograničenih, mekih eritemno-braonkastih nodulusa ili plaka, sa sjajnom povrsinom na kojoj se vide teleangiektazije i dilatirani folikularni otvori, što daje lezijama izgled pomorandžine kore. Definitivna dijagnoza granuloma faciale se postavlja na osnovu prisustva klinički tipičnih lezija i potvrdnog histopatološkog nalaza. Granuloma faciale ima hroničan tok sa intermitentnim akutnim kliničkim pogoršanjem. Ne zahvata unutrašnje organe. U velikom broju slučajeva bolest je refraktorna na različite destruktivne ili antiinflamatorne tretmane. Zbog toga granuloma faciale predstavlja dijagnostički i terapeutski izazov.
Prikaz slučaja: Prikazujemo 65-godišnju ženu sa petomesečnom anamnezom o kontinuiranom povećanju asimptomatske, infiltrirane lezije na nosu. Pre četiri meseca, specijalista za plastičnu hirurgiju je postavio kliničku dijagnozu bazocelularnog karcinoma i uradio ekscizionu biopsiju središnjeg dela lezije, a od strane patologa postavljena je histopatološka dijagnoza granuloma pyogenicum. Histološka interpretacija opisivala je prisustvo gustog inflamatornog infiltrata sastavljenog od eozinofila u kombinaciji sa neutrofilima, histiocitima i limfocitima, sa brojnim dilatiranim kapilarima. I pored ovog nalaza, konsultovani dermatolog je smatrao da se radi o granuloma annulare i tretirao je pacijenticu krioterapijom. Krioterapija sa tekućim azotom izazvala je pogoršanje lezije, odnosno njeno povećanje na periferiji. Pacijentica je tražila ekspertsko misljenje na Univerzitetskoj Klinici za Dermatologiju u Skoplju. Pregledom je utvrđeno prisustvo eritemo-lividnog plaka na nosu, jasno ograničenog, sa dimenzijama 3 x 2.5cm. U centru lezije bio je vidljiv atrofični cikatriks na mestu prethodne biopsije. Površina plaka imala je izgled pomorandžine kore sa dilatiranim folikularnim otvorima i teleangiektazijama (Slike 1a-c). Pacijentica je inače bila zdrava sa urednim laboratorijskim nalazima, bez eozinofilije u perifernoj krvi. Urađena je revizija histološkog preparata koji je pacijentica donela.
Histopatologija: U revidiranom histološkom preparatu bio je prisutan normalan epidermis i gust mešani

inflamatorni infiltrat u gornjem i srednjem dermisu. Infiltrat je bio sastavljen od brojnih eozinofila, neutrofila, i manjeg broja limfocita, histiocita i plazma ćelija. Traka normalnog kolagena, t.z. "Grenz zona" tipično je separirala inflamatorni infiltrat od epidermisa i pilosebacealnih jedinica. Bio je prisutan i vaskulitis sa fibrinoidnim depozitima unutar i oko krvnih sudova sa perikapilarnom ekstravazacijom eritrocita. Viđena je i diskretna fibroza (Slike 2,3,4). Na osnovu ovih histopatoloških promena postavljena je dijagnoza granuloma faciale.

Lečenje: Terapija topičnim srednje i jako potentnim kortikosteroidima pokazala je samo minimalno i prolazno poboljšanje. Posle prekida tretmana pojavio se brzi recidiv. Zatim je ordinirana lokalna terapija sa takrolimusom (0.1% mast), 2 x dnevno u trajanju od 2 meseca, a onda jedanput mesečno narednih 2 meseca. Lezija se poboljšala posle 4 mesečnog tretmana sa izuzetkom perzistentnog slabo infiltriranog i pigmentiranog ruba. Pacijentica je prekinula tretman zadovoljna rezultatom, ali jedan mesec posle prekida terapije pojavili su se novi nodulusi na periferiji lezije. Zbog toga što ova promena za pacijenticu više nije pretstavljala značajan estetski problem, ona je odbila dalje tretmane.

Komentar: dijagnoza granuloma faciale se samo u oko 10% slučajeva postavlja na osnovu kliničkog nalaza. Definitivna dijagnoza se postavlja na osnovu podudaranja kliničkih i histopatoloških karakteristika.

Zaključak: Slučaj koji je prikazan, ukazuje na potrebu da dijagnoza granuloma faciale bude uključena u diferencijalnu dijagnozu kod svih infiltriranih nodularnih ili plakoznih lezija na licu, pa i kod ekstrafacijalnih lokalizacija. Za verifikaciju dijagnoze neophodna je biopsija i korektna histopatološka interpretacija nalaza od strane dermatopatologa. Terapija granuloma faciale je još jedan izazov za kliničare jer promene najčešće pretstavljaju značajan estetski problem za pacijenta, a do sada nema sigurnih dokaza o postojanju jedinstvenog preporučenog efikasnog terapijskog protokola.

Ključne reči

Granulom + dijagnoza; Neoplazme kože; Kriohirurgija; Tacrolimus; Topikalna primena; Histolohija