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A Case of Granulomatous Rosacea: Successful treatment with Topical Azelaic acid 20% cream

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VERSITA

Abstract

Granulomatous rosacea is considered to be the only true variant of rosacea. Diascopy of larger lesions often reveals apple-jelly nodules, indicating their granulomatous histology. Other signs and symptoms of rosacea are not required to make a diagnosis of granulomatous rosacea. The response to treatment may be slow, which must be the most important consideration for both the clinician and the patient. We present an otherwise healthy 62–year-old non-atopic woman with a 15-year history of episodic facial flushing, often accompanied by a burning sensation without sweating. Exclusively affecting the face, lesions had a high tendency to spread each year. The patient was a lifelong non-smoker. A seller on the local market, she spent most of her time outdoors. She had no positive family history of rosacea. At the time of presentation, she was not taking any medications, except for topical neutral creams. Multiple reddish-brown papules without comedones, associated with telangiectasia were scattered over the erythematous background on the chin, forehead, cheeks, nose, glabella and eyelids, while small pustules clustered over the eyelids. The nasolabial folds, neck and ears were not affected. There was neither lymphadenopathy, nor ocular involvement. Based on the history, physical, laboratory and other relevant investigations including histopathology, the diagnosis of granulomatous rosacea was established. The therapy was conducted with topical azelaic acid 20% cream, twice daily for six months. Clinical evaluation was done every 14 days during the first month, and once monthly during the next five months. Affter two weeks, there was a significant decrease in the mean inflammatory lesion count. At the end of the therapy, telangiectasia and facial erythema almost disappeared. There were no side effects. Apart from several short episodes of erythema, during the five-year-long follow-up, there were no other signs of the disease. In conclusion, azelaic acid 20% cream may be an effective and safe treatment option for some patients with granulomatous rosacea.

Key words

Words: Rosacea; Granulomatous Disease, Chronic; Administration, Topical; Dicarboxylic Acids

Rosacea represents a common inflammatory condition that is more frequent after the age of thirty, and is diagnosed almost three times more often in women than in men (1). More than 1% of all patients seen i dermatology units suffer from rosacea, but its exact prevalence in the general population is lacking (2).

Rosacea is a highly heterogeneous entity with uncertain etiology (3). It is characterized by presence of one or more of the following signs with a central face distribution: flushing, persistent erythema, papules and pustules without comedones, and telangiectasia (4).

Granulomatous rosacea is a rare variant and a dinstinct form of rosacea. Actually, granulomatous rosacea is considered to be the only true variant of rosacea (4, 5). It presents with multiple, hard, less inflammatory, monomorphic reddish-brown papules or nodules, located on the cheeks and periorificial facial skin. In acne agminata, also considered a variant of rosacea, moreover, a self-limiting variant of the granulomatous form of rosacea, the lesions may cluster around the mouth or on the eyelids or eyebrows, so that the term 'agminata' is appropriate (3). However,

the term 'acne rosacea' is used synonymously with rosacea, but should better be avoided, since the epidemiology, etiology and pathology of rosacea are quite distinct from those in acne vulgaris. It only denotes the occurrence, in both diseases, of papules and pustules on the face (3).

Some lesions contain granulomas which can be epithelioid, elastolytic or pallisaded around altered collagen accumulations. Foreign-body type giant cells may also be observed. Such findings can accurately be predicted by clinical examination. Diascopy of larger lesions often reveals apple-jelly nodules indicating their granulomatous histology and central caseation. The background facial skin is otherwise normal (5). Other signs and symptoms of rosacea are not required to make a diagnosis of granulomatous rosacea (5). However, the response to treatment may be slow, which is the most important consideration for both the clinician and the patient (3).

Azelaic acid (1,7-heptanedicarboxylic acid) is a naturally occurring saturated dicarboxylic acid. It is a relatively safe, though mildly irritant agent (the local irritant reactions are often mild or transient) with several effects important for dermatology. Besides its depigmenting effects and antikeratinizing properties, azelaic acid 20% cream is effective in the treatment of acneiform lesions. This is likely due to a combination of anti-microbial and anti-inflammatory properties. It can inhibit growth of *Propionibacterium acnes* and *Staphylococcus epidermidis*, and inhibits production of free radicals by polymorphs. The latter property may also explain why it is effective in rosacea. It may also prove to have a role as an antimycotic, inhibiting growth of dermatophytes, and as a topical antimicrobial agent with activity against antibiotic resistant *Staphylococcus aureus* (3). Azelaic acid 15% gel was approved by the US Food and Drug Administration (FDA) in 2002, for the topical treatment of inflammatory papules and pustules of mild to moderate rosacea (6).

We present a 62–year-old woman with granulomatous rosacea, who was succesfully treated by topical azelaic acid cream.

Case report

History

An otherwise healthy 62–year-old non-atopic woman had a 15-year history of episodic facial flushing. From the very beginning, the flushing was often accompanied by a burning sensation without sweating. Exclusively affecting the face, lesions had a high tendency to spread each year. Erythema, which gradually became more persistent and easily triggered by minor irritants, was meanwhile accompanied by erythematous papules and pustules with increasingly prominent telangiectasia. At that time, she was treated by a general practioner, by topical corticosteroids. She was a lifelong non-smoker. As a seller on the local market, she spent most of her life outdoors and had no positive family history of rosacea. At the time of presentation, she was not taking any medications, except for topical neutral creams.

Physical examination

When first seen by us, the patient was in a good general health condition. The pertinent findings were confined to the facial skin. The lesions affected the central convex areas of the face. There were multiple reddish-brown papules, 3-5 mm in diameter, without comedones, and small pustules scattered over the erythematous background on the chin, forehead, cheeks, nose, glabella and eyelids. Erythema was

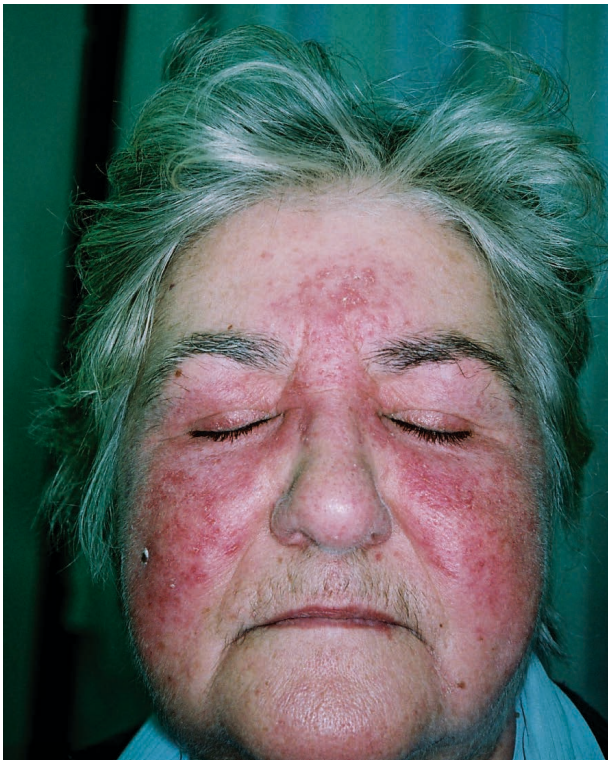

Figure 1. Before treatment: nasolabial folds, neck and ears were not affected

associated with increasingly prominent telangiectasia. Small pustular lesions clustered over the eyelids (Figures 1, 2, 3). The nasolabial folds, neck and ears were not affected. A marked edema of the skin was located over glabella. There was no lymphadenopathy, or ocular involvement.

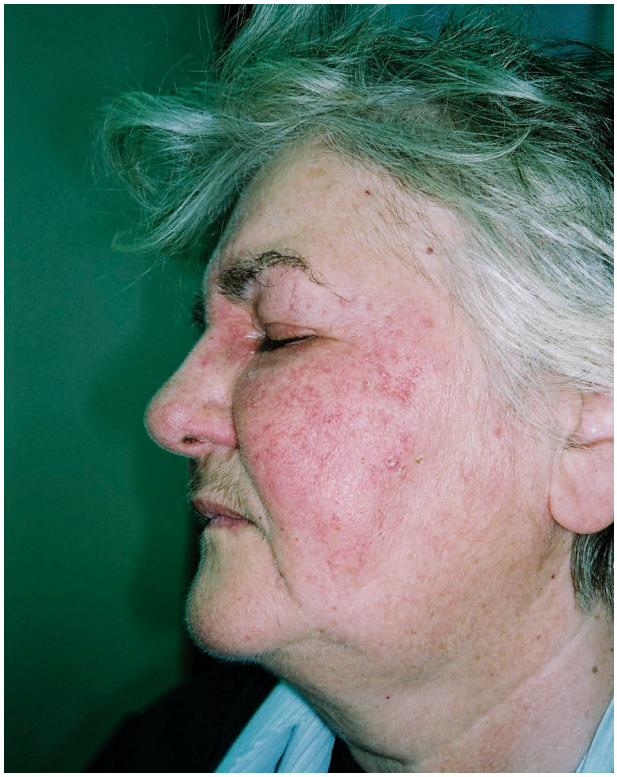

Figure 2. Before treatment: erythema associated with increasingly prominent telangiectasia

Laboratory and other relevant investigations

A complete blood count with differential counts, erythrocyte sedimentation rate, rutine serum biochemical analysis, urinalysis, serum protein electrophoresis, serum autoimmune antibodies, serum complement components, thyroid function, viral serologies, vaginal smear, Pap test, abdominal ultrasound, chesr x-ray, were all within normal limits. The purified protein derivative skin test (PPD) was negative.

Histopathology

Skin biopsy was performed, and a skin sample of the papule taken from the cheek was sent for histopathological analysis. It revealed moderate

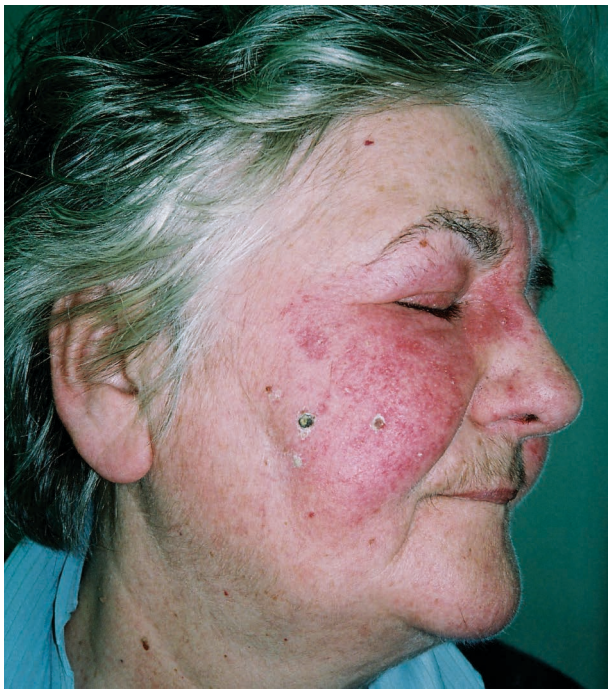

Figure 3. Before treatment: small pustular lesions clustered over the eyelids

hyperkeratosis of the epidermis with mild follicular plugging, dilated upper dermal capillaries, a non specific lymphohistiocytic perivascular infiltrate and dilated hair follicles. No *Demodex folliculorum*

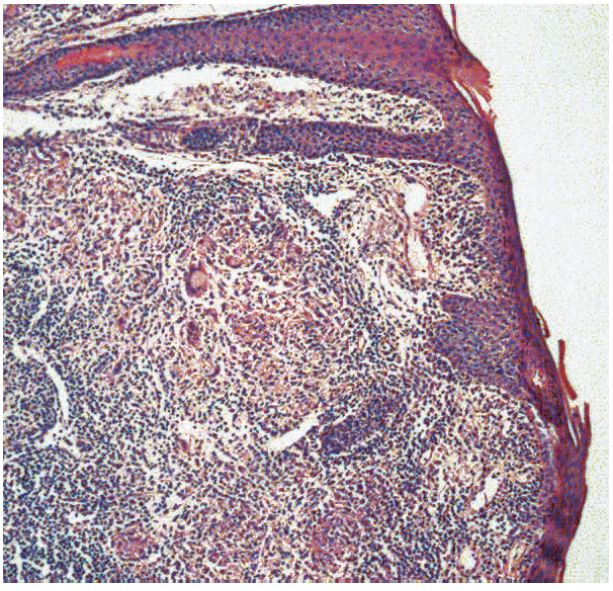

Figure 4. Skin biopsy with moderate epidermal hyperkeratosis and granuloma in the upper dermal part (HE x 50)

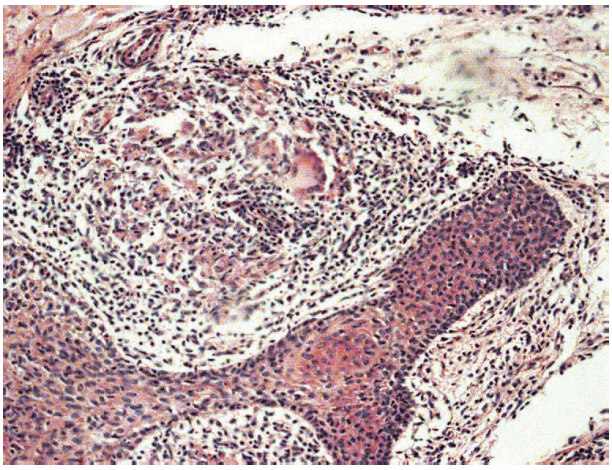

Figure 5. Skin biopsy with granuloma in the upper dermis. Granuloma with multiple giant cells of foreign body type and Langerhans cells type, without necrosis (HE x 200)

mites were found. The upper and middle dermis contained noncaseating tuberculoid granulomas with lymphocytes, epithelioid histiocytes, plasma cells, multinucleated foreign-body type, giant cells, and occasional Langhans' cells. The finding was consistent with granulomatous dermatitis, preferentially granulomatous rosacea (Figures 4, 5).

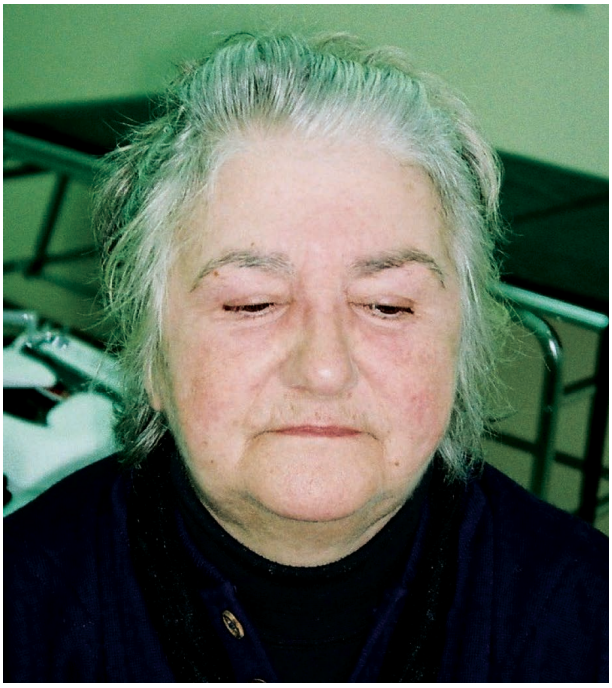

Figure 6. At the end of the treatment: a significant improvement

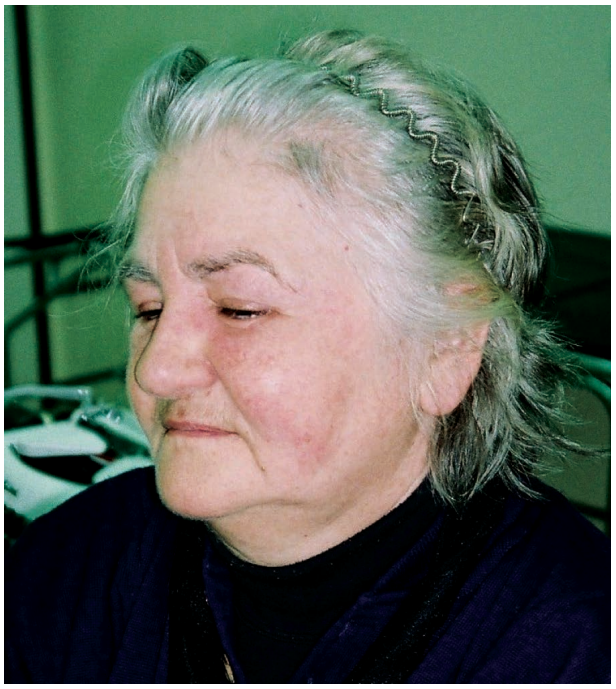

Figure 7. At the end of the treatment: facial erythema almost completely disappeared

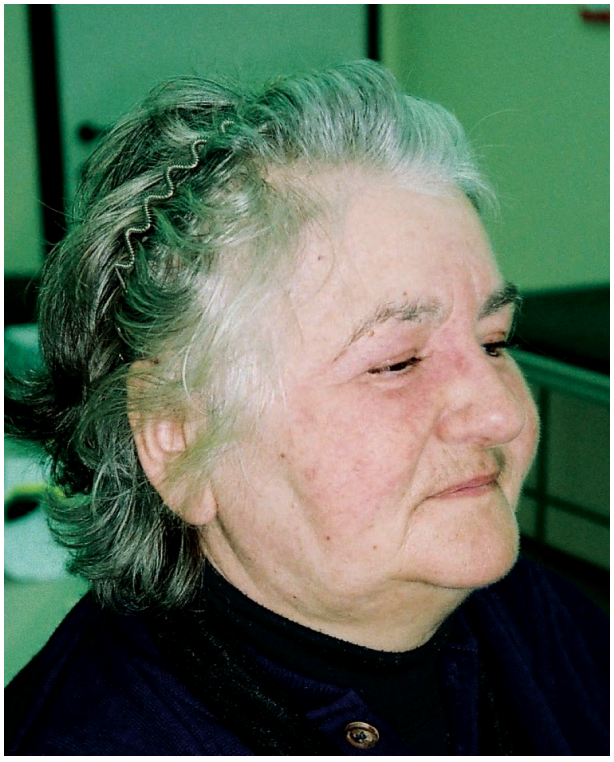

Figure 8. At the end of the treatment: dilatation of the small blood vessells almost completely disappeared

Therapy

Our patient was initially treated with oral 100 mg doxycycline once daily, and oral metronidazole 400 mg twice a day over 10 days. The therapy was discontinued after ten days, when gastrointestinal symptoms with nausea, vomiting, malaise, and stomach pain occurred. Local therapy was continued with topical azelaic acid 20% cream twice a day. The patient was advised to apply the cream gently in a circular manner, for at least six months. Follow-up evaluation was done every 14 days during the first month, and once monthly during the next five months of treatment. On the first control, there was a significant decrease in the mean inflammatory lesion (papulas and pustules) count. At the end of therapy, dilatation of small blood vessells and facial erythema almost disappeared (Figures 6, 7, 8). There were no side effects observed, and/or reported by the patient. After cessation of topical azelaic acid therapy, the patient was advised to use neutral creams and UV protecting creams with a sun protection factor-SPF > 15.

Apart from several short episodes of erythema, during the five-year follow-up, there were no other signs or symptoms of the disease.

Discussion

Based on the history, physical examination, laboratory and other relevant investigations, including histopathological analysis, the diagnosis of granulomatous rosacea was established in our patient (4). The age of onset, history of flushing and burning without sweating, absence of comedones and clear nasolabial folds, differentiated our case from a late-onset of acne vulgaris, postmenopausal flushing, corticosteroid-induced rosacea, seborrhoeic dermatitis, acne agminata, and granulomatous perioral dermatitis in children (3). Unlike in rosacea, telangiectasia and flushing are not common in perioral dermatitis. Perioral dermatitis, like seborrhoeic dermatitis, affects the nasolabial area. Scaling (present in our patient) is not a feature of rosacea, but is common not only in seborrheic, but also in contact dermatitis. However, rosacea and contact dermatitis often seem to occur concurrently (7). Acne agminata is seen mainly in young adults and adolescents. It is a synonym for *'lupus miliaris disseminatus'* which originates from a historical classification. It now seems most unlikely to be tuberculous in etiology, since several studies failed to demonstrate *Mycobacterium tuberculosis* or other mycobacterial agents by culture (3). Whilst the clinical appearance, distribution and histology of lesions are similar with granulomatous rosacea, acne agminata may represent a self-limiting variant of the granulomatous form of this disease. Some authors believe that the natural history and the tendency to affect younger males and females approximately equally, means that they are not a form of rosacea. However, it may be difficult to distinguish it from micropapular sarcoidosis. Similar to our study, a chest X-ray, tuberculin skin test and antistreptolysin 0 titre (ASOT) may be obtained in such instances to exclude causes such as sarcoidosis, tuberculosis or streptococcal infection (8).

Granulomatous infiltrates are reported to occur in about 10% of all cases of rosacea, while caseation necrosis, which was not a feature in our patient, has only been identified in about 10% of these patients (9).

For prevention and better treatment of rosacea, it is important to establish its etiopathogenesis. Rosacea represents a common disease, but its etiology is still a mistery (10). Several endocrinological, pharmacological, immunological, infectious, alimentary, climatic and thermal factors are implicated as triggers for rosacea (3, 5). However, no true relations have been established between most of these factors and rosacea. Thus, in a recent study done by Abram et al, there is no relation between rosacea and *Helicobacter pylori* infection, caffeine intake or alcohol consumption (11). Significant risk factors associated with rosacea included: age, photosensitive skin types (by Fitzpatrick), positive family history, outdoor working conditions and ex-smoking status (10). These findings suggest that rosacea is related to photoaging. Moreover, it has been proposed that damage to dermal connective tissue, often caused by solar irradiation, may be the initiating factor. This may result in a dysfunction of the unsupported facial blood vessels and consequent endothelial damage, leakage, edema and inflammation. It has been suggested that abnormal vascular reactivity plays a central role (3). It is the heat, not the caffeine content of hot drinks, that causes flushing (3,10).

Smoking seems to prevent several granulomatous diseases, which could be a result of a decreased inflammatory response in smokers. Thus, rosacea

was previously considered predominantly a disease of non-smokers. However, in a recent study done by Abram et al, the risk of getting rosacea was higher among ex-smokers (previous smoking period with at least 1 cigarette per day, but not any more), than among current smokers (at least 1 cigarette per day), or lifelong non-smokers (never smoked). The authors argue that the withdrawal of the immunosuppressive effect of smoking acts as a trigger for the disease onset (10).

Our patient had several risk factors: outdoor working conditions, advanced age, sun reactive skin type II, and lifelong non smoker category (never smoked).

The first step in therapy of rosacea should begin with education of patients to use sunscreens and mild cleaners, as well as avoid risk factors including common irritants. Curently, there is no cure for rosacea. It seems that standard medical therapies have focused mainly to minimizing inflammation (1, 11-14). Thus, the main goal of the treatment is disease control. Reduction of the inflammatory component of rosacea by broad-spectrum antibiotics may slow down its progression (3). Similar to our case, troublesome side effects and compliance have been their major limitations. Combinations of topical and systemic treatment are often used in patients with severe forms of the disease, and may be more effective than either used alone. Effective oral agents include tetracyclines and azithromycin (3, 14).

Topical antibiotics like clindamycin, erythromycin, and tetracycline are the first choice therapy for inflammatory lesions, in addition to metronidazole and azelaic acid (3, 6). Metronidazole 1% gel once a day, and azelaic acid 15% gel twice a day alone, or in combination, are the best evaluated topical agents (6). Metronidazole can be used with or without oral antibiotics. Moreover, metronidazole 400 mg daily over a 4-month period, followed by metronidazole 200 mg daily, markedly reduces facial swelling (3). Topical pimecrolimus 1% and tacrolimus 0.3 - 0.1%, have recently been proposed, but only as alternative (unapproved) agents for rosacea (12, 14).

In a recent study done by Mostafa et al, it was found that in comparison with metronidazole 0.75% gel and permethrin 5% cream, azelaic acid 20% cream was significantly more effective reducing the mean inflammatory lesion count, but not erythema. However, patients who used azelaic acid 20% cream were significantly more satisfied with azelaic acid cream with regard to cosmetic results (13).

It is important to explain to patients (with papulopustular lesions), that none of the above measures will significantly suppress the troublesome flushing or the burning discomfort which often accompanies this condition. Treatment of flushing and burning is the most difficult in rosacea.

In our case, once the therapy with oral doxycycline and metronidazole was discontinued, azelaic acid 20% cream was introduced, regarding all the above mentioned reports on azelaic acid effects, obtained in the treatment of patients with papulopustular rosacea (3, 6, 13).

In conclusion, azelaic acid 20% cream may be an effective and safe treatment option for some patients with granulomatous rosacea.

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Granulomatozna rozacea – lokalno lečenje azelaičnom kiselinom u obliku 20% krema – prikaz slučaja

Sažetak

Uvod: Rozacea predstavlja čestu inflamatornu dermatozu, koja se značajno češće javlja posle tridesete godine života i skoro je tri puta češća kod žena nego kod muškaraca. Rozacea predstavlja heterogeni entitet nepoznate etiologije, karakterističnih, jednog ili više, sledećih znakova: iznenadni naleti rumenila (eng. *flushing*), perzistentni eritem, papule i pustule bez komedona, teleangiektazije.

Granulomatozna rozacea, koja predstavlja kliničku varijantnu oboljenja, manifestuje se multiplim, tvrdim, manje inflamiranim, monomorfnim crvenkastosmeđim papulama i/ili nodusima lokalizovanim na obrazima i periorificijalnoj koži lica. Akne agminata predstavljaju varijantu granulomatozne rozacee, a lezije se često grupišu oko usta, očnih kapaka ili obrva, što opravdava naziv *agminata*. Suprotno tome, naziv akne, odnosno *acne rosacea,* koji se često koristi kada je rozacea u pitanju, trebalo bi izbegavati s obzirom da se etiologija, epidemiologija i patologija rozacee potpuno razlikuje od vulgarnih akni. U ovom slučaju termin *acne* označava za oba oboljenja pojavu papula i pustula lokalizovanih na licu.

Neke lezije granulomatozne rozacee sadrže granulome, koji mogu biti epiteloidni, elipsoidni, elastoidni ili biti palisadno raspoređeni oko izmenjenih kolagenih vlakana u koži. Granulomi mogu biti formirani i od džinovskih višejedarnih ćelija tipa „oko stranog tela“ i/ili Langhans višejedarnih džinovskih ćelija. Dijaskopskim pregledom većih lezija dobija se karakteristična „boja želea od jabuka“, koja ne samo da ukazuje na granulomatozni patohistološki supstrat nego i na centralnu nekrozu granuloma. Okolna koža može biti klinički nepromenjena u granulomatoznoj rozacei, a ostali simptomi i znaci koji predstavljaju kriterijume za dijagnozu klasične rozacee (ranije navedeni), ne moraju biti prisutni. Povoljan terapijski odgovor pacijenata sa ovim oblikom rozacee može biti značajno usporen, što ima veliki značaj i za lekara i za pacijenta.

Dikarboksilna kiselina, po svom hemijskom sastavu azelaična kiselina, ispoljava nekoliko efekata koji su značajni za dermatologiju: inhibicija keratinizacije, depigmentacija, antizapaljensko delovanje, antimikrobno delovanje (inhibiše rast *Propoinibacterium acnes* i *Staphylococcus epidermidis*), antimikotično delovanje (inhibicija rasta dermatofita), inhibicija produkcije slobodnih radikala iz polimorfonuklearnih granulocita.

Ova poslednja osobina objašnjava povoljan terapijski efekat azelaične kiseline u lečenju pacijenata sa rozaceom. Azelaična kiselina u obliku pripravka za lokalnu primenu, na osnovu svojih antimikrobnih efekata, može da se koristi za sprečavanje antibiotske rezistentnosti na *Staphylococcus aureus.* Lečenje rozacee lokalnom primenom azelaične kiseline u vidu 15% gela je FDA (eng. *Food and Drug Administration*) zvanično odobrila 2002. godine.

Cilj rada: Prikazujemo slučaj pacijentkinje obolele od granulomatozne rozacee, koja je uspešno lečena lokalnom primenom azelaične kiseline.

Prikaz slučaja: Pacijentkinja stara 62 godine, neatopičar, dobrog opšteg stanja, u momentu pregleda dala je podatak da unazad 15 godina ima povremene nalete iznenadnog rumenila lica. Na samom početku bolesti ove epizode su bile praćene

pečenjem, ali ne i pojačanim znojenjem. Vremenom tegobe su se pojačavale, crvenilo lica je postajalo trajno prisutno, pojačavalo se prilikom izlaganja različitim iritansima (npr. začinjena hrana, alkohol, toplota), a na koži su počele da se pojavljuju bubuljice i čvorići, kao i prošireni kapilari. Lečenje se zasnivalo na kortikosteroidnim kremama, po savetu lekara opšte prakse. U momentu kada se javila dermatologu koristila je samo neutralne kreme.

U momentu dermatološkog pregleda, promene su bile ograničene na kožu lica, u vidu multiplih, crvenkastosmeđih papula, 3-5 mm u dijametru, bez komedona i malih pustula, koje su bile diseminirane na eritematoznoj koži obraza, čela, nosa, glabele i očnih kapaka.

Teleangiektazije su bile jasno izražene, a male pustulozne lezije grupisane na očnim kapcima. Koža je bila pošteđena promena u predelu nazolabijalnih brazda, ušnih školjki i nosa. Otok na licu je bio najizraženiji u predelu glabele. Bolest nije zahvatala regionalne limfne žlezde.

Sve relevantne laboratorijske, imunološke, ultrazvučne i RTG analize (pluća), kao i kožni testovi (PPD), bili su u granicama fizioloških vrednosti.

Histopatološka analiza: Isečak kože uzet sa papule podvrgnut je histopatološkoj analizi: epidermis je lako hiperkeratotičan, sa umereno izraženim folikularnim keratinskim čepovima; prošireni kapilari u gornjem dermisu obloženi su nespecifičnim histiocitnim infiltratom, uočava se proširenje folikula dlaka i odsustvo *Demodex folliculorum*; gornji i srednji dermis sadrže tuberkuloidne granulome bez kazeozne nekroze, sastavljene od limfocita, epiteloidnih histiocita i plazma ćelija, a uočavaju se i višejedarne džinovske ćelije tipa oko stranog tela i pojedinačne Langahansove ćelije. Nalaz ukazuje na granulomatozni dermatitis, u prvom redu na granulomatoznu rozaceu.

Lečenje: Lečenje je započeto peroralnim davanjem doksiciklina u dozi od 100 mg dnevno i metronidazolom u dozi od 800 mg dnevno (podeljeno u dve pojedinačne doze) u toku deset dana. S obzirom da se kod pacijentkinje javio osećaj mučnine, povraćanje i bolovi u stomaku, sistemska terapija je obustavljena. Lečenje je nastavljeno isključivo lokalnom terapijom i to sa azelaičnom kiselinom u obliku 20% krema, koji je nanošen dva puta dnevno na obolelu kožu tokom šest meseci. U toku prvog meseca lečenja pacijentkinja je kontrolisana svakih 14 dana, a potom jednom mesečno tokom narednih pet meseci.Već na prvoj kontroli uočavalo se značajno smanjenje broja inflamiranih lezija, papula i pustula. Posle šest meseci lečenja crvenilo i prošireni kapilari su se gotovo potpuno (> 85%) izgubili. Lečenje nije bilo praćeno neželjenim efektima. Pacijentkinji je savetovano da koristi neutralne kreme i kreme za zaštitu od UV zračenja (zaštitni faktor > 15). Tokom sledećih pet godina pacijentkinja je imala nekoliko kratkotrajnih epizoda crvenila lica bez drugih simptoma i znakova oboljenja.

Diskusija: Postavili smo dijagnozu granulomatozne rozacee na osnovu anamneze, fizičkog pregleda i relevantnih analiza, uključujući i patohistološku. Životno doba na početku bolesti, napadi rumenila i osećaj pečenja bez znojenja, odsustvo komedona i promena na nazolabijalnim brazdama, jesu karakteristike koje razlikuju rozaceu od akni vulgaris u starijem dobu, valunga u postmenopauzi, kortikosteroidima izazvane rozacee, seboroičnog dermatitisa, akne agminata i granulomatoznog perioralnog dermatitisa kod dece (juvenilna rozacea). Teleangiektazije i naleti rumenila kod naše pacijentkinje isključuju perioralni dermatitis. Nazolabijalne brazde su zahvaćene kod perioralnog dermatitisa i seboroičnog dermatitisa. Deskvamacija (viđena kod naše pacijentkinje) nije karakteristična za rozaceu; po pravilu se javlja kod seboriočnog, ali i kod kontaktnog dermatitisa. Štaviše, rozacea i kontaktni dermatitis se javljaju udruženo mnogo češće nego što se na to pomišlja.

Akne agminata se javljaju u mlađem životnom dobu i kod adolescenata. Sinonim *Lupus miliaris disseminatus* potiče iz stare klasifikacije. Sa današnje tačke gledišta isključena je tuberkulozna etiologija (izostanak kultivacije tipičnih i atipičnih mikobakterija). Izgled, distribucija i histološka građa lezija kod granulomatozne rozacee i akne agminata se praktično ne mogu razlikovati, stoga neki autori smatraju akne agminata kliničkom varijantom granulomatozne rozacee.

Promene kod akne agminata se javljaju ranije, podjednako često kod osoba muškog, odnosnog ženskog pola, što po nekim autorima izdvaja akne agminata kao poseban entitet. Relevantne

analize, uključujući RTG pluća, tuberkulinski test, antistreptolizinski titar (ASTO), koje smo sproveli kod naše pacijentkinje, mogu isključiti sarkoidozu, tuberkulozu ili streptokoknu infekciju.

Granulomatozni ćelijski infiltrat se može javiti kod oko 10% svih pacijenata sa rozaceom, dok se kazeozna nekroza (nije je bilo kod naše pacijentkinje) može dokazati kod samo 10% ovih pacijenata.

Radi bolje prevencije i lečenja oboljenja potrebno je dobro poznavanje njegovog etiopatogenetskog mehanizma. Iako se rozacea smatra čestim oboljenjem (dijagnostikuje se kod 1% svih dermatoloških pacijenata), njena etiologija ostaje misterija.

Endokrinološki, farmakološki, imunološki, infektivni, alimentarni, klimatski i termalni faktori se smatraju okidačima za pojavu rozacee. Međutim, značaj većine ovih činilaca nije statistički dokazan. Ispitivanja novijeg datuma nisu potvrdila značajnu ulogu infekcije *Helicobacter pylori*, konzumacije kafe ili alkohola.

Značajni faktori rizika od nastanka rozacee bili su starost, fotosenzitivni tipovi kože (po Fitzpatricku I,II), pozitivna porodična anamneza (najznačajnija), obavljanje posla na otvorenom prostoru i prestanak pušenja.

Iz svega navedenog se može zaključiti da je rozacea izraz „fotostarenja" (eng. p*hotoaging*). Pretpostavlja se da oštećenje vezivnog tkiva u dermisu, koje se često viđa nakon solarne iradijacije, može biti inicijalni događaj i rezultovati disfunkcijom krvnih sudova sa konsekutivnim oštećenjem endotela, transudacijom, edemom i inflamacijom.Takođe se ističe centralna uloga abnormalne vaskularne reaktivnosti. Toplota, a ne kofein u toploj kafi izaziva napad rumenila (*flushing*).

Veći broj do sada sprovedenih ispitivanja ukazao je na preventivnu ulogu pušenja u nastanku granulomatoznih oboljenja, a kao moguće objašnjenje navodi se smanjen inflamatorni odgovor kod pušača. Zato je rozacea smatrana bolešću nepuša. U već ranije navedenoj studiji o faktorima rizika od nastanka rozacee ističe se statistički značaj statusa „bivšeg pušača" (najmanje jedna cigareta dnevno ranije, a nijedna sada), koji se pokazao značajnijim okidačem od statusa nepušača (nijedna cigareta tokom celog života). Nagli prekid imunosupresivnog delovanja koje ima pušenje može da deluje kao okidač.

Edukacija predstavlja prvi korak u lečenju rozacee, a ona podrazumeva ne samo izbegavanje faktora rizika, nego i upotrebu krema za zaštitu od sunca. Za sada ne postoji nijedan lek koji bi doveo do potpunog izlečenja rozacee. Standardne terapijske metode dovode do smanjenja inflamacije. Zato je glavni cilj lečenja rozace kontrola njenog toka.

Upotrebom antibiotika širokog spektra (antiinflamatorni efekat tetraciklina npr. doksiciklina i/ili makrolida, npr. azitromicina), može se usporiti progresija oboljenja. Kao i u našem slučaju, pojava neželjenih efekata primene sistemskih antibiotika često ograničava njihov trajni terapijski efekat.

U težim oblicima oboljenja uvek treba kombinovati sistemsku i lokalnu terapiju, jer se ona pokazala efikasnijom od upotrebe isključivo sistemske ili isključivo lokalne terapije. Lokalna primena antibiotika (klindamicin, eritromicin i tetraciklini) u kombinaciji sa metronidazolom i azelaičnom kiselinom predstavljaju prvu liniju izbora za lokalno lečenje rozacee.

Najveći broj studija o lokalnom lečenju rozacee odnosi se na pojedinačnu ili istovremenu primenu metronidazol 1% gela koji se nanosi jednom dnevno i azelaične kiseline 15% gela, koji se nanosi dva puta dnevno. Lečenje metronidazolom (sistemski i/ili lokalno) može se kombinovati sa sistemskom primenom antibiotika. Metronidazol u dnevnoj dozi od 400 mg tokom četiri meseca, a potom u dnevnoj dozi od 200 mg može u značajnoj meri da smanji otok kože na licu.

Lokalna primena pimekrolimusa 1% i takrolimusa 0,3-0,1% u lečenju rozacee još nije zvanično odobrena.

Najnovije studije su istakle superiornost antiinflamatornog efekta (smanjenje broja papula i pustula, ali ne i eritema) i kozmetičke prihvatljivosti azelaične kiseline u obliku 20% krema u odnosu na metronidazol 0,75% gel i permetrin 5% krem. Zato je značajno objasniti pacijentu sa rozaceom da nijedna od gore navedenih metoda lečenja, neće značajno uticati na iznenadne napade rumenila, crvenilo i osećaj pečenja.

Imajući sve ovo u vidu, nakon prekida desetodnevne terapije započete sistemskom primenom doksiciklina i metronidazola, kod naše pacijentkinje je nastavljena lokalna terapija sa azelaičnom kiselinom u obliku

20% krema, koja je uspešno sprovedena bez ikakvih neželjenih efekata.
Zaključak: Lokalna primena azelaične kiseline u obliku 20% krema može biti efikasna i bezbedna terapijska opcija kod nekih pacijenata sa granulomatoznom rozaceom.

Ključne reči

Rozacea; Hronična granulomatozna bolest; Lokalna primena; Dikarboksilne kiseline