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EFIKASNOST DAPSONA U TERAPIJI DISEMINOVANOG GRANULOMA ANNULARE – PRIKAZ SLUČAJA
EFFICACY OF DAPSONE IN TREATMENT OF DISSEMINATED GRANULOMA ANNULARE – CASE REPORT

Maša GOLUBOVIĆ[1,2], Ivana BINIĆ[1,2] and Vesna KARANIKOLIĆ[1,2]

[1]Univerzitetski Klinički centar Niš, Klinika za dermatovenerologiju, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet. Niš, Srbija

[1]University Clinical Center Niš, Dermatovenerology Clinic, Niš, Serbia
[2]University of Niš, Faculty of Medicine, Niš, Serbia

Correspondence: Maša Golubović, E-mail: masabinic@gmail.com

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Sažetak

Granuloma annulare je neinfektivna benigna granulomatozna dermatoza nepoznate etiologije. Karakteriše se granulomatoznom inflamacijom derma i manifestuje se pojavom papula anularne distribucije. Najčešća klinička prezentacija je lokalizovana forma, koja je obično samoograničavajuća i dolazi do spontane regresije promena bez terapije. Generalizovana forma može da se održava godinama i često ima nezadovoljavajući odgovor na terapiju. Prikazujemo pacijenta muškog pola starosti 77 godina, sa diseminovanom formom, koji nije imao poboljšanje promena na dve primenjene terapijske opcije. Nakon uključivanja leka dapson u terapiju u dozi od 100 mg dnevno, došlo je do potpune rezolucije promena.
Ključne reči: *granuloma anulare; dapson; dermatološki agensi; ishod lečenja; znaci i simptomi*

Abstract

Granuloma annulare is a benign noninfectious granulomatous dermatosis with unknown etiology. It is characterized by granulomatous inflammation of the dermis and commonly manifests with papules in an annular distribution. The most common clinical type of granuloma annulare is localized and it is usually self-limited and resolves without therapy. The generalized form of granuloma annulare may persist for decades and is less responsive to treatment. We present a case of a 77-year-old male patient with disseminated granuloma annulare who failed three different treatment options and then was given Dapsone at a dose of 100mg per day. After ten months, the complete resolution of skin lesions was observed.
Key words: Granuloma Annulare; Dapsone; Dermatologic Agents; Treatment Outcome; Signs and Symptoms

Uvod

Granuloma annulare (*GA) je neinfektivna benigna granulomatozna dermatoza nepoznate etiologije. Karakteriše je granulomatozna inflamacija derma i manifestuje se pojavom papula anularne distribucije. Opisana je povezanost sa određenim stanjima, kao što su dijabetes melitus, HIV, hiperlipidemija, oboljenja štitaste žlezde i maligniteti [1]. Najčešća klinička prezentacija je lokalizovana forma GA, koja je obično samoograničavajuća i dolazi do regresije promena bez terapije. Generalizovana forma GA može da se održava godinama i često ima nezadovoljavajući odgovor na terapiju [2]. Terapijske preporuke se često menja-*

Introduction

Granuloma annulare (GA) is a benign noninfectious granulomatous dermatosis with unknown etiology. It is characterized by granulomatous inflammation of the dermis and commonly manifests with papules in an annular distribution. It has a possible association with many conditions, such as diabetes mellitus, HIV, hyperlipidemia, thyroid disease, and malignancy [1]. The most common clinical type of GA is localized and it is usually self-limited and resolves without therapy. The generalised form of GA may persist for decades and is less responsive to treatment [2]. A gold standard of care has yet to be created to guide clinical management.

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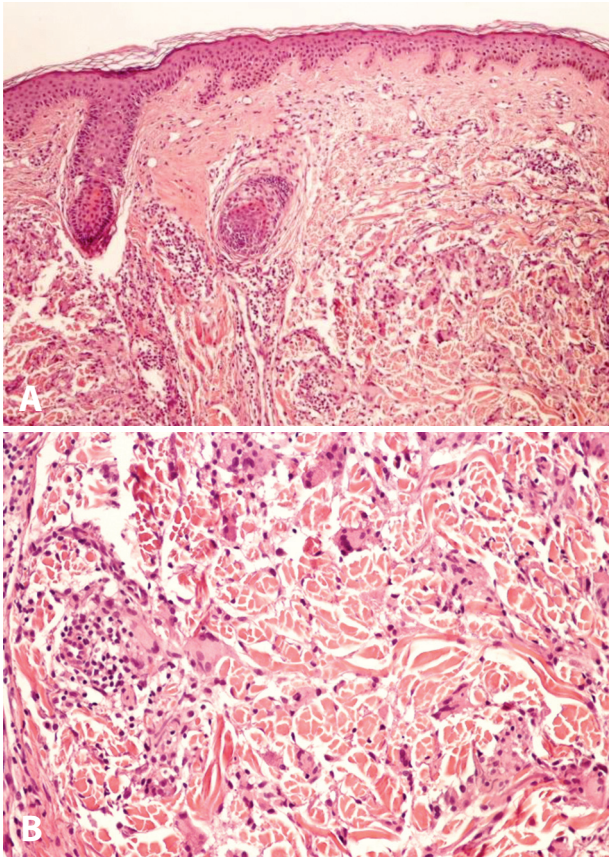

Slika 1. A. *H&E, x 10: Hiperkeratoza, papilomatoza i fokalna spongioza epiderma. U dermu su prisutni granulomi i perivaskularni zapaljenski infiltrat izgrađen od limfocita i plazmocita.* ***B.*** *H&E, x 20: granulomi izgrađeni od histiocita, retkih limfocita i multinuklearnih džinovskih ćelija.*

Figure 1. A. H&E, x10: Hyperkeratosis, papillomatosis and focal spongiosis of the epidermis. Granulomas and a perivascular inflammatory infiltrate made up of lymphocytes and plasmocytes are present in the dermis. **B.** H&E, x20: granulomas composed of histiocytes, rare lymphocytes, and multinucleated giant cells.

ju i dopunjuju, tako da još uvek ne postoji jasan algoritam za lečenje.

Prikaz slučaja

Pacijent muškog pola, starosti 77 godina, javio se na pregled zbog pojave eritemnih papula, unazad četiri meseca. Pojava promena bila je praćena povremenim pruritusom. Nije imao pridružene bolesti, kao ni hroničnu terapiju. Kliničkim pregledom utvrđeno je prisustvo brojnih eritemnih papula i anularnih pla-

Case report

A 77-year-old male patient was examined in our Clinic with a four-month history of erythematous papules, which had appeared gradually. The patient occasionally had pruritus. He had no history of chronic diseases and therapy. Physical examination revealed erythematous papules and annular plaques several centimeters in diameter with irregular edges slightly infiltrated, symmetrically distributed on shoulders, upper arms, and upper back. A skin biopsy showed several granulomas surrounded by histiocytes and lymphocytes within the dermis. Laboratory tests, including biochemistry and complete blood count, revealed no abnormal findings, and fasting plasma glucose levels were normal. Also, the antigen/antibody test for HIV was done, and it was negative. Screening for thyroid diseases was within the reference limits. Clinical features combined with histopathological findings suggested a diagnosis of disseminated GA (**Figures 1 and 2).**

The patient had no pronounced subjective symptoms and was not motivated to use systemic therapy, so the treatment was started with high-potency topical corticosteroids, betamethasone 0.5 mg/g. After eight weeks of therapy, there was no significant improvement of lesions. The second line of treatment was cryotherapy on the edges of the most pronounced skin lesions once a week and after that UVB phototherapy, both ineffective. A Saalmann UVB lamp (270-350 nm) was used, a total of 24 treatments were performed over a period of 8 weeks. The dosage was adjusted according to the phototype of the patient and the local protocol. Following a year of unsuccessful treatment attempts, dapsone was started as a monotherapy at a dose of 100 mg daily (after it was found that the patient's methemoglobin levels were normal). After six weeks, the improvement of skin lesions was observed. Clinical symptoms improved gradually; after ten months of therapy, only residual macules and brown marks remained. Results of the periodic laboratory tests performed during treatment were normal, and no adverse effects were observed.

Discussion

GA is considered a benign dermatosis that is usually self-limiting. Its cause has yet

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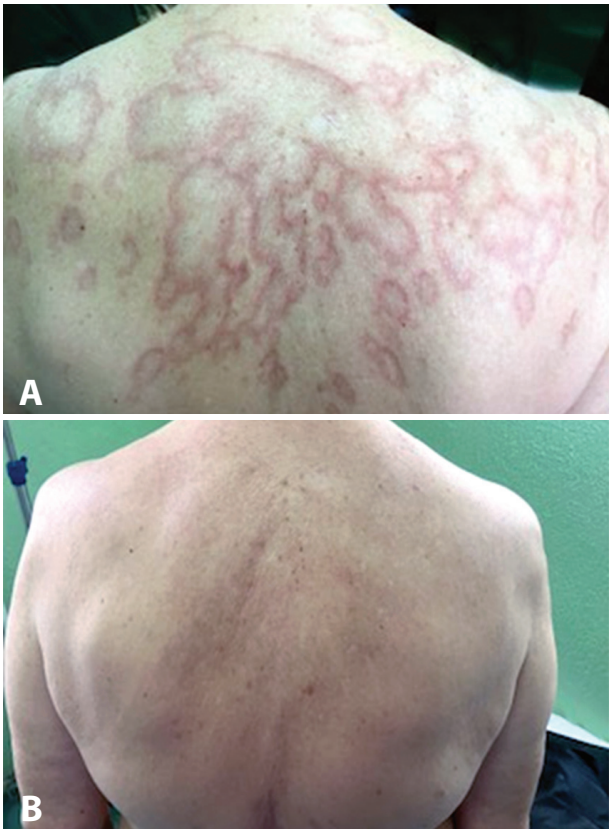
kova, dijametra do par centimetara, lako infiltrovanih ivica, simetrično raspoređenih na koži ramenog pojasa, gornjih ekstremiteta i gornje polovine leđa. Urađena je biopsija promena, patohistološki nalaz: u dermu prisutni granulomi okruženi histiocitima i limfocitima. Urađene su laboratorijske analize, kompletna krvna slika sa leukocitarnom formulom, biohemijske pretrage (hepatogram, lipidogram, glukoza, urea, kreatinin), rezultati su bili u granicama referentnih vrednosti. Test na HIV (Ag/At) bio je negativan. Skrining za oboljenja štitaste žlezde bio je u granicama referentnih vrednosti. Klinička i patohistološka korelacija je ukazala na diseminovani Granuloma annulare ***(Slike 1 i 2)****.*

Pacijent nije imao izražene subjektivne simptome i nije bio motivisan za lečenje sistemskom terapijom, te je započeta terapija sa visoko potentnim topikalnim kortikosteroidom, betametazonom 0,5 mg/g. Nakon dva meseca terapije po protokolu, terapijski efekat nije bio zadovoljavajući. Sledeća terapijska opcija bila je krioterapija na rubovima najizraženijih promena, jednom nedeljno, zatim fototerapija UVB; bez značajnih rezultata. Koristili smo Saalmann UVB lampu (270-350 nm), ukupno 24 tretmana su izvedena tokom perioda od 8 nedelja. Doziranje je prilagođeno u skladu sa fototipom pacijenta i lokalnim protokolom. Nakon godinu dana neuspešne terapije, uključen je lek dapson u dozi od 100 mg dnevno (nakon provere nivoa methemoglobina u krvi). Šest nedelja od početka terapije, dolazi do značajne regresije promena na koži. Klinički simptomi su se postepeno poboljšavali; nakon deset meseci prisutne su bile samo rezidualne hiperpigmentovane makule.

Diskusija

Granuloma annulare se smatra dermatozom benignog toka koja je obično i samoograničavajuća. Uzrok nastanka još uvek nije poznat, mada većina autora smatra da je u pitanju imunoreakcija sa mogućim delovanjem i na ćelijski imunitet i na imunokomplekse. Većina slučajeva GA se smatra idiopatskim. Međutim, objavljeno je i javljanje oboljenja nakon uboda insekta, fototerapije, traume, različitih infekcija i drugih različitih okidača. Pacijenti sa bolestima štitaste žlezde, dijabetesom melitus (posebno tipom 1), dislipidemijom i HIV-om imaju povećanu učes-



Slika 2. A. *Anularni eritemni plakovi sa nepravilnim ivicama na koži gornje polovine leđa.* ***B.*** *Rezidualne hiperpigmentovane makule nakon deset meseci terapije dapsonom.*

Figure 2. A. Annular erythematous plaques with irregular defined borders on upper back. **B.** Residual hyperpigmented macules after ten months therapy with Dapsone.

to be determined, though most authors consider it an immune reaction with possible action on both cell immunity and immune complexes. Most cases of GA are considered to be idiopathic. However, the appearance of the disease following insect bites, phototherapy, trauma, different infections, drug therapy, and other possible triggers has been reported. Patients with thyroid disease, diabetes mellitus (especially type 1), dyslipidemia, and HIV have an increased frequency of GA compared with the general population [2].

In their review of granulomatous cutaneous drug eruptions, Shah et al. identified a number of iatrogenic causes of GA, including allopurinol, amlodipine, anti-TNFα agents (infliximab, adalimumab, etanercept, and tha-

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talost GA u poređenju sa opštom populacijom [2]. U svom pregledu granulomatoznih kožnih erupcija lekova, Šah (Shah) sa saradnicima je identifikovao brojne jatrogene uzroke GA, uključujući alopurinol, amlodipin, anti-TNFa agense (infliksimab, adalimumab, etanercept i talidomid), botulinum toksin, dabrafenib, injekcije za desenzibilizaciju, inhibitore imunoloških kontrolnih tačaka, intranazalni imunitis, intranazalna infekcija B i vakcinacija protiv tetanusa), levetiracetam, paroksetin, pegilovani IFNa, sekukinumab, tocilizumab, topiramat i vemurafenib [3].

Najčešće forme GA su lokalizovani, generalizovani, supkutani i perforirajući GA. Varijante GA koje se smatraju atipičnim uključuju folikularni, pač (patch) tip, linearni i fibroelastolitički GA gigantskih ćelija. Prevalencija diseminovanog GA je oko 15% svih slučajeva, osim kod pacijenata zaraženih virusom humane imunodeficijencije; gde je diseminovani GA najčešća varijanta [4]. Bolest se češće javlja kod starijih osoba; 70% pacijenata je starije od 40 godina. Klinička manifestacija uključuje dva različita obrasca: anularne plakove do nekoliko centimetara u prečniku ili mnogobrojne papule koje mogu biti boje kože ili eritemolividne. Većina autora smatra da diseminovani GA traje duže i ima lošiji odgovor na terapiju u odnosu na lokalizovane varijante. Odluka o terapiji ovih pacijenata zavisi od proširenosti promena, prisustva ili odsustva svraba i psihičkog stanja pacijenta [5]. Predloženi su brojni tretmani za diseminovani GA, sa veoma promenljivim ishodima. To uključuje sistemsku i topikalnu primenu kortikosteroida, antimikrobne agense, hlorambucil sulfon, antimalarike, estre fumarične kiseline, fototerapiju, sistemske retinoide, kalijum jodid, tiroksin, dipiridamol, pentoksifilin, defibrotid, niacinamid, nikotinamid, topijski vitamin E, i odnedavno, topijske imunomodulatore, JAK inhibotore – tofacitinib i biološke lekove (adalimumab, etanercept, infliksimab, dupilumab). Što se tiče nivoa dokaza efikasnosti navedenih terapijskih opcija, samo fotodinamička terapija je u grupi B (nasumično kontrolisano ispitivanje manjeg kvaliteta ili prospektivna studija), dok druge terapije imaju nivo dokaza C (studija slučaj – kontrola ili retrospektivna studija) ili D (slučaj serije ili izveštaji o slučajevima) [6].

Iako većina autora smatra da je dapson moguća opcija terapije za diseminovani GA, objavljeno je malo slučajeva. Od objavljenih lidomide), botulinum toxin, dabrafenib, desensitization injections, immune checkpoint inhibitors, intranasal calcitonin, gold, immunizations (hepatitis B and anti-tetanus vaccination), levetiracetam, paroxetine, pegylated IFNα, secukinumab, tocilizumab, topiramate, and vemurafenib [3].

The most common forms of GA are localized, generalized, subcutaneous, and perforating GA. Varieties of GA considered atypical include follicular, patch-type, linear, and fibroelastolytic giant cell GA. Prevalence of disseminated GA is about 15% of all cases, except in patients infected with the human immunodeficiency virus; disseminated GA is the most common variant in these patients [4]. The mean age of onset is higher than for the localized variants; 70% of patients are over 40 years of age. Clinical manifestation includes two different patterns: annular plaques of several centimeters in diameter and many skin-colored or violaceous erythematous papules. Most authors consider that disseminated GA has a longer duration and it is less response to treatment than the localized variant. Whether or not to treat each patient should be essentially based on the extension of the disease, the presence or absence of pruritus, and the patient's psychological state [5]. Several treatments for disseminated GA have been proposed, with highly variable outcomes. These include systemic and topical corticosteroids, antimicrobial agents, chlorambucil sulfone, antimalarial drugs, fumaric acid esters, phototherapy, systemic retinoids, potassium iodide, thyroxin, dipyridamole, pentoxifylline, defibrotide, niacinamide, nicotinamide, topical vitamin E, and, more recently, topical immunomodulators, JAK inhibitors - tofacitinib and biological drugs (Adalimumab, Etanercept, Infliximab, Dupilumab). Regarding to level of evidence for efficacy of mentioned treatments, only photodynamic therapy is in group B (lesser quality randomized controlled trial or prospective study), while other therapies have level od evidence C (case-control study or retrospective study) or D (case series or case reports) [6].

While most authors consider dapsone a possible treatment option for disseminated GA, few series have been reported. Of the published cases with a good response to the drug, most showed improvement after 4 to 12 weeks. Residual macules and hyperpigmented marks

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slučajeva sa dobrom reakcijom na lek, većina je pokazala poboljšanje nakon četiri do 12 nedelja lečenja, a veliki procenat pacijenata nije dobio recidiv više meseci nakon prekida primene dapsona. Doza koju gotovo svi autori preporučuju je 100 mg dnevno. Pronašli smo malo slučajeva u literaturi gde diseminovani GA nije reagovao na dapson, a većina tih pacijenata takođe nije pokazala dobar odgovor i na druge primenjene terapijske opcije [7].

Takođe smo pronašli nekoliko slučajeva pacijenata kod kojih je dapson morao biti obustavljen zbog neželjenih efekata; ovi efekti uključivali su glavobolju i umor, ali i druge, ozbiljnije nuspojave kao što su agranulocitoza i aplastična anemija [8].

Dapson je sulfonski preparat koji se koristi u mnogim dermatološkim oboljenjima. Ima sposobnost da blokira sintezu dihidrofolične kiseline i to je ono što mu daje antibakterijska svojstva. Dodatno, on inhibira proizvodnju reaktivnih vrsta kiseonika, smanjuje uticaj eozinofilne peroksidaze na mast-ćelije i suprimira inflamatorne reakcije posredovane neutrofilima. Stoga se može koristiti za lečenje širokog spektra virusnih i inflamatornih bolesti kože [9]. Glavni neželjeni efekti dapsona uključuju hemolitičku anemiju i metemoglobinemiju. Laboratorijskim testovima pre uključivanja terapije treba isključiti bolesti krvi, srca, jetre i bubrega, trudnoću, kao i deficit glukoza-6-fosfat dehidrogenaze ili folne kiseline. U toku terapije potrebno je obavljati analize krvi i urina svake nedelje tokom prvog meseca, a kasnije na mesečnom nivou [5].

Zaključak

Prikazali smo pacijenta sa diseminovanom formom Granuloma annulare koji nije imao poboljšanje promena nakon nekoliko terapijskih opcija. Posle uvođenja leka dapson, dolazi do potpune regresije kožnih lezija. Takođe je i nekoliko meseci nakon završetka lečenja, pacijent bez aktivnih promena na koži. Iako ne možemo isključiti mogućnost da je do nestanka lezija došlo zbog prirodnog toka bolesti, jasno kliničko poboljšanje kože i pruritusa nakon početka lečenja navodi nas da smatramo da je lek uzrok remisije. Naše iskustvo nas je navelo da predložimo ovu opciju lečenja kao efikasnu alternativu.

following treatment with dapsone. of treatment, and a high percentage showed no recurrence months after suspension of dapsone .The dosage recommended by almost all authors is 100 mg daily. We found few cases in the literature of disseminated GA that did not respond to dapsone, and most of those cases also showed no response to other treatments [7].

We also found a few cases of patients in whom dapsone had to be suspended due to adverse effects; these effects included headache and fatigue and other, more severe side effects such as agranulocytis and aplastic anemia [8].

Dapsone is a sulfone with many dermatologic indications. Dapsone's ability to block the synthesis of dihydrofolic acid is what gives it its antibacterial properties. Additionally, it inhibits the production of reactive oxygen species, lowers the impact of eosinophil peroxidase on mast cells, and suppresses inflammatory reactions mediated by neutrophils. Thus, it can be used to treat a wide range of viral and inflammatory skin disorders [9]. The main side effects of dapsone include hemolytic anemia and methemoglobinemia. Blood dyscrasias, heart, liver, and kidney abnormalities, pregnancy, and glucose-6-phosphate dehydrogenase or folic acid deficit should be ruled out with laboratory tests before beginning treatment. During treatment, blood and urine tests should also be performed every week for the first month and every month after that [5].

Conclusion

We presented a case of a patient with disseminated GA who has failed several treatments and, after initiating Dapsone, showed complete resolution of cutaneous symptoms and remained free of the disease for several months after treatment was stopped. While we cannot rule out the possibility that the disappearance of the lesions was due to the natural course of the disease, the clear clinical improvement of the skin and the pruritus after instating treatment leads us to consider the drug as the cause of remission. Our experience led us to propose this treatment option as an effective alternative.

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