GROVER'S DISEASE IN A PATIENT WITH ATOPIC DERMATITIS – A CASE REPORT

GROVEROVA BOLEST KOD PACIJENTA SA ATOPIJSKIM DERMATITISOM – PRIKAZ SLUČAJA

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Summary
Introduction. Grover’s disease is characterized by pruriginous polymorphic rash with a variable course and duration. Although the etiology is still unknown, the disease is often associated with other dermatoses, malignant diseases, use of certain medications, as well as immunosuppression. Case Report. We report a case of a 70-year-old male patient who was referred for examination to the Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, due to a rash that lasted for nine months. The first lesions on the skin appeared around the nipples as exudative eczematous plaques. A few months later, identical lesions appeared on the lower legs. During treatment with systemic antihistamines and topical corticosteroids, there were episodes of transient improvements and re-exacerbations. In the meantime, erythematous brownish, round and oval papules appeared on the abdomen and the back, accompanied by intense itch. Laboratory findings revealed eosinophilia and elevated serum immunoglobulin E levels. A skin biopsy of the back lesion was performed and the histopathological examination confirmed the diagnosis of Grover’s disease. After the systemic treatment using corticosteroids and antihistamines, with gradual dose reduction and application of topical corticosteroids and emollients, complete regression of the skin lesions was achieved. Conclusion. Since the clinical manifestations of the disease may be nonspecific and discrete, dermatopathological analysis is of crucial importance in making the correct diagnosis. In patients with atopy, the treatment with systemic corticosteroids, antihistamines and topical agents may lead to regression of skin lesions with a significant improvement in the quality of life.

Key words: Dermatitis, Atopic; Acantholysis; Skin Diseases; Signs and Symptoms; Diagnosis; Morphological and Microscopic Findings; Glucocorticoids; Histamine Antagonists

Introduction
Grover’s disease is a benign dermatosis of unknown etiology with a variable duration. It is characterized by polymorphous papulovesicular rash followed by intense itch. The disease is predominantly seen in Caucasian middle-aged men. Although it may be self-limiting, in some cases treatment is necessary, with varying degrees of success, especially in patients suffering from other derma-

Sažetak
Uvod. Groverovu bolest karakteriše pojava polimorfne pruriginozne ospe različitog toka i dužine trajanja. Iako neznačajne etiologije, bolest može često biti udružena sa drugim dermatozama, malignitetima, primenom određenih lekova, kao i kod imunosuprimiranih bolesnika. Prikaz slučaja. Prikazujemo pacijenta starosti 70 godina koji se javio na pregled na Kliniku za kožno-venerične bolesti Kliničkog centra Vojvodine, zbog ospe koja je trajala devet meseci. Prve promene na koži javile su se u predelu oko mamila u vidu ekzematoidnih plakova sa vlaženjem. Nekoliko meseci kasnije javili su se identični plakovi i na potkolenicama. Tokom lečenja sistemskim antihistaminicima i lokalno kortikosteroidima, dolazilo je do prolaznog poboljšanja i ponovne egzacerbacije. U međuvremenu su se javile promene u vidu eritematozno-braonkastih okruglih i ovalnih papula na koži leđa i prednjeg trbušnog zida koje su bile praćene intenzivnim osjećajem svraba. Laboratorijski nalazi su pokazali prisustvo eozinofilije i povišenih vrednosti serumskih imunoglobulina E. Urađena je biopsija promene na koži leđa i histopatološkom analizom je potvrđena dijagnoza Groverove bolesti. Nakon sprovedene sistemskog terapije kortikosteroidima i antihistaminicima, sa postepenim snižavanjem doze, uz aplikaciju topikalnih kortikosteroida i emolijenasa, postignuta je potpuna regresija promena na koži. Zaključak. S obzirom na to da klinička manifestacija bolesti može biti nespecifična i diskretna, dermatopatološka analiza je od posebnog značaja u pravilnom postavljanju dijagnoze. Kod pacijenata sa atopijom, sprovođenje sistemskih terapije kortikosteroidima i antihistaminicima, uz primenu lokalne terapije, može dovesti do regresije kožnih promena uz značajno poboljšanje kvaliteta života. Ključne reči: atopijski dermatitis; akantoliza; kožne bolesti; znaci i simptomi; dijagnoza; morfološki i mikroskopski nalazi; kortikosteroidi; antihistaminici

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toses or in transplant and immunosuppressed patients [1–4].

The aim of this paper was to emphasize the importance of proper diagnosis of Grover’s disease, as well as to indicate the possibility of its association with atopy, which may lead to certain therapeutic challenges.

**Case Report**

We present a 70-year-old male patient who was referred for examination to the Clinic of Dermatovenerology Diseases, Clinical Center of Vojvodina, due to a pruriginous rash that lasted for nine months. The medical history data showed that the first skin lesions appeared on the chest bilaterally, and a few months later identical plaques appeared on the lower legs as well. During the treatment with systemic antihistamines and topical corticosteroids, there were episodes of transient improvement followed by exacerbations. After the skin lesions spread to the abdomen and the back, accompanied by intense itch, the patient was referred to our clinic. At the time of admission, the patient was afebrile, in a good general condition, with noticeable eczematous exudative plaques in the perimamillary region and on the lower legs, with erythematous-brownish round and oval papules on the skin of the abdomen and the back (Figures 1 and 2). Laboratory findings revealed eosinophilia (11.5%) and elevated serum immunoglobulin E levels, while the inflammatory and biochemical parameters were within the reference range. The mycological and microbiological analysis of the affected perimamillary skin was negative. Having revised previous histopathological biopsy findings of the perimamillary area, a nonspecific chronic dermatitis was described, while Paget’s disease was excluded. Due to inconclusive findings, another skin biopsy of the skin lesion on the back was performed. The dermatopathological analysis confirmed the diagnosis of Grover’s disease. There was an epidermis of uneven thickness with diffuse hyperkeratosis and focal parakeratosis, with irregularly elongated rete ridges. A perivascular patchy focally denser inflammatory infiltrate composed of lymphocytes and a smaller number of eosinophilic granulocytes was visible in the upper dermis. The infiltrate partially invaded the epidermis with focal acantholysis and spongiosis. Skin adnexa were reduced, atrophic in appearance, while sweat glands had proper features (Figure 3).
Figure 3. Grover’s disease: There are a few acantholytic cells surrounded by focal spongiosis. The infiltrate composed of lymphocytes and eosinophils is visible in the upper dermis.

The patient complained about skin dryness and itching. He presented with pruritic erythematous plaques on the eyelids, in cubital and popliteal regions, that indicated atopic dermatitis. A standard inhalant allergy test was done and sensitization to grass pollen was determined, which confirmed the atopic constitution in our patient. Considering long duration of skin lesions and unsatisfactory response to topical therapy, a systemic therapy with levocetirizine and methylprednisolone at a dose of 40 mg with gradual dose reduction was administered. Additionally, a fluocinolone acetonide ointment was used twice a day, as well as appropriate skin care with emollients. After finishing the treatment, a complete regression of skin lesions was achieved.

Discussion

The disease was first described in 1970 by Grover who reported about six patients with a nonspecific papulovesicular rash with histological features similar to Darier’s disease as well as Hailey-Hailey disease, but the clinical manifestations indicated a separate entity [5]. After that, Chalet gave a more detailed presentation of the clinical picture and potential four types of acantholysis: Darier-like, pemphigus-like, spongiotic and Hailey-Hailey-like, which has been confirmed in recent publications. Fernandez-Figueras et al. reported an extended description of the histological findings of this dermatosis. Based on the fact that Grover’s disease is histologically characterized by acantholysis, which is often associated with visible dyskeratosis and eczematous lesions as in our patient, these authors identified other possible histological patterns such as pokokeratotic, lentiginous, vesicular, lichenoid and dysmaturative. Moreover, they also pointed to the appearance of neutrophil granulocytes in dermal infiltrates, apart from lymphocytes and eosinophils. According to this study, a vascular degeneration in the form of endothelial tumefaction due to cytoplasmic edema and erythrocyte extravasation can often be found [6]. Other researchers showed that early histological lesions in Grover’s disease are represented by elongation of rete ridges, mild focal acantholysis and occurrence of eosinophils, which can be helpful in dermatopathological analysis of discrete nonspecific lesions if the clinical correlation is feasible [7].

The etiology is still unknown. Triggering factors such as increased sweating, heat and sun exposure were described, which would indicate that the disease has a seasonal character and occurs more often in summer, but according to other authors, Grover’s disease appears more frequently in winter months because of skin dryness and impaired epidermal integrity [1–4, 8]. A potential mechanism for the development of skin lesions could be damage to the epidermis by the toxic effects of sweat uric acid after occlusion of the gland ducts, although this has not been completely proven [1, 4]. Furthermore, Phillips et al. examined the autoimmune mechanism of Grover’s disease, but even this study did not provide a clear insight into the etiology of the disease [9].

Although it was originally regarded as a transient acantholytic dermatosis, a more appropriate term would be just Grover’s disease, on the account of the fact that it has a variable course and duration. Quirk and Heenan defined three variants of the disease: transient eruptive with a sudden onset of pruriginous rash that recedes within a few weeks; persistent pruritic with a slightly less pronounced itch than in the previous variant, but with a prolonged duration and poor response to the therapy; and a chronic asymptomatic with persistent papules on the trunk and in the submammary region mimicking folliculitis that cannot be histologically confirmed [10]. Skin lesions are typically polymorphous in the form of papulovesicles or smooth light erythematous or brownish papules, with crusts or keratotic surface, in nummular, herpetiform or zosteriform distribution or may confluent into plaques [4]. The skin lesions mainly affect the trunk and the back, upper extremities and thighs, but may also have an atypical extensive presentation especially in patients suffering from malignancy, during the course of oncologic treatment or in transplants [11–20]. Given that Grover’s disease has been shown to be associated with hematological or visceral malignancies, it is of the utmost importance to examine the patient in that direction as well [4].

From the dermatological point of view, in relation to Grover’s disease, folliculitis, miliaria, dermatitis herpetiformis, insect stings, herpes viral infections, benign familiar pemphigus (Hailey-Hailey disease), pemphigus foliaceus and pemphigus vulgaris, Darier’s disease as well as Galli-Galli disease should be considered in the differential diagnosis [1–4]. In accordance with the literature data reporting cases of coexistence of Grover’s disease and pemphigus foliaceus, as well as pityriasis rubra pilaris-like Grover’s disease, a thorough dermatopathological analysis is crucial in making an accurate diagnosis [21–23]. Furthermore,
recent literature data have revealed that Grover’s disease may occur in patients with COVID-19 disease, but it is still unknown what the exact role of a new coronavirus is in the etiology of Grover’s disease [24]. In our case report, it is of special significance to point to the possibility of association of Grover’s disease and atopic dermatitis, which is consistent with the literature data [25, 26]. Our patient had eosinophilia, elevated serum immunoglobulin E levels of 700 IU/ml and pruritic erythematous plaques on the eyelids, in cubital and popliteal region with a marked skin xerosis of the whole body. The standard allergy test to inhalant allergens confirmed the sensitization to grass pollen, and with all previously mentioned, it indicated an atopic constitution in our patient.

In patients suffering from both atopy and Grover’s disease, the treatment can be particularly challenging. Apart from avoidance of provoking factors and skin care with emollients, topical corticosteroids such as triamcinolone acetonide or fluticasone propionate applied twice daily, are recommended as first line therapy [27, 28]. In resistant cases, instead of topical corticosteroids, application of D vitamin analogues can be beneficial due to anti-inflammatory effects and impact on keratinization. Persistent forms may have a satisfying response to low doses of systemic retinoids or corticosteroids, regardless of the topical therapy. It has also been shown that phototherapy may be beneficial in cases with a severe clinical form. Novel studies highlight subcutaneous administration of etanercept, tumor necrosis-alpha blocker, in achieving a complete resolution while pointing at the same time to the potential mechanism of the disease, as well as a potential of photodynamic therapy with aminolevulinic acid in chronic cases. In addition to all of the above, the use of systemic antihistamines is highly recommended in order to relieve itching [28].

**Conclusion**

Grover’s disease is a relatively common skin disorder that is often unrecognized. Given that the clinical picture may be nonspecific and discrete, a dermatopathological analysis is of utmost importance in making the correct diagnosis and exclusion of other acantholytic dermatoses. Although of unknown etiology, Grover’s disease may often occur in patients with skin xerosis and atopic dermatitis, which may result in a prolonged treatment with systemic corticosteroids and antihistamines.

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