

# GROVER'S DISEASE – PERSISTENT ACANTHOLYTIC DERMATOSIS

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## Summary

*Grover's disease is a monomorphic papulovesicular rash, asymptomatic or pruriginous, occurring mostly in Caucasian males over the age of 40.*

*64 year old patient is admitted to the hospital for pruriginous eruption consisting of erythematous papules, some covered by vesicles, found on the mid chest and upper limbs. Based on the clinical aspect, histopathological examination and direct immunofluorescence, Grover's disease was diagnosed.*

*After receiving Acitretin 0,3 mg/kg/day treatment for 3 months, the patient's condition improved, no new skin lesions appeared and the old ones subsided.*

*Grover's disease remains a challenge both to the patient and the clinician because of its unpredictable evolution, varied response to treatment and, to this day, unknown etiopathogenesis, making a new therapeutic approach difficult.*

**Key-words:** Grover, pruriginous rash, acantholysis.

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## Introduction

Grover's disease also known as transient or persistent acantholytic dermatosis, is a monomorphic papulovesicular rash, asymptomatic or pruriginous, acquired[1]. It is mainly seen in Caucasian males over the age of 40. No correlations with genetic factors or infectious agents could be found therefore the etiology of the disease remains unknown; most authors associate the skin eruption and its exacerbation with sweating, excessive heat, xeroderma and other skin conditions (psoriasis, eczema) but also with nondermatological malignant conditions [2].

Its progression is unpredictable; it can manifest itself as a transient skin eruption, a persistent pruritus or a chronic asymptomatic form [3].

## Case Presentation

We are presenting the case of a 64 year old patient, from an urban area, who is admitted to the hospital for an itchy eruption consisting of erythematous papules, some covered by vesicles, some excoriated, found on the mid chest and upper limbs. The lesions first appeared 5 years ago namely a few pruriginous erythematous papules on the mid chest, which the patient did not get treated at the time. For about a year now, the rash has been growing larger, new lesions have appeared and the itching has intensified.

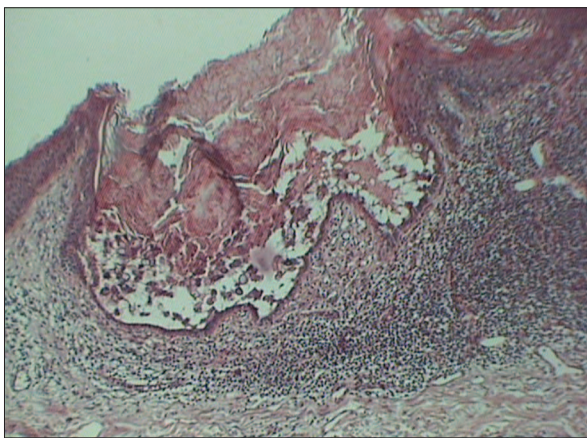
The patient's medical history reveals benign prostatic hyperplasia currently treated with Omnic 0.4 mg 1 tab./day and Uroflow 2 mg 2 tab./day, with no other significant pathology or family history, no history of neoplasms.

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*Fig. 1 and 2. Eruption consisting of erythematous papules, some with vesicular outline on the mid chest*



*Fig. 3. Darier-like pattern with suprabasal acantholysis and dyskeratotic cells; hyperkeratosis, acanthosis and parakeratosis in the epidermis and perivascular inflammatory infiltrate of lymphocytes in the dermis*

The physical examination performed on admission found a normoponderal patient, with a stable cardiorespiratory status, BP – 120/80 mmHg, oriented to time and place, otherwise clinically normal. The paraclinical tests were normal.

A skin lesion biopsy was done and histopathological examination and direct immunofluorescence (DIF) were performed. The

histopathology revealed a Darier-like pattern with suprabasal acantholysis and dyskeratotic cells; hyperkeratosis, acanthosis and parakeratosis in the epidermis and perivascular inflammatory infiltrate of lymphocytes in the dermis. DIF was negative.

Based on the clinical aspect, histopathological examination and direct immunofluorescence, Grover's disease was diagnosed. With no

associated systemic pathology, moderate-potency topical steroids treatment was decided; after about one month of therapy the symptoms had not subsided. Because the rash persisted despite the topical medication, systemic therapy was introduced: Prednisone 30 mg/day for 2 weeks, progressively reducing the dose in the course of a two-month period. UVA and UVB phototherapy was performed, twice a week for 4 weeks, with a slight improvement of the rash. After quitting the Prednisone therapy, there was a quick relapse and Acitretin 0.3 mg/kg/day therapy was instituted for 3 months, during which time no new skin lesions appeared and the pruritus subsided. Because of the persistent eruption and the risk of relapse, the patient remains under directly observed therapy at our clinic. About 3 months after quitting the treatment, the patient has no new skin lesions and the old ones have subsided.

## Discussions

Grover's disease or transient acantholytic dermatosis is a self-limiting skin condition, non-familial, non-immune-mediated, with the clinical appearance of a pruriginous papulovesicular rash. The disease was first described by Dr. Ralph Grover in 1970. Although the terms of Grover's disease and transient acantholytic dermatosis are interchangeable, the former is preferred because in most cases the disease is persistent and the acantholysis may be absent on the histopathology[4]. Grover's disease is thought to occur frequently; most cases are found in Caucasian males over the age of 40 and the sex ratio is 3:1 for men. Although the disease is usually self-limiting, its duration and progression are directly correlated with age. In other words, elderly patients are prone to extended and long-lasting rashes[5].

Although the pathogenesis of this skin condition remains unknown, many authors link it to excessive heat and sweating. One of the theories states that eccrine duct occlusion is the cause of the clinical manifestation of Grover's disease. In small patient lots, sunlight exposure was considered a precipitating factor in 26% of cases, whilst 23% reported heat, physical activity and sweat to be aggravating factors. That is also the case of our patient in whose rash appeared

during the warm season, after sunlight exposure. In spite of all this, attempts of reproducing the disease with artificial sunlight or ultraviolet radiation have proven unsuccessful[6]. In many case studies, the physical blockage of the ducts of sweat glands was attributed to prolonged bed rest. In a large patient lot, 21 % of patients with Grover's disease were bedbound. It was considered that the occlusion leads to the infiltration of the adjacent epidermis with the molecules found in sweat glands, causing acantholysis. In spite of this, immunohistochemical studies have proven the absence of molecules like carcinoembryonic antigen and/or epithelial mucins in the epidermis[7].

A series of desmosomal plaque protein modifications in the context of the acrosiringium's acantholysis and spongiosis have been found in Grover's disease, proving the involvement of the eccrine apparatus in the disease pathogenesis[8]. However, in Grover's disease, the palms and soles that are abundant in eccrine glands, are unscathed. Although an eccrine etiologic mechanism seems to be responsible for the clinical manifestations in some patients, the pathogenesis of the disease remains unsolved.

A connection between Grover's disease and malignant disorders has been found. It is most often associated with solid tumors, especially of the genitourinary tract but also with stomach, lung, prostate or kidney adenocarcinomas [9]. The skin condition was found in 6 % of patients with leukemia. However, there appears to be no direct connection, as there was no diskeratosis or leukemic infiltrate obstruction in the ducts of sweat glands. In the presented study case no underlying malignancy has been found but we would emphasize that the patient remains under directly observed therapy at our clinic. Grover's disease is often associated with other skin conditions such as eczema, especially seborrheic and asteatotic, psoriasis, actinic keratosis [10]. The only medications associated with the onset of Grover's disease have been sulfadoxine-pyrimethamine, an antimalarial and recombinant human Interleukin 4 (IL4)[11]. In the current case, the patient's only comorbidity was the prostate adenoma for which he was being treated with Tamsulosin and Tolterodine.

The clinical manifestation of the disease is a pruriginous eruption consisting of papules and vesicles, some with excoriations, found on the mid chest and upper limbs, proximal. There are three clinical forms of Grover's disease:

a) Transient skin eruption: few lesions, severe itching with sleep disruption, exacerbated by heat. This form subsides in a few weeks' time and responds well to treatment.

b) Persistent form: less severe itching but the lesions persist for months or even years, moderate treatment response.

c) Chronic asymptomatic form: characterized by persistent papules, typically in the submammary area, simulating folliculitis [12].

Our patient presented with the persistent form, with moderate pruritus, persistent and newly appearing lesions for several months.

The positive diagnosis of Grover's disease relies on the suggestive clinical appearance and on the histopathological examination. The acantholysis in Grover's disease can have different patterns, resembling Darier's disease, pemphigus vulgaris, pemphigus foliaceus, Hailey-Hailey disease and spongiotic dermatitis. These patterns can be singular or pathognomonically, combined. Deeper sectioning or multiple biopsies are frequently required to differentiate the different types of acantholysis. In the three largest studies with detailed histopathological tissue analysis of Grover's disease (n=523), the most frequent acantholysis pattern was the one found in pemphigus vulgaris (47%), followed by the one similar to that of Darier's disease (18%), spongiotic dermatitis (9%), pemphigus foliaceus (9%), combined (8%) and Hailey-Hailey disease (8%) [13].

The Darier pattern consists of suprabasal acantholysis and dyskeratotic and apoptotic cells dispersed in the entire epidermis, pattern that was also found in our patient's histopathological examination. In the Hailey-Hailey disease pattern, the acantholysis is suprabasal and involves the entire epidermis, with no significant dyskeratosis. In the pemphigus vulgaris model, suprabasal acantholysis is prevalent and the basal keratinocytes show the characteristic „row of tombstone“ appearance. The spongiotic pattern is characterized by intra-epidermal edema leading to separation of keratinocytes and

revealing the intercellular connections [14]. Perivascular lymphohistiocytic infiltrate can be found in the papillary dermis. Eosinophils have been identified in a quarter of biopsies positive for Grover's disease and are useful for differentiating Darier-like pattern in Grover's disease from Darier's disease in which they are usually absent [15].

Direct immunofluorescence is usually negative or nonspecific in Grover's disease. Still, there are authors that have reported positive DIF in this condition, but the aspect is inconsistent, with both intercellular and basal laminar IgG, IgM, C3 and even IgA deposits [16].

Because of its particular clinical appearance, Grover's disease is generally easy to diagnose. A rare condition in the clinical differential diagnosis is Galli-Galli disease, the acantholytic form of Dowling-Degos disease. Galli-Galli disease is found, the same as Grover's disease, mostly in male adults and is clinically characterized by slightly keratotic papules, of different colors, which are focally confluent in a reticulate pattern just like in Dowling-Degos disease. Another distinction between the two is that Galli-Galli disease can extend to a larger area, affecting the hands and feet. Skin biopsy helps the diagnosis because in Galli-Galli disease we observe the elongation of the epidermis crests and the absence of the different acantholysis types found in Grover's disease [17]. Another differential diagnosis is with acne, acute febrile neutrophilic dermatosis, bullous Impetigo, candidiasis, contact dermatitis, dermatitis herpetiformis, cutaneous drug reactions, folliculitis [18].

The treatment in Grover's disease is difficult to evaluate because in most cases the disease regresses spontaneously or fluctuates. Avoiding heat and excessive sweating and using emollients can be helpful. In cases of mild disease, moderately-potent topical steroids, calamine, menthol solutions can be used to reduce itching. Other reported topical medications are retinoids, lactic acid 12 %, urea 10 % topical cream, zinc oxide ointment [19].

Systemic therapy is recommended in cases of extensive eruption with intense pruritus and persistent despite correctly applied topical medication. Prednisone with an initial dose of 25 mg is efficient but relapse is frequent after

quitting the treatment. In many case reports in specialized literature systemic retinoids: etretinate, acitretin and isotretinoin have proven to be efficient [20]. Phototherapy, PUVA or narrow band UVB (311 nm) can be efficient in reducing symptoms. An exacerbation of the eruption can occur initially. It has been noted that after 10 phototherapy sessions, the itching is reduced and after 20 sessions the itching is gone [21].

## Conclusions

Although it is a frequent condition, the pathogenesis of Grover's disease remains unsolved. The dermatosis can have a long chronic progression with remission and relapse periods even when correctly treated. Because this

skin condition has been associated both with dermatologic and non-dermatologic conditions such as solid tumors or blood cancers, a careful patient assessment is advised.

The prognosis varies and is difficult to evaluate as it can be influenced by treatment response or by a possible coexistence with other benign and malignant conditions. Grover's disease remains a challenge both to the patient and the clinician because of its unpredictable evolution, varied response to treatment and, to this day, unknown etiopathogenesis, making a new therapeutic approach difficult.

We reported the case of a Caucasian male patient aged 64 with typical clinical appearance of Grover's disease, the persistent form, with no other coexisting conditions.

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Conflict of interest  
NONE DECLARED

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