

Grover Disease (Transient Acantholytic Dermatitis)

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• Grover disease, also known as transient acantholytic dermatosis, is a papulovesicular rash of the upper trunk, generally among older white males; it is usually pruritic but temporary. Grover disease is characterized by 4 different acantholytic histologic patterns, and it has been associated with numerous disorders, including hematologic malignancies. Follow-up and treatment are often difficult to evaluate secondary to the spontaneous remittance and occasional fluctuant course of the disease. Our objective will be to discuss the diagnostic considerations of Grover disease and focus on the postulated pathogenesis, including concurrent disorders and the role of the pathologist in examining skin biopsies of this nonhereditary vesicobullous disorder. Although recognized as a common condition, Grover disease's pathogenesis still remains unknown. Because Grover disease has been associated frequently with other dermatologic and nondermatologic skin conditions, inspection for other pathologic processes within the skin biopsy is essential to rule out other concomitant disorders, including hematopoietic malignancies.

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Transient acantholytic dermatosis is a self-limited, primary, nonfamilial, non-immune-mediated acantholytic skin disorder that manifests as pruritic, discrete, edematous papules and/or a vesiculopapular rash and is more commonly referred to as Grover disease, after Dr Ralph Grover, who first reported the condition in 1970.¹ Although the diagnostic terms *Grover disease* and *transient acantholytic dermatosis* can be used interchangeably, here we will use the more clinical conventional and widely recognizable term *Grover disease*. Grover disease may also be the more appropriate terminology, because it is most likely a condition/syndrome caused by various etiologies resulting in the same clinical manifestations. In addition, the term *transient acantholytic dermatosis* is misleading, considering Grover disease can, in fact, be persistent and show morphologies other than acantholysis.

After the original description of Grover disease, Grover and Rosenbaum² discovered a clinically significant association between Grover disease and other dermatitides. Cancer, including acute leukemia, was soon linked with Grover disease.³ Here, we will discuss the clinical and histopathologic features of Grover disease. Subsequently, we will discuss the diagnostic considerations, focusing on the postulated pathogenesis and the role of the pathologist in searching for concurrent dermatologic and nondermatologic disorders within skin biopsies.

CLINICAL FEATURES

The prototypic presentation of Grover disease consists of a self-limited papulovesicular rash on the upper trunk of an older white male (Figure 1). The rash begins as a sudden onset of small papules and fragile vesicles, which can quickly form crusts and keratotic erosions. The 4 largest clinical and clinicopathologic case series published in the English literature have been combined (n = 509) here, where possible, to hopefully provide a more accurate and true reflection of the natural history and demographic data of Grover disease.⁴⁻⁷ The frequency of Grover disease diagnosed between 2 institutions was 0.1%.^{6,7} Grover disease has a male predilection (male to female ratio of 2.4:1) and a mean age at diagnosis of 61.0 years,⁴⁻⁷ but the disorder can be found throughout a wide age range (22–100 years).⁶ The characteristic distribution of the lesions has them most commonly located along the trunk and proximal extremities (99% and 35%, respectively).^{5,7} Some patients are asymptomatic, but most present with pruritis. As mentioned previously, although the alternative term *transient acantholytic dermatosis* is synonymous with Grover disease, the duration of disease may actually extend for many months, and reports of chronic relapsing disease are not an uncommon occurrence. Therefore, some authors have proposed a more accurate term, *persistent and recurrent acantholytic dermatosis*.⁸ The transient and chronic relapsing nature of Grover disease may cause delay in the diagnosis, because the papulovesicular rash may resolve prior to a scheduled dermatologic appointment. In one of the retrospective cohort studies where follow-up was most thorough, 46% of cases recurred, 43% resolved, and 11% persisted.⁵ The average length of duration has reportedly varied from 2 to 4 weeks.^{4,7}

The itching and papulovesicular rash are frequently exacerbated by heat, sweating, ultraviolet light exposure, and hospitalization. The seasonal association of Grover disease is more controversial. An association with the winter months has been found by some authors^{4,6} but not identified by others.⁷ Most series have noted the connection with hospitalization or bedridden patients.^{4,5,7} Again, the

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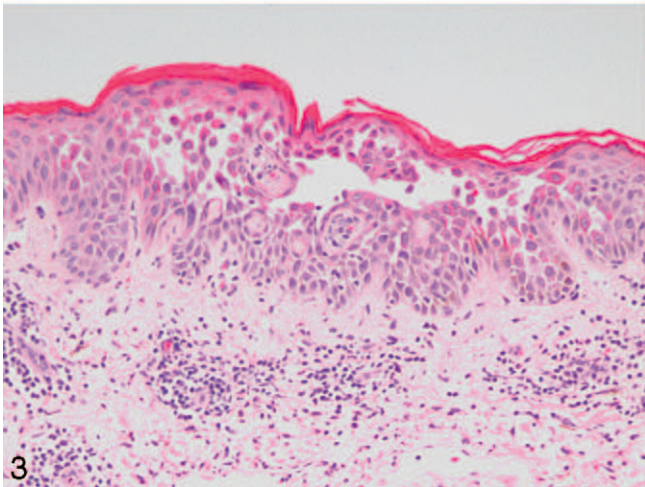
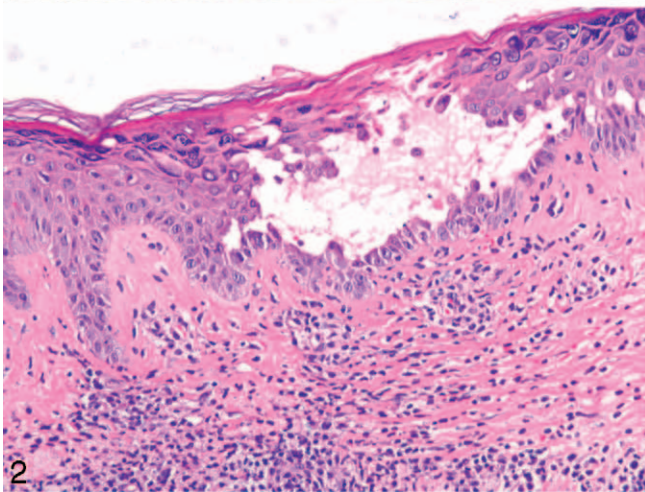


Figure 1. Pruritic erythematous rash consisting of patches, papules, and plaques across the patient's upper chest (hematoxylin-eosin, original magnification $\times 20$).

Figure 2. Darier-like pattern consists of suprabasal acantholysis of keratinocytes with scattered dyskeratotic cells within various levels of the epidermis (hematoxylin-eosin, original magnification $\times 20$).

Figure 3. Hailey-Hailey-like pattern of nondyskeratotic subbasal acantholysis throughout the entire epidermis (hematoxylin-eosin, original magnification $\times 20$).

self-limited, recurrent nature of Grover disease may explain the higher incidence of detection in hospitalized patients compared with the general population. Although most studies report no association with certain drugs,^{4,5} rare case reports have implicated interleukin 4 and D-penicillamine in precipitating Grover disease.^{9,10} Further discussion of exacerbating factors of Grover disease regarding the pathogenesis comes later.

Grover disease has been found to coexist with numerous other dermatoses in 11% of cases⁵; these include asteatotic eczema, allergic contact dermatitis, atopic dermatitis, irritant contact dermatitis, and psoriasis.^{2,11} Also found to be associated with Grover disease are malignant disorders, including skin cancer and hematologic malignancies, the latter occurring in 8% of cases.⁵ Desch and Smoller³ noted a similar association between intraepidermal blistering disorders, including Grover disease, in 6% of patients with acute myelogenous leukemia. The following discussion of the potential pathogenesis of Grover disease will continue to examine these associations.

HISTOPATHOLOGY

Histologically, the acantholysis seen in Grover disease occurs in a variety of different patterns in small, circumscribed foci resembling Darier-White disease, pemphigus vulgaris, pemphigus foliaceus, Hailey-Hailey disease, and a spongiotic dermatitis. These patterns may occur singly, or pathognomically in combination. Often, deeper sections are required to appreciate the different patterns of acantholysis, or multiple biopsies are needed to obtain the various diagnostic acantholytic patterns. When the 3 largest studies with detailed histopathologic analyses of all of their cases of Grover disease are combined ($n = 523$), the most common pattern of acantholysis is a pemphigus vulgaris-like pattern (47%), followed by (in decreasing order of frequency) Darier-like (18%), spongiotic (9%), pemphigus foliaceus-like (9%), mixed (9%), and Hailey-Hailey-like (8%) patterns.⁴⁻⁶

The Darier-like pattern consists of suprabasal acantholysis of keratinocytes with scattered apoptotic or dyskeratotic cells within various levels of the epidermis (Figure 2). The Hailey-Hailey-like pattern consists of subbasal acantholysis of all levels of the epidermis without significant dyskeratosis—the so-called dilapidated brick wall appearance (Figure 3). The pemphigus vulgaris-like pattern appears as predominantly and limited to suprabasal acantholysis, with the basal keratinocytes remaining attached to the basement membrane forming the characteristic tombstone appearance (Figure 4). And, finally, as one might expect, the spongiotic-like pattern displays edema within the epidermis, with resulting separation of the keratinocytes and the revelation of their intracellular bridges (Figure 5).

There also tends to be a superficial, perivascular, lymphohistiocytic infiltrate in the superficial dermis. Eosinophils have been identified in nearly one quarter of biopsies of Grover disease,⁵ which has been found by some authors to be useful in distinguishing between predominant Darier-like pattern of Grover disease and Darier disease, in which they are usually absent.¹²

Direct immunofluorescence has been negative or non-specific in most cases of Grover disease.^{4,5} However, some authors have reported positive direct immunofluorescence in Grover disease, but these patterns have varied and have been inconsistent, including both intercellular and base-

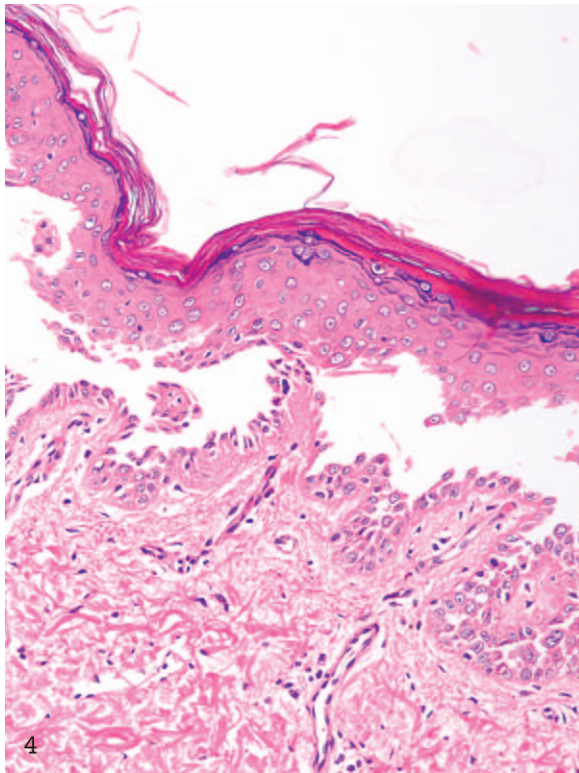


Figure 4. *Pemphigus vulgaris*-like pattern of suprabasal acantholysis with tombstoning of suprabasal keratinocytes (hematoxylin-eosin, original magnification $\times 20$).

ment membrane involvement of granular immunoglobulin (Ig) G, IgM, C3, and even IgA.^{13,14} These results may suggest different etiologies of Grover disease, but to date no one has associated the unique direct immunofluorescence findings with described clinical subgroups of Grover disease,¹⁵ nor has anyone correlated the direct immunofluorescence findings with the various histologic patterns identified in Grover disease.

Because Grover disease has been associated with so many inflammatory and neoplastic conditions, it is important to examine each biopsy for additional diagnoses, especially concurrent hematologic malignancies, including leukemias, which may alert clinicians of progressing disease.

PATHOGENESIS

Etiologic Role of the Eccrine Apparatus

It has been postulated that occlusion of damaged eccrine ducts is the cause of the manifestations of Grover disease. This theory has arisen because of the constant association of Grover disease in most case reports and small series with sun exposure, heat, and sweating. Sunlight was reported as an exacerbating factor in 26% of cases, whereas 23% stated that heat, exercise, and sweating exacerbated their condition.⁵ However, attempts to reproduce Grover disease with sunlight or artificial ultraviolet light have been unsuccessful,¹⁶ and the disease has actually been found to occur more commonly in the winter season.⁶

Physical occlusion of sweat ducts has been anecdotally attributed to bed confinement in many case studies. In a large series, bed confinement was found in 21% of patients with Grover disease.⁵ It has been hypothesized that the

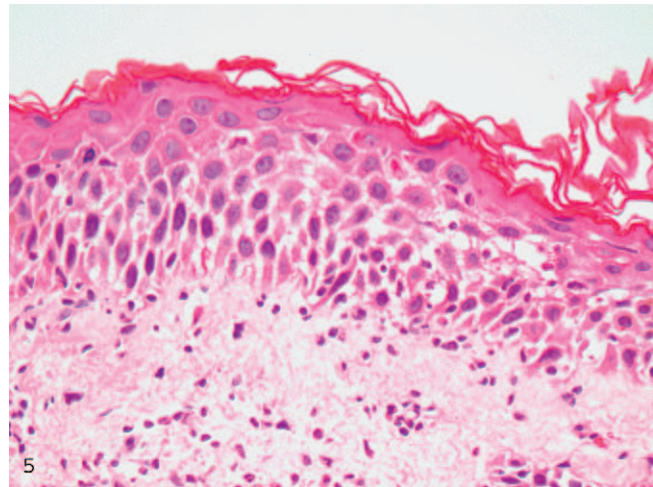


Figure 5. *Spongiotic-like pattern with epidermal edema separating keratinocytes displaying their desmosomal attachments (hematoxylin-eosin, original magnification $\times 40$).*

occlusion leads to “internal sweating” or seepage of molecules in sweat into the adjacent epidermis, leading to acantholysis; however, no evidence of leakage of sweat molecules, such as carcinoembryonic antigen and/or epithelial mucins, by immunohistochemistry has been shown.¹⁷ In addition, no histologic or immunohistochemical evidence of a relationship between the acantholytic areas and the eccrine apparatus has been identified.^{5,18}

Altered desmosomal plaque proteins within the acantholysis or spongiosis in the acrosyringium has been recognized in Grover disease, further supporting an eccrine contribution.¹⁹ A syringomatous, hyperplastic, reactive proliferation has been described in Grover disease; conversely, these changes can occur in other non-eccrine-related inflammatory skin conditions, and most cases of Grover disease do not show evidence of this phenomenon.²⁰ Peculiarly, Grover disease spares the palms and soles, which have a high concentration of eccrine glands. Although an etiologic eccrine mechanism appears responsible for the manifestations of Grover disease in a subgroup of patients, the pathogenesis of Grover disease remains elusive.

Etiologic Role of Myeloid Sarcoma

Grover disease was identified in 6% of patients with leukemia,³ compared with an incidence of 0.8% in the hospital setting⁷—evidence supporting a relationship. However, the affiliation appears not to be direct, because of the lack of evidence of direct dyskeratosis or occlusion of sweat ducts by the leukemic infiltrates. An indirect association can be postulated because of the possibility that the chemotherapy used to treat leukemia can be excreted in sweat and could accumulate in the epidermis, causing epidermal toxicity.¹⁵ Otherwise, an association including a paraneoplastic phenomenon appears unlikely, because of the fact that most cases of Grover disease are not associated with malignancies.

The relationship may be a coincidence caused by a selection bias—patients getting medical attention are more likely to have more than one disease.⁵ Finally, the inflammatory oncotaxis phenomenon, which is defined as the homing of malignant cells to abnormal skin, has been proposed as an explanation for the increased incidence of he-

matopoietic malignancies in patients with Grover disease.²¹ Either way, although both dermatologic and non-dermatologic concurrent conditions, including myeloid sarcoma, are associated with Grover disease, neither appear to play a primary role in the pathogenesis of the disease process.

Etiologic Role of the Immune System

Various acantholytic patterns, including focal acantholytic dyskeratosis and Hailey-Hailey-like acantholysis, can occur as incidental histologic findings in skin biopsies taken for other diagnostic purposes,^{22–25} and even in solitary tumors.^{26,27} It has been hypothesized that these incidental histologic findings found adjacent to other skin tumors may harbor random acquired mutations, from the so-called field cancerization effect,²² identical to the mutations found in their respective genodermatosis (ie, *ATP2A2* gene mutations encoding a calcium ion pump in Darier disease).²⁸ In addition to the clinical presentation and associated inflammatory infiltrate, these incidental histologic findings and solitary tumors are identical on hematoxylin-eosin microscopy to the Darier-like pattern and Hailey-Hailey-like patterns of acantholysis seen in Grover disease. Although similar mutations have not been identified in Grover disease,²⁹ this does not negate the possibility that Grover disease may represent a host inflammatory response to disseminated lesions described previously that contain altered antigens from aberrant molecular alterations that the immune system now recognizes as foreign.

In conclusion, a single definitive pathogenesis of Grover disease still remains unknown. This conclusion only further supports the fact that Grover disease may still best be considered a syndrome rather than a distinct entity and that the multiple etiologies likely result in the similar clinical pictures that we recognize as Grover disease.

DIFFERENTIAL DIAGNOSIS

Rarely does Grover disease present a clinical diagnostic difficulty, because of its characteristic classic clinical signs and symptoms described previously. A rare entity in the clinical differential includes Galli-Galli disease, which is an acantholytic variant of Dowling-Degos disease. Galli-Galli presents similarly to Grover disease in predominantly adult males as small, slightly keratotic, variably colored papules; however, focally, a reticulated pattern, as seen in Dowling-Degos disease, should be appreciated.⁸ Also differing from Grover disease is the distribution of disease—Galli-Galli can affect a larger portion of the body, including the hands, groin, and lower extremities. Skin biopsy can help distinguish these 2 entities, because Galli-Galli disease shows similar elongation and interdigitating downgrowths of the rete ridges found in Dowling-Degos disease, and absence of the various acantholytic patterns seen in Grover disease.

The histologic differential diagnosis of Grover disease is broader, because it typically displays various proportions of various intraepidermal acantholytic patterns. Therefore, Grover disease must be distinguished morphologically from Darier disease, pemphigus vulgaris, pemphigus foliaceus, benign familial pemphigus (Hailey-Hailey disease), and various spongiotic dermatoses. Although rare, finding more than one of the above acantholytic patterns in a single skin biopsy would favor the diagnosis of Grover disease. More commonly, multiple

skin biopsies are required to document the diagnostic various acantholytic patterns. Additionally, the various acantholytic patterns are typically only focally found within the skin biopsies of Grover disease, whereas a diffuse involvement of the biopsy specimen would favor the other diseases in the differential. Specifically, Darier disease usually lacks an eosinophilic infiltrate, and pemphigus vulgaris and foliaceus display the characteristic IgG and C3 expression on direct immunofluorescence in a fishnet pattern between individual keratinocytes.

CURRENT TREATMENT AND PROGNOSIS

Follow-up and treatment are often difficult to evaluate secondary to the spontaneous remittance and occasional, fluctuant course of the disease. However, about half of the patients with Grover disease respond to topical corticosteroids. Systemic steroids have induced sustained remission. Additionally, acitretin and phototherapy have been shown to reduce associated symptoms.³⁰ Avoidance of exacerbating factors, such as heat, sweating, and sunlight, results in improvement of the clinical signs and symptoms. Follow-up of 28 patients with Grover disease at the Mayo Clinic demonstrated that 43% resolved, only 11% had persistent disease, and the remaining patients recurred.⁵

CONCLUSIONS

Although recognized as a common condition, Grover disease's pathogenesis still remains unknown. A strong relationship with exercise, heat, sunlight, and bed confinement places the eccrine apparatus as a primary suspect. Because Grover disease has frequently been associated with other dermatologic and nondermatologic skin conditions, inspection for other pathologic processes within the skin biopsy of Grover disease is essential to rule out other concomitant disorders, including hematopoietic malignancies.

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