Grover's disease

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Mild cases of Grover's disease (acantholytic dermatosis) do not need to be treated. If symptomatic, potent topical corticosteroids are usually effective but simple measures such as reducing overheating and sweating, using simple moisturisers, having short showers and avoiding soap will help.

Case presentation

A 73-year-old man presented with a pruritic papular mildly scaly red rash on his trunk, particularly his back and chest (Figures 1a to c). This had developed six months earlier and had fluctuated in severity since but overall had slowly worsened.

Initially the patient was diagnosed by his family GP with folliculitis and treated with cephalexin capsules with no improvement. Subsequently he was given betamethasone 0.02% cream daily for a week, which helped but did not settle the rash. He had previously worked in an office but was a keen sportsperson and had significant sun damage as a result. He had no personal or family history of atopy and was taking no new medications. His history suggested no allergic causes.

The patient had hypertension and hypercholesterolaemia, both of which were well controlled with irbesartan and fluvastatin tablets. Three years prior to the presentation he had a partial colectomy for a Dukes A level colon cancer.

Diagnosis

The diagnosis was Grover's disease (acantholytic dermatosis).

Differential diagnoses

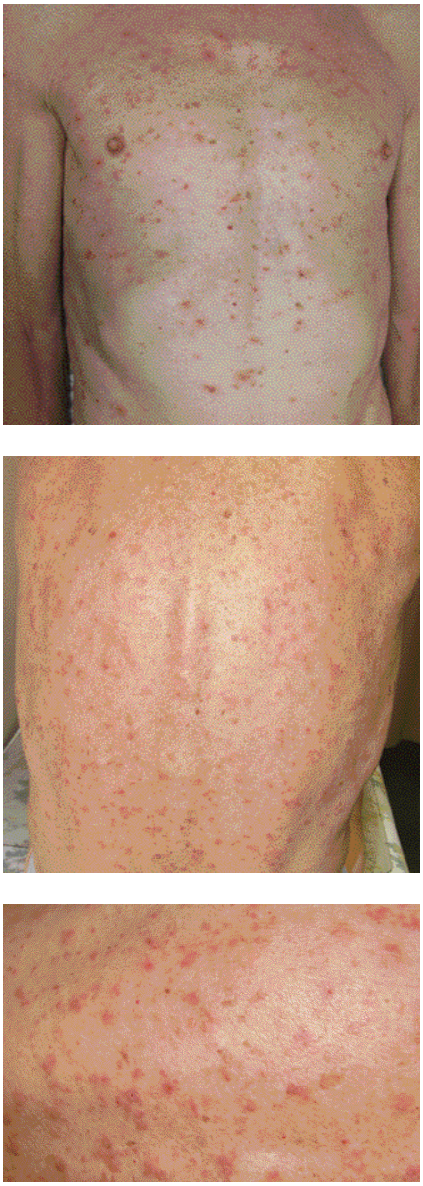
Late-onset dermatitis

Dermatitis (eczema) can be papular, although there are usually also areas of more typical red, lightly scaly plaques with an indistinct (smudgy) border with more normal skin. In Grover's disease, the papules are more discrete, often with a mild to moderate sandpaper-like roughness. Biopsies may be required to distinguish the two entities.

There are many possible causes of dermatitis, which can be endogenous (including atopic dermatitis) or exogenous (including irritant or allergic contact dermatitis). Atopic dermatitis is most often seen in children or young adults but can occur at any age and is quite common even later in life. The patient described had no past or family history of atopy and no history suggesting an allergic precipitant. It is also quite common for dermatitis of an unknown cause to occur in older people. Occasionally, dermatitis is drug-induced (there are many potential culprits but it is a rare event for any one drug).

Miliaria rubra

Miliaria rubra can closely resemble Grover's disease, and heat and sweating may also play a role in this disease. Miliaria rubra is due to occlusion of the eccrine duct and is seen most often in febrile bedridden patients, particularly if they are laying on occlusive plastic-lined mattresses with insufficient absorptive material to soak up their sweat. The sweat probably swells the skin enough to block the epidermal component of the acrosyringeal duct leading to rupture of the duct and inflammatory miliaria. It therefore occurs on the occluded areas, usually the back.



Figures 1a to c. A 73-year-old man with a six-month history of an itchy papular rash mainly on his chest (a, top) and back (b, middle and c, bottom).

Folliculitis

With folliculitis there are pustules as well as red papules. There are occasional reports of Grover's disease being pustular. Folliculitis is common on the trunk and in patients of most ages. It is mostly caused by bacteria, usually *Staphylococcus aureus*, but occasionally can be caused by fungi or yeasts, usually *Malassezia* species.

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Insect bite reactions

Insect bite reactions can cause smooth red swellings. The individual lesions are usually larger than the small papules of Grover's disease and are more scattered. Various insects may be the cause – for example, mosquitoes, fleas, bed bugs, and *Cheyletiella* and bird mites. Identifying the source of the biting insect can be a challenge.

Scabies can also resemble Grover's disease,[1] but usually the distinction between the two conditions is easy. Scabies particularly affects the distal limbs and genitals and is sometimes widespread. Visible burrows, vesicles and excoriations are often present in affected individuals, and other close contacts may be itchy. It is confirmed by finding the Sarcoptes scabiei mites on a potassium hydroxide preparation of a skin scraping from the burrows.

Papular drug eruptions

Papular drug eruptions are common and resemble morbilliform viral eruptions such as rubella. They are not (mainly) restricted to the trunk, the papules tend to coalesce into small plaques and there is usually a clear relation to the intake of the causative drug.

Papular pityriasis rosea

Papular pityriasis rosea is a less common variant of the relatively common pityriasis rosea. Similar to the commonly seen form, the papules are mainly on the trunk and proximal limbs, they may be preceded by a larger herald patch and the rash settles within 10 weeks. The papular form is more commonly seen in children. Itch is either absent or less severe than in those with Grover's disease.

Darier-White disease

Darier-White disease (keratosis follicularis) is a rare inherited disorder of keratinisation, that shares some clinical features of Grover's disease. Its histopathology is also very similar to that of Grover's disease. The rash usually appears in teenagers and consists of a more confluent papular red, somewhat greasy-scaly rash with a rough sand-papery feel. It particularly affects the upper trunk but less severely also the face, scalp and flexures. There are also more subtle palmar pits and keratoses and characteristic nail changes, including white-red longitudinal streaks and subungual keratoses.

Various neurological problems have been linked to Darier-White disease but it appears these are chance associations. Darier-White disease is an autosomal dominant genodermatosis due to mutations in the *ATP2A2* gene, which encodes the calcium pump protein sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase isoform 2 (*SERCA2*). The reason that these mutant proteins cause the skin disease is unclear. These mutations are not found in patients with Grover's disease.[2]

Secondary syphilis

Secondary syphilis appears three weeks to three months after the primary lesions (up to 25% still have a healing chancre), typically with a pale red to pink macular rash and later becoming a coppery red coloured papular rash. Later there is a tendency for necrosis or sometimes psoriasiform thickening to occur. The papular rash is more widespread than that in Grover's disease and typically involves the palms and soles and is minimally itchy.

Comment

Ralph Grover is an American dermatologist who described it in 1970. He termed it 'transient acantholytic dermatosis', but subsequently it has been recognised to vary from transient to quite persistent, in some cases lasting many years. It usually appears suddenly but often fluctuates in severity. In most people it is itchy, consisting of many small- to medium-sized, mild to moderately scaly red papules. It varies from mild and asymptomatic to substantial with debilitating itch. It mostly affects the trunk, particularly the mid- to upper part, and can extend onto the neck and sometimes the proximal limbs. It usually spares the scalp, palms and soles. The level of pruritus may be well out of proportion to the number of papules seen. Three main presentations have been described, which are outlined below.[3]

- Transient eruptive, lasting a few weeks with a sudden onset of itch and few to many papules. The itch may be out of proportion to the number of papules, may disturb sleep and is usually aggravated by heat. Therapy speeds recovery.
- Persistent pruritic, lasting months to years (reported mean duration of 11 months to 6.9 years). The itch is less severe than the transient form. Therapy is less reliably effective.
- Chronic asymptomatic, occurring mostly in men, with the papules located especially on the lower chest and upper abdomen. Clinically, it resembles low-grade chronic folliculitis (usually without pustules).

Grover's disease is not an uncommon problem but there are no good epidemiological studies. It more commonly occurs in men older than 40 years (male to female ratio 3:1). It is more likely to be persistent in elderly patients. Uncommon clinical variants include vesicular, bullous, pustular, acneiform and, rarely, zosteriform (unilateral) cases. Oral involvement has also been described but is rare.

Although the cause of Grover's disease is not known, it seems to be more common in men with sun damaged skin. Some cases of the transient form arise soon after a single sunburn. One of Ralph Grover's original six cases occurred after a sunlamp burn. The disease has also been reported to be a consequence of ionising radiation.[4] It can occur as a result of heat or sweating, including in patients who are bedridden (similar to miliaria rubra as described above but this condition does not appear to be related to acantholysis of the epidermal part of the eccrine duct).[5,6]

Grover's disease may be more common in atopic individuals and is related to

xerosis of the skin.[7] A retrospective study of a large US database of skin biopsies found that Grover's disease was diagnosed three times more frequently in the winter than in summer, suggesting that winter-time dry skin was a significant factor in causing the disease.[8]

There have also been some unconvincing reports of drug-induced Grover's disease (e.g. sulfadoxine pyrimethamine, ribavirin, cetuximab and recombinant human interleukin-4). In addition, there have been a small number of reports of Grover's disease occurring in people on renal dialysis.[9] One study reported on a series of oncology patients with Grover's disease but the author concluded that Grover's disease was not due to the malignancies themselves.[10] It has been suggested by another author that a subset of patients develop Grover's disease as a result of mercury toxicity, usually from a high seafood diet, and that a low seafood diet or mercury chelation therapy clears this form;[11,12] however, this issue has not been further investigated.

If there is doubt about the diagnosis, histopathology of a simple 3 mm punch biopsy is quite helpful in ruling out other conditions. Loss of cohesion between keratinocytes (acantholysis) causing clefts and vesicles is a characteristic feature of Grover's disease. The degree of acantholysis varies widely in biopsy specimens and multiple levels may be needed to see it. Dyskeratosis also occurs. Grover's disease has a number of histological patterns that resemble other skin conditions, most commonly Darier-White disease. It can also sometimes resemble other dermatoses, including dermatitis, although acantholysis and dyskeratosis remain as features.[13,14]

Treatment

Mild cases of Grover's disease do not need to be treated. If patients are symptomatic, simple measures such as avoiding overheating and sweating, treating dry skin with a simple moisturiser, having short showers and avoiding soap will help.

If needed, Grover's disease will most often respond to daily or twice daily applications of mid-potency to potent topical corticosteroids such as betamethasone valerate 0.02%, triamcinolone acetonide 0.02%, methylprednisolone aceponate 0.1% or mometasone furoate 0.1%. These should be applied until the papules clear, and then used as needed for recurrences. Cream formulations may be sufficient; however, the ointments are more effective but more messy. If there is coexisting chronic folliculitis, the ointment may aggravate this by its occlusive effects. Calcipotriol cream applied twice daily to the affected areas may also be effective in treating Grover's disease.[15] Additional benefit may be seen by using calcipotriol plus betamethasone valerate ointment. (The ointment form of purely calcipotriol has recently been discontinued by the Australian supplier.) Antihistamine tablets may help reduce the itch and sedating ones will aid sleeping. The dose may have to be higher to maximise effect. For more severe cases, prednisolone 25 mg a day, reducing the dose over 7 to 14 days, will provide good but often only temporary relief.

In more severe and persistent cases, the vitamin A analogue acitretin at a low dose of 10 to 20 mg per day seems to work well.[16] Isotretinoin, a close relative of acitretin, at a dose of 10 to 40 mg a day also seems to work well.[17] However, there have been no properly controlled trials in use of these drugs in Grover's disease. Both of these retinoids can only be prescribed by dermatologists. They are usually used for a month or two and then withdrawn. They can, however, be used for a prolonged time in persistent cases if other treatments are contraindicated or ineffective. Retinoids have a range of side effects, particularly cheilitis, dry skin, retinoid dermatitis and mild skin fragility, but also epistaxis, dry eyes, mood changes, hyperlipidaemia and hepatitis. Pregnancy is strictly contraindicated in women taking these medications, but men can safely father a child while taking these drugs.

Although ultraviolet damage seems to be an aetiological factor in Grover's disease, it can also be a useful therapy, probably because of its anti-inflammatory effect. Most often narrow band ultraviolet B (NB-UVB) phototherapy is used, which is given three times a week in a gradually increasing dose regimen until the rash clears (usually in one to two months). UVA phototherapy with additional psoralen (PUVA) can also be used,[18] but in practice NB-UVB has supplanted its use. Sunburn, skin cancer and photoageing are the main side effects. Retinoids can be used safely with phototherapy and probably enhance its effectiveness. If Grover's disease tends to recur when phototherapy is stopped, retinoids can be continued to maintain control.

Anecdotally, some dermatologists report successful treatment of Grover's disease with oral tetracycline antibiotics and oral azole antifungal agents such as ketoconazole or itraconazole. Unfortunately, there is no published evidence to support the use of these agents. In some cases their effectiveness may be due to the additional presence of bacterial or *Malassezia* folliculitis for which these agents are known to be effective.

Conclusion

Grover's disease is a papular red rash that is not uncommon, sometimes quite itchy, occurring mainly on the trunk and more often in older men. It may be short-lived or persistent. Its cause is poorly understood but chronic sun damage may be a factor. If patients are symptomatic, the disease can usually be suppressed with mid- to more potent topical corticosteroids. Topical calcipotriol, oral retinoids and UVB phototherapy may be needed for more recalcitrant cases. MT

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

Medicine Today 2010; 11(5): 69-71

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