

## BRIEF ARTICLE

## Recalcitrant Grover's Disease Successfully Managed with Dupilumab and Naltrexone in a Middle-Aged Woman: A Case Study

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### ABSTRACT

**Introduction:** Grover's disease, or transient acantholytic dermatosis, is a common benign papulovesicular disorder that often affects elderly men. It is typically managed with topical therapeutics in this population. We present here an uncommon case of Grover's disease, occurring in a relatively younger patient, that was recalcitrant to typical therapeutics modalities.

**Case Report:** A 45-year-old woman presented to our clinic with a several month history of discrete, pink, ill-defined pruritic papules on her torso with sparing of her extremities. Grover's disease was diagnosed based on her clinical presentation and subsequently biopsy confirmed. She failed multiple topical medications, oral acitretin, and only experience minimal relief when transitioned to Naltrexone. Dupilumab was added to her regimen, with rapid improvement. She was eventually transitioned down to dupilumab monotherapy and has remained clear since.

**Conclusion** Grover's disease is not common among middle-aged women. Novel therapies, such as biologics, have been efficacious in elderly (especially male) populations with this condition. Our case demonstrates the importance of attempting new treatment modalities such as dupilumab for patients with recalcitrant disease. Novel application of these biologic treatments may be needed in particular for atypical cases, such as when patients do not fit the known epidemiologic profile.

### INTRODUCTION

Grover's disease, also known as transient acantholytic dermatosis, is an acquired dermatologic condition characterized by a pruritic, erythematous, and scaly papulovesicular eruption affecting the trunk. The cause remains unknown, though condition worsening has been associated with heat, sweat, renal failure, and malignancy.<sup>1</sup> The diagnosis is primarily

clinical, though biopsy can be helpful in atypical cases.

Grover's disease is relatively uncommon, and prevalence is primarily limited to older adults. To date only a few empiric epidemiologic studies have been performed. One of these, a 30-month retrospective assessment of 3,750 patients with dermatologic consultations during their hospitalization, showed the prevalence of Grover's disease was 0.8% with a Male: Female ratio of 1.8.<sup>2</sup> A second study with

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outpatient data from the United States largely recapitulated both the prevalence and gender ratio.<sup>3</sup> In both, the average patient with Grover's disease was older than 64 years. There is presently no standard of care for Grover's disease, though most patients are started on topical steroids, calcineurin inhibitors, retinoids, or antibiotics. Dupilumab has recently been used to treat the intense pruritus associated with Grover's disease. The theoretical mechanism supporting the use of dupilumab in Grover's disease is well-described, and is thought to target pruritoceptive pathways.<sup>5</sup> However, reports of treatment with dupilumab are few, and have been largely limited to assessment in male, elderly patients. We present here a middle-aged woman with refractory Grover's disease who eventually responded to treatment with Dupilumab.

## CASE REPORT

A 45-year-old woman presented to our clinic with a several month history of discrete, pink, ill-defined papules on her torso with sparing of her extremities (**Figure 1**). The lesions had an insidious onset, were intermittently pruritic, and were exacerbated with sweating and heat. The patient had been following a gentle skin care regimen with intermittent trials of topicals including 1% hydrocortisone cream, baby power and miconazole powder without significant improvement. She denied any personal or family history of similar skin lesions or any other dermatologic conditions. Upon clinical evaluation, Grover's disease was suspected. Consistent topical use of triamcinolone 0.1% ointment over 2-3 weeks was recommended in addition to 25mg oral diphenhydramine twice daily. When this regimen only provided partial relief, topical steroids were escalated to using topical clobetasol 0.05% cream daily for two weeks. The lesions initially resolved on this regimen

but eventually recurred within the subsequent three months, prompting a skin biopsy to confirm the diagnosis. On histology, focal acantholysis and dyskeratosis were observed, consistent with the suspected Grover's disease.

After confirming the diagnosis, the patient was started on topical calcipotriene 0.005% cream daily for a month. After which, topical 0.1% triamcinolone cream daily was added to the calcipotriene regiment. Due to lack of significant improvement after three months, the patient was initiated on 10 mg daily oral acitretin for three months, which was then increased to 17.5mg daily for three months, and later escalated to 25mg daily. After two weeks on 25mg of acitretin, the patient experienced dermatitis and hair loss. Her acitretin dose was subsequently lowered back to 17.5 mg daily. The patient was also started on a naltrexone 1.5 mg daily with escalation to 4.5mg daily. After two months on the 17.5mg daily dose of acitretin and 4.5mg daily dose of naltrexone, the patient continued to experience worsening hair loss. Acitretin was discontinued.

After multiple first and second line therapies failed to manage the condition, alternative novel management approaches were discussed, and dupilumab (Dupixent) 300mg every-other-week SQ were started. The patient was continued on the naltrexone as well and noticed a major improvement in her condition within a few weeks. After two months on the dupilumab, naltrexone was discontinued. The patient initially experienced rebound pruritus for two weeks upon discontinuation of the naltrexone, however this pruritus progressively resolved. Six months after starting dupilumab she remained completely clear of new skin lesions and reported no pruritus (**Figure 2**).



**Figure 1.** Before treatment, anterior view.



**Figure 2.** After treatment, anterior and posterior view.

## DISCUSSION

The successful management of Grover's disease with dupilumab, a monoclonal antibody that binds to interleukin-4 (IL-4) receptors, has only been reported in a few instances. Existing cases are amongst men above the age of 70, with only a single case reported of a woman in her 50s.<sup>5-8</sup> There is theoretical support for use of dupilumab among post-menopausal women along with elderly men, given that women older than the age of 50 develop an increased proportion of T-helper 1 lymphocytes (Th1 cells) and pro-inflammatory cytokine secretion.<sup>9,10</sup> This known increased Th1 immunologic profile has been hypothesized as the mechanism by which dupilumab may be efficacious in post-menopausal women, as previously reported.<sup>5</sup> Therefore, we questioned the potential efficacy in a pre-menopausal woman nearly 20 years younger than the average age of reported success with dupilumab. However, the decision to start this biologic was made due to her failure to respond completely to other therapies. Fortunately, her condition was greatly improved with dupilumab and eventually stabilized on monotherapy.

Given the significant improvements seen in our patient's condition, this case serves to support the wider clinical use of dupilumab in younger females. In addition, this case suggests that the pruritus and dermatologic manifestations of Grover's disease may be mediated by IL-4, regardless of patient age or hormonal status. This IL-4 based mechanism is implicated in the pruritoceptive pathway.<sup>5</sup> However, improved pruritus observed in our case with the additional use of naltrexone also suggests that neuropathic pruritus may be implicated as well in Grover's disease pathophysiology. The combination of dupilumab with naltrexone was extremely successful in relieving pruritus. Naltrexone has

not been widely studied for use in Grover's disease specifically, though the anti-pruritic effects have been discussed in both theoretical and practical studies of older adults.<sup>11,12</sup>

## CONCLUSION

Our case highlights dupilumab and naltrexone to successfully manage Grover's disease in a pre-menopausal woman. Our case demonstrates the importance of early consideration of dupilumab for immunologic targeting of pruritoceptive itch pathways in Grover's disease. In addition, we report on the potential use of naltrexone as a bridge therapy to temporarily target neuropathic itch. Clinicians should thoughtfully investigate pruritus in younger women and maintain a high index of suspicion for Grover's disease.

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