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# Successful treatment of two individual cases of generalized granuloma annulare with amoxicillin/clavulanic acid and a combination of doxycycline and pentoxifylline

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## Abstract

Granuloma annulare is a benign inflammatory skin disease potentially related to a delayed hypersensitivity reaction to the dermis. Generalized granuloma annulare (GGA) manifests as diffuse skin-colored to erythematous annular or nummular plaques affecting at least the trunk and either upper or lower extremities, or both. GGA is resistant to many therapeutic modalities, making it difficult to treat. Different therapeutic approaches to GGA have been attempted but definitive treatment for this disease remains elusive. This article focuses on the use of amoxicillin/clavulanic acid and a combination of doxycycline and pentoxifylline therapy as treatment options for GGA in two patients with histopathology-proven interstitial GGA. Both amoxicillin/clavulanic acid and doxycycline inhibit bacterial cell growth, raising the possibility that a bacterial pathogenesis may be of significance in GGA. This is the first reported case of successful treatment of GGA with these regimens.

*Keywords: amoxicillin, clavulanic acid, doxycycline, granuloma annulare, pentoxifylline*

## Introduction

Granuloma annulare (GA) is generally a benign granulomatous skin disease that resolves within two years, but can occasionally be widespread. GA is characterized by raised erythematous or skin-colored annular plaques, most often on the hands and feet. Generalized granuloma annulare (GGA) is a less common variant, accounting for approximately

15% of all cases, with plaques on the trunk as well as on the extremities [1, 2]. GGA may persist for decades, with treatment resistance and a chronic course [1]. Current options for treatment of GGA include topical agents, phototherapy, and systemic medications. The pathogenesis is not entirely known, but comprehensive reviews suggest a type III immune-mediated reaction that leads to chronic vasculitis versus a delayed-type hypersensitivity reaction with secondary changes of vasculature and surrounding tissue [3]. Our aim in presenting these cases is to introduce two new therapeutic approaches to treating GGA, a disease to which definitive treatment fails to exist. In addition, we introduce the possibility that a bacterial pathogenesis may exist in GGA.

## Case Synopsis

Patient A, a 55-year-old woman with past medical history of adrenal gland insufficiency, presented with a nine-month history of scattered skin-colored and erythematous thin, annular plaques involving her trunk and extremities. Laboratory testing was unremarkable. Medications at the time of presentation included levothyroxine, cortef (5 mg/day), vitamin D3, DHEA, alpha lipoic acid, coenzyme Q 10, vitamin B12, L-arginine, chlorophyll liquid, and melatonin. A biopsy was performed and histopathology was consistent with interstitial type generalized GA, demonstrating superficial and mid-dermal interstitial granuloma formation with mucin and an interstitial and perivascular lymphocytic infiltrate.

The patient was initially started on pentoxifylline 400mg three times daily for six months without improvement. The patient returned one month later, noting marked improvement of her skin after finishing a course of amoxicillin/clavulanic acid 875/125mg (ACA) twice daily for ten days that she received for the treatment of an upper respiratory infection. She was no longer taking pentoxifylline at that time. The patient was then started on a monthly treatment regimen with rifampin, ofloxacin, and ACA owing to reports of success with this modified therapy, with only mild improvement [4]. A trial of ACA twice a day for ten days was initiated. The patient noted marked improvement in the skin lesions one month later and was switched to a modified regimen consisting of ACA 2×/day for one week every month. She has since noted dramatic improvement and sustained control of her disease using this regimen.

Patient B, a 64-year-old man, presented with a 6-month history of a generalized eruption on the abdomen, shoulders, and upper chest. The rash had a gradual onset and was not pruritic or otherwise symptomatic. The patient had a past medical history of hypothyroidism, but was otherwise healthy. Medications at time of presentation included pravastatin, thyroid supplementation, zinc, vitamin C, Tylenol PM, lisinopril, losartan, fish oil, and ibuprofen 1×/week. Histopathology of a representative lesion, as with patient A, was consistent with an interstitial GA.

The patient was initially started on doxycycline 100mg two times daily and pentoxifylline 400mg three times daily. The patient returned two months later with significant improvement, and he remained stable on this regimen. Two years later, an attempt was made to decrease the oral regimen, but when doxycycline and pentoxifylline were stopped the patient had a notable recurrence of the eruption.

## Case Discussion

Although different therapeutic approaches to GGA have been reported, definitive treatment for this disease remains elusive. First line therapies include psoralens with ultraviolet A (PUVA), photodynamic

therapy, and hydroxychloroquine for generalized disease [3]. Previous studies have shown antibiotic combinations to help clear GA, including the ROM therapy that consists of rifampin, ofloxacin, and minocycline [4, 5].

ACA inhibits the peptidoglycan synthesis in bacterial cell walls, whereas clavulanic acid inhibits beta-lactamase-producing bacteria [6]. It is unclear if this mechanism of action is significant in its efficacy in GGA, or if the immune modulating properties are solely responsible for the clinical improvement. Studies have shown successful treatment of GGA with pentoxifylline, suggesting a model of immune-mediated vasculitis in the pathogenesis of this disease [7]. Clinical benefit has also been documented in patients treated with doxycycline [8]. Doxycycline inhibits protein synthesis by binding to 30S and potentially 50S ribosomal units, whereas pentoxifylline improves blood flow by decreasing blood viscosity and increasing red blood cell flexibility, potentially increasing tissue oxygenation [9]. Pentoxifylline has additional anti-inflammatory effects including decreasing neutrophil chemotaxis and function as well as inhibiting tumor necrosis factor-alpha [10].

Importantly, both ACA and doxycycline inhibit bacterial cell growth, raising the possibility that a bacterial pathogenesis may be of significance in GGA. Both patients tolerated the treatment well and continue to have clearance of their GGA with these regimens.

## Conclusion

Generalized granuloma annulare (GGA) is a benign inflammatory skin disease that manifests as diffuse plaques affecting the trunk and extremities. In this study, two new therapeutic approaches to treating GGA are introduced through individual patient case studies. Successful treatment of GGA with amoxicillin/clavulanic acid and combination therapy of doxycycline and pentoxifylline is observed. In consideration of the success of these regimens, a bacterial pathogenesis may be of significance in the pathogenesis of GGA.

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