

Granuloma Annulare Treated With Rifampin, Ofloxacin, and Minocycline Combination Therapy

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Background: Granuloma annulare (GA) is a benign, usually self-limiting, dermatosis, that typically presents as asymptomatic, flesh-colored or erythematous papules, frequently arranged in an annular or arciform pattern on the distal extremities. Although localized GA is most commonly observed, a generalized or disseminated form can occur. The etiology of GA is unknown; however, multiple inciting factors have been proposed. Histologically, GA is characterized by foci of degenerative collagen associated with palisading, sometimes infiltrating granulomatous inflammation.

Observations: We report 6 cases with biopsy-proved GA, resistant to the standard modalities of treatment that resolved after 3 months with monthly rifampin (600 mg), ofloxacin (400 mg), and minocycline hydrochloride (100 mg) combination therapy. Rifampin, ofloxacin, and mi-

nocycline combination therapy has been successfully used to treat patients with paucibacillary leprosy. Given reports that prolonged antibiotic agents are a useful treatment for GA, rifampin (600 mg), ofloxacin (400 mg), and minocycline hydrochloride (100 mg) combination therapy was initiated in these patients. Complete clearance of the plaques was achieved 3 to 5 months after the initiation of treatment. Some patients experienced postinflammatory hyperpigmentation.

Conclusion: Although our treatment was effective, further studies may be needed to confirm the success of this therapeutic option for patients with recalcitrant lesions of GA.

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HISTOLOGICALLY, GRANULOMA annulare (GA) is characterized by foci of degenerative collagen associated with palisading, sometimes infiltrating, granulomatous inflammation.¹ Many therapies have been described to manage GA including psoralen UV-A treatment, systemic corticosteroids, dapsone, pentoxifylline, hydroxychloroquine, isotretinoin, chlorambucil, interferon gamma, cyclosporine, potassium iodide, nicotinamide, niacinamide, salicylate acids, chlorpropamide, thyroxine, and dipyridamole.² Shelley² reported successful treatment of GA by treating underlying infections with antibiotics such as cefaclor, cefixime, penicillin, amoxicillin, ciprofloxacin, erythromycin, clarithromycin, and trimethoprim-sulfamethoxazole.

We report 6 cases of resistant GA that resolved after a 3-month treatment course of rifampin (600 mg), ofloxacin (400 mg), and minocycline hydrochloride (100 mg) combination therapy administered monthly. Rifampin, ofloxacin, and minocycline combination therapy has been suc-

cessfully used to treat patients with paucibacillary leprosy that has morphologic and histologic similarities to GA.

REPORT OF CASES

This study was approved by the Institutional Review Board (IRB) of Henry Ford Hospital, Detroit, Michigan. A total of 6 patients, living in the Great Lakes region of the United States, with GA, who failed to respond to topical corticosteroids and other standard therapies for GA, were treated for 3 months with a combination of rifampin, ofloxacin, and minocycline. Histopathologic examination of all cases were consistent with GA; acid-fast bacilli stain was negative. Patients were followed up to assess efficacy and adverse events of the treatment. All patients tolerated the combination therapy well.

CASE 1

A 60-year-old woman presented with a 1-year history of a pruritic rash on her arms and legs. She was treated with a combi-

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Figure. Multiple erythematous papules and annular plaques of granuloma annulare on the back before (A) and clearance of papules and annular plaques 3 months after (B) combination therapy with rifampin, ofloxacin, and minocycline hydrochloride was started.

nation of liquid nitrogen and pimecrolimus with limited success. Her medical history was significant for hypertension and hypercholesterolemia. Physical examination revealed erythematous papules and annular plaques on her arms and legs. Pathologic findings were consistent with early interstitial GA. After 8 months of failed therapy, oral antibiotic therapy was considered and combined therapy with rifampin, ofloxacin, and minocycline was started.

Three months later she returned with significant improvement of her GA lesions. After 4 months, she had complete clearance, with residual postinflammatory hyperpigmentation.

CASE 2

A 44-year-old woman presented with a 5-year history of a mildly pruritic rash involving the dorsum of the hand that had been resistant to previous therapies including hydrocortisone, 1%, pimecrolimus, desoximetasone, and mometasone furoate. Medical history was significant for asthma, depression, cesarean sections, and urinary urgency. On physical examination, erythematous annular plaques were on the dorsum of the hand. The patient returned 2 weeks later for suture removal, at which time the lesions had not changed; combined therapy with rifampin, ofloxacin, and minocycline was started. Three months later she returned with significant improvement of her lesions. At 5 months, she had complete clearance of the lesions, leaving only residual hyperpigmentation. The patient reported insomnia on the night of treatment and discoloration of her body fluids.

CASE 3

A 69-year-old woman presented with a 1-year history of itchy papules on hands, arms, trunk, and legs. The lesions had been resistant to therapies including clarithro-

mycin; tacrolimus; fluticasone propionate; intralesional triamcinolone acetonide, 40 mg/mL; liquid nitrogen; and excimer laser. Medical history included hypertension and hypercholesterolemia. Physical examination disclosed erythematous papules and annular plaques. Treatment with excimer laser and clarithromycin were both tried with limited results in this patient who had failed to respond to topical therapy. Combination therapy with rifampin, ofloxacin, and minocycline was started for a total of 3 months, after which her condition was completely cleared, with postinflammatory pigmentation.

CASE 4

An 81-year-old woman presented with a 6-month history of an asymptomatic rash on her trunk and extremities. The lesions had been resistant to treatment with topical triamcinolone, 0.1%. Her medical history was noncontributory. Physical examination disclosed erythematous papules and small annular plaques. Combination therapy with rifampin, ofloxacin, and minocycline was started for a total of 3 months. After 4 months, she had complete clearance of the lesions, with only residual pigment in the area (**Figure**).

CASE 5

A 49-year-old man presented with a 2-year history of an asymptomatic rash on his arms that never completely faded away. The patient's medical history was significant for hypertension and a 20-year history of cigarette smoking. The lesions had been resistant to topical triamcinolone therapy. Physical examination disclosed erythematous scaly annular patches and plaques, with raised borders, on the ventral surface of his arms. The patient also had rosacea on the face for which he was prescribed metronidazole lotion and actinic keratosis. Combination therapy with rifampin, ofloxacin, and minocycline was started on a monthly basis for 3 months. The patient had complete clearance of the lesions, with residual hyperpigmentation in the area.

CASE 6

A 44-year-old man presented with a 5-year history of GA. Topical triamcinolone treatment had failed. Physical examination disclosed erythematous papules and annular plaques on the dorsum of the right hand and on his feet. Combination therapy with rifampin, ofloxacin, and minocycline was started for a total of 3 months. He had complete clearance of the lesions, with only postinflammatory pigmentation.

COMMENT

Modalities of treatment that are effective in localized GA, such as high-potency topical corticosteroids, cryotherapy, or intralesional injections of glucocorticosteroid, are inadequate for generalized GA, in which large areas of the body need to be treated.

Tuberculoid or paucibacillary leprosy can appear similar to GA both clinically and histologically. Tuberculoid

leprosy is a granulomatous condition with few or no bacilli observed. Tuberculoid leprosy presents as well-demarcated plaques with often slightly elevated erythematous borders. Histologically, this form of leprosy shows a dermal granulomatous infiltrate composed of epithelioid cells, Langhans giant cells, and lymphocytes.³ Granuloma annulare lesions have a similar but distinct appearance demonstrating foci of degenerative collagen associated with palisading around an anuclear dermis with mucin deposition, sometimes infiltrating granulomatous inflammation composed of histiocytes, lymphocytes, and fibroblasts.⁴ This granulomatous appearance of the biopsy specimen and the annular clinical appearance combine to form the descriptive term *granuloma annulare*. In addition, both tuberculoid leprosy and GA respond to therapy with dapsone as well as prolonged antibiotic use.^{5,6}

Since rifampin, ofloxacin, and minocycline combination therapy has been effective in treating tuberculoid leprosy, this therapy was thought to likely be effective against GA, which has clinical and histologic similarities to tuberculoid leprosy. In addition, empirical antibiotic therapy for GA has been reported on a continuous basis.⁷ We believe that intermittent dosing used in millions of patients also could be used safely.⁶ The treatment is inexpensive, has few adverse effects, and is a commonly used treatment worldwide for paucibacillary leprosy.⁶ In addition to its antimicrobial effects, rifampin has also proved to influence antibody formation and cellular immune response, specifically delayed-type hypersensitivity.⁸ Most frequent adverse effects include orange-red discoloration of urine and permanent staining of soft contact lenses.³ Tetracyclines are broad-spectrum antibiotics that interfere with protein synthesis, inflammation, immunomodulation, cell proliferation, and angiogenesis, even in subantibiotic concentrations.⁹ Minocycline has been shown to reduce collagenase activity on gingival fibroblasts from diabetic rats and in the synovial tissue of patients with rheumatoid arthritis.¹⁰ Minocycline also interferes with lymphocyte proliferation, especially T cells, and has anti-inflammatory effects that are likely related to its antioxidant activity.¹⁰ Adverse effects most commonly include gastrointestinal tract symptoms including epigastric burning, abdominal discomfort, nausea, and vomiting.³ In 2008, Duarte et al⁷ described a patient with GA who failed to respond to treatment with intense pulsed light and dapsone. A 10-week course of doxycycline (100 mg/d) resulted in almost complete resolution of the lesions, even after a considerable follow-up period.

Although GA often resolves spontaneously, these patients failed to respond to multiple therapeutic interventions. To our knowledge, no data exist that definitively prove that GA is infectious, and multiple attempts to identify a causative agent have been unsuccessful.¹ However, antimicrobial agents have been used successfully in dermatology for noninfectious conditions for de-

caes. For example, dapsone has been used for treatment of noninfectious conditions such as dermatitis herpetiformis, autoimmune bullous diseases, neutrophilic dermatoses, and some vasculitis syndromes.¹¹ Also hydroxychloroquine, an antimalarial agent, has been used to treat noninfectious disorders including lupus (discoid and systemic) and photodermatoses.¹¹ The success of these agents led us to attempt to treat recalcitrant cases of GA with agents that treat a condition that has similar morphologic and pathologic features. Further placebo-controlled studies will be needed to determine if combination therapy with rifampin, ofloxacin, and minocycline may be a viable option for recalcitrant lesions of GA. Patients often developed a postinflammatory hyperpigmentation after treatment. If successful in others' hands, this treatment option would increase the therapeutic options for patients with recalcitrant lesions of GA.

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