Orofacial Granulomatosis Responding to Weekly Azithromycin Pulse Therapy

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Orofacial granulomatosis (OFG), also termed granulomatous cheilitis, oral granulomatosis, and cheilitis granulomatosa, is an uncommon disorder. The presentation can be very varied; pathogenesis is not very clear; and the treatment result is often disappointing. It is characterized by persistent enlargement of the soft tissues of the lip, oral mucosa, and the area around the mouth. Other granulomatous disorders like sarcoidosis, Crohn disease, leprosy, and tuberculosis must be ruled out before making this diagnosis. We describe herein an index case and 4 subsequent cases of idiopathic OFG that responded dramatically and almost completely to treatment with weekly oral azithromycin pulse doses.

Report of the Index Case

A 50-year-old woman presented with erythematous edematous swelling on her face of 3 years’ duration. She had repeated episodes of erythematous edematous diffuse swelling of her upper lip. Gradually, the upper lip became persistently swollen with extension of redness and swelling beyond the lip margins that slowly involved the philtrum, both nasolabial folds, and the cheeks (Figure, A). She had occasional pruritus and burning in the affected area. Her dental hygiene was poor, but she never had dental fillings. She could not associate flare of symptoms with any specific food intake. She did not have known significant medical illness or any systemic symptoms.

On examination, her tongue was not swollen and there were no fissures. There was neither lesional sensory deficit nor any thickened nerve in the vicinity. Findings of her facial nerve examination were also normal. Further investigations determined that her blood cell counts, liver function, kidney function, angiotensin-converting enzyme levels, serum calcium levels, and chest radiograms were all normal. The induration response to the Mantoux test measured 5 × 8 mm, and stool tested negative for occult blood.

Mucosal biopsy from the upper lip on histopathologic examination revealed acanthotic epidermis and dense granulomatous inflammation in the dermis. There were multiple discrete, noncaseating, compact epithelioid cell granulomas surrounded by dense lymphocytic infiltrate. Special stainings for acid-fast bacilli and fungus were negative. From the clinical and biopsy findings, a diagnosis of OFG was made.

Therapeutic Challenge

Various treatments for OFG have been tried: oral corticosteroids; intralesional corticosteroids, alone or combined with pingyangmycin (bleomycin A5); antibiotics like dapsone, metronidazole, clofazimine, and minocycline; thalidomide; biologics (infliximab, adalimumab); and dietary restrictions. When medical treatment failed, surgery (reductive cheiloplasty) has been performed.

Our patient had previously received a 6-month course of clofazimine with little improvement. During 2 months of treatment with intralesional triamcinolone injections at monthly intervals along with...
oral metronidazole, there was approximately 20% improvement, but she developed gastrointestinal intolerance of metronidazole. Consequently, metronidazole therapy was stopped, and intraleisional injections were continued for another 4 months without any further significant response.

Solution
Because OFG is considered to be a kind of delayed hypersensitivity response to an unrecognized antigen, we prescribed azithromycin, 500 mg, weekly pulse therapy (3 consecutive days every week) for its antimicrobial and anti-inflammatory properties. After 1 month of this therapy, there was slight reduction in swelling, and at the end of 3 months, there was 80% to 90% improvement in symptoms with significant reduction in redness and swelling. Azithromycin pulse therapy was continued for another 2 months and then stopped because the lesions had disappeared completely (Figure, B). There were no treatment-related complications and no recurrences during the 6-month follow-up period.

Other Cases
Subsequently, we treated 4 more patients with idiopathic OFG with azithromycin, 500 mg, weekly pulse therapy with good response. A response was apparent in every patient after 1 month of treatment, and all lesions had improved significantly after 3 months of therapy. Epidemiological characteristics, disease profiles, prior treatment histories, and responses to azithromycin treatment of all these patients are summarized in the eTable in the Supplement.

Discussion
Orofacial granulomatosis is a relatively uncommon granulomatous disorder that usually affects young adults and has nearly equal incidence in both sexes. The signs and symptoms include persistent enlargement of soft tissues in and around the mouth and gingiva, oral ulceration, and cobblestoning of the tongue. When it is associated with facial nerve paralysis and fissured tongue, it is labeled as Melkerson-Rosenthal syndrome.

Idiopathic OFG is diagnosed when specific granulomatous diseases have been excluded. This disorder is considered to be a delayed hypersensitivity response to an unidentified antigen with a variable response in different individuals. Continuous exposure to the putative antigen is considered to lead to chronic submucosal T-cell-mediated inflammatory response and finally result in granuloma formation in the lamina propria and in and around lymphatic channels. The inflammation with resultant edema leads to swelling of the soft tissues. The suspected sources of the antigen include metals, food additives and preservatives, and microbes, such as spirochetes.

We have treated 5 patients with OFG successfully with azithromycin weekly pulse therapy. Azithromycin is a macrolide antibiotic with antimicrobial action and in addition has anti-inflammatory and immunomodulatory properties. It reduces the production of pro-inflammatory cytokines and interleukins (ILs) like IL-1, IL-6, IL-8, tumor necrosis factor, and interferon γ. Azithromycin also affects the cell junctions located in the membranes of epithelial cells. The drug induces the production of proteins that form the tight junctions and thereby strengthens the epithelial barrier and potentially reduces the transgression of putative antigens into the submucosa. Azithromycin may alter the growth and number of different microbes in oral cavity, thereby altering the antigenic load.

Other antibiotics that have proven benefit in the treatment of OFG include minocycline, clofazimine, and metronidazole, and all of these also produce their effect through anti-inflammatory and immunomodulatory properties. It was interesting to note that some of the patients who did not respond to clofazimine and metronidazole showed improvement with azithromycin. There are 2 previous single-patient case reports of successful use of roxithromycin for OFG. In one of these reports, the patient did not respond to azithromycin, 1500 mg/wk, therapy when given for a duration of 10 weeks. It is difficult to explain why treatment with azithromycin failed in this patient.

The treatment of idiopathic OFG is challenging because of its chronicity, generally poor response to treatment, and aesthetic impact. Our 5 patients showed a very fast and almost complete improvement with weekly azithromycin pulse therapy. We postulate that this beneficial effect is possibly mediated by its anti-inflammatory, immunomodulatory, and antibacterial properties; the effects on mucosal barrier; and by regulating the microbial flora of the oral cavity.