Acute-Onset, Painful Acrall Granuloma Annulare

A Report of 4 Cases and a Discussion of the Clinical and Histologic Spectrum of the Disease

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Background: Granuloma annulare is a benign cutaneous inflammatory disease of unknown etiology most commonly presenting on the hands and feet and consisting of asymptomatic to mildly pruritic, flesh-colored to erythematous annular plaques. To our knowledge, an acute-onset, painful acral eruption has not been previously recognized.

Observations: We report 4 patients who presented with acute-onset, painful acral granuloma annulare.

Conclusions: It is possible for granuloma annulare to present as a painful eruption with an acute onset and an acral distribution. Biopsy results are a crucial factor when establishing the diagnosis of this atypical clinical presentation of granuloma annulare.

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Granuloma Annulare (GA) is a benign cutaneous inflammatory disease of unknown etiology most commonly presenting on the hands and feet.1 The eruption most often consists of asymptomatic to mildly pruritic flesh-colored to erythematous annular plaques. Spontaneous resolution usually occurs within 2 years of initial presentation; however, recurrence at the original site approaches 40%.1

Five clinical morphologic patterns of GA have been recognized: localized, generalized, perforating, subcutaneous, and patch type. Histopathologically, localized GA consists of foci of granulomatous inflammation and collagen alteration in the upper to middle dermis. There is an infiltration of histiocytes, lymphocytes, and occasional giant cells with peripheral palisading of the infiltrate around degenerative collagen bundles. Deposition of acid mucopolysaccharides on and between collagen fibers is also characteristic. Dabbs and Winkelmann2 found this classic pattern in only 25% of original biopsy specimens reviewed. Generalized cases typically present with an interstitial histiocytic infiltrate with less apparent collagen alteration. In their review, 53% of generalized GA lesions displayed some form of collagen necrobiosis, whereas 79% of localized GA cases exhibited collagen alteration. The prevalence of eosinophils has been reported to range from 3.5% to 40%.3 Romero and Kantor3 found eosinophils to be predominantly perivascular when present and more often associated with a palisaded pattern and necrobiosis.

We report 4 patients with an atypical clinical presentation characterized by an acute onset, acral location, and pain with emphasis on the importance of the clinicopathologic correlation in establishing the correct diagnosis.

REPORT OF CASES

OBSERVATIONS

Table 1 summarizes the clinical characteristics of 4 women with an unusual presentation of GA (also see Figure 1). Case 1

Patient 1 was a 42-year-old, previously healthy woman who awoke with a painful rash on her hands, legs, and feet. Five days later, she developed arthralgias of the knees and ankles. Her only medications were multivitamins and supplemental calcium. The patient’s condition was initially evaluated by a rheumatologist and an expert in infectious diseases who noted an elevated erythrocyte sedimentation rate of 56 with otherwise unremarkable findings from laboratory evaluations for cryoglobulins, anti-neutrophilic cytoplasmic antibody, anti-
cardiolipin antibodies, factor V Leiden mutation, hepatitis B serology, rheumatoid factor, rapid plasma reagin, Lyme disease titers, urinalysis, and complete metabolic profile.

She was treated with oral colchicine and valdecoxib, which improved her arthralgias, but she continued to develop cutaneous lesions. Findings from biopsies performed at another institution had been interpreted as demonstrating an occlusive vasculopathy with dermal necrosis, and Dego disease was strongly suggested to be the differential diagnosis. She was subsequently referred to our practice (J.P.C.).

Physical examination revealed tender, erythematous, annular plaques on her hands with an erythematous, firm, dermal nodule on her toe and postinflammatory pigmentary alteration involving her legs (Figure 2 and Figure 3). Findings from repeated laboratory tests revealed a positive qualitative cryofibrinogen on 1 occasion. Results from all other laboratory testing was either in the reference range or negative, including findings for rheumatoid factor, antinuclear antibody, anti-Ro/SSA, anti-La/SSB antibodies, antineutrophilic cytoplasmic antibody, antcardiolipin antibody, anti–double-stranded DNA antibody, creatine kinase, erythrocyte sedimentation rate, cryoglobulins, C-reactive protein, hepatitis C antibody, glucose 6-phosphate dehydrogenase, and β-2 glycoprotein 1 antibody.

The initial biopsy results from the patient’s left thigh were reviewed. Irregular epidermal acanthosis, spongio-
sis, and focal parakeratosis were noted, overlying a broad zone of necrobiosis with scattered neutrophils surrounded by a palisaded infiltrate of histiocytes. A perivascular and periappendageal lymphocytic infiltrate was also noted; however, there was only a focal suggestion of fibrin deposition in a vessel lumina to suggest a vasculitic process.

Repeated biopsy specimens were subsequently obtained from the patient’s left second toe, finger, and palm. Results of the biopsy of the toe showed irregular epidermal acanthosis and an underlying dermis with a superficial and deep perivascular and interstitial lymphohistiocytic infiltrate. Histiocytes seemed to palisade around zones of necrobiotic collagen (Figure 4). There was no definitive evidence of vascular damage. A colloidal iron stain demonstrated increased mucin in the areas of necrobiosis. Results from the biopsy (Figure 5) of her left second finger revealed an interstitial histiocytic infiltrate in the upper and middle reticular dermis admixed with a perivascular lymphocytic infiltrate with interstitial mucin deposition on colloidal iron staining. The third biopsy specimen showed a perivascular and interstitial infiltrate composed of histiocytes, lymphocytes, and giant cells. The histiocytes seemed to focally palisade around areas of mild necrobiosis (Figure 6). Vascular damage was not appreciated, and interstitial mucin deposition was seen on a colloidal iron stain. Periodic acid–Schiff staining was negative for pathogenic fungi in all of the bi-
opposite specimens. These findings were felt to be histologically consistent with a diagnosis of GA.

The patient’s cutaneous disease and arthralgias resolved within 4 weeks after initiating treatment with 200 mg of oral hydroxychloroquine sulfate twice daily. After 10 months of successful therapy, the patient decided to discontinue treatment in October 2004.

**Table 2**

Granuloma annulare may clinically mimic lichen planus, insect bites, sarcoidosis, annular elastolytic giant cell granuloma, foreign body granuloma, erythema multiforme, and acute febrile neutrophilic dermatosis. Histopathologically, GA may be included in the spectrum of other interstitial or palisading granulomatous dermatitides (Table 2), including interstitial granulomatous dermatitis with arthritis (cord and plaque types), interstitial granulomatous drug reaction, annular elastolytic giant cell granuloma, necrobiosis lipoidica diabetica, cutaneous extravascular necrobiosis granuloma, rheumatoid nodules, sarcoidosis, and infectious granuloma. A clinicopathologic correlation is essential to establish a final diagnosis given the substantial overlap in histopathologic features of the various granulomatous dermatitides.

Patients 1 and 3 presented with arthralgias, which increased our concern that their disease might represent an early manifestation of an autoimmune disease. A variety of clinical presentations, including papules, plaques, or linear cords, often with a bilateral and symmetrical distribution, have been reported under a variety of monikers, including interstitial granulomatous dermatitis with arthritis, Churg-Strauss granuloma, palisaded neutrophilic and granulomatous dermatitis, rheumatoid papule or vasculitis, and, more recently, interstitial granulomatous dermatitis with plaques. All of these conditions may clinically mimic generalized GA and are to be considered manifestations of a number of immunologically mediated diseases, including, but not limited to, rheumatoid arthritis, collagen vascular disease, Wegener granulomatosis, inflammatory bowel disease, and lymphoproliferative disorders. These conditions may also mimic GA from a histologic standpoint, although the diffuse interstitial pattern often exhibits numerous eosinophils, few to absent giant cells, and scant mucin deposition, in contrast to conditions found in GA. The palisaded pattern, with the formation of basophilic necrobiotic zones containing neutrophils and neutrophilic debris with variable vascular fibrin deposition (or so-called Churg-Strauss granuloma), may more closely mimic GA histologically. The diffuse interstitial pattern was not seen in our patients’ biopsy specimens, nor did their clinical presentation reveal the intracrinous and symmetrically distributed lesions typically noted in interstitial granulomatous dermatitis and other related disorders. Although fibrin deposition and perivascular neutrophils were seen in the biopsy findings from patient 1, overt changes of vasculitis were not seen, and these findings have been reported in patients with GA. In addition, the negative findings from serologic studies in our patients and the absence of clinical findings to substantiate a diagnosis of autoimmune disease would further refute one of the immunologically mediated conditions mimicking GA.

Given the rapid progression of arthritic symptoms in our third patient, we considered multicentric reticulohistiocytosis in her differential diagnosis; however, the patient did not develop mucosal involvement, and her biopsy results did not reveal findings consistent with that diagnosis.

An interstitial granulomatous drug reaction may also mimic GA and has been attributed to angiotensin-converting enzyme inhibitors, calcium channel blockers, B-blockers, antihistamines, anticonvulsants, antidepressants, and lipid-lowering agents. Patients with interstitial granulomatous drug reactions present with intracrinous erythematous to violaceous annular plaques, although papules have also been reported. Biopsy findings from these patients resemble a GA pattern or a GA-like pattern but may be distinguished from other interstitial granulomatous dermatitides by the presence of vacuolar interface changes, focal basal and suprabasilar dyskeratosis, absent vaculoplastic changes, and variable lymphoid atypia and mucin deposition. Although patients 1 and 2 had been taking an angiotensin-converting enzyme inhibitor, they did not have intracrinous involvement, and findings from their biopsies did not demonstrate vacuolar changes and lymphoid atypia.

Annular elastolytic giant cell granuloma is characterized by annular erythematous plaques with hypopigmented centers on sun-damaged skin of the face, neck, or other exposed areas. There have also been reports of papular lesions occurring on nonexposed skin. The presence of elastolysis with dermal elastic fibers within the cytoplasm of histiocytes and the absence of collagen necrobiosis and mucin are the primary features that distinguish annular elastolytic giant cell granuloma from GA. Although there was evidence of focal elastophagocytosis in 1 patient, it was accompanied by collagen necrobiosis and mucin deposition, which are generally not observed in patients with annular elastolytic giant cell granuloma.

Also included in the differential diagnosis of palisading granulomas are necrobiosis lipoidica, rheumatoid nodules, and cutaneous sarcoidosis. The presence of plasma cells, increased numbers of giant cells, less mucin depo-
sition, and the depth of granulomatous inflammation help histopathologically to distinguish necrobiosis lipidica from GA.14 Our patients did not have previous diagnoses of diabetes mellitus, none presented with pretibial plaques characteristic of necrobiosis lipidica, and their biopsy specimens did not have histologic findings to suggest such a diagnosis.

Rheumatoid nodules are estimated to occur in approximately 20% of patients with rheumatoid arthritis and are usually associated with high titers of rheumatoid factor. Two of our patients had arthritic complaints, and another had an elevated serum rheumatoid factor level, but neither met the criteria defined by the American College of Rheumatology for rheumatoid arthritis. In addition, our patients did not present with nodules on the bony prominences but did have tender papules and plaques, with results from their biopsies showing upper to middle dermal involvement. With careful clinicopathologic correlation and the presence of mucin rather than fibrin deposition, GA may be differentiated from rheumatoid nodules.

Sarcoidosis is a disease of unknown etiology with cutaneous findings occurring in approximately 20% to 30% of patients with systemic disease. The cutaneous manifestations are variable, including brown erythematous or purple papules and plaques that may appear annular.16 There was an initial concern that patient 2 had cutaneous sarcoidosis because of her clinical presentation; however, biopsy findings did not reveal naked sarcoidal granulomas, x-ray films of her chest did not reveal hilar adenopathy, and findings from serologic studies were negative for sarcoidosis.

The clinical presentation of GA is variable and may be associated with mild pruritus or occasional burning. Our patients presented with painful papules and plaques. One patient also presented with a dermal nodule on her foot. These symptoms are unusual, and, to our knowledge, this is the first documented presentation of GA associated with pain. Weston and Morelli17 previously reported a case of “painful” GA due to Munchausen syndrome by proxy. This case report documented a mother’s complaint that her child’s eruption was painful and disabling in order to subject the child to unnecessary surgical procedures for financial gain. However, on repeated physician examination, the papules were non-tender. Whether the symptoms in our patients are attributable to the GA lesions themselves or due to locality is uncertain.

These 4 cases should alert clinicians to become aware of patients who present with similar clinical findings and symptoms of tenderness and/or pain and to consider GA in their differential diagnosis. Laboratory investigation should focus on a patient’s symptoms and clinical examination to exclude other possible etiologies. Single- or multiple-agent therapy with topical and/or intraleisional corticosteroids, nicotinamide, hydroxychloroquine, or other treatment modalities should also be guided by these principles.18

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REFERENCES


News and Notes

First Congress of the International Dermoscopy Society.
Naples, Italy, April 27 to 29, 2006. The recently founded International Dermoscopy Society organizes a meeting designed for all colleagues interested in the diagnosis and management of pigmented skin lesions. Special emphasis is given on guidelines for management, standardization of reports, and, particularly, on the development of machine vision in dermoscopy. In addition, seminars in discussion format and half-day workshops with special emphasis on pertinent issues in dermoscopy will be conducted.

The detailed program is presented on the Web site: http://www.dermoscopy-ids.org.

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