Granuloma annulare

Pathogenesis, disease associations and triggers, and therapeutic options

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Learning objectives
After completing this learning activity, the learner should be able to review the systemic workup, disease associations, triggers (medications and others) of GA, and present a review of the available treatments (and evidence supporting each) and a proposed list of labs to check, studies to order, and an algorithm of treatment for GA.

Disclosures
Editors
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Granuloma annulare (GA) represents a cutaneous reaction pattern of unknown cause with a variety of previously described potential disease associations and triggers. This review attempts to synthesize the available data regarding potential etiopathogenesis, reviews the available data on potential GA disease associations and work-up indicated for patients with GA, and discusses potential inciting triggers. In the final part, this article describes the available treatments options and supporting data, and provides a framework for approaching management of patients with GA. The previous accompanying article provided a comprehensive overview of the available information known about the clinical variants, epidemiology, genetics, and histology of GA. (J Am Acad Dermatol 2016;75:467-79.)

Key words: annular elastolytic giant cell granuloma; granuloma annulare; granulomatous dermatitis.

PATHOGENESIS

The pathogenesis of granuloma annulare (GA) is unknown. There have been a number of hypotheses regarding the underlying etiology of GA; however, most of these hypotheses are supported by relatively limited evidence. In a 1977 study, Dahl et al[1] reasoned that because lesions of GA often show blood vessel thickening, occlusion or other damage to blood vessels ultimately may be responsible for the development of GA. To test this, 58 specimens from patients with GA were studied, and the authors found that immunoglobulin M (IgM), complement, and fibrinogen were present in blood vessels in areas of GA. This led the authors to postulate that the underlying mechanism behind GA Is an immune-mediated, type III reaction leading to chronic vasculitis.[1] A similar hypothesis has been suggested for necrobiosis lipoidica (NL),[2] and both conditions may be associated with diabetes and microvascular damage. In addition, an ultrastructural study of

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patients with localized GA (LGA) and generalized GA (GGA) found that in 4 patients, masses of intercellular fibrin and thickened basal lamina around capillaries was seen more commonly in lesions of patients with GGA.[3]

Contemporaneously with the Dahl et al,[1] Umbert et al[4] proposed an alternative mechanism. They postulated that cell-mediated immunity underlies the pathogenesis of GA, based on their data that lymphokines, including macrophage-inhibiting factor (MIF), lead to sequestration of macrophages and histiocytes in the dermis. Upon lysosomal enzyme release by these sequestered cells, connective tissue damage results, which culminates in GA.[4] In a further study, the same authors found that activation of macrophages and fibroblasts are involved in the pathogenesis of GA, and postulated that their findings showing fibrin and rare IgM and C3 deposition around vessels did not suggest an immune-complex mediated disease, but more likely delayed-type hypersensitivity with secondary tissue and vessel changes.[5] Ten biopsy specimens obtained from patients with early LGA lesions in a separate study had negative findings on direct immunofluorescence, further suggesting that immune-complex deposition is not the primary process leading to GA.[6]

While the etiopathogenesis of GA is not known, there are multiple studies that lend some additional support to the hypothesis that GA may be triggered by delayed hypersensitivity. In a study of 8 skin samples obtained from patients with GA, the infiltrate was comprised primarily of helper T cells, leading the authors to hypothesize that through interaction with histiocytes, these helper T cells lead to granuloma formation and GA.[7] A 1999 study[8] showed that large numbers of T cells in lesions of GA were $CD3^+$ and expressed receptors for interferon gamma. In addition, the authors noted that macrophages were differentiated to aggressive effector cells expressing tumor necrosis factor—alfa (TNF-α) and matrix metalloproteinases, which could contribute to the underlying tissue destruction and inflammation.[8] Active collagen synthesis in lesions of GA has been shown by Northern and in situ hybridization studies. In this paper, the authors showed a low level of transforming growth factor—beta, and elevation in interleukin-1 (IL-1) and -2 (IL-2) receptors, leading them to postulate that collagen synthesis is ultimately regulated by helper T cells through the activation of macrophages and subsequent secretion of fibroblast-activating chemokines.[9] They postulate that this collagen synthesis is important as a reparative phenomenon in patients with GA. Local production of IL-2 has also been shown in lesions of GA, and was not found in peripheral blood mononuclear cells.[10]

Additional studies that may shed some light on the pathogenesis of GA have been conducted. One study of neutrophil migration found that neutrophil chemotaxis was impaired in the body of GA patients, while normal in vitro.[11] The authors hypothesized that in patients with defective neutrophil chemotaxis, macrophages take over their role at an inflammatory site, leading to the granulomatous inflammation seen in GA, rather than suppurative neutrophilic inflammation.[11] Eosinophils, though occasionally identified in lesions of GA, are more likely bystanders than actively involved in etiopathogenesis.[12] Heparan sulfate (HS) is normally attached to the surface of keratinocytes, but has been shown to be present in the interstitium in patients with GA.[13] Elevated levels of serum lysozyme were found in patients with GGA as opposed to LGA and normal controls.[14] TIMP metallopeptidase inhibitor 1 (collagenase) mRNA has been shown to be elevated at the outer edges of palisaded granulomas in patients with GA.[15] The overall significance of these findings in the pathogenesis of GA is unknown, and additional studies are clearly needed.

Some argue that elastic fiber degeneration is the underlying dermal alteration in GA and not collagen, based on electron microscopy results and special studies for elastic fibers.[16,17] Macrophage metalloelastase (a matrix metalloproteinase) has been shown to be elevated in areas of elastin degradation in several granulomatous conditions, including GA.[18] GA-related elastic fiber destruction has also been reported to culminate in mid-dermal elastolysis.[19] These findings may hint at a common thread between GA and annular elastolytic giant cell granuloma (AEGCG).

An infectious etiology has been postulated; however, studies to date have largely been negative.[20] While some infectious agents, including HIV, infectious hepatitis, and Borrelia species have been reported as triggers in some cases, the occurrence of GA may represent a nonspecific cutaneous reaction in these patients rather than a direct result of the infection. A further discussion of infectious triggers of GA can be found below.

Overall, at least some variants of GA may be ultimately caused by a delayed-type hypersensitivity to an as yet unknown source. Perhaps, given the multitude of reported triggers, associations, and presentations, it is possible that there is no one, singular "cause" of GA but rather multiple pathways that ultimately culminate in this condition.[21] The reported triggers and multiple diseases reported to be associated with GA are discussed below.

ASSOCIATIONS

GA may occur as an isolated, idiopathic entity, but reports persist describing GA in the setting of a variety of systemic processes. The most widely reported diseases associated with GA are diabetes and hyperlipidemia, though rare reports have also described GA in the setting of malignancies, systemic infections, and thyroid disease. There are also numerous reports of drug-induced forms of GA.

The story of GA and diabetes has evolved over many decades, with numerous papers both supporting[22-29] and refuting[30-33] a connection between the 2 conditions. In a 1989 paper by Winkelmann et al,[34] 20% of patients with GGA were diagnosed with diabetes mellitus. An important caveat noted in this paper also applies to many studies that came both before and after: "A preselected population of more difficult cases seen at tertiary referral institutions … represents a fraction of the entire group with a given disorder and yields epidemiologically skewed inferences about associations between diseases."[34] With that important caveat, there are a number of studies—mostly from large institutions—suggesting an association between GA and diabetes. In 1984, a study of 557 patients with GA found that 24 (4%) had diabetes.[26] In a comprehensive study of GA in a Korean population, 4 of 52 patients with GA were found to have diabetes (8%), a higher rate than that of the general Korean population.[35] A retrospective case-control study of 61 patients later showed that insulin-dependent diabetes was significantly increased in patients with GA, and the authors noted a higher prevalence of diabetes mellitus (DM) in patients with LGA versus GGA.[28] Twelve of 84 patients (14%) with GA were found to have diabetes in 1 paper, with 5 having generalized GA.[29] In a study of 52 patients with GA (13 with GGA and 39 with LGA), patients with LGA had similar rates of carbohydrate intolerance as controls, but a significantly higher percentage of patients with GGA (77%) had carbohydrate intolerance.[23] Lending some strength to the reported association between GA and DM, diabetes has been reported in association with other cutaneous reactive granulomatous processes, most notably NL.[36]

Some reports also describe a lack of association between GA and DM. In a study of 126 patients with GA, no association was found between GA and DM when compared to controls.[31] Controls were patients with psoriasis, which is now thought to have a potential connection to DM.[37] No significant difference between 16 patients with GA and matched controls was found when using several markers of glucose tolerance.[32] In another report of 23 patients with LGA or GGA, only 1 patient was diagnosed with DM.[30] There are also 2 separate studies from India that looked at the cutaneous manifestations of 500 patients with type I diabetes[38] and 500 patients with predominately type II diabetes,[39] and only 1 patient in each study (0.2%) was found to have GA.

In the end, despite a large number of studies published on GA and DM, definitive evidence for an association is lacking. Future studies attempting to connect DM to GA must be well designed and controlled, as the aforementioned studies often used different methods of assessing for diabetes, often did not differentiate between clinical variants of GA (or used different definitions of GA subtypes), or did not assess for likely confounders, including age and comorbidities. Screening is inexpensive; in patients with risk factors or symptoms suggesting glucose intolerance, physicians should consider testing.

In addition to DM, several other conditions have been suggested to be associated with GA. A recent study of 140 patients showed that 80% had dyslipidemia, as compared to about 52% of controls.[40] Improvement of dyslipidemia led to concurrent improvement of GGA in a 62-year-old Japanese woman, though there could have been other reasons for her improvement.[41] Autoimmune thyroiditis also may be associated with GA, based on small studies and series.[42-44] GA, type I DM, and autoimmune thyroiditis have been reported in the same patient.[45] Other granulomatous conditions have been described in association with thyroid disease, suggesting that GA and thyroid disease may be related in some patients.[46,47]

It has been postulated that GA may be associated with an infectious agent, but studies have been mixed. A small study of 10 patients did not reveal any molecular or culture-based evidence for a bacterial, mycobacterial, or fungal cause.[20] A similar study looking for Bartonella species in 18 cases of previously diagnosed GA also yielded negative results.[48] A number of European studies have suggested a connection between GA and Borrelia species. In one such study, patients with GA were more likely than controls to have detectable levels of *Borrelia burgdorferi* DNA in their urine.[49] Another study showed that 127 of 157 patients with GA had evidence of Borrelia by focus-floating microscopy.[50] A third study found that pseudorosettes are a common finding in patients with GA, and may be predictive of borrelial infection in European patients with GA.[51] In 2002, Winkelmann[21] presented a case of tuberculosis (Tb) in which the patient also had GA (based on a polymerase chain reaction study of a lesion that was negative for *Mycobacterium tuberculosis*). The author postulated that historical

cases of GA attributed to Tb were noninfectious, but represented a Tb-related immune response manifesting as GA.[21] It is worth noting that tuberculoid or granulomatous reactions to tuberculosis infection may mimic GA. Viruses have also been suggested as associated with GA, and a case of GGA in a patient with chronic hepatitis C virus improved after interferon-alfa therapy.[52] Similarly, a case of GGA in a patient with chronic hepatitis B virus infection also improved after interferon-alfa therapy; polymerase chain reaction studies performed on lesional skin biopsy specimens from this patient were positive for hepatitis B virus DNA.[53]

Hypothesizing that patients with GA are at risk of developing "odd sequelae," Dahl[54] studied 32 patients seen at the Mayo Clinic and found that after at least 20 years of follow-up, most patients with GA heal, remain "remarkably healthy, and do not ordinarily develop other odd diseases." A recent study found no association between GA and uveitis (in contrast to a previous report[55]), and screening eye examination is not routinely recommended for asymptomatic patients with GA.[56] GA has also been reported in the settings of sarcoidosis[57,58] and Sweet syndrome.[59]

GA has been reported in temporal association with various malignancies, but a recent review on the subject concluded that no causative relationship has been proven.[60] Cases reported have ranged from GA preceding diagnosis of malignancy by 5 years, occurring concurrently, or developing as much as 27 years after the cancer. That said, there have been a number of case reports describing patients with GA and malignancy, including Hodgkin[61-63] and non-Hodgkin[64-67] lymphoma, leukemia,[68,69] and visceral malignancies, typically adenocarcinoma.[70,71] A variety of GA subtypes were described in these patients, who were typically >60 years of age.[72] Two association studies attempting to define whether a correlation exists between malignancy and GA concluded that there is no relationship.[72] At this point, expert consensus remains that clinicians should consider screening for malignancy in older patients with GA, or those with atypical, widespread, or recalcitrant clinical presentations.[60,66] Before a true association between GA and any of the conditions mentioned above can be determined, additional large-scale, controlled studies are necessary.

GA and its connection to HIV deserves special mention. The first discussion of GA in the setting of HIV/AIDS was probably in 1985, when it was noted that a number of noninfectious dermatoses including GA may have an increased incidence in patients with AIDS.[73] A report of perforating GA in a patient with AIDS was described in 1987,[74] and several patients were subsequently reported to have "atypical" forms of GA—namely with disseminated papules or perforating GA.[75,76] Four patients reported in 1989 were described as having a papular form of GGA, or an "extensive" LGA that appeared clinically similar to Kaposi sarcoma.[77] In 1999, Toro et al[78] published a study of 34 patients with GA and HIV. In these patients, 59% presented with AIDS, and unusual features of GA included oral lesions in 1 and perforating lesions in 2 patients. Moreover, GA was found to be generalized in 20 patients (59%) reported in this study, and in 15 of 23 (65%) of patients reported previously, suggesting that patients with HIV are more likely to have generalized disease than the general population. Clinically, the lesions were predominately papular rather than annular. Histopathologic findings included an interstitial pattern in 8 patients, palisaded in 18, perforating in 2, and mixed palisaded and interstitial in 6; no clinicopathologic correlation was discussed.[78] An editorial published at the same time drew attention to 2 HIV-infected individuals who presented with photodistributed GGA.[79] Six additional cases of HIV-associated GA were reported in 2000, with most patients presenting with papular lesions on extensor surfaces.[80] Some highly atypical cases of GA have also been reported in patients with HIV, including generalized umbilicated papules[81] and a macular form with $CD8^+$ T cells as the predominate infiltrate.[82]

There are reports of antiretroviral drugs both improving[83-85] and triggering[86] GA. Because AIDS is a problem with cell-mediated immunity, GA associated with HIV was initially interpreted as evidence against the hypothesis that GA is a delayed-type hypersensitivity reaction. However, given the complex interplay between HIV and the immune system, the story is probably not so straightforward. It is difficult to know whether the reported cases of GA are in fact true GA or rather are reactive granulomatous responses caused by HIV or antiretroviral drugs. Nonetheless, because many HIV patients in the general population are asymptomatic, the US Centers for Disease Control and Prevention currently recommends wider screening for HIV. As such, clinicians should assess patient risk factors and strongly consider HIV testing in patients with a new presentation of GA. Patients with perforating GA, or those with GGA with papules in particular should be screened, because these seem to be the predominant GA variants associated with HIV.

TRIGGERS

In addition to the reported associations between GA and the above systemic diseases, there have also been a number of reported triggers of GA. Some of the more unique triggers of the disease include a lightning strike, termed "lightning-strike granuloma,"[87] tattoo (caused by red pigment, developed after 37 years),[88] a bee sting,[89] and GA induced by an octopus bite.[90] GA has also been reported as a contact dermatitis[91] and as an isomorphic response after saphenectomy.[92]

There have been many other triggers reported to lead to the development of GA. In particular, GGA has been reported as developing after several vaccinations, including Bacillus Calmette–Guérin,[93-96] hepatitis B,[97] tetanus and diphtheria toxoid,[98] and an antitetanus[99] vaccination. With that said, the inarguable health benefits of vaccinations far outweigh the exceedingly rare potential risk of GA development in all cases.

In a series of 5 patients, Kapoor et al[100] present a succinct review of the differences between an isotopic response (ie, developing a unique skin disease at the site of another healed and unrelated skin disease) and an isomorphic response (ie, the Koebner phenomenon). In these 5 patients, GA developed as an isotopic response at sites of previous herpes zoster infection. Multiple other case reports have demonstrated the same phenomenon,[101-105] and GA has also been reported after varicella infection in 2 children.[106,107] A case of GA after herpes zoster infection also showed features of an isomorphic response in an isolated report.[108]

A number of medications have been implicated in triggering GA, though most are only in isolated case reports. These medications include TNF-α inhibitors, allopurinol,[109] topiramate,[110] and gold therapy (for rheumatoid arthritis).[111] While some cases of GA associated with infectious hepatitis have improved after treatment with interferon, reports of interferon-alfa–induced GA have also been reported.[112] LGA has also been reported after injection of collagen for soft-tissue augmentation[113] and after mesotherapy.[114]

TREATMENT

In 1982, Wilkin et al[115] wrote "in general, successful treatment of any disease is probably inversely related to the number of recommended regimens." It is not surprising that they were writing about GA, because there have been numerous reported treatment options for GA, many of which are supported by only small, uncontrolled case studies or series. In fact, in a series of 67 patients with GA, there was no significant difference between duration of disease between treated and untreated patients.[116] Further, it is estimated that around 50% of patients with LGA will spontaneously remit within 2 years, although recurrence is also common.[117-120] While some initial reports suggested potassium iodide as an effective therapy for patients with GA,[121,122] a 1994 double blind, placebo controlled trial[123] showed that the results were no better than placebo, prompting the authors to note "because of the potential for spontaneous waxing and waning of this disease, case reports and open studies that lack placebo control may give a false impression of efficacy of individual therapies." This concept is important to keep in mind when interpreting the available data on treatment options for GA that are discussed below.

Despite the relative lack of evidence for effective therapies for GA, many patients desire treatment for symptomatic or cosmetic reasons, and it is important to discuss what options do exist. The intralesional injection of triamcinolone has strong expert consensus as a first-line therapy, but few studies have been designed to test this. In 1975, 52 patients with LGA were treated with intralesional injection of triamcinolone 5 mg/mL or sterile saline.[117] Sixty-eight percent of those injected with steroid experienced complete clearance compared to 44% in the sterile saline group. Partial clearance was better in the saline group (33% vs 24%), and <50% of patients in both groups had recurrence of lesions after improvement. Because injection of medication leads to localized trauma of the skin, it is important to note that lesions of GA have also been shown to improve after trauma alone. Robinson, in 1953, described improvement after incision of lesions (he had previously noted improvement in lesions after biopsy).[124] Biopsy alone has also been reported to improve lesions of patch GA[125] and GGA.[126] Several reports of improvement after "scarification" (ie, the use of a 19-gauge needle drawn across the lesions until capillary bleeding occurs) have been described as successful.[115,127] Improvement has also been described by "repetitive pricking"[128] and cryotherapy.[129]

A number of studies have examined the role of phototherapy in treating GA. Psoralen plus ultraviolet A light phototherapy (PUVA) was first described as effective in patients with GGA in a report of 5 patients who improved within 1 month (after 2-3 treatments per week) of starting therapy.[130] In a follow-up report, an isolated patient with GGA was treated with bath PUVA and experienced improvement with this modality after 15 treatments.[131] Bath PUVA was also reported to

improve an 11-year-old with GA.[132] One report of PUVA for GGA without long-term treatment[133] prompted 3 additional reports of GGA that improved with PUVA but did require maintenance therapy to help prevent relapse.[134] In a retrospective study of 33 patients with GGA treated with PUVA (with the inclusion of 7 patients multiple times because they had experienced relapse in their disease and required additional therapy with PUVA), clearance was achieved in 50%, a partial response was seen in 41%, and only 9% showed no improvement. In long-term follow-up, 15 of 19 patients remained clear of disease at 6 months, 6 of 19 remained clear at 12 months, and 3 remained clear at 2 years.[135] Topical PUVA has also been described as therapy for LGA. In a study of 4 patients, all experienced improvement in the lesions after 4 weeks, with no recurrences after 4 months of follow-up.[136] UVA-1 therapy has also been described as effective in patients with GGA, although this modality is not widely available. In 1 report, 4 patients improved at least partially after 3 weeks of UVA-1, with 5 days per week of treatment.[137] A subsequent study of 20 patients with disseminated GA (ie, no clear description of the clinical findings) found that half experienced "excellent results" with 5 times weekly UVA-1 therapy.[138] Building on this, 4 patients were reported to have improvement in their "multiple localized GA" with higher doses of UVA-1.[139] In a study of 20 patients, 13 had their disease ameliorated after therapy with UVA-1.[140] While larger studies comparing different treatment modalities and placebo are needed, these findings do suggest that PUVA, or UVA-1 if available, should be considered for therapy of GA, particularly in patients with widespread disease.

Other forms of phototherapy have also been described as effective for patients with GA. Narrowband ultraviolet B light phototherapy was shown to improve disease in 1 patient after 24 total treatments.[141] The excimer laser has also been described in reports of improving cases of GGA.[142] It should be noted that while AEGCG may simply represent GA occurring on sun-damaged skin, there have been rare reports of GA occurring in a seasonal pattern, possibly correlated with increased exposure to ultraviolet light.[143] Similarly, a case of photo-induced GA has been reported after receiving paroxetine,[144] suggesting that the role of ultraviolet radiation in GA is incompletely understood.

A number of lasers have been used to treat patients with GA, and some early reported success was described with use of a pulsed-dye laser (PDL).[145,146] However, in the largest study to date, 13 patients with GA (all women, with 5 localized cases and 8 generalized cases) were treated with PDL and the results were disappointing. After 3 sessions, <33% of skin lesions treated showed improvement, and the treatment was associated with adverse effects, including postinflammatory hyperpigmentation. The authors did find that lesions of LGA improved more often than GGA (56% of LGA lesions treated showed improvement after 3 sessions compared to 14% for GGA). The authors did not compare treated lesions to untreated lesions.[147] Other lasers reported as successful in isolated case reports include an yttrium laser[148] and a neodymium-doped yttrium aluminium garnet laser.[149] Photodynamic phototherapy (PDT) has also been discussed as a therapy for patients with GGA and LGA, with some limited data suggesting a potential role for this therapy in refractory cases.[150-152]

Antimalarial drugs have been described for GGA since the first report of chloroquine 250 mg twice daily was reported as effective after just 2 months of therapy in 1959.[153] Hydroxychloroquine was first reported as effective in patients with GGA in 1987.[154] In a study of 6 children treated with antimalarials (4 with chloroquine and 2 with hydroxychloroquine), all achieved remission within 4 to 6 weeks of instituting treatment.[155] In a study of 9 patients treated for 4 months with hydroxychloroquine (9 mg/kg/d for 2 months followed by 6 mg/kg/day for 1 month, followed by 2 mg/kg/day for 1 month with half this dose used in the 1 child in the study), all achieved remission without relapse in the 9-month follow-up period.[156] One report of GGA in a photodistribution responded to therapy with chloroquine, with multiple recurrences when taken off the medication.[157] Hydroxychloroquine therapy is generally efficacious, and this therapy probably merits first-line consideration in patients with generalized disease—at least until additional studies are conducted to confirm or deny this conclusion.

TNF-α inhibitors have shown promise in treating widespread and recalcitrant granulomatous dermatitidis, including GA. Case reports have described effectiveness in treating patients with GGA with a combination of adalimumab and methotrexate,[158] adalimumab alone,[159-161] and etanercept.[162] GA with extensive involvement of the extremities has responded to infliximab[163,164] and adalimumab.[165] A recent study reported 7 patients with generalized GA, all of whom initially responded to adalimumab, which was well tolerated in this cohort.[166] Similar to psoriasis and sarcoidosis where these drugs are used to treat the disease, TNF-α inhibitors have also been reported to trigger GA in a few instances.[167,168] Additional studies are needed to show the risk/benefit profile of using TNF-α inhibitors to treat patients with GA and to justify their regular use.

Fumaric acid esters have received considerable attention in Europe for successfully treating noninfectious granulomatous processes generally, and GA specifically.[169-174] Currently, fumaric acid esters are not widely used in the United States, with the first approval (for multiple sclerosis) occurring in 2013. Similarly, tranilast is a medication unavailable in the United States that has been described as effective in Japan for atopic dermatitis, and recently granulomatous diseases, such as sarcoidosis and GA. It is hypothesized that tranilast directly affects the monocyte–macrophage lineage cells, which could explain its effectiveness for these granulomatous conditions.[175]

In 1954, vitamin E was first described as a treatment for GA (along with pantothenic acid derivatives), and 8 of 9 patients treated showed complete resolution.[176] In a retrospective cohort study of patients with "disseminated" GA (defined as having >10 lesions over at least 3 anatomic regions), the authors compared 21 patients treated with oral vitamin E to 17 patients treated with a "wait and see" approach. They found complete healing in 40% of patients, and improvement in an additional 30% of the patients treated with doses of vitamin E between 400 and 600 IU. However, lesions spontaneously disappeared in 31% and improved in 25% of untreated control patients.[177] Three patients with disseminated (apparently used in this article as equivalent to generalized) GA were treated with oral vitamin E and zileuton (a 5-lipoxygenase inhibitor). All 3 patients resolved after 2 to 3 months of therapy with minimal adverse effects.[178]

In keeping with Wilkins et al's premise[115] that successful treatment is probably inversely related to the number of recommended regimens, there have been many additional treatments described as effective in small case reports or series. These include doxycycline,[179] rifampin, ofloxacin, and minocycline,[180,181] dapsone,[182-184] clofazimine,[59] allopurinol,[185] cyclosporine,[186-188] methotrexate,[189] hydroxyurea,[190] alkylating agents, including chlorambucil,[191-194] niacinamide,[195,196] defibrotide,[173] oral calcitriol,[197] topical imiquimod cream,[198-201] topical pimecrolimus 1% cream,[202] topical tacrolimus 0.1% ointment,[203-206] intralesional interferon-beta,[207] intralesional interferon-gamma,[208] isotretinoin, both alone[209-216] and in conjunction with topical pimecrolimus,[217] and etretinate.[215,218] Efalizumab, a T cell modulator that is no longer available, has also been reported as effective for patients with recalcitrant GA.[219] Surgical excision is a reported option for lesions of subcutaneous GA, though recurrence is common.[220,221] In the end, there are multiple options for treating patients with GA, with limited evidence supporting any particular regimen. Clearly, however, more research is needed in this area.

In conclusion, there are 3 relatively common clinical variants of GA (ie, localized, generalized, and subcutaneous), and a number of rare subtypes. The histology is notable for mucin, with 2 patterns of granulomatous inflammation (ie, palisading and interstitial) typically seen. While the etiology is not known, GA may represent a reaction to a number of different stimuli leading to a common pathway, possibly mediated by delayed-type hypersensitivity and connective tissue damage. GA may be associated with HIV, diabetes, dyslipidemia, malignancy (especially hematologic), and thyroid disease, although stronger studies are needed to clarify these possible associations. Infections other than HIV and certain vaccines may also trigger GA, in addition to multiple other rarely reported stimuli. GA often self-resolves, but patients frequently seek treatment, and while data are lacking for many aspects of GA, treatment options in particular suffer from a paucity of large clinical trials. LGA may respond to intralesional glucocorticoid, and widespread disease is probably best initially treated with antimalarial drugs or phototherapy. GA is a common entity with a wide range of clinical presentations. It suffers from a lack of quality data, and additional studies are necessary to better elucidate the cause, triggers, associations, and treatment of this condition.

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Answers to CME examination

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