Granuloma annulare

Clinical and histologic variants, epidemiology, and genetics

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Learning objectives
After completing this learning activity, the learner should be able to recognize history, pathogenesis, genetics, epidemiology, clinical and histological presentation of GA.

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Granuloma annulare (GA) is a poorly understood condition characterized by a set of clinical morphologic variants with 2 predominant histopathologic patterns of inflammation. This review provides a comprehensive overview of the available information about the clinical variants and histopathologic features, current epidemiologic data, and potential genetic underpinnings of GA. Much of the current understanding of GA is based on retrospective studies, case series, and case reports; this review aims to synthesize the available information and present it clearly for practicing dermatologists. (J Am Acad Dermatol 2016;75:457-65.)

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

Granuloma annulare (GA) is a relatively common skin disorder of uncertain etiology. Thomas Colcott Fox first described the entity in 1895 as "ringed eruption," and over the next decade additional similar reports were described. In 1902, Radcliffe Crocker used the term GA, and a review by Graham Little in 1908 described previous cases of the entity under this name, which became the standard term describing this condition.[1] Over the past century, many case reports and small studies have been published further characterizing different aspects of this condition. While the cause remains unknown, HIV, diabetes, dyslipidemia, malignancies, thyroid disease, and other conditions have all been described as potentially connected to GA with varying levels of evidence. GA is often localized to the hands and feet, is minimally symptomatic, and frequently self-resolves. However, because of the appearance, tendency to recur, and occasional widespread presentation, patients often desire treatment. While there are many treatment options, limited data are available to guide clinical management. This review will serve to describe the clinical and histologic features of the different

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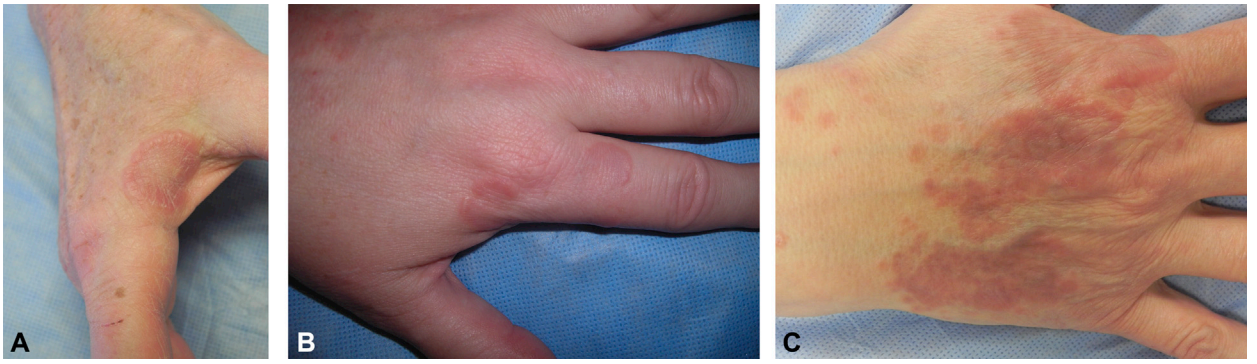

Fig 1. Localized granuloma annulare. Erythematous annular plaques may be singular (**A**) or multiple (**B**). Localized granuloma annulare may also present as papules coalescing into circular plaques (**C**).

subtypes of GA and to describe available data on the epidemiology, genetics, pathogenesis, disease associations, triggers, and treatment options.

CLINICAL VARIANTS

The term GA appropriately describes the classic variant characterized by ringed erythematous plaques with granulomatous inflammation seen histologically. However, GA now encompasses a spectrum of disease. The most common variant of GA is localized GA (LGA), and other well defined forms include generalized GA (GGA) and subcutaneous GA (SGA). Over time, clinicians have described more atypical, rare variants. These descriptions are frequently presented as isolated case reports or small case series, making a synthesis of the clinical morphologic variants a challenge. Nevertheless, this section will work to clarify the different subtypes and clinical variants of GA.

LGA is the prototypical subtype of GA, and is characterized by pink to red nonscaly papules and plaques often in an annular configuration on the extremities. The hands and feet in particular are commonly involved (Fig 1).[2-4] This subtype is often cited as characterizing around 75% of the reported cases of GA, and has a tendency to remit within 2 years.[2,3,5-7]

In 1989, Winkelmann published a study of 100 cases of patients with GGA.[8] This represents one of the largest series of patients with this entity, and is quite helpful in describing the clinical pattern and morphology. Generalized GA was defined as "affecting at least the trunk and either upper or lower, or both, extremities" (Fig 2). Patients were divided into 2 morphologic groups: 67 patients with predominately annular lesions comprised of individual coalescing papules arranged in ring-like configurations, and 33 patients with predominately nonannular lesions consisting of symmetrically scattered, often coalescing papules favoring the chest and back (Fig 3). Over time, many published reports of GA have described patients' eruptions as "generalized GA" without strictly adhering to the definition used by Winkelmann in his report. This lack of consistency among subsequent reports of "generalized GA" makes analysis of the available data difficult. Adding further confusion to the literature is the term "disseminated GA." In their 1989 paper on GGA, Winkelmann and Dabski[8] rejected 15 cases of patients with extensive involvement of the extremities only, considering them "disseminated, but not truly generalized." This seems to be an informal use of the English word "disseminated," rather than Winkelmann's consideration of "disseminated GA" as a separate and distinct variant of GA. Unfortunately, this term has subsequently been used loosely in the literature, ranging from case reports seemingly using disseminated to mean the same as generalized[3,9-11] or as a description of cases characterized by nonannular papules (which Winkelmann had considered in his original definition of GGA).[6] Given the confusion since Winkelmann's 1989 paper, GA with extensive involvement of the extremities is likely better considered a form of generalized GA rather than its own subtype. Additional studies would need to be conducted to determine whether this difference has any clinical significance, which might justify use of both disseminated and generalized in describing GA.

A particularly noteworthy subtype of granuloma annulare is the subcutaneous variant (SGA). Painless, firm subcutaneous nodules characterize this entity, also known as pseudorheumatoid nodule. SGA is seen nearly exclusively in children, often on the lower extremities (Fig 4), although cases with

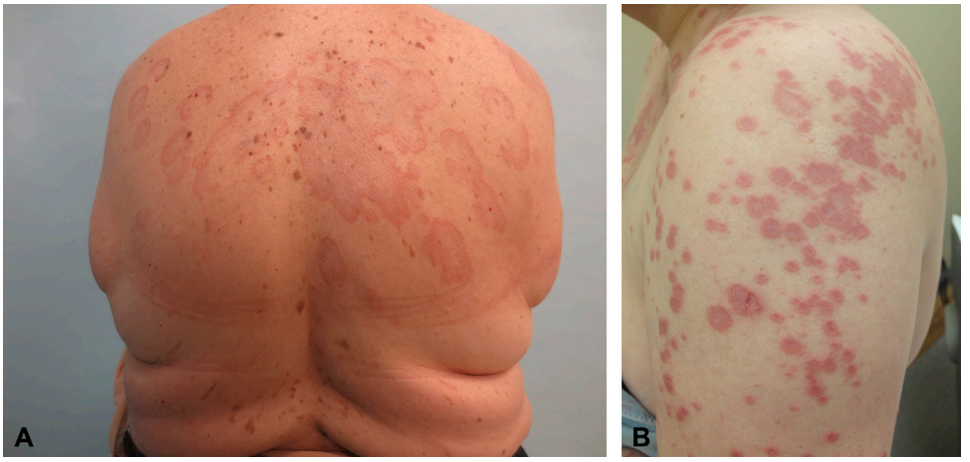

Fig 2. Generalized granuloma annulare. Patients may present with annular plaques on the trunk (**A**) and extremities (**B**).

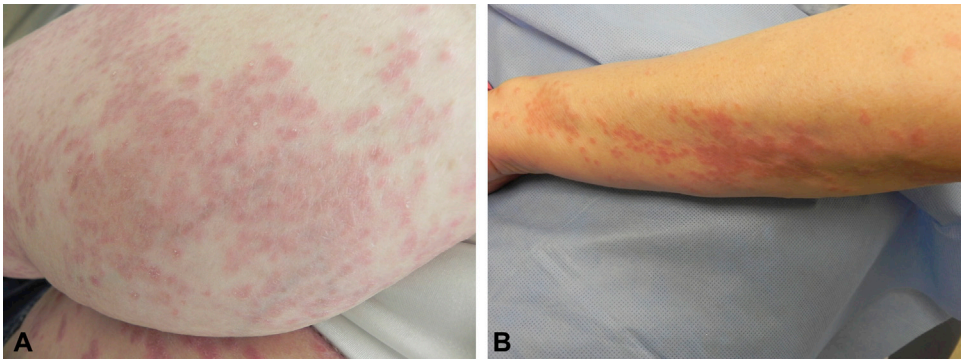

Fig 3. Generalized granuloma annulare with disseminated papules coalescing into plaques on the posterior arm of one patient (**A**) and forearm of another (**B**). Photograph **A** courtesy of Dr Kathy Schwarzenberger.

forehead and scalp involvement have also published. Similar to the other subtypes of GA, the lesions show a tendency to regress with time but may recur.[12-19]

While LGA, GGA, and SGA are the most widely recognized clinical phenotypes of GA, a number of rare variants have been reported. Of these less common forms, perforating GA (PGA) is perhaps the best described. PGA seems to have been first reported in 1971, and can present either localized to the extremities or generalized to involve the trunk and extremities.[20] The primary lesion in most reports is an umbilicated papule with a central crust or hyperkeratotic core (Fig 5).[20-24] The lesions may become pustular[25] or ulcerate.[26] Large flat patches of GA have also been reported[27,28] ("patch" or occasionally "macular" GA), but given the overlap between this condition and reactive granulomatous eruptions, such as interstitial granulomatous dermatitis, it may be challenging to distinguish between these 2 entities. Extremely rarely reported variants of GA include palmoplantar, blaschkolinear, pustular, and visceral.[27-38] In addition, depending on the author, annular elastolytic giant cell granuloma (AEGCG), also known as actinic granuloma, may[30,39] or may not[40] represent a photoinduced subtype of GA, or simply GA appearing on sun-damaged skin (Fig 6). One case of GGA on predominately photoexposed areas resolved with features of anetoderma after 5 to 6 months.[41] Descriptions of the clinical variants of GA appear in Table I.

EPIDEMIOLOGY

There have been no large-scale, population-based studies documenting the overall incidence or prevalence of GA, although 1 review article published in 1980 reported that 0.1% to 0.4% of new patients presenting to dermatologists were diagnosed with GA.[2] Overall, the condition is most commonly reported in patients in the first 3 to 5 decades of life, with a female to male ratio of around 1-2:1.[2,6,7,42-45] However, it is important to

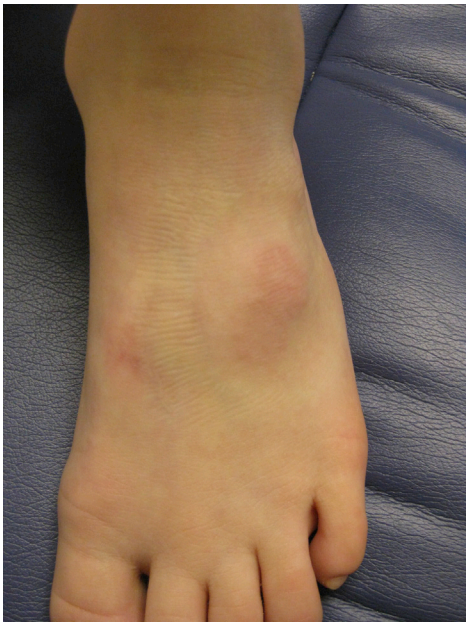

Fig 4. Subcutaneous granuloma annulare is more common in children and presents as a firm, painless nodule. Photograph courtesy of Dr Melinda Jen.

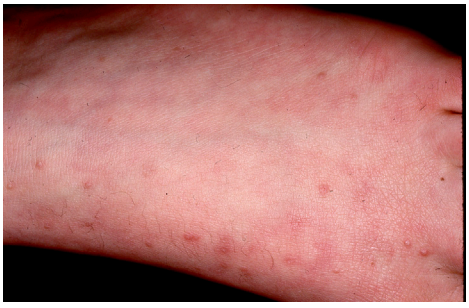

Fig 5. Perforating granuloma annulare is a rare subtype and can present with umbilicated papules with central plugs of keratinaceous material. Photograph courtesy of Dr William D. James.

note that by not differentiating between clinical variants of GA, these data may be skewed, because SGA tends to occur more commonly in children,[12,14-18] while GGA is often reported in elderly patients.[8,46,47] One study of Korean patients presenting with GGA described a bimodal distribution in age (44% presented within the first decade of life, and 44% presented over the fifth decade of life).[44] This bimodal age distribution of GGA has been reported before,[2] but is not always replicated.

As noted above, SGA is reported almost exclusively in children, with an age range of around 1 to 14 years of age.[12,14-18] One patient was reported as having lesions present at birth.[13] PGA has been reported to be more common in children,[22,23] but it may also affect adults.[20,21,25,48] Patch GA is typically described in women between 40 and 74 years of age.[27,28,49]

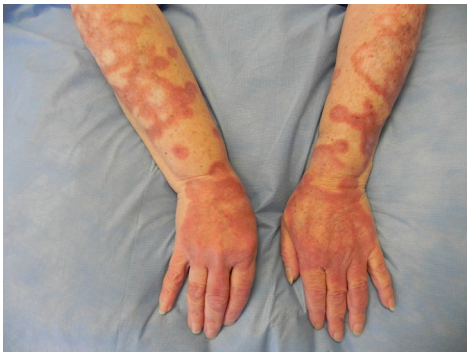

Fig 6. Annular elastolytic giant cell granuloma is considered by some a distinct entity, but shares some clinical and histologic features of granuloma annulare. Annular elastolytic giant cell granuloma typically presents with photoexposed annular plaques with central pallor and atrophy.

GENETICS

A relative paucity of data exists on the genetics of GA. In 1987, Winkelmann reported that there were <20 cases of GA described in at least 2 immediate family members.[50] An additional familial case of generalized PGA was reported 1 year later.[51] GGA and human leukocyte antigen (HLA)-Bw35 may have an association.[52] HLA-Bw35 has also been associated with thyroid disease,[53] which is in itself reported to be associated with GA.[54] Further evidence for a familial association comes from the first published report of adalimumab use in GA, a 67-year-old woman with disseminated (based on the authors' description, this seems consistent with generalized) GA received 40 mg of adalimumab per week for 3 months with marked improvement in her disease. After her identical twin sister experienced similar results, the patients were found to harbor the HLA-AH8.1 genotype, which has been associated with increased production of tumor necrosis factor−alfa by peripheral blood mononuclear cells.[55]

HISTOLOGY

Histologically, mucin coupled with a palisading or interstitial pattern of granulomatous inflammation represents the principal finding in all subtypes of GA, but other patterns may rarely be seen.[4,56-61] The palisading pattern is characterized by a central zone of necrobiotic collagen surrounded by palisading histiocytes and varying numbers of lymphocytes (Fig 7). The interstitial pattern is characterized by collections of histiocytes scattered between and

Table I. Clinical variants of granuloma annulare

Type	Classic description	Estimated frequency	Note
Common			
Localized	Annular plaques, limited, classically on the hands or feet	+++++	Most common and well-recognized form of GA
Generalized	Annular plaques or papules, diffuse, classically on the extremities and trunk	+++	Extensive involvement of the extremities probably fits into this subtype, and given the confusion in the literature, "disseminated" GA is likely best thought of as a form of GGA in the absence of better data
Subcutaneous	Subcutaneous nodules	+++	Almost exclusively seen in children
Uncommon			
Perforating	Umbilicated papules with keratotic core	+	May be more common than reported given the difficulty of histologically locating the area of perforation. Probably associated with HIV, especially when disseminated
AEGCG	Sun-exposed lesions, atrophic white center	+	Considered by some to represent a distinct entity, AEGCG shares many overlapping clinical and histologic features with GA
Patch	Red-brown or violaceous patches, extremities > trunk	+	Can be localized or generalized. There have been few reports in the literature, but almost exclusively described in women
Palmoplantar	Acral papules	Rare	Typically painful, and more often seen on the palms

AEGCG, Annular elastolytic giant cell granuloma; *GA*, granuloma annulare; *GGA*, generalized granuloma annulare.

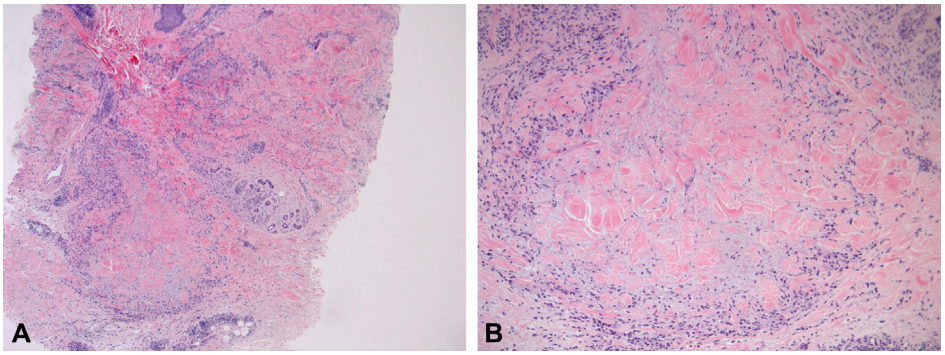

Fig 7. **A** and **B**, Palisading granuloma annulare. Lymphohistiocytic inflammation surrounds central altered collagen with palisades of histiocytes. Mucin is prominent. (Hematoxylin–eosin stain; original magnification: **A**, ×40; **B**, ×100).

around collagen bundles and blood vessels in the papillary and mid dermis (Fig 8). A recent study of 35 cases of GA described these 2 patterns in addition to sarcoidal granulomas and a mixed variant, although correlation with clinical morphology was lacking.[58] Winkelmann characterized 207 cases of GA and found that 71% showed the interstitial pattern, while 26% showed palisading granulomas.[62] This study also described mononuclear perivascular inflammation in all cases, and upon electron microscopy revealed histiocytic and macrophagic vasculopathy with small-vessel degeneration in areas of well-developed GA.[62] Multiple clinical and histologic morphologies in the same patient have also been described.[61]

While many studies group all clinical variants of GA together,[56] a paper by Yun et al[44] studied 54 patients in Korea with GGA using the clinical definition put forth by Winkelmann. They found that the 2 predominate histologic patterns were nearly equal in numbers (52% were characterized as palisading; 48% were characterized as interstitial). Mucin was seen in 94% of cases, an eosinophilic infiltrate in 44%, and nuclear dust in 33%. No vasculitis was seen. In 1 paper comparing GGA with LGA, only minor differences were seen on

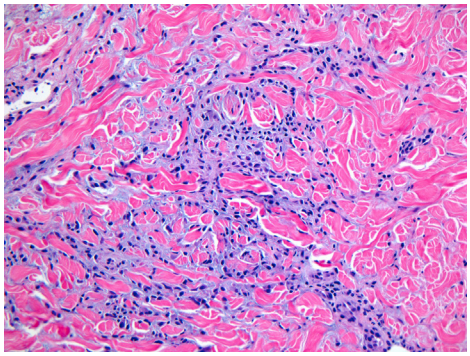

Fig 8. Interstitial granuloma annulare. Histiocytes intercalate between the collagen bundles singularly or in small aggregates. Mucin is again a prominent feature. Distinguishing interstitial granuloma annulare from reactive granulomatous processes, such as interstitial granulomatous dermatitis, may be challenging. (Hematoxylin–eosin stain; original magnification: ×100).

histologic examination, and no specific findings to allow for a diagnosis of GGA versus LGA based solely on histology were found.[4]

The typical findings seen in patients with SGA consist of multiple nodules in the subcutaneous layer and reticular dermis with degenerated collagen surrounded by palisading histiocytes and a peripheral zone of lymphocytes. Mucin is also seen in these deeper lesions.[12-19] Occasionally, histiocytes are more dispersed in the reticular dermis and subcutaneous layer, without the classic palisading pattern.[16] SGA in particular can mimic sarcoidosis clinically, and the presence of sarcoidal (or epithelioid nodules) histologically can make the diagnosis particularly difficult.[61] Eosinophils can be seen, and may be more common in SGA than in other variants of GA.[17] A comparison of LGA and SGA showed classic palisading granulomas in all cases (13 LGA and 8 SGA).[60]

Perforating GA is characterized by mucinous collagen degeneration surrounded by palisading granulomas, with transepithelial elimination of altered collagen.[20,22,23,25] This entity may be more common than is reported, given that transepidermal elimination of collagen may be missed without careful examination of serial histologic sections.[21,22] Histologic findings in the patients with patch GA described by Mutasim and Bridges[27] were consistent with the interstitial pattern of GA.

Other granulomatous disorders can mimic GA histologically. Necrobiosis lipoidica (NL) in particular can appear similar to GA under the microscope, because both entities are characterized by altered collagen. Despite this, the simultaneous occurrence of NL and GA is only rarely reported.[63,64] Several studies have been designed to differentiate between these conditions, including a 1986 study that showed 12 of 13 cases of GGA and 15 of 32 cases of LGA had intracellular elastin noted on hematoxylin–eosin staining, as opposed to 0 of 20 cases of NL.[65] Lysozyme staining has been reported as present in lesions of GA as opposed to NL and rheumatoid nodules (RN), which may also be confused with GA histologically.[66] The monoclonal antibody PG-M1 (a member of the CD-68 cluster) has been suggested as a reliable marker of histiocytes in lesions of GA, though more recently CD-123 staining was found to be denser in lesions of GA than RN or NL. This suggests a greater role for plasmacytoid dendritic cells in GA than previously thought.[67,68] A novel immunohistochemical stain for adipophilin has been shown to be a potentially useful marker for distinguishing GA, NL, and sarcoidosis. Staining for this marker in GA showed patterns corresponding to the distribution of histiocytes, with both intracellular and extracellular staining. Interstitial GA demonstrated more focal adipophilin expression than cases of palisaded GA.[69] GA and other granulomatous conditions, including NL and sarcoidosis, have been shown to have strong positivity for *gli-1*, which has been suggested as a potential target for therapeutic inhibition in patients with these conditions.[70] Other reactive granulomatous dermatoses, such as palisading neutrophilic and granulomatous dermatitis (PNGD), interstitial granulomatous dermatitis (IGD), interstitial granulomatous drug reaction (IGDR), and sarcoidosis can also mimic GA, and the characteristics that may distinguish these entities are described in Table II.

AEGCG shares significant clinical and histologic overlap with GA. While it may best be thought of as a variant of GA, AEGCG is felt by some to be a distinct entity. The histology of AEGCG demonstrates a nonpalisading granulomatous infiltrate of histiocytes, foreign body–type multinucleated giant cells, and lymphocytes in the mid to papillary dermis. Altered collagen, mucin, and lipid deposition are often absent.[71] Elastophagocytosis can be seen, characterized by elastic fibers highlighted within giant cells. Given that GA may also show elastophagocytosis and elastic fiber reduction,[4,65] that histologic feature alone may not reliably distinguish the 2 entities.

In conclusion, this review has discussed the historical context of GA, provided an overview of the different clinical and histologic subtypes of GA, and discussed the relatively limited data on the epidemiology and genetics of the condition. The accompanying continuing medical education article addresses the pathogenesis, disease associations and

Table II. Histopathologic comparison of the most common presentations of granuloma annulare, palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, and annular elastolytic giant cell granuloma

	GA	PNGD	IGD	AEGCG
Classic morphology	Annular plaques on the dorsal surfaces of the hands and feet	Papules on the elbows	Palpable cords on the trunk	Photodistributed annular plaques with atrophic centers
Histology	Palisading variant—central zone of altered homogenized collagen with mucin, surrounded by palisaded histiocytes and varying numbers of lymphocytes and neutrophils; interstitial variant—aggregates of histiocytes intercalating between and around collagen bundles with interstitial mucin	Varies by chronicity. Intense neutrophilic inflammation, with or without signs of leukocytoclasis and vasculitis, altered collagen, sparse palisades of histiocytes, and small granulomas. Mucin is minimal to absent	Scattered interstitial histiocytes in small aggregates with rare giant cells, often surrounding "rosettes" of altered collagen, which may be "detached" and "floating." Vasculitis is absent. Mucin is minimal to absent	Histiocytes grouped in aggregates and small granulomas around altered connective tissue. Elastophagocytosis may be evident on routine histologic sections or special stains. Elastic fibers are reduced or absent on special stains. Mucin is minimal to absent

AEGCG, Annular elastolytic giant cell granuloma; *GA*, granuloma annulare; *IGD*, interstitial granulomatous dermatitis; *PNGD*, palisaded neutrophilic and granulomatous dermatitis.

triggers, and potential therapeutic options for patients with GA.

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