Annular elastolytic giant cell granuloma in a woman with metabolic syndrome

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Abstract

Annular elastolytic giant cell granuloma is a rare granulomatous skin condition. It belongs to a group of skin and elastic fiber disorders. When it affects sun-exposed skin, it is also called actinic granuloma. The etiology and pathogenesis are still debated. However, sun-induced actinic damage to elastic fibers is acknowledged as the primary triggering factor, though the pathogenesis of instances in sun-covered areas is unknown. The most commonly linked systemic illness is diabetes mellitus. Different case reports show an association of this disease with hematological conditions, infections, sarcoidosis, and protoporphyria. Multisystemic involvement was also reported in a case. The disease is clinically recognized by erythematous non-scaly annular patches and plaques with raised borders and hypopigmented or skin-colored centers, sometimes atrophic. It is usually asymptomatic or mildly itchy. The presence of an inflammatory infiltration with non-palisading granulomas, multinucleate large cells, elastin degradation, and elastophagocytosis, as well as the absence of necrobiosis and mucin, are histopathological characteristics. We report a 5-year history of annular elastolytic giant cell granuloma in a 66-year-old woman with a history of type two diabetes mellitus, hypertension, and fatty liver disease (steatosis). She presented with asymptomatic polymorphic erythematous skin lesions mainly in sun-exposed areas.

Keywords: actinic granuloma, annular elastolytic, diabetes mellitus, elastophagocytosis, giant cell

Introduction

Annular elastolytic giant cell granuloma (AEGCG), as initially described by O'Brien in 1975, is a rare granulomatous skin condition. It belongs to a group of skin and elastic fiber disorders. The word actinic granuloma refers to its environmental factor, distinguishing it from other granulomas that are frequently confused with it [1]. The disease is clinically recognized by erythematous non-scaly papules that extend to form annular patches and plaques with raised borders and hypopigmented or skin-colored centers, sometimes atrophic (wrinkled tissue paper picture). It is usually asymptomatic or mildly itchy. Also, usually no alteration in sensation is noted. There is no yellow discoloration or telangiectasia. The lesions may reach several centimeters in diameter and they can be single, multiple, or generalized. Sun-exposed areas, such as the arms, forearms, dorsum of the hands, upper chest, upper back, legs (especially in women), face, and scalp, are common sites. Hair and other skin appendages are usually not affected. The oral mucosa and conjunctiva are usually spared. However, actinic granuloma of the conjunctiva has been reported [2]. Patients may also present with reticular, macular rash and non-scarring alopecia. Patients with skin phototypes one and two appear to be more affected than those with darker skin [1]. The outcome is variable. The disease may remain for months to years, although spontaneous resolution has been reported. The mean age of onset is 60 years old, with a slight female predominance of 1.5:1 [3]. Children and young age groups have also been reported to be affected.

Histologically, four variants have been described and more than one type may be seen in the same patient [4]. The most common one is the giant cell variant, which accounts for more than 50% of cases. It is distinguished by an interstitial infiltration constituted primarily of foreign body giant cells and surrounded by diffuse actinic elastosis. Some elastic fibers are digested by these massive cells (elastophagocytosis). The second most prevalent form is the necrobiotic variety, also known as the vascular variant. It resembles the first type. However, necrobiosis foci have also been observed. The histiocyte pattern, in which histiocytes are the predominant cells in the infiltrate, is the third pattern. These cells also produce elastase, which causes elastolysis. The last type is a sarcoid-like granuloma, which is assumed to represent an annular type of cutaneous sarcoidosis. Orcein stain shows the presence of small number of elastic fibers in these cell types. Histiocytes and various inflammatory cells can also be found [4]. In 1979, Hanke and co-workers used the term "AEGCG" for the first time for the lesions previously called O'Brian actinic granuloma, Miescher granulomatosis, and atypical necrobiosis lipoidica [5].

Difficulties in the categorization of AEGCG, among many other granulomatous skin diseases, are common. However, the presence of an inflammatory infiltration with non-palisading granulomas, multinucleate large cells, elastin degradation, and elastophagocytosis, as well as the absence of necrobiosis, lipid, and mucin, are histopathological features that aid in the diagnosis. These features are helpful in differentiating this entity from other granulomatous disorders like granuloma annulare, necrobiosis lipoidica, infectious granuloma, and sarcoidosis. Histopathological changes in elastic fibers can be either congenital or acquired. Congenital disorders include Buschke–Ollendorf syndrome and juvenile elastoma, which represent an increase in elastic fibers. Pseudoxanthoma elasticum and primary anetoderma represent degeneration. Acquired disorders include solar elastosis, mid-dermal elastolysis, and secondary anetoderma [6]. An inflammatory variation or prodromal stage of mid-dermal elastolysis may be represented by an annular elastolytic giant cell granuloma [7]. An association with different systemic diseases, mainly diabetes, was reported. Management is controversial, with variable treatment response. The efficacy of topical corticosteroids, tacrolimus, and systemic agents such as hydroxychloroquine, tetracyclines, methotrexate, pentoxifylline, and phototherapy has been reported to be variable [4].

Case Synopsis

A 66-year-old woman presented with asymptomatic skin lesions. Her skin eruption was distributed on sun-exposed areas such as arms, forearms, the dorsum of the hands, and scalp. Five years prior, she noticed the appearance of a rash for the first time on her arms without any known cause. Then new patches continued to arise continuously without remission in other areas, mainly in the summer period. Nonspecific diagnoses were made and various topical agents were tried without benefit.

The patient has had a known history of hypertension for 7 years (controlled with indapamide diuretics and amlodipine) and diabetes mellitus type two for 6 years (controlled with metformin, glimepiride, and insulin). She also had a history of liver steatosis and dyskinesia of the bowel, so she was constantly using ursodeoxycholic acid. The family history of skin diseases was unremarkable.

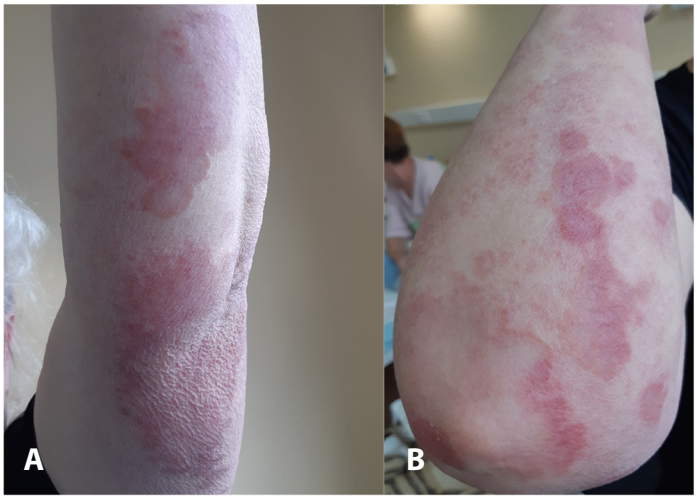

Figure 1. ***A)*** *On the left arm and forearm, there are erythematous non-scaly patches and plagues, some of which are annular in shape with raised well-defined borders and hypopigmented or skin-colored centers, with atrophy (cigarette paper changes).* ***B)*** *On the right elbow and forearm, there are erythematous, non-scaly annular patches with variable diameters. Some have a hypopigmented center.*

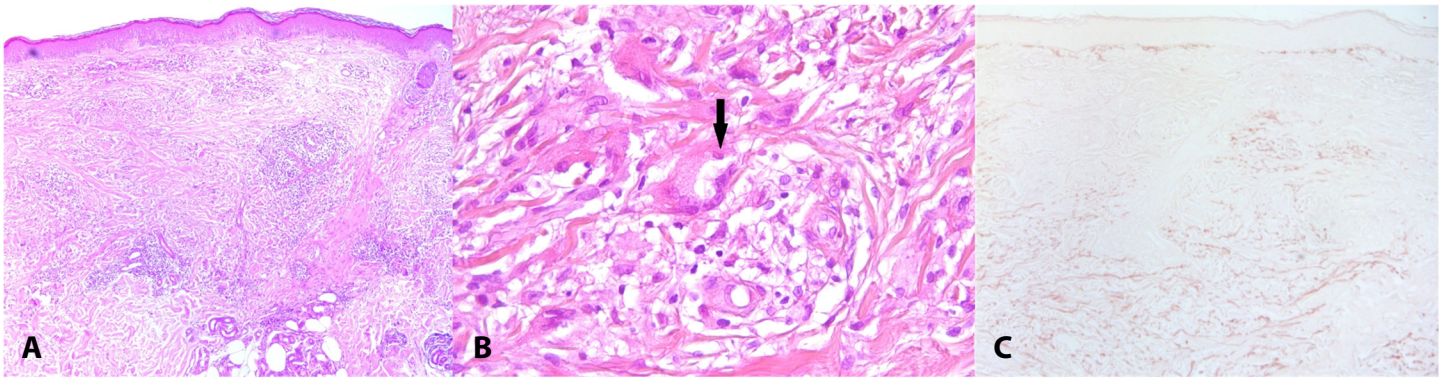

Figure 2. ***A)*** *Histological examination revealed a normal epidermis with slight atrophy. In the mid and upper dermis, there is an interstitial granulomatous infiltrate of multinucleated giant cells with a mixed inflammatory infiltrate.* ***B)*** *A black arrow points to some giant cells that have fragmented elastic fibers in their cytoplasm (elastophagocytosis).* ***C)*** *Orcein stain shows scant elastic fibers which were absent in some areas of granulomatous changes (elastin degenerations).*

On general examination, the patient was oriented, afebrile, without lymphadenopathy. She was obese with a body mass index of 32.3 (normal range 18.5 to 24.9). She has no other complaints except for dry skin (xerosis). Her rash was characterized by erythematous non-scaly patches and plaques, some of which were annular in shape with raised well-defined borders and hypopigmented or skin-colored centers. Atrophy (cigarette paper appearance) was noted mainly on the arms as shown in (**Figure 1A**, **B**). The diameter of lesions varied by up to several centimeters. In the occipital area of the scalp, there was non-scaly erythema with diffuse hair thinning (non-scarring alopecia). On the upper back and chest, a non-specific macular rash in a photo-distribution was also seen. There were no lesions on the oral mucosa or conjunctiva.

Complete blood count, C-reactive proteins, erythrocyte sedimentation rate, urinalysis, renal and thyroid function, and serum level of angiotensin-converting enzyme were normal. Both the antinuclear antibody and the viral screen were negative, as was the syphilis serology test. Elevated liver enzymes: alanine aminotransferase 70U/L (normal 7-55U/L), aspartate aminotransferase 103U/L (normal 8-48U/L), and random blood sugar 7mmol\L, (normal level 3.5–6.1mmol\L) were observed. Except for hepatomegaly, the abdominal ultrasound was normal. The chest X-ray was also normal.

A biopsy revealed a normal epidermis with slight atrophy. In the mid and upper dermis, there was a non-palisading granulomatous infiltrate of multinucleated giant cells with a mixed inflammatory infiltrate as shown in (**Figure 2A**). Some giant cells showed fragmented elastic fibers in their cytoplasm (elastophagocytosis) as shown in (**Figure 2B**). Orcein stain showed scant elastic fibers which were absent in some areas of granulomatous changes (elastin degenerations) as illustrated in (**Figure 2C**). There were no signs of vasculitis, necrobiosis, mucin, lipid, or eosinophils. Fungal stains and Ziehl–Neelsen were negative. Treatment was started with topical tacrolimus (Protopic) 0.1% ointment twice a day for 4–6 weeks. In addition, she was given systemic methylprednisolone, 36mg daily for two weeks, pentoxifylline tablets, 400mg three times a day, and omeprazole capsules, 20mg twice daily. The patient was seen after one months with partial improvement as illustrated in (**Figure 3**). She was advised to continue topical tacrolimus and pentoxifylline twice daily for another month and asked to return for follow up.

Case Discussion

Elastolytic actinic giant cell granuloma is a rare distinct entity among other granulomatous skin disorders because of the controversiality of categorization, etiopathogenesis, and treatment. Furthermore, the disease's coexistence has been reported with various systemic diseases. There have been several pathophysiology hypotheses proposed. Solar radiation, according to O'Brien, is the

initial trigger that causes damage to the elastic tissue in the upper and mid-dermis. This degraded tissue is subsequently targeted by inflammatory cells (CD4+ cells) in an attempt to repair the injured skin but instead causes granulomatous inflammation [4]. Ragaz and Ackerman vehemently contested this notion, insisting that these granulomas were simply an anatomical variety of granuloma annulare [8]. McGrae proposed an immunological response to deteriorated elastic tissue mediated by lymphocytes, with a preponderance of helper T cells in the lymphocytic infiltration. Factor XIIIa and macrophages would be induced to produce granulomas and giant cells by elastin peptides [9]. Macrophages in the infiltration make matrix metalloproteinase (MMP 12). This helps to explain why elastic fibers break down and multinucleated giant cells arise [10]. The immunological theory could explain the development of AEGCG in sun-protected areas and the absence of involvement in areas with no elastin, such as scars and striae distensae [11]. Our case is better explained by the actinic hypothesis due to the rash arising in sun-exposed areas only and exacerbations mainly in the summer period.

There is a long list of other granulomatous and non-granulomatous skin disorders that may have a similar clinical picture to AEGCG and can be differentiated based on careful assessment, investigations, and histopathology, despite the common overlap between them in many reported cases. We exclude many of these disorders in our case, including granuloma annulare (no necrobiosis or mucin, and no palisading collagen degeneration), necrobiosis lipoidica (no necrobiotic foci), sarcoidosis (no naked granuloma, no elastin changes, normal angiotensin converting enzyme level, no hilar lymphadenopathy in chest X-ray, and unremarkable systemic review), subacute lupus (negative antinuclear antibody and unremarkable systemic review), infectious granulomas (negative Ziehl–Neelsen stains, negative fungal stains, no lymphadenopathy, no fever, normal complete blood count, C-reactive proteins normal, negative syphilis serology, and no travel history), and granulomatous mycosis fungoides (negative immunophenotyping). Granulomatous mycosis fungoides may have a similar clinical picture, mechanism of elastolysis, and histopathological features to AEGCG. This is evident in granulomatous slack skin, a special variant of CD4+ cutaneous T-cell lymphoma [12]. Annular lichen planus is another clinical entity in the differential diagnosis that can be differentiated based on histology, which shows no granulomatous changes in addition to a positive direct immunofluorescence assay.

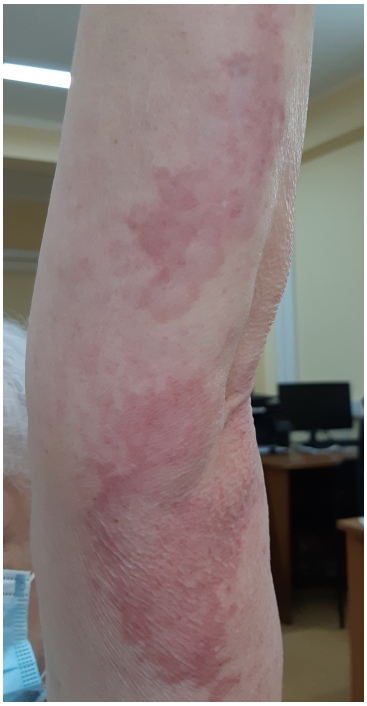

Figure 3. *On the left upper arm, there is a slight fading of erythema, with flattening of the borders and plagues.*

Systemic associations with AEGCG have been observed in many cases. But the most frequently reported disease is diabetes, despite the fact that there are no relations mentioned in the first description of this entity. Diabetes mellitus has been found to be more prevalent in AEGCG patients than in the general population. According to one case series study, 40% of patients with this skin condition had diabetes, which was higher in the necrobiotic pattern than in the giant cell group, which could be explained by hyperglycemia-induced vascular injury [13]. Many studies point to a significant contribution of diabetes mellitus to the loss of elastin fibers and correlations between fasting plasma glucose values and the degree of elastin degradation [14]. Glycation of elastic fibers enhances immunological reactions, which may contribute to giant-cell granuloma formation. These hypotheses could support

diabetes's auxiliary role in the development of these skin lesions in this case. Our patient also had hypertension, which may have aided in the progression of elastin degeneration and glycation [15]. But perhaps there is no significant correlation between them, as it was observed in 20% of the patients in one study, which is similar to the prevalence in the general population [13].

Despite observed coexistence in some cases, the role of liver diseases in the etiology of EGCG remains unclear. Dyslipoproteinemia, metabolic abnormalities, and vascular disturbances, may play a role [16,17]. However, the patient in this case had non-alcoholic fatty liver, which may be related principally to her obesity. Various other systemic disorders have been reported to coexist with this entity, like sarcoidosis [18], Hashimoto thyroiditis [19], vitiligo [20], temporal arteritis [21], implantation of cardiac pacemakers [22], stroke [23], Lyme disease [24], lymphoma [25], leukemia [26], syphilis [27], and protoporphyria [28]. A case of systemic elastolytic granulomatosis has also been described [29].

Many different treatment methods have been tried, with varying degrees of effectiveness. Because spontaneous resolution of this entity has been documented in certain cases, a true evaluation of the treatment's efficacy can be challenging [30,31]. Topical and systemic corticosteroids, pimecrolimus and tacrolimus, psoralen ultraviolet A (PUVA) and narrow band ultraviolet B, cyclosporine, pentoxifylline, dapsone, systemic retinoids, and fumaric acid esters all had varying degrees of success [3]. One case responded successfully to minocycline treatment after failure of management with corticosteroids [32]. In one of the case series studies, the anti-malarial agent hydroxychloroquine showed good effects [33]. Despite the fact that methotrexate is ineffective in some cases, one case report of resisted generalized AEGCG revealed a successful outcome [34].

Although these skin lesions remained in our patient for five years and increased constantly, we cannot predict the chance of spontaneous resolution in the future. Good results with topical tacrolimus, systemic corticosteroids, and pentoxifylline treatments were also observed in previous cases [5,35-37], respectively.

Conclusion

Annular elastolytic giant-cell granuloma is an uncommon granulomatous skin disease with controversial etiology, pathogenesis, and treatment modalities. Sun exposure and actinic damage could both play a significant role. Immunological responses to trauma, infectious agents, and metabolic disorders may all play a role in the progression of this disease. Associations with hematologic disorders and cancer may be the result of an immune response to tumor antigens. Cross reactions may also explain why this entity coexists with some autoimmune diseases. The complexity of understanding such a diverse range of presentations and associations creates treatment challenges.

Potential conflicts of interest

The authors declare no conflicts of interest.

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