Generalized perforating granuloma annulare associated with latent tuberculosis successfully treated with isoniazid: case report and review

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Abstract

Generalized perforating granuloma annulare (GPGA) is a very rare form of granuloma annulare, with only 31 reported cases to the best of our knowledge. Furthermore, GPGA is a chronic disease that mimics many diseases, with no known exact etiology, resulting in a lack of specific clinical criteria leading to a lack of guidelines for diagnosis and therapy. In GPGA, papules are the predominant lesions followed by central crusting/scaling or umbilication; pustules, plaques, annular lesions or nodules are less frequent. We report a 66-year-old woman who presented with a 7-month history of mostly asymptomatic generalized infiltrated, flesh-colored to red-brown umbilicated or crusted papules. Histopathological findings were compatible with perforating granuloma annulare. Diagnostic workup revealed latent tuberculosis. To the best of our knowledge, this is the second published case of GPGA associated with latent tuberculosis and the first one that was successfully treated by isoniazid monotherapy. From our case we can speculate and support the theory that GPGA is a phenotypic granulomatous response to multiple etiologies and/or antigenic stimulation and that testing for tuberculosis should be seriously considered in the evaluation of patients with GPGA.

Keywords: granuloma, annulare, isoniazid, latent tuberculosis, therapy

Introduction

Perforating granuloma annulare (PGA) is an extremely rare clinical and histological variant of granuloma annulare (GA), localized most commonly on upper extremities and dorsal hands [1-3]. Studies suggest the prevalence of PGA to be up to 5% of GA [1]. Furthermore, generalized perforating granuloma annulare (GPGA) is even more rare with only 31 reported cases, up to April 2022 to the best of our knowledge. In this report, we present the first case of GPGA associated with latent tuberculosis successfully cured by isoniazid monotherapy.

We also present a short review of literature. A Medline database search was undertaken in April 2022 using terms "disseminated perforating granuloma annulare" and "generalized perforating granuloma annulare". The revision of aforementioned case reports and their references and the inclusion or exclusion of certain cases was done by following the criteria of Dabski and Winkelmann [4]; only cases with extensive lesions on both trunk and extremities were classified as generalized and thus included.

Case Synopsis

A 66-year-old woman was admitted with a 7-month history of gradually progressive and generalized skin lesions. Our patient presented with infiltrated, flesh colored to red-brown papules, mostly asymptomatic, often covered with crust or umbilicated. These were disseminated distribution on the scalp, face, trunk, gluteus, and upper and lower extremities (predominantly on the extensor areas), (**Figure 1A-E**). Individual pustules were also present. No atrophic scars were noticed. Multiple

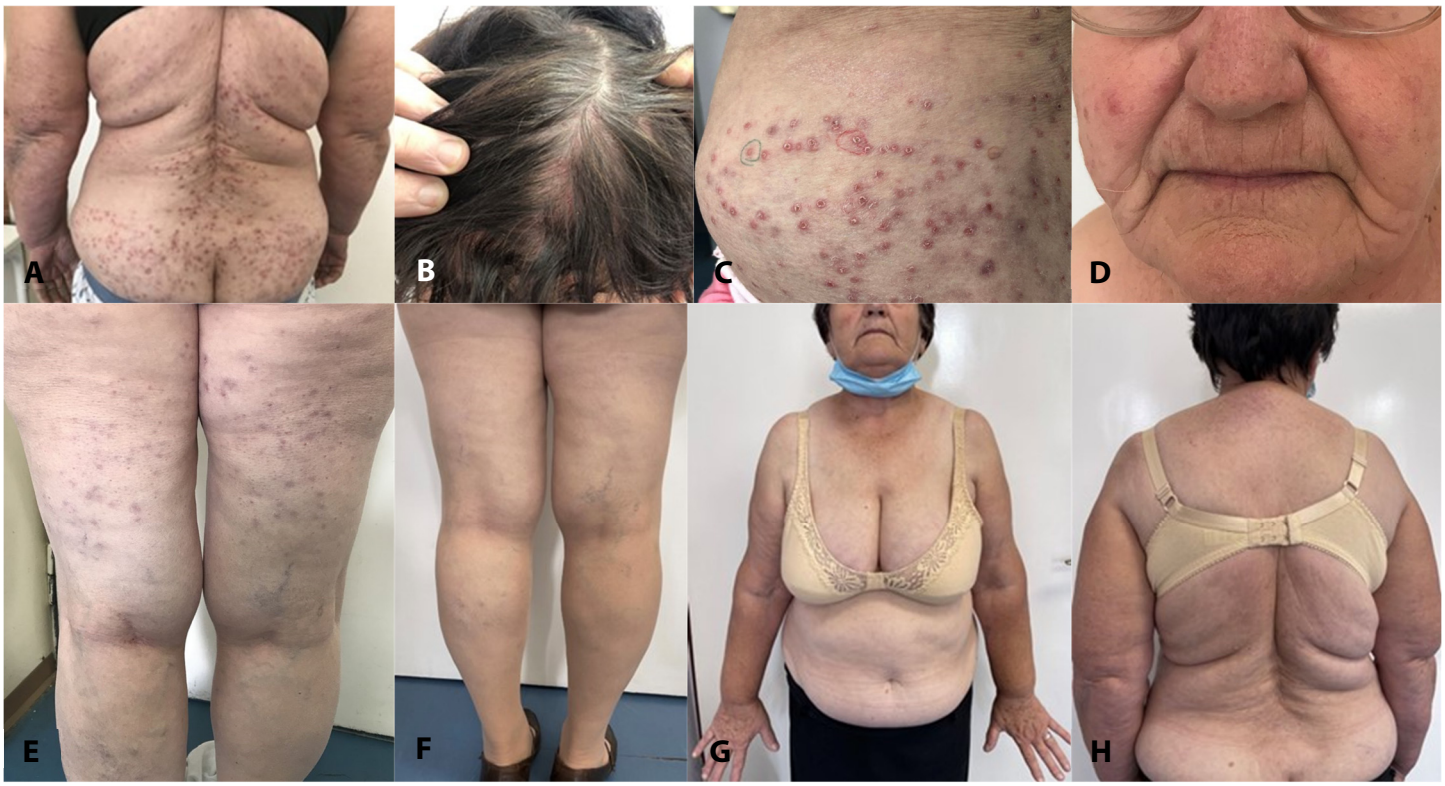

Figure 1. ***A-E)*** *Skin lesions upon admission in patients;* ***F-H)*** *Skin lesions after two months of isoniazid therapy.*

(five in total: lumbosacral region, upper extremity, scalp and two from the trunk) 4mm skin punch biopsies were performed. Histopathology revealed shallow ulceration filled with fibrin, rare neutrophils, and focally rare collagen fibers in the central epidermis. Below the ulceration, in the superficial and mid-dermis, focally fused degeneration of collagen with a focus of histiocytes and mucin was noted (**Figure 2A-E**). Findings were compatible with PGA.

History of trauma, ultraviolet exposure, and insect bites was absent. Co-morbidities included arterial hypertension. Extensive laboratory evaluation revealed normal complete blood count, biochemical

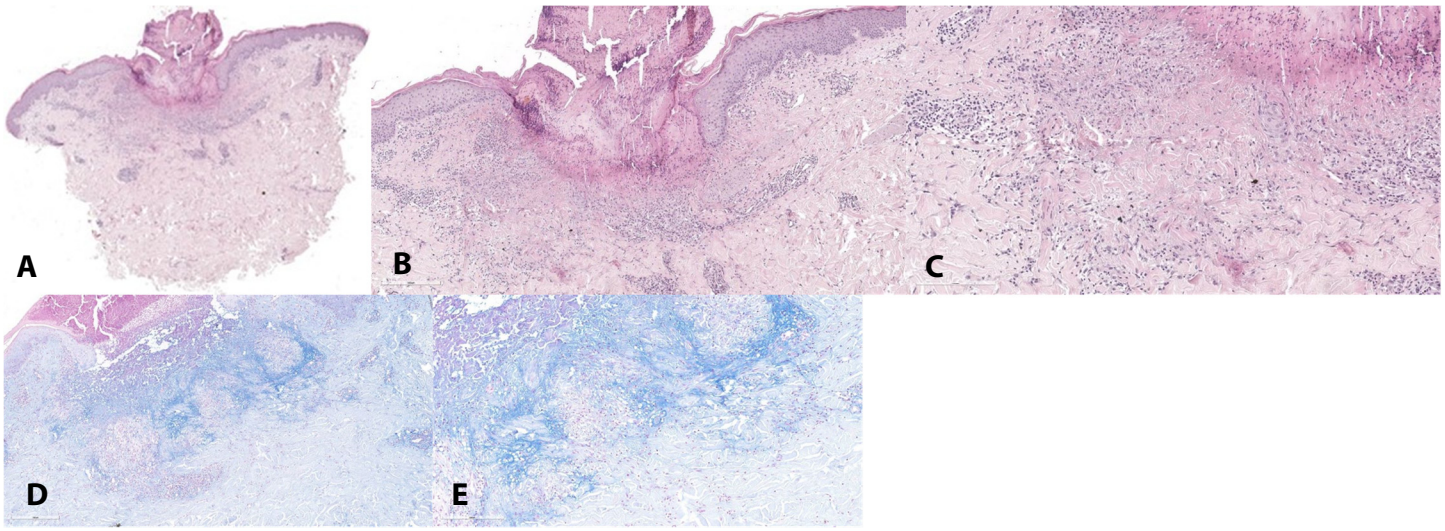

Figure 2. ***A-C)*** *H&E punch biopsy of umbilicated papule on the trunk revealed shallow ulceration filled with fibrin and rare neutrophils, 40×.* ***B, C)*** *Below the ulceration, in the superficial and mid-dermis, focally fused degeneration of collagen with a focus of histiocytes was noted;* ***B)*** *100×,* ***C)*** *200×.* ***D, E)*** *Alcian blue staining: mucin deposition in granuloma was confirmed with histochemical staining stain;* ***D)*** *100×,* ***E)*** *200×.*

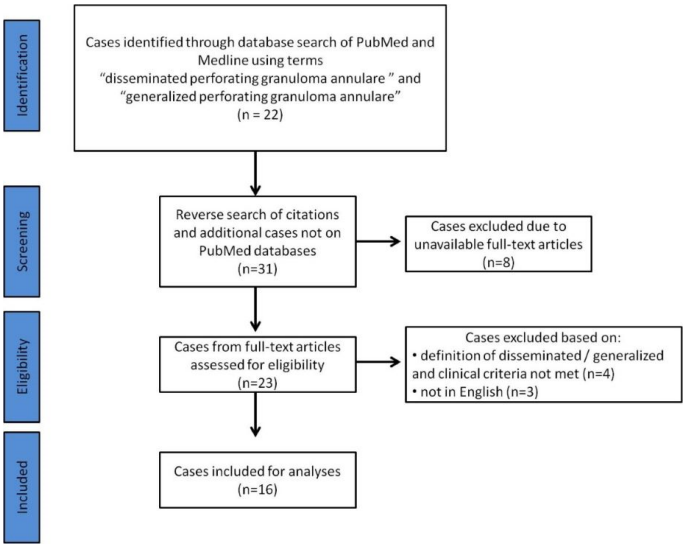

Figure 3. *Flow chart of the systematic literature review.*

parameters, and urine analysis. Hemoglobin A1c, calcinuria, angiotensin-converting enzyme, chitotriosidase (a reliable and sensitive biomarker of sarcoidosis), and parathyroid hormone were within normal range as were immunological and virological analyses. QuantiFERON TB gold test was positive. Protein purification derivatives (PPD) test was extremely positive (>2cm). Sputum and urine samples for acid-fast bacilli smear and Lowenstein culture were negative. Thoracal computed tomography was within normal limits. Pulmonary consultations concluded a diagnosis of latent tuberculosis. Polymerase chain reaction (PCR) detection of *Mycobacterium tuberculosis* from a lesional skin biopsy specimen was negative. Only prophylactic therapy of latent tuberculosis (isoniazid 300mg daily and vitamin B6) was initiated and continued for 6 months. Skin lesions ceased within two weeks and a complete regression, without scarring, was obtained after two months (**Figure 1F-H**). Regression was maintained even after isoniazid discontinuation. In the follow-up period of 26 months, no new lesions occurred.

Case Discussion

Herein, we presented a case of GPGA associated with latent tuberculosis successfully cured by isoniazid monotherapy. We also provide a comprehensive review of literature applying stringent criteria for the diagnosis of GPGA according to the criteria of Dabski and Winkelmann [4]. Only cases with extensive lesions affecting at least the trunk and either extremity were regarded as generalized and thus included. As illustrated in **Figure 3**, total of 31 cases were identified through database search of PubMed and Medline and through reverse search of citations and additional cases not available in PubMed databases. Eight cases were unavailable for full-text and our review, thus were excluded from the analysis. An additional three cases were excluded as the articles were not in English. Finally, four cases were excluded as the definition of generalized and other clinical criteria were not met. A total of 16 cases of GPGA were compiled in addition to our case and summarized for comparison in **Table 1** [1,3,5-15].

Perforated GA represents 5% of all GA cases [1]. Although rarely reported in literature, a generalized form of PGA can be seen in 29.5% [16] to 33% [1] of PGA cases. Our stringent literature review, including the currently presented case, shows equal occurrence of GPGA in men and women, unlike previously reported female-to-male ratio of 1.3:1 [16]. It was reported both in adults (11 cases) and in children (5 cases).

Clinically, GPGA and PGA differ from typical GA. Proposed clinical criteria for perforating granuloma annulare and generalized perforating granuloma annulare, along with clinical features in studies by Penas et al. [1] and Zhong et al. [10] are summarized in **Table 2**. Generalized perforating granuloma annulare predominately presents with multiple, grouped papules with central crust, scale, and/or umbilicated or pustules leading to atrophic hypo- or hyperpigmented scars. Localization is mostly on the extensor surfaces [1,16]. In GPGA specifically, papules are the predominant lesion (94% of cases), followed by central crusting/scaling (83%), umbilication (72%), pustules (33%), plaques or annular lesions (17%), and nodules (11%), [16]. In our patient, the full spectrum of skin changes except annular lesions was present. Our patient had no atrophic scars although scarring can be seen in up to 42% of GPGA cases [16]. Of note, our patient had disseminated papulopustules on the scalp, a localization not typical for GPGA. In fact, scalp lesions were shown in only one GPGA case previously [3].

Table 2. *Proposed clinical criteria for perforating granuloma annulare and generalized perforating granuloma annulare and clinical features summarized and differences by studies Penas et al [1] and Zhong et al [10].*

	Generalized perforating granuloma annulare	Localized perforating granuloma annulare
Location of lesions	Extensive lesions on both trunk and extremities	Minimal or extensive lesions on either extremities or trunk
Histological differences	None	None
Ratio female : male	1.1 : 1 [1] - 1.3 : 1 [10]	2.2 : 1 [1] - 1.9 : 1 [10]
Mean age of onset (years)	33 (1) - 36 (10)	30 (1) - 31 (10)
Mean evolution time, years (SD)	4.6 (10) - 8.4 (1)	2.2 (1) - 2.3 (10)
Associated diabetes mellitus (%)	19% (1) - 26% (10)	13% (10) - 16% (1)

The extremely variable clinical presentation leads to an extensive differential diagnosis. Papulonecrotic tuberculid (PNT) has a similar clinical appearance to PGA with widely distributed, mostly asymptomatic symmetric lesions especially on the extensors of the extremities and gluteus. Central necrosis in individual lesions and varioliform-like scarring is exhibited [2]. Such scarring was not noted in our patient. Still, PNT was in the differential diagnosis especially when PPD was highly positive despite active tuberculosis being excluded. Due to this, one can question (as we did during the workup) if this is GPGA associated with latent tuberculosis or a form of PGA-like tuberculoid (reported previously by Jordaan et al. [17]). Ultimately in our case, multiple factors, especially the histology from multiple biopsies from several lesions which showed typical findings of PGA and the absence of necrosis and vascular involvement, allowed PNT to be excluded. In addition, PCR for *Mycobacterium* species in lesional skin was negative.

The etiology and reported association of other diseases with GPGA are scarce [1,16]. Our literature review of cases revealed only summer worsening [6], UV [7], neural atrophy [8], oral candidiasis [10], IgG kappa myeloma [13], as associated conditions. Latent tuberculosis and GPGA have been reported in only one case so far. This was in a 4-year-old boy, treated with low-dose hydroxychloroquine but not isoniazid or other therapy targeting the latent tuberculosis [15]. In our review, only three out of 16 GPGA cases were evaluated for tuberculosis; two were negative [13,14] and one was positive for latent tuberculosis [15]. Furthermore, Santos et al. [9] reported a case showing spontaneous resolution with only glucose control and Satta et al. [13] reported complete resolution in a patient with IgG kappa myeloma after hematological therapy only. These cases, along with ours, give further credence to the theory that GPGA is caused by antigenic stimulation. This lack of diagnostic evaluation underlies the lack of awareness of the association between GPGA and tuberculosis. Association between PGA and tuberculosis has also been reported in only one case of localized PGA on the extremities associated with lymph node tuberculosis, but not latent tuberculosis [2].

In PGA, and especially GPGA, there are no exact guidelines for treatment. An extensive work-up is needed to reveal all possible etiological factors. In published GPGA cases a variety of therapeutic options were used, all with variable success ranging from complete or partial clearance to no improvement. Only one patient was treated with isoniazid, although unsuccessfully [5]. To the best of our knowledge, our case is the only reported GPGA treated exclusively by isoniazid treatment of the latent tuberculosis, not the GA, resulting in complete resolution within two months.

Conclusion

In conclusion, GPGA is an extremely rare, chronic disease that mimics many diseases. There is a lack of specific diagnostic and therapeutic guidelines due to inadequate knowledge of exact etiological mechanisms. This case raises questions regarding the extremely rare association of GPGA with latent tuberculosis and testing for tuberculosis should be seriously considered in the evaluation of patients with GPGA. Finally, isoniazid could be a potentially effective, but severely underused therapy leading to

quick resolution of the, often chronic, symptoms and lesions observed in GPGA, especially in patients with latent tuberculosis and possibly even in other forms of GPGA.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Clinical features, localization, symptoms, laboratory findings, workup and treatment of published cases of generalized perforating granuloma annulare.*

Cases	Age,sex	Duration	Localization	Clinical picture	Inciting factors	Diabetes Mellitus	Quantiferon/ PPD	Therapy
1. Delaney et al. 1973 [5]	60, M	12 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules + Umb – Crust/Ero + Scars +	N/S	Yes	N/S	INH *
2. Duncan et al. 1973 [6]	Case 1, 3, M;	Case 1, 1.5 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero + Scars –	Summer; Insect bites	N/S	N/S	N/S
	Case 2, 6, F	Case 2, 3 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero – Scars –	Summer; Insect bites	N/S	N/S	N/S
3. Izumi et al. 1973 [7]	6, F	4 yr	Face + Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero – Scars –	UV	N/S	N/S	Liquid nitrogen and vitamin A (200,000 units/day – 2 m) *; No therapy **
4. Jacyk et al. 1974 [8]))	42, F	1 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero + Scars –	Neural atrophy (15 yr)	N/S	N/S	prednisone 500mg total dosage-24 d **; At 3 years follow up: no recurrences.
5. Penas et al. 1997 [1]	Case 1, 50, F	30 yr	N/S	N/S	N/S	N/S	N/S	Topical and oral prednisone *
	Case 2, 32, F	3 m	N/S	N/S	N/S	N/S	N/S	None *
6. Santos et al.1999 [9]	59, F	3 m	Face – Trunk + Ext + Scalp –	Papules + Pustules + Umb + Crust/Ero + Scars –	N/S	Yes	N/S	Oral flucloxacillin, erythromycin, hydroxyzine *; Glucose control (1 yr) *** (SR);
7. Choi et al. 2003 [10]	2 m, F	15 d	Face + Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero +	Oral candidiasis (1 m)	No	N/S	Prednicarbate cream (1 m) **

				Scars –				
8. Villegas et al. 2003 [11]	84, M	13 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules + Umb + Crust/Ero – Scars –	N/S	N/S	N/S	Pentoxifylline 3x500mg (7 m), Acitretin 35mg QD (8 m) **; Prednisone (30mg QD)**; PUVA plus prednisone (10 mg EOD) ***;
9. Dornelles et al. 2011 [12]	49, M	10 m;	Face – Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero + Scars +	N/S	Yes	N/S	Dapsone 100mg QD (30 d) **
10. Zhong et al. 2016 [16]	34, M	11 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero + Scars –	N/S	N/S	N/S	Liquid nitrogen, topical CTS ***
11. Satta 2018 [13]	70, M	N/S	Face – Trunk + Ext + Scalp –	Papules + Pustules + Umb + Crust/Ero + Scars –	MGUS - 3 yr; IgG kappa myeloma	No	Quantiferon –	Hemotological therapy ***
12. Deza et al. 2019 [14]	70, M	15 yr	Face – Trunk + Ext + Scalp –	Papules + Pustules + Umb – Crust/Ero – Scars –	N/S	N/S	PCR –; Qunatiferon –	topical antibiotics, doxycycline, oral terbinafine, dapsone, isotretinoin, and colchicine *; Acitretin 10mg QD (6 m) **
13. Xu et al. 2019 [15]	4, M	1 m	Face + Trunk + Ext + Scalp –	Papules + Pustules – Umb + Crust/Ero + Scars –	Latent tuberculosis	N/S	T-SPOT.TB +	HCQ 25mg QD, Tacrolimus 0.03%, Dexamthasone cream (6 m) ***
14. Salzmann et al. 2021 [3]	42, M	18 m	Face + Trunk + Ext – Scalp +	Papules + Pustules – Umb + Crust/Ero – Scars –	N/S	No	N/S	Topical CTS, PUVA * 100mg QD and intalesional triamcinolone 10mg/ml (6 cycles every 4 weeks) ** after 18 m
15. Kapetanovic et al. 2023	66, F	7 m	Face + Trunk + Ext + Scalp +	Papules + Pustules + Umb + Crust/Ero + Scars +	Latent tuberculosis	No	PCR +; Quantiferon +	INH 300mg QD, Vitamin B6 (6 m) ***

*, no improvement; **, partial improvement; ***, complete resolution; +, present; –, absent
CTS, corticosteroids; d, day; EOD, every other day; Ero, erosions; Ext, extremities; F, female; HCQ, hydroxychloroquine; INH, Isoniazid; M, male; m, month; MGUS, Monoclonal gammopathy of undetermined significance; N/S, not stated; PCR, polymerase chain reaction; PPD, protein purified derivative; PUVA, psoralen and ultraviolet A; QD, once daily; SR, spontaneous resolution; Umb, umbilicated; UV, ultraviolet; yr, year