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Original Research Article

CLINICAL PROFILES AND EPIDEMIOLOGICAL TRENDS IN GRANULOMA ANNULARE: A CROSS-SECTIONAL OBSERVATIONAL STUDY IN TERTIARY CARE HOSPITAL

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ABSTRACT

Background: Granuloma annulare (GA) is a benign, self-limiting, inflammatory dermatosis characterized by annular or arcuate plaques formed by dermal papules. The exact etiology remains uncertain, but proposed mechanisms include a delayed-type hypersensitivity reaction and associations with systemic conditions such as diabetes mellitus and dyslipidemia. GA presents in several clinical variants, each with distinct morphological and epidemiological features. The present study aimed to evaluate epidemiological and clinical pattern of granuloma annulare and their correlation with dermoscopic and histopathological features in a tertiary care centre from north India.

Materials and Methods: The present study assessed 40 subjects. A detailed clinical history was obtained for each participant, followed by a thorough clinical examination and dermoscopic evaluation. Quantitative variables included age and disease duration, while qualitative parameters such as gender, symptoms, lesions morphology, dermoscopy features, and histopathological data were also recorded.

Results: The study results demonstrated a female predominance among patients with Granuloma annulare, with a mean age of 33.3 ± 14.82 years. Atypical clinical presentation was observed in 30 % of the subjects. The most common dermoscopic features was yellowish-orange structureless areas in non-vascular pattern, present in 80% of cases, while in vascular pattern, dotted or linear-irregular vessels observed most commonly in 55% of subjects. Histopathological evaluation most frequently revealed palisading pattern in 62.5% of subjects followed by interstitial pattern (22.5 %).

Conclusion: GA requires a multidisciplinary approach encompassing clinical evaluation, dermoscopy, and histopathological examination for optimal diagnostic precision, especially for atypical pattern. Biopsy is the gold standard in differentiating it from other differentials of Granuloma annulare.

Keywords: Granuloma annulare, Dermoscopy, Histopathology.

INTRODUCTION

Granuloma annulare (GA) is a granulomatous disorder of unknown etiology, which known of its transient, benign course and usually self-limiting.[1] First description of its lesion given by Colcott Fox in 1895 and name given by Radcliffe-Crocker in 1902.[2,3] From most studies, it has estimated that the annual incidence of granuloma annulare (GA) to range from 0.1% to 0.4%, with a female predominance has been noted in several epidemiological studies.[1] GA may occur at any

age, although it is reported most commonly in the first 3 to 5 decades of life.[4]

Etiopathogenesis of GA remains unclear, but multiple hypotheses have been proposed. Some believe that granuloma annulare is caused by a delayed-type hypersensitivity reaction, more specifically a Th1 reaction involving IFN-gamma stimulating macrophages to release matrix metalloproteinases. Many trigger factors as well as associated disorders have been found in various studies of GA. More recent studies suggest a possible role of immune dysregulation, microangiopathic changes, and changes in collagen structure, reflecting the complex pathogenesis of the disease.[4,5]

Clinically, GA exhibits considerable diversity and is typically classified into localized, generalized, subcutaneous, perforating, and atypical variants.[4] Localized GA is the most common form and usually presents as asymptomatic, annular plaques on the extremities, particularly the dorsal hands and feet.[4] Generalized GA, although less frequent, is more chronic and may present with widespread papules and plaques involving the trunk and limbs; this variant is more often associated with systemic disease such as metabolic abnormalities.[6]The subcutaneous variant, predominantly seen in children, presents as deep, firm nodules and may mimic rheumatoid nodules or benign soft-tissue tumors.[7]Perforating GA is characterized by transepidermal elimination of degenerated collagen and is more commonly reported in individuals with diabetes mellitus.[5]

Histopathologically, GA is defined by areas of necrobiotic collagen surrounded by palisading histiocytes, lymphocytes, and mucin deposition—patterns that can be categorized into palisading or interstitial types.[4,8] The palisading pattern shows central necrobiosis with surrounding granulomatous inflammation, whereas the interstitial pattern features histiocytes interspersed between collagen bundles with minimal necrobiosis.[8] These histological patterns aid in differentiating GA from other granulomatous conditions such as necrobiosis lipoidica, rheumatoid nodules, and sarcoidosis.

MATERIALS AND METHODS

The present descriptive, cross-sectional observational study was conducted to evaluate the clinical and epidemiological characteristics of patients with granuloma annulare (GA). In addition, dermoscopic features were assessed and correlated with histopathological findings. The study was carried out in the Department of Dermatology, Venereology and Leprosy after obtaining approval from the Institutional Ethics Committee. Verbal and written informed consent were obtained from all participants prior to enrolment. All patients of any age and gender who presented during the defined study period, had a confirmed diagnosis of GA, and were willing to participate were included in the study.

For each enrolled subject, demographic details such as age and gender were recorded. A comprehensive clinical history was obtained, including duration, smoking history, recent viral infection, family history, associated comorbidities, vaccination history, drug intake, prodromal symptoms, and other disease-related symptoms. This was followed by a detailed physical examination of all subjects to assess the site of lesions, size as well as the distribution and morphology of skin lesions. Dermoscopic evaluation was then performed using a video dermatoscope, and clinical photographs were obtained for documentation. Relevant investigations, including skin biopsy, were carried out to confirm the diagnosis of granuloma annulare. The collected data were statistically analyzed using SPSS (Statistical Package for the Social Sciences) software, version 24.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the findings, and results were presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables.

RESULTS

This descriptive cross-sectional observational study was conducted to evaluate the clinical pattern and epidemiological profile of patients diagnosed with granuloma annulare from a region in North India. The study also evaluated their histopathological correlation and dermoscopic features. Total 40 patients diagnosed with granuloma annulare were enrolled in the study. A detailed clinical history was obtained, followed by thorough clinical examination and dermoscopic evaluation in all cases. The majority of participants were female (n =26, 65 %). [Graph 1] The age of subject ranges from 10 year to 64 years with mean age of presentation 33.3 ± 14.82 years. The highest prevalence was observed in the 20-29 years age group (n=15, 37.5 %). [Graph 2]

None of the subjects reported a positive family history. A slightly higher case of granuloma annulare was observed during the summer season. Majority of cases gave no history of prodromal symptoms. [Table 1] A history of stress and depression present in 17.5% (n=7) of subjects, while 5% (n=2) of subjects have positive HIV status. History of smoking, Non-migraine headache, Atopy and recent viral infection were present in 22.5 %, 5 %, 2.5 % and 12.5 % of cases respectively, while DM, Hypothyroidism, liver disease, Hypertension and dyslipidemia were present in 15 %, 5 %, 2.5 %, 10 %, and 12.5 % of cases, respectively. One Patient also have history of recent SARS CV-2 vaccine (Covaxin), while one patient was on amlodipine.

In most cases, lesions were asymptomatic and itching were present in few cases 15 %, especially in generalized type of granuloma annulare. Only 2

subjects gave history of mild burning sensation, that also in generalized type of granuloma annulare. On morphology, majority of cases present with typical localized pattern 70 % (n=28) appeared as annular plaques or grouped papules arrange in annular pattern with a central clearing and a well-defined raised border. Size ranges from 0.5 cm to 4 cm. Second most frequent clinical pattern 20 % (n=8) was generalized granuloma annulare in which multiple lesions involved trunk and extremities and had bilateral symmetrical distribution. Other pattern was observed were subcutaneous GA (n=2), then perforating and patch type GA with single case of each. [Graph 3]

On dermoscopy, the most frequent non-vascular findings was yellowish-orange structure less areas, detected in 80 % lesions (diffusely and focally distributed), seen in most localized and generalized GA. Next frequent finding was whitish shiny streaks, observed in 60 % lesions (including irregular, globular or irregular+ globular areas). Regarding vascular findings, most frequent finding was dotted or linear-irregular vessels, observed in 55 % lesions, followed by annular or arcuate arrangement of vessels 45 % lesions. Other dermoscopic findings includes peripheral reddish rim (50 %), browning/orange-brown background (35 %), whitish border (40 %), and central hypopigmentation (25 %) of lesions. Central keratotic plug was observed in perforating GA. Vascular pattern and erythematous halo were more prominent in early lesions, while in late lesions yellow-orange structure less areas and white shiny streaks were more prominent feature.

In histopathology, most of cases (62.5 %) had palisading pattern showed histiocytes arranged in a palisading pattern around a central zone of collagen degeneration with abundant mucin in mid dermis Multinucleated giant cells, perivascular lymphocytic infiltrate and scattered eosinophils were occasional findings. It followed by interstitial pattern (22.5 %) showed loose interstitial infiltrate of histiocytes between collagen bundle with mild to moderate mucin and no discrete necrobiotic foci in mid and upper dermis. 12.5 % subjects show mixed pattern, while subcutaneous pattern showed palisading granulomas surrounding foci of degenerated collagen in subcutis was correspond to subcutaneous pattern of GA.

Figure 1: Showing gender distribution (percentage-wise)

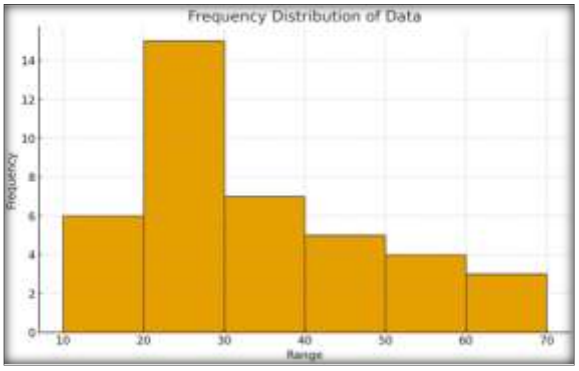

Figure 2: Showing number of cases in different age group

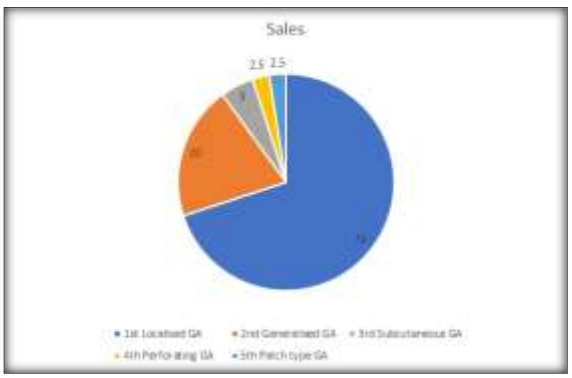

Figure 3: Showing distribution of clinical patterns of granuloma annulare (GA) [percentage-wise]

Table 1: Prodromal symptoms distribution in the study subjects

S. No.	Symptoms	Number	Percentage
1.	None	25	62.5
2.	Headache	5	12.5
3.	Diarrhoea	1	2.5
4.	Cold and cough	4	10
5.	Arthralgia	2	5
6.	Myalgia	1	2.5
7.	Fever	4	10

DISCUSSION

In this observational study, evaluation of 40 patients with granuloma annulare done through comprehensive clinical history-taking, physical examination, and dermoscopic assessment. The ages of the participants ranged from 10 to 64 years, mean age of presentation 33.3 ± 14.82 years. Most cases were seen in the 20-to-29-year age group (37.5 %),

with Localized GA appear more in younger age group while generalized GA in older age group. These findings are corresponding to previous literature of PietteEW,[4] in 2016 and Schmieder SJ et al,[1] in 2023. Many previous studies show female predominance for GA.[1,9] In study by Sari Aslani F female to male ratio in GA cases was 3.85:1.[9] In our study, we also find female predominance (F:M - 1.86:1). However, some studies do not show female predominance. In study by Cheng Y-W, et al, Male to female ratio was found slightly more than one.[10] Another study by Yun JH, et al showed the similar findings.[11] In Malhotra S study, they found more cases of GA during summer season.[12] In this study, we found cases of GA appear slightly more during summer season. Family history in GA is rarely reported and we did not find positive family history in our study.

Unfortunately, there is a lack of large-scale studies examining the role of infectious agents in triggering GA, although both viral and bacterial factors have been proposed. GA associated with viral infections has been reported, including cases linked to Epstein–Barr virus,[13]human immunodeficiency virus,[14] and varicella zoster virus (VZV).[15] More recently, two instances of GA following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have also been documented.[16,17] In our study, we also identified two cases of GA in patients with positive HIV status. GA has been reported as a cutaneous manifestation of HIV infection, particularly in the setting of advanced disease or significant immunosuppression. The generalized form of GA is much more common in HIV positive patients than in immunocompetent individuals.[18] There is growing evidence that stress may contribute to the development or exacerbation of granuloma annulare, although the underlying mechanism remains unclear. Belzer et al study investigated anxiety and depression in the patients with GA and reported a positive association.[19]Studer et al study also examined precipitating factors in GA and found stress present in 15 % of cases.[20] In our study, stress was identified in 17.5 % of subjects. Smoking has been associated with an increased likelihood of developing GA, possibly due to shared immunological mechanism seen in other granulomatous disorders. Almazan E et al study reported a higher prevalence of smoking history among patients with GA, noting that individuals with GA were more likely to have ever smoked (50% vs 38% in controls).[21] In our study, 22.5 % (n=9) of subjects had a history of smoking.

Granuloma annulare has occasionally been reported following vaccination, although this association remains rare and not definitively established.[22] Cases has been described after several vaccines, including COVID-19 vaccines,[23]suggesting that immune activation rather than a specific vaccine component may be responsible. In our study, one patient reported a history of recent vaccination. Another potential trigger for granuloma annulare is medication exposure. Several drugs have been implicated in inducing GA. In a January 2021 review, Shah et al. summarized granulomatous cutaneous drug eruptions and identified multiple iatrogenic causes of GA, including allopurinol, amlodipine, anti-TNFα agents, immune checkpoint inhibitors and several others.[24] Consistent with the findings reported by Lim AC,[25]one patient in our study was taking amlodipine.

Granuloma annulare has been linked to several comorbidities. In our study, diabetes mellitus (DM) and dyslipidaemia were the most common. Although the association between GA and DM remains debated, multiple studies have reported a higher prevalence of DM, among patients with generalized GA compared with those who have the localized form. A retrospective cohort study of 51,169 patients with GA, found that 21.1% of patients with GA had DM, compared with 13.3% of matched controls.[26] The same study also demonstrated a significant association between GA and hyperlipidaemia. Another case–control study similarly reported a statistically significant link between GA and dyslipidaemia, particularly elevated total cholesterol, triglyceride, and LDL levels, underscoring the potential role of lipid metabolism disturbances in GA pathogenesis.[27] In our study, additional comorbid conditions included hypertension (10%), hypothyroidism (5%), and liver disease (2.5%).

Granuloma annulare can present with different morphological pattern. In our study, among all GA cases, the localized annular form was the most common clinical presentation, followed by the generalized form. The typical sites of involvement for localized GA were the dorsum of the hands, feet, ankles, and elbows, whereas the generalized variant more often affected the extremities and trunk. These findings are consistent with most published literature, including the study of clinical variants of GA by Piettiet al.[4] Less common variants observed in our cohort included subcutaneous GA (n = 2), as well as perforating GA and patch-type GA, one case each. In majority of cases, cutaneous lesions were asymptomatic, while in few cases lesions were associated with itching and mild burning sensation.

Dermoscopy has emerged as a valuable non-invasive tool in the evaluation of GA, aiding in differentiation from clinically similar conditions and improving diagnostic confidence. Although GA is primarily a histopathological diagnosis, characteristics dermoscopic pattern correlate strongly with underlying granulomatous inflammation, mucin deposition, and vascular changes. Dermoscopic features in GA includes vascular and non-vascular patterns. In this study, dermoscopy showed yellowish-orange structure less areas as most common non vascular pattern (80%) followed by white shiny streak (60%). Another study by Errichetti E found whitish areas (64 %) as most common non-vascular findings, followed by

yellowish-orange structure less areas (60 %).[28] In vascular pattern, the same study observed unfocused vessels in 22 (88.0%) lesions, with sparsely distributed dotted ones being the most common, followed by linear-irregular and branching vessels. We found dotted or linear-irregular vessels as most frequent vascular finding, observed in 55 % lesions, followed by annular or arcuate arrangement of vessels 45 % lesions. A study by Bombonato C et al, analysing dermoscopy of GA according to histological subtypes, observed a strict association between yellowish-orange structure less areas, especially those having diffuse distribution, and a palisading granuloma histological pattern, thereby confirming the well-known dermoscopic-pathological correlation.[29] Similarly, focally distributed yellowish-orange structure less areas were also detected in lesions displaying

In the present study, the predominant pattern observed was the palisading granulomatous pattern, which is classically described as the hallmark of GA. This pattern is typified by foci of necrobiotic (degenerating) collagen in the dermis, surrounded by a rim of palisading histiocytes, lymphocytes, and occasional eosinophils. The presence of abundant dermal mucin, demonstrated on special stains such as alcian blue or colloidal iron, further supports the diagnosis and helps distinguish GA from other necrobiotic granulomatous disorders. In addition to the palisading pattern, a significant proportion of cases in our study showed the interstitial pattern, in which histiocytes are dispersed between collagen bundles without forming well-defined granulomas. Study by Stefanaki K at el (2007) and Cohen PR (2015) also observed similar pattern.[30,31] However, Umbert P and Winkelmann RK (1977) characterized 207 cases of GA and found that 71% showed the interstitial pattern, while 26% showed palisading granulomas.[32] The subcutaneous variant of GA, seen predominantly in pediatric age groups, is characterized by granulomatous inflammation involving the lobules and septa of subcutaneous fat, forming discrete nodules. While less common, its recognition prevents misdiagnosis as panniculitis or deep fungal/infectious processes. Similarly, the perforating variant, though rare, displays transepidermal elimination of degenerated collagen and may clinically mimic perforating dermatoses.

The variability in histopathological patterns seen across our cases underscores the dynamic nature of GA as a spectrum rather than a single fixed histological entity. Several authors suggest that the palisading pattern may evolve into the interstitial pattern during resolution, or vice versa, depending on lesion age and immunologic activity. Overall, the findings of the present study reinforce the significance of histopathology in confirming GA, especially in cases where clinical features are atypical or overlap with other annular dermatoses. The identification of necrobiotic collagen with palisading or interstitial histiocytes, along with mucin deposition, remains pivotal for diagnosis, and the combination of patterns observed reflects the heterogeneous and evolving nature of the disease.

CONCLUSION

Granuloma annulare exhibits diverse morphological patterns and may be influenced by multiple precipitating factors, including infections, medications, stress, and systemic conditions. It is also associated with a range of comorbidities, most notably diabetes mellitus and dyslipidaemia. Given this clinical heterogeneity, accurate diagnosis requires a comprehensive approach integrating clinical evaluation with dermoscopic and histopathological findings. Continued research with larger cohorts is needed to further clarify etiologic factors and optimize diagnostic and management strategies.

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