International Journal of Dermatology

Report

Clinical features, histology, and treatment outcomes of granular parakeratosis: a systematic review

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Conflict of interest: None.

Funding source: None.

doi: 10.1111/ijd.16107

Abstract

Background Granular parakeratosis is a rare disorder characterized by erythematous-brown hyperkeratotic papules and erythematous patches with scaling, occurring predominantly in the flexures and sites of occlusion. While the exact underlying pathogenesis remains unknown, there has been a wide variety of precipitating factors and treatment options reported in the literature.

Objective We systematically reviewed and identified precipitants of granular parakeratosis, as well as its clinical and histologic features and treatment outcomes.

Method A comprehensive literature search was conducted using MEDLINE and Embase in March 2021.

Results A total of 60 studies with 129 patients were included for analysis. An inciting factor was identified in 53.4%, the most common being topical agents including zinc oxide (17.1%), deodorant/antiperspirant (15.5%), and those containing benzalkonium chloride (7.0%). The majority presented with bilateral (68.2%) eruption of hyperkeratotic papules or erythematous patches and plaques, most frequently involving the axilla (56.5%). The prevailing histologic feature was retained keratohyalin granules within the stratum corneum in punch biopsy (97.2%) and curette (100%) specimens. Treatment options with reported success ranged from topical corticosteroids and systemic antibiotics to surgical interventions.

Conclusion We provide a systematic review of reported precipitants, clinical features, and treatment options that clinicians should consider when granular parakeratosis is considered.

Introduction

Granular parakeratosis is an enigmatic dermatologic disorder characterized by erythematous scaly patches, papules, and plaques predominantly involving the flexures (Fig. 1). First described by Northcutt et al. in 1991 as *axillary granular parakeratosis* and attributed to contact reaction to antiperspirants, it is currently conceptualized as a disorder of keratinization with an expanding list of postulated etiological factors and treatment options reported.[1,2] More recently, *hyperkeratotic flexural erythema* has been an alternative term proposed to recognize its heterogeneous clinical presentation and histologic features.[3]

Granular parakeratosis is considered rare, based on previous estimates of incidence at 0.005%.[4] However, estimates of incidence and prevalence are likely skewed by under-recognition of this clinical entity, which in turn is further compounded by under-reporting in the literature.[4]

We systematically reviewed the literature on granular parakeratosis to provide insights into their etiologic factors, clinical features, histologic findings, and treatment outcomes.

Methods

The systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive literature search was conducted using MEDLINE and Embase from inception to March 16, 2021, using the terms "granular parakeratosis" or "hyperkeratotic flexural erythema".

The authors screened initially by title and abstract. Articles were included if they: (i) documented patient(s) diagnosed with granular parakeratosis clinically or histologically, (ii) were written in English with either observational or interventional study design, and (iii) were accessible through the researchers' affiliated institutions. Independent full-text review was then conducted.

The authors (K. I. and A. L.) conducted abstract screening and data extraction independently of each other. Any discrepancies were resolved by discussion between the authors. Data extraction included study design, patient information (age, gender, ethnicity, comorbidities), clinical

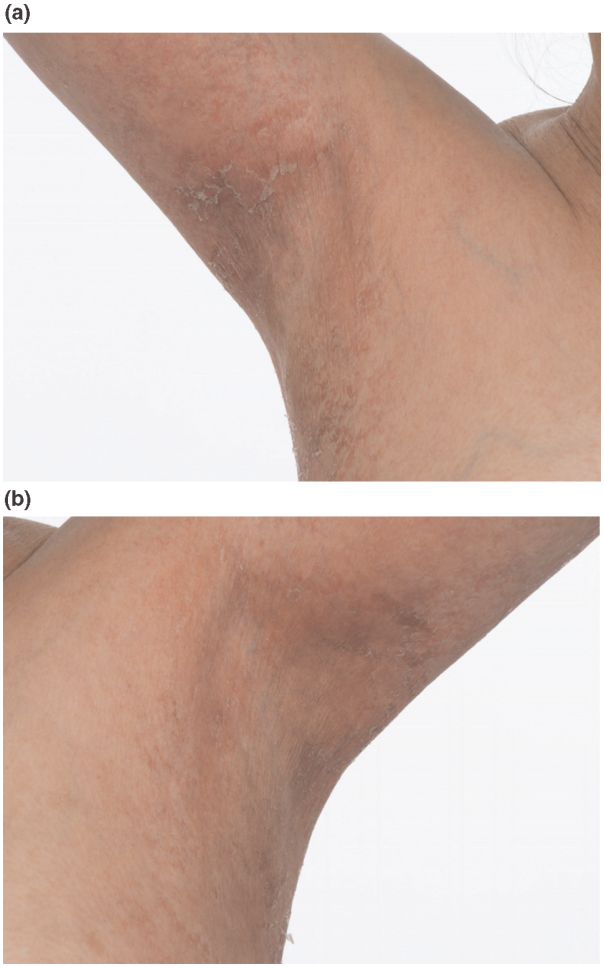

Figure 1 Granular parakeratosis characterized by a symmetrical flexural, erythematous, hyperkeratotic eruption involving the right (a) and left (b) axillae

characteristics (postulated triggers, clinical findings, symptoms, anatomic site, time course), histologic findings, treatment, and outcomes.

Results

Search results

The systematic literature search identified 193 studies (Fig. 2), of which 75 were duplicates and removed. Following abstract screening, 34 articles were removed as they did not meet eligibility criteria, leaving 84 studies that were analyzed for full-text review. Of these, 24 studies were excluded due to incorrect study design ($n = 6$), incorrect disease ($n = 6$), and the full texts being inaccessible ($n = 6$) or not published in English ($n = 6$). On completion of full text review, 60 studies were included for analysis. A summary of each study including design, patient demographics, clinical and histologic features, and treatment outcomes is provided in Data S1.

Study characteristics

The 60 studies identified included 46 case reports and 14 case series with a total of 129 patients diagnosed with granular parakeratosis (Data S1). The mean age at diagnosis was 37.8 years (range 0–83 years), of whom 69.0% ($n = 89/129$) were female. The most commonly reported comorbidities were eczema (6.2%, $n = 8/129$) and obesity (3.9%, $n = 5/129$). The mean duration of granular parakeratosis prior to diagnosis was 19.2 months (range 4 days–20 years).

Precipitants

An etiologic factor was identified in 59.7% ($n = 77/129$) (Table 1). Topical products accounted for 43.4% ($n = 56/129$), the most commonly implicated being zinc oxide, deodorant/antiperspirant, and products containing benzalkonium chloride. Occlusive environments such as diapers were implicated in 13.2% ($n = 17/129$). Causal relationship with systemic medication exposure – namely simvastatin, doxorubicin, and probiotics – were proposed in 2.3% ($n = 3/129$). Although predominantly an acquired disorder, one congenital case has been reported.

Clinical characteristics

The most frequent clinical presentations of granular parakeratosis were papules coalescing into plaques (53.5%, $n = 69/129$) with erythematous/brown coloration and hyperkeratotic texture, or as hyperkeratotic erythematous patches and plaques (32.6%, $n = 42/129$) (Table 1). Other common features include a papillomatous appearance and brown peeling crust/scale. Symptoms such as pruritus, burning, and tenderness were reported in 43.4% ($n = 56/129$) whereas 21.7% ($n = 28$) remained asymptomatic. Granular parakeratosis most commonly involved the axillae (56.5%, $n = 73/129$) and groin (31.8%, $n = 41/129$), with 68.2% ($n = 88/129$) of presentations being bilateral. A fluctuant nature, such as recurrence with hot climates, was reported in 7.9% ($n = 9/129$).

Histologic features

Histology was available in 90.7% ($n = 117/129$) (Table 2). Punch biopsies were performed in 82.2% ($n = 106/129$). Supportive findings included hyperkeratosis, parakeratosis, retained keratohyalin granules within the stratum corneum, psoriasiform or papillomatous epidermal hyperplasia, and lymphocyte-predominant interstitial or perivascular infiltrate in the superficial dermis. Curetted scale revealing parakeratosis with retained keratohyalin granules was used as an alternative to biopsy in 8.5% ($n = 11/129$).

Treatment and outcomes

Treatment outcomes were reported in 65.1% ($n = 84/129$) (Table 2). Spontaneous clearing between 2.5 and 12 months occurred in 4.7% ($n = 6/129$), while stopping an identified etiologic factor led to resolution between 1 week and 12 months in 21.7% ($n = 28/129$). Topical treatments were employed in

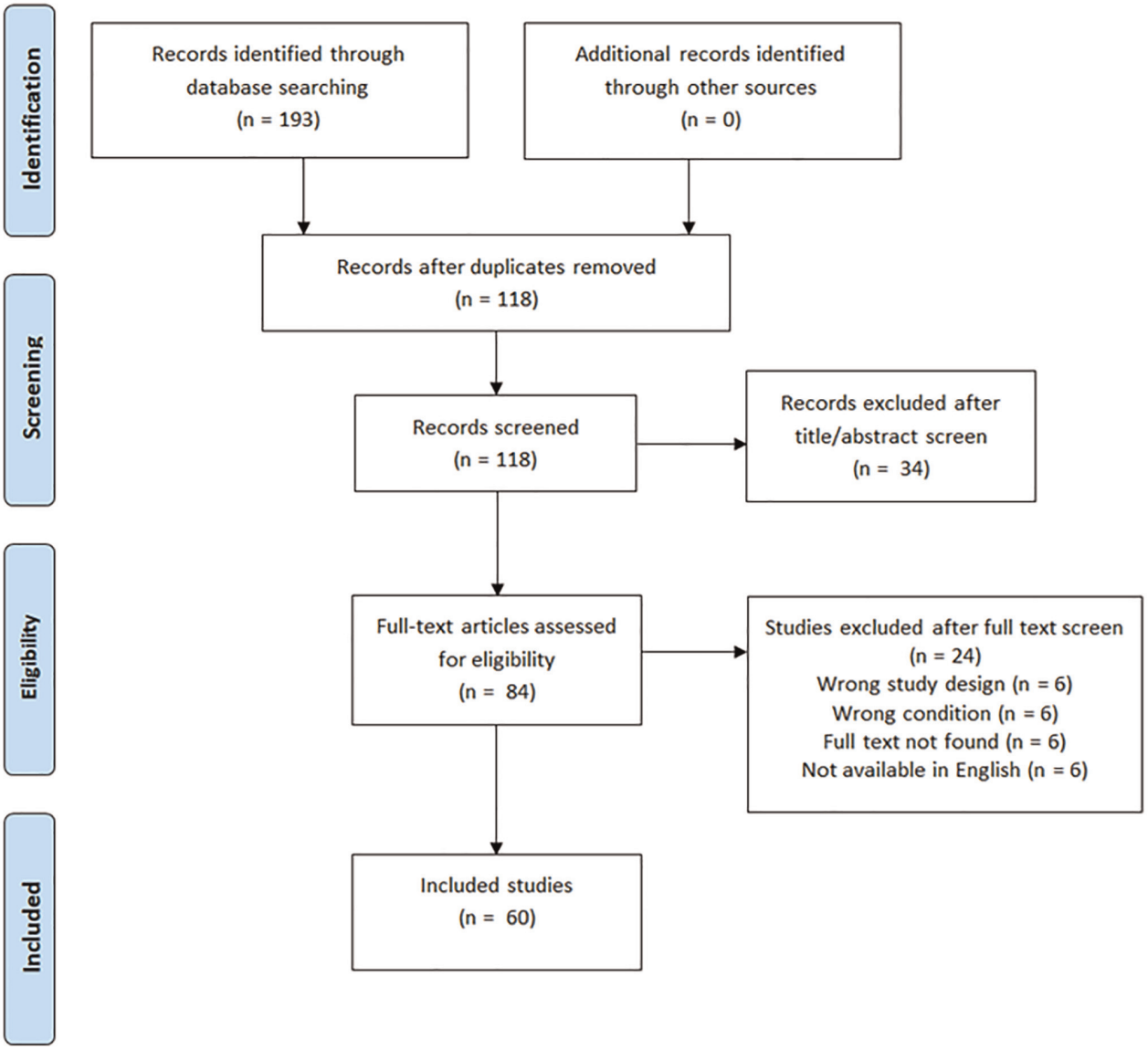

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for identifying studies that reported granular parakeratosis

23.3% (n = 30/129) including keratolytic agents, corticosteroids, vitamin D analogues, retinoids, and calcineurin inhibitors. Systemic medications were administered in 10.1% (n = 13/129) including antibiotics, isotretinoin, triazole antifungals, and dexamethasone. Other treatment modalities reported included mammopexy, laser, clostridium botulinum injections, and cryotherapy.

Discussion

The primary objective of this study was to create a comprehensive review of granular parakeratosis. The latency in diagnosis, with a mean duration of 19.2 months and range of up to 20 years, highlights that granular parakeratosis is an underrecognized entity for which clinical diagnosis may be missed or delayed. An interrogation of histologic database by Scheinfeld et al., where only one of 18 histologically confirmed cases of granular parakeratosis had an accompanying correct clinical diagnosis, further corroborates this view that granular parakeratosis is likely more frequently encountered than previously reported.[4]

The evolution in nomenclature of granular parakeratosis has followed developments in recognition of its distribution. Northcutt et al. first described in 1991 a case series of four patients

Table 1 Clinical features of granular parakeratosis

Postulated etiology	
Topical agents	
Zinc oxide	22 (17.1%)
Deodorant/antiperspirant	20 (15.5%)
Benzalkonium chloride	9 (7.0%)
Talcum powder	1 (0.8%)
Depilatory cream	1 (0.8%)
Wax hair removal	1 (0.8%)
Calamine lotion	1 (0.8%)
Frequent emollient (not specified)	1 (0.8%)
Occlusion	
Heat, sweating, and friction	8 (6.2%)
Diaper	7 (5.4%)
Obesity	2 (1.6%)
Other	
Congenital	1 (0.8%)
Systemic medications	
Pegylated liposomal doxorubicin	1 (0.8%)
Simvastatin	1 (0.8%)
Probiotic	1 (0.8%)
Not identified	41 (31.8%)
Not reported	19 (14.7%)
Morphology	
Papules coalescing into plaques	
Erythematous/brown	65 (50.4%)
Hyperkeratotic	60 (46.5%)
Peeling brown crust/scale	11 (8.5%)
Fissures/erosions/maceration	6 (4.7%)
Papillomatous/verrucous	4 (3.1%)
Scaling and erythema	
Hyperkeratotic erythematous patch/plaque	42 (32.6%)
Papillomatous/verrucous	10 (7.8%)
Lichenified	3 (2.3%)
Maceration	3 (2.3%)
Satellite pustules	2 (1.6%)
Double-edged scale	1 (0.8%)
Other	
Hyperkeratotic balanoposthitis	1 (0.8%)
Pigmented macule	1 (0.8%)
Not reported	12 (9.3%)
Symptoms	
Pruritus	40 (31.0%)
Burning	10 (7.8%)
Pain/tenderness	6 (4.7%)
Asymptomatic	28 (21.7%)
Not reported	55 (42.6%)
Anatomic site	
Body folds	
Neck	9 (7.0%)
Axilla	73 (56.5%)
Inter/submammary	14 (10.9%)
Infra-pannus	2 (1.6%)
Groin/inguinal folds	41 (31.8%)
Buttocks/intergluteal cleft	8 (6.2%)
Knee flexures	5 (3.9%)
Other	
Face	2 (1.6%)
Torso (abdomen/back)	11 (8.5%)
Anogenital	13 (10.1%)
Thighs	5 (3.9%)
Laterality	
Unilateral	17 (13.2%)
Bilateral	88 (68.2%)
Not specified	24 (18.6%)

with axillary involvement and ascribed the term *axillary granular parakeratosis* – befitting for both its clinical and histologic features.[1] In 1998, Mehregan et al. adapted the term to *intertriginous granular parakeratosis* after describing a case with inguinal involvement.[5] Metze et al. later expanded it to *granular parakeratosis* recognizing other sites of involvement outside of the axillae and groin.[2] This holds true with the findings of our systematic review, where only a minority of patients developed granular parakeratosis in non-intertriginous sites including the face (1.6%), torso (8.5%), and thighs (3.9%).

Insights into its pathogenesis have similarly evolved. Initial cases of axillary involvement, each associated with deodorant/antiperspirant use, led to a deduction that a compound within deodorant/antiperspirant acted as an external stimulus that induces epidermal proliferation and/or blocks breakdown of filaggrin precursors.[1,6–8] Recognition of inguinal involvement under occlusion of diapers highlighted the role of environmental modification, further exacerbated by topical application of zinc oxide, which can increase epidermal turnover.[9–13] Indeed, zinc oxide, deodorant/antiperspirant, and occlusive factors collectively accounted for 45.7% of postulated etiological factors. The next most commonly implicated precipitant was benzalkonium chloride, a quaternary ammonium cationic detergent found in household laundry detergents. This, combined with reported resolution observed following treatment with systemic antibiotics, has lent support to the role of an altered microbiome in the development of granular parakeratosis.[3,14–16] However, rare reports of congenital onset, and development of granular parakeratosis following administration of systemic medications, highlight that the exact pathogenesis remains elusive and is a subject that warrants further investigation.[17–19]

Notably, our review highlights that findings of parakeratosis and retention of keratohyalin granules within the stratum corneum, despite its name, is not always present on histologic examination of granular parakeratosis. Kumarasinghe et al. propose that the histologic features may fluctuate developing on the stage of clinical progression and ascribed the term *hyperkeratotic flexural erythema* as a better encompassing description.[3] Clinicians must recognize granular parakeratosis in their differential diagnoses for intertriginous exanthems in order to ensure correct clinical–pathological correlation when supportive features such as epidermal hyperplasia are noted, even if the classic histologic findings are not present. Curetted or peeled samples of desquamative scale were sufficient for histologic confirmation in 11 patients and present a useful noninvasive alternative to punch biopsies.[11,13,20]

Table 2 Histologic features and treatment of granular parakeratosis

Histology	
Biopsy modality	
Punch biopsy	106 (82.2%)
Curette of scale	11 (8.5%)
Not biopsied	9 (7.0%)
Not reported	3 (2.3%)
Biopsy features	
Hyperkeratosis	82 (77.4%)
Parakeratosis	97 (91.5%)
Retained keratohyalin granules within stratum corneum	103 (97.2%)
Epidermal hyperplasia	63 (59.4%)
Inflammatory infiltrate	
Lymphocyte (interstitial, superficial dermis)	28 (26.4%)
Lymphocyte (perivascular, superficial dermis)	42 (39.6%)
Lymphocyte (perifollicular)	2 (1.9%)
Lymphocyte and eosinophils	4 (3.8%)
Lymphocyte and neutrophils	1 (0.9%)
Other	
Vacuolization in stratum granulosum	13 (12.3%)
Hypergranulosis	8 (7.5%)
Dyskeratotic keratinocytes	2 (1.9%)
Involvement of dilated follicular infundibulum	6 (5.7%)
Eccrine ostia prominence	2 (1.9%)
Fibrosis in papillary dermis	7 (6.6%)
Curette features	
Parakeratosis with retained keratohyalin granules	11 (100%)
Successful treatment	
Spontaneous clearing	6 (4.7%)
Stop precipitant	
Alone	22 (17.1%)
Combined with topical treatment	6 (4.7%)
Topical	
Corticosteroid	8 (6.2%)
Vitamin-D analogue	6 (4.7%)
Retinoid	4 (3.1%)
Calcineurin inhibitor	1 (0.8%)
Glycolic acid	1 (0.8%)
Salicylic acid	4 (3.1%)
Other combinations	6 (4.7%)
Oral	
Antibiotics	7 (5.4%)
Isotretinoin	3 (2.3%)
Antifungal triazole	2 (1.6%)
Dexamethasone + ebastine	1 (0.8%)
Other	
Mammopexy	1 (0.8%)
Change to cooler climate	2 (1.6%)
Laser combined with topical retinoid	1 (0.8%)
Clostridium botulinum injection (50 units per axilla)	2 (1.6%)
Cryotherapy	1 (0.8%)
Treatment or outcome not reported	45 (34.9%)

Treatment efficacy of granular parakeratosis is difficult to assess in the absence of randomized controlled trials, especially where a minority of cases (4.7%) reported spontaneous clearing. Based on the findings of our review, a pragmatic approach includes first identification and removal of potential triggers, environmental modification to avoid heat and occlusion where possible, followed by stepwise introduction of topical then systemic agents in order to minimize the risk of inflicting iatrogenic adverse effects. Although asymptomatic in 21.7%, the spectrum of symptoms reported by patients also ranged from pruritus (31.0%) and burning (7.8%) to pain (4.7%), and thus treatment escalation needs to be tailored accordingly.

The main limitation of this review is the small sample size and observational findings accrued from case reports and case series. In the absence of epidemiological, case–control, or randomized controlled studies, conclusions drawn regarding the incidence, triggers, and efficacy of different treatment modalities should be interpreted with a degree of caution. That said, our systematic review of the literature to characterize granular parakeratosis affords insights and inferences that may guide clinical practice. Larger studies are warranted to confirm the generalizability of our findings and to further explore the pathogenesis of granular parakeratosis.

Conclusion

Our systematic review demonstrates that granular parakeratosis is a rarely reported dermatosis that typically manifests at sites of occlusion in association with a variety of inciting triggers and spectrum of clinical manifestations. Dermatologists and clinicians should consider topical and/or systemic medications and environmental factors that may be implicated in its development. Removal of the postulated trigger does not necessarily result in resolution, and an array of topical, systemic, and surgical adjunctive treatments have been reported in case reports and case series.

Acknowledgment

The patient photographed in this manuscript has provided informed consent for publication of images. Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

Author contributions

K. I. and A. L. jointly designed the study, performed the systematic review, and jointly wrote the manuscript.

Data availability statement

We have provided data relating to this study in the supplemental material.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Summary of study characteristic, patient demographics, granular parakeratosis characteristics and treatment outcomes.