Ann Dermatol. 2024 Feb;36(1):58-61
https://doi.org/10.5021/ad.22.229
pISSN 1013-9087·eISSN 2005-3894

AD ANNALS of DERMATOLOGY

Brief Report

Check for updates

A Comparative Study on Clinico-Histopathological Features of Granulomatous Rosacea and Lupus Miliaris Disseminatus Faciei

So Hee Park [1], **Sang Woo Ahn** [2], **Seung Hee Jang** [2], **Seong Min Hong** [2], **Woo Jung Jin** [2], **Jung Eun Seol** [2], **So Young Jung** [1], **Hyojin Kim** [2]

[1]Department of Dermatology, Haeundae Paik Hospital, College of Medicine, Inje University, Busan, Korea
[2]Department of Dermatology, Busan Paik Hospital, College of Medicine, Inje University, Busan, Korea

Dear Editor:

Granulomatous rosacea (GR) was considered as a variant of rosacea apart from four subtypes: erythematotelangiectatic (ET), papulopustular (PP), ocular, and phymatous[1]. However, granuloma was also found in ET or PP form of rosacea, so GR was considered as a histologic variant rather than a distinct clinical subtype[2]. The updated classification unified the subtypes to encompass wide range of phenotypic combinations, focusing on the subclinical histological inflammation[3]. In other words, GR could still be interpreted as a histologic variant, featured by distinctive granulomatous inflammation indicating the underlying chronic and severe tissue reaction[3,4].

Lupus miliaris disseminatus faciei (LMDF) manifests as multiple discrete yellow-brown, dome-shaped papules on the centrofacial area[5]. The etiology of tuberculosis was refuted, suggesting the immune reaction to the antigens from injured hair follicles or *Demodex folliculorum*[6]. Histologic hallmark is epithelioid granuloma surrounding caseation necrosis, which can be obscure in early or late stage[7].

Differential diagnosis of them is important because of the differences in therapeutic responsiveness and prognosis[8]. GR was known to be improved by tetracycline, but LMDF was known to show relatively favorable response on corticosteroid. GR tends to show chronic progress but LMDF can resolve spontaneously within 2 years, accompanying pitted scars. Overlapping clinical manifestations and histology between them can easily lead to misdiagnosis[5,6,8]. Therefore, this study investigated the perceptional pattern to reflect real-world dilemma in diagnosis, correlating the clinical appearance and histopathology.

Patients were selected who received biopsy on suspicion of GR or LMDF in the Busan Paik and Haeundae Paik Hospital between 1995 and 2020. Five dermatologists reviewed all photographs without clinical or histopathological information. Any training or opinion exchange was not given to minimize the confirmation bias.

The subjects were classified into five groups: 'GR,' 'LMDF,' 'Indeterminate GR (I-GR),' 'Indeterminate LMDF (I-LMDF),' or 'Others.' If 4–5 physicians had impressions of GR or LMDF, the subjects were assorted into 'GR' or 'LMDF' groups respectively. If 2–3 physicians did, the subjects were included in 'I-GR' or 'I-LMDF' groups respectively. The subjects were classified into 'Others' if none or 1 impression of GR or LMDF was given. This study was approved by Inje University Institutional Review Board (No.: 2021-04-039).

A total of 62 case were enrolled and their clinico-histopathologic features were described in **Table 1**. The 'GR' group showed significantly higher female proportion than 'LMDF' group (1:3.5 vs. 1:0.8), with a higher mean age (51.7 vs. 44.4). Vascular symptom and history of aggravation on external stimuli were significantly more common in 'GR' group than 'LMDF' group (77.7%

Received: Jan 4, 2023
Revised: Aug 9, 2023
Accepted: Aug 9, 2023
Published online: Jan 25, 2024

Corresponding Author:
Hyojin Kim
Department of Dermatology, Busan Paik Hospital, College of Medicine, Inje University, 75 Bokji-ro, Busanjin-gu, Busan 47392, Korea.
Email: derma09@hanmail.net

Table 1. The clinical and histopathologic features of the subjects

Variables	Total	GR	I-GR	I-LMDF	LMDF	Others
No.	62	18	10	8	13	13
Age (mean ± SD)	47.3±13.8	51.7±11.9	46.9±14.7	47.9±15.6	44.4±13.0	44.2±15.4
Sex (male:female)	1:1.3	1:3.5	1:0.6	1:3.0	1:0.8	1:0.8
Vascular symptom	53.2%	77.7%*	60.0%	50.0%	23.0%	46.1%
Aggravation on external stimuli	40.3%	61.1%*	40.0%	37.5%	15.3%	38.4%
Lesion distribution						
Eyelid	45.1%	27.7%	50.0%	75.0%*	84.6%*	7.7%
Forehead	77.4%	83.3%	70.0%	75.0%	92.3%	61.5%
Nose	70.9%	83.3%	90.0%	50.0%	100.0%	23.0%
Perioral area	64.5%	61.1%	50.0%	87.6%	76.9%	53.9%
Cheek	85.4%	100.0%	80.0%	62.5%	92.3%	76.9%
Chin	72.5%	88.9%	50.0%	75.0%	69.2%	69.2%
Extrafacial area	8.1%	11.1%	0.0%	12.5%	7.7%	8.3%
Lesion appearance						
Background erythema	59.6%	88.9%*	60.0%	37.5%	46.2%	46.2%
Telangiectasia	58.0%	93.3%*	90.0%*	50.0%	30.8%	30.8%
Deep-seated papule	32.2%	22.2%	10.0%	50.0%	76.9%*	7.7%
Pustule	16.1%	33.3%	0.0%	0.0%	23.0%	7.7%
Histopathology						
Caseation necrosis	17.7%	5.6%	10.0%	37.5%*	38.5%*	7.7%
Epithelioid granuloma	59.6%	55.6%	60.0%	75.0%	84.6%	30.8%
Capillary dilatation	83.8%	88.9%	90.0%	87.5%	84.6%	69.2%
Solar elastosis	53.2%	61.1%	70.0%	50.0%	46.2%	38.5%
Demodex folliculorum	14.5%	27.8%	10.0%	12.5%	7.7%	7.7%

GR: granulomatous rosacea, I-GR: indeterminate granulomatous rosacea, I-LMDF: indeterminate lupus miliaris disseminatus faciei, LMDF: lupus miliaris disseminatus faciei, SD: standard deviation.
*$p<0.05$.

vs. 23%, 61.1% vs. 15.3%). Other clinical impressions were folliculitis, acne vulgaris, contact dermatitis, seborrheic dermatitis, ET rosacea, and PP rosacea.

Representative clinical pictures were shown in **Fig. 1**. Eyelid involvement was significant in 'LMDF' and 'I-LMDF' groups (84.6%, 75%). It gradually increased from 'GR' (27.7%) to 'LMDF' group (84.6%). The 'LMDF' group showed significantly higher incidence of deep-seated papules (76.9%), however background erythema (88.9%) and telangiectasia (93.3%) were significant in 'GR' group. Telangiectasia gradually decreased from 'GR' (93.3%) to 'LMDF' group (30.8%). Unlike previous studies, extrafacial involvement was not significantly different between 'GR' group (11.1%) and 'LMDF' group (7.7%), which might be attributed to the small subject number in this study.

Representative histological images were shown in **Fig. 2**. Caseation necrosis was significant in 'LMDF' and 'I-LMDF' groups (38.5%, 37.5%). The proportion of epithelioid granuloma gradually increased from 'GR' (55.6%) to 'LMDF' group (84.6%). In contrast, capillary dilatation, solar elastosis, and *D. folliculorum* were more common in 'GR' group, albeit statistically insignificant. CD3 (pan T-cell marker) and CD8 (cytotoxic T-cell marker) were positive in both 'GR' and 'LMDF' groups, however CD68

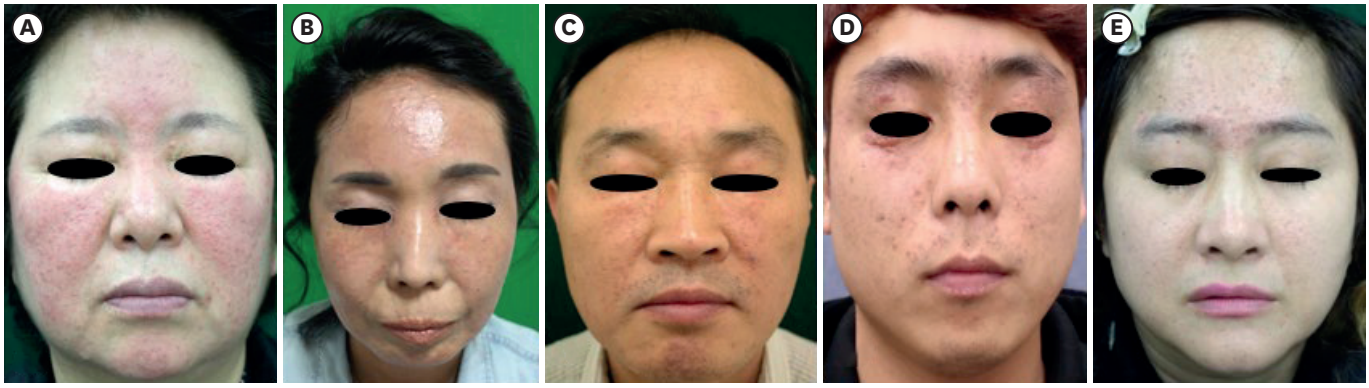

Fig. 1. The representative clinical pictures of each group. (A) Granulomatous rosacea. (B) Indeterminate granulomatous rosacea. (C) Indeterminate lupus miliaris disseminatus faciei. (D) Lupus miliaris disseminatus faciei. (E) Others.

AD ANNALS of DERMATOLOGY

(macrophage marker) stain was weaker in the former. Although both diseases have pathophysiology of the T-cell-attracting chemokines and subsequent cytokine cascades, macrophage activity might be more markedly upregulated in the LMDF as indicated in the previous report[9].

Previously known features of LMDF distinctive from GR were the predilection of young men, eyelid and perioral involvement, absence of background erythema or vascular symptoms, less reactivity to external stimuli, favorable response to corticosteroid, and self-limited course with scarring[5,6,8]. Histologically, LMDF shows larger-sized granuloma and central necrosis with less capillary dilatation, solar elastosis, or *D. folliculorum* than GR[5,6].

In this study, 'GR' group showed significantly higher proportion of female, background erythema, and telangiectasia, while 'LMDF' group showed significant eyelid involvement and deep-seated papules. In other words, physician's perceptual pattern was focused on sex, erythema, telangiectasia, eyelid invasion, and deep-seated papules to get impression.

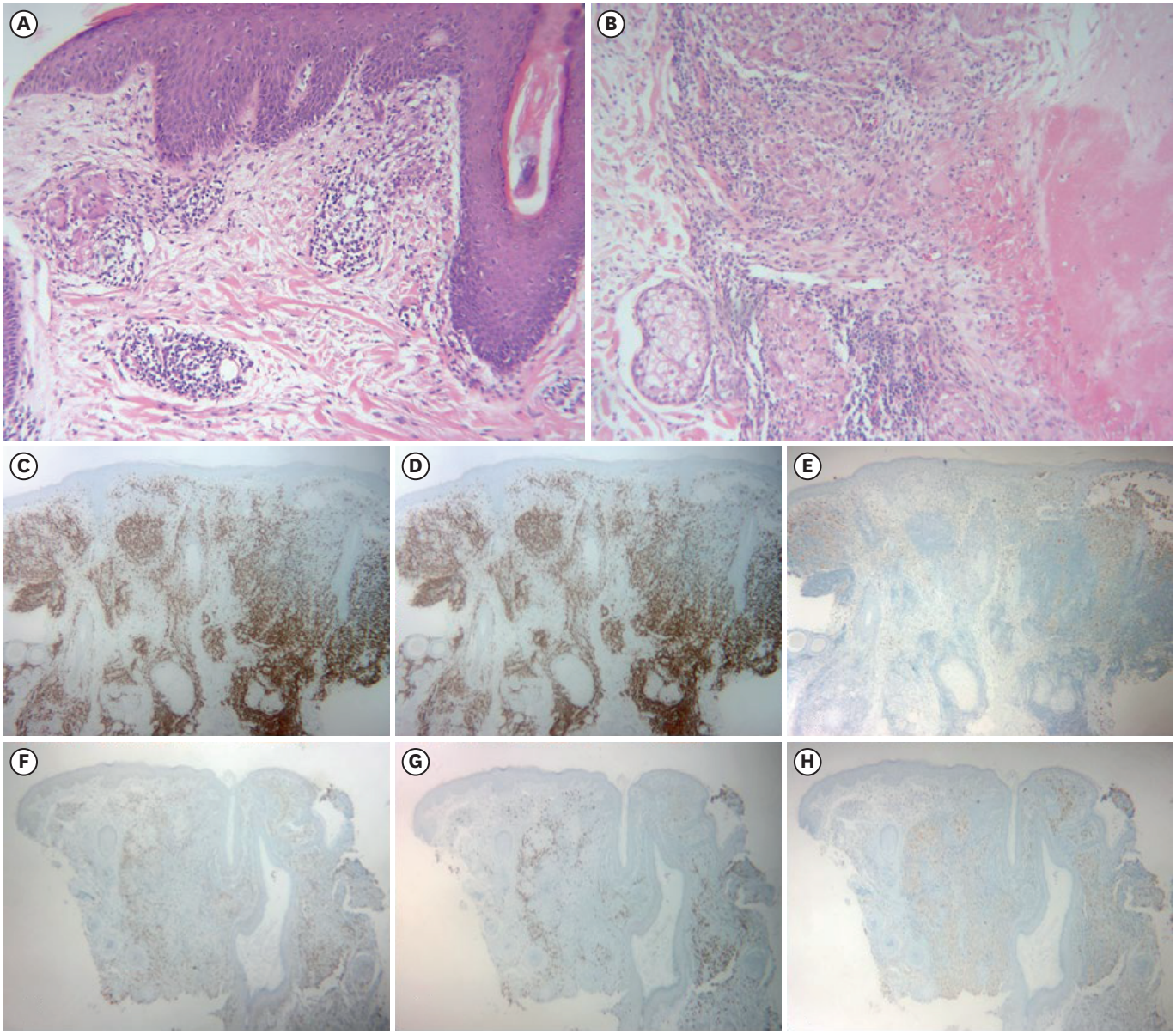

Fig. 2. Histopathology. (A) Granulomatous rosacea showed dermal epithelioid granuloma, solar elastosis, capillary dilatation, and *Demodex folliculorum* (H&E; ×100). (B) Lupus miliaris disseminatus faciei showed caseation necrosis and adjacent epithelioid granuloma (H&E; ×100). (C-E) Infiltrated cells of granulomatous rosacea were positive on CD3 and CD8 (T cell markers), but weakly positive on CD68 (macrophage marker). (CD3 ×40, CD8 ×40, CD68 ×40) (F-H) Infiltrated cells of lupus miliaris disseminatus faciei were positive on CD3, CD8, and CD68. (CD3 ×40, CD8 ×40, CD68 ×40). H&E: hematoxylin and eosin.

https://doi.org/10.5021/ad.22.229

Interestingly, clinical classification well predicted the histological features. 'LMDF' group showed significant caseation necrosis, while 'GR' group showed slightly more capillary dilatation, solar elastosis, and *D. folliculorum*. Prevalent deep-seated papules of 'LMDF' group might indicate the histological granuloma with caseation necrosis. Significant telangiectasia of 'GR' group might indicate the histological capillary dilatation, while background erythema might reflect the histological photoaging manifested as solar elastosis, and *Demodex*-related inflammation with vasodilation.

The proportion of caseation necrosis in 'LMDF' group was consistent with the previous studies (20%–43%)[7]. The absence of caseation necrosis could be attributed to the biopsy of early or late lesion, and distinction with GR was challening in those cases[7]. The proportion of caseation necrosis in 'GR' group was also consistent with previous studies (10%), and consideration of other information, including vascular symptoms or therapeutic response, was required to rule out LMDF[8].

D. folliculorum was more common in 'GR' group than 'LMDF' group (27.8% vs. 7.7%), suggesting closer relationship with the former. Although several reports considered *D. folliculorum* to induce LMDF through delayed hypersensitivity reaction, this study might reflect the well-established strong relationship of *D. folliculorum* with rosacea through toll-like receptor 2, cathelicidin, and activation of macrophage and CD8-positive cytotoxic T cell[10].

This study has limitations in that the subject number was small and the subjects were not initially confirmed as GR or LMDF. Therefore, other diseases such as folliculitis or acne vulgaris would have acted as confounding factors. In addition, this study could not evaluate the prognostic factors of GR and LMDF because of several missing data about therapeutic progress, not unified treatment regimen, and variable follow-up period. It would be helpful to perform prospective study with standardized management protocol with objective method for evaluation of therapeutic response.

This study clearly showed the perceptional pattern in evaluating granulomatous facial dermatoses. In other words, this study implicated the risk of misdiagnosis of GR or LMDF based merely on clinical appearance or histopathology. To avoid the diagnostic pitfalls, comprehensive information, including vascular symptoms, aggravating factors, and treatment progress, would be necessary.

ORCID iDs

So Hee Park
https://orcid.org/0000-0002-9600-799X
Sang Woo Ahn
https://orcid.org/0000-0003-4820-3870
Seung Hee Jang
https://orcid.org/0000-0002-8343-209X
Seong Min Hong
https://orcid.org/0000-0002-8273-7350
Woo Jung Jin
https://orcid.org/0000-0003-4499-8901
Jung Eun Seol
https://orcid.org/0000-0002-3029-9635
So Young Jung
https://orcid.org/0000-0003-0155-5473
Hyojin Kim
https://orcid.org/0000-0003-0987-4938

FUNDING SOURCE

None.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

DATA SHARING STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

REFERENCES

1. Sánchez JL, Berlingeri-Ramos AC, Dueño DV. Granulomatous rosacea. Am J Dermatopathol 2008;30:6-9. PUBMED | CROSSREF
2. Aroni K, Tsagroni E, Lazaris AC, Patsouris E, Agapitos E. Rosacea: a clinicopathological approach. Dermatology 2004;209:177-182. PUBMED | CROSSREF
3. Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, et al. Standard classification and pathophysiology of rosacea: the 2017 update by the National Rosacea Society Expert Committee. J Am Acad Dermatol 2018;78:148-155. PUBMED | CROSSREF
4. van Zuuren EJ, Arents BW, van der Linden MM, Vermeulen S, Fedorowicz Z, Tan J. Rosacea: new concepts in classification and treatment. Am J Clin Dermatol 2021;22:457-465. PUBMED | CROSSREF
5. van de Scheur MR, van der Waal RI, Starink TM. Lupus miliaris disseminatus faciei: a distinctive rosacea-like syndrome and not a granulomatous form of rosacea. Dermatology 2003;206:120-123. PUBMED | CROSSREF
6. Chougule A, Chatterjee D, Yadav R, Sethi S, De D, Saikia UN. Granulomatous rosacea versus lupus miliaris disseminatus faciei-2 faces of facial granulomatous disorder: a clinicohistological and molecular study. Am J Dermatopathol 2018;40:819-823. PUBMED | CROSSREF
7. el Darouti M, Zaher H. Lupus miliaris disseminatus faciei--pathologic study of early, fully developed, and late lesions. Int J Dermatol 1993;32:508-511. PUBMED | CROSSREF
8. Seo JI, Shin MK. Lupus miliaris disseminatus faciei versus granulomatous rosacea: a case report. Case Rep Dermatol 2021;13:321-329. PUBMED | CROSSREF
9. Alexanian C, Liakos W, Toussi A, Kao J, Cheng MY, Wang EA, et al. Immune profiling of lupus miliaris disseminatus faciei and successful management with anti-tumour necrosis factor therapy. Clin Exp Dermatol 2021;46:910-914. PUBMED | CROSSREF
10. Luo Y, Wu LX, Zhang JH, Zhou N, Luan XL. Demodex-induced Lupus miliaris disseminatus faciei: a case report. Medicine (Baltimore) 2020;99:e21112. PUBMED | CROSSREF