ORIGINAL ARTICLE

Predictive Model for Differential Diagnosis of Inflammatory Papular Dermatoses of the Face

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Background: The clinical features of inflammatory papular dermatoses of the face are very similar. Their clinical manifestations have been described on the basis of a small number of case reports and are not specific. **Objective:** This study aimed to use computer-aided image analysis (CAIA) to compare the clinical features and parameters of inflammatory papular dermatoses of the face and to develop a formalized diagnostic algorithm based on the significant findings. **Methods:** The study included clinicopathologically confirmed inflammatory papular dermatoses of the face: 8 cases of eosinophilic pustular folliculitis (EPF), 13 of granulomatous periorificial dermatitis-lupus miliaris disseminatus faciei (GPD-LMDF) complex, 41 of granulomatous rosacea-papulopustular rosacea complex (GR-PPR) complex, and 4 of folliculitis. Clinical features were evaluated, and area density of papular lesions was quantitatively measured with CAIA. Based on these variables, we developed a predictive model for differential diagnosis using classification and regression tree analysis. **Results:** The EPF group showed lesion asymmetry and annular clusters of papules in all cases. The GPD-LMDF complex group had significantly higher periocular density. The GR-PPR complex group showed a higher area density of unilateral cheek papules and the highest total area density. According to the predictive model, 3 variables were used for differential diagnosis of the 4 disease groups, and each group was diagnosed with a predicted probability of 67%~100%. **Conclusion:** We statistically confirmed the distinct clinical features of inflammatory papular dermatoses of the face and proposed a diagnostic algorithm for clinical diagnosis. **(Ann Dermatol 32(4) 298~305, 2020)**

-Keywords-
Algorithms, Computer-assisted, diagnosis, Decision trees, Facial dermatoses, Granulomatous rosacea, Perioral dermatitis

INTRODUCTION

Various inflammatory skin diseases characterized by erythematous papules that most often affect the face include clinically common folliculitis and rosacea, and relatively rare eosinophilic pustular folliculitis (EPF), granulomatous periorificial dermatitis (GPD), and lupus miliaris disseminatus faciei (LMDF). These have similar clinical manifestations and therapeutic responses, but are separate clinical entities with differences in epidemiology, accompanying symptoms, histopathology, etiopathogenesis, and prognosis[1-6].

Until now, the clinical features of these inflammatory papular dermatoses on the face have been described on the basis of a small number of case reports and personal observations, but these are not pathognomonic[4,7-10]. Consequently, histological examination has been considered indispensable for differential diagnosis, although the pathologic results may not always be diagnostic and can be similar to each other. In practice, however, the location and

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distribution of inflammatory papules on the face seem to be slightly different in each disease. Objective verification of these subtle differences would help dermatologists diagnose these diseases clinically.

In previous studies, the clinical and pathologic images of various skin diseases were quantitatively analyzed using computer-aided image analysis (CAIA)[11-14]. The CAIA parameters derived from these studies made it possible to objectively differentiate clinically similar diseases or different histological subtypes within a disease. This study aimed to use CAIA to objectively compare the clinical features and parameters of inflammatory papular dermatoses of the face and to develop a formalized diagnostic algorithm based on significant findings that can be obtained in clinical practice without histological examination.

METHODS AND MATERIALS

Subjects

Clinical photographs and histological slides were collected from patients who underwent assessment for inflammatory papules of the face in Seoul National University Bundang Hospital between January 2005 and July 2019. Three experienced dermatologists (CWC, SC, and SWY) classified the photos into 4 groups (Fig. 1): EPF, GPD-LMDF complex, granulomatous rosacea-papulopustular rosacea complex (GR-PPR complex), and folliculitis, based on clinical photos, medical histories, and biopsy reports. Photographs that did not fit any of the 4 groups and those that caused ambiguity in diagnosis were excluded. The study protocol was approved by the Institutional Review Board (IRB) of
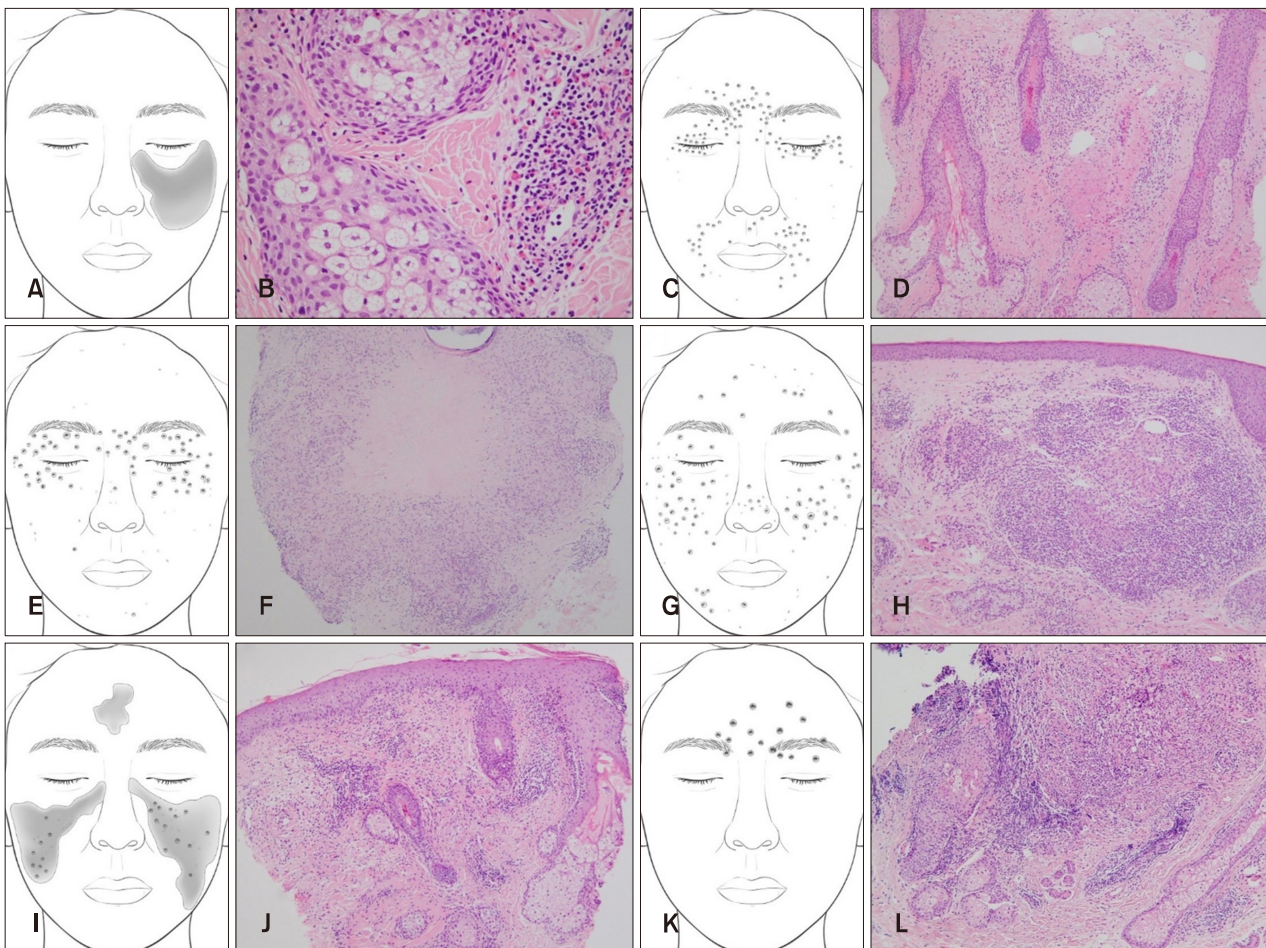

Fig. 1. Inflammatory papular dermatoses of the face confirmed with biopsy. Illustrations of the clinical features: (A) EPF, (C) GPD, (E) LMDF, (G) GR, (I) PPR, (K) folliculitis. Histopathological features: (B) Perifollicular eosinophilic infiltration (H&E, ×400). (D) Perivascular and perifollicular lymphoneutrophilic infiltration (H&E, ×100). (F) Granulomatous inflammation with necrosis (H&E, ×100). (H) Perifollicular granulomatous inflammation with focal central suppuration (H&E, ×100). (J) Perivascular and perifollicular lymphoneutrophilic infiltration (H&E, ×100). (L) Dense perifollicular lymphohistiocytic infiltration (H&E, ×100). EPF: eosinophilic pustular folliculitis, GPD: granulomatous periorificial dermatitis, LMDF: lupus miliaris disseminatus faciei, GR: granulomatous rosacea, PPR: papulopustular rosacea.

Seoul National University Bundang Hospital (IRB number: B-1803-457-101) and conducted according to the principles of the Declaration of Helsinki.

Evaluation of clinical features

Clinical features were evaluated by an independent investigator (BRK) using the collected facial photographs. The symmetry of the papular lesions, the presence of annular clustering of papules, and the presence of pustules were investigated. In addition, the face was divided into 6 segments (periocular, nasal, perioral, forehead, right cheek, and left cheek areas), and the distribution of inflammatory papules was investigated.

Quantification of area density of papular lesions with computer-aided image analysis

To objectively quantify the degree of compactness, the area fraction of the inflammatory papules in each facial segment was measured using Image J software (ver. 1.47;

National Institutes of Health, Bethesda, MD, USA). After selecting each segment of the face with the image brush tool, the area of each segment was determined using the measurement tool. Using the region of interest tool, inflammatory papules distributed in each segment could be selected cumulatively, and the area of these papules was measured. Finally, the area fraction of papular lesions in each segment was obtained by dividing the area of the inflammatory papules in each segment by the area of each segment. The larger the value of the area fraction of papules, the denser the papules in each segment. We defined this as the area density of papular lesions in the segment. The total area density indicated the sum of the area densities of 6 facial segments.

Building a predictive model based on clinical features and computer-aided image analysis parameters

We used classification and regression tree (CART) analysis to identify the predictive model for diagnosis of the in-

Table 1. Demographics and clinical features of patients with inflammatory papular dermatoses of the face

Variable	EPF (n = 8)	GPD-LMDF complex (n = 13)	GR-PPR complex (n = 41)	Folliculitis (n = 4)
Age (yr)	38.5 ± 10.9	48.5 ± 10.2	48.5 ± 12.8	48.8 ± 9.2
Sex				
Male	2 (25.0)	2 (15.4)	12 (29.3)	2 (50.0)
Female	6 (75.0)	11 (84.6)	29 (70.7)	2 (50.0)
Symmetry				
Yes	0 (0.0)	11 (84.6)	41 (100.0)	4 (100.0)
No	8 (100.0)	2 (15.4)	0 (0.0)	0 (0.0)
Annular clusters				
Yes	8 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	0 (0.0)	13 (100.0)	41 (100.0)	4 (100.0)
Periocular involvement				
Yes	0 (0.0)	12 (92.3)	14 (34.1)	1 (25.0)
No	8 (100.0)	1 (7.7)	27 (65.9)	3 (75.0)
Nasal involvement				
Yes	0 (0.0)	6 (46.2)	30 (73.2)	1 (25.0)
No	8 (100.0)	7 (53.8)	11 (26.8)	3 (75.0)
Perioral involvement				
Yes	0 (0.0)	8 (61.5)	32 (78.0)	2 (50.0)
No	8 (100.0)	5 (38.5)	9 (22.0)	2 (50.0)
Forehead involvement				
Yes	0 (0.0)	3 (23.1)	32 (78.0)	4 (100.0)
No	8 (100.0)	10 (76.9)	9 (22.0)	0 (0.0)
Cheek involvement				
Yes	8 (100.0)	1 (7.7)	41 (100.0)	3 (75.0)
No	0 (0.0)	12 (92.3)	0 (0.0)	1 (25.0)
Pustule				
Yes	0 (0.0)	0 (0.0)	10 (24.4)	2 (50.0)
No	8 (100.0)	13 (100.0)	31 (75.6)	2 (50.0)

Values are presented as mean ± standard deviation or number (%). EPF: eosinophilic pustular folliculitis, GPD-LMDF: granulomatous periorificial dermatitis-lupus miliaris disseminatus faciei, GR-PPR: granulomatous rosacea-papulopustular rosacea.

flammatory papular dermatoses of the face. CART analysis is a machine-learning method for constructing predictive models, and simulates the clinical decision-making process. It uses a generalization of the binomial variance called the Gini index; advantages of its use include quick prediction and easy visual recognition of important variables[15,16]. We started with a single node and then assessed binary distinctions that provide most information about the class until a stop criterion was satisfied. The stop criterion was set so that the number in each node was at least 10.

Statistical analysis

Comparisons of continuous variables were performed using the Kruskal–Wallis test and the Mann–Whitney method was used for *post-hoc* analysis. The 2-proportion z-test was used to examine the distributions of the categorical variables. The results were judged as significant at $p < 0.05$, with an adjusted p-value for multiple comparisons.

Data were analyzed using Stata/SE, version 14 (Stata Corp., College Station, TX, USA), and the CART was constructed with R, ver. 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic data, clinical features, and results of the comparative analysis of clinical features are summarized in Table 1 and Fig. 2. The study included clinicopathologically confirmed inflammatory papular dermatoses of the face: 8 cases of EPF, 13 of GPD-LMDF complex, 41 of GR-PPR complex, and 4 of folliculitis. The EPF patients tended to have a younger mean age than the other 3 groups; except in the folliculitis group, female patients predominated. The EPF group showed lesion asymmetry and annular clusters of papules in all cases. Compared with the other groups, 92.3% of The GPD-LMDF complex
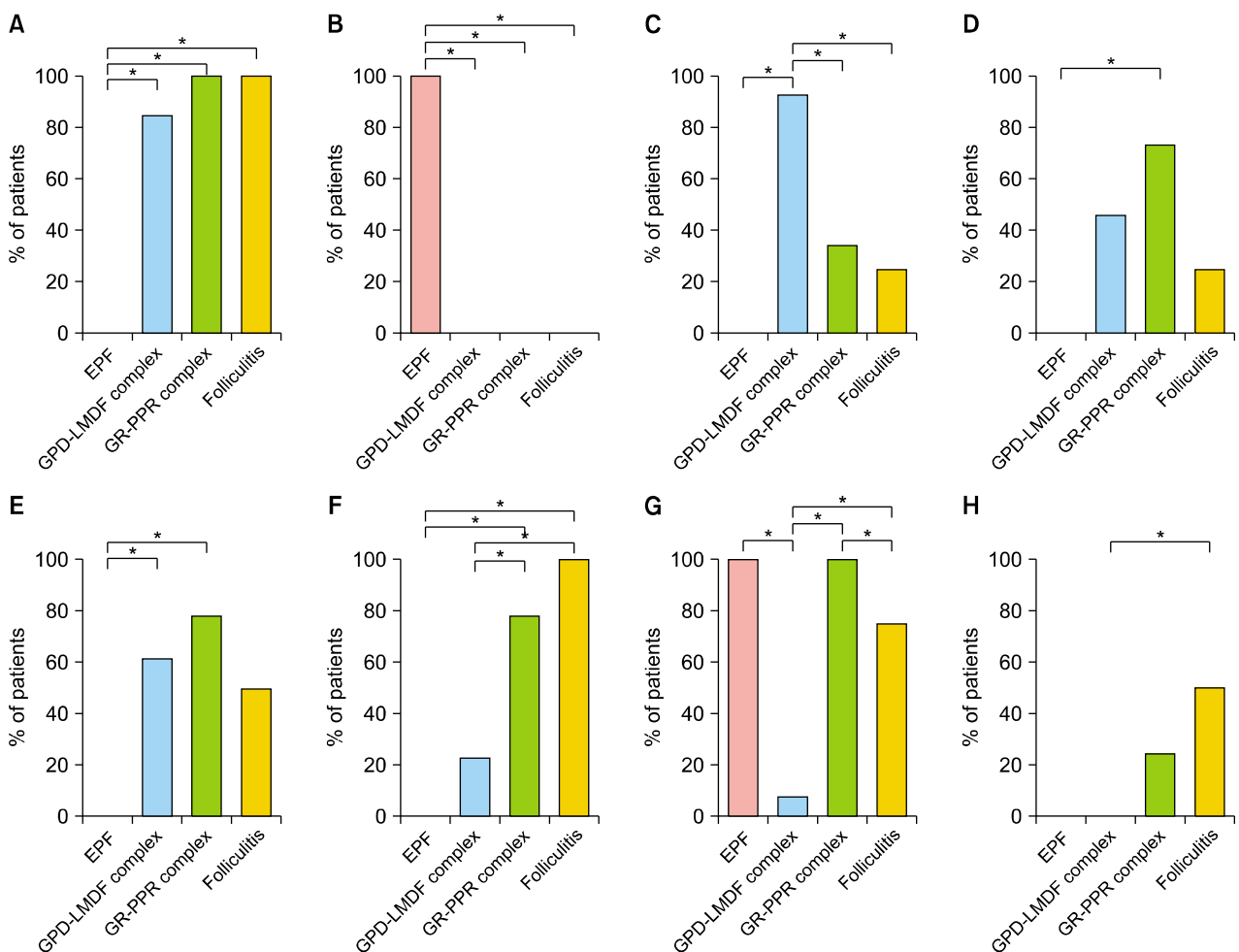

Fig. 2. Group comparison of clinical features using the 2-proportion z-test: (A) Symmetry, (B) annular clusters, (C) periocular, (D) nasal, (E) perioral, (F) forehead, (G) cheeks, (H) pustule. EPF: eosinophilic pustular folliculitis, GPD-LMDF: granulomatous periorificial dermatitis-lupus miliaris disseminatus faciei, GR-PPR: granulomatous rosacea-papulopustular rosacea. *$p < 0.008$.

patients had a significant periocular distribution of lesions, whereas 73.2% of the GR-PPR complex patients were more likely than the other groups to have nasal lesions. The distribution of inflammatory papules in the perioral area, forehead, and cheeks and the presence of pustules were not characteristics that distinguished among the 4 groups.

Table 2 and Fig. 3 show the results of comparative analy-

Table 2. Area density of papules in facial segments using computer-aided image analysis

Variable	EPF (n = 8)	GPD-LMDF complex (n = 13)	GR-PPR complex (n = 41)	Folliculitis (n = 4)	p-value[†]
Forehead	0.00 ± 0.00	0.01 ± 0.01	0.05 ± 0.07	0.02 ± 0.01	< 0.001*
Periocular	0.00 ± 0.00	0.09 ± 0.09	0.02 ± 0.03	0.00 ± 0.01	< 0.001*
Nasal	0.00 ± 0.00	0.04 ± 0.08	0.10 ± 0.14	0.01 ± 0.02	0.003*
Right cheek	0.05 ± 0.15	0.02 ± 0.06	0.25 ± 0.19	0.02 ± 0.01	< 0.001*
Left cheek	0.25 ± 0.17	0.01 ± 0.02	0.28 ± 0.21	0.03 ± 0.04	< 0.001*
Perioral	0.00 ± 0.00	0.06 ± 0.10	0.06 ± 0.07	0.01 ± 0.01	0.001*
Total	0.30 ± 0.28	0.23 ± 0.20	0.76 ± 0.48	0.08 ± 0.04	< 0.001*

Values are presented as mean ± standard deviation. The unit is a fraction. *Statistically significant ($p < 0.05$). [†]The means and standard deviations of area density were compared among the 4 groups using the Kruskal–Wallis test. EPF: eosinophilic pustular folliculitis, GPD-LMDF: granulomatous periorificial dermatitis-lupus miliaris disseminatus faciei, GR-PPR: granulomatous rosacea- papulopustular rosacea.
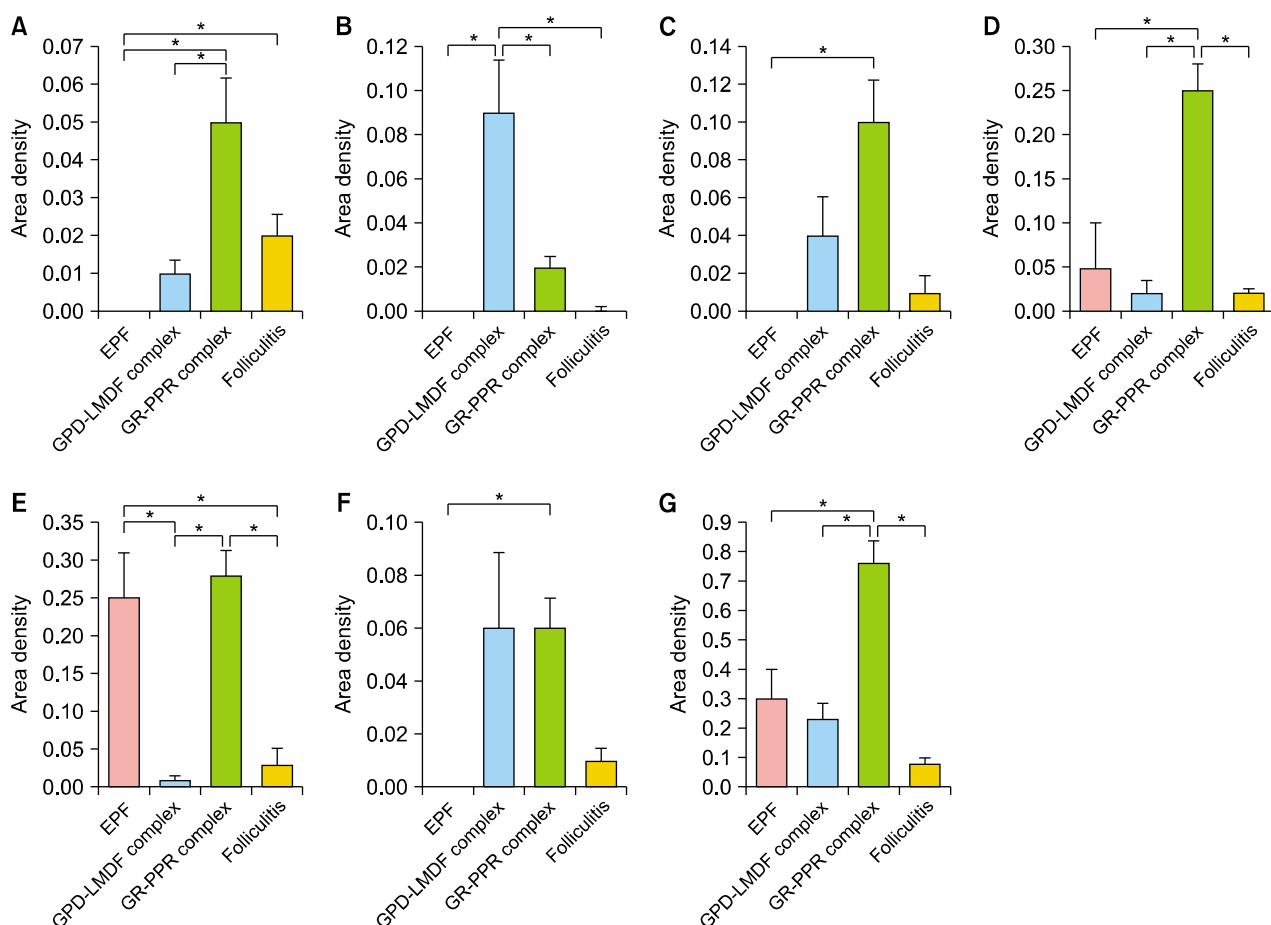

Fig. 3. *Post-hoc* analysis of the area density of papules in facial segments using the Mann-Whitney method: (A) Forehead, (B) periocular, (C) nasal, (D) right cheek, (E) left cheek, (F) perioral, (G) total. The unit is a fraction. EPF: eosinophilic pustular folliculitis, GPD-LMDF: granulomatous periorificial dermatitis-lupus miliaris disseminatus faciei, GR-PPR: granulomatous rosacea-papulopustular rosacea. *$p < 0.008$.
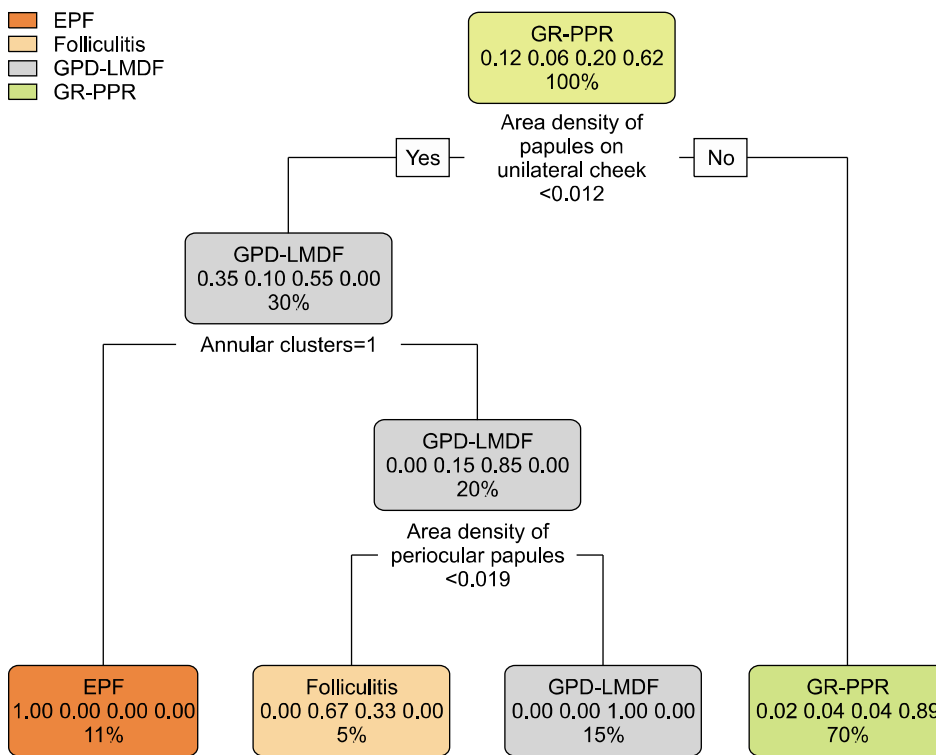
Fig. 4. Predictive model for differential diagnosis of inflammatory papular dermatoses of the face using classification and regression tree analysis. Each node shows the predicted class, the predicted probability of each class, and the percentage of observations in the node, respectively. EPF: eosinophilic pustular folliculitis, GPD-LMDF: granulomatous periorificial dermatitis-lupus miliaris disseminatus faciei, GR-PPR: granulomatous rosacea-papulopustular rosacea.

sis of area density of papular lesions between the 4 groups. Consistent with clinical features, the GPD-LMDF complex group had a significantly higher periocular density, and the GR-PPR complex group had a higher nasal density. We could not clinically distinguish between the 4 groups according to whether or not papules were present on the cheeks; however, a comparison of the area density of papules extracted by CAIA showed that the GR-PPR complex group had a higher area density on the right or left cheek and the highest total area density among the groups.

The predictive model for differential diagnosis of inflammatory papular dermatoses of the face using CART analysis is shown in Fig. 4. During construction of the classification tree, 3 important variables among the clinical features and CAIA parameters shown in Table 1 and 2 were used for diagnosis: area density of unilateral cheek papules, presence of annular clusters, and area density of periocular papules. An area density of unilateral cheek papules $\geq$0.012 enabled diagnosis of GR-PPR with predicted probability of 89%. Lesions then showing an annular cluster among the remaining 3 groups enabled an EPF diagnosis with 100% predicted probability. Finally, a periocular papule area density of $\geq$0.019 enabled a diagnosis of GPD-LMDF complex with 100% predicted probability, while an area density of <0.019 diagnosed folliculitis with 67% predicted probability.

DISCUSSION

This study identified significant clinical variables that distinguish between 4 groups of inflammatory papular dermatoses on the face and proposed a diagnostic algorithm to facilitate differential diagnosis. According to our predictive model, only 3 of 10 clinical features and 7 CAIA parameters, i.e., (1) area density of unilateral cheek papules; (2) presence of annular clusters; and (3) area density of periocular papules, were required for differential diagnosis of the 4 disease groups, and each group was diagnosed with a predicted probability of 67%~100%.

In general, the diagnosis of folliculitis and rosacea is made based on the typical clinical presentation, and histologic examination is rarely necessary to exclude other diagnoses. On the other hand, the diagnosis of rarely seen, facial papular dermatoses such as EPF, GPD, and LMDF can be challenging if not suspected, and evaluation should include a thorough clinical history, physical examination, and skin biopsy. The inconsistent descriptions of clinical manifestations of these entities in different reports probably reflect misdiagnosis due to lack of histologic confirmation and rarity of the disease itself. In this context, we collected as many biopsy-confirmed cases as possible over 10 years to completely exclude ambiguity of diagnosis, and ultimately selected cases that were consistently diagnosed by 3 dermatologists. Therefore, our study has the

strength of analyzing only cases with a definite diagnosis. Our results show that the GPD-LMDF complex differs from other groups in that papules are more likely to be distributed around the eyes, and that GR-PPR complex has the highest density of papules throughout the face, with a high probability of papular distribution on the nose and cheeks compared with other groups. This suggests differences in the pathophysiology involving follicles in GPD-LMDF complex and rosacea cases. The face has 3 types of hair follicles: vellus, sebaceous, and terminal. The GPD-LMDF complex originates in and involves the vellus follicles, while rosacea mainly involves the sebaceous follicles[17]. Because the location and distribution of these follicles differ on the face, the predisposing site in which the inflammatory papules develop is different for each disease. Sebaceous follicles with large and multilobulated sebaceous glands are more commonly present on the face than elsewhere, while vellus follicles are 3～4 times more numerous than sebaceous follicles on the face. Therefore, rosacea that involves sebaceous follicles specifically vulnerable to inflammation has the highest density of papules; therefore, if inflammatory papules occur in periorificial areas, and especially the periorbital area, where sebaceous follicles are rarely found, GPD or LMDF causing inflammation of the vellus follicle should be considered in the initial differential diagnosis.

Similar to previous reports[6,18,19], EPF patients in our study had asymmetrical, annular plaques comprised of follicular papulopustules. Although clinical findings of EPF differ depending on the affected site (facial or extrafacial) or type (classic, immunosuppression-associated, or infancy-associated), our study only included patients with facial, classic EPF and showed annular appearance in all cases, suggesting that this is a unique feature distinguishing it from other diseases. In addition, except in cases of folliculitis, female predominance was observed in EPF, GPD-LMDF complex, and GR-PPR complex. Although facial EPF[19] and perioral dermatitis[3,20] have been reported to predominantly affect female in previous studies, there were no sex differences in classic EPF and rosacea, probably because a comparison was not made according to the subtype of rosacea or affected sites of EPF[6,21]. The more frequent inflammation of the pilosebaceous unit of the face in female than in male is likely related to the use of topically applied preparations such as cosmetics, or reflects the role of sex hormones.

Our study has several limitations. First, since only definite cases were included, the number of subjects in each group, especially those with EPF and folliculitis, was small. EPF is a rare disease that has been reported in about 300 cases worldwide in the 40 years since Ofuji proposed

a new clinical entity[22]. Because folliculitis is very common and most cases can be diagnosed clinically, only a few patients underwent biopsy. Additionally, accuracy of the predictive model was not tested with a new data set. Nonetheless, we statistically confirmed the distinct clinical features of inflammatory papular dermatoses of the face and proposed an algorithm for use in clinical diagnosis. Objective clinical recognition using CAIA could help to identify these diseases and could be the basis for a diagnostic system using artificial intelligence.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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