

RESEARCH PAPER



Clinical and histopathological characteristics in patients with scarring folliculitis type of acne inversa

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ABSTRACT

Objective: This study was designed to study the clinical and histopathological characteristics of patients with the scarring folliculitis type acne inversa in Chinese population.

Methods: A total of 21 patients with acne inversa and 6 controls without known dermatological disease were recruited from outpatient department of dermatology and orthopedic surgery. Two-millimeter punch biopsies were taken from 8 patients with acne inversa and 6 controls, fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin prior to histopathological analysis.

Results: There were 12 patients (57.14%) belonging to the scarring folliculitis type presented with double comedones, papules, nodules, depressed scars, and were mainly Hurley stage I (66.67%). Many of the scarring folliculitis type were smokers (58.33%), some had a history of occupational exposure (41.67%) and some were overweight (50%), the mean BMI of which is $25.18 \pm 3.16 \text{ kg/m}^2$. Histopathological changes such as perifollicular inflammation can be observed in scarring folliculitis type of acne inversa and controls as well. However, epidermal hyperplasia, follicular hyperplasia, sebaceous gland disappearance, destruction of hair follicle and sebaceous gland, collagen hyperplasia, perivascular inflammation, granulomatous inflammation, Micro thrombus were only seen in scarring folliculitis type. The mean surface area in patients ($8073.36 \pm 15798.43 \mu\text{m}^2$) was smaller than that in controls ($302059.08 \pm 502813.78 \mu\text{m}^2$), with statistically significant difference. ($P = 0.024$).

Conclusion: The scarring folliculitis type in acne inversa in Chinese population could be characterized by depressed scars, double-ended comedones, epidermal cysts and had high proportion of smokers, or occupational exposure with lower Hurley stage, as well as diminished sebaceous gland. Further studies are needed to clarify the relations between the clinical subtypes of acne inversa and their corresponding genotypes.

ARTICLE HISTORY

Received 7 June 2017
Accepted 26 July 2017

KEYWORDS



acne inversa; Chinese population; clinical and histopathological characteristics; the scarring folliculitis type

Introduction

Acne inversa is also known as “hidradenitis suppurativa”, “follicular occlusion triad” (acne conglobata, hidradenitis suppurativa, dissecting cellulitis) or “follicular occlusion tetrad (together with pilonidal sinus)”. The pathogenesis of acne inversa is complex and remains unclear until now, which may consists of endogenous and exogenous factors such as genetics, hormones, cigarette smoking and so on.¹

The most commonly used classification for evaluating the severity of acne inversa is Hurley classification,² however, few were classified according to skin lesions. In

2015, van der Zee et al. identified 6 clinical subtypes: The regular type, Frictional furuncle type, Scarring folliculitis type, Conglobata type, Syndromic type, Ectopic type.³ According to van der Zee et al, patients with the scarring folliculitis type of acne inversa are presented with small and superficial inflammatory lesions, depressed cribriform scarring and cigarette smoking. It is supposed that different types may had different etiology. The clinical classification according to lesion types may help elucidating the etiology of acne inversa. The objectives of this study were to explore the clinical and histopathological characteristic between scarring folliculitis type and

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This paper is part of the special section based on the 3rd ICSGAD conference held in September 2016.

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regular types in patients with acne inversa, which could help to reveal the clinical characteristics and mechanisms in acne inversa.

Results

A total of 21 patients aged from 16 to 25 years (mean age, 27.29 ± 5.35 years, male/female = 2) and 6 control subjects with no known dermatological disease (mean age 26.33 ± 4.76 years, male/female = 2) were interviewed. There was no significant difference in age ($P = 0.698$) and gender ($P = 1$) between acne patients and controls.

Clinical characteristics

The distribution of patients according to clinical characteristics is described in Table 1. Among 21 patients, 12 patients (57.14%) belonged to the scarring folliculitis type of acne inversa, 9 patients (42.86%) belonged to the regular type of acne inversa; 13 patients (27.4%) were of Hurley stage I and 8 patients (38.10%) stage II. Of the 21 patients, 11 patients (52.38%) had chemicals exposure (smokers and occupational exposure), 9 patients (42.86%) were smokers, the mean cumulative smoking dose (number of cigarettes smoked daily \times 365 \times number of years) was 46829.50 ± 42981.25 . A total of 5 patients had a history of occupational exposure, one was chef, one worked in a printing plant, one worked in a packing plant (Fig. 1), they were

smokers as well. In addition to smokers, one out of the five patients had a history of occupational exposure to dust, one was chef. The total occupational exposure time for each patient mentioned above was more than 1 years (At least 4 days a week).

Table 1 also compares diseases characteristics between two subtypes of acne inversa about lesion types, Hurley stage, locations, chemical exposure, BMI and family history and so on. Compared with the regular type, the scarring folliculitis type had a higher proportion of gluteal or groin involvement (22.22% versus 75%) with statistically significant difference ($P = 0.03$), a higher proportion of double-ended comedones (0% versus 30%), epidermal cysts and/or macrocysts (0% versus 30%), depressed scars (44.44% versus 83.33%) and Hurley stage I (55.56% versus 66.67%), a higher proportion of chemicals exposure (22.22% versus 75%) with statistically significant difference ($P = 0.03$), a higher proportion of smokers (22.22% versus 58.33%) and occupational exposure (0% versus 33.33%), higher mean BMI (23.50 ± 4.23 kg/m² versus 25.18 ± 3.16 kg/m²), a higher proportion of overweight (33.33% versus 50%), a lower proportion of Family history of acne inversa (33.33% versus 16.67%).

Histopathological characteristics

14 punch biopsies were made, among which 8 patients were scarring folliculitis type, 6 were controls. The

Table 1. Comparison of the characteristics between scarring folliculitis type of acne inversa and regular type of acne inversa.

Variables	Scarring folliculitis type (N = 12),100%	Regular type (N = 9), 100%	Overall patients (N = 21)100%	P value (Scarring folliculitis type versus regular type)/ OR (95% CI)
Hurley stage				
Stage I	8(66.67%)	5(55.56%)	13(61.90%)	—
Stage II	4(33.33%)	4(44.44%)	8(38.10%)	0.673/-
Lesion types				
Double-ended comedones	3(25%)	0(0%)	3(14.29%)	0.229/-
Papules and nodules	12(100%)	8(88.89%)	20(95.24%)	0.429/-
Epidermal cysts and/or macrocysts	3(25%)	0	3(14.29%)	0.229/-
Depressed scars	10(83.33%)	4(44.44%)	14(66.67%)	0.519/-
Locations				
Armpit and/or breast	6(50%)	4(44.44%)	10(47.62%)	1/-
Ears and/or chest and/or back and/or others	8(66.67%)	7(77.78%)	15(71.43%)	0.659/-
Gluteal and/or groin	9(75%)	2(22.22%)	11(52.38%)	0.03*/10.5(1.36–81.05)
Chemicals exposure	9(75%)	2(22.22%)	11(52.38%)	0.03*/10.5(1.36–81.05)
Smokers	7(58.33%)	2(22.22%)	9(42.86%)	0.184/-
Occupational exposure	5(41.67%)	0(0%)	5(23.81%)	0.045/2.286(1.311–3.984)
Mean BMI(kg/m ²)	25.18 ± 3.16	23.50 ± 4.23	24.46 ± 3.6	0.309/-
Overweight	6(50%)	3(33.33%)	9(42.86%)	0.660/-
Family history of acne inversa	2(16.67%)	3(33.33%)	5(23.81%)	0.611/-

Fisher's exact test for categorical variables, Student's t-test for quantitative variables. †Reference category; *, $P < 0.05$; BMI, body mass index; SD, standard deviation.



Figure 1. A patient with scarring folliculitis type of acne inversa who was smokers and worked in a packing plant. (a) Double comedones on the forehead (black arrows). (b) Double comedones (black arrows) on the neck and an epidermal cyst (red arrow) on the mandibular. (c) Follicular papules (folliculitis) on the back. (d) Hypertrophic scar on the buttock.

histopathological characteristics of acne inversa and controls are displayed in Table 2.

Except low-grade inflammation surrounding hair follicle and epidermal hyperpigmentation, there is no specific changes in controls. However, epidermal hyperplasia, follicular hyperplasia, sebaceous gland disappearance, destruction of hair follicle and sebaceous gland, collagen hyperplasia, perivascular inflammation, granulomatous inflammation, micro thrombus were only seen in scarring folliculitis type. (Table 2, Fig. 2).

Table 2. Qualitative histopathological changes observed in patients with scarring folliculitis type of acne inversa and controls.

Histopathological changes	Scarring folliculitis type (N = 8),%	Controls (N = 6),%
Epidermal hyperpigmentation	8(100%)	1(16.67%)
Epidermal hyperplasia	4(50%)	0(0%)
Sebaceous gland disappearance	6(75%)	0(0%)
Perifollicular inflammation	2(25%)	1(16.67%)
Destruction of hair follicle and sebaceous gland	3(37.5%)	0(0%)
Collagen hyperplasia	4(50%)	0(0%)
Granulomatous inflammation	1(12.5%)	0(0%)
Micro thrombus	3(37.5%)	0(0%)
Perivascular inflammation	6(75%)	0(0%)
Follicular hyperplasia	2(25%)	0(0%)

Sebaceous glands size

The surface area of sebaceous glands is represented in Fig. 3a: the mean surface area in patients with scarring folliculitis type ($8073.36 \pm 15798.43 \mu\text{m}^2$) was smaller than that in controls ($302059.08 \pm 502813.78 \mu\text{m}^2$), with statistically significant difference ($P = 0.024$). When considering only the biopsies from the patients with acne inversa (9 sections in 3 patients) that contained sebaceous glands (Fig. 3b), the mean surface area of sebaceous glands in patients ($21528.97 \pm 19790.81 \mu\text{m}^2$) was also smaller than that in controls ($302059.08 \pm 502813.78 \mu\text{m}^2$), with statistically significant difference ($P = 0.03$).

Discussion

In our study, two subtypes of acne inversa were observed. The regular type corresponds to typical lesions in acne inversa such as papules, comedones, nodules, abscesses, cysts, hypertrophic scar and so on. However, the scarring folliculitis type comprised 57.14% of the subjects, in addition to typical lesions mentioned above, it was characterized by high prevalence of papules and/or nodules, depressed scars, double-ended comedones, epidermal cysts and of groin and buttocks involvement and had high proportion of

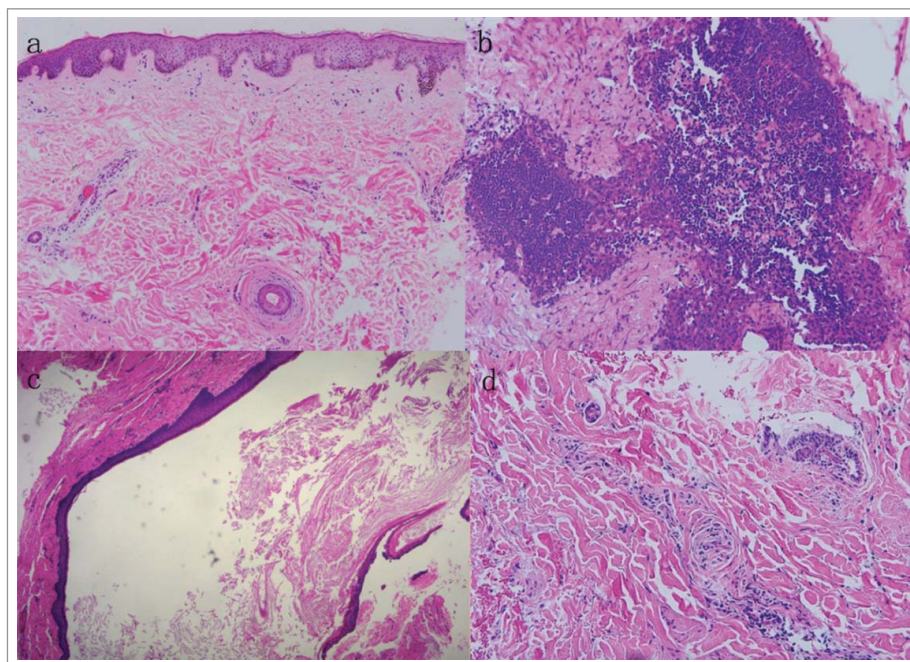


Figure 2. Histopathological changes in patients with scarring folliculitis type of acne inversa. (a) Epidermal hyperpigmentation and fibrosis surrounding hair follicles. (HE × 200). (b) Granulomatous inflammation. (HE × 100). (c) Epidermal cyst. (HE × 200). (d) Destruction of hair follicle and sebaceous gland and collagen hyperplasia. (HE × 200).

smokers, occupational exposure, Hurley stage I and overweight, which is similar to previously reported.³ A study from France conducted by F Canoui-Poitaine et al.⁴ identified acne inversa subtypes by latent class analysis in a cohort of 618 patients. They identified 3 phenotypes: axillary-mammary type, follicular type, gluteal type, which is different from the classification we used in this study. Both the classification we used in this study suggested by van der Zee et al and the classification proposed by F Canoui-Poitaine et al has

not been further validated against risk factors or treatment outcomes.

The double-ended comedones is frequently seen in patients with the scarring folliculitis type of acne inversa, but actually they are sinus instead of true comedones. On the other hand, there is a strong relationship between smoking and acne inversa as previously described,¹ but very few studies have analyzed the relationship between other chemicals exposure and acne inversa.

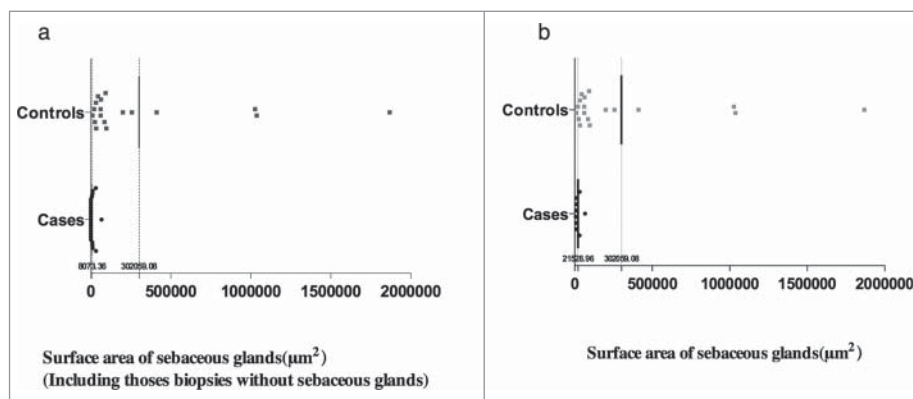


Figure 3. (a) Comparison of surface area of sebaceous glands between patients and controls, the mean surface area of sebaceous glands (below the dotted line) in patients is smaller than controls ($8073.36 \pm 15798.43 \mu\text{m}^2$ versus $302059.08 \pm 502813.78 \mu\text{m}^2$, $P = 0.024$). (b) Surface area of sebaceous glands where the biopsies with no visible sebaceous glands have been omitted, the mean surface area of sebaceous glands (below the dotted line) in patients is lower than controls ($21528.97 \pm 19790.81 \mu\text{m}^2$ versus $302059.08 \pm 502813.78 \mu\text{m}^2$, $P = 0.03$).

Histopathological changes such as epidermal hyperpigmentation and inflammation surrounding hair follicle can be observed in both scarring folliculitis type and regular type of acne inversa. hyperpigmentation of the basal keratinocytes might be interpreted as post inflammatory changes, and indicates a higher regional level of inflammatory activity in patients.⁵ However, epidermal hyperplasia, follicular hyperplasia, sebaceous gland disappearance, destruction of hair follicle and sebaceous gland, collagen hyperplasia, perivascular inflammation, granulomatous inflammation, micro thrombus were only seen in scarring folliculitis type. Pathological characteristics such as follicular hyperplasia, absence of sebaceous gland, granulomatous inflammation, micro thrombus have rarely been reported in the literature. Our study report the mean size of sebaceous glands in acne inversa patients was smaller than that in controls, which is consistent with another study,⁵ suggesting pilosebaceous unit may play a central role in the pathogenesis of acne inversa. Whether the shrinkage of the sebaceous glands is a primary event or a consequence of prior events in the pathogenesis remains to be revealed.

The potential pathogenic effects of smoking and other chemicals exposure in acne inversa pathogenesis may be could explained by the following evidence: Cigarette contain dioxins, benzopyrene, nicotine and dioxin-like chemicals.¹ People with occupational exposure may be exposed to dioxins, polycyclic aromatic hydrocarbons (PAHs). The aryl hydrocarbon receptor (AhR) and its downstream gene Cytochrome P450 1A1(CYP1A1) could be activated by these chemicals, thus affecting the differentiation of sebaceous gland cells by switching human sebaceous into keratinocyte-like differentiation in chloracne pathogenesis.⁶ Though shrinkage of the sebaceous glands were observed in patients with acne inversa in our study, whether dioxins or dioxin-like chemicals take part in the pathogenesis has to our knowledge not been studied.

The proportion of family history of acne inversa in subjects is 23.81%, indicating that inheritance may play a key role in the pathogenesis of acne inversa, with no subtype difference ($P = 0.611$). Decreased Notch signaling, due to loss-of-function mutations in the γ -secretase genes [presenilin1 gene (PSEN1), presenilin enhancer gamma secretase subunit gene (PSENEN), and nicastrin gene

(NCSTN)] is hypothesized to play an important role in the pathogenesis of acne inversa, and have been correlated to epidermal and follicular alterations, with absent or impaired formation of the sebaceous glands in mouse models.⁷⁻⁹

There are some limitations of the current study. A selection bias in a hospital-based study design is possible. Secondly, classification methods require a large number of patients, the sample size of subjects is not enough for more precisely statistics. Thirdly, we relied solely on the classification suggested by van der Zee et al to classify acne inversa which remained to be further validated. Fourthly, calculating the surface areas of sebaceous glands is not precise enough for calculating the size of sebaceous glands. In the further study, we will calculate the volume of the sebaceous glands which is estimated by the Cavalieri principle.⁵

Until now there are still no published data regarding the subtypes of acne inversa from the Chinese mainland. In conclusion, in addition to typical lesions of acne inversa, the scarring folliculitis type was characterized by high prevalence of papules and/or nodules, depressed scars, double-ended comedones, epidermal cysts and of groin and buttocks involvement and had high proportion of smokers, occupational exposure, Hurley stage I and overweight. However, further studies should be conducted to evaluate whether these subtypes are significant in terms of genetic background, disease course, and respond to treatment.

Patients and methods

Patient recruitment

Twenty-one patients with an established diagnosis of acne inversa based on the modified Dessau definition¹⁰ were recruited from our outpatient department of dermatology and six healthy controls without known dermatological disease were recruited from outpatient department of orthopedic surgery. The protocol was reviewed and approved by the Human Ethics Committee of our hospital. A written informed consent was obtained from each participant or the custodial parents of underage children. Patients were excluded if they had used systemic retinoids or antibiotics in the past 12 weeks. Pregnant or lactating women were also excluded.

Clinical assessment

Demographic and clinical characteristics of patients were recorded by trained interviewers, including socio-demographic profile (age, gender), relevant medical history such as severity of lesions, type of lesions, affected sites, age of onset, course of acne, height and weight (by anthropometric measurement), history of smoking, history of chemical exposures, family history of acne inversa and accompanied diseases.

Hurley staging² was used to assess the severity of acne inversa, and the clinical subtypes proposed by van der Zee et al. including six subtypes (the regular type, frictional furuncle type, scarring folliculitis type, conglobata type, syndromic type, ectopic type) was used to classify acne inversa according to different clinical presentations simultaneously. All of the 3 Hurley stages can occur in these subtypes.³ The above process were performed at the first time of diagnosis by two board dermatologists using uniform criteria in good agreement.

After anthropometric measurement, BMI was calculated and categorized according to the Cooperative Meta-Analysis Group of the Working Group on Obesity in China with recommended cut-off criteria for overweight and obesity described by Zhou et al. Subjects ≥ 18 years old were classified into one of the following categories: underweight (BMI < 18.5), normal weight (BMI: 18.5–23.9), overweight (BMI: 24–27.9) and obese (BMI ≥ 28).¹¹ Due to the lack of general consensus on BMI thresholds in young people < 18 years old, we adopted the cut-off criteria modified for overweight and obesity in Chinese people described by Group of China Obesity Task Force.¹²

Histopathological assessment

We took two-millimeter punch biopsies from the back and face regions in 8 acne inversa patients with scarring folliculitis type, 6 controls and subjected them to histopathological analysis. The biopsies were fixed in formalin, embedded in paraffin and stained with haematoxylin and eosin.

The qualitative histological study was also conducted from all biopsies, describing the morphology of the hair follicles and sebaceous gland, basal layer hyperpigmentation, inflammation and scarring and so on.

The process of calculating the size of sebaceous glands in cases and controls were performed by light microscope [Olympus CX1, Tokyo, Japan] with a built-in camera (digital camera UCMOS05100KPA, Olympus). Using $\times 10$ objective lens, surface areas of all sebaceous glands in three sections were measured using software Adobe Photoshop (version: 13.0), outlining sebaceous gland boundaries, with calculation of average value in $1 \mu\text{m}^2$.¹³

Statistical analysis

Analysis was performed with IBM SPSS Statistics (IBM Corp. Released 2011, version 20.0, Armonk, NY, US). Statistical tests included mean \pm standard deviation, Two-sample t-test and chi-squared test, continuity correction, likelihood ratio, Fisher's Exact Test. All p values were two-tailed and the level of statistical significance was set at 0.05.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

Funding organizations: National Natural Science Foundation of China (Number: 81472894), Shanghai Municipal Commission of Health and Family Planning (Number: 20134037).

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