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ORIGINAL RESEARCH

Correlation Between the Koebner Phenomenon and Clinical Features in Vitiligo

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Purpose: To investigate the correlation between the presence of the Koebner phenomenon (KP) and clinical features of patients with vitiligo.
Patients and Methods: The clinical characteristic data, including age, age of onset, disease duration, gender, clinical stage, clinical type, family history, and comorbid immune-related diseases, of 1472 patients with/without KP were analyzed with SPSS 17.0 software.
Results: Of the 1472 patients, 290 (19.70%) were positive for KP. The clinical course (6.95 vs 5.62, P = 0.015), percentage of patients with progressive stage (78.97% vs 70.05%, P = 0.002), the acrofacial type (4.49% vs 1.69%, P = 0.004), comorbid immune-related diseases (28.29% vs 19.04%, P = 0.001) and lesion area ≥2% (47.24% vs 38.24%, P = 0.005) in KP-positive group were significantly greater than those in KP-negative group. Binary logistic regression analysis found that progressive stage (P = 0.003, OR = 1.60, 95% confidence interval (CI): 1.17–2.18), area of skin lesion ≥2% (P = 0.008, OR = 1.44, 95% CI: 1.10–1.88) and comorbid immune-related diseases (P = 0.001, OR = 1.63, 95% CI: 1.21–2.20) were significantly associated with KP.
Conclusion: The presence of KP in patients with vitiligo is associated with clinical progression, the acrofacial type, comorbid immune-related disease and a larger lesion area. This study suggested the presence of KP may be an indicator of disease activity and aggression, and underlay its importance in the management of disease.
Keywords: vitiligo, Koebner phenomenon, clinical features

Introduction

Vitiligo is a common depigmentation of the skin and mucous membranes with a prevalence of approximately 0.5–2% in various populations abroad and approximately 0.56% in China.[1,2] Genetic predisposition, abnormal immune response, intervention of environmental factors and the evolution under treatment were reported to be associated with the prognosis of this disease.[3] Irritation of the skin by various environmental stressors (eg, burns, friction, insect bites, surgical incisions, and allergic and irritant reactions) can lead to the development of new lesions at the damaged site (regular skin/noninvolved skin), known as anaplasia or the Koebner phenomenon (KP).[4] KP is a well-known and common phenomenon in dermatology;[5] however, the exact mechanism of its occurrence has yet to be clarified. KP can occur in numerous skin conditions, such as vitiligo, psoriasis, lichen planus, folliculitis, dermatophytosis, drug reactions, and after UV irradiation therapy.[4,5] Epidemiological studies have shown that the incidence of KP among vitiligo patients is approximately 21–62%.[6] On the basis of the pathophysiology and clinical features, KP may be associated with the clinical course, clinical stage, and clinical type of vitiligo. In 2023, KP-positive patients were found with higher area of skin lesion, body mass index and longer disease duration in a Chinese study.[7] Hasan et al found that the onset age larger or equal to 30 was increased in KP-positive vitiligo patients.[8] In this study, the presence of KP in vitiligo patients and the correlation between KP and other clinical features were evaluated.

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Materials and Methods

General Information

The clinical data of vitiligo patients were obtained from the sample resource laboratory of the Institute of Dermatology, Anhui Medical University, which were collected from 16 clinics during August 2009 to October 2010 in this study. All the patients met the diagnostic criteria of the Vitiligo European Task Force (VETF)[9] and were diagnosed by outpatient physicians and trained professionals who completed administered a detailed self-designed questionnaire of vitiligo. All the patients provided informed consent and signed an informed consent form for participation in the study. The study complies with the Declaration of Helsinki.

Assessment of Clinical Features

The clinical information of the vitiligo patients were collected using a self-designed questionnaire with demographic and clinical information. The demographic information included gender, age, ethnicity, contact address, survey date and name of investigator, while the clinical information consisted of the following: 1. Age of onset, measured in years (with early onset defined as onset at age ≤20 years and late onset as onset at >20 years);[10] 2. Disease duration, measured in years; 3. Clinical stage (classified as progressive or stable); 4. Clinical type (classified as sporadic, segmental, generalized, acrofacial, mucosal and mixed); 5. Family history (with a positive family history defined as having at least one affected individual among the patient's third-degree relatives); 6. Comorbid immune-related diseases, such as autoimmune thyroid disease, allergic diseases (allergic rhinitis, asthma, etc), chronic hepatitis B, diabetes mellitus, rheumatoid arthritis, alopecia areata, psoriasis, etc.; 9. Cumulative skin lesion area as a percentage of body surface area; 10. Presence or absence of the combined KP. The patients who did not complete each of the above information were excluded. Finally, the data of the clinical features from 1472 patients were included in this study.

Statistical Analysis

The questionnaire data was tested by the reliability and validity analysis, and the Cronbach's Alpha coefficient was 0.716, which indicate a good reliability. The data on various clinical characteristics were statistically analyzed using the SPSS 17.0 statistical package. Measurement and count data are presented as the mean ± standard deviation and frequency, and compared with t test and $\chi 2$ test, respectively. (if the frequency < 5, Fisher's exact test was used). Binary logistic regression analysis was used to explore the significance in various clinical features. These differences were considered statistically significant at $P < 0.05$.

Results

Information on the clinical characteristics of the 1472 vitiligo patients is shown in Table 1. The average age of the patients was 29.34 ± 15.38 years; the average age of onset was 24.08 ± 14.72 years the average duration of disease was 5.88 ± 8.34 years. A total of 782 (53.13%) patients were males and 690 (46.87%) were females; 1057 (71.81%) were in the progressive stage and 415 (28.19%) were in the stable stage; 1309 (88.92%) patients were sporadic type, 75 patients had segmental type (5.10%), 49 (3.33%) were generalized type, 33 (2.24%) were acrofacial type, 2 (0.14%) were the mucosal type, and 4 patients were the mixed type (0.27%).

A total of 1315 patients (89.33%) had no family history and 157 patients (10.67%) had a family history. Three hundred and seven patients (20.85%) had comorbid immune-related diseases, including 89 (6.05%) with comorbid allergic diseases, 77 (5.23%) with thyroid disease, 50 (3.40%) with chronic hepatitis B, 22 (1.49%) with diabetes mellitus, 22 (1.49%) with rheumatoid arthritis, 19 (1.29%) with alopecia areata, and 14 (0.95%) with psoriasis. KP was present in 290 patients (19.70%) and absent in 1182 patients (80.30%).

A comparison of the clinical characteristics between KP-positive and KP-negative groups is shown in Table 2. Compared with KP-negative patient group, there were significant differences in the clinical course, clinical stage, clinical type, comorbid immune-related diseases, and lesion area in KP-positive patient group ($P < 0.05$), but there were no significant differences in age, age at onset, gender or family history between KP-positive and KP-negative groups ($P > 0.05$). The duration of disease was significantly greater in KP-positive group than in KP-negative group (6.95 vs 5.62, $P = 0.015$); the

Table 1 Clinical Characteristics of 1472 Vitiligo Patients

Clinical Features	Value
Mean age (year)	29.34±15.38 (1–82)
Mean age at onset (year)	24.08±14.72 (0.8–81)
Age at onset ≤20	753 (51.15%)
Age at onset >20	719 (48.85%)
Disease duration (year)	5.88±8.34 (0.1–60)
Gender	
Male	782 (53.13%)
Female	690 (46.87%)
Clinical stage	
Progressive stage	1057 (71.81%)
Stable stage	415 (28.19%)
Clinical type	
Sporadic	1309 (88.92%)
Segmental	75 (5.10%)
Generalized	49 (3.33%)
Acrofacial	33 (2.24%)
Mucosal	2 (0.14%)
Mixed	4 (0.27%)
Family history	
Yes	157 (10.67%)
None	1315 (89.33%)
Comorbid immune-related diseases	307 (20.85%)
Allergic disorders	89 (6.05%)
Thyroid disease	77 (5.23%)
Chronic hepatitis B	50 (3.40%)
Diabetes mellitus	22 (1.49%)
Rheumatoid arthritis	22 (1.49%)
Alopecia areata	19 (1.29%)
Psoriasis	14 (0.95%)
Other	14 (0.95%)
None	1165 (79.15%)
Koebner phenomenon	
Yes	290 (19.70%)
None	1182 (80.30%)

Table 2 Comparison of Clinical Characteristics Between the KP Positive and Negative Groups

Clinical Characteristics	Koebner Phenomenon		*P*
	Yes (n=290)	None (n=1182)	
Mean age (year)	28.61±15.82	29.52±15.27	0.366*
Mean age at onset (year)	23.55±15.32	24.21±14.58	0.485*
Age at onset ≤20	154 (53.10%)	599 (50.68%)	0.459
Age at onset >20	136 (46.90%)	583 (49.32%)	
Disease duration (year)	6.95±8.61	5.62±8.25	**0.015***
Gender			
Male	160 (55.17%)	622 (52.62%)	0.436
Female	130 (44.83%)	560 (47.38%)	

(*Continued*)

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Table 2 (Continued).

Clinical Characteristics	Koebner Phenomenon		*P*
	Yes (n=290)	None (n=1182)	
Clinical stage			
Progressive stage	229 (78.97%)	828 (70.05%)	**0.002**
Stable stage	61 (21.03%)	354 (29.95%)	
Family history			
Yes	33 (11.38%)	124 (10.49%)	0.660
None	257 (88.62%)	1058 (89.51%)	
Clinical Type			
Sporadic	249 (85.86%)	1060 (89.68%)	0.063
Segmental	15 (5.17%)	60 (5.08%)	0.947
Acrofacial	13 (4.49%)	20 (1.69%)	**0.004**
Generalized	12 (4.14%)	37 (3.13%)	0.391
Mucosal	0 (0%)	2 (0.17%)	–
Mixed	1 (0.34%)	3 (0.25%)	0.585
Comorbid immune-related diseases			
Yes	82(28.29%)	225(19.04%)	**0.001**
None	208(71.71%)	957(80.96%)	
Area of skin lesion			
<2%	153 (52.76%)	730 (61.76%)	**0.005**
≥2%	137 (47.24%)	452 (38.24%)	

Notes: * is *t*-test P-value, the rest is $\chi 2$ test P-value. Bold text indicates the data is statistically significant.

Table 3 Binary Logistic Regression Analysis for the Clinical Features Associated with Koebner Phenomenon

Clinical Characteristics	P	OR	95% CI	
			Lower	Upper
Gender (Male vs Female)	0.483	1.10	0.85	1.43
Disease duration (>5 years vs ≤5 years)	0.291	0.85	0.63	1.15
Clinical stage (Progressive vs Stable stage)	**0.003**	1.60	1.17	2.18
Area of skin lesion (≥2% vs <2%)	**0.008**	1.44	1.10	1.88
Comorbid immune-related diseases (Yes vs No)	**0.001**	1.63	1.21	2.20

Notes: Bold text indicates the data is statistically significant.
Abbreviations: OR, odds ratio; CI, confidence interval.

percentage of patients in the progressive stage was higher in KP-positive group than in KP-negative group (78.97% vs 70.05%, $P = 0.002$); the percentage of patients with the acrofacial type was greater in KP-positive group than in KP-negative group (4.49% vs 1.69%, $P = 0.004$); the percentage of patients with comorbid immune-related diseases was higher in KP-positive group than in KP-negative group (28.29% vs 19.04%, $P = 0.001$); and the percentage of patients with lesion area ≥2% was significantly higher in KP-positive group than in KP-negative group (47.24% vs 38.24%, $P = 0.005$). Binary logistic regression analysis was conducted with different clinical features (Table 3). Clinical stage ($P = 0.003$, OR = 1.60, 95% confidence interval (CI): 1.17–2.18), area of skin lesion ($P = 0.008$, OR = 1.44, 95% CI: 1.10–1.88) and Comorbid immune-related diseases ($P = 0.001$, OR = 1.63, 95% CI: 1.21–2.20) were significantly associated with KP.

Discussion

The pathogenesis of vitiligo is still unclear, although several factors, such as genetic factors, autoimmune factors, and neurological factors, have been hypothesized to play roles. Currently, a combination of genetic factors and autoimmune factors leading to damage to melanocyte function and apoptosis are the main factors in the pathogenesis of vitiligo.

However, several studies have shown that the age of onset, clinical type, and comorbid immune diseases of patients with vitiligo were different; for example, patients with segmental vitiligo have an earlier age of onset, while patients with non-segmental vitiligo have a greater risk of comorbid autoimmune diseases.[11,12] In this study, the correlation of disease duration, clinical stage, clinical type, area of skin lesion and comorbid immune-related diseases with KP in vitiligo patients were identified which provided a basis for disease assessment and prognosis.

The mean age of onset and percentage of patients with progressive disease reported in this study were 24.08 years and 71.81%, respectively, which are in line with other reports (24.20 years and 70.10%, respectively).[11,12] The mean duration of disease, the percentage of positive family history, and the percentage of patients with comorbid immune-related diseases were lower than those reported abroad (7.00 years, 20.50%, and 28.30%, respectively).[12,13] Autoimmune thyroid disease, chronic hepatitis B, and allergic diseases predominated among the combined immune-related diseases, indirectly suggesting an essential role of autoimmunity in the pathogenesis of the disease. Among the clinical types, the sporadic type was present in 88.92% of patients with a percentage slightly higher than the 84.50% reported abroad.[12] These differences may be related to differences in ethnicity, geographic location, genetic heterogeneity, and environmental factors, leading to alterations in the pathophysiological basis of the disease.

The exact mechanism by which KP occurs in vitiligo patients is unclear. Various possible mechanisms, including immunological mechanism, inadequate melanocyte adhesion, oxidative stress, and neurovascular factors, may lead to depigmentation.[5,14] In immunological mechanism, trauma is considered to activate innate and adaptive immunity through interferon-γ-CXCL10-CXCR3B signaling, which may play a role in the occurrence of KP in vitiligo.[15] The stimulation of environmental factors leads to the increase of reactive oxygen species in epidermal melanocytes, which changes mitochondrial function and leads to endoplasmic reticulum stress and ultimately destroys melanocytes.[16] Exogenous injury can reduce the level of E-cadherin in melanocytes which leads to detachment and is thought to be a pathogenesis of KP.[17] Furthermore, growth factor deficiency and other factors may also participate in the pathogenesis of KP in vitiligo.[4] The prevalence of KP in patients reported in this study was 19.70%, which is similar to that reported abroad (21–62%) and may be related to the fact that the occurrence of KP is influenced by several factors.[5,6] KP is often overlooked in clinical diagnosis, yet it may be a significant predictor of the extent and activity of the disease in later stages.[18] A recent study suggested that KP can be a clinical marker to assess the progression and prognosis of vitiligo.[19] Khurrum et al performed a correlation analysis of the clinical characteristics of 381 patients with vitiligo, which found that patients with positive of KP were associated with a longer disease duration, a progressive clinical stage, and clinical types of limited and mixed forms.[12] In this study, the sample size was further expanded to show that KP-positive patients had a more prominent clinical course and a greater proportion of patients with progressive disease than KP-negative patients, with statistical differences between two groups ($P < 0.05$). These were consistent with the results of the above study.[12]

We found comorbid immune-related diseases were more common in KP-positive patients in this study, which indirectly supports the critical role of immunological mechanisms in the development of KP. Vitiligo has been reported to be associated with numerous diseases. Recently, a systematic review and meta-analysis found that alopecia areata, discoid lupus erythematosus, Sjogren's syndrome, myasthenia gravis, systemic lupus erythematosus, and several other diseases were associated vitiligo,[20] while another study found vitiligo patients with a high morbidity risk of several psychiatric disorders.[21] The relationship between comorbid immune-related diseases and KP has not been reported previously.

Vitiligo mainly affects the external appearance of patients. Therefore, the larger the affected area, the more negative impact on the patient. Recently, increased area of skin lesion was found to be associated with higher depression and poorer quality of life.[22] Area of skin lesion ≥2% was significantly higher in KP-positive group in this study which was consistent with the result in an earlier study.[18] Although we have found a correlation between the present of KP and various clinical features of vitiligo, the causal relationship cannot be determined yet. Further analysis of the confounding variables, such as treatment history or environmental factors, should also be addressed in future.

Conclusion

This study was to explore the correlation between the presence of KP and the other clinical features of vitiligo patients. The progressive stage, acrofacial type, comorbid immune-related diseases and larger lesion area were related to positive KP. The study suggested the presence of KP may be an indicator of disease activity and aggression, and underlay its

importance in the management of the disease. This study also provided a reference to explore the correlation between the present of KP and clinical features of other diseases.

Ethical Approval

This study was approved by the ethical review committee of the First Affiliated Hospital of Anhui Medical University (Anhui, China).

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Disclosure

The authors report no conflicts of interest in this work.

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