Clinical significance of Koebner's phenomenon in vitiligo: a hospital-based epidemiological investigation from China

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To the Editor: Vitiligo is an asymptomatic but cosmetically disfiguring disorder that results in depigmented patches in the skin. The prevalence of vitiligo was 0.56% in China according to our study in 2008.[1] Based on clinical features, vitiligo can be classified into four subtypes: segmental (SV), non-segmental (NSV), mixed, and unclassified vitiligo. It also can be divided into active and stable phases according to the disease activity.[2] Koebner's phenomenon (KP), also known as the isomorphic response, had been defined as the development of new lesions of a dermatosis over the sites of mechanical trauma. Unlike other disease (such as psoriasis), KP in vitiligo is related to daily activities, especially to chronic friction. The Vitiligo European Task Force (VETF) has recently updated the definition and classification of KP for vitiligo.[3]

To observe the clinical features of KP in Chinese vitiligo patients based on the new KP classification, a hospital-based study was conducted between June 2019 and February 2020 in the Department of Dermatology, Peking University People's Hospital. The present study was approved by the Ethics Committee of Peking University People's Hospital (2023PHB067-001). The survey was conducted by trained professional dermatologists, using a standardized questionnaire, followed by a complete physical examination. All the patients signed an informed consent form. According to the new VETF classification of KP, KP1 was diagnosed based on history. KP2A was diagnosed based on clinical examination and was defined as depigmentation corresponding either to areas of repeated pressure or friction (hands, elbows, knees, ankles, etc) or areas of chronic friction related to clothes/accessory. KP2B was defined as depigmentation clearly induced by trauma (linear, punctiform, crenate). KP3 referred to experimentally induced KP and was not elicited. Furthermore, the definition of KP1 was extended in our study, including but not limited to 1 year. The Vitiligo Disease Activity was scored on a 6-point scale, comprising active vitiligo lesions during the last 6 weeks (score +4), 3 months (score +3), 6 months (score +2), 12 months (score +1), stable for at least 1 year (score 0), stable for at least 1 year and spontaneous repigmentation (score −1). The body surface area (BSA) involvement was divided into three levels: Grade I, BSA $\leq$ 1%; Grade II, 1% < BSA $\leq$ 5%; and Grade III, BSA > 5%. The body mass index (BMI) of each patient was calculated, using the formula of weight divided by the square of height (kg/m^2). The data were analyzed using SPSS Statistics ver. 24.0 (IBM Co., Armonk, NY, USA). A P value <0.05 was taken as statistically significant.

A total of 418 vitiligo patients completed the questionnaire and clinical examination. As shown in Table 1, 68 (16.3%) were SV, 288 (68.9%) were NSV, ten (2.4%) were mixed vitiligo, and 52 (12.4%) were unclassified vitiligo. The ages of the patients were in the range of 0.5 to 82.0 years, while the mean age was 33.4 ± 14.9 years. The male-to-female ratio was 1.2:1 (229 male and 189 female). The affected BSA ranged from 0.5% to 90%. KP occurred in all types of vitiligo, including 19.1% (13/68) in SV, 90% (9/10) in mixed vitiligo, 75.7% (218/288) in NSV, and 36.5% (19/52) in unclassified vitiligo. Mixed vitiligo had the highest incidence of KP ($P < 0.001$). Among patients with progression, 67.3% (216/321) had KP, with a significant difference compared with 44.3% (43/97) in stable vitiligo ($P < 0.001$).

The mean onset age of vitiligo had no statistical difference between the two groups ($P = 0.055$). The median disease duration was 3.0 years in the KP-positive group ($n = 245$) *vs*. 2.0 years in the KP-negative group ($n = 152$, $P < 0.001$). The number of leukoderma were 14.0 ± 12.3 in the KP-positive group *vs*. 4.4 ± 3.5 in the KP-negative group ($P < 0.001$). The incidence of KP was different between different BSA affected levels: 48.9%

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Table 1: Clinical characteristics of 418 vitiligo patients with Koebner's phenomenon.

Items	Value	KP+	KP−	*P* values
Number of patients (%)	418	259 (62.0)	159 (38.0)	
Male, *n* (%)	229 (54.8)	142 (62.0)	87 (38.0)	N.S.
Female, *n* (%)	189 (45.2)	117 (61.9)	72 (38.1)	
Age (years), mean ± SD	33.4 ± 14.9	35.2 ± 14.0	30.5 ± 15.8	0.001
Age at onset (years), mean ± SD*	27.8 ± 15.4	28.9 ± 15.1	26.0 ± 15.6	N.S.
BMI, mean ± SD	22.3 ± 3.7	22.7 ± 3.5	21.6 ± 3.9	0.003
Type of vitiligo, *n* (%)				<0.001
Segmental	68 (16.3)	13 (19.1)	55 (80.9)	
NSV	288 (68.9)	218 (75.7)	70 (24.3)	
Mixed	10 (2.4)	9 (90.0)	1 (10.0)	
Unclassified	52 (12.4)	19 (36.5)	33 (63.5)	
Disease activity				<0.001
Progressive, *n* (%)	321 (76.8)	216 (67.3)	105 (32.7)	
Stable, *n* (%)	97 (23.2)	43 (44.3)	54 (34.0)	
Duration of vitiligo (years), median*	0.0–53.0	3.0	2.0	0.001
BSA affected with vitiligo, *n* (%)				<0.001
Grade I (BSA ≤ 1%)	235 (56.2)	115 (48.9)	120 (51.1)	
Grade II (1%<BSA ≤ 5%)	137 (32.8)	101 (73.7)	36 (26.3)	
Grade III (BSA > 5%)	46 (11.5)	43 (93.5)	3 (6.5)	
VIDA, mean ± SD	2.3 ± 1.8	2.6 ± 1.7	1.82 ± 2.0	0.001
Number of leukoplakia, mean ± SD	10.5 ± 11.0	14.0 ± 12.3	4.4 ± 3.5	<0.001
Autoimmune diseases, *n* (%)	59 (14.1)	40 (15.4)	19 (11.9)	N.S.
Family history vitiligo, *n* (%)	55 (13.2)	37 (14.3)	18 (11.3)	N.S.
Presence of halo nevi, *n*%	33 (14.1)	19 (7.3)	14 (8.8)	N.S.

* Including 397 patients, not including the answer 'doubtful'. KP: Koebner's phenomenon; N.S.: Not significant; NSV: Non-segmental; VIDA: Vitiligo disease activity.

(115/235) in Grade I group, 73.7% (101/137) in Grade II group, and 93.5% (43/46) in Grade III group ($P < 0.001$). The BMI of the KP-positive group was 22.7 ± 3.5, which was higher than 21.6 ± 3.9 in the KP-negative group ($P = 0.003$). According to the logistic regression analyses, BMI values >18.5 (OR, 2.938; 95% CI, 1.591–5.424; $P < 0.001$) were significantly associated with KP. To summarize, KP-positive patients had a longer disease duration, higher BMI, higher BSA levels, and more vitiligo lesions.

Among the 259 patients with KP, 159 developed KP1 (38.0%), 202 developed KP2A (48.3%), and 48 developed KP2B (11.5%). The same patient can have different types of KP at the same time. A total of 4379 leukoplakia were recorded, and the top 10 sites of leukoderma were the back of the hand, belt areas, digit, wrist flexion, shank extensor side, proximal interphalangeal joint, forehead, proximal knuckle plane, fingertip, and back of the foot. The top three sites of KP1 prone sites were the back of the hand, belt department, and shank extensor side. KP2A prone sites were the belt department, wrist flexor side, and digit. KP2B prone sites were the back of the hand, forearm extensor side, and shank extensor side.

KP, evaluated by medical history (KP1) and clinical examination (KP2A and KP2B), can be used as a clinical parameter for vitiligo, which can help in the prediction of prognosis, clinical course, and response to treatment. Unlike previous reports, our study showed that KP can also occur in SV patients. Mixed vitiligo had the highest incidence of KP (90%, 9/10), higher than in NSV patients (75.7%, 218/288, $P < 0.001$). These observations suggest that patients with SV should also pay attention to the prevention of KP and that the pathogenesis of SV and NSV may be intertwined.

Our study also showed that KP of vitiligo can occur after almost all wounds; when we extended our medical history to >1 year, we found that many patients had trauma or scars that had occurred many years ago even before the onset of vitiligo, and KP1 appeared on the old injury site after the onset of vitiligo or during its progression. KP1 can also be caused by years of lifestyle habits, exercise, etc. Vitiligo is also related to daily activities, especially repeated friction, which is the same as KP2A. Our leukoplakia statistics revealed that new leukoplakia were very closely related to chronic friction, but less related to clear trauma. Therefore, the pathogenesis of vitiligo KP may be different from that of classic KP such as psoriasis, and making this distinction is important for accurately ascertaining the pathogenesis of vitiligo.

In our investigation, the mean BMI of the KP-positive group was higher than that of the KP-negative group, which may be related to increased friction caused by obesity. However, further studies are needed to ascertain whether there is an intrinsic related mechanism. Furthermore, according to the prone sites of KP, it is obvious that the friction caused by behavioral habits and clothing should be reduced to avoid new KP. In some obstinate cases of vitiligo, it should be analyzed whether there are KP-inducing factors, such as glasses' frame compression, belt friction, shaving habits, and so on.

The limitations of this study are the lack of data from more centers and the inadequate sample size.

Conflicts of interest

None.

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Erratum

Erratum: Applications of human amniotic fluid stem cells in wound healing

Following the original article's publication,[1] the authors identified the following errors:

There is a typo error on the first affiliation. "Department of Plastic Surgery and Burns, The Affiliated Hospital of Zunyl Medical University, Zunyl, Guizhou 563003, China" should be "Department of Burns and Plastic Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563003, China"

The second affiliation "Department of Plastic Surgery and Burns, Fuling Central Hospital, Chongqing 408000, China." should be "Department of Burns and Plastic Surgery, Chongqing University Fuling Hospital, Fuling, Chongqing 408000, China".

Reference

1. Luo H, Wang Z, Qi F, Wang D. Applications of human amniotic fluid stem cells in wound healing. Chin Med J 2022;135:2272–2281. doi: 10.1097/CM9.0000000000002076.