

Sparing phenomenon in dermatology: Case reports and literature review

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Summary

Sparing phenomenon in dermatology is the phenomenon that the skin lesions of existing skin diseases do not appear in skin areas with certain characteristics. This phenomenon is recorded across various skin diseases. It is not only serve as a helpful clinical sign in the differential diagnosis of multiple dermatological conditions but also opens up a direction for further research on the pathogenesis of disease that remain poorly understood. Moreover, it may suggest the possibility of application in new treatment therapies. In Vietnam, this phenomenon has been rarely discussed in the literature. In this article, we present three clinical cases with sparing phenomenon and provide an overview of this finding based on international literature.

Keywords: Sparing phenomenon; inverse Koebner phenomenon; Renbook phenomenon; isotopic non-response, reverse isotopic.

1. Background

Sparing phenomenon refers to the absence of specific dermatological disease's cutaneous lesions in specific areas that posses distinctive characteristic: particular anatomic regions, skin previously or currently affected by other skin diseases, or areas exposed to physical, chemical factors¹. This phenomenon was first described in 1981, Cochran and Wilkin recorded a drug-induced eruption case. In which, there were no cutaneous lesions on the skin area that had been irradiated for Wilms tumor treatment². To date, sparing phenomenon has been documented in variety dermatological conditions. Albeit, its pathogenesis has not been fully elucidated, this clinical finding contributes to differential diagnosis, aids in predicting lesion progression, and may reflect underlying pathogenic mechanisms.

To our best knowledge, in Vietnam, there have been no previous reports on the sparing phenomenon. In this study, we report three clinical cases and provide a literature review on this intriguing phenomenon.

II. CASE REPORTS

Case 1

A 45-year-old male patient with scattered gray hair presented with hair loss in the forehead and temples. The hair loss area is 5x6cm in size. There were gray hairs in the middle of affected area. Hair loss only occurred in the surrounding black hair, not affecting the gray hair. (Figure 1A)

Case 2

A male patient presented with hyperpigmentation macules and patches around the right armpit, with fine scaly surface. KOH test reveals budding yeasts. The patient was diagnosed tinea versicolor. No similar lesions were found in central of the right armpit. The patients had not received any treatment prior to presentation. (Figure 1B).

Received: 25/6/2025, *Accepted:* 6/10/2025

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Case 3

The 10-year-old patient was diagnosed with plaque psoriasis 6 years ago. The condition responded poorly to the treatment and progressively extended over time. The patient presented with multiple well-demarcated red plaque with minimal silvery-white scale distributed across the body. Notably, no psoriatic lesions were detected in the elbow areas (Figure 1C-D).



Figure 1. A: The gray hairs remained in affected in hair loss area. B: The lesion is sparing in the armpit. C-D: A patient with progressive psoriasis showing no psoriasis lesions over typical pressure-bearing areas.

III. DISCUSSION AND LITERATURE REVIEW

The sparing phenomenon can be divided into 3 groups: classic sparing, inverse Koebener, comorbid sparing.

The first with classic sparing refers to the phenomenon observed in certain dermatological conditions that specific areas of the skin are unaffected or rarely affected, despite active lesions being present in adjacent areas or the skin disease is widespread. This phenomenon has been recorded in many diseases³, including:

Atopic dermatitis: in children wearing diapers, atopic dermatitis lesions typically spare at the diaper area^{4,5}. Several studies have hypothesized that wearing diapers helps prevent and improves skin

barrier function. The increased humidity in this region improves the skin barrier function and reduces transepidermal water loss⁶. The presence of sweat and urine enhances hydration. Furthermore, sweat contains antimicrobial peptides that may inhibit pathogenic bacteria related to atopic dermatitis^{7,8}. Additionally, fecal microbiota may stimulate protective immune responses and compete with atopic dermatitis-related pathogens⁹⁻¹¹. The diaper may also physically limit scratching in the area⁵. This feature helps support the diagnosis and differentiation of atopic dermatitis from other skin diseases commonly found in infants and children such as seborrheic dermatitis.

Alopecia areata: in the hair loss area, gray hairs are preserved. The disease only affects pigmented hairs. Current evidence suggests that alopecia areata is considered a T-cell-mediated autoimmune disease. In which, loss of protection due to the immune privilege of hair follicles plays an important role. Melanocytes of hair follicles are one of the targets of attack¹². In clinical case number 1, our patient had scattered gray hair on the head, the gray hairs in the hair loss area were the same length as the remaining hair areas, ruling out the possibility that the gray hairs in the hair loss area were new hairs growing back in the remission phase of alopecia areata. Thus, the gray hairs in the hair loss area are an example of this common exemption phenomenon.

Pityriasis versicolor: lesions are rarely present in the armpit area^{4,13}. This may be due to the lipophilic nature of *Malassezia* species, which preferentially colonize sebum-rich areas such as the chest and back. Although the axillae are moist and warm, they contain fewer sebaceous glands and thus provide a less favorable environment for *Malassezia* growth⁴. Moreover, the armpit area also has a distinct and diverse microbial community¹⁴, which may competitively inhibit *Malassezia* colonization. Our clinical case number 2 patient had not received any treatment before coming to the clinic, there was no different care between the armpit, forearm and arm skin. The absence of lesions in the axillae in this case could be explained by the factors mentioned above.

Nose sign (Beak sign): In cases of facial contact dermatitis or erythroderma, the nasal area is often spared. Some authors have proposed that this is due to the high density of sebaceous glands in the nasal region. Sebum may act as a physical barrier, preventing penetration of water-soluble allergens and irritants, thus protecting the area from contact dermatitis. In erythroderma, it has been hypothesized that the nose is more frequently exposed to sunlight, which may suppress keratinocyte proliferation. In addition, habitual touching or rubbing of the nose when feeling anxious may reduce scale accumulation in this area^{3,15,16}.

Above, we have outlined this phenomenon through common diseases that demonstrate typical patterns of classic sparing, although the underlying pathogenesis remains incompletely understood. In addition, there are various diseases with classic sparing phenomenon that have been recorded: butterfly rash in lupus erythematosus are often absent in the nasolabial folds (areas with little exposure to light); in tinea cruris, scrotum is typically spared (lower keratinization, richer blood supply, lower pH), erysipelas affects the ear area but cellulitis does not (Milium's ear sign, because the ear area does not have a deep dermis and fat).

Classic sparing plays an important role in clinical diagnosis and differential diagnosis. Furthermore, it provides valuable insights for future research into disease pathogenesis and the development of targeted therapeutic approaches.

Secondly, inverse Koebner is a phenomenon in which disease-specific skin lesions do not appear in the area that was previously mechanically damaged, in contrast to Koebner (Figure 2A)¹, where trauma induces lesions. Inverse Koebner has been described in diseases such as psoriasis, vitiligo, IgA vasculitis, bullous pemphigoids^{1,17-19}. The pathogenesis of this phenomenon is not fully understood.

Psoriasis is a disease with typical Koebner phenomenon, reports also recorded the Inverse

Koebner in psoriasis³. In such cases, psoriatic lesions were absent in previously traumatized skin areas caused by electrocautery, sanding dermabrasion, radiation therapy, or surgical incisions. The hypothesis suggests that these procedures may destroy dermal papillae, thereby inhibiting the epidermal hyperplasia that characterizes the pathogenesis of psoriasis²⁰. The authors also suggested that post-radiation cellular changes, such as Langerhans cell depletion, vascular wall alterations, decreased vascular activity, and radiation-induced cytokine imbalance, may suppress the expression of type 1 pro-inflammatory cytokines, contributing to the sparing^{21,22}. Inverse Koebner in irradiated skin areas is also seen in many other skin diseases such as vitiligo, drug-induced exanthems, and drug-induced acneiform eruptions³.

Some reports describe psoriatic erythroderma patients who exhibited sparing in areas of pressure, such as beneath tight waistbands (Figure 2B)³ or in limbs encased in casts following trauma²⁰, suggesting that mechanical pressure may contribute to reverse sparing. Our clinical case 3, the patient was having widespread active psoriasis but had no psoriatic lesions over the elbows, which are pressure-bearing areas. There was no history of preexisting skin disease or trauma at those sites, supporting the diagnosis of Inverse Koebner. Inverse Koebner due to pressure has also been reported in bullous pemphigoid, IgA vasculitis. It is hypothesized that mechanical pressure reduces blood flow through superficial dermal vessels, thereby impairing the deposition of immune complexes to levels insufficient to cause visible lesions^{17,18}. In people using sunbeds for tanning, it was also noted that there was no tanning in pressure areas such as the shoulder scapular area and sacrum. This is explained by the fact that UVA-induced melanogenesis requires oxygen, and pressure on the skin may reduce local oxygenation, thus preventing pigmentation in those areas³.

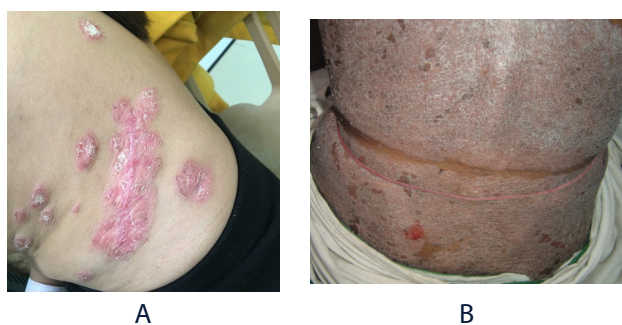


Figure 2. A: Koebner in psoriatic. B : Inverse Koebner in psoriatic erythroderma patient³

Inverse Koebner has been reported in various dermatological conditions triggered by different etiologies, with distinct hypothetical mechanisms of pathogenesis. Investigating this phenomenon may offer new therapy for managing skin disorders.

The third is comorbidity sparing phenomenon refers to cases where a particular dermatological disease does not affect the skin area that are currently or previously involved with another skin disorder³. Up to now, there have been many cases of co-morbidity sparing phenomenon described. In terms of the "comorbidity" of the disease, it can be divided into:

Reverse isotopic (True comorbidity sparing): the patient presents with simultaneous skin manifestations of two different skin diseases, but one condition spares the area affected by the other³

Isotopic non-response (Secondary comorbidity sparing): The current skin disease does not affect an area previously involved by a different skin condition³.

Reverse isotopic has been reported in many cases. Among them, the spared diseases those whose lesions do not appear on the areas affected by another skin conditions are often T cell-mediated inflammatory skin disorders, such as allergic contact dermatitis lesions sparing areas with insect bite reactions (Figure 3A)²⁵ or herpes zoster¹; alopecia areata sparing at the skin area with psoriasis, vascular nevus (Figure 3B)²³; drug eruptions do not affect the skin area with tinea versicolor³. In addition, in the skin area with tinea versicolor, avoidance of lesions of skin diseases such as polymorphous light

eruption, drug-induced papular rash, acute generalized exanthematous pustulosis (AGEP) has also been recorded (Figure 4A)³. In these cases, the authors hypothesized that the presence of *Malassezia* species may play a role in mediating comorbidity sparing by altering the local cutaneous immune environment^{3,24}.

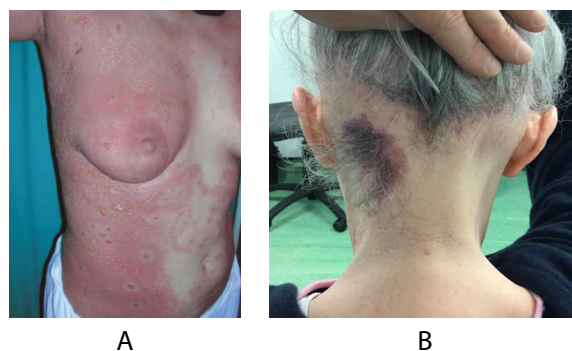


Figure 3. Reverse isotopic. A: Contact dermatitis lesions do not affect the skin surrounding insect bite reactions²⁵. B: alopecia areata does not affect hairs located within vascular nevi²³

Isotopic non-response have been reported in many diseases. Drug eruptions are a common skin disease that exhibits co-occurrences. The two drugs most commonly reported are ampicillin and cotrimoxazole¹. The skin affected by herpes zoster is resistant to many other dermatological diseases: leprosy, contact dermatitis, cutaneous lymphoma. There is no clear relationship between the first and second diseases. The time interval between the two lesions ranges from a few weeks to 20 years¹.

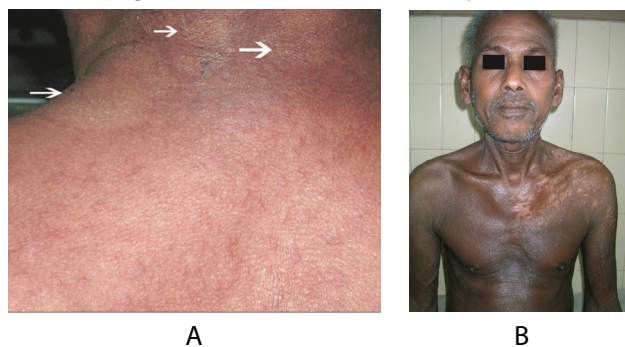


Figure 4. A: Drug-induced maculopapular eruptions spare skin areas with prior tinea versicolor lesions (reverse isotopic)³. B: cutaneous lymphoma lesions spare areas previously affected by herpes zoster (isotopic non-response)¹

The exact pathogenesis of comorbidity sparing is still unclear, possible hypotheses about the pathogenesis of this phenomenon include¹:

Structural changes (cells, blood vessels, nerves) caused by the initial injury can prevent the appearance of a second disease at the same location.

Microenvironmental changes (immune pathways and cytokines) in the affected skin area due to the first injury lead to resistance to the next disease at the same location.

A combination of both reasons.

IV. CONCLUSION

The phenomenon of immunity can be found in many different diseases and is an intriguing but often overlooked finding. The phenomenon of immunity contributes to differential diagnosis and prognosis of lesion progression. Studying the mechanism of this phenomenon helps open up new research directions to better understand the pathogenesis of the disease, the interactions between dermatological diseases, and contribute to research on new treatments.

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