REVIEW ARTICLE

The Woronoff Ring in Psoriasis and the Mechanisms of Post-inflammatory Hypopigmentation

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The Woronoff ring is a ring-like hypopigmentation zone around regressing psoriasis lesions. Although it was first described more than 100 years ago, its aetiology has remained a mystery. Recent insights into the pathogenesis of psoriasis can now explain the origin of the Woronoff ring. Psoriasis involves an HLA-class I-restricted autoimmune response of CD8^{+} T cells against melanocytes in the epidermis. The pathogenic CD8^{+} T cells are not cytotoxic, but are characterized by the production of interleukin-17, interleukin-22 and tumour necrosis factor-α. Interleukin-17 and tumour necrosis factor-α act synergistically on melanocytes by increasing proliferation while inhibiting melanogenesis. This reduces the cellular melanin content despite an increased number of melanocytes in psoriatic lesions. As a consequence, during healing the prior influence of interleukin-17 and tumour necrosis factor-α, despite the increased density of melanocytes, leaves a hypopigmented zone at the edge of regressing psoriasis lesions, which becomes visible as the Woronoff ring. This mechanism can explain a long-discussed puzzling phenomenon in dermatology.

Key words: psoriasis; Woronoff ring; melanocytes.

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SIGNIFICANCE

The Woronoff ring is a depigmented zone arising around healing psoriasis plaques. Analysed in detail for the first time approximately 100 years ago, our current understanding of the pathogenesis of psoriasis enables its explanation due to the cytokine pattern of the T-cell-mediated pathogenic melanocyte-specific psoriatic autoimmune response. The production of interleukin-17 and tumour necrosis factor-α causes suppression of melanin synthesis with a simultaneous increase in melanocyte proliferation. This results in an inflammation-induced hypopigmentation surrounding the healing psoriasis lesions. The emergence of the phenomenon is thus coherently integrated into our immunological understanding of psoriatic pathogenesis.
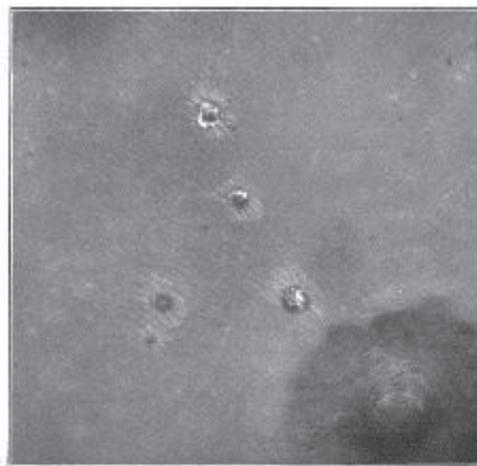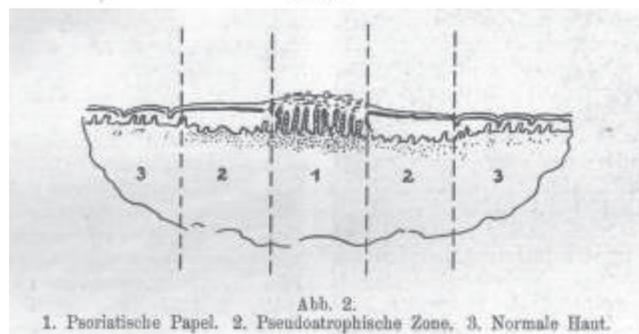

Abb. 1.

Abb. 2.
1. Psoriatische Papel. 2. Pseudoatrophische Zone. 3. Normale Haut.

Fig. 1. The pseudoatrophic zone around the psoriatic papules and scheme of histological changes. From the original publication by Woronoff, 1926 (1).

Nearly 100 years ago, Dr D. L. Woronoff, a dermatologist at the clinic for skin diseases of Moscow University in Russia, published his investigations on a pale annular zone that was known to appear around healing psoriasis lesions, and was thought to be caused by a spastic vessel contraction or hypopigmentation (1). He described the clinical appearance of these rings as a "pseudoatrophic" annular zone surrounding acanthotic psoriatic plaques, and gave a precise histological description (**Fig. 1**). He reported that this zone was histologically distinct from both the psoriasis plaque and the surrounding normal skin due to the absence of parakeratosis in the stratum granulosum, a broadened stratum Malpighii due to more layers of living cells leading to increased epidermal thickness, and irregularly shaped papillae without dilation of the capillaries. He concluded

that this zone, which he sketched in a scheme (Fig. 1), inhibited further development of the psoriatic plaque and was more likely to result in regression of psoriasis lesions. Since he also observed these changes around corymbiform syphilitic skin lesions, he concluded that these "achromatic phenomena" were to the utmost extent better able to withstand all possible pathological stimuli than normal skin.

Based on these studies, the annular zones of hypopigmentation developing around psoriatic skin lesions are referred to as the Woronoff ring. The Woronoff ring is a phenomenon that is mentioned in major dermatological textbooks as a morphologically distinct alteration of healing psoriasis plaques, and it has been occasionally addressed in the medical literature with only a few photographic illustrations. The width is usually between 2 and 6 mm, with regional fluctuations, and increases with the size of the central psoriatic plaque (2). The Woronoff ring has been observed after ultraviolet (UV) phototherapy or photochemotherapy (3), topical treatment, such as anthralin (4) or glucocorticosteroids, or systemic treatments including fumaric acid esters (5) or the tumour necrosis factor (TNF)-α antagonist adalimumab (6), but it may also occur spontaneously. The nature of the Woronoff ring is still not fully explained. This article discusses the aetiology of the Woronoff ring in terms of new insights into the pathogenesis of psoriasis, using the example of a patient who developed Woronoff rings around regressing psoriasis plaques under UV (311 nm) radiation therapy.

CASE REPORT

A 71-year-old female patient with a long history of psoriasis had undergone phototherapy with UVB (311 nm) radiation. The resolving psoriasis plaques developed annular zones of hypopigmentation and, further outward, circumferential hyperpigmentation (**Fig. 2**A). A biopsy from a whitish Woronoff ring showed a dense population of c-Kit+ melanocytes in the basal epidermal layer (Fig. 2B) compared to lesional and normal skin (Fig. 2 C, D).

DISCUSSION

Different approaches have tried to explain the aetiology of the Woronoff ring. Disturbed vascularization, as discussed in early descriptions, appeared unlikely as a cause, since injections of prostaglandin E_2 (7), histamine phosphate and metacholine chloride (8) produced wheals with surrounding red flare involving both the Woronoff ring and adjacent normal skin. Furthermore, by measuring the cutaneous and subcutaneous blood flow in the Woronoff ring by the ^{133}Xe washout method, cutaneous vasoconstriction corresponding to a white dermographism could be excluded as the cause of the white discoloration (9). A major cause of the Woronoff ring was suspected in alterations in prostaglandin metabolism. Observation of a decreased level of prostaglandins in the tissue corresponding to the Wornoff ring has led to the hypothesis that UV therapy induces an inhibitor of prostaglandin synthesis, which causes the white ring by reducing inflammation (10). In addition, diminished inflammation in the Woronoff ring was attributed to a decreased level of endoglin, a scavenger of transforming growth factor beta (11). A histological study using the Masson-Fontana stain observed a marked decrease in the amount of basal-zone epidermal melanin in both the halo and the psoriatic lesions (8).

Recent insights into the psoriatic pathogenesis now provide another explanation for the aetiology of the Woronoff ring. The HLA-class I allele, HLA-C*06:02, is the main psoriasis risk gene (12). Psoriasis develops upon epidermal recruitment, activation and clonal expansion of CD8+ T cells (13, 14). CD8+ T cells recognize peptides that are presented by HLA-Class I molecules. Because the peptide antigens are derived from intracel-
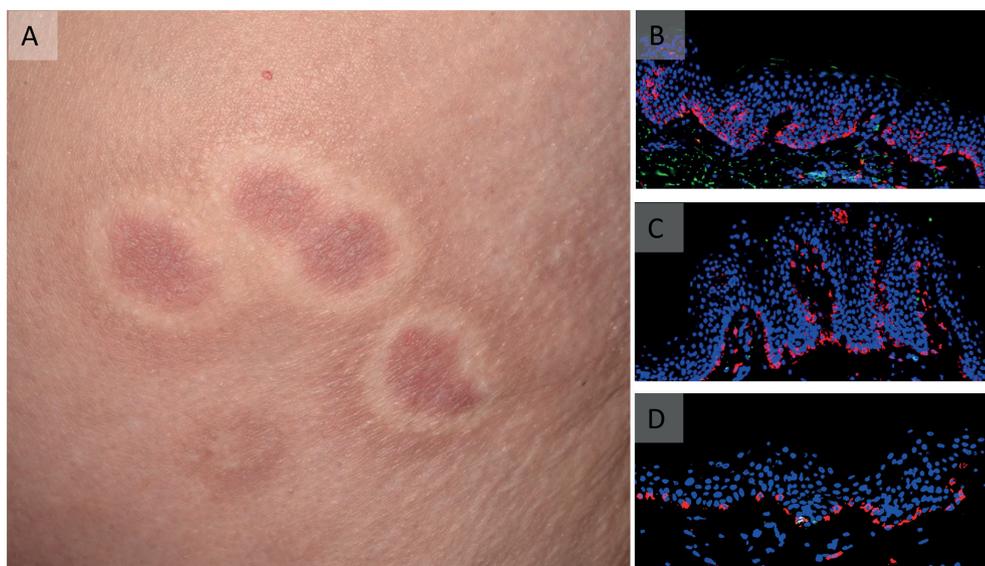
Fig. 2. Clinical features and immunostaining of melanocytes in patient and control skin. (A) Woronoff rings developing as depigmented zones around regressing psoriasis lesions during UVB (311 nm) radiation on the buttocks. Note the slight hyperpigmentation surrounding the depigmented halo. (B) Dense population of c-Kit+ melanocytes (red) in the basal epidermal layer of a biopsy from a Woronoff ring compared with (C) a psoriasis lesion or (D) normal skin; blue: DAPI. Staining by Akiko Arakawa, MD, PhD. Original magnification ×25.

lular proteins, an HLA-class I-restricted pathogenic CD8$^+$ T-cell response is primarily directed against a particular target cell type expressing the parent protein of said antigenic peptides (15, 16). In fact, in psoriasis HLA-C*06:02 mediates an autoimmune response against melanocytes through autoantigen presentation as the underlying pathomechanisms of T-cell mediated chronic inflammation (17).

The pathogenic psoriatic CD8$^+$ T cells represent a particular subtype of epidermal CD8$^+$ tissue-resident memory cells. Such CD8$^+$ T cells are characterized by the expression of CD103 and by CD69, and develop in the skin from epithelium-infiltrating precursor cells (18). CD103 is the α subunit of the $\alpha_E\beta_7$ integrin receptor, binds E-cadherin, which is highly expressed on epithelial cells and thus promotes lodging of CD8$^+$ T cells in the epidermis (19), while CD69 inhibits egress of T cells from tissue via the sphingosine 1-phosphate receptor 1 (20, 21). The epidermal psoriatic CD8$^+$ T cells belong to the T$_{helper/cytotoxic}$17 (T$_{h/c}$17) T cell type and produce the cytokines interleukin (IL)-17, TNF-α and IL-22 (22), which are the signature cytokines of the lesional psoriatic immune response (23). These cytokines promote the epithelial hyperplasia, accumulation of neutrophilic granulocytes and production of antimicrobial peptides, and thus convey the clinical manifestation of psoriasis with the scaly erythematous squamous plaques.

In addition to these clinically apparent cytokine effects, IL-17 and TNF-α have another impact: they alter the functional state of melanocytes. IL-17 and TNF-α synergize in reducing skin pigmentation while promoting melanocyte proliferation (24). They inhibit pigmentation-related signalling and melanogenesis by suppressing pigmentation-related genes and lowering cellular tyrosinase levels in melanocytes, thereby reducing cellular melanin content. IL-17 and TNF-α further jointly induce the expression of melanocyte mitogens, including CXCL1 and IL-8, thus enhancing melanocyte proliferation. In psoriasis, epidermal melanocytes are under the constant influence of IL-17 and TNF-α. Accordingly, the combined effect of these 2 cytokines causes hypopigmentation and, at the same time, increases the number of melanocytes by stimulating melanocyte proliferation, which is reflected by the expression of the proliferation marker Ki67 on melanocytes in psoriatic lesions (24). This impact on melanocytes can now explain the emergence of the Woronoff ring. During healing, the effect of IL-17 and TNF-α leaves a hypopigmented zone on the edge of regressing lesions, where melanogenesis is still suppressed despite the increased density of melanocytes along the basement membrane (Fig. 2B) seen in lesional psoriatic skin (24, 25). The progressive recovery of pigmentation genes, along with the numerically increased melanocytes can then lead to an abundant melanin production and thus cause post-inflammatory hyperpigmentation. This is already evident here as a hyperpigmented zone around the Woronoff ring (Fig. 2A) and can eventually induce hyperpigmentation of the entire lesion. Accordingly, selective therapeutic blockade of TNF-α or IL-17 caused rapid recovery of pigmentation and post-inflammatory hyperpigmentation in healing psoriatic lesions of treatment responders (24). The ring may develop if the psoriasis plaques regress centripetally and not evenly over the entire lesion, so that a remaining central plaque is surrounded by a healed skin zone. If the psoriasis lesions evenly heal, either a uniform post-inflammatory hyperpigmentation or hypopigmentation may remain at the site of the former psoriasis plaque, as is often observed.

At the same time, these findings raise the question of how psoriasis differs from vitiligo. Both diseases are based on an autoimmune response against melanocytes. The pathogenic T cells of vitiligo correspond with the expression of CD8$^+$CD103$^+$CD49a$^+$ to a tissue-resident memory phenotype, which is characterized by a high production of interferon (IFN)-γ and has the protective purpose to mediate local immunity to viruses (26). CD49a is the α-subunit of the $\alpha_1\beta_1$ integrin receptor and is expressed on ~15% of all skin-derived T cells (27). The CD8$^+$CD103$^+$CD49a$^+$ T cells express cytotoxic granules including granzymes and perforins and have a high cytotoxic potential, which can be further amplified by IL-15 (26). When activated in an autoimmune response against melanocytes they promote T-cell-mediated killing of melanocytes and induce the persistent depigmentation of vitiligo through the permanent elimination of melanocytes. The melanocyte-specific CD8$^+$CD103$^+$ psoriatic T cells are clearly distinguished from the melanocyte-specific CD8$^+$ T cells of vitiligo by the absence of the expression of CD49a, by a different cytokine transcription profile and a lack of cytotoxicity, which even IL-15 cannot overcome (26). Instead, they belong to the T$_{h/c}$17 phenotype, whose actual role is the antimicrobial immune defence against extracellular bacteria and fungi (23, 28). When activated against melanocytes in psoriasis, they are not cytotoxic, but induce an antimicrobial, yet sterile, immune reaction. Psoriasis can therefore be considered as a T-cell-mediated antibacterial defence reaction against melanocytes (29, 30). The reason for the different functional outcomes of the melanocyte-specific autoimmune response in psoriasis and vitiligo may lie in the different genetic predisposition of the 2 diseases. According to genome-wide association studies, psoriasis and vitiligo arise on a different genetic background and HLA-association, which may then decide the respective functional differentiation of the pathogenic immune response (31, 32).

REFERENCES

1. Woronoff, DL. Die peripheren Veränderungen der Haut um die Effloreszenzen der Psoriasis vulgaris und Syphilis corymbosa. Dermatologische Wochenschrift 1926; 82: 249–257.
2. Groebe G, Marsch WC, Holzmann H. Woronoff rings in a mathematical model. Hautarzt 1990; 41: 226–228.
3. Lowe NJ, Bures F. Woronoff's rings with PUVA therapy. Arch Dermatol 1978; 114: 278–280.
4. Gupta AK, Ellis CN, Goldfarb MT, Voorhees JJ. Woronoff ring during anthralin therapy for psoriasis. Arch Dermatol 1986; 122: 248.
5. Torley D, Leman J, Burden AD. The Woronoff ring and fumaric acid ester flush. Clin Exp Dermatol 2011; 36: 416–417.
6. Park KK, Swan JW, Eilers D, Tung R, Koo J. Woronoff ring associated with adalimumab therapy for psoriasis. Cutis 2014; 93: E1–2.
7. Penneys NS, Ziboh V, Simon P, Lord J. Pathogenesis of Woronoff ring in psoriasis. Arch Dermatol 1976; 112: 955–957.
8. Koplon BS, Waterson KW, Shapiro L. The Woronoff ring of psoriasis: study of a patient. Intern J Dermatol 1971; 10: 233–236.
9. Klemp P, Bojsen J. Local variation in cutaneous and subcutaneous blood flow measured by CdTe(C1) minidetectors in normal and psoriatic skin. J Invest Dermatol 1986; 86: 109–114.
10. Penneys NS, Ziboh V, Lord J, Simon P. Inhibitor(s) of prostaglandin synthesis in psoriatic plaque. Nature 1975; 254: 351–352.
11. van de Kerkhof PC. The Woronoff zone surrounding the psoriatic plaque. Br J Dermatol 1998; 139: 167–168.
12. Nair RP, Stuart PE, Nistor I, Hiremagalore R, Chia NV, Jenisch S, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Hum Genet 2006; 78: 827–851.
13. Di Meglio P, Villanova F, Navarini AA, Mylonas A, Tosi I, Nestle FO, Conrad C. Targeting CD8(+) T cells prevents psoriasis development. J All Clin Immunol 2016; 138: 274–276.
14. Conrad C, Boyman O, Tonel G, Tun-Kyi A, Laggner U, de Fougerolles A, et al. Alpha1beta1 integrin is crucial for accumulation of epidermal T cells and the development of psoriasis. Nat Med 2007; 13: 836–842.
15. Blum JS, Wearsch PA, Cresswell P. Pathways of antigen processing. Ann Rev Immunol 2013; 31: 443–473.
16. Neefjes J, Jongsma ML, Paul P, Bakke O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nat Rev Immunol 2011; 11: 823–836.
17. Arakawa A, Siewert K, Stohr J, Besgen P, Kim SM, Ruhl G, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. J Exp Med 2015; 212: 2203–2212.
18. Mackay LK, Rahimpour A, Ma JZ, Collins N, Stock AT, Hafon ML, et al. The developmental pathway for CD103(+)CD8+ tissue-resident memory T cells of skin. Nat Immunol 2013; 14: 1294–1301.
19. Watanabe R, Gehad A, Yang C, Scott LL, Teague JE, Schlapbach C, et al. Human skin is protected by four functionally and phenotypically discrete populations of resident and recirculating memory T cells. Science Transl Med 2015; 7: 279ra239
20. Skon CN, Lee JY, Anderson KG, Masopust D, Hogquist KA, Jameson SC. Transcriptional downregulation of S1pr1 is required for the establishment of resident memory CD8+ T cells. Nat Immunol 2013; 14: 1285–1293.
21. Mackay LK, Braun A, Macleod BL, Collins N, Tebartz C, Bedoui S, et al. Cutting edge: CD69 interference with sphingosine-1-phosphate receptor function regulates peripheral T cell retention. J Immunol 2015; 194: 2059–2063.
22. Ortega C, Fernandez AS, Carrillo JM, Romero P, Molina IJ, Moreno JC, Santamaria M. IL-17-producing CD8+ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. J Leukoc Biol 2009; 86: 435–443.
23. Lowes MA, Suarez-Farinas M, Krueger JG. Immunology of psoriasis. Ann Rev Immunol 2014; 32: 227–255.
24. Wang CQF, Akalu YT, Suarez-Farinas M, Gonzalez J, Mitsui H, Lowes MA, et al. IL-17 and TNF synergistically modulate cytokine expression while suppressing melanogenesis: potential relevance to psoriasis. J Inv Dermatol 2013; 133: 2741–2752.
25. Abdel-Naser MB, Liakou AI, Elewa R, Hippe S, Knolle J, Zouboulis CC. Increased activity and number of epidermal melanocytes in lesional psoriatic skin. Dermatol 2016; 232: 425–430.
26. Cheuk S, Schlums H, Gallais Serezal I, Martini E, Chiang SC, Marquardt N, et al. CD49a expression defines tissue-resident CD8(+) T cells poised for cytotoxic function in human skin. Immunity 2017; 46: 287–300.
27. Purwar R, Campbell J, Murphy G, Richards WG, Clark RA, Kupper TS. Resident memory T cells T(RM)) are abundant in human lung: diversity, function, and antigen specificity. PloS One 2011; 6: e16245.
28. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol 2010; 28: 445–489.
29. Prinz JC. Psoriasis vulgaris – a sterile antibacterial skin reaction mediated by cross-reactive T cells? An immunological view of the pathophysiology of psoriasis. Clin Exp Dermatol 2001; 26: 326–332.
30. Prinz JC. Melanocytes: target cells of an HLA-C*06:02-restricted autoimmune response in psoriasis. J Inv Dermatol 2017; 137: 2053–2058.
31. Shen C, Gao J, Sheng Y, Dou J, Zhou F, Zheng X, et al. Genetic susceptibility to vitiligo: GWAS approaches for identifying vitiligo susceptibility genes and loci. Front Gen 2016; 7: 3.
32. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of psoriasis: a comprehensive review. J Autoimmun 2015; 64: 66–73.