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REVIEW ARTICLE

Pityriasis versicolor alba

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ABSTRACT

Pityriasis versicolor alba is a hypopigmented or depigmented variant of pityriasis versicolor characterized by maculous, partly pityriasiform, scaly depigmented lesions occurring particularly in seborrhoeic areas. Long-persisting hypopigmentation after healing of the pityriasis versicolor was first described by Gudden in 1853. Hypopigmentation and depigmentation were later differentiated as an independent variant of the disease. In 1848, Eichstedt recognized the pathogen-related character of pityriasis versicolor in its hyperpigmented form. Today it is generally accepted that the disease is caused by yeasts of the genus *Malassezia*, of which nine species are differentiated. It is controversial whether a single species is responsible for the disease. The pathogenesis of depigmentation has not been established. A screening effect by the scale layer as well as toxic effects on pigment synthesis by fungal metabolites have been discussed. With regard to the second mechanism, the newly discovered tryptophan-derived metabolites of *M. furfur* might be significant. Evidence-based data concerning the therapy of pityriasis versicolor alba do not exist. According to current recommendations, pityriasis versicolor should be rapidly treated with antimycotics, followed by ultraviolet therapy to induce maturation of existent melanosomes and accelerate repigmentation. However, depigmented lesions are difficult to improve by ultraviolet therapy.

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Introduction

Pityriasis versicolor (PV) is the most common dermatosis worldwide associated with alterations in pigmentation.[1] It is a superficial mycosis caused by yeasts of the genus *Malassezia*.[2] These yeasts are part of the normal human skin flora, occurring predominantly in seborrhoeic areas due to their lipid dependency (except for *M. pachydermatis*).[3] Several predisposing factors to the disease have been described, of which hyperhidrosis is the most important one.[2,4] However, the pathogenesis of PV remains to be elucidated. Furthermore, it remains to be clarified whether an individual species of the nine known *Malassezia* species is responsible for the disease, and if so, which in particular.[2,5,6] According to recent data, importance is attached to *M. globosa*, which might explain the globose shape of cells in lesions of PV.[5,6]

Two forms of PV are differentiated according to the clinical appearance.[2] The hyperpigmented form shows bran-like scaly yellowish-red and brownish macules particularly in the seborrhoeic areas. Hypopigmentation and depigmentation have been differentiated from this hyperpigmented form as an independent variant and named as pityriasis versicolor alba (PVa).[7–9] Numerous publications have dealt with the clinical picture of the hyperpigmented form. The authors agree about the clinical data concerning hyperpigmented foci, pityriasiform scaling, demonstration of the causative agent ('spaghetti and meat balls') and fluorescence of the lesions. Clinical data about the hypopigmented form, especially concerning duration of depigmentation (variations from weeks to months are given), occurrence of scaling and presence or absence of the causative agent within the depigmented lesions are rare and often controversial.

The pathogenesis of depigmentation still remains to be elucidated. As ultrastructural examinations of depigmented skin areas show extensive damage to melanocytes several hypotheses deal with toxic influences on melanogenesis and melanocytes by fungal metabolites such as, for example, dihydrocarboxylic acids and products of lipoperoxidation.[10,11] Apart from these metabolites the newly discovered tryptophan-derived metabolites of *M. furfur* might be significant in the pathogenesis of depigmentation as they can explain some clinical phenomena of the disease.

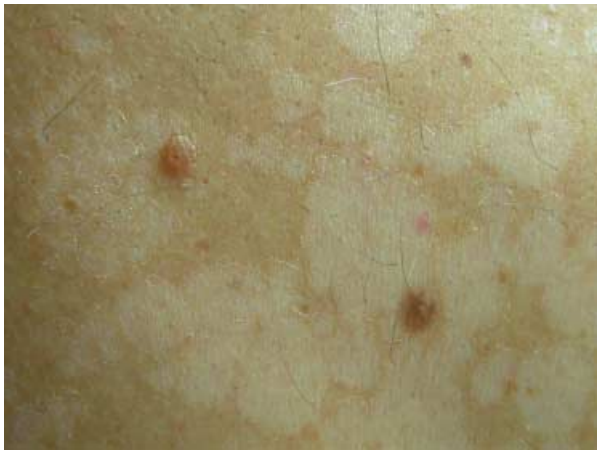

fig. 1 Depigmentation of pityriasis versicolor.

Evidence-based data concerning therapy of the depigmented form of PV are not available. Current recommendations do not differentiate between the hyperpigmented and the depigmented form. But there is unanimity about the difficulties of improving the depigmented lesions by ultraviolet (UV) therapy.

Clinic of pityriasis versicolor alba

Clinically, PVa is characterized by depigmented or hypopigmented macules particularly in the seborrhoeic areas (fig. 1). Depigmentation after healing of lesions of the hyperpigmented form of PV has been known for a long time.[12,13] In most cases, depigmentation develops following the hyperpigmented stage of PV, either spontaneously or under the influence of UV light.[14–18] Many patients do not notice the hypopigmented changes until exposure to sunlight.[17] However, only two-thirds of patients with PV develop depigmentation during the healing process.[18] PVa can also occur without any hyperpigmented pre-stage. Hypopigmentation and depigmentation as an independent variant of the disease, especially on black skin, have been described by Pardo-Castello,[7] Jeliffe and Jacobson[8] and Marples.[9] Even though children are far less frequently affected by PV than adults, 72% of them show the hypopigmented or depigmented form.[19] Simultaneous occurrence of hyperpigmentation and depigmentation is possible.[1,20,21]

Depigmentation and hypopigmentation in PVa are 'long' persisting.[12,22,23] Data range between 6 months in patients without regular UV irradiation and 3–6 weeks in those receiving UV therapy.[14,24,25] In contrast to other depigmentation diseases such as vitiligo, depigmented lesions in PVa are less sensitive to UV light. Independently of each other, Ruete,[20] Kistiakowsky[24] and Wertheim[26] described the complete absence of erythema in depigmented areas during UV irradiation, while the unaffected skin showed marked UV-induced inflammatory reaction.[20,24,26] According to Barney, depigmentation cannot be influenced not even by phototoxic agents.[23] Likewise, therapy studies by El-Gothamy and Abdel-Fattah failed to demonstrate an additional effect of photosensitizing agents in terms of reversibility of depigmentation.[18]

Table 1 Clinical phenomena of depigmented lesions

Demonstration of pathogen	Early depigmentation: yes Late depigmentation: no
Desquamation	Early depigmentation: yes Late depigmentation: no
Fluorescence	Only demonstrable while demonstration of pathogen?

While demonstration of yeast cells and hyphae in hyperpigmented areas is thought to be certain,[27] controversial data exist concerning demonstration of the infectious agent in depigmented areas: both positive[28–30] and negative results[16,18,21,31] have been reported. In comparative studies Galadari and El Komy found lower numbers of pathogens in depigmented areas than in hyperpigmented lesions.[30]

In the older literature there are observations reporting high numbers of pathogens (yeast cells and hyphae) in early lesions of PVa, followed by reduction (only demonstration of hyphae) and finally even pathogen-free depigmented areas[14,24,26] Such a time course could explain the recent controversial findings and shows that depigmentation may outlast the presence of *Malassezia* yeasts. This would also explain the non-response of PVa to antimycotics.

Fine desquamation is characteristic of hyperpigmented lesions in PV.[32] It is not regularly developed in depigmented areas of PVa. While depigmentation with scaling has been reported,[25,33] depigmented areas without any desquamation[23] represent problems in the differential diagnosis of PVa with other depigmenting diseases, particularly with vitiligo.[16] In the older literature time course dependent presence of scaling is described. So there is marked scaling of early depigmented lesions, followed by complete regression during an intermediate stage in which desquamation is only demonstrable in the marginal region.[7,24,26]

Apart from the presence of the pathogen and pityriasiform scaling fluorescence of lesions under UV light is thought to be a third characteristic of the hyperpigmented form of PV. Wood's light examination of the patient (long-wave UV light, approximately 366 nm) allows us to assess the disease extent based on the yellow-greenish fluorescence of affected skin areas.[4,34] Data concerning fluorescent depigmented areas are rare. Lockshin described fluorescence of depigmented lesions, which was no longer demonstrable after pathogen eradication (Table 1).[16]

Histology and electron microscopy of pityriasis versicolor alba

As in hyperpigmented lesions, yeast cells and hyphae in depigmented areas are predominantly found in the upper

two-thirds of the horny layer. Only sporadically they occur in the deeper portions of the horny layer.[20,35,36] The epidermis has been found to be thickened or thinned.[20,30,37] The cellular turnover of the affected (hypopigmented) areas is normal.[29]

In the hyperpigmented form of PV, the dermis shows inflammatory changes with mild superficial and perivascular lymphocytic infiltrate.[18,30,38,39,40] In the case of PVa, the inflammatory infiltrate is markedly less pronounced.[30] There is no evidence of vasculitis or significant inflammation apart from a few scattered lymphocytes in perivascular location.[29]

Epidermal pigmentation in the depigmented areas seems to be decreased compared with normal skin.[30] On histological examination depigmented areas show an equal number of melanocytes compared with normal skin.[18,29] There is no description of pigment incontinence so depigmentation does not result from destruction of melanocytes. The DOPA reaction in skin specimens of depigmented lesions is predominantly positive.[16,28,33] Ruete is the only author describing a completely negative DOPA reaction in the depigmented area, which, however, was demonstrated in only one skin sample.[20]

Light microscopy of depigmented PVa as well as of hyperpigmented areas of PV reveals lower pigment density within the melanocytes in the DOPA reaction and Fontana–Masson stain compared with normal skin of the same individual.[18]

According to Charles light microscopy of hypopigmented areas shows morphologically altered melanocytes characterized by enlargement of the cells and marked dendrites.[29] Electron microscopic examinations confirm these findings by showing degeneratively altered melanocytes with mitochondrial and cytoplasmic vacuoles of varying intensity, visible cytoskeleton and cessation of melanin production up to plasmolysis of melanocytes.[30,39] The number of melanosomes in the keratinocytes of the spinous cell layer is significantly lower compared with normal skin (3.5 vs. 21.3).[30,40] Individual melanosomes are reduced in size and form aggregates instead of being scattered as in normal skin (Table 2).[30,39] Accumulation of melanosomes within melanocytes and their dendrites as a consequence of a partial block in the transfer of melanosomes to keratinocytes as described by Charles *et al.* was not confirmed by Breathnach and Galadari.[29]

Table 2 Histology of depigmented lesions

Inflammatory infiltrate	Sparse (few lymphocytes around vessels), no sign of vasculitis
Melanocytes	Present, no difference in number in compared with normal surrounding skin Disturbance of shape, mitochondrial and cytoplasmic vacuoles
Melanosomes	Number of melanosomes in the keratinocytes of the spinous cell layer is significantly lower Partly reduction in size forming aggregates

Table 3 Pathogenesis of depigmentation

Pseudo-leucoderma	Light filtering effect by scales and fungal layer
Leucoderma	Disturbance of melanogenesis and/or destruction of melanocytes by fungal metabolites: acelaic acid; lipoxygenase; tryptophan metabolites

For a long time, depigmentation has been understood as a pseudo-leucoderma resulting from the light filtering effect by the scales and the fungal layer (Table 3).[14,24,26,31,41] This thesis was supported by the observation of depigmentation arising on previously hyperpigmented areas during UV irradiation.[24,39] In particular, the complete absence of erythema in the affected lesions despite marked environmental skin reaction to UV irradiation was considered the main argument against postinflammatory hypopigmentation and in favour of a (physical) light filter. However, three reasons are against such a pseudo-leucoderma resulting from a purely physical filter effect of the fungal layer towards UV irradiation:

- Clinical observation of depigmentation in unexposed skin such as the genitoanal region[22,42,43] and depigmentation of black skin.[8,35,44] As early as in 1935 Sulzberger assumed the presence of 'an agent that actively removes skin pigment'.[31]
- Significantly delayed repigmentation of depigmented lesions despite no longer scaling; a fact that caused Barney in 1932 to assume destruction or 'paralysation' of pigment forming cells, as even the use of bergamot oil during UV irradiation failed to achieve repigmentation of white lesions within 3–6 weeks.[7,23]
- Histologically and electron microscopically visible melanocytic damage with impaired melanogenesis.

So today depigmentation in PVa is thought to be true leucoderma.

The complex process of melanogenesis offers numerous targets for interactions of the causative agent or its metabolites with melanin production. While Charles *et al.* assumed a blockage of melanosome transfer from the dendrites of melanocytes to the surrounding keratinocytes, other electron microscopic findings rather suggest disturbed melanogenesis on a previous level as well as impairment of melanocytes.[29,30,39]

Here the studies focus on the influence of tyrosinase, which plays a key role in melanogenesis by catalysing the first two steps of melanin formation. Jung and Bohnert demonstrated inhibition of this enzyme by an extract of scales of PV.[25] The inhibitory effect was later ascribed to dicarboxylic acids, which can be isolated from cultures of *Malassezia* yeasts, although these had actually not been demonstrated in the scale extract.[45,46] In particular azelaic acid ($HOOC\text{-}(CH_2)_7\text{-}COOH$) inhibits the key enzyme of melanogenesis *in vitro* and thus interferes with the first steps of melanin formation.

However, subsequent studies showed that concentrations of azelaic acid *in vivo* were too low for inhibition of tyrosinase and or damage to melanocytes (Table 3).[11,47,48] De Luca *et al.*[11] propose the effects of lipoperoxides and by-products causing damage to melanocytes. Formation of lipoperoxides can be regularly found in cultures of *Malassezia* yeasts.[11] As these are part of the

resident skin flora, depigmentation caused by lipoperoxides would occur in any human at any time.

Another interesting finding is the newly discovered tryptophan-dependent secondary metabolism of *M. furfur*. It was shown that *M. furfur* produces a brown pigment on a medium consisting of a lipid source and tryptophan as the main nitrogen source.[49] Under UV light, this pigment exhibits yellowish-green fluorescence, and chromatographic separation reveals a variety of differently coloured bands as well as fluorochromes. Given the similarities between the pigment formation with differently coloured bands with their fluorescence and the polychromatous lesions of PV and their green-yellowish fluorescence the composition of the produced pigment was specified and the structures of some components of the pigment were elucidated. Thereby substances that have been isolated were detected by means of bioassays developed on the basis of different clinical phenomena of PV. The isolated components are hitherto unknown mostly complex indole derivatives with interesting pharmacological properties.[50–53] Thus, inhibition of tyrosinase could be demonstrated on screening the chromatographically separated pigment *in vitro*. During further thin-layer chromatographic separation enzyme inhibition was reproducibly assigned to a particular band ($R_f = 0.39–0.43$ in fraction 6) and finally to a single peak on high-performance liquid chromatography separation of this thin-layer band.[54,55] Inhibition of the DOPA reaction by substances from pigment produced by *M. furfur* in skin sections was demonstrated as well.[56] Initial studies with melanocyte cultures have shown damage to melanocytes by components of pigment produced by *M. furfur*, particularly by malassezin.[50,57] Looking upon melanin as a polyindole derivative, it is conceivable that indole compounds produced by *M. furfur* interact with melanin synthesis.

Among the tryptophan metabolites potent broad-spectrum UV filters could be shown with the lipophilic substance pityriacitrine and pityrialactone.[51,52,58] The screening effect of these compounds might explain why patients with PVa do not get sunburn in the depigmented areas, although the disease frequently occurs in sunny regions close to the Equator. The yellow inherent colour of pityriatricine would also explain why depigmentation in PVa is not pure white as in vitiligo, but slightly yellowish.[59]

Pigment production could be shown only in *M. furfur* and in some strains of *M. pachydermatis*.[60] However, *M. furfur sensu strictu* seems to be a very uncommon species in PV lesions, whereas actually *M. globosa* is proposed to be the pathogen of PV being isolated from between 25 and 97% of the patients.[38] On the other hand the same species *M. globosa* can be isolated in 51–71% from the trunk of healthy objects as well.[6,61] Therefore, pigment production might represent a new concept, which might elucidate some phenomena of the disease unexplained to date: therefore, fluorescence, hyper- and depigmentation as well as the coexistence of hyper- and depigmented lesions as a transitional state between pigment synthesis by the yeasts and suppression of melanogenesis could be explained.

Therapy

Data concerning therapy of PVa are rare. Treatment options separating between the hyperpigmented and the hypopigmented form are not available.[1,2] In particular, depigmentation in PVa itself is difficult to treat. It is long-persisting even under UV irradiation, as shown by Kistiakovskys and Wertheim.[24,26] Jung and Bohnert described repigmentation during UV therapy within 3 weeks after pathogen eradication.[25] A therapeutic study concluding 79 patients suffering from the hyperpigmented and the depigmented form of PV/PVa showed no effect of an additional UV therapy or an additional combination of UV therapy and photosensitizing agent (meladinine) vs. antimycotic treatment alone.[18] Unfortunately, this study does not show how patients with the hyperpigmented form and those with the hypopigmented form were distributed to the different treatment groups. Irrespective of which additional therapy had been used, lesions in all three groups healed within 6 weeks of local antimycotic treatment, two-thirds with hypopigmentation, one-third without hypopigmentation. Therefore it is recommended that patients with PV/PVa should receive antimycotic therapy as soon as possible in order to minimize the effect of the disease on skin pigmentation. If taken at all, UV therapy should be given only after complete eradication of the fungus. Should the potent UV filter pityriacitrin in fact be of pathogenetic significance, this could explain the low success of UV therapy.[42]

Malassezia yeasts are sensitive to azole-type, allylamine-type and hydroxypyridone-type antimycotics.[2] PV is primarily treated with topical preparations whereon it responds well. As endogenous factors of the patient such as hyperhidrosis are thought to be of great importance, recurrence is common (up to 60% in the first year and up to 80% in the second year, data referring to PV without differentiation between the hyper- and hypopigmented form).

Consequently, therapy of PV has to be divided into the treatment of the actual episode itself and prophylaxis of further (probable) relapses. Especially in cases of frequent recurrence as well as very extensive disease, oral therapy with ketoconazole, fluconazole or itraconazole can be performed.[2] Oral antimycotics of the allylamine-type are not effective.[62] Different schemes for oral therapy are available:

- Ketoconazole is given at a daily dose of 200 mg over 10 days or 400 mg/monthly.[63,64] As the drug is released with eccrine sweat it is important to inform the patient not to take showers. Itraconazole can be given as well. In an open study it was shown that treatment regimens with a single dose 400 are as effective as 200 mg/d for 7 days.[65] Comparing itraconazole with ketoconazole it has been shown that itraconazole either 200 mg/d for 1 week or 100 mg/d for 2 weeks is as effective as ketoconazole at a dose of 400 mg/week for 2 weeks.[66]
- Fluconazole can be given at a dose of 50 mg/d for 2 weeks or 200 mg as a single dose that can be repeated after 2 weeks.[67]
- Prophylaxis of the disease can be performed by oral application of azoles. Therapy with ketoconazole 400 mg once a

month or 200 mg at three successive days once a month, respectively, as well as itraconazole 400 mg one dose once a month for 6 months is recommended for patients suffering from frequent recurrence.[68,69]

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