Progressive macular hypomelanosis (PMH) treatable but often misdiagnosed
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PROPIONIBACTERIUM ACNES AND THE PATHOGENESIS OF PROGRESSIVE MACULAR HYPOMELANOSIS
ABSTRACT

Introduction: Progressive macular hypomelanosis is a common hypopigmentation mainly on the central parts of the trunk, predominantly in young adults, especially women. It is often mistaken for pityriasis versicolor and pityriasis alba. It occurs in all races and has been described in many parts of the world. We discovered follicular red fluorescence restricted to lesional skin. We suspected a relation with a porphyrin-producing bacteria residing in sebum of the pilosebaceous duct, and we therefore performed a study in 8 patients.

Results: In all biopsy specimens taken from lesional skin of 8 women, we could demonstrate gram-positive bacteria in the pilosebaceous duct, and a mild perifollicular lymphocytic infiltrate was seen. In all but 1 patient, *Propionibacterium acnes* was yielded from cultured biopsy specimens taken from follicular lesional skin. Healthy follicular skin did not show bacteria in histological sections, and cultures did not yield anaerobic bacteria.

Conclusions: There seems to be a relation between the presence of *P. acnes* and the hypopigmented macules. We propose that a factor is produced by these strains of *P. acnes*, which interfere with melanogenesis. Based on these observations, we are undertaking a clinical trial to find a treatment for this troubling, intractable disease.
INTRODUCTION

Progressive macular hypomelanosis (PMH) of the trunk is characterized by ill-defined nummular, hypopigmented, nonscaly macules on the front and back of the trunk, with confluence of the macules in and around the midline (Figure 1A,B). It occurs in young adults of both sexes, but primarily women. Progressive macular hypomelanosis of the trunk is described by Guillet et al. (1988, 1992), in people of mixed racial (white and black) ancestry originating from the French Caribbean. This entity was also described or at least recognized independently by several investigators from different parts of the world, using the following variety of descriptive terms: cutis trunci variata in Venezuela (Borelli 1987), Creole dyschromia in the French West Indies (Lesueur et al. 1994), idiopathic multiple large-macule hypomelanosis in the United States (Sober, Fitzpatrick, 1996), and nummular and confluent hypomelanosis of the trunk by our group in the Netherlands (Menke et al. 1989, 1997, 1998). From comparison of the clinical descriptions, it seems reasonable to assume that they all refer to the same pigmentary disorder.

The pathogenesis of PMH of the trunk is unknown, although several hypotheses have been offered. According to Guillet et al. (1988), this disorder is caused by a “melting” of genes of white and black parents. This view is based on the fact that the disorder

Figure 1A Progressive macular hypomelanosis in a male patient of skin type V, with a typical distribution of confluent hypopigmented macules on the back.

Figure 1B Progressive macular hypomelanosis in a female patient of skin type V with hypopigmented lesions on the abdomen.
is seen in people of mixed racial origin and furthermore on the ultrastructural finding of stage IV single melanosomes (in black skin) in healthy-looking skin and small stages I through III aggregated melanosomes (in white skin) in the hypopigmented spots. However, our observation that the disorder also occurs in people of other racial origin, including “pure” white patients, is an argument against this racial theory (Menke et al. 1997). Moreover, our own electron microscopic investigations do not confirm these findings (GN Relyveld, KP Dingemans, W Westerhof, unpublished data, May 2002). Borelli (1987) suggests that this is a genodermatosis, but hard facts in support of this idea are lacking in his article. A hereditary factor, as in many other disorders, might indeed play a role; additional research is needed to clarify this point. In a comment on a publication by Lesueur et al. (1994), Sober (1996) and FitzPatrick (1996) state that this disorder has been seen in African Americans in Boston, Massachusetts, as well as in the West Indies, and they think that it might be related to tinea versicolor. However, the causative organism of tinea versicolor, the yeast Malassezia furfur (also known as Pityrosporum orbiculare / ovale), was never identified by us (and others) in skin lesions of this disorder, and we have never seen a case of PMH of the trunk that evolved from a preceding tinea versicolor. We also could not relate it to atopy as in pityriasis alba or to contact dermatitis, psoriasis, or seborrheic eczema, which cause postinflammatory hypopigmentation. Other hypomelanoses due to microorganisms (eg, leprosy or pinta) were excluded (Menke et al. 1998).

We propose a new hypothesis on the pathogenesis of PMH of the trunk. We noticed that patients with PMH of the skin show pointed red fluorescence in a follicular fashion inside the hypopigmented spots, when observed under Wood’s light (Figure 2). The number of fluorescing follicles is generally higher on the lateral side of the

Figure 2 Red fluorescence in a follicular pattern, restricted to lesional skin.
trunk, where isolated nummular hypopigmented spots are present; here probably the hypopigmentation is slowly expanding. Usually the healthy pigmented skin of the trunk does not show any fluorescence. However, in the healthy-looking skin close to the rim of the hypopigmented macules, a follicular fluorescence can sometimes be seen. On meticulous inspection, a nearby, often small, probably incipient hypopigmented spot, only a few millimeters in diameter around that fluorescing follicle, can be seen. Based on these observations, we now hypothesize that there might be a relation between the red fluorescing follicles and the hypopigmented macules.

Dermatologists are familiar with the phenomenon of red follicular fluorescence, which is caused by the presence of Corynebacterium species or Propionibacterium acnes, producing porphyrins that are responsible for the fluorescence induced by UV radiation as under Wood’s light (Bommer 1927). We therefore investigated 8 patients for the presence of P. acnes in lesional skin.

**METHODS**

**Patients**

We included 8 patients with PMH in this study to investigate the possible relation between the red fluorescing follicles (P. acnes) and the hypopigmentation. All were women aged 18 to 38 years (mean age, 29 years). All 8 patients had ill-defined nummular, hypopigmented, nonscaly macules on the front and back of the trunk, with confluence of the macules in and around the midline. Participants were from different ethnic backgrounds. They originated from the Netherlands (skin type III), Turkey or Morocco (skin type IV), and Suriname (Hindustani or Creole people with skin type V) (Table I). They all gave their informed consent to this study.

**Histological investigation**

We obtained 2-mm biopsy specimens from the lesional follicular skin, healthy follicular skin, and inter-follicular lesional and healthy skin. Hematoxylin-eosin, gram, and periodic acid–Schiff staining were performed. A gram stain finding is one of the cornerstones for bacterial identification, but it also serves as a useful technique for rapid detection of microorganisms in clinical samples.
MICROBIOLOGICAL INVESTIGATION

Sampling and Culture Conditions

The skin was first disinfected with 70% alcohol, without other antibacterial agents, to eliminate superficial skin flora. After the skin dried, 2-mm biopsy specimens were obtained from lesional skin containing a fluorescent hair follicle and from nonlesional skin containing a nonfluorescent hair follicle.

We also obtained biopsy specimens from inter-follicular healthy and lesional skin. For microbiological culture, all biopsy specimens were cut transversally, and the dissected sides were immediately swapped on blood-culture agar plates (Colistin Nalidixic Agar; Becton, Dickinson and Company, Franklin Lakes, NJ) with thioglycolate-enriched broth. One half was cultured under aerobic conditions (5% carbon dioxide at 37°C), and the other half was cultured under anaerobic conditions (80% nitrogen/10% hydrogen/10% carbon dioxide) for 48 hours at 37°C.

Identification

Anaerobic colonies were subcultured under aerobic and anaerobic conditions for 48 hours. The anaerobic colonies underwent gram staining. The gram-positive rods were identified with a commercial identification kit (Rapid ID 32A; bioMérieux Vitek Inc, Lyon, France).

Propionibacterium acnes is a gram-positive, non–spore-forming, anaerobic bacteria. Bacteria were identified per morphologic colony type.

Table I Demographic Data on the Progressive Macular Hypomelanosis Patients in this Study

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Skin type</th>
<th>Sex</th>
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<th>Site of Lesions</th>
<th>Duration, y</th>
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</thead>
<tbody>
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<td>F</td>
<td>28</td>
<td>B, A, F</td>
<td>11</td>
</tr>
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<td>2</td>
<td>III</td>
<td>F</td>
<td>38</td>
<td>B, A</td>
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</tr>
<tr>
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<td>III</td>
<td>F</td>
<td>25</td>
<td>B, A</td>
<td>5</td>
</tr>
<tr>
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<td>III</td>
<td>F</td>
<td>37</td>
<td>A</td>
<td>4</td>
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<tr>
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<td>IV</td>
<td>F</td>
<td>31</td>
<td>B, UA</td>
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<td>V</td>
<td>F</td>
<td>27</td>
<td>A</td>
<td>Unknown</td>
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<td>V</td>
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<td>8</td>
<td>IV</td>
<td>F</td>
<td>28</td>
<td>B</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: A, Anterior side of the trunk; B, back of the trunk; F, face; UA, upper arms.
ANTIBIOTIC SENSITIVITY OF P. ACNES ISOLATES

An antimicrobial sensitivity test was performed with the disk diffusion method with agar plates supplemented with 5% sheep’s blood. The plates were incubated at 37°C for 24 to 48 hours under anaerobic conditions. The antimicrobial agents used in this study included penicillin, amoxicillin, amoxicillin-clavulanate combination, piperacillin-tazobactam combination, erythromycin, clindamycin, and metronidazole.

RESULTS

Histological findings

Histological examination of the hypopigmented lesions revealed only a decrease of melanin content in the epidermis compared with the adjacent healthy skin; there were no abnormalities in the dermis. There were no signs of eczema as in pityriasis alba, seborrheic eczema, or psoriasis. In the lesional skin of all patients, there was sometimes a mild perifolliculitis (Figure 3A). In the stratum corneum, no spores, hyphae, or bacteria were seen. In the specimens stained with periodic acid–Schiff, no spores or hyphae were found in middle portion of pilosebaceous duct; however, they contained a pure population of gram-positive bacteria (Figure 3B), which showed a rodlike structure with arborizing growth pattern that was consistent with features of P. acnes. The findings were also positive for periodic acid–Schiff reaction but not for acid-fast staining.

Figure 3A Hematoxylin-eosin staining of follicular lesional skin shows a mild perifollicular infiltrate of lymphocytes (original magnification x100). B Gram staining of a cross section of a pilosebaceous duct with a high population density of microorganisms, which on culture yield appear to be Propionibacterium acnes (original magnification x400).
Microbiological findings
The cultures from inter-follicular skin of lesional and healthy skin of patients with PMH were negative for *P. acnes*. In biopsy specimens from lesional follicular skin of all patients, *P. acnes* could be isolated except in patient no.7. The histological picture of the hair follicles in her lesional skin, however, demonstrated gram-positive bacteria typical of *P. acnes*. Patient no.8 showed a positive culture yield in clinically normal skin (Table II). This biopsy specimen was taken from a close distance to the lesional skin. No *P. acnes* was found in cultures of nonfollicular lesional and healthy skin.

*Propionibacterium acnes* isolates demonstrated high-level in vitro sensitivity to penicillin, amoxicillin, amoxicillin-clavulanate, piperacillin-tazobactam, erythromycin, and clindamycin and resistance to metronidazole (Table II).

**DISCUSSION**
We observed red fluorescence in a follicular pattern inside lesional skin of patients with PMH, which coincides with the presence of *P. acnes* yielded from cultures of lesional skin follicles. They could not be retrieved from healthy skin.

The phenomenon of red punctate fluorescence, using examination of facial skin under Wood’s light, was first described by Bommer in 1927. The foci of light correspond to porphyrin produced by *P. acnes*, which resides within the hair follicle unit. Using photographic methods, the fluorescence can be demonstrated on film (Burkhart 2001). McGinley *et al.* (1980) revealed that a density of 1000 *P. acnes*
organisms was required for follicular fluorescence to occur, and that the intensity was proportional to the numbers obtained by bacteriologic culture of *P. acnes.* *Propionibacterium acnes* is a major inhabitant of adult human skin, and high population densities are associated with skin sites possessing high numbers of sebum-excreting sebaceous follicles (McGinley *et al.* 1978). It is generally considered that this organism has a low virulence in humans. The population densities of these bacteria are low in children, who have low sebum excretion rates (Leyden *et al.* 1975). *Propionibacterium acnes* colonizes the infra-infundibular portion of follicles of sebaceous glands. Sebaceous follicles are most common in the acne-prone areas, such as the cheeks, nose, and forehead, and the midline of the chest and back (Toyoda and Morohashi 2001). This organism is not pathogenic by normal standards because in case of acne, there is minimal correlation between the number of bacteria and the severity and type of acne.

We did not notice acne lesions on the back, the chest, or the face in any of our patients. They also had no history of acne. Although for acne, Koch’s famous postulates for the definition of infection have not been met, and we believe in a specific role of *P. acnes* in the promotion of hypopigmentation in PMH. At the periphery of the confluent lesions, small, round hypopigmented macules arise. The fluorescent follicle is always at the center of the lesion, suggesting the diffusion of a hypopigmenting factor migrating from the follicular orifice.

It is possible that *P. acnes* produces a depigmenting agent or a factor that interferes with the melanogenesis in the skin, resulting in hypopigmented spots. The type of

<table>
<thead>
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<th>Patient</th>
<th>Lesional Skin</th>
<th>Nonlesional Skin</th>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Amoxicillin-Clavulanate</th>
<th>Piperacillin-Tazobactam</th>
<th>Erythromycin</th>
<th>Clindamycin</th>
<th>Metronidazole</th>
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Abbreviations: R, resistant; S, sensitive; - , negative; + , positive.
mechanism we now propose is not new in the biology of pigmentation disorders. In 1986, Nazzaro-Porro et al. (1986) suggested that the hypopigmentation in pityriasis versicolor is probably due to toxic lipoperoxides formed by the action of *Pityrosporon ovale* on the unsaturated lipids of the skin surface.

Previously, we investigated 50 patients with skin types III, IV, and V and the typical distribution of ill-defined nummular and confluent non-scaly hypopigmented lesions around the midline of the trunk. They were examined for follicular fluorescence in lesional and healthy skin and compared, for the presence of this fluorescence, with 10 patients with pityriasis versicolor and 5 patients with pityriasis alba (W Westerhof, HE Menke, unpublished data, 1999). To observe the red follicular fluorescence, a completely dark room is essential, with the use of a strong Wood’s lamp. The fluorescent tubes need to warm up, and the observer has to adapt to the dark environment for at least 3 minutes.

In all 50 patients with clinical signs of PMH, we saw red follicular fluorescence restricted to lesional skin. In the patients with pityriasis versicolor and pityriasis alba, no red fluorescence could be discerned in lesional and normal skin.

No effective treatment of PMH is available at present. Topical and systemic antifungal treatment and topical steroids are ineffective. We never observed spontaneous regression of the lesions; on the contrary, the disorder appeared to be stable or showed a slow progression over time in about 200 patients followed up by us for more than 10 years. With phototherapy or after extensive sun exposure, the white spots can disappear or become less apparent. However, a couple of weeks or months after cessation of this treatment, the induced repigmentation fades away and the hypopigmented spots reappear at exactly the same sites. We are presently undertaking a clinical trial to test a treatment regimen that is directed against the *P. acnes*, while stimulating melanogenesis (GN Relyveld, M Kingswijk, JB Reitsma, W Westerhof, unpublished data, starting in August 2002).