Propionibacterium acnes and the Pathogenesis of Progressive Macular Hypomelanosis

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Background: 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.

Observation: 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.

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sicolor, the yeast Malassezia furfur (also known as Pit-

yrosporum 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, pso-

riasis, or seborrheic eczema, which cause postinflamma-
tory hypopigmentation. Other hypomelanoses due to mi-
croorganisms (eg, leprosy or pinta) were excluded.8

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 ob-
served under Wood light (Figure 2). The number of fluo-
rescescing follicles is generally higher on the lateral side
of the 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 hy-
popigmented macules, a follicular fluorescence can some-
times be seen. On meticulous inspection, a nearby, of-
ten 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 pres-
ence of Corynebacterium species or Propionibacterium ac-

nes, producing porphyrins that are responsible for the fluo-
rescence induced by UV radiation as under Wood light.9
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 ac-

nes) and the hypopigmentation. All were women aged 18 to 38
years (mean age, 29 years). All 8 patients had ill-defined num-
mular, 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 Cre-
ole people with skin type V) (Table 1). They all gave their
informed consent to this study.

HISTOLOGICAL INVESTIGATION

We obtained 2-mm biopsy specimens from the lesional follicu-
lar skin, healthy follicular skin, and interfollicular 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 interfollicular 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 (Colestin Nalidixic Agar; Becton, Dickinson and Company, Franklin Lakes, NJ) with thioglycolate-enriched broth. One half was cultured under aerobic conditions (3% 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.

**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.

**MICROBIOLOGICAL FINDINGS**

The cultures from interfollicular skin of lesional and healthy skin of patients with PMH were negative for...
**COMMENT**

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 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. McGinley et al 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 sebaceous glands. The population densities of these bacteria are low in children, who have low sebum excretion rates. *Propionibacterium acnes* colonizes the infrainfundibular 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. 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.

*P. acnes*. In biopsy specimens from lesional follicular skin of all patients, *P. acnes* could be isolated except in patient 7. The histological picture of the hair follicles in her lesional skin, however, demonstrated gram-positive bacteria typical of *P. acnes*. Patient 8 showed a positive culture yield in clinically normal skin (Table 2). 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 2).

**Table 2. Culture of Biopsy Specimens for Propionibacterium acnes Sensitivity/Resistance**

<table>
<thead>
<tr>
<th>Patient No.</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>
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Abbreviations: R, resistant; S, sensitive; −, negative; +, positive.

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 mechanism we now propose is not new in the biology of pigmentary disorders. In 1986, Nazzaro-Porro et al 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 nonscaly 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.W., H.E.K., unpublished data, 1999). To observe the red follicular fluorescence, a completely dark room is essential, with the use of a strong Wood 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

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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 (G.N.R., M.M.K., J.B. Reitsma, MD, PhD, W.W., unpublished data, starting in August 2002).

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**REFERENCES**


