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Role of *Staphylococcus aureus* in the pathogenesis of folliculitis decalvans

Aleksandra Jedlecka[1], Małgorzata Grabarczyk[1], Kinga Kubicka-Szweda[1], Aleksandra Siegmund[1], Bartosz Miziołek[2, 3], Beata Bergler-Czop[2]

[1]*Students Research Club at the Department of Dermatology, Medical University of Silesia, School of Medicine in Katowice, Poland*
[2]*Department of Dermatology, Medical University of Silesia, School of Medicine in Katowice, Poland*
[3]*Department of Internal Medicine and Rheumatology, Leszek Giec Upper-Silesian Medical Centre of the Silesian Medical University in Katowice, Poland*

ABSTRACT

Folliculitis decalvans (FD) is an inflammatory cicatricial alopecia. Its aetiology remains unclear but an imbalance of skin microbiota seems to play a special role in the pathogenesis. The normal subepidermal microbiota resides in hair follicles and protects from opportunistic infections. Previously *Staphylococcus aureus* (*S. aureus*) was postulated to play the main role in the pathogenesis of the disease, but recent findings show it is rather opportunistic than a specific pathogen in FD. *Staphylococcus aureus* colonizing FD does not seem to be more virulent than one isolated from the general population, however, only a partial response to standard anti-staphylococcal antibiotic treatment suggests rather gram-negative aetiology. Antibiotic therapy may prove effective to reduce bacterial load below the threshold that triggers the immune system, but the microbiota found in FD after antibiotic treatment is not entirely restored to normal. Unbalanced microbiota with the reservoir of commensal and opportunistic bacteria in hair follicles may stoke unspecific responses of the immune system, therefore causing chronic inflammation.

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Key words: folliculitis decalvans, microbiota, *Staphylococcus aureus*

INTRODUCTION

Folliculitis decalvans (FD) is a rare inflammatory disease that affects the scalp and belongs to the group of scarring alopecia. The first description of the disease by Quinquaud [1] dates back to 1888. Its prevalence in the population and disease risk factors cannot be determined due to the deficiency of epidemiological studies. The disease mainly affects young male adults. It starts to develop from the occipital scalp (Fig. 1), but there is a gradual progression to the vertex and the temple [2]. Scalp biopsy reveals a dense perifollicular infiltration consisting mainly of neutrophils, later with an addition of lymphocytes. The inflammation may lead to irreversible destruction of the hair follicle with scarring, which produces small alopecic patches [3, 4].

The hypothesis of the microbiome in folliculitis decalvans

In 1963, Bogg [5] hypothesized that a skin microbiome and the presence of some specific organisms on the skin could contribute to FD. An imbalance of the bacterial biofilm in the follicular unit is believed to attract phagocytes that cause

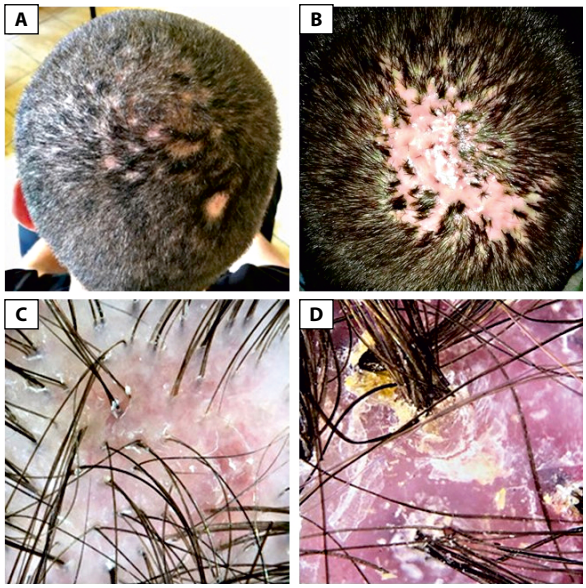

Figure 1. Clinical **(A, B)** and trichoscopy **(C, D)** pictures of folliculitis decalvans. The disease starts on the occipital scalp **(A)** but may progress involving the vertex **(B)**. Trichoscopy shows the initially merging of two neighbouring follicles, but later there are seen tufts of multiple hairs in one follicular unit

Address for correspondence:
Bartosz Miziołek, MD, PhD, Department of Dermatology, Medical University of Silesia, School of Medicine in Katowice, Poland, tel/fax. +48 32 259 1581, e-mail: bmiziolek@gmail.com

a loss of integrity of follicular walls [6]. A study by Uchiyama et al. [7] revealed the growth of *S. aureus* on the scalp in the majority of patients with FD, but only a partial response to standard anti-staphylococcal treatment rises a question about the composition and role of the microbiome in FD [8]. There are two hypotheses on the role of *S. aureus* in the pathogenesis of FD. The first says that FD is a chronic recurrent folliculitis caused by *S. aureus* [9]. The second indicates FD to be dermatitis with inflammation induced by an unknown factor, while *S. aureus* is only an opportunistic bacterium [10].

Staphylococcus aureus and folliculitis decalvans

Recently Matard et al. [10] compared epidermal and subepidermal bacterial flora in FD patients to healthy controls. Their results showed *S. aureus* to be a rather opportunistic bacterium than the main pathogen with a specific role in FD. *S. aureus* colonized non-lesional and subepidermal skin in 80% of cases. Anti-staphylococcal antibiotic treatment allowed *S. aureus* to disappear in all studied areas, but it was associated with incomplete restoration of normal epidermal and subepidermal microbiota. These data imply a break in the epidermal barrier integrity and suggest that an abnormal non-lesioned skin microbiota persists in FD. In every patient, the same staphylococcal strain and toxin profile was isolated from all sampled areas.

In 1979, Rogolsky [11] proposed FD to be caused by toxic substances produced by bacteria on the skin, and Marrack & Kapler [12] described these toxic substances as "superantigens" in 1990. The toxin profiles and antibiograms of *S. aureus* in the study of Matard et al. [10] were typical for those with no particular pathogenicity. One-third of patients with FD harboured *S. aureus* strains without superantigenic toxins. In every FD patient, the harboured *S. aureus* strain exhibits no particular pathogenicity or virulence factors. The normal subepidermal microbiota with a reservoir in hair follicles probably assures balance in the skin. The microbiota seen in FD after antibiotic treatment is not entirely restored to that of healthy control skin, but rather includes transient abnormal flora, suggesting the persistent defect in the epidermal barrier and no integrity of the skin layers. It may promote subepidermal invasion of *S. aureus* or other opportunistic bacteria. Antibiotic therapy may be effective to reduce the bacterial load below the threshold that triggers the innate immune system and its inflammatory response, although it fails to restore the normal composition due to the persistence of an unbalanced follicular microbiota. This unbalanced, abnormal microbiota, coupled with a "reservoir" effect of the subepidermal pathogenic flora may explain the indefinite chronicity of FD.

The study of Matard et al. [10] found, however, *Cutibacterium acnes* (*C. acnes*) to be the dominant component of both superficial and subepidermal microbiota in normal scalp.

Involvement of other bacteria

Previously, Matard et al. [13] examined plucked hairs from four patients by field emission scanning electron microscopy and confocal laser scanning microscopy. They were compared to three healthy controls. This pilot study showed the presence of bacterial biofilm in the infra infundibular part of human scalp hair follicles in both FD patients and healthy controls. A pathogenic shift in a commensal biofilm was proposed to induce the development of FD. Detected bacteria were very similar to those described as *C. acnes*. Interestingly, a great majority of antibiotics prescribed due to the assumed responsibility of *S. aureus* in FD remain active also against *C. acnes*. It might explain temporary improvements obtained with anti-staphylococcal antibiotics [14].

Pharmacotherapy in FD is based on long-term antibiotic therapy, aimed mainly at *S. aureus*, but sometimes combines several antibiotics from different groups [15]. The World Health Organization's (WHO) Global Antimicrobial Surveillance System in 2021 listed *S. aureus* among bacteria with ever-increasing antibiotic resistance which potentially may affect the effectiveness of antibiotics in the treatment of FD [16]. Clindamycin, rifampicin and tetracyclines and macrolides belong to the most commonly applied antibiotics in FD [15, 17]. Asfour et al. [18], in a retrospective data analysis, found *S. aureus* in FD patients to be significantly more resistant to macrolides and tetracyclines compared to the populational data reported by WHO. The long-lasting therapies using these groups of antibiotics in patients with FD predispose to the development of this bacterial resistance [14, 15].

An anti-staphylococcal treatment may, however, promote the growth of gram-negative strains on the scalp. Tietze et al. [19] investigated the change of bacterial flora in patients with FD receiving treatment with isotretinoin. Most of the cultures were positive for staphylococci, therefore the patients received targeted antibiotics. The cultures from lesioned skin were reinvestigated after anti-staphylococcal treatment and gram-negative strains comprised 21% of all cultures. They included *Klebsiella*, *Serratia* and *Citrobacter bacteria*. More than half of them were resistant to antibiotics: clindamycin, rifampicin and doxycycline [19]. Samrao & Mirmirani [20] performed a chart review of 34 patients with a known diagnosis of FD. The majority of cultures were positive for staphylococci, but gram-negative infections comprised 33% of all cultures: *Escherichia coli*, *Enterobacter aerogenes*, *Klebsiella pneumoniae*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Citrobacter koseri*

and *Serratia marcescens*. Overproduction of sweat and sebum creates a favourable environment for gram-negative rod infections. A long-term antibiotic treatment that suppresses commensal flora of skin may predispose to gram--negative folliculitis, therefore repeated bacterial cultures should be considered in patients with FD who lose response to the standard anti-staphylococcal antibiotic treatment.

CONCLUSION

The ubiquity of bacterial biofilms in the anaerobe part of the hair follicle of FD and healthy subjects suggests they are commensal biofilms with a possible pathogenic shift in FD. The scalp in patients with FD shows the same toxin profile of staphylococcal strains like the one in healthy people. *S. aureus* shows the typical toxin profiles and antibiograms with no particular pathogenicity. An overload of *S. aureus* is not necessary to activate the patient's immune system over the scalp. The microbiota seen in FD patients after anti-staphylococcal antibiotic treatment is not entirely restored to that of healthy control but rather include transient abnormal flora, suggesting the persistent defect in the epidermal and subepidermal barrier. The irreversibly damaged integrality of the skin layers in FD patients may explain the chronic character of FD. Probably, the balance of normal microbiota protects from opportunistic infections or the growth of abnormal flora. Dysfunction of the normal commensal bacterial flora, increased production of sebum and sweat and a modified innate immune system response are conducive to gram-negative infections which do not respond to standard antibiotic treatment.

Conflict of interest

The authors have no conflicts of interest to declare. This work has not been previously published and is not being considered by any other journal.

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