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GRAM-NEGATIVE FOLLICULITIS. A RARE PROBLEM OR IS IT UNDERDIAGNOSED? CASE REPORT AND LITERATURE REVIEW

GRAM-UJEMNE ZAPALENIE MIESZKÓW WŁOSOWYCH. RZADKI PROBLEM CZY RZADKO DIAGNOZOWANY? OPIS PRZYPADKU I PRZEGLĄD PIŚMIENNICTWA

Sierra-Téllez Daniela[1], Ponce-Olivera Rosa María[1], Tirado-Sánchez Andrés[1], Hernández Marco Antonio[2], Bonifaz Alexandro[2]

[1]*Dermatology Department, General Hospital of Mexico.*
[2]*Micology Section, Dermatology Department, General Hospital of Mexico.*
danaya_25@hotmail.com

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Abstract
Gram-negative folliculitis may be the result of prolonged antibacterial treatments in patients with acne and rosacea. It is caused by alteration of facial skin flora and the nasal mucous, a decrease of Gram-positive bacteria and a proliferation of Gram-negative bacteria (for example *Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens, Klebsiella* sp. and *Proteus mirabilis)*. It should be considered in patients with acne who have not had a clinical improvement after 3-6 months of treatment with tetracyclines. The disease is underestimated, probably because bacteriological studies are rarely requested and the increased use of oral isotretinoin for acne management. One of the most effective treatments for Gram-negative folliculitis is oral isotretinoin (0.5-1 mg / kg / day for 4-5 months). We report the case of Gram negative folliculitis successfully treated with oral isotretinoin.

Streszczenie
Gram-ujemne zapalenie mieszków włosowych może być wynikiem długotrwałego leczenia przeciwbakteryjnego u pacjentów z trądzikiem i trądzikiem różowatym. Jest to spowodowane zmianą flory bakteryjnej skóry twarzy i błony śluzowej nosa, zmniejszeniem ilości bakterii Gram-dodatnich i wzrost liczby bakterii Gram-ujemnych (na przykład Escherichia coli, Pseudomonas aeruginosa, Serratia marcescens, sp Klebsiella. i Proteus mirabilis). Należy rozważyć u pacjentów z trądzikiem, którzy nie mieli poprawy klinicznej po 3-6 miesiącach leczenia tetracyklinami. Częstotliwość tej choroby jest zaniżona, prawdopodobnie dlatego, że badania bakteriologiczne rzadko są wykonywane i istnieje zwiększone używanie doustnej izotretynoiny w leczeniu trądziku. Jednym z najbardziej skutecznych metod leczenia Gram-ujemnych zapaleń mieszków włosowych jest doustna izotretynoina (0,5-1 mg / kg mc. / dobę przez 4-5 miesięcy). Prezentujemy przypadek Gram-ujemnego zapalenia mieszków włosowych skutecznie leczonego doustną izotretynoiną.

Key words: folliculitis; Gram-negative; acne; isotretinoin
Słowa klucze: zapalenie mieszków włosowych; Gram-ujemne; trądzik; izotretynoina

Introduction

Gram-negative folliculitis (GNF) is a hair follicle infection by Gram-negative organisms that can occur as a complication in patients receiving prolonged treatment with broad spectrum antibiotics for the treatment of acne vulgaris and rosacea. It must be suspected in a sudden exacerbation of acne treatment or in patients non-responding to conventional acne treatments [1].

There are two clinical variants of GNF; type I, is the most common, about 80% of cases, with the presence of multiple papules and pustules in the middle of the face; the type II occurs in 20% of cases and is characterized by inflammatory nodules or cysts [1-4].

Oral isotretinoin is the treatment of choice at doses of 0.5 to 1mg/kg/day for 4-5 months [4]. Its mechanism of action is to control the proliferation of Gram-negative bacteria through microenvironmental changes produced in the skin and nasal mucous [5,6].

Case report

A 24-year old female came to our service with a skin disease that affects the perioral zone, characterized by multiple papules and pustules (Fig. 1A). Patient started one week before their assessment and with a

history of having received tetracycline hydrochloride for 2 months for mild to moderate acne, as well as topical clindamycin intermittently for six months.

The patient underwent clinical examination and laboratory test such as Gram stain (Fig. 1C) and culturing on McConkey agar (Fig. 1D). A treatment with oral isotretinoin was proposed with resolution of the skin disease within a 3 month treatment period (Fig. 1B).

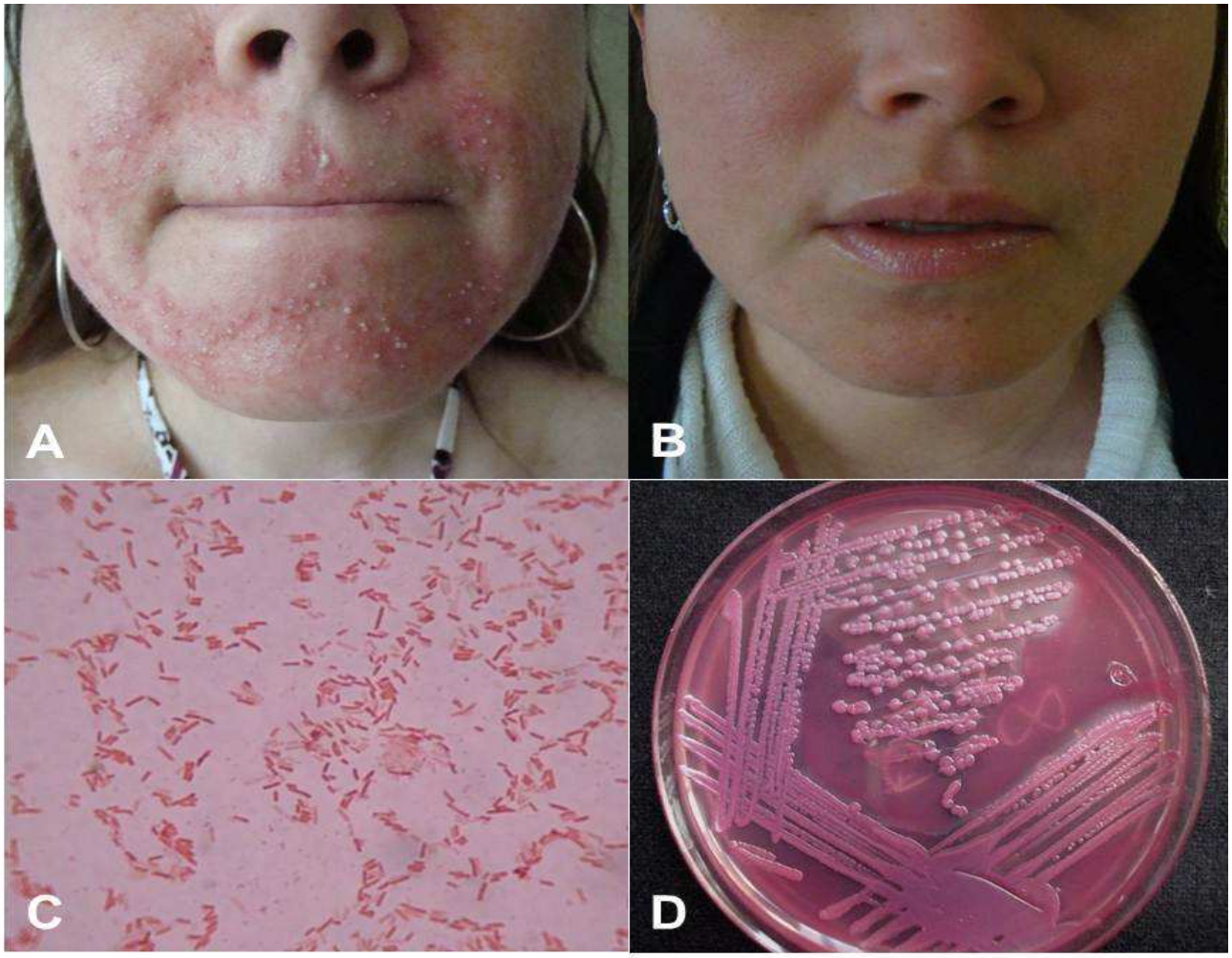

Figure 1. A. Perioral pustules. B. Post-treatment control. C. Gram-negative bacilli (x100). D. Lactose +, red-pink colonies (McConkey agar). *Escherichia Coli*

Discussion

Gram-negative folliculitis was first reported in 1968 by Fulton et al [1], in a group of patients with acne vulgaris resistant to conventional treatments [1-4]. It is a hair follicle infection that occurs mainly in patients with inflammatory acne or rosacea that have long treatments with broad spectrum antibiotics, mainly tetracycline [3-5]. It should be suspected when there is an increase in pustules with resistance to systemic treatment [4,6]. It is reported a prevalence of 4%. Prolonged treatment alters the normal bacterial flora of the nasal mucous and adjacent skin with reduced Gram-positive bacteria and coagulase positive aerobic diphtheroids, with an increase in Gram-negative bacilli mainly enteric bacteria [2-4].

Its characteristic features include: predominance in male gender, severe seborrhea, papules, pustules and perinasal and/or perioral involvement, recurrent folliculitis of the scalp, and prolonged antibacterial pretreatment, asymptomatic intervals tend to be shortened, acne and rosacea resistant to conventional treatment and isolation repeatedly of Gram-negative bacteria in cultures of pustules and facial nasal mucous [2-3].

Gram-negative folliculitis has been reported after eradication of recurrent staphylococcal pyodermas and prolonged treatment with topical antibacterials. Bartholow & Maibach [7], described a patient with acne who had been treated with topical clindamycin, followed by benzoyl peroxide and topical erythromycin and developed GNF due to *E. coli*. Fulton et al [1], described patients using antibacterial soaps, which selectively inhibit Gram-positive bacteria [8].

Leyden et al [9], clinically differentiated two types of GNF. The type I, superficial or pustular, is the most common (80-90%), with presence of multiple papules and pustules in the middle of the face, 3 to 6 mm in diameter with an erythematous halo, mainly caused by *E. coli, Klebsiella* sp., *Enterobacter* sp. and *P. aeruginosa.* The type II, deep or nodular (10-20%), is characterized by deep and painfully inflammatory nodules or cysts, on the face, neck and/or chest, caused by *Proteus mirabilis*.
Sebaceous follicles are colonized with these bacteria, mainly in the perioral and perinasal zone, with subsequent follicular and perifollicular inflammation with formation of papules and pustules [3,4,10,11].
Marples et al [12], confirmed an inverse ratio between nasal carriers of *S. aureus* and enterobacteria. The proportion of Gram-negative bacteria results in a 1% of the total flora under normal conditions. In the case of nasal carriers this ratio increases 3-4%, being nasal cavity the reservoir for facial cases of GNF [2,3].
The role of immune mechanisms of defense as a factor in the development of the GNF in patients with acne is not clear yet. Neubert et al [3], report that in addition to seborrhea and microflora changes induced by antibiotics, there are various mechanisms in the host immune defense, which appear to be an important factor in the GNF, induced by a depressed cell-mediated immunity, as evidenced by weak or absent response of hypersensitivity, which results in increased susceptibility to infections, showing a decrease of serum IgM, with a weak or absent response to enterobacterial antigens, similar events occur in patients with type V dysgammaglobulinemia (selective deficiency of IgM), which are liable to septicemia episodes by Gram-negative bacteria, and a deficiency in the complement system causing alterations in opsonization, chemotaxis and bacterial lysis. There is also evidence that chemotaxis of neutrophils may be inhibited by IgE-mediated histamine release, which is elevated in these patients.

It is well known that tetracyclines, the most commonly used systemic antibiotic in acne and rosacea, impair protein synthesis and function of lymphocytes and neutrophil chemotaxis, increasing the risk of bacterial infection [3,4].
The diagnosis should be confirmed with a smear of the pustules. The lesions (pustules) and the anterior nasal mucosa should be sampled for bacteriological studies. Treatment antibiotics must be withdrawn [4,10]. Oral isotretinoin is the treatment of choice [4-5,11,13]. Oral doses ranged from 0.5 to 1mg/kg/day for a period of 4-5 months, remission of the symptoms of facial and nasal colonization is achieved since the first three months of treatment [5]. The therapeutic success of isotretinoin in the GNF is due to decreased secretion of the sebaceous glands (thereby reducing the amount of sebum in more than 90%) and reduction of the follicular space size and anti-inflammatory effect, returning the environment uninhabitable for Gram-negative bacteria [5,8]. The most effective dose with a lower recurrence rate is 1mg/kg/day [4,11,13].
Systemic antibiotics such as cephalosporins combined with oral isotretinoin for 2 weeks are often useful on patients with frequent relapses [4]. Ampicillin and trimethoprim-sulfamethoxazole are reported with good results with remission of lesions in two weeks, with subsequent gradual reduction in dose. The clinical course determines the time of withdrawal, with remission rates ranged from 4 to 48 months [3] (Tab. I).
Finally, we concluded the gram-negative folliculitis is an underdiagnosed disease, probably because the increased use of oral isotretinoin for acne management. We must suspected it when there is an exacerbation of centrofacial papules, pustules and/or nodules and cyst in patients with inflammatory acne or rosacea that have long treatments with broad spectrum antibiotics, non-responding to conventional treatments. We must request the bacteriological studies before initiating the oral isotretinoin.

Literature Reference	**Patients**	**Clinical Status**	**Agent**	**Treatment**
Neubert et al [10]	n= 46	Centrofacial folliculitis combined with open and/or closed comedon.	*Klebsiella* spp., *Escherichia coli*, *Enterobacter* spp., and *Proteus* spp.	Isotretinoin, mean duration 18.6 weeks, mean total dosage 109 mg/kg.
James et al [5]	n=21	Patients with nodulocystic acne with several facial pustules resistant to all therapies.	*Escherichia aerogenes.*	Isotretinoin 0.48-0.74 mg/kg/day for 20 weeks.

	n=11	Patients with nodulo-cystic acne with several facial pustules resistant to all therapies.	*Escherichia aerogenes, Proteus mirabilis, Klebsiella pneumoniae, E. coli* and *S. marcescens.*	Isotretinoin 1mg/kg/day for 5 months.
Leyden et al [9]	n=35	Folicular pustules grouped around the nose.	Lactose fermenting Gram-negative rods often *Klebsiella, Enterobacter*.	Ampicillin 1gr/day for 7-14 days, lowered to a maintenance level 250mg twice daily.
	n=15	Deep, nodular and cystic lesions.	*Proteus.*	Ampicillin 1gr/day for 7-14 days, lowered to a maintenance level 250mg twice daily.
Eady et al [13]	n= 8	Non-responding acne patients.	Gram-negative rods.	Trimethoprim or co-trimoxazole.
Presented Case	n=1	Perioral pustules with acne resistant to all therapies.	*Escherichia coli.*	Isotretinoin, 0.3mg/kg/day for 10 months.

Table 1. Summary of Gram-negative Folliculitis. Case Reports

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Hernández Marco Antonio, Bonifaz Alexandro

Professor Antonio Chuh

I congratulate the authors for having documented an unusually severe case of Gram-negative folliculitis (GNF) necessitating systemic retinoid therapy. Marked clinical remission was seen at three months. I wonder whether there was a clinical relapse in the few months after cessation of systemic retinoids.

The epidemiology, pathophysiology, symptomatology, and management of GNF were well reviewed by the authors. I entirely agree with them that this condition is under-diagnosed and under-treated. The incidence is unknown as we lack the denominator to start with.

For patients with flares of acne vulgaris or rosacea, GNF should be considered. I have been seeing patients with perioral and periorbital dermatitis exacerbated by GNF. A descriptive study for GNF for this group of patients would be highly worthwhile.

In patients with nodulocystic acne, open- and closed-comedones could be mistaken for GNF. For these patients, we have found that digital epiluminescence dermatoscopy can be of much diagnostic assistance. We hope to document such images when we see further patients with GNF captured digitally to be submitted as case reports.

Antonio Chuh
Adjunct Associate Professor
School of Public Health
The Chinese University of Hong Kong

Professor Mehmet Doganay

Folliculitis is a typical pyoderma located within hair follicles and apocrine regions. Hair follicles can become inflamed by physical injury, chemical irritant or infection that leads to folliculitis. The lesions are characterized with a small, erythematous and sometimes pruritic papules by central pustule and fine surrounding collar of desquamation. It may be deep seated or superficial. The most common form is superficial folliculitis that manifest as a tender or painless pustule that heals without scarring. The lesion may be appearing as single or multiple on the skin bearing hair including the head, neck, trunk, buttocks and extremities. Fever or associated systemic symptoms rarely exist. Folliculitis sometimes can progress to form subcutaneous abscess (furuncles) or carbuncle (1,2).

Staphylococcus aureus is the usual cause of folliculitis. Gram-negative bacteria and fungi are less frequently responsible from folliculitis. Among gram-negative bacteria, *Klebsiella spp. Escherichia coli, Enterobacter spp. , Proteus spp* and *Pseudomonas spp*. are more frequently isolated (2,3). The face is generally involve in gram-negative folliculitis and the majority of patients have a history of long-term antibiotic therapy for acne. It can be treated with isotretinoin, but it should not be forgotten of the side effect, including birth defect (2).

In this issue of Our Dermatology Online Journal, Sierra-Téllez Daniela and et al (4) reported a case with *E. coli* folliculitis on the face The history of patient , clinical features and etiologic agent are well described in this case report. The patient's lesion picture and demonstration of etiological agent in microscopy and on bacteriologic media are very educative materials for young physicians. The patient had also received tetracycline hydrochloride for 2 months for mild to moderate acne, as well as topical clindamycin intermittently for six months. The data for the combination with topical treatments (topical benzoyl peroxide or retinoids) suggest synergistic effects. In this case the combined use of topical and systemic antibiotics is not suitable for acne treatment. A healing was obtained in this case with the therapy of oral isotretinoin.

This paper shows that in a resistant to conventional therapy in cases with acne, some rare etiological agents should be considered.

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Mehmet Doganay, M.D.
Professor in Infectious Diseases
Department of Infectious Diseases,
Faculty of Medicine,Erciyes University,
38039- Kayseri / Turkey
Email. mdoganay@erciyes.edu.tr