CASE REPORTS

Sporotrichoid Cutaneous Infection by Mycobacterium Haemophilum in an AIDS Patient

D Cameselle,^a J Hernández,^a A Francès,^b T Montenegro,^c F Cañas,^d and L Borrego^a

^aServicio de Dermatología, ^bUnidad de Enfermedades Infecciosas y Medicina Tropical, ^cServicio de Anatomía Patológica, and ^dServicio de Microbiología, Hospital Universitario Insular, Las Palmas de Gran Canaria, Spain.

Abstract. We report a case of primary cutaneous infection by *Mycobacterium haemophilum* after the bite of an aquarium fish in a severely immunodepressed AIDS patient. Clinical features consisted in nodular and ulcerative lesions that followed a sporotrichoid pattern. Histological study of nodular lesions showed a granulomatous dermatitis with numerous acid-fast bacilli. The mycobacterium was identified 3 months later by genetic hybridization from a cultive in solid medium. Combined therapy with isoniazid, rifampin, clarithromycin, ethambutol, amikacin and ciprofloxacin resulted in complete resolution of the lesions. Infection by *Mycobacterium haemophilum* is a rare mycobacteriosis that usually affects immunodepressed patients. The most common clinical manifestations are cutaneous lesions but the development of sporotrichoid nodular lymphangitis is exceptional.

Key words: Mycobacterium haemophilum, immunosuppression, sporotrichoid, HIV, AIDS.

INFECCIÓN CUTÁNEA ESPOROTRICOIDE POR *MYCOBACTERIUM HAEMOPHIL*UM EN UN PACIENTE CON SIDA

Resumen. Presentamos un caso de infección primaria cutánea por *Mycobacterium haemophilum* tras la mordedura de un pez de acuario en un paciente con sida, gravemente inmunodeprimido. Las manifestaciones cutáneas consistieron en lesiones nodulares y ulcerativas que seguían un trayecto esporotricoide. El estudio histológico de las lesiones nodulares mostró una dermatitis granulomatosa con numerosos bacilos ácido-alcohol resistentes. La micobacteria se identificó tres meses después mediante hibridación genética a partir de un cultivo en medio sólido. Se instauró terapia combinada con isoniazida, rifampicina, claritromicina, etambutol, amikacina y ciprofloxacino con curación de las lesiones. La infección por *Mycobacterium haemophilum* es una micobacteriosis poco frecuente que aparece habitualmente en el paciente inmunodeprimido. Las lesiones cutáneas son las manifestaciones clínicas más frecuentes, pero en forma de linfangitis nodular esporotricoide es excepcional.

Palabras clave: Mycobacterium haemophilum, inmunodepresión, esporotricoide, VIH, sida.

Introduction

Mycobacterium haemophilum infection is a rare mycobacteriosis that occurs in immunosuppressed adults. It is caused by a slow-growing nontuberculous mycobacterium, which is acquired through environmental exposure, although its natural habitat, mode of transmission, and incubation period are unknown. The most common

Correspondence:

Daniel Cameselle Martínez. Servicio de Dermatología. Hospital Universitario Insular de Gran Canaria. Avda. Marítima del Sur, s/n. 35016 Las Palmas de Gran Canaria. Spain dani.camel@hotmail.com

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clinical presentations are skin lesions, although lung and joint infections have also been described.^{1,2} The difficulty in isolating the bacterium in standard culture media often delays diagnosis and initiation of appropriate treatment. The nutritional requirements of the bacterium also make it extremely difficult to perform susceptibility studies.

Case Description

We present the case of a 37-year-old man with known human immunodeficiency virus (HIV)-positive status for the past 12 years, poor compliance with antiretroviral therapy, no check-up visits in the past year, and several previous admissions due to opportunistic HIV-associated infections. He was admitted to our hospital with ascending



Figure 1. Sporotrihcoid nodules on left arm.



Figure 2. Ulcerative nodules on left arm.

lymphangitis in the upper right arm that had started 2 weeks earlier and had been followed by a chain of painful, inflammatory nodular lesions that appeared along the lymphatic path and that had became ulcerative and suppurative. The patient had an aquarium and reported having been bitten by a tropical fish (blue African cichlid from Lake Tanganyika) on the left index finger 2 months earlier. He reported pain in the left knee and spread of the skin lesions to the right limbs 5 days prior to admission; he had no fever or malaise.

Clinical examination revealed several subcutaneous erythematous nodules that moved when touched; there were visible sporotrichoid lesions at the bite site and along the extensor surface and inner side of the left arm (Figure 1); some of the lesions had ulcerated and were seeping purulent exudate (Figure 2). There were similar isolated skin lesions on the right arm and on both legs, and signs of arthritis in the left knee.

The tests performed on admission revealed a CD4+ count of 26 cells/µL, a viral load of 740 000 copies/mL, and unremarkable chest radiograph findings. The joint fluid obtained by arthrocentesis showed inflammatory characteristics. Both the sputum smear and culture were negative and the radiograph of the left knee was normal. Blood cultures were also negative. The histologic study of 2 nodular lesions revealed an epidermis with acanthosis, inflammation, and a nonspecific superficial and deep dermal granulomatous reaction, characterized by poorly differentiated nonsuppurative granulomas and epithelial lymphocytes and histiocytes without giant cells (Figures 3 and 4). The microbiological cultures of the skin specimens were negative and numerous acid-fast bacteria were observed in both specimens (Figure 5). Polymerase chain reaction results were negative for Mycobacterium tuberculosis.

Broad-spectrum empirical therapy with isoniazid, rifampicin, ethambutol, amikacin, clarithromycin, and

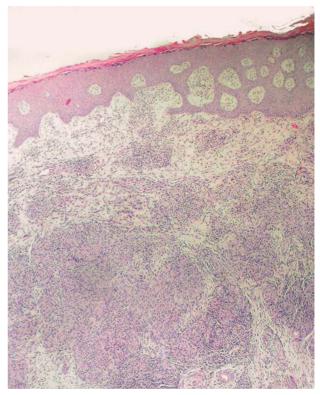


Figure 3. Inflammation and granulomatous reaction under a hyperplastic epidermis. Hematoxylin–eosin, original magnification ×400.

ciprofloxacin was administered during the first days of hospitalization; antiretroviral treatment, with tenofovir, lamivudine, and efavirenz, was reinstated and administered simultaneously, although it had to be interrupted after 8 days as the patient developed a severe skin rash as a reaction to efavirenz. Although the patient showed initial clinical improvement, he developed a paradoxical inflammatory reaction on the hands in the third week of therapy,

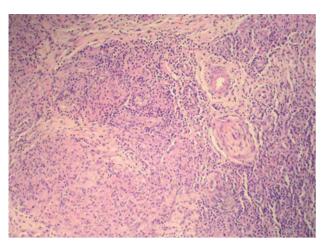


Figure 4. Granulomas without necrosis, formed by epithelial lymphocytes and histiocytes. Hematoxylin–eosin, original magnification ×100.

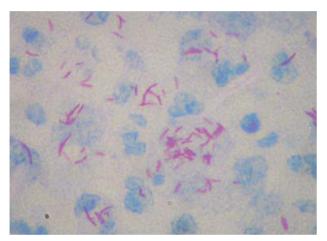


Figure 5. Acid-fast bacteria.

accompanied by fever and malaise. The antibiotics were maintained and the patient improved following the administration of short-acting corticosteroids, which brought the condition into remission. Three months later, an atypical mycobacterium was detected in an iron-replete culture medium; it was identified as *M haemophilum* by amplification of specific DNA sequences (GenoType Mycobacterium CM/AS 12). Tests performed on the strain showed it to be resistant to first-line antituberculous drugs (isoniazid, rifampicin, ethambutol, and amikacin) and susceptible to ciprofloxacin, clarithromycin, cotrimoxazole, and tetracyclines.

Five months after admission to hospital, the patient continued to receive triple antibiotic therapy with ofloxacin, clarithromycin, and minocycline; tolerance was good and the skin lesions resolved gradually.

The patient stopped coming for check-up visits when he returned to his native Germany.

Discussion

There has been growing interest in infections caused by atypical mycobacteria, including *M haemophilum*, in recent years due largely to the HIV pandemia and the increasing number of patients receiving immunosuppressive therapy.

Mhaemophilum is a slow-growing, aerobic, nonchromogenic acid-fast bacterium that was first discovered in 1978 by Sompolinsky et al^{3,4} in a 51-year-old Israeli woman with Hodgkin disease and generalized skin ulcers. The authors reported that the bacterium had a low incubation temperature, similar to that of Mycobacterium marinum and Mycobacterium ulcerans, and that culture media had to be enriched with iron to promote growth, distinguishing it from other atypical mycobacteria. Since then, fewer than 150 cases of infection due to M haemophilum have been described in the medical literature.^{1,5-7} It typically presents as a superficial infection in immunosuppressed adults and can lead to potentially serious systemic infections. The most common clinical manifestations are a broad spectrum of skin lesions ranging from localized disease to systemic disease with cutaneous dissemination.8 Skin lesions tend to be multiple and can present as erythematous papules, plaques, nodules, necrotic abscesses, or chronic ulcers. They generally affect the limbs, and joints in particular, although sporotrichoid spread is not characteristic of M haemophilum infection.^{1,2} Purpuric and annular lesions have also been described.9 Skin lesions typically evolve from papules to asymptomatic pustules, and eventually very painful deep-seated ulcers. Less common clinical presentations include bacteremia, pneumonia, lymphangitis, arthritis, tenosynovitis, and osteomyelitis.¹⁰ Patients with cutaneous and articular manifestations have a more favorable prognosis than those with pulmonary involvement.²

Histologically, there are no differences between infections caused by M haemophilum and those caused by other atypical mycobacteria.¹¹ Microscopic examination of skin lesions reveals deep granulomatous dermatitis, with or without caseating necrosis; the granulomas are often poorly differentiated and frequently affect the panniculus adiposus in patients with AIDS. The histopathological pattern is strongly influenced by the time since onset, particularly in immunosuppressed patients. Early lesions include an inflammatory infiltrate that is composed mostly of neutrophils or a mixture of neutrophils with granulocytes, lymphocytes, monocytes, and occasionally, multinucleated giant cells and foamy macrophages. Subsequent lesions are characterized by a granulomatous inflammatory reaction. Acid-fast bacteria are often detected in immunosuppressed patients using specific staining techniques.¹²

Microbiological diagnosis is difficult. Generally speaking, biopsies have a greater diagnostic yield than cotton swabs or pads. Under direction examination, *M haemophilum* turns red following Ziehl–Neelsen staining. Although this technique detects the presence of acid-fast bacteria, it does not distinguish between different species, meaning that a culture is always necessary.⁵ The nutritional requirements for culture of *M* haemophilum distinguish it from other atypical bacteria. Unlike its homologues, M haemophilum grows specifically in a standard mycobacterial culture medium (solid or liquid) that has been enriched with iron.^{1,2,13,14} An excellent low-cost alternative is the use of a culture with fresh, hemolyzed blood.¹⁵ M haemophilum requires a lower temperature (between 30°C and 32°C) and a longer incubation period than other atypical mycobacteria to achieve optimal growth. The bacterium is probably not detected as often as it should be because of its growth requirements and the fact that successful isolation depends greatly on the method used.^{2,16} Bacteria grown in culture are identified on the basis of standard biochemical tests, growth characteristics, the chromatographic analysis of membrane lipids, and in more recent years, molecular genetic studies of mycobacterial DNA. An increasing number of mycobacterial species are being identified thanks to this new technique, and recent advances in the field have provided essential information on the clinical spectrum of the diseases they cause. They have also paved the way for the detection of bacteria in biological samples or in solid or liquid media using methods such as polymerase chain reaction.^{5,15,17}

Since the first case of infection due to *M haemophilum* was published in 1978,^{3,4} there have been reports of skin lesions caused by this bacterium in patients who have undergone kidney transplants,^{1,18-21} bone marrow transplants,^{2,22,23} heart transplants,²⁴⁻²⁶ as well as in patients with lymphoma,^{2,18,27} rheumatoid arthritis,²⁸ and Crohn disease.¹

The first report of an infection due to M haemophilum in a patient with AIDS was published in 1987, when Males et al²⁹ reported isolating the bacterium from the joint fluid of a 32-year-old man with septic arthritis and skin lesions. An additional 2 cases involving disseminated cutaneous infection in patients with AIDS were published a year later.⁶ By 2001, 90 cases of *M* haemophilum infection had been reported worldwide. The majority of the patients had developed skin and soft tissue manifestations²; 72 were adults and they al were all immunosuppressed due to AIDS or immunosuppressive therapy received prior to organ transplantation.^{2,21,23,29-31} Nonetheless, several cases of cervicofacial lymphadenitis due to M haemophilum have been reported in immunocompetent children,^{1,1,3,32-34} with a clinical picture similar to that produced by other mycobacteria (Mycobacterium avium complex, M tuberculosis, and Mycobacterium scrofulaceum). There have also been anecdotal reports of infection in otherwise healthy adults with skin lesions.⁷

Because relatively few cases of the disease are seen and the bacterium is difficult to isolate in the laboratory, the true epidemiological impact of *M haemophilum* infection is unknown.^{1,31}

The environment is probably the reservoir of infection, as is the case with other atypical mycobacteria, but little is known about the natural habitat of the bacterium or the mechanism by which it infects humans. One recent study reported a series of cases in cities near large expanses of water (lakes and oceans) although it has not been possible to isolate the bacterium from aquatic environments.³ Nosocomial human-to-human transmission was also suggested as a possible cause of infection following an outbreak of cases in several hospitals in the metropolitan areas of New York between 1989 and 1991. The only epidemiological link detected between the patients, however, was that they were all immunosuppressed.^{1,22,23,31,35} Of the few series that have been published to date, none has been able to establish a link between a specific exposure scenario and transmission.^{1,2,30,31}

M haemophilum has a very different antimicrobial susceptibility pattern to that of other atypical mycobacteria. The studies published to date have all used different susceptibility analysis methods^{13,22,29,30,33,36} and there are no established antibiotic protocols for treating infected immunosuppressed patients. *M haemophilum* is resistant to first-line antituberculous drugs (isoniazid pyrazinamide and ethambutol) and has a susceptibility of just 56% to rifampicin.¹⁰

The bacterium is, however, susceptible to other antibiotics such as ciprofloxacin, clarithromycin, and rifabutin, all of which are drugs used to treat infections caused by other atypical mycobacteria.^{1,2,30,31} It occasionally shows susceptibility to tetracyclines and cotrimoxazole.¹ In a series published by Bernard et al³⁶ involving 17 isolates from 12 immunosuppressed patients, the most effective antibiotics against *M haemophilum* were rifamycins, macrolides, quinolones, clofazimine, and amikacin. The authors also noted that 2 patients with progressive or recurrent disease developed resistance to rifamycins during treatment. There have been occasional reports of a lack of correlation between in vitro susceptibility and clinical response to treatment.³⁷

Although there are no standard protocols for susceptibility studies designed to determine minimum inhibitory concentrations of antimicrobial agents against *M* haemophilum, clinical experience indicates that antibiotic therapy in association with clarithromycin, ciprofloxacin, and rifampicin or rifabutin is a reasonably adequate empirical treatment option.^{2,28} In patients with more serious disease, including lung disease, the addition of amikacin, possibly in combination with doxycycline or minocycline, is recommended.² Clinical response to treatment is varied, even when the above antibiotics are used. Prolonged maintenance therapy lasting months or even years with several drugs is generally necessary, particularly in patients with sustained immunosuppression.¹⁰

Given that M haemophilum is not normally pathogenic in immunocompetent individuals, the most efficient treatment in some cases seems to be reconstitution of the immune system in hosts with potentially reversible immunosuppression.³⁸

We have presented a case of sporotrichoid cutaneous infection due to *M haemophilum* in an immunosuppressed patient.

In our review of the literature we found no reports of sporotrichoid nodular lymphangitis secondary to *M* haemophilum. While it is true that this clinical form is well documented for a number of infections caused by other atypical bacteria such as *M* marinum,³⁹ Mycobacterium chelonae,⁴⁰ and Mycobacterium kansasii,⁴¹ to the best of our knowledge, this is the first time that it has been described for *M* haemophilum.

Conflicts of Interest

The authors declare no conflicts of interest.

References

- 1. Saubolle MA, Kiehn TE, White MH, Rudinsky MF, Armstrong D. Mycobacterium haemophilum: microbiology and expanding clinical and geographic spectra of disease in humans. Clin Microbiol Rev. 1996;9:435-47.
- Shah MK, Sebti A, Kiehn TE, Massarella SA, Sepkowitz KA. Mycobacterium haemophilum in immunocompromised patients. Clin Infect Dis. 2001;33:330-7.
- Sompolinsky D, Lagziel A, Naveh D, Yankilevitz T. Mycobacterium haemophilum sp. nov., a new pathogen of humans. Int J Syst Bacteriol. 1978;28:67-75.
- 4. Sompolinsky D, Lagziel A, Rosenberg I. Further studies of a new pathogenic mycobacterium (M. haemophilum sp. nov.). Can J Microbiol. 1979;25:217-26.
- 5. Valdés F, Cid A. Micobacterias atípicas (review). Actas Dermosifiliogr. 2004;95:331-57.
- Rogers PL, Walker RE, Lane HC, Witebsky FG, Kovacs JA, Parrillo JE, et al. Disseminated Mycobacterium haemophilum infection in two patients with the acquired immunodeficiency syndrome. Am J Med. 1988;84:640-2.
- Smith S, Taylor GD, Fanning EA. Chronic cutaneous Mycobacterium haemophilum infection acquired from coral injury. Clin Infect Dis 2003;37:e100-1.
- Geisler WM, Harrington RD, Wallis CK, Harnisch JP, Liles WC. Broad spectrum of dermatologic manifestations caused by Mycobacterium haemophilum infection. Arch Dermatol. 2002;138:229-30.
- 9. Friedli A, Krischer J, Hirschel B, Saurat JH, Pechere M. An annular plaque due to Mycobacterium haemophilum infection in a patient with AIDS. J Am Acad Dermatol. 2000;43:913-5.
- Lefkowitz RA, Singson RD. Considering Mycobacterium haemophilum in the differential diagnosis for lytic bone lesions in AIDS patients who present with ulcerating skin lesions. Skeletal Radiol. 1998;27:334-6.
- 11. Bartralot R, Pujol RM, García-Patos V, Sitjas D, Martín-Casabona N, Coll P, et al. Cutaneous infections due to nontuberculous mycobacteria: histopathological review of 28

cases. Comparative study between lesions observed in immunosuppressed patients and normal hosts. J Cutan Pathol. 2000;27:124-9.

- Von Stebut E, Wiest K, Braeuninger W. Chronic infiltrates and persisting ulcerations on the arms and legs. Arch Dermatol. 2005;141:897-902.
- McBride ME, Rudolph AH, Tschen JA, Cernoch P, Davis J, Brown BA, et al. Diagnostic and therapeutic considerations for cutaneous Mycobacterium haemophilum infections. Arch Dermatol. 1991;127:276-7.
- Vadney FS, Hawkins JE. Evaluation of a simple method for growing Mycobacterium haemophilum. J Clin Microbiol. 1985;22:884-5.
- Bruijnesteijn van Coppenraet LE, Kuijper EJ, Lindeboom JA, Prins JM, Claas EC. Mycobacterium haemophilum and lymphadenitis in children. Emerg Infect Dis 2005;11:62-8.
- Martín-Casabona N, Rosselló-Urgell J. Micobacterias ambientales en España: aislamientos en el periodo 1976-1996. Med Clin (Barc). 2000;115:663-70.
- Tortoli E, Nanetti A, Piersimoni C, Cichero P, Farina C, Mucignat G, et al. Performance assessment of new multiplex probe assay for identification of mycobacteria. J Clin Microbiol. 2001;39:1079-84.
- 18. Dawson DJ, Jennis F. Mycobacteria with a growth requirement for ferric ammonium citrate, identified as Mycobacterium haemophilum. J Clin Microbiol. 1980;11:190-2.
- Davis BR, Brumbach J, Sanders WJ, Wolinsky E. Skin lesions caused by Mycobacterium haemophilum. Ann Intern Med. 1982;97:723-4.
- 20. Ryan CG, Dwyer BW. New characteristics of Mycobacterium haemophilum. J Clin Microbiol. 1983;18:976-7.
- Branger B, Gouby A, Oules R, Balducchi JP, Mourard G, Fourcade J, et al. Mycobacterium haemophilum and Mycobacterium xenopi associated infection in a renal transplant patient. Clin Nephrol. 1985;23:46-9.
- 22. Kiehn TE, White M, Pursell KJ, Boone N, Tsivitis M, Brown AE, et al. A cluster of four cases of Mycobacterium haemophilum infection. Eur J Clin Microbiol Infect Dis. 1993; 12:114-8.
- White MH, Papadopoulos E, Small TN, Kiehn TE, Armstrong D. Mycobacterium haemophilum infections in bone marrow transplant recipients. Transplantation. 1995;60: 957-60.
- 24. Cooper DK, Lanza RP, Oliver S, Forder AA, Rose AG, Uys CJ, et al. Infectious complications after heart transplantation. Thorax. 1983;38:822-8.
- Lederman C, Spitz JL, Scully B, Schulman LL, Della-Latta P, Weitzman I, et al. Mycobacterium haemophilum cellulitis in a heart transplant recipient. J Am Acad Dermatol. 1994;30: 804-5.
- Fairhurst RM, Kubak BM, Pegues DA, Moriguchi JD, Han KF, Haley JC, et al. Mycobacterium haemophilum infections in heart transplant recipients: case report and review of the literature. Am J Transplant. 2002;2:476-9.
- Artenstein AW, Fritzinger D, Gasser RA Jr, Skillman LP, McEvoy PL, Hadfield TL. Infection due to Mycobacterium haemophilum identified by whole cell lipid analysis and nucleic acid sequencing. Clin Infect Dis. 1994;19:1155-7.
- Darling TN, Sidhu-Malik N, Corey GR, Allen NB, Kamino H, Murray JC. Treatment of Mycobacterium haemophilum infection with an antibiotic regimen including clarithromycin. Br J Dermatol. 1994;131:376-9.

- 29. Males BM, West TE, Bartholomew WR. Mycobacterium haemophilum infection in a patient with acquired immune deficiency syndrome. J Clin Microbiol. 1987;25:186-90.
- Dever LL, Martin JW, Seaworth B, Jorgensen JH. Varied presentations and responses to treatment of infections caused by Mycobacterium haemophilum in patients with AIDS. Clin Infect Dis. 1992;14:1195-200.
- Straus WL, Ostroff SM, Jernigan DB, Kiehn TE, Sordillo EM, Armstrong D, et al. Clinical and epidemiologic characteristics of Mycobacterium haemophilum, an emerging pathogen in immunocompromised patients. Ann Intern Med. 1994;120:118-25.
- 32. Dawson DJ, Blacklock ZM, Kane DW. Mycobacterium haemophilum causing lymphadenitis in an otherwise healthy child. Med J Aust. 1981;2:289-90.
- Thibert L, Lebel F, Martineau B. Two cases of Mycobacterium haemophilum infection in Canada. J Clin Microbiol. 1990;28:621-3.
- Armstrong KL, James RW, Dawson DJ, Francis PW, Masters B. Mycobacterium haemophilum causing perihilar or cervical lymphadenitis in healthy children. J Pediatr. 1992;121:202-5.
- Centers for Disease Control (CDC). Mycobacterium haemophilum infections-New York City metropolitan area, 1990-1991. MMWR Morb Mortal Wkly Rep. 1991;40: 636-7.

- Bernard EM, Edwards FF, Kiehn TE, Brown ST, Armstrong D. Activities of antimicrobial agents against clinical isolates of Mycobacterium haemophilum. Antimicrob Agents Chemother. 1993;37:2323-6.
- Soubani AO, al-Marri M, Forlenza S. Successful treatment of disseminated Mycobacterium haemophilum infection in a patient with AIDS. Clin Infect Dis. 1994;18:475-6.
- 38. Paech V, Lorenzen T, von Krosigk A, von Stemm A, Meigel WM, Stoehr A, et al. Remission of cutaneous Mycobacterium haemophilum infection as a result of antiretroviral therapy in a human immunodeficiency virus-infected patient. Clin Infect Dis. 2002;34:1017-9.
- Hanau LH, Leaf A, Soeiro R, Weiss LM, Pollack SS. Mycobacterium marinum infection in a patient with the acquired immunodeficiency syndrome. Cutis. 1994;54:103-5.
- Murdoch ME, Leigh IM. Sporotrichoid spread of cutaneous Mycobacterium chelonei infection. Clin Exp Dermatol. 1989;14:309-12.
- Dore N, Collins JP, Mankiewicz E. A sporotrichoid-like Mycobacterium kansasii infection of the skin treated with minocycline hydrochloride. Br J Dermatol. 1979;101:75-9.