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Cutaneous nocardiosis: A great imitator

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Abstract Nocardiosis is caused by Gram-positive aerobic bacilli of the *Nocardia* genus, which are saprophytes living in the soil. It is a rare and opportunist disease with a localized or disseminated infection. When occurring in patients who are immunocompromised, involvement is usually systemic, most commonly represented by pulmonary disease. It can also be acquired through direct inoculation, entailing primary skin and subcutaneous tissue infections, frequently presenting as a localized nodular process. Cutaneous nocardiosis can manifest as a lymphocutaneous infection, actinomycetoma, superficial skin infection, or secondary infection from hematogenic dissemination. Diagnosis is made by identification of the organism in the culture of a clinical sample. Staining for acid-alcohol–resistant bacteria and, especially, Gram staining, is particularly relevant to obtain a rapid and presumptive diagnosis, while awaiting culture results. First-line medication is sulfamethoxazole-trimethoprim, which may be used with other antimicrobials, if necessary. Nocardiosis may be considered a major mimicker of several cutaneous diseases that present difficult, and often, delayed diagnoses.
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Introduction

Nocardiosis is a possible cause of lung and systemic infection in patients who are immunocompromised, despite its possible isolated occurrence. *Nocardia* are Gram-positive bacilli dwelling in the soil, with over 50 known species. They are not part of the normal human flora and, when isolated, should be carefully scrutinized. The disease has been reported worldwide, regardless of age or ethnicity, with a two to three times greater prevalence in men.[1–3]

Disseminated nocardiosis occurs when two or more noncontiguous sites are affected. The sites involved with greatest frequency are the lungs, central nervous system, and skin.[4] Some risk factors can lead to disseminated nocardiosis, among which are HIV infection, alcohol abuse, organ transplantation, advanced chronic obstructive pulmonary diseases, and autoimmune diseases.[2]

Cutaneous nocardiosis is characterized by such clinical manifestations, as lymphocutaneous infection (ie, sporotrichoid) (Figures 1-4), actinomycetoma, superficial skin infection (ie, pustules, ulcers, granulomas, abscesses, or cellulitis), or as a secondary infection by hematogenic dissemination. The most common agent related to lymphocutaneous nocardiosis is *Nocardia brasiliensis.*[3,5]

In addition to the clinical diagnosis, isolation of *Nocardia* and identification of the organisms from a clinical sample is necessary. As the colonies may take up to 2 weeks to appear, it is important to inform the laboratory in case of suspecting

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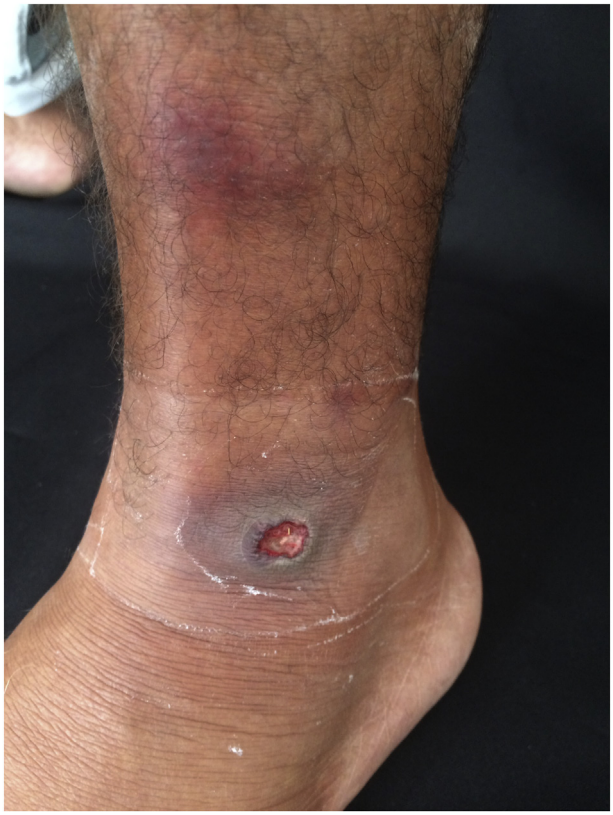

Fig. 1 Ulcerated lesion at the left lateral malleolus (with permission from Secchin et al.[3]).

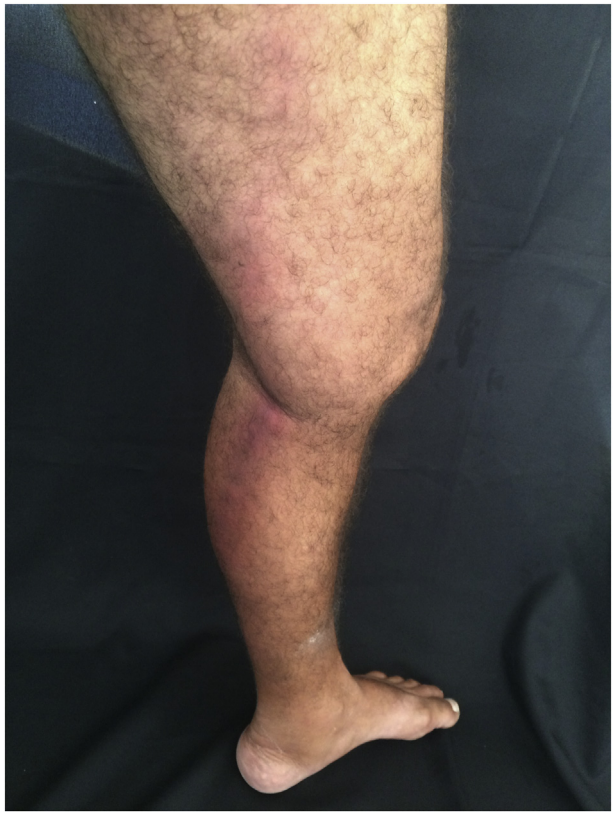

Fig. 2 Ascending lymphangitis in the left lower limb (with permission from Secchin et al.[3]).

an infection by *Nocardia* in order to take appropriate measures to optimize recognition of the organism.[1–3]

The main differential diagnoses include sporotrichosis, infection by atypical mycobacteria (*M. marinum* and *M. chelonae*), leishmaniosis (*Leishmania braziliensis*), and tuberculosis.[6]

Initial treatment is based on therapy with antimicrobials, with the first choice being sulfamethoxazole-trimethoprim, both for the cutaneous and pulmonary forms; however, if the disease is disseminated, the choice must be imipenem associated with amikacin.[1]

We focus on nocardiosis as being a major mimicker of some cutaneous diseases, some of which include sporotrichosis, tuberculosis, atypical mycobacteria, leishmaniosis, syphilis, abscess, cellulitis, deep mycoses, skin cancer, and lupus erythematosus.

Cutaneous manifestations of nocardiosis

Cutaneous nocardiosis can be classified by the following features: (1) mycetoma, lymphocutaneous infection; (2) superficial infections of the skin; and (3) disseminated infection with cutaneous involvement.

Mycetoma is a hardened, chronic, tumor mass associated with fistulae that drain granules from inside the lesion, and, occasionally, from the underlying bone. Mycetoma is worldwide the most common cutaneous manifestation of *N. brasiliensis.*

In case of lymphocutaneous or sporotrichoid infections, the initial infection site becomes acutely inflamed, with secondary lesions occurring alongside the drainage of lymph vessels. Possibly, nocardiosis may be the most common alternative diagnosis to sporotrichosis in this cutaneous manifestation.

Superficial cutaneous infections include cellulitis, abscesses, ulcers, and granulomas. Those infections are difficult to distinguish from their morphologic clinical appearance of the common bacterial causes of the same process. In disseminated infection, the incidence of skin involvement is approximately 10%.[3,7]

Diseases mimicking nocardiosis

Sporotrichosis

The etiology of sporotrichosis comprises several species of fungi of the *Sporothrix* genus with the main transmission occurring by direct inoculation (contact with soil or felines). It may clinically appear on the skin in the

Fig. 3 *Nocardia brasiliensis* colony in Sabouraud agar medium (with permission from Secchin et al.[3]).

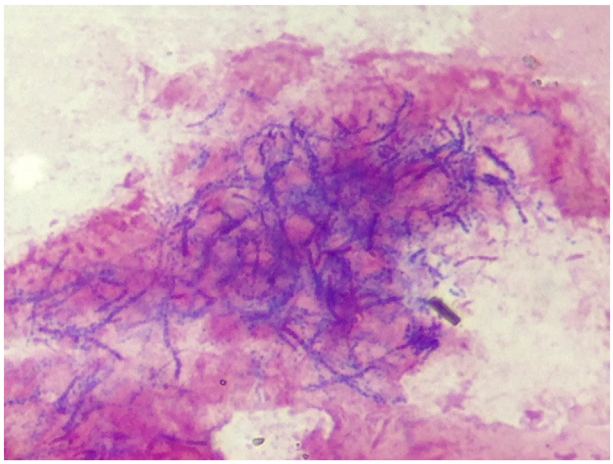

Fig. 4 Gram-positive thin and branched bacterial filaments (Gram, X 1,000) (with permission from Secchin et al.[3]).

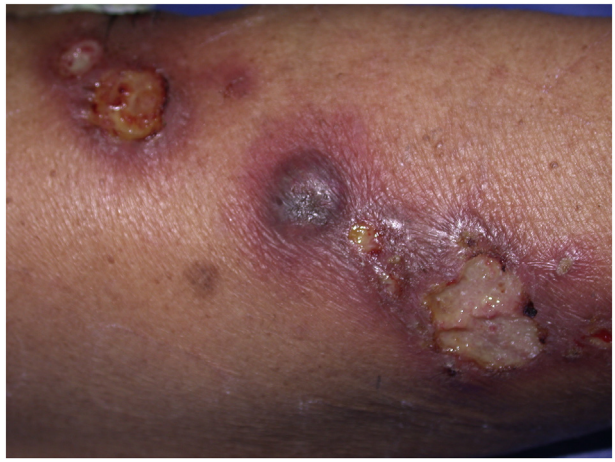

Fig. 5 Sporotrichosis ulcers in a patient with multiple myeloma.

lymphocutaneous, fixed cutaneous, and multiple inoculation forms (Figures 5 and 6).[8]

Nocardiosis in the sporotrichoid form is the most commonly observed presentation, whereas the lymphocutaneous form is the one most described.

In 1988, a patient was reported with primary cutaneous nocardiosis mimicking sporotrichosis. There were nodules and linear pustules on the dorsum of the right hand, extending to the forearm.[9] Another case reported in 2017, concerned cutaneous nocardiosis, mimicking cutaneous lymphatic sporotrichosis, clinically with ulceration and lymphangitis, with onset 1 week after an insect bite on the left leg.[3]

Tuberculosis

Cutaneous tuberculosis is caused by infection from *Mycobacterium tuberculosis*. It can be classified by the following features: (1) tuberculosis from inoculation by exogenous source; (2) endogenous source; and (3) hematogenic spread.

Clinically it may present as a verrucous or ulcerated form, as subcutaneous nodules, or as gumma, among others (Figures 7 and 8).[10]

Visceral tuberculosis is rarely associated concurrently with cutaneous involvement, but in case this happens, it is usually either scrofuloderma or lupus vulgar.

Scrofuloderma results from extension of an infection to structures adjacent to the skin, such as bones, lymph nodes, joints, or epididymis (Figure 9). The most common sites are the cervical region, axillae, and groin. Clinically, it begins as a subcutaneous nodule that gradually increases, becoming confluent, ulcerating, and forming sinus tracts with purulent secretion.[11] This clinical form can mimic cutaneous nocardiosis.

Atypical mycobacteriosis

In a cutaneous infection due to atypical mycobacteriosis, also called nontuberculous mycobacteria, the species can be

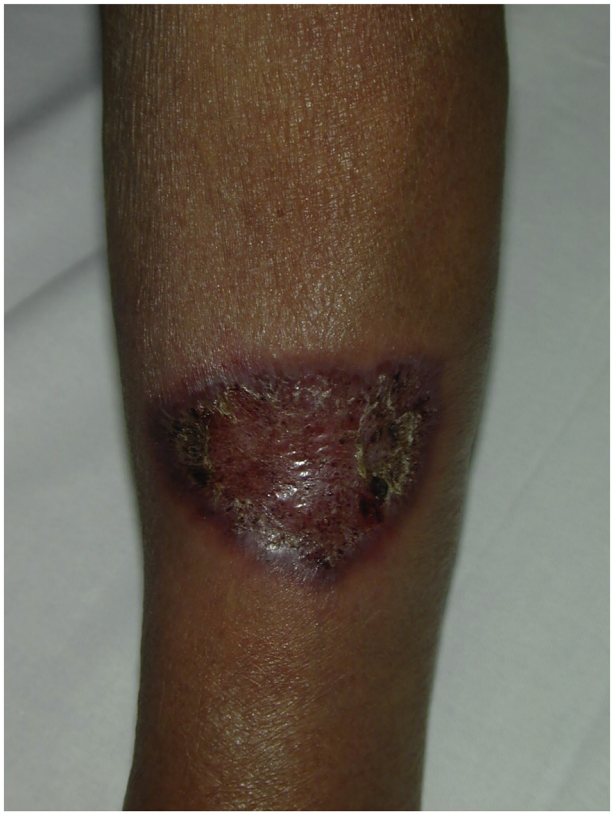

Fig. 6 Single lesion of sporotrichosis.

classified according to its response to light and speed of growth. Each species has its own clinical form.

The members of the complex comprising *M. abscessus* (*M. abscessus*, *M. massiliense*, and *M. bolletii*) are the main nontuberculous mycobacteria associated with cutaneous involvement together with *Mycobacterium fortuitum* and *Mycobacterium chelonae*. An atypical mycobacteriosis is caused by infection of posttraumatic lesions, infections

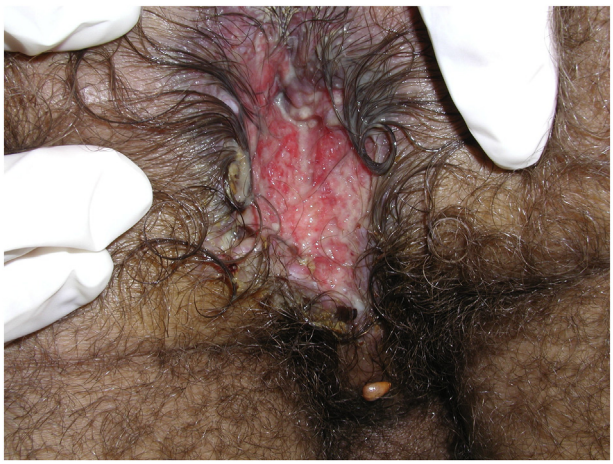

Fig. 7 Perianal tuberculosis ulcer.

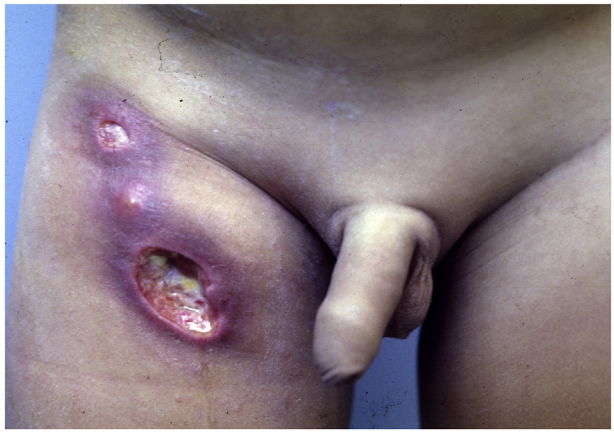

Fig. 8 Tuberculosis gumma.

associated with catheters, postsurgical infections, and trauma-related infections. *M. chelonae* and *M. abscessus* usually present with multiple cutaneous lesions, whereas *M. fortuitum* tends to appear as a single lesion. These lesions can present as erythematous nodules, cellulitis, abscesses, and ulcers, subject to evolve to the sporotrichoid presentation as occurs in cutaneous nocardiosis (Figures 10 and 11).[11–13]

Leishmaniasis

Leishmaniasis is caused by a protozoa of the *Leishmania* genus, transmitted through insect bites of phlebotomine insects. The different species entail characteristic clinical syndromes, with the most common form being localized cutaneous leishmaniosis.[14]

The primary cutaneous localized cutaneous leishmaniosis lesion frequently consists in papules, either single or multiple, appearing in the skin of the affected individual at the site of a bite by a phlebotomine sand fly, normally in exposed areas such as the face, neck, and extremities. Evolution is insidious until an ulcer is formed, penetrating into the deep portion of the dermis. It is usually round with a reddish, granular base,

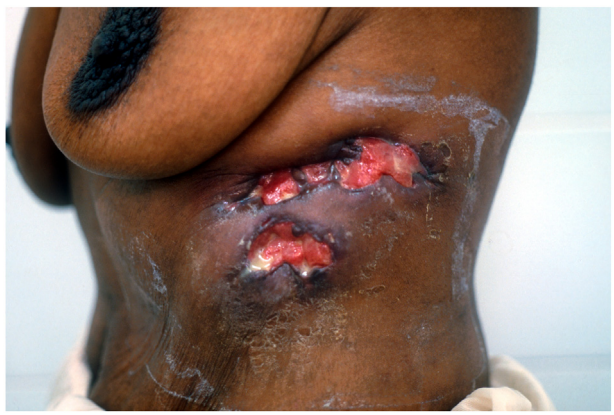

Fig. 9 Scrofuloderma.

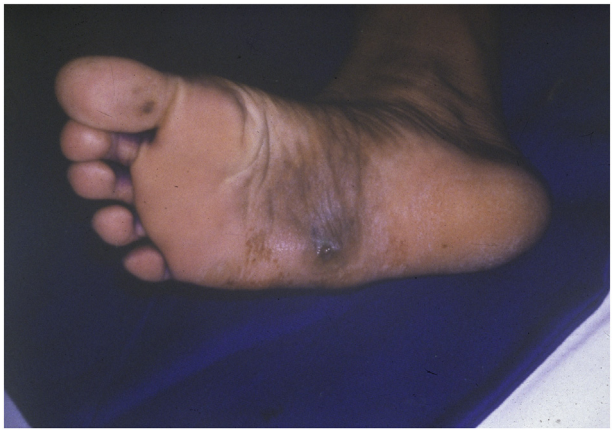

Fig. 10 Atypical mycobacteriosis due to M. aviumin an Aids patient.

sometimes covered by a serous hemorrhagic or serous purulent crust. It is generally painless or with low sensitivity, with infiltrated borders (Figure 12). Lymphadenopathy may develop as the first sign of the disease (Figure 13). Secondary bacterial or fungal infections may occur, with *Staphylococcus* species being more common.[14,15]

Leishmaniasis can present with atypical lesions of lupoid, eczematous, erysipeloid, and verrucous aspect. It can also manifest in the following forms: (1) dry ulcers; (2) zosteriform, sporotrichoid, and cancroid disposition; (3) paronychia; or (4) annular and volcanic erythematous ulcers. Some patients have shown similarity with deep and subcutaneous mycosis or with malignancies as lymphoma, pseudolymphoma, and basocellular or spinocellular carcinoma.[15]

Syphilis

Early malignant syphilis is a rare but severe manifestation of secondary syphilis, which has its start as an ulcer usually in the genital area where inoculation occurred followed by

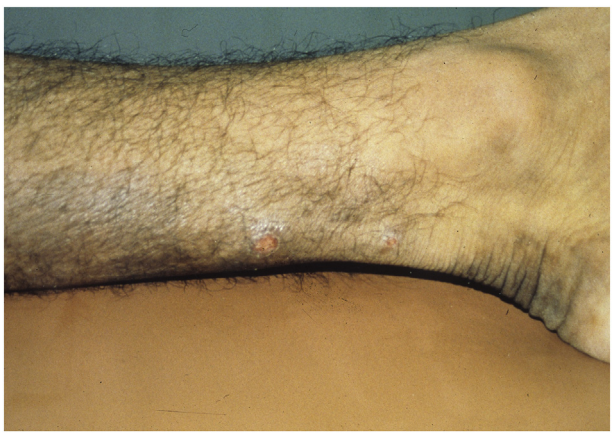

Fig. 11 Atypical mycobacteriosis due to M. aviumin an Aids patient.

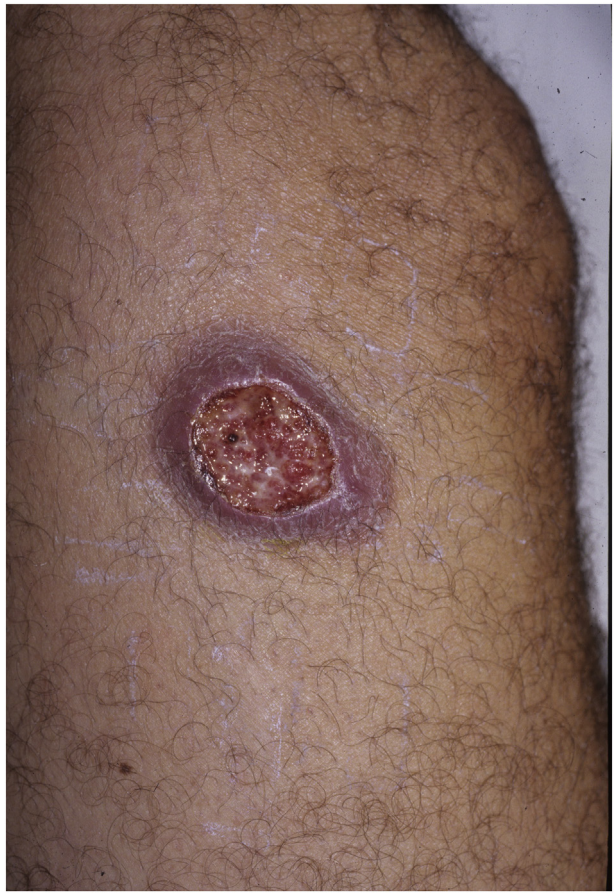

Fig. 12 Leishmaniasis ulcer.

the onset of asymmetric multiple erythematous papules. The papules evolve into well-defined, ulcerated, necrotic plaques of round or oval shape on the scalp, face, trunk, and extremities (Figure 14). Lesions in different stages may be present; these include papules, nodules, pustules, and ulcerations covered with rupioid crusts with the mucosa also subject to being affected.[16,17]

Late or tertiary syphilis may present with mucocutaneous, cardiac, ophthalmic, and neurologic or bone involvement. Skin is the most affected organ, with a variable clinical presentation according to the level of commitment, subject to being hypodermal (syphilitic gumma) or dermoepidermal (psoriasiform plaques or nodules).

The gumma form presents initially as firm and painless subcutaneous nodules that later develop into ulcerations with drainage of necrotic material.[16–18]

Abscesses and cellulitis

These are infections caused by more common bacteria, such as *Staphylococcus aureus* or *Streptococcus pyogenes*, which cause an acute infection that may clinically resemble nocardiosis and, therefore, should be distinguished based on the results of Gram staining and culture.

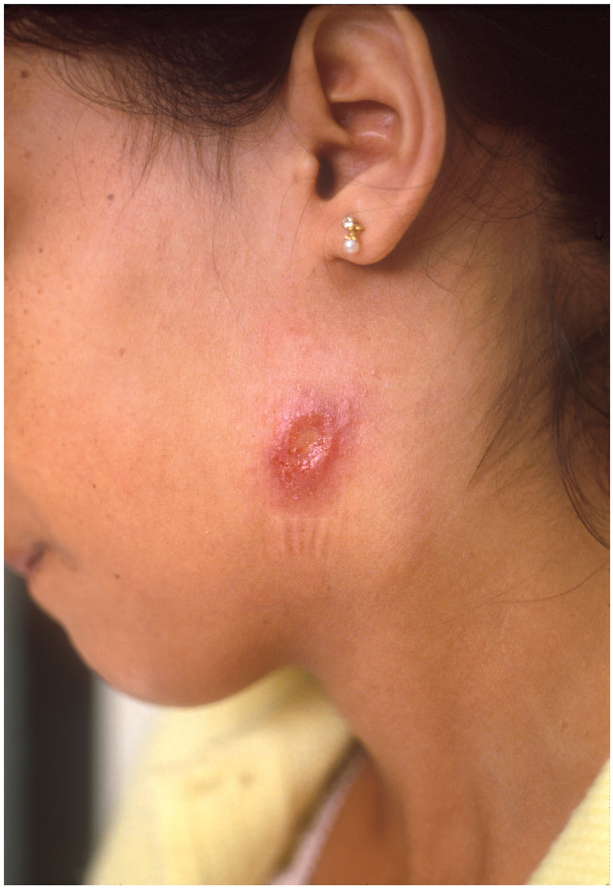

Fig. 13 Leishmaniasis ulcer and lymphadenopathy.

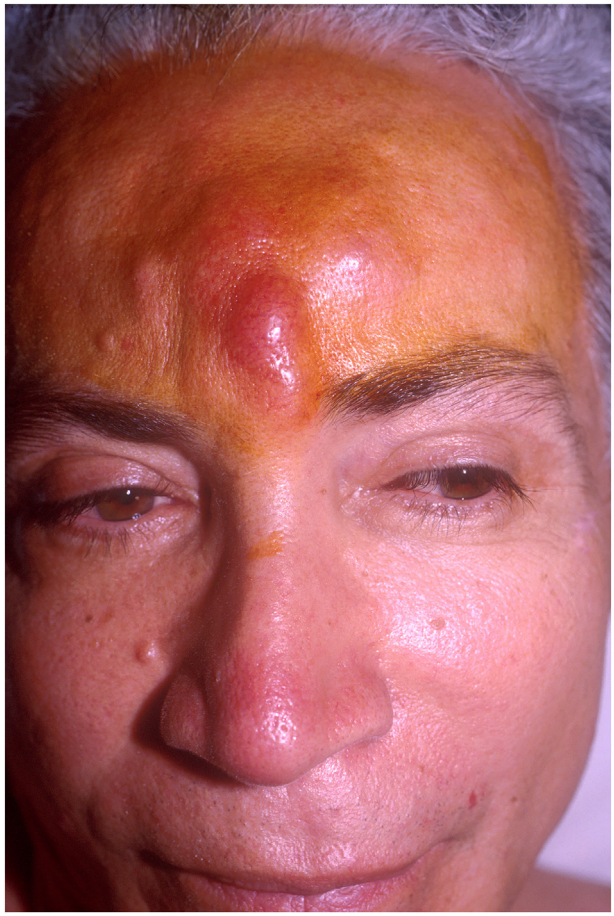

Fig. 14 Late syphilis in an AIDS patient.

Acute superficial secondary cutaneous infections by *Nocardia* can manifest as cellulitis or subcutaneous abscesses, with onset from days to weeks after direct skin inoculation, and can be associated with minor systemic clinical manifestations. *N. brasiliensis* is the most common species causing acute cutaneous lesions.[19,20]

A child with acute infection was recently reported with the formation of abscesses in the fourth and fifth fingers of the left hand, secondary to *Nocardia brasiliensis*.[20] Another patient, classified as immunocompetent, developed cellulitis in the right hand and disseminated subcutaneous nodules in the legs after a kidney transplantation. Culture evidence of *Nocardia asteroids* was obtained.[19]

Histoplasmosis

This is a systemic mycosis caused by *Histoplasma capsulatum,* a dimorphic fungus, of the capsulatum variety. Involvement of mucosa is characteristic in chronic disseminated forms and granulomatous ulcerative lesions are common in the oral mucosa, tongue, nasal septum, and larynx (Figure 15).

The reported cutaneous manifestations include granulomatous plaques, deep nodules, erythematous papules, eczema, erythematous plaques, pustules, papulonecrotic lesions, exfoliative erythrodermia, and subcutaneous nodules. In patients with AIDS, disseminated lesions mimicking molluscum contagiosum are commonly observed.[21,22]

Paracoccidioidomycosis

This is a chronic systemic mycosis, in subacute or in rare cases, acute form, caused by *Paracoccidioides brasiliensis*

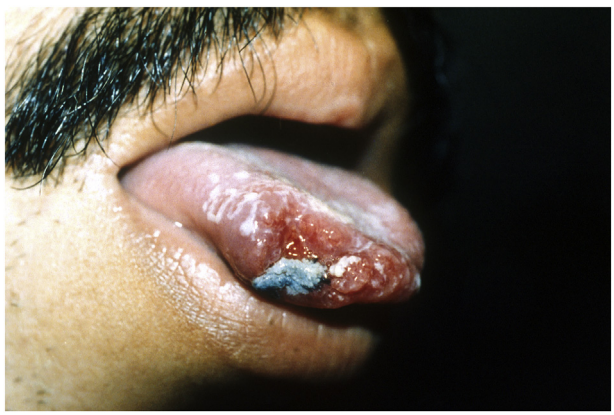

Fig. 15 Histoplasmosis ulcer.

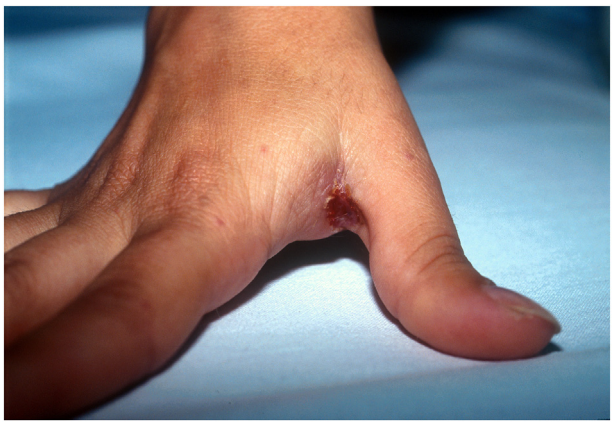

Fig. 16 Paracoccidioidomycosis ulcer on the hand.

and *Paracoccidioides lutzii*. The cutaneous lesions are often located around the nose and mouth (face center), subject to assume several forms, some beginning as small pustules that change into ulcerated papules, of 2.0 to 3.0 mm, and which later may become ulcers with hematic crusts (Figures 16 and 17).

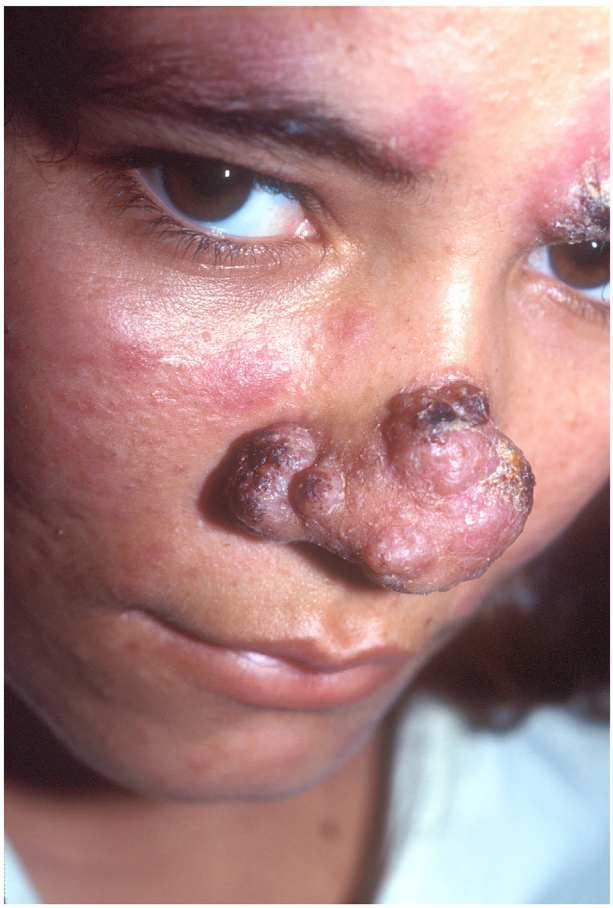

Fig. 17 Paracoccidoidomycosis verrucous lesions on the face (same patient as in Figure 16).

In some cases, nodular lesions can develop fistulae that trail the course of a lymph node. Cold subcutaneous abscesses are also observed with overlying erythema, from which it is possible to aspirate a dark exudate.[21,22]

Skin cancer

One case report[23] reported, in 2000, a patient with a diagnosis of suspected lung carcinoma, associated with several nodular, subcutaneous, erythematous lesions in the left forearm. The skin lesions were considered cutaneous metastases from a possible lung cancer. The pathologic diagnosis was only made with the postmortem examination that indicated nocardiosis of the lungs with hematologic dissemination to the esophagus, pleura, and to the subcutaneous skin of the left forearm.

Lupus erythematosus

Primary cutaneous nocardiosis from *Nocardia asteroides* may mimic lupus erythematosus with painless, hardened, erythematous lesions with follicular obstruction in the malar region. Due to suspicion for lupus erythematosus, an intermittent previous treatment with systemic steroids was carried out, which probably lead to the opportunist skin infection manifesting as infiltrated and hardened plaques.[24]

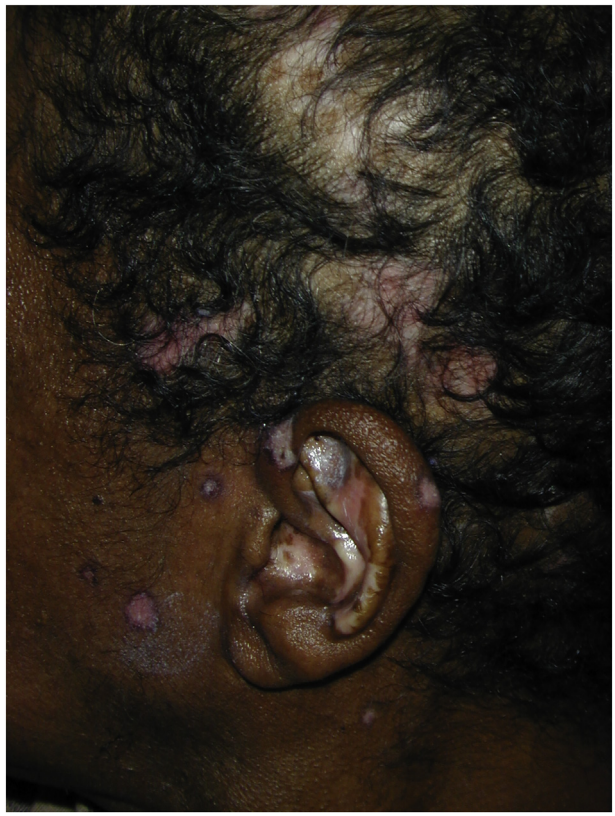

Fig. 18 Lupus erythematosus on the ear and scalp.

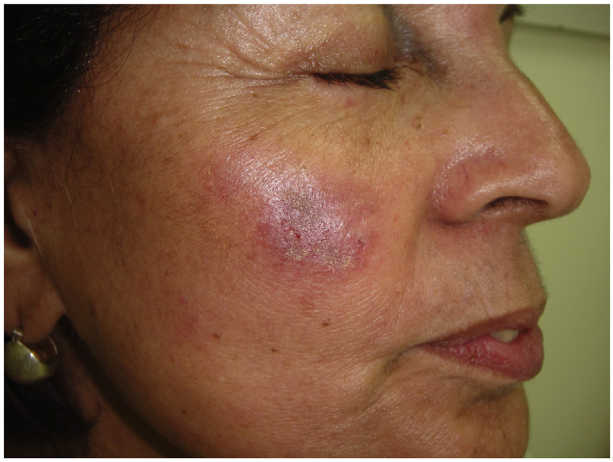

Fig. 19 Lupus erythematosus on the cheek.

Systemic lupus erythematosus is an autoimmune disease with a wide spectrum of clinical and immunologic features, often with cutaneous involvement. In acute cutaneous lupus erythematosus, the classic malar eruption ("butterfly wings" distribution) occurs, characterized by erythematous maculae, papules, and plaques in the central areas of the face including the nose, chin, forehead, and malar region, typically without affecting the nasolabial folds and periorbital regions. Additionally, it may involve the ear lobes, scalp, and neck. Erosions and ulcerations of the oral or nasal mucosa may also accompany the cutaneous lesions (Figures 18 and 19).[25]

Conclusions

Nocardiosis is a rare and opportunistic disease with localized or disseminated infection caused by Gram-positive aerobic bacilli of the genus *Nocardia.* Clinical presentations may be acute, subacute, or more often, chronic. It presents with several differential diagnoses, making it difficult to establish the etiology of the disease and emphasizing the importance of being aware of the clinical characteristics of each of these cutaneous diseases.

The clinical presentation of these lesions can mimic several other diseases, and may delay or hamper a precise diagnosis, submitting patients to unnecessary treatments, sometimes worsening the clinical picture, and eventually contributing to the transmission chain of the agent.

A histopathologic exam, direct mycology analysis, and Gram staining are advised to distinguish between the different cutaneous lesions that may be mimicked by each other.

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