CASE REPORT

Cutaneous nocardiosis by a new pathogenic species: *Nocardia grenadensis*

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SUMMARY

Nocardiosis is a rare, predominantly opportunistic, suppurative disease caused by bacteria of the order Actinomycetales. There are currently more than 100 species of *Nocardia* described, less than half are pathogenic to humans. Cutaneous nocardiosis can be caused by direct inoculation from a contaminated material or by secondary dissemination. The authors present a 70-year-old man with an autoimmune haemolytic anaemia treated with prednisolone and azathioprine. The patient presented multiple erythematous tender nodules with linear distribution and proximal progression along the left upper limb with 2 months of evolution. The skin biopsy revealed non-specific inflammation with areas of abscess. Culture was positive for bacteria of the genus *Nocardia*, and molecular techniques revealed *Nocardia grenadensis*. The patient was treated with minocycline with good response, but the disease recurred. *N. grenadensis* was first identified in 2012 in a bioprospecting process. The authors now describe the first case of cutaneous nocardiosis caused by *N. grenadensis*.

BACKGROUND

Bacteria from the genus *Nocardia* are members of the order Actinomycetales.¹ These aerobic Gram-positive saprophytic bacteria, found ubiquitously in the environment, are responsible for the localised or disseminated infection known as nocardiosis.²

In 1995 only 15 species of *Nocardia* were known. Currently there are more than 100 species of *Nocardia* described, although less than half are pathogenic to humans.³ Modern molecular methods such as the 16S rRNA gene sequencing have made an important contribution to the increasing number of new species identified in the last decades.⁴

Another important contributing factor is the bioprospecting phenomenon. Because of the important role of *Nocardia* in biotechnology and in the medicine field for the production of antibiotics and enzymes, an active search for new species is thriving.³

In 2012, a new species of *Nocardia* was isolated on soil extract agar from sand collected at a depth of 5 m in the Caribbean Sea near Grenada, and was called *Nocardia grenadensis*.⁵

The authors report the first case of cutaneous nocardiosis, and the second clinical isolation, caused by this new species of *Nocardia*.

CASE PRESENTATION

The authors present a 70-year-old man with a medical history relevant for diabetes mellitus, hypertension, congestive heart failure and autoimmune haemolytic anaemia. Among others, the patient was treated with prednisolone 60 mg/day and azathioprine 50 mg/day since the diagnosis of autoimmune haemolytic anaemia 3 years ago.

The patient was admitted to the internal medicine department for a community-acquired pneumonia (*Streptococcus pneumoniae* identified on sputum culture and positive pneumococcal urinary antigen test), left lumbar pain (MRI revealed an inflammatory process involving L3–L4 and the left psoas muscle) and exacerbation of the haemolytic anaemia needing a red blood cell transfusion. His pneumonia resolved with an antibiotic regimen consisting of ceftriaxone and clarithromycin. Based on classical presentation and good response of the pneumonia and the absence of suspicion of nocardiosis at that time, no other tests such as bronchoscopy were performed. The lumbar inflammatory process was approached surgically, but the microbiological exam was negative for micro-organisms.

The patient was internally referred to the dermatology department due to multiple painful nodules with linear distribution and proximal progression from the left wrist along the medial aspect of the left forearm and arm with 2 months of evolution. The patient used to garden and remembered an injury in the left wrist just before the first lesion appeared.

Clinical examination revealed several erythematous tender nodules, some of them covered with a haemorrhagic crust, with a linear distribution along the medial aspect of the left upper limb (figure 1). A thick cord-like structure was palpable between the nodules but no regional lymph nodes were noted.

INVESTIGATIONS

With clinical differential diagnosis of sporotrichosis, nocardiosis and atypical mycobacteria, a skin biopsy of the upper, and therefore more recent, nodules was performed for histological examination. This examination revealed epidermal acanthosis and deep dermis inflammatory infiltrate involving lymphocytes, histiocytes and neutrophils with areas of abscess formation, but the histochemical study was negative for micro-organisms.

The purulent content of the nodules was collected and sent to the laboratory for microbiological examination. Mycobacterium culture and

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Figure 1 Multiple erythematous tender nodules, some of them covered with a haemorrhagic crust, with a linear distribution along the medial aspect of the left upper limb.

fungal PCR were negative. The agent grew on sheep blood agar after 24 hours of incubation at $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$ in a 5% carbon dioxide atmosphere. Acid-fast, Gram-positive branching rod bacteria were identified by direct examination. 16S rRNA gene sequencing (999 bp fragment amplified with primers 5'-ccagcagccgcgtaataacg-3' and 5'-atcggtacctgttacggacttc-3') identified the organism as *N. grenadensis* (the percentage of sequence similarity with the reference for *N. grenadensis* was 99.57%). The National Center for Biotechnology Information (NCBI) Blast limited to sequences from type material was the database used to check the identification of *N. grenadensis* (NCBI accession number NR_117107.1).

TREATMENT

Combining the clinical findings and the microbiological study results (only with proven *Nocardia* isolation on the skin), we established the diagnosis of lymphocutaneous nocardiosis.

Treatment was initiated with minocycline 100 mg twice daily with concomitant gradual weaning of the steroid dose.

OUTCOME AND FOLLOW-UP

At week 6 of treatment the clinical lesions were almost completely resolved. However, at week 8 a relapse occurred even with the antibiotic regimen, with a new tender nodule arising proximally to the previous ones (figure 2). The treatment was switched to trimethoprim-sulfamethoxazole (TMP-SMX per os) 160/800 mg two times a day (2id). At that same visit, an infiltrated 15 cm wide erythematous plaque was noted in the presternal area. The skin biopsy unfortunately revealed skin involvement by a B cell lymphoma. The search for *Nocardia* was negative in the histological exam.

The patient died 2 months after the diagnosis of follicular lymphoma in spite of chemotherapy.

DISCUSSION

Nocardiosis is a predominantly opportunistic infection, although up to one-third of cases are found in immunocompetent hosts.⁶ Patients with cell-mediated immunosuppression, including those with HIV infection, haematological or solid organ malignancies, submitted to solid organ and haematopoietic stem cell transplantation, or long-term steroid treatment, are particularly at risk.⁶ Other risk factors for cutaneous nocardiosis

Figure 2 A relapse at week 8 of treatment with minocycline. Note a newer erythematous nodule arising proximally to the previous ones.

include rural work or gardening.⁴ Concomitant comorbidities like diabetes mellitus, alcoholism or cytomegalovirus infection may also contribute to the development of the disease.⁶

Although an internationally accepted classification of cutaneous nocardiosis is still lacking, most published articles typically categorised the disease into primary or disseminated. The latter, classically found in immunosuppressed patients, occurs by haematological dissemination in the setting of other organ infection, usually the lung.⁴ This category implies isolation of *Nocardia* in at least two organs, and clinically manifests with pustules, abscesses and nodules most commonly involving the trunk and proximal extremities.¹ Primary cutaneous nocardiosis results from direct inoculation of an infected material, and can be subdivided according to clinical characteristics into superficial, lymphocutaneous and nocardial mycetoma.⁷ Superficial infection clinically resembles classic streptococcal or staphylococcal soft tissue infection, with pustules, abscesses and cellulitis, although with a more indolent course.^{6,8} Lymphocutaneous nocardiosis is characterised by an ulcerated nodule or plaque at the inoculation site, followed by an ascending lymphangitis and multiple nodules along the course of the regional lymphatic vessels. It represents up to one-third of all cases of cutaneous nocardiosis and usually affects the face or the extremities.⁹ Nocardial mycetoma is a granulomatous infection of the dermal and subcutaneous tissue which may extend to the muscle or even the bone. It typically presents as an inflammatory plaque with characteristic draining sinuses containing grains. This lesion should be differentiated from mycotic mycetoma, which is clinically similar, by laboratory evaluation. In this patient, the diagnosis of lymphocutaneous nocardiosis was made based

on clinical evaluation, isolation of *Nocardia* species on the skin and the possible point of entrance through a lesion when gardening in a chronically immunodepressed patient. It is, however, possible that the lumbar inflammatory process could be caused by *Nocardia* infection as no other cause was advanced. As mentioned, any bronchoscopy or PCR search for *Nocardia* was not performed in the sputum as the pulmonary presentation was, at the time, considered as a classical pneumococcal pneumonia and treated as such with good results. Nonetheless, we cannot completely exclude the possibility of pulmonary nocardiosis. There are even cases reported of primary cutaneous nocardiosis with pulmonary dissemination in immunosuppressed patients.¹⁰ Attending to the criteria the fact is that *Nocardia* was not isolated from the surgically collected lumbar material nor the lung, and so primary cutaneous nocardiosis is the prevalent hypothesis.

The clinical diagnosis of cutaneous nocardiosis is difficult because the clinical findings can be similar to other, sometimes more common infections, like streptococcus or staphylococcus (superficial), sporotrichosis (lymphocutaneous) or deep mycosis (mycetoma).⁹

The isolation and classification of *Nocardia* are laborious, and clinical suspicion of nocardiosis should always be communicated to the laboratory. *Nocardia* is a Gram-positive, variably acid-fast, strictly aerobic bacteria that forms branched filaments that fragment into pleomorphic rod-shaped or coccoid elements.⁷ The colonies have a chalky white or cotton-ball appearance on blood agar plates. As mentioned there is a crescent number of new *Nocardia* species, which makes it difficult to classify them based only on the morphological characteristics and acid-fastness. The new molecular method based on 16S rRNA gene is nowadays the best way for *Nocardia* identification.¹¹

Treatment should be offered in all cases of *Nocardia* infection as these micro-organisms should be considered pathogenic and not part of the normal human microbiota, and so susceptibility tests are advised. Being a rare disease, there are no clinical trials reporting the best initial empiric treatment, dosage and duration. However, most consensus and expert opinions agree that sulfonamides are the most common choice.¹ TMP-SMX is the most used drug. Adverse reactions to TMP-SMX have been reported and include myelosuppression, hepatotoxicity and renal insufficiency.⁶ Although these effects are most commonly seen at high dosages, we empirically opted for an alternative treatment given our patient's previously known autoimmune haemolytic anaemia. Also, the percentage of nocardial resistance to TMP-SMX is rising.¹² We chose to initially treat him with minocycline, which seems a good option for patients who cannot be treated with sulfonamides.⁴ The duration of treatment for cutaneous nocardiosis is still a subject of debate, with authors recommending 1–12 months of treatment depending on the subtype and presence of immunosuppression.^{4,6}

Usually the prognosis of primary cutaneous nocardiosis is good, although with high rates of relapse even during maintenance therapy if antibiotic levels are not optimal.⁴ In our case a relapse did occur at week 8 of the minocycline regimen and was switched to TMP-SMX. Unfortunately, the patient was diagnosed with a disseminated B cell lymphoma and died within 2 months.

A new *Nocardia* species, called *N. grenadensis*, was first reported in 2012.⁵ The micro-organism was characterised during a bioprospecting process. It was recovered on soil extract agar from 1g of a sample originating from sand collected at a depth of 5 m in the Caribbean Sea near Grenada, hence the name *grenadensis*. Sequence similarity calculations (according to

16S rRNA sequencing) show that this new species is related to *N. speluncae* (99.2%), *N. jinanensis* (99.2%) and *N. rhamnophilae* (98.6%).⁵ From our research only one case report of *N. grenadensis* has been published.³ That case, published in 2016, reported the first clinical isolation of *N. grenadensis*, by 16S rRNA gene sequencing, from the sputum of a Spanish patient suspected of having tuberculosis. However, to the best of our knowledge, up to date no paper has reported isolation of this new *Nocardia* species on the skin. Here, we reported the first case of cutaneous nocardiosis caused by *N. grenadensis*.

Learning points

- ▶ Nocardiosis is a rare, predominantly opportunistic, suppurative disease caused by bacteria of the order Actinomycetales.
- ▶ Cutaneous nocardiosis can be caused by direct inoculation from contaminated material or by secondary dissemination.
- ▶ Modern molecular methods such as 16S rRNA gene sequencing have made an important contribution to the increasing number of new species identified in the last decades.
- ▶ The isolation and classification of *Nocardia* are laborious, and clinical suspicion of nocardiosis should always be communicated to the laboratory.
- ▶ Treatment should be offered in all cases of *Nocardia* infection as these micro-organisms should be considered pathogenic and not part of the normal human microbiota.

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