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Nocardia spp infections among hematological patients: results of a retrospective multicenter study

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SUMMARY

Objectives: To describe the clinical characteristics and prognostic factors of hematological patients affected by *Nocardia spp* infections.
Methods: We retrospectively evaluated all the cases diagnosed in four Italian institutions.
Results: Between 2002 and 2012, 10 cases of nocardiosis were recorded. The median age of the patients was 66 years (range 24–85 years). The underlying hematological disease was a lymphoproliferative disorder in all but two patients. Eight patients (80%) showed active underlying hematological disease, relapsed or refractory in five (50%); one patient had a history of previous allogeneic bone marrow transplantation. Eight patients (80%) were on steroid therapy; lymphopenia was present in 8/10 (80%) patients. All patients showed lung involvement. Six patients were affected by disseminated nocardiosis. Three patients (30%) were nocardemic and three (30%) showed central nervous system involvement. Skin, lymph nodes, and bone were involved in one patient each. The median overall survival was 65 days. Older age, a longer period between hematological diagnosis and *Nocardia spp* infection, and relapsed/refractory hematological disease were associated with a worse prognosis.
Conclusions: Although rare, nocardiosis should be considered in the differential diagnosis of pulmonary and central nervous system lesions among hematological patients. Lymphoproliferative disorders, prolonged steroid treatment, lymphopenia, and active hematological disease are the conditions that are worth considering as predisposing factors for the development of this disease.

1. Introduction

Infections due to *Nocardia spp* are rare; localized skin forms are often seen among categories with limited exposure, such as agricultural workers.[1,2] Although uncommon, disseminated infections are severe and life-threatening and affect mainly immunodeficient patients.[3] The most common localization is the lung, but central nervous system (CNS), soft tissue, blood, and lymph nodes are also involved in disseminated nocardiosis.[1,2]

Due to the rarity of the disease and to the relative difficulty and slowness of growing cultures, the diagnosis of *Nocardia spp* infection may be underestimated. Differential diagnoses include bacterial lung abscess, aspergillosis or other invasive mould infections, actinomycosis, tuberculosis, and other malignancies.[3–5]

Large series of nocardiosis are uncommon and often refer to heterogeneous patients with different underlying diseases.[3,6–9] Chronic obstructive pulmonary disease (COPD), renal failure, and diabetes mellitus (DM) are predisposing factors, as well as immunodeficiency following prolonged steroid therapy, autoimmunity, HIV positivity, cancer, and solid organ or bone marrow transplantation. Of note, mortality due to nocardiosis ranges between 7% and 44%;[2] disseminated infections, with nocardemia and brain abscesses, are responsible for an even higher death rate.[3]

Hematological patients are considered a risk category for nocardiosis because of intrinsic and therapy-related immunodeficiency. The recent introduction in clinical practice of new, highly immunosuppressive therapeutic agents in the non-transplant setting may be responsible for the increased incidence of nocardiosis observed during recent years.[2,10] In order to better identify the clinical and prognostic characteristics of nocardiosis, as well as the type of underlying immunodeficiency predisposing

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to its development among hematological patients, we retrospectively collected data of cases diagnosed in different Italian hematology units. The exposure to antibiotic prophylaxis and the therapeutic approach were also evaluated.

2. Patients and methods

2.1. Patients and setting

Between October 2002 and November 2012, patients with a diagnosis of *Nocardia spp* infection admitted to four Italian hematology wards of tertiary care centers or university hospitals participating in the SEIFEM (Sorveglianza Epidemiologica Infezioni Fungine nelle Emopatie Maligne) group were included in the study. The study was approved by the ethics committee.

The clinical charts of all patients included in this study were retrospectively reviewed. Information was analyzed on age, gender, habits (smoking), place of residence, professional exposure (type of job), comorbidities (DM, COPD, chronic renal failure), time from hematological disease to Nocardia infection, underlying immunocompromised conditions (including underlying hematological disease, neutropenia and lymphopenia, history of immunosuppressant drug use, and corticosteroid therapy), possible prophylaxis with co-trimoxazole, type of therapy delivered, and outcome.

2.2. Definitions

A diagnosis of nocardiosis required a histological finding or at least one positive culture from respiratory samples (including expectorated sputum and bronchoalveolar lavage), blood, or abscess drainage, and the presence of pertinent clinical symptoms and signs. Nocardiae were isolated from BACTEC blood culture broth media; nocardiae from tissue specimens, as well as bronchoalveolar lavage and sputum samples, were isolated from blood agar plates. If a Nocardia infection was suspected, a Kinyoun acid-fast stain was performed. Molecular techniques were not routinely performed.

Infections by pathogens other than Nocardia were also excluded with standard microbiological tests.

'Pulmonary' nocardiosis was defined when signs and symptoms were limited to the lungs; 'disseminated' nocardiosis was defined when the isolation of *Nocardia spp* was demonstrated from specimens from two or more non-contiguous organs, such as lung, lymph node, skin, and brain, or from blood.

2.3. Statistical analysis

Analyses of differences between groups were performed using the Mann–Whitney test or Fisher's exact test. A p-value of <0.05 was considered to be statistically significant.

3. Results

3.1. Characteristics of patients

Between 2002 and 2012, 10 cases of nocardiosis were observed in four different hematology centers.

The male/female ratio was 8/2; the median age at diagnosis of Nocardia infection was 66 years (range 24–85 years). Only one patient had professional exposure (farmer) and 4/10 were smokers. The majority of them lived in the countryside (7/10). Comorbidities were reported in 5/10 patients (two DM, two chronic renal failure, and one COPD).

Underlying hematological diseases were B cell non-Hodgkin lymphoma (NHL) ($n = 3$), T-NHL + myelofibrosis ($n = 1$), multicentric Castleman disease ($n = 1$), hairy cell leukemia ($n = 1$), idiopathic thrombocytopenic purpura (ITP) ($n = 1$), chronic lymphocytic leukemia + ITP ($n = 1$), hypereosinophilic syndrome (HES) ($n = 1$), and Sézary syndrome ($n = 1$). One patient (B-NHL) developed nocardiosis after allogeneic stem cell transplantation (alloSCT).

The median time from the diagnosis of the hematological disease to Nocardia infection was 5 months (range 0–30 months). All but two patients (80%) showed active underlying hematological disease and five were considered (50%) relapsed or refractory.

In only one patient was the identification of the species available (*Nocardia asteroides*); susceptibility data were available only in two cases and revealed resistance to ciprofloxacin in both cases and to amoxicillin–clavulanate in one. Both cases were susceptible to linezolid, amikacin, imipenem, and co-trimoxazole.

Table 1 shows the patient clinical characteristics.

3.2. Previous treatment and immunological status

Eight out of 10 patients (80%) were on corticosteroid therapy, started at least 3 weeks before the diagnosis of nocardiosis. The median duration of corticosteroid therapy was 3.5 months (range 3–11 months) and the median dose delivered was 25 mg/day of prednisone or equivalent (range 10–50 mg/day).

Two patients (20%) were receiving hydroxyurea and one patient received anthracycline-containing chemotherapy for three cycles 3 months before the diagnosis of nocardiosis and then only steroid therapy. One patient (10%) received immunochemotherapy (rituximab + anthracycline-containing chemotherapy) immediately before Nocardia infection. One patient (10%), affected by Sézary syndrome, was on photopheresis. Concerning co-trimoxazole prophylaxis, only two patients (20%) were receiving this. The single alloSCT patient was receiving prednisone and cyclosporine because of graft versus host disease (GVHD).

Table 1
Patient characteristics (sex, age, underlying hematological disease, status of hematological disease, and time from hematological disease to nocardiosis)

Patient	Sex/age, years	Underlying hematological disease	Status	Time from hematological disease to nocardiosis (months)
1	Male/67	MF + peripheral T-NHL	Refractory	18
2	Male/71	MCD	Refractory	18
3	Male/71	HES	Refractory	10
4	Female/85	DLCL	Refractory	6
5	Male/70	ITP	Refractory	3
6	Male/63	ITP + B-CLL	Partial remission	3[a]
7	Female/65	SS	Diagnosis	4
8	Male/62	MCL	Disease beginning	1
9	Male/55	HCL	Disease beginning	0
10	Male/24	DLCL	Complete remission	30

CLL, chronic lymphocytic leukemia; DLCL, diffuse large cell lymphoma; HCL, hairy cell leukemia; HES, hypereosinophilic syndrome; ITP, idiopathic thrombocytopenic purpura; MCL, mantle cell lymphoma; MCD, multicentric Castleman disease; MF, myelofibrosis; NHL, non-Hodgkin lymphoma; SS, Sézary syndrome.
[a] From ITP diagnosis.