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MAJOR ARTICLE

Nocardia Infection in Patients With Anti–Granulocyte-Macrophage Colony-Stimulating Factor Autoantibodies: A Prospective Multicenter French Study

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Background. Nocardiosis, a bacterial opportunistic infection caused by *Nocardia* spp, has recently been reported in patients with anti–granulocyte-macrophage colony-stimulating factor (GM-CSF) autoantibodies, but insufficient data are available about disease presentation, outcomes, and occurrence of autoimmune pulmonary alveolar proteinosis (aPAP) in this population.

Methods. We performed a prospective, multicenter, nationwide study in France and included patients with a *Nocardia* infection who had anti-GM-CSF autoantibodies. We describe their clinical, microbiological, and radiological characteristics, and their outcome at 1 year of follow-up.

Results. Twenty patients (18 [90%] male) were included, with a median age of 69 (interquartile range, 44–75) years. The organs most frequently involved were the brain (14/20 [70%]) and the lung (12/20 [60%]). Half of the infections were disseminated (10/20 [50%]). *Nocardia* identification was predominantly made in abscess fluid (17/20 [85%]), among which 10 (59%) were brain abscesses. The 1-year all-cause mortality was 5% (1/20), and only 1 case of aPAP (1/20 [5%]) occurred during the follow-up period.

Conclusions. Nocardiosis with anti-GM-CSF autoantibodies is associated with a low mortality rate despite a high incidence of brain involvement. Although the occurrence of aPAP was infrequent during the 1-year follow-up period, long-term clinical data are needed to fully understand the potential relationship between nocardiosis, anti-GM-CSF autoantibodies, and aPAP.

Keywords. anti-GM-CSF autoantibodies; autoimmune pulmonary alveolar proteinosis; central nervous system infection; *Nocardia*; nocardiosis.

Nocardia is an environmentally ubiquitous gram-positive filamentous bacteria that can cause severe opportunistic infections called nocardiosis [1]. Inhalation is the main mode of *Nocardia* acquisition, so the most commonly involved organ is the lung. However, dissemination to other organs, such as the brain, occurs in about one-third of cases [1]. Invasive nocardiosis is usually observed among immunocompromised hosts, notably solid organ transplant [2–4] and hematopoietic cell transplant [5, 6] recipients, patients receiving corticosteroid therapy [7], and those with primary immunodeficiencies [8] or patients with chronic bronchopulmonary disease. However, 20%–40% of cases of invasive nocardiosis occur among apparently immunocompetent patients without chronic bronchopulmonary disease [7, 9, 10].

Anticytokine autoantibodies, an emerging cause of adult-onset immunodeficiency, are considered to constitute autoimmune phenocopies of inborn errors of immunity [11]. For example, autoantibodies against type I interferons (IFNs)

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have recently been shown to increase the risk of critical coronavirus disease 2019 (COVID-19) and influenza pneumonia [12, 13]. Furthermore, anti–granulocyte-macrophage colony-stimulating factor (anti-GM-CSF) autoantibodies have been identified in patients with disseminated cryptococcosis or invasive nocardiosis [14–17]. Pulmonary alveolar proteinosis (PAP) is a rare lung disease characterized by the accumulation of surfactant proteins and lipids in the pulmonary alveoli, which leads to progressive respiratory failure and an increased susceptibility to infections, primarily nocardiosis and, to a lesser extent, mycobacterial infections [18, 19]. Interestingly, about 90% of patients diagnosed with acquired PAP have anti-GM-CSF autoantibodies in their serum (autoimmune PAP [aPAP]) [20]. Despite a limited number of case reports and small retrospective series on nocardiosis associated with anti-GM-CSF autoantibodies in the literature [15, 16, 21–26], these data are insufficient to describe the key clinical features and assess the prognosis of this condition.

We therefore performed a prospective, multicenter, nationwide study in France with the main objective to describe the characteristics and outcomes of nocardiosis in patients with anti-GM-CSF antibodies. Our secondary objective was to assess the temporal relationship between *Nocardia* infection and aPAP occurrence in these patients.

METHODS

Inclusion Criteria and Study Design

Patient meeting all of the following criteria were included: (1) isolation of *Nocardia* spp in a clinical sample, (2) clinical and/or radiological signs of nocardiosis, (3) diagnosis made between 1 September 2020 and 1 September 2022, and (4) presence of anti-GM-CSF autoantibodies in serum determined at the Immunology Laboratory of the University Hospital of Rennes (see the section "Anti-GM-CSF Autoantibodies Identification" below).

Because the presence of anti-GM-CSF autoantibodies is a possible cause of invasive nocardiosis [17], biological sampling to identify these autoantibodies was considered as standard of care for cases of nocardiosis occurring in apparently immunocompetent patients. Apparently immunocompetent patients are defined as patients who lack any identified risk factors or conditions associated with nocardiosis, such as solid organ transplant, hematopoietic stem cell transplant, patients receiving high-dose corticosteroid therapy or immunosuppressive agents, or those with primary immunodeficiencies. During the study period, identification of anti-GM-CSF autoantibodies was performed in a single immunology laboratory in France (CHU Rennes). If anti-GM-CSF autoantibodies were identified, the patient's medical history was screened. If the patient met the study inclusion criteria, the physician responsible for their care was informed and study inclusion proposed.

This was a prospective multicenter study in France. In September 2020, we used the Infectio-Flash mailing list to inform all French infectious disease specialists about the possible inclusion in the study of patients who met the predefined inclusion criteria. Additionally, we notified pneumologists through different research networks, including Orpha Lung [27], RESPIRARE [28], RESPIFIL [29], GREPI [30], and the French Nocardiosis Observatory [31].

Microbiology

Two methods were used to confirm the presence of *Nocardia* spp in a clinical sample:

1. Microbiological definition: detection by culture of gram-positive, filamentous, branching bacteria, identified at the molecular level (16S ribosomal RNA [rRNA] gene sequencing or positive polymerase chain reaction [PCR]) as *Nocardia* spp. Identification of *Nocardia* at the genus level could also be performed by matrix-assisted laser desorption/ionization–time-of-flight spectrometry (MALDI-TOF) [32–34].
2. Histological definition: presence of bacterial clusters formed by gram-positive, filamentous, branching bacteria within a biopsied organ, associated with an inflammatory reaction. To confirm that these gram-positive bacteria were actually *Nocardia* spp, a molecular confirmation (identification *Nocardia* spp by PCR, refer to the paragraph below) was necessary to confirm identification, directly on the tissue sample.

To accurately identify the *Nocardia* spp, molecular biology techniques such as amplification and sequencing of a gene fragment coding for the 16S rRNA or *hsp65* genes were required. MALDI-TOF could also be used, but was considered reliable only for identification of *Nocardia farcinica* and *Nocardia cyriacigeorgica* [32–35].

The in vitro classification of pathogens as "resistant," "intermediate," or "susceptible" was made by assessing antibiotic susceptibility using broth microdilution (according to the Clinical and Laboratory Standards Institute standard [34, 36]), Etest strips on agar plate [37], or antibiotic disk diffusion methods [38].

Anti–GM–CSF Autoantibody Identification

Serum samples were sent to the Immunology Laboratory of the University Hospital of Rennes. Anti-GM-CSF antibody titers were determined using a functional assay measuring the ability of antibodies to neutralize the effect of recombinant GM-CSF on the growth of the GM-CSF–dependent erythroblastic cell line TF1. In brief, serial dilutions of sera were incubated with 1 ng/mL GM-CSF (Cellgenix, Freiburg, Germany) and TF1 cells. The proliferation of TF1 cells was measured by

Table 1. Patient Characteristics

Characteristic	Total, No. (%)
No. of patients	20 (100)
Male sex	18 (90)
Age at diagnosis, y, median (IQR)	69 (44–75)
Comorbidities	
Solid organ transplantation	0 (0)
Hematopoietic cell transplantation	0 (0)
Autoimmune disease	0 (0)
Neoplasia[a]	3 (15)
HIV infection	0 (0)
Corticosteroid use[b]	3 (15)
Immunosuppressive drug, biotherapy, or DMARD	0 (0)
Primary immunodeficiency	0 (0)
Chronic pulmonary disease[c]	3 (15)
Diabetes mellitus[d]	2 (10)
Smoking[e]	8 (40)

Abbreviations: DMARD, disease-modifying antirheumatic drug; HIV, human immunodeficiency virus; IQR, interquartile range.

[a]Two with nonmetastatic tumor considered in remission and 1 with metastatic tumor (prostate cancer) considered in remission.

[b]Two with a maximum dosage of 0.5 mg/kg/day of prednisone equivalent had discontinued the treatment for >30 days before *Nocardia* diagnosis and 1 with a dosage of 1 mg/kg/day of prednisone equivalent at the time of *Nocardia* diagnosis.

[c]Three with chronic obstructive pulmonary disease.

[d]One requiring insulin therapy.

[e]Three current smokers and 5 past smokers.

incorporation of tritiated thymidine for each dilution. The resulting count-per-minute sigmoidal curve enabled calculation of the dilution of serum that inhibited 50% of TF1 cell proliferation (IC_{50}) [39]. Sera were considered positive if the titer was strictly greater than 1:1.

Clinical Data, Definitions, and Follow-up

The date of diagnosis was defined as the day on which the first clinical sample that provided identification of *Nocardia* spp was collected.

Patient characteristics, including age, sex, comorbidities, antibiotic prophylaxis at the time of nocardiosis diagnosis, and other(s) potential opportunistic infection(s) within 6 months prior to the diagnosis, were collected. Clinical presentation, biological blood values, and microbiological and radiological findings at the time of *Nocardia* diagnosis were recorded. Dissemination was defined as the involvement of at least 2 noncontiguous organs.

To evaluate the treatment of nocardiosis, we recorded the antimicrobial agents used, appropriateness of the initial regimen prescribed in the first 2 weeks of therapy (defined as the administration of antibiotics with in vitro activity against the infecting strain [40]), and use of bactericidal antibiotics (eg, amikacin, carbapenems, and third-generation cephalosporins [restricted to ceftriaxone and cefotaxime]) in the initial 2 weeks of treatment [3]. We also recorded the occurrence of antibiotic-related adverse effects and the need for surgery or admission to an intensive care unit (ICU). Last, we recorded the total duration of antibiotic treatment and introduction of secondary antibiotic prophylaxis at the end of the curative treatment.

Relapse was defined as the presence of clinical and radiological signs of nocardiosis following the discontinuation of antimicrobial therapy for nocardiosis, with isolation of the same *Nocardia* sp as that identified during the initial diagnosis [41].

The presence of anti-GM-CSF autoantibodies was an inclusion criterion, so the diagnosis of aPAP was established based on a suggestive chest computed tomography (CT) scan and a compatible cytological appearance identified during bronchoalveolar lavage or through histological confirmation obtained from pulmonary biopsy [20].

The outcome for this study was all-cause mortality 12 months after the diagnosis of nocardiosis. Long-term follow-up (10 years) is ongoing.

Statistical Analysis

Continuous variables are presented as mean (interquartile range [IQR]) or median (IQR). Categorical variables are presented as numbers and frequencies. Survival was assessed using Kaplan-Meier curves.

Ethics

The local ethics committee approved the study (CERAPHP Centre reference 2019-06-05). Oral and written information about the study protocol were given to the patient on inclusion. As it was a noninterventional cohort, no written informed consent was required from included patients. The study was declared to the General Data Protection Regulation (reference 20200519161604). All decisions related to diagnosis or treatment were left to the physician in charge of the patient.

RESULTS

Patient Characteristics

Twenty-one cases of nocardiosis in patients with anti-GM-CSF autoantibodies were identified from 14 French centers between September 2020 and September 2022. Among them, 1 patient died early and we were unable to retrieve their clinical data (Supplementary Figure 1). As a result, 20 patients were included (18 men [90%]), with a median age of 69 (IQR, 44–75) years (Table 1 and Supplementary Table 1). Within the 6 months preceding the nocardiosis diagnosis, 3 patients (15%) had taken corticosteroids, with 2 of them having discontinued prednisone at least 30 days before the diagnosis. None of the patients had other immunosuppressive conditions or had used immunosuppressive drugs prior to *Nocardia* infection. Three patients (15%) were current smokers at the time of diagnosis (Table 1).

Characteristics of *Nocardia* Infections

The median time from initial symptoms to diagnosis was 19 (IQR, 10–35) days. The organ most frequently involved was

Table 2. Nocardiosis Characteristics

Characteristic	Total, No. (%)
No. (%) of patients	20 (100)
Antibiotic prophylaxis at time of infection	0 (0)
Opportunistic infection[a]	0 (0)
Coinfection at time of diagnosis[b]	2 (10)
Time from first symptoms to diagnosis, d, median (IQR)	19 (10–35)
Involved organs	
Brain	14 (70)
Lung	12 (60)
Skin and soft tissue	6 (30)
Skin and soft tissue as only site of infection	1 (17)
Joint(s) and bone(s)	1 (5)
Other[c]	4 (20)
Disseminated infection[d]	10 (50)
Clinical signs	
Fever >38°C	5 (25)
Chills	3 (15)
Dyspnea	6 (30)
Chest pain	3 (15)
Cough	8 (40)
Sputum production	2 (10)
Acute respiratory distress	2 (10)
Headache	7 (35)
Coma	1 (5)
Seizure	3 (15)
Focal neurologic signs	10 (50)
Weight loss	10 (50)
Asthenia	14 (70)
Cutaneous lesions	5 (25)
Arthritis	0 (0)
Subcutaneous swelling	6 (30)
Vision loss	1 (5)
Biological results on the day of diagnosis	
WBC count, × 1000/μL, median (IQR)	11.9 (7.6–18.2)
Neutrophil count, × 1000/μL, median (IQR) (n = 19)	7.5 (4–16)
Lymphocyte count, × 1000/μL, median (IQR) (n = 19)	1 (0.7–1.8)
GFR[e], mL/min/1.73 m^2, median ± SD (n = 19)	87 (59–98)
C-reactive protein, mg/L, median (IQR)	19 (10–109)
Radiological characteristics	
Brain imaging	20 (100)
CT scan	17 (85)
MRI	16 (80)
Type of brain abscess (n = 14)	
Multiple lesions	10 (71)
Bihemispheric	6 (43)
Supratentorial	11 (79)
Infratentorial	3 (21)
Lung CT scan	20 (100)
Type of lung involvement (n = 12)	
Nodules	9 (75)
Excavated (n = 9)	3 (33)
Lung consolidation	6 (50)
Pleural effusion	4 (33)
Interstitial syndrome	4 (33)
Multilobar involvement	8 (67)
Bilateral involvement	8 (67)

Abbreviations: CT, computed tomography; GFR, glomerular filtration rate; IQR, interquartile range; MRI, magnetic resonance imaging; SD, standard deviation; WBC, white blood cell.

[a]Within 6 months prior to *Nocardia* diagnosis.

[b]One bacterial infection with *Pseudomonas aeruginosa* and 1 viral infection with cytomegalovirus.

[c]Other organs: pericarditis (n = 1), intraocular (n = 2), kidney (n = 2), testis (n = 1).

[d]Defined as the involvement of at least 2 noncontiguous organs.

[e]As estimated by Modification of Diet in Renal Disease formula.

the brain (14/20 [70%]) followed by the lungs (12/20 [60%]). Half of the infections were disseminated (10/20 [50%]), with the majority of these involving the brain (9/10). Skin or soft tissue involvement was reported in 6 patients, with 1 of them presenting as primary cutaneous nocardiosis following direct inoculation without involvement of any other body site. Additional infection sites are shown in Table 2.

Brain imaging was performed in all patients, with 16 (80%) undergoing magnetic resonance imaging. Among the 14 patients with brain involvement, 3 (21%) had no neurological symptoms. Brain abscesses were the predominant presentation in these patients (14/14 [100%]), with the majority having multiple lesions (10/14) and bihemispheric involvement (6/14) (Table 2).

Chest CT was performed in all patients, predominantly revealing nodules (9/12), most of which were bilateral (7/9); 3 were excavated nodules (Table 2).

Nocardia was identified in abscess fluid in 17 patients (85%), with 10 of these cases involving brain abscesses (Supplementary Table 2). Molecular biology techniques were performed to identify bacterial isolates at the species level in 15 (75%) cases and at the genus level in 6 (30%) cases. MALDI-TOF was used to identify *Nocardia* at the species level in 5 cases (25%) (*N farcinica*). *Nocardia farcinica* was the species most commonly identified (7/20 [35%]), followed by *Nocardia abscessus* complex (5/20 [25%]). All patients with *N farcinica* (7/7) infections and 4 of 5 with *N abscessus* complex infections had brain involvement. At the time of diagnosis, only 2 coinfections were reported, 1 with *Pseudomonas aeruginosa* and 1 with cytomegalovirus.

Treatment

Bactericidal antibiotics were used in 19 (95%) of the patients. Antibiotic-related adverse effects were reported in 12 (60%) of the patients (Table 3). After exclusion of 1 patient who

Table 3. Treatment Characteristics

Treatment	Total, No. (%)
Association of 2 appropriate antibiotics during the first 2 wk of treatment[a]	10 (50)
Use of bactericidal antibiotics[b]	19 (95)
Duration of antibiotic treatment, mo, median (range)	12 (9–12)
Occurrence of antibiotic-related adverse effects	12 (60)
Need for surgery	9 (45)
Need for ICU admission	6 (30)
Secondary prophylaxis with TMP-SMX after the curative antibiotic treatment (n = 19)[c]	11 (58)

Abbreviations: ICU, intensive care unit; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Appropriate antibiotic is defined as a drug with demonstrated in vitro activity against the isolated *Nocardia* strain.

[b]Bactericidal antibiotic: amikacin, carbapenems, and third-generation cephalosporins restricted to ceftriaxone and cefotaxime.

[c]After exclusion of 1 patient who died.

died while receiving curative antibiotic treatment, secondary antibiotic prophylaxis with trimethoprim-sulfamethoxazole was prescribed to 11 (58%) patients after their curative treatment. Surgical intervention was required for 9 patients (45%); 6 patients (30%) required ICU admission. None of the 20 patients received specific adjunctive therapies used for aPAP, such as subcutaneous or inhaled GM-CSF, or rituximab.

Outcome and Occurrence of PAP

None of the 20 patients were lost to follow-up at 1 year. The 1-year all-cause mortality rate was 5% (1/20); taking into account the early death of the identified but not included patient, the actual mortality rate was 9% (2/21). One case of relapse was reported during the 1-year follow-up period (see detailed case in Supplementary Results).

The median anti–GM–CSF autoantibody titer was 1:321 (IQR, 1:166–1:569) AU/mL. During the 1-year follow-up, control lung CT scans were performed in 12 patients (60%) and pulmonary function tests in 7 (35%). No cases of aPAP were diagnosed before or at the time of nocardiosis diagnosis. One case of asymptomatic aPAP (5%) was diagnosed 7 months following the nocardiosis diagnosis, and this patient did not require specific treatment. No additional opportunistic infections were reported.

DISCUSSION

In this prospective multicenter study of *Nocardia* infection associated with anti-GM-CSF autoantibodies, we describe frequent brain involvement with a low mortality rate and infrequent occurrence of PAP over a 1-year follow-up period.

To our knowledge, this is the first prospective study in this group of patients. In a literature search, we identified an additional 20 reported cases of nocardiosis in patients with anti-GM-CSF autoantibodies [15, 16, 19, 21–26]. In these cases as in our cohort most patients (17/20, 85%]) were men, and the median age was 43 (IQR, 39–52) years. Brain involvement was present in 12 of 20 cases (60%) and no deaths were reported (Table 4). In our study, brain involvement was highly prevalent, affecting 70% of patients. This rate is higher than that reported in previous studies of nocardiosis in immunosuppressed patients, specifically solid organ [2-4] and hematopoietic cell [5, 6] transplant recipients, in whom rates ranged between 25.6% and 32%. Among patients with primary immunodeficiency, such as in chronic granulomatous disease, cerebral involvement of nocardiosis appears to be even less frequent (6.7%) [8]. While it is possible that previous studies may have underestimated the incidence of brain involvement due to lack of cerebral imaging in all asymptomatic patients, our findings suggest a particularly high prevalence of brain involvement in patients with anti-GM-CSF autoantibodies, as reported in previous case reports (Table 4).

In vitro, human monocytes produce GM-CSF in the presence of *Nocardia*, indicating a central role of the GM-CSF pathway in nocardiosis pathogenesis [15]. Anti-GM-CSF neutralizing autoantibodies are polyclonal antibodies that block GM-CSF receptor signaling, resulting in impaired phosphorylation of signal transducer and activator of transcription (STAT) 5 [15]. This disruption affects various cellular processes of innate immunity in the lungs, including Toll-like receptor activation, phagocytosis, bactericidal activity, oxidative burst, cell adhesion, and surfactant catabolism in neutrophils and alveolar macrophages [15, 16]. Anti-GM-CSF autoantibodies have also been associated with cryptococcal meningitis, another infection that involves the brain in apparently immunocompetent hosts [14, 16, 17]. One can therefore hypothesize that these autoantibodies play a critical role in predisposing individuals to central nervous system (CNS) infections. The role of GM-CSF in the CNS inflammatory response has been investigated in inflammatory neurological diseases [42–44]. These studies suggest that interleukin 23– and interleukin 1β–driven T cells induce the production of GM-CSF, which in turn facilitates the infiltration of phagocytes into the CNS and activates CNS-resident phagocytes (microglia), thereby contributing to myeloid-mediated tissue immunopathology. Furthermore, anti-GM-CSF autoantibodies can be detected in the cerebrospinal fluid of patients with cryptococcal meningitis, albeit at lower concentrations than in the circulation [14, 16]. Based on these distinct pathophysiological considerations, it can be suggested that *Nocardia* has the ability to cross the alveolar barrier, even in the absence of clinical lung involvement, and migrate more readily to the brain parenchyma. Notably, within our cohort, lung nocardiosis was observed in "only" 60% of cases, in sharp contrast with previous studies involving immunocompromised hosts [2, 4–6, 8], which reported lung involvement in 85%–90% of patients.

Despite the high prevalence of brain involvement and disseminated infection in our cohort, the overall 1-year mortality

Table 4. Published Reports of Nocardia Infection in Patients With Anti–Granulocyte-Macrophage Colony-Stimulating Factor Autoantibodies

Reference	Sex/ Age, y	Clinical Features	Site of Infection	*Nocardia* Species	Comorbidities	Coinfection	Outcome[a]	Relapse	PAP Diagnosis
Rosen et al [15]	M/44	Confusion, headache, blurry vision	Brain	*N paucivorans*	…	…	Alive	…	No[b]
	M/73	Fever, cough, hemoptysis, asthenia, cutaneous lesions, confusion	Brain, lung, skin	*Nocardia* spp	…	*Aspergillus fumigatus*	Alive	Neurologic relapse	No
	M/61	Focal neurological signs, headache, seizures	Brain, lung	*N farcinica*	…	…	Alive	Neurologic relapse	No
	F/52	Not specified	Brain, lung	*N asteroides*	Diabetes mellitus	*Cryptococcus* spp	Alive	…	No
Hammound et al [25]	M/50	Focal neurological signs	Brain, lung	*N paucivorans*	…	…	Alive	…	No
Berthoux et al [22]	M/40	Focal neurological signs	Brain	*N abscessus*	…	…	Alive	…	Yes[c]
Yamaguchi et al [21]	M/37	Cough	Lung	Not specified	…	…	Alive	…	Yes[c]
Ekici et al [24]	M/62	Fever, sweat, chest pain	Lung	*N brasiliensis*	MGUS	…	Alive	…	Yes[c]
Wu et al [23]	M/42	Not specified	Lung[d]	Not specified	…	…	Alive	…	Yes[c]
Lee et al [26]	M/50	Alteration in mental status	Brain	Not specified	…	…	Alive	…	Yes[c]
Mabo et al [19]	M/55	Not specified	Lung, muscle	Not specified	…	*Pseudomonas aeruginosa*	Alive	…	Yes[c]
	F/35	Cough	Lung	*N amamiensis/ pneumoniae*	…	…	Alive	…	Yes[c]
	F/48	Weight loss	Brain, lung	Not specified	…	…	Alive	…	Yes[c]
	M/41	Dyspnea	Lung	*N abscessus*	…	…	Alive	…	Yes[c]
	M/37	Cough, dyspnea, weight loss	Lung	Not specified	Cardiomyopathy	*Staphylococcus aureus*, *Mycobacterium chimaera*	Alive	…	Yes[c]
	M/34	Cough, dyspnea	Brain	*N abscessus*	Hemochromatosis, prostate cancer	…	Alive	…	Yes[c]
	M/56	Cough, dyspnea, weight loss	Lung	*N abscessus*	…	…	Alive	…	Yes[c]
	M/34	No symptoms	Brain	*N abscessus*	…	…	Alive	…	Yes[c]
	M/40	Dyspnea	Brain	*N paucivorans*	…	…	Alive	…	Yes[c]
	M/43	Cough	Brain	*N paucivorans*	…	…	Alive	…	Yes[c]

Other cases of nocardiosis associated with PAP have been described, but the presence of anti-GM-CSF antibodies was not specified.

Abbreviations: F, female; GM-CSF, granulocyte-macrophage colony-stimulating factor; M, male; MGUS, monoclonal gammopathy of undetermined significance; PAP, pulmonary alveolar proteinosis.

[a]Outcome at the end of follow-up.

[b]Infiltrates on lung CT scan but normal respiratory function tests; PAP diagnosis not retained.

[c]PAP diagnosis (n = 15): before nocardiosis diagnosis (n = 4), at the time of nocardiosis diagnosis (n = 5), after nocardiosis diagnosis (n = 6, the median duration from nocardiosis diagnosis to PAP diagnosis was 2 months [IQR 1–4]).

[d]Absence of brain imaging.

rate was remarkably low, in contrast to higher rates observed in solid organ (16.2%) and hematopoietic cell (40%) transplant patients [3–6]. Interestingly, this mortality rate is comparable to that observed in patients with a primary immunodeficiency, particularly in chronic granulomatous disease [8]. It is worth noting that previous studies have not definitively determined whether dissemination is responsible for higher mortality compared to localized disease [3, 45]. In a recent study [10] exploring factors associated with nocardiosis dissemination, in which isolated brain involvement was considered as disseminated infection, the overall mortality rate was significantly higher in the disseminated subgroup. However, it is important to highlight that a majority of patients had comorbidities, with 54.5% of them being classified as immunocompromised. Based on our data and another recent study [9], it can be suggested that dissemination per se is not a prognostic factor, and the presence of comorbidities and/or immunocompromised conditions plays a more significant role in determining prognosis.

Anticytokine autoantibodies are commonly detectable in sera from healthy individuals, with a variable prevalence [46, 47]. Anti-GM-CSF autoantibodies have been identified in healthy controls and intravenous immunoglobulin, but at levels 10- to 1000-fold lower than in patients with PAP [48]. Moreover, the differences between healthy individuals and aPAP patients regarding the targeted GM-CSF epitopes, binding affinity, or the relative composition of neutralizing and nonneutralizing GM-CSF autoantibodies remain unknown.

In our cohort, only 1 case of aPAP occurred at 1 year, but it is premature to conclude that there is a low risk of PAP following nocardiosis in patients with anti-GM-CSF autoantibodies. Indeed, among the 20 cases published so far, aPAP was diagnosed in 4 patients before, 6 patients after, and in 5 patients at the time of diagnosis of nocardiosis. Conversely, among patients previously diagnosed with PAP, *Nocardia* infection was the most common opportunistic infection, comprising approximately 44% of the infections [18, 19]; additionally, patients who developed nocardiosis had higher anti-GM-CSF autoantibody titers at the time of aPAP diagnosis [19]. On the other hand, including patients with anti–GM–CSF autoantibodies and a diagnosis of nocardiosis, cryptococcosis, or aPAP, patients with aPAP tended to have higher levels of anti–GM-CSF autoantibodies; however, there was no significant difference between groups in terms of the neutralizing activity of anti-GM-CSF autoantibodies [16]. Long-term clinical and biological data will be crucial to assess the potential overlap in clinical phenotypes and definitively establish the temporality between these different entities.

Our study has several limitations, including its small sample size, but it was a prospective study with minimal missing data. As the decision to test for anti-GM-CSF autoantibodies in patients with nocardiosis was left to the physician in charge, it is possible that we missed some patients who were not tested. However, as the detection of anti-GM-CSF autoantibodies was performed in a single routine laboratory in France, we can be certain that we included all cases of nocardiosis among those who tested positive for anti-GM-CSF autoantibodies during the study period.

In conclusion, in this first prospective, multicenter study of nocardiosis in patients with anti-GM-CSF autoantibodies, we report common brain involvement but a low mortality rate. The occurrence of aPAP over the first year after diagnosis is infrequent, but further long-term follow-up studies are ongoing to establish its temporal relationship with nocardiosis.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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