Nocardiosis is a rare cause of infection that usually affects immunocompromised adult patients and might not be recognized by pediatricians. We report a fatal case of disseminated nocardiosis in a previously healthy child initially admitted for an abdominal mass with suspicion of a renal malignant tumor. The patient, originating from Mali without any medical history, displayed abdominal pain with progressive altered general status. Laboratory and imaging findings revealed lymphocytic meningitis and disseminated abscesses in the brain and the cerebellum and a large number of cystic lesions of the kidney. Despite being administered wide-spectrum antibiotics and antituberculous and antifungal therapies with an external ventricular drainage for intracranial hypertension, the patient died 6 days after his admission. *Nocardia* spp was cultured from a renal biopsy and the cerebrospinal fluid. Species identification and antibiotic susceptibility were obtained later, revealing a multidrug-resistant isolate of the *Nocardia elegans/aobensis/africana* complex. This case reveals the difficulties of diagnosing nocardiosis, in particular in children not known to be immunocompromised, because we face multiple differential diagnoses and the importance of treating nocardiosis appropriately because of intrinsic resistance issues.

*Nocardiosis* is primarily an opportunistic infection caused by *Nocardia* spp, a ubiquitous aerobic actinomycete commonly found in the environment. Ninety species of *Nocardia* are currently known to exist, and 30 species are considered clinically important, including *Nocardia cyriacigeorgica, Nocardia farcinica/kroppenstedtii complex, Nocardia nova, Nocardia abscessus, Nocardia brasilienis, Nocardia wallacei,* and *Nocardia beijingensis,* with a distribution that differs significantly around the world.1-3 The antimicrobial susceptibility pattern of *Nocardia* spp differs between species.4 After an exogenous contamination (eg, cutaneous traumas, inhalation), *Nocardia* spp can cause cutaneous or invasive diseases, the latter mainly affecting immunosuppressed patients.2 Systemic infections can be localized in the lung (60%–70% of cases), the central nervous system (CNS) (5%–6% of cases), or disseminated (13% of cases).2 Diagnosis of nocardiosis can be difficult both clinically and microbiologically and is often delayed, which contributes significantly to mortality.2 We report here the case of a supposedly immunocompetent child from Mali presenting a disseminated nocardiosis because of an uncommon resistant species.

Fulminant Nocardiosis Due to a Multidrug-Resistant Isolate in a 12-Year-Old Immunocompetent Child

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abstract

*Nocardiosis* is an uncommon disseminated infection due to filamentous aerobic bacteria of the *Nocardia* genus. Although most cases occur in immunocompromised patients, initiation of antibiotics on an abnormal abdominal mass with suspicion of a renal malignant tumor in a previously healthy 12-year-old child was performed. The patient presented with fever, altered general status, and abdominal pain. Imaging revealed lymphocytic meningitis and disseminated abscesses in the brain and cerebellum and a large number of cystic lesions of the kidney. Despite being administered antibiotics, antifungal therapies, and an external ventricular drainage, the patient died 6 days after admission. *Nocardia elegans/aobensis/africana* was identified as the causative agent. This case reveals the difficulties of diagnosing nocardiosis, in particular in children not known to be immunocompromised, because we face multiple differential diagnoses and the importance of treating nocardiosis appropriately because of intrinsic resistance issues.

Dr Senard drafted the initial manuscript; Dr Blanot managed the patient and reviewed the text; Dr Jouvion interpreted histopathologic slides and reviewed the text; Dr Rodríguez-Nava performed *Nocardia* identification and susceptibility testing and reviewed the text; Prof Lortholary managed the patient and reviewed the text; Dr Join-Lambert conducted laboratory testing and critically reviewed and revised the manuscript; Dr Toubiana managed the patient, coordinated and supervised data collections and the draft of the manuscript, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspect of the work.

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References

A 12-year-old patient of Malian origin was admitted to our hospital for a renal mass. The patient had no personal or family medical history. His current medical history started in Mali with cough, fever, asthenia, and anorexia associated with progressive abdominal pain and vomiting. There was no evidence of a previous cutaneous wound. Five months later, he was hospitalized as his state worsened with persistent fever and headache, significant loss of weight (~10 kg), and macroscopic hematuria. Blood tests revealed anemia (7 g/dL), an elevated erythrocyte sedimentation rate (135 mm/hour), and a normal renal function. Ultrasonography results revealed left hydronephrosis with a heterogeneous kidney, hypodensities, and calcifications. Intravenous urography results revealed a nonfunctioning left kidney. A renal malignant tumor (ie, nephroblastoma) was suspected, and the patient was transferred to our hospital in France.

At admission, the patient was afebrile, pale, had diffuse abdominal and back pain, and a conserved hemodynamic state. A neurologic examination revealed meningeal and pyramidal irritation. Blood test results revealed an acute inflammatory syndrome with an elevated white blood cell count (23,400/mm³, 82% of polymorphonuclear neutrophils) and high C-reactive protein and procalcitonin levels (123 mg/L and 1.28 μg/L, respectively). The results of a whole-body tomodensitometry revealed numerous lesions in the brain and the cerebellum after contrast injection, a pulmonary consolidation of the left lower lobe, and a large number of cysts in the kidney (Fig 1A). The CSF was purulent with 1320 cells/µL (89% of polymorphonuclear neutrophils). The results of a direct examination and Gram-staining of CSF were negative. The isolate was identified to the genus level as Nocardia spp by the Andromas matrix-assisted laser desorption/ionization–time of flight mass spectrometry system. The condition of the patient worsened and the patient died on day 6 of hospitalization because of cerebral herniation. The autopsy revealed a purulent peritonitis and multiple abscesses of the left kidney and brain, located in the supratentorial area and in the posterior fossa (Fig 3 A–C).

**FIGURE 1**
A. Abdominal and chest computed tomography. Shown is a multilocular abdominal mass of fluid density with septations in the left kidney. Thin septations and gas in some cysts were enhanced in postcontrast images. Pulmonary consolidation of the left lower lobe is also shown. B. Cerebral MRI. Multiple abscesses are shown, disseminated in the brain and cerebellum; meningitis, left ventriculitis, and ischemic injury in the area of the left middle cerebral artery are also shown.
Histopathological analysis of the brain revealed multifocal abscesses (generally located at the gray-white matter junction) that extended to the ventricles and meninges and were associated with a diffuse edema. Gomori-Grocott staining results revealed multifocal aggregates of rod-shaped bacteria forming branching filaments, which is a morphology compatible with Nocardia spp (Fig 3 D–O). Nocardia isolates were sent to the French reference center for Nocardia for species identification and antimicrobial susceptibility testing. The isolate belonged to the N. elegans/aobensis/africana complex, as assessed by a 1372-nucleotide fragment of the rrs gene sequencing with similarities of 98.4%, 98.1%, and 97.96%, respectively. The isolate was highly resistant to imipenem (minimum inhibitory concentration >32 µg/mL) and only susceptible to sulfamethoxazole/trimethoprim, moxifloxacin, linezolid, and tigecycline (Table 1).

**DISCUSSION**

We describe here a rare case of fatal systemic nocardiosis in a child who was HIV-negative without any previous history of infection. The subacute clinical course and the multiple organ involvement in the immunocompetent child initially misled the physicians to a diagnosis of neoplasia or tuberculosis. The Nocardia isolate belonged to the rare N. elegans/aobensis/africana complex and was particularly resistant to antibiotics.

Nocardiosis is a rare disease, but its incidence seems to be increasing worldwide, reaching 0.45 to 0.87 per 100,000 inhabitants in northern countries. In Africa, the few reported cases of invasive nocardiosis mainly affected adult patients who are HIV-positive. Most of the other adult patients who develop nocardiosis have an underlying disease, such as organ transplantation, hematologic malignancy, or low CD4 T-lymphocyte counts, or are under immunosuppressive treatment such as glucocorticoids. Although less frequent than in adults, nocardiosis has also been reported in immunosuppressed children with relative similar characteristics (including renal transplantation, anti-tumor necrosis factor α treatment, and chronic granulomatous disease) and in patients with cystic fibrosis. In immunosuppressed patients, nocardiosis should be considered as a differential diagnosis of many other opportunistic diseases that are associated with abscesses in lungs and the CNS, such as fungi (eg, *Cryptococcus* spp, *Aspergillus* spp), toxoplasmosis, or nontuberculous mycobacteria.

Only a few cases of invasive nocardiosis have been reported in immunocompetent children, involving brain or lung disease in most of the cases, sometimes mimicking a tumor, lung metastases, or juvenile idiopathic arthritis. Authors have systematically reported initial misdiagnosis in immunocompetent children, sometimes misled by a transient improvement under a broad-spectrum antibiotic. Regarding our patient, the lung, brain, and renal localizations of the disease led to a suspicion of tuberculosis or parasitic (cysticercosis), fungal, or multiresistant pyogenic infection, with subsequent adjunction of large empirical antibiotic therapy and antituberculous and antifungal agents. Computed tomography images of consolidation and nodules that progress to cavitation are typical but not systematic. Cerebral MRI can detect ring-enhancing lesions with occasional surrounding edema and mass effect, as observed in pyogenic abscesses, toxoplasmosis, and lymphoma. The delay in diagnosis and the inappropriate antibiotic treatment were fatal for our patient, reflecting the importance of a microbiological diagnosis of the disease. Indeed, the mortality of systemic nocardiosis is high (estimated between 14%–40%) depending on CNS involvement and dissemination, underlying comorbidities, and antimicrobial susceptibility of the isolate.

The microbiological diagnosis of *Nocardia* can be a difficult task in the microbiology laboratory because *Nocardia* can require 2 to 21 days to grow on routine culture media depending on the species. Moreover, because of rapidly evolving taxonomy, species identification often requires advanced molecular identification methods. Consequently, microbiologists must be informed of the suspected diagnosis. Matrix-assisted laser desorption/ionization--time of flight
mass spectrometry is a reliable method to identify *Nocardia* isolates,\textsuperscript{5,26} but in our case, identification was only obtained at the genus level, probably because the spectrum of the isolate was not in the database. Species identification of this *Nocardia* isolate required molecular methods, revealing that the strain was close to the *N. elegans/aobensis/africana* complex,\textsuperscript{3} recently discovered species with high phylogenetic similarities. *N. africana* was discovered in 2001 in Sudan in 8 patients with lung disease,\textsuperscript{27} and *N. elegans* has been isolated in sputum, skin abscess, and vitreous fluid.\textsuperscript{28} The species found here is also close to *N. aobensis*, which was discovered in Japan in 2004 from 5 pulmonary isolates.\textsuperscript{30}

In this case report, we highlight that empirical treatment strategy can be inactive because of antimicrobial resistance. Our strain showed a drug resistance pattern similar to *N. elegans* and *N. aobensis*.\textsuperscript{29,30} However, unlike *N. aobensis* and *N. elegans*, our strain was resistant to all β-lactams, aminoglycosides, and quinolones except for moxifloxacin, which represents a characteristic feature of our strain. The strain was susceptible only to sulframethoxazole/trimethoprim, linezolid, tigecyclin, and moxifloxacin. Sulframethoxazole/trimethoprim constitutes historically the cornerstone of

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<th>Table 1: Antimicrobial Susceptibility of the <em>Nocardia</em> Isolate (µg/mL)</th>
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I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, sensitive.

* Antimicrobial susceptibility testing was performed by using the microdilution method according to the Clinical and Laboratory Standards Institute standard M24-A2 (CLSI, 2011).

FIGURE 3
Gross examination and histopathological analysis of the brain. Gross examination revealed suppurative meningitis, multifocal abscesses located at the gray-white matter junction, and cerebral edema with herniation (A–C). Histopathological analysis confirmed the gross examination results, with multifocal abscesses located in the cortex, the smallest measuring ∼800 µm in diameter, well delineated (D), circled by a marked activation of microglial cells, gliosis, and peripheral infiltration of neutrophils (E). The largest abscesses could measure several millimeters in diameter (F) and were also well delineated (G). In the center of these large abscesses, we observed cell debris (necrosis) and fragmented neutrophils (pus) (H). An extension to the meninges (I) and ventricles (J–L) was also detected with either destruction of choroid plexus (J and K) or infiltration of the ventricles by neutrophils (L). Abscesses and extension to the meninges and ventricles were also detected in the cerebellum (M and N). Gomori-Grocott staining (O) revealed the presence of positive filamentous bacteria forming small aggregates, a morphology compatible with *Nocardia* spp.
nocardioms treatment because of its large spectrum of efficiency whatever the species of Nocardia involved and also because of a good tissue diffusion pattern.\textsuperscript{25,31} However, a combined antibiotic therapy (generally the addition of amikacin and carbapenem) is preferred for immunosuppressed patients with local disease or for disseminated infections when the diagnosis is suspected.\textsuperscript{2} Because the antibiotic susceptibility profile of Nocardia spp depends on the species,\textsuperscript{4} the antibiotic regimen should be guided by the involved species.\textsuperscript{10} The treatment could be then simplified with the results of antibiotic susceptibility testing.\textsuperscript{10} Finally, an early combined surgical approach might have also been beneficial for our patient.\textsuperscript{2}

CONCLUSIONS
Our patient presented with fatal invasive nocardiosis because of a rare multi-resistant isolate. Such nocardiosis has, to our knowledge, never been described in an immunocompetent child. Regarding the high mortality rate of disseminated nocardiosis, this diagnosis should be considered early when facing an infection with multiple organ sites not responding to conventional antibiotics. Considering the various antibiotic susceptibility patterns of Nocardia spp, diagnostic procedures should be rapidly performed to confirm the diagnosis, identify the isolate to the species level, and complete susceptibility testing. Clinical severity, geographical background, and antibiotic resistance associated with the suspected species should be taken into account by practitioners when choosing the empirical antimicrobial combination treatment.

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ABBREVIATIONS
CNS: central nervous system
CSF: cerebrospinal fluid

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