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Nocardia brasiliensis Infection Mimicking Juvenile Idiopathic Arthritis in a 4-Year-Old Girl

abstract

Nocardia are ubiquitous environmental saprophytes that cause pneumonia and disseminated disease in immunocompromised patients. They can also cause localized cutaneous and soft tissue infections in healthy people after direct percutaneous inoculation. *Nocardia* arthritis is rare in both forms of the disease. Here we present the first published case of a child with septic arthritis caused by *N brasiliensis*. Importantly, this otherwise well 4-year-old girl had no known history of trauma but presented with transient cutaneous lesions and a 6-week history of arthritis involving the right fourth digit proximal interphalangeal joint without accompanying fever or raised systemic inflammatory markers. She received a diagnosis of juvenile idiopathic arthritis and underwent antiinflammatory and immunosuppressant therapy. After 2 months she developed frank septic arthritis, which necessitated a surgical joint washout, from which an intraoperative swab grew *N brasiliensis*. The patient received 6 months of high-dose trimethoprim–sulfamethoxazole and remains well more than 4 years after treatment. This unusual case highlights the importance of considering an indolent infection from slow-growing organisms, including *Nocardia*, when diagnosing the oligoarthritis subtype of juvenile idiopathic arthritis. This is especially relevant when a single joint is involved and response to antiinflammatory therapy is suboptimal because antiinflammatory agents may mask evolving signs of infection. *Pediatrics* 2013;132:e1424–e1427

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KEY WORDS

arthritis, juvenile idiopathic arthritis, oligoarthritis subtype, *Nocardia*, septic arthritis, trimethoprim–sulfamethoxazole

ABBREVIATIONS

CRP—C-reactive protein
ESR—erythrocyte sedimentation rate
JIA—juvenile idiopathic arthritis
PIPJ—proximal interphalangeal joint
RF—rheumatoid factor
TMP-SMX—trimethoprim–sulfamethoxazole

Dr Kapur drafted the initial manuscript; Dr Adib reviewed and revised the manuscript; Dr Grimwood conceived the case report and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Nocardia are aerobic, filamentous Gram-positive bacteria belonging to the *Actinomycetales* order.¹ They are ubiquitous environmental saprophytes and are found in soil, decaying organic matter, and water worldwide. Important human pathogens in the *Nocardia* genera include *N asteroides* and *N brasiliensis*. The organisms are readily aerosolized with dust, and in immunocompromised patients inhalation can lead to pulmonary involvement and dissemination, especially in those with chronic granulomatous disease or impaired cell-mediated immunity after bone marrow and organ transplantation, HIV infection, or long-term corticosteroid therapy.² These organisms can also cause localized cutaneous and lymphocutaneous infections in healthy children by direct inoculation after soil contamination of open wounds.³ Typically, *N asteroides* results in pulmonary and disseminated disease, whereas *N brasiliensis* is more often associated with cutaneous and soft tissue infections.⁴

Arthritis is a rare presentation of *Nocardia* infection. Most reported cases involve immunocompromised adults with disseminated disease or previously healthy people after a penetrating injury to the affected joint.^{4–8} To our knowledge only 3 cases of *Nocardia* septic arthritis have been reported in children.^{9–11} All were previously healthy children who had sustained a recent percutaneous injury to the knee or adjacent soft tissues, after which *N asteroides* was isolated from the septic joint. We now report a pediatric case of *N brasiliensis* arthritis involving the proximal interphalangeal joint (PIPJ) of the right fourth digit. This occurred without a known history of trauma and was diagnosed and treated initially as juvenile idiopathic arthritis (JIA).

CASE REPORT

A previously healthy 4-year-old girl presented to her family physician with

swelling and erythema at the base of the right fourth digit and with 2 small erythematous vesicular lesions on the palmar aspect of the right fourth metacarpal. There was no known history of injury, and a cutaneous infection was suspected. She received oral flucloxacillin, and over the next 7 days the palmar lesions resolved. However, the swelling progressed distally during the next 4 weeks to involve the PIPJ. This was accompanied by localized joint pain, tenderness, and restricted movement. There was no fever, respiratory symptoms, adenopathy, new cutaneous lesions, or rash. She saw her pediatrician, who noted the fusiform, boggy swelling of the right fourth digit PIPJ and slight erythema in the same finger but no tenderness. The full blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and plain hand radiograph were normal. A whole-body bone scan showed hyperemia of the right fourth digit PIPJ with increased bone tracer uptake. The patient was treated expectantly for 10 days, but because no improvement occurred she was referred for a rheumatology consultation at our institution.

The pediatric rheumatologist noted a maternal history of palindromic arthritis, confirmed the previous clinical observations, and made a diagnosis of oligoarthritis subtype JIA. Antinuclear antibodies and rheumatoid factor (RF) were negative, and an ophthalmology examination for uveitis was normal. The joint was injected with a long-acting corticosteroid, triamcinolone acetonide, although an aspirate for synovial fluid for microscopy and culture was not undertaken at this time. Complete resolution of the joint abnormalities and return of normal function followed within a few days of the procedure. However, this effect was not sustained, and after 2 months the swelling recurred, and she received a second intraarticular corticosteroid injection.

The patient also began once-weekly, low-dose (15 mg/m²) oral methotrexate. This time the PIPJ swelling did not improve. When the patient was seen 3 weeks later, marked pain and erythema were present, as was a small, tense, and tender subcutaneous pustule in the volar aspect of the affected finger. The CRP and ESR had increased to 18 mg/L and 28 mm/hr, respectively. A diagnosis of septic arthritis was made, and she underwent urgent surgical drainage and joint washout before commencing intravenous flucloxacillin and cefotaxime. Large quantities of purulent debris and granulation tissue were observed in the soft tissue. A synovial biopsy reported focal necrosis with neutrophils, lymphocytes, and multinucleated giant cells consistent with septic arthritis. The incision was left open initially to facilitate drainage.

Gram stain of the purulent synovial fluid did not demonstrate any organisms, but aerobic cultures of this material on blood and chocolate agar plates grew dry, cream-colored, pitted colonies after 3 days from which filamentous Gram-positive branching rods were identified. The organism was non-acid fast on Ziehl–Neelsen stain and acid fast on modified Ziehl–Neelsen stain, suggesting *Nocardia*, and the organism was confirmed as *N brasiliensis* by sequencing with the 16s ribosomal DNA primer.¹² The isolate was susceptible to trimethoprim–sulfamethoxazole (TMP–SMX), tobramycin, amikacin, and minocycline, had intermediate susceptibility to amoxicillin–clavulanate and cefoxitin, and was resistant to erythromycin, ciprofloxacin, and imipenem.

Chest and brain imaging found no evidence of dissemination. The antibiotics were changed to intravenous TMP–SMX (5 mg/kg every 6 hours TMP component) and cefotaxime (50 mg/kg every 8 hours). All other drugs were ceased.

Over the next 10 days and after 2 additional joint washouts, the arthritis improved. After 2 weeks of intravenous antibiotics she was sent home on a 6-month course of oral TMP-SMX (5 mg/kg every 8 hours of TMP). The CRP normalized before hospital discharge, and the ESR became normal 2 months later. At the end of treatment the right fourth digit PIPJ was normal other than for a slight flexion deformity. Screening evaluation of her immune function revealed negative HIV serology and normal neutrophil oxidative burst, T- and B-cell lymphocyte subsets, and serum immunoglobulins. More than 4 years later she remains well off all treatments, without recurrence or signs of other joint involvement.

DISCUSSION

This case of *N brasiliensis* septic arthritis in a previously healthy, immunocompetent child shows that the organism can infect a joint without a known history of percutaneous inoculation. Furthermore, the subacute presentation and absence of fever and raised systemic inflammatory markers

in this young girl led to an initial diagnosis of JIA oligoarthritis subtype and treatment with antiinflammatory agents.

Previous case reports of septic arthritis from *N brasiliensis* have included only adults, and in each case the knee was involved.^{13–16} In 2 patients immunocompromised from long-term corticosteroid therapy, septic arthritis arose from pulmonary infection and hematogenous dissemination.^{13,14} The remaining 2 cases had a history of knee trauma.^{15,16}

In contrast, the 3 prior pediatric case reports involved previously healthy children who had sustained a percutaneous wound to the knee before developing features of septic arthritis and isolation of *N asteroides* from synovial fluid (Table 1).^{9–11}

JIA includes all forms of arthritis of unknown etiology that persists for at least 6 weeks and has its onset before 16 years of age.^{17,18} It is the most common chronic rheumatologic childhood disease, with its oligoarthritis subtype being an important differential diagnosis in any subacute mono-

arthritis in children. The diagnosis of JIA is mainly clinical, with antinuclear antibodies, RF, or HLA-B27 genotype helping in subclassification into respective subtypes. RF is of additional value only in polyarticular JIA. The most useful radiologic investigation is MRI, although even this investigation does not always differentiate between septic and noninfective causes of synovitis. Such differentiation is essentially made on clinical grounds, with patients with septic arthritis expected to have a toxic appearance, marked painful limitation of joint movement from involuntary muscle spasm, and short duration of symptoms from the time of onset. In comparison, peripheral joints with synovitis from JIA are usually swollen, but generally not markedly tender, and often without substantial restriction of movement, especially early in the disease. Elevated systemic inflammatory markers may also not be present. Screening for uveitis should always be done in oligoarticular JIA. Commonly, monoarthritis in oligoarticular JIA involves large joints, especially the knee joints.

TABLE 1 Reported Cases of *Nocardia* Arthritis in Children

Case	Underlying Disease	Joint	Inoculation Route	<i>Nocardia</i> sp	Time to Initial Presentation ^a	Culture Diagnosis ^b	Inflammatory Markers ^c	Definitive Treatment	Outcome
9-yr-old boy ⁹	Nil	Knee	Puncture wound	<i>N asteroides</i>	7 d	3 d	Not reported	Arthrocentesis × 2 IV ampicillin first 3 wk Oral TMP-SMX next 3 wk	Cure
11-yr-old boy ¹⁰	Nil	Knee	Thorn puncture wound	<i>N asteroides</i>	3 d	12 d	ESR 22 mm/h	Arthrotomy, removal of thorn Oral TMP-SMX for 3 mo	Cure
9-yr-old girl ¹¹	Nil	Knee	Rooster puncture wound	<i>N asteroides</i>	8 wk	18 d	CRP 98 mg/L ESR 69 mm/h	Arthrocentesis × 3 Surgical drainage × 3 IV and oral TMP-SMX for 4 mo IV amikacin for 6 wk Oral azithromycin for 1 mo	Cure
Current case: 4-yr-old girl	Nil	Proximal interphalangeal joint	Possible percutaneous route	<i>N brasiliensis</i>	4 mo	3 d	CRP 2 mg/L ESR 6 mm/h	Surgical drainage and washout × 3 IV TMP-SMX + cefotaxime for 2 wk Oral TMP-SMX for 6 mo	Cure

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IV, intravenous; TMP-SMX, trimethoprim-sulfamethoxazole.

^a Time from the inoculation injury to hospitalization; for the current case it refers to the time from start of initial symptoms to hospitalization.

^b Time taken for cultures to grow the organism.

^c The results of systemic inflammatory markers when first measured.

Small joint monoarthritis should therefore be investigated for unusual organisms, including joint aspiration for culture or molecular diagnostic testing whenever possible. Similarly, other conditions such as psoriatic arthritis should be also considered. Therefore, differentiating indolent small joint septic arthritis (especially if caused by unusual organisms) from oligoarthritis in the immunocompetent host may be challenging, particularly if constitutional, microbiological, and hematologic abnormalities are absent. Because *Nocardia* is a slow-growing organism, the diagnosis can be delayed while one is waiting for the organisms to appear on culture. Indeed, *Nocardia* should be included among pathogens such as *Mycobacteria*, *Actinomyces*, *Borrelia*

burgdorferi (Lyme disease), and fungi (eg, *Sporothrix* and *Candida*) that can cause subacute or chronic infective arthritis and be confused initially with JIA.¹⁹

Although inoculating *Nocardia* into the joint de novo from a contaminated intraarticular needle is possible theoretically, the prior cutaneous lesions supports instead an unrecognized inoculation event followed by contiguous spread to the nearby PIPJ.^{4,8} Indeed, the initial skin lesions with symptoms and signs of inflammation migrating to a neighboring joint would be unusual for JIA. Furthermore, because the child remains free of JIA symptoms 4 years after treatment, this provides additional evidence that JIA is very unlikely to have been the primary event.

In summary, *N brasiliensis* is a soil-dwelling organism that should be considered in the differential diagnosis of arthritis in children when there is delayed presentation or history of trauma to the joint or adjacent soft tissues within 1 to 2 months of symptom onset. Because the organism can be slow growing, cultures should be held for 2 to 3 weeks. As this case illustrates, the prolonged latency period and absence of both fever and a systemic inflammatory response initially can make clinical differentiation from JIA difficult. However, this and the 3 previously reported pediatric cases also suggest that an excellent prognosis is expected with a timely microbiological diagnosis and appropriate surgical and medical management.

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