SAJS

Case Report

Disseminated nocardiosis masquerading as abdominal tuberculosis

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Summary

A 32-year-old patient was admitted with a community-acquired pneumonia. She had clinical evidence of AIDS and chest X-ray features consistent with pulmonary tuberculosis. While in the ward she developed an acute abdomen necessitating laparotomy, at which a diagnosis of abdominal tuberculosis was made. Sputum and intraoperative pus specimens grew a multiresistant *Nocardia brasiliensis*. Microbiological investigations for tuberculosis were negative. The patient died after a short ICU admission from multiple organ dysfunction syndrome.

Nocardia species are long, filamentous, Gram-positive, aerobic organisms belonging to the actinomycete group, which often aggregate in branching chains.[1,2] They are weakly acid-fast and can be stained using a modified acid-fast technique (Kinyoun stain).[3] *Nocardia* species mainly cause opportunistic disease in humans with compromised immunity.[1,4] The lung is most commonly involved, followed by the central nervous system and skin.[2,5-9] Although *Nocardia brasiliensis* is a documented human pathogen, the literature reports *Nocardia asteroides* as the more prevalent species. However, *N. brasiliensis* occurs more frequently in immunocompetent individuals, suggesting greater virulence, and the clinical spectrum in this group of patients is limited to lymphocutaneous disease following traumatic inoculation of the skin.[2]

The pathogenesis of *Nocardia* infection is not fully understood although there is evidence that the bacteria are facultative intracellular pathogens with specific virulence characteristics capable of evading the host immune surveillance. However, after phagocytosis, virulent *Nocardia* species inhibit phagolysosomal fusion thereby evading oxidative death and survive as cell wall-deficient forms (L-forms). The specific immune response provided by activated T-lymphocytes is responsible for direct death or cytokine-mediated elimination of the organism. Specific antibodies have a limited role in the elimination of this pathogen.[6] Human infection is acquired mostly by inhalation, but may also occur by percutaneous inoculation.[5] We describe a patient with AIDS and peritonitis in whom a diagnosis of *Nocardia* peritonitis was missed because of the clinical similarity between *Nocardia* and tuberculous peritonitis.

Case report

A 32-year-old HIV-positive woman was admitted with a community-acquired pneumonia to our tertiary care hospital in February 2002. She had been referred by a local clinic with a 1-month history of productive cough, chest pain, loss of weight and night sweats. In addition, she had vomiting and abdominal pain of one week's duration. In June 2001 the patient had been diagnosed with pulmonary tuberculosis using chest radiography and sputum, and had been compliant on antituberculous treatment (rifampicin, isoniazid, ethambutol, pyrazinamide) for 8 months.

On admission the patient was emaciated, pale, had a pyrexia of 40°C, blood pressure (BP) 108/70 mmHg, pulse 148 beats/minute, oral thrush and generalised lymphadenopathy. Examination of her respiratory system revealed tachypnoea and bi-basal crepitations. She also had a tender abdomen with a 6 cm hepatomegaly. Splenomegaly was absent and no other masses were palpated. Her white cell count was 7 X 10^9/l (range: 4 - 11 X 10^9 /l) with an absolute lymphocyte count of 0.4 X 10^9/l (range: 1.5 - 4 X 10^9/l). Haemoglobin was 5.7 g/dl (range: 11.5 - 13.5 g/dl) and a platelet count of 124 X 10^9/l (range: 150 - 450 X 10^9/l) was recorded. Based on the United States Centers for Disease Control (CDC) criteria,[10] a clinical diagnosis of AIDS was made. Chest X-ray showed extensive bilateral shadowing consistent with severe community-acquired pneumonia and there were features consistent with pulmonary tuberculosis. After sputum specimens were taken, antituberculous therapy was recommenced empirically.

A sputum specimen received a day after admission was reported to have filamentous branching Gram-positive bacteria on microscopy. A diagnosis of nocardial pneumonia was made following a positive Kinyoun stain and the patient was commenced on co-trimoxazole.

Two days later she developed worsening abdominal pain and vomiting and an erect plain abdominal X-ray showed 'fluid levels'. After excluding pyelonephritis and gynaecological pathology, a clinical diagnosis of acute intestinal obstruction was entertained. The patient was initially managed non-operatively but she subsequently developed peritonitis which necessitated emergency laparotomy. This revealed thin pus in the peritoneal cavity. The omentum was shortened, thickened, contained pus-filled cavities and was adherent to the proximal small bowel. There was a kink in the mid-jejunum causing complete obstruction. The bowel in this area

was thin-walled but still macroscopically viable, with no perforation. The rest of the small intestine was thick-walled, with multiple nodular lesions measuring 1 - 2 mm that were suggestive of tubercles. There was no macroscopic evidence of caseation or lymphadenopathy. The supra-colic compartment was not involved in this process. The liver and other intra-abdominal organs appeared normal. The findings were macroscopically suggestive of abdominal tuberculosis.

Intraoperative pus specimens were sent for microbiological evaluation and an omental biopsy was sent for histological examination. Postoperatively the patient was managed in the intensive care unit for acidosis and renal failure. She deteriorated progressively despite resuscitation and died 2 days after surgery from multiple organ dysfunction syndrome.

The pus sent from theatre showed the same Kinyoun-positive bacilli as in the sputum. Dry, white colonies grown from sputum and pus specimens were cultured on blood and chocolated agar after 48 hours of incubation in 8% CO_2 at 37°C. The organism was identified as *N. brasiliensis* on specific biochemical tests. Susceptibility testing using the E-test method showed resistance to co-trimoxazole and imipenem while cefotaxime, tetracycline and amikacin retained susceptibility. Acid-fast staining and 8-week selective culture for *Mycobacterium* species were negative. Histological examination of the omental biopsy confirmed nocardiosis.

Discussion

Nocardiosis infection is a relatively common opportunistic infection in the immune-compromised host and the environment is the main source of the organisms.[8,11,12] The frequent antecedents are AIDS, immunosuppressive drug treatment, corticosteroid therapy, continuous ambulatory peritoneal dialysis (CAPD) and chronic illness.[1] Infections due to this organism are being reported with increasing frequency, the reasons being the wider use of immunosuppressive therapy, the AIDS pandemic, more invasive diagnostic approaches to infection in immune-compromised hosts, and a heightened index of suspicion among physicians.[13]

Most cases of *Nocardia* infection are of the pulmonary or disseminated types, *N. asteroides* being the principal pathogen.[12] Pulmonary nocardiosis is difficult to differentiate from tuberculosis and the two infections may co-exist.[11,13,14] Consequently infection with this organism is frequently underdiagnosed.[12] In most HIV-infected patients *Nocardia* infection is disseminated at the time of diagnosis and is characterised by an indolent course that may be difficult to differentiate from other systemic infections.[5]

This case illustrates the disseminated nature of this disease, its similarity to abdominal tuberculosis and the co-existence of pulmonary tuberculosis and nocardiosis. Findings at laparotomy appeared to be consistent with miliary tuberculosis except for the absence of intra-abdominal lymphadenopathy. This is not surprising, as patients with AIDS may not manifest a typical inflammatory response, and involution and degeneration of lymph nodes have been reported.[13] Although we did not have a CD_4 cell count for our patient, she did have clinical and laboratory evidence of severe immune suppression.

In populations where HIV-associated tuberculosis is common, it is possible that some patients with a negative smear for pulmonary tuberculosis may have nocardiosis.[11,15] South Africa is currently experiencing an uncontrolled tuberculosis epidemic,[11] and has among the highest HIV prevalence rates in southern Africa and in the world.[16] Consequently, nocardiosis and the difficulty in differentiating this infection from tuberculosis will continue to be a challenge to clinicians in this country.

Eight cases of nocardial peritonitis have been reported in the literature in the last three decades,[17-24] as shown in Table I. The most common organism in these reports was *N. asteroides*. The present case is the second case of *Nocardia* peritonitis due to *N. brasiliensis*, the first one having been reported by Bonacini and Walden in 1990.[18] The only case of *Nocardia* peritonitis due to *Nocardia farcinica* was reported by Liassine and Rahal in 1992.[21]

High doses of sulphonamides have remained the standard treatment.[8] Recently, however, co-trimoxazole has been used extensively and has been shown to be even more effective in disseminated disease.[5,25] The *in vitro* susceptibility results using the E-test method unexpectedly showed complete resistance to co-trimoxazole in this isolate. Resistance of this actinomycete to sulphonamides and co-trimoxazole has been shown to occur before the present case, by Aswapokee *et al.*[26] in 1977 and Jones *et al.*[4] in 2000. Interpretation of *in vitro* results is difficult and few studies have evaluated conventional susceptibility test methodology for these micro-organisms and, to date, there are no standards provided by the National Committee for Clinical Laboratory Standards.[27]

Ineffective antimicrobial therapy could have contributed to this patient's demise, but disseminated disease and a severely compromised immune system were probably overriding factors. It is likely that early pulmonary nocardiosis was missed in 2001 when the patient was treated for tuberculosis as the patient reported poor response to prolonged antituberculous therapy. Inappropriate antimicrobial agents for nocardiosis and immunosuppression contributed to abdominal dissemination of this infection.

Mortality from nocardial peritonitis ranges between 25% and 60%.[9,11,24] The patient reported here succumbed to her illness because of disseminated disease and resistance to the

TABLE I. CASES OF NOCARDIA PERITONITIS REPORTED IN THE LAST TWO DECADES

Author	Year	Aetiology	Predisposing condition
Arfania *et al.*[17]	**1981**	***N. asteroides***	**CAPD**
Rubin *et al.*[24]	**1987**	***N. asteroides***	**CAPD**
Bonacini and Walden[18]	**1990**	***N. brasiliensis***	**AIDS**
Chan *et al.*[19]	**1990**	**Not specified**	**CAPD**
Kaczmarski *et al.*[20]	**1990**	***N. asteroides***	**CAPD**
Liassine and Rahal[21]	**1992**	***N. farcinica***	**CAPD**
Lopes *et al.*[22]	**1993**	***N. asteroides***	**CAPD**
Rodriguez *et al.*[23]	**1994**	***N. asteroides***	**HIV infection**
Present case	**2003**	***N. brasiliensis***	**AIDS**

CAPD = continuous ambulatory peritoneal dialysis.

empirical antibiotics used. Of the 8 cases reported in the literature the only death was in a patient with peritonitis due to *N. brasiliensis*, reported by Bonacini and Walden.[18] That patient, too, was treated with inappropriate broad-spectrum antibiotics.

In patients with features suggestive of abdominal tuberculosis found to be smear-negative for tuberculosis, and in those who do not respond to empirical antituberculous therapy, a high index of suspicion on the part of the clinician and the laboratory personnel is essential and *Nocardia* must be considered. The microbiology laboratory needs to be alerted to the possibility of unusual infections so that the specific isolation conditions of unusual pathogens can be accommodated. We support the view of Curry,[8] viz. that because the treatment of nocardiosis is different from the treatment for the disorders it masquerades as, it is important to establish a firm diagnosis, preferably by culture. Incubation of culture plates must be prolonged to facilitate the detection of the slow-growing *Nocardia* species.[13] The diagnosis is especially important as nocardiosis is a treatable condition and aggressive management is essential. It is our recommendation that patients with suspected *Nocardia* peritonitis be commenced on treatment with co-trimoxazole after appropriate specimens have been sent for culture and susceptibility testing.

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REFERENCES

1. von Lichtenberg F. Infectious disease. In: Cotran RS, Kumar V, Robbins SL, eds. *Robbins Pathologic Basis of Disease*. Philadelphia: WB Saunders. 1989: 307-433.
2. Fergie E, Purcell K. Nocardiosis in South Texas children. *Pediatr Infect Dis J* 2001; **20:** 711-714.
3. Kinyoun JJ. A note of Uhlethuth's method for sputum examination for tubercle bacilli. *Am J Public Health* 1915; **5:** 867-870.
4. Jones N, Khoosal M, Louw M, Karstaed A. Nocardial infection as a complication of HIV in South Africa. *J Infect* 2000; **41:** 232-239.
5. Javaly K, Horowitz HW, Wormser GP. Nocardiosis in patients with human immunodeficiency virus infection. *Medicine* 1992; **71:** 128-138.
6. Beaman BL, Beaman L. Nocardia species: Host parasite relationships. *Clin Microbiol Rev* 1994; **7:** 213-264.
7. Lakshmi V, Sundaram C, Meena AK, Murthy JM. Primary cutaneous nocardiosis with epidural abscess caused by *Nocardia brasiliensis*: a case report. *Neurology India* 2002; **50:** 90-92.
8. Curry WA. Human nocardiosis. *Arch Intern Med* 1980; **140:** 818-826.
9. Sorell TC, Iredell JR, Mitchell DH. *Nocardia* species. In: Mandell GL, Bennet JE, Dolin R, eds. *Principles and Practice of Infectious Disease*. New York: Churchill Livingstone, **2000:** 2637-2645.
10. Bartlett JG, Gallant JE. Natural history and classification. In: Bartlett JG, Gallant JE, eds. *Medical Management of HIV Infection*. Baltimore, Maryland: Johns Hopkins University; 2001:1-4.
11. Marquez-Diaz F, Soto-Ramirez LE, Sifuentes-Osornio J. Nocardiosis in patients with HIV infection. *AIDS Patient Care and STDs* 1998; **12:** 825-831.
12. Baily GG, Neill P, Robertson VJ. Nocardiosis: a neglected chronic lung disease in Africa? *Thorax* 1988; **43:** 905-910.
13. Smego RA, Gallis HA. The clinical spectrum of *Nocardia brasiliensis* in the United States. *Rev Infect Dis* 1984; **6:** 164-180.
14. Greenberg AE, Lucas S, Tossou O, *et al*. Autopsy proven causes of death in HIV-infected patients treated for tuberculosis in Abidjan, Côte d'Ivoire. *AIDS* 1995; **9:** 1251-1254.
15. Lucas SB, Hounou A, Peacock C, *et al*. Nocardiosis in HIV positive patients: an autopsy study in West Africa. *Tuber Lung Dis* 1994; **75:** 301-307.
16. UNAIDS. AIDS epidemic update, 2002. **www.unaids.org** 2002.
17. Arfania D, Everett ED, Nolph KD, Rubin J. Uncommon causes of peritonitis in patients undergoing peritoneal dialysis. *Arch Intern Med* 1981; **141:** 61-64.
18. Bonacini M, Walden JM. *Nocardia brasiliensis* peritonitis in a patient with AIDS. *Am J Gastroenterol* 1990; **85:** 1432-1433.
19. Chan DTM, Cheng IKP, Chan PCK, Mok KY. Nocardia peritonitis complicating continuous ambulatory peritoneal dialysis. *Perit Dial Int* 1990; **10:** 99.
20. Kaczmarski EB, Wilkie M, Thornhill C, *et al.* Problems encountered in diagnosis of *Nocardia asterioides* peritonitis complicating CAPD. *Perit Dial Int* 1990; **10:** 106.
21. Liassine N, Rahal K. Peritonite a *Nocardia farcinica* chez un sujet en dialyse peritoneal continue ambulatoire. *Arch Inst Pasteur Algeric* 1992; **58:** 95-102.
22. Lopes JO, Alves SH, Benevenga JP, *et al*. *Nocardia asteroides* peritonitis during continuous ambulatory peritoneal dialysis. *Rev Inst Med Trop Sao Paulo* 1993; **35:** 377-379.
23. Rodriguez M, Forne M, Viver J, *et al*. *Nocardia asteroides* peritonitis in a patient with cirrhosis and human immunodeficiency virus infection. *Clin Infect Dis* 1994; **18:** 1010-1011.
24. Rubin J, Kirchner K, Walsh D, *et al.* Fungal peritonitis during continuous ambulatory peritoneal dialysis: A report of 17 cases. *Am J Kidney Dis* 1987; **10:** 361-368.
25. Smego RA, Moeller MB, Gallis HA. Trimethoprim-sulphamethazole therapy for *Nocardia* infections. *Arch Intern Med* 1983; **143:** 711-718.
26. Aswapokee P, Aswapokee N, Chirawong P, Leelarasamee A. Pulmonary nocardiosis in a patient receiving immunosuppressive agent. *Southeast Asian J Trop Med Public Health* 1977; **8:** 317-321.
27. Ambaye A, Kohner PC, Wollan PC, *et al.* Comparisons of agar dilution, broth microdilution, disk diffusion E-test, and BACTEC radiometric methods for antimicrobial susceptibility testing of clinical isolates of the *Nocardia asteroides* complex. *J Clin Microbiol* 1997; **35:** 847-852.