Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jor

Original Article

Musculoskeletal melioidosis: An under-diagnosed entity in developing countries

Hitendra G. Patil^{a,*}, Manit Gundavda^a, Vivek Shetty^a, Rajeev Soman^b,
Camilla Rodriques^c, Vikas M. Agashe^a

^a Department of Orthopaedics, Hinduja Hospital and MRC, Mahim, India

^b Infectious Diseases, Hinduja Hospital and MRC, Mahim, India

^c Infection Control Committee, Hinduja Hospital and MRC, Mahim, India

ARTICLE INFO

Article history:

Received 1 April 2015

Accepted 30 August 2015

Available online 19 September 2015

Keywords:

Melioidosis

Burkholderia pseudomallei

Musculoskeletal infection

ABSTRACT

Background: Melioidosis is a saprophytic infectious disease caused by Gram-negative soil-dwelling bacillus *Burkholderia pseudomallei*.

Materials & methods: We report three cases of musculoskeletal melioidosis that are presented to our department from 2011 to 2013.

Results: One of the patients died due to post-septicemic ARDS. The other two patients have recovered fully and are followed up for minimum of 6 months. There were no recurrences.

Conclusions: Though musculoskeletal infection due to melioidosis is not common in India, new cases are being reported from Karnataka, Goa and Southern Maharashtra. The need for diagnosing this entity is due to the fact that the septicemic form has a mortality rate that exceeds 90%, and though culture sensitivity report shows susceptibility to various antibiotics, the infection responds to only specific set of antibiotics i.e. intravenous ceftazidime and combination of trimethoprim and sulfamethoxazole.

© 2015 Prof. PK Surendran Memorial Education Foundation. Published by Elsevier, a division of Reed Elsevier India, Pvt. Ltd. All rights reserved.

1. Introduction

Melioidosis is a saprophytic infectious disease caused by Gram-negative soil-dwelling bacillus *Burkholderia pseudomallei*.¹ Also known as Vietnamese time bomb (due to prolonged incubation period US servicemen got the infection after many year returning from Vietnam).² Musculoskeletal melioidosis is endemic in parts of southeast Asia (including Thailand, Laos and southern China, Singapore, Malaysia, Burma and

Vietnam), Taiwan and northern Australia.³ Musculoskeletal infection due to melioidosis is not common in India. However, several cases of soft tissue infection have been reported in the past. New cases are being reported from Karnataka, Goa and southern Maharashtra.⁴ We report three cases of musculoskeletal melioidosis that are presented to our department from 2011 to 2013. Two patients recovered fully, and there were no recurrences at follow-up ranging from a minimum of 6 months to 30 months. One patient died due to septicemia.

* Corresponding author.

E-mail address: hitendrapatil@kem.edu (H.G. Patil).

<http://dx.doi.org/10.1016/j.jor.2015.08.001>

0972-978X/© 2015 Prof. PK Surendran Memorial Education Foundation. Published by Elsevier, a division of Reed Elsevier India, Pvt. Ltd. All rights reserved.

2. Case 1

A 43-year-old diabetic male presented two and half months after he was being treated for osteomyelitis left Femur at other institution. Tracing the history, he had developed fever along with left lower thigh pain in September 2011. Diagnosis of osteomyelitis was made and was treated with debridement. The intraoperative specimen grew acinetobacter (Gram-negative bacilli), which was resistant to aminoglycoside and colistin. Based on culture report, orthopaedic surgeon started appropriate antibiotics treatment, but pain, fever and discharge persisted. The surgeon reexplored as the patient was not improving on antibiotics and the second intraoperative culture grew *E. coli* (another Gram-negative bacilli), which was also resistant to aminoglycoside and colistin. Based on sensitivity report, intravenous antibiotics were given. Several antibiotics were tried by the surgeon, but the infection could not be brought under control. The patient was presented to our department two and a half months after onset of first symptom with marked swelling along previous incision on the lateral aspect of the left thigh with persistent discharge. He also had an abscess on medial aspect of left thigh and left ankle as well as right inguinal lymphadenopathy. He was running high fever for most of the past 10 weeks, and his WBC counts were varying between 15,000/mm to 28,000/mm with markedly raised ESR and CRP. MRI scan was suggestive of osteomyelitis with soft tissue abscess, and changes were more extensive as compared to previous scan. The patient underwent a thorough debridement and scraping of the osteomyelitic cavity after making a large window. The abscesses on the medial side of thigh and ankle were drained, but the enlarged lymph node on the right side was not addressed surgically. Specific inquiry by the infection specialist revealed that he had travelled to mines in Goa, a few months ago. Based on the history and presentation (multifocal infection, toxic state, no response to conventional antibiotics and in vitro resistance to aminoglycoside and colistin) the infection specialist suspected melioidosis, and the same was informed to the Microbiologist. The sent intraoperative culture grew *Burkholderia pseudomallei*, which was resistant to aminoglycoside and colistin. He was started on intravenous injection of Ceftazidime 2 g 8 hourly for 2 weeks and then was orally given a combination of tablets containing 160 mg Trimethoprim and 800 mg Sulfamethoxazole 8 hourly for 6 months. The wounds were managed with the help of negative suction therapy and skin grafting. Patient improved rapidly with right Inguinal node disappearing in a matter of 3 weeks. At three-month follow-up wound healed completely and no sign of active infection, and there is no recurrence of infection at thirty months follow-up.

3. Case 2

A 63-year-old male case of chronic osteomyelitis of right tibia since 1995 presented in our department in June 2013 with pain swelling and discharging sinus on medial aspect of proximal one-third of right leg with difficulty in walking. Patient was a known case of diabetes on treatment. He had sustained a right tibia fracture in 1995 and was treated with plating and local rotation flap; later on, he had developed osteomyelitis. On

examination, erythema and local warmth and tenderness were noted in right leg. The discharging sinus was present on medial aspect of right leg. Based on X-ray and MRI findings, diagnosis of osteomyelitis was made and debridement and saucerisation were done. Intraoperative tissue specimen was subjected for culture test to check the growth of *Burkholderia pseudomallei*. He was started on iv injection ceftazidime 2 g 8 hourly for 2 weeks and then orally tablet containing 160 mg trimethoprim and 800 mg sulfamethoxazole combination 8 hourly for 12 weeks. In August 2013, local rotation flap was done to cover the exposed bone. On follow-up three months, since starting of antibiotics, the flap was taken well and no signs of active infection. No recurrence of infection was observed at 6-month follow-up.

4. Case 3

A 48-year-old female, a known case of diabetics, was admitted in our department in July 2013 with multiple swellings over the body, at right shoulder, interscapular region, right hand and elbow, right leg and foot with high grade fever since 2 months. Incision and drainage were done for the abscesses and she was started on intravenous antibiotic Teicoplanin 400 mg iv once a day and Meropenem 2 g iv thrice a day in the view of systemic infection. But on third postoperative day, she complained of breathlessness and found to have tachycardia, so was shifted to ICU. She developed ARDS with multiorgan failure and went in hypercalemic arrest on 4th postoperative day and could not be revived. Though intraoperative cultures were negative, the blood culture on 3rd postoperative day from ICU grew *Burkholderia pseudomallei*. Unfortunately, by the time report arrived, the patient had succumbed to septicemia with multi-organ failure and did not survive.

5. Discussion

Melioidosis is an infection caused by facultative intracellular Gram-negative bacilli *Burkholderia pseudomallei*. It is a saprophyte found in the soil and surface water in endemic areas.⁵ Melioidosis is prevalent in many parts of India, but is under-diagnosed and under-reported.⁶ The clinical spectrum of melioidosis is variable and includes latent infection, local cutaneous lesions, subacute pneumonia, focal organ abscesses, musculoskeletal infection and lethal fulminant septicemia.^{7,8}

Musculoskeletal melioidosis is a well-recognized manifestation of the disease, but is relatively rare even in endemic areas.⁹ The diagnosis in our first two cases was delayed for 10 weeks in one and possibly many years in the second, while the third patient had fulminant septicemia and could not be revived stressing the importance of this entity.

Human infection occurs, when the organism gains entry through broken skin, by inhalation, and perhaps ingestion. In addition, laboratory-acquired infection through contaminated equipments and inhalation have been reported in the literature.^{10,11} Following an incubation period lasting a few days to many years, melioidosis may present as an acute, subacute or chronic illness. Clinically, it mimics pyogenic bacterial infection, Gram-negative sepsis, tuberculosis or even polyarthritis,⁶ so it has been referred to as the "remarkable

imitator” and the “mimicker of maladies”.^{6,12} The important clue to diagnosis is travel to or residence in an endemic area. Most important risk factor is diabetes mellitus, others being thalassaemia, kidney disease, occupation (rice paddy farmers) and cystic fibrosis.¹³

Histopathology may show necrotizing granuloma without acid fast bacilli, which may confuse the picture with tuberculosis.⁶ Confirmation of a diagnosis of melioidosis depends heavily on the clinical, microbiology laboratory and specifically on recovering *B. pseudomallei* isolate by culture from blood, sputum, cerebrospinal fluid or other bacteriology specimen. But microbiological diagnosis is tricky as it closely resembles common contaminant pseudomonas species and is easily misidentified as pseudomonas or any other Gram-negative organism in microbiology laboratories especially in a small set up in developing countries.¹⁴ Lack of accurate microbiological services may result in under-reporting of cases and an under-estimate of the global burden of this infection.¹⁵ When dealing with such an infection in the small set up, where facilities are not adequate, the clue which raises suspicion is pseudomonas/ Gram-negative bacilli isolated in culture with resistance to colistin and Aminoglycoside (to which it is usually susceptible). Other important additional clue is travel to, or residence in, an endemic area e.g. coastal regions of Karnataka, Goa or south Maharashtra. Though culture sensitivity report shows susceptibility to various antibiotics, it does not respond to all susceptible antibiotics, which stress the importance of diagnosing this infection. The treatment effective for this entity is intravenous injection ceftazidime alone or ceftazidime plus combination of trimethoprim and sulfamethoxazole for minimum of 10–14 days or patient's temperature has returned to normal for more than 48 h and to prevent recurrence combination of trimethoprim and sulfamethoxazole could be given orally with or without doxycycline for 12–20 weeks.^{5,7,15} As far as prognosis is concerned, septicemic form has a mortality rate that exceeds 90%. In melioidosis, recurrent infections can occur in about 2–9% due to either relapse (same strain, unknown mechanism) in two-thirds of cases, especially in the first year and the rest due to re-infection with new strain.¹⁶

6. Conclusion

Melioidosis is increasingly recognized around the world. It has been noted that published case reports and series are likely to represent only the 'tip of the iceberg' i.e., melioidosis is far more common than previously recognized, as culture facilities for bacterial isolation are not available in most of the rural tropics, where the infection is likely to be prevalent.¹⁷ Any delay in diagnosis and treatment of this infection may be harmful, because the disease possesses the potential for recurrence and may become an acute, fulminant and fatal infection. Though culture sensitivity report shows susceptibility to various antibiotics, it does not respond to all susceptible antibiotics, which stresses the importance of diagnosing this infection. Diagnosis is often missed in labs with small setup especially in developing countries. When encountered with culture report of Gram-negative infection, which is resistant to aminoglycoside and colistin, diagnosis of *Burkholderia pseudomallei* should be kept

in mind, especially when there is history of travelling to endemic area. Though culture sensitivity report shows sensitivity to several antibiotics, recommended treatment is intravenous ceftazidime alone or with combination of trimethoprim and sulfamethoxazole for minimum of 10–14 days and to prevent recurrence combination of trimethoprim and sulfamethoxazole orally with or without doxycycline be used for 12–20 weeks.

Conflicts of interest

The authors have none to declare.

REFERENCES

1. Vuddhakul V, Tharavichitkul P, Na-Eng N, et al. Epidemiology of *Burkholderia pseudomallei* in Thailand. *Am J Trop Med Hyg.* 1999;60:458–461.
2. Whitmore A, Krishnaswami CS. An account of the discovery of a hitherto undescribed infective disease occurring among the population of Rangoon. *Indian Med Gaz.* 1912;47:262–267.
3. Vidyakshmi K, Lipika S, Vishal S, Damodar S, Chakrapani M. Emerging clinico-epidemiological trends in melioidosis: analysis of 95 cases from western coastal India. *Int J Infect Dis.* 2012;16:e491–e497.
4. Rao PS, Dhawan R, Shivananda PG. *Burkholderia pseudomallei* infections: case reports of five cases. *Trop Doctor.* 2002;32:174–175.
5. Mathew S, Perakath B, Mathew G, et al. Surgical presentation of melioidosis in India. *Natl Med J India.* 1999;12:59–61.
6. John TJ. Emerging and re-emerging bacterial pathogens in India. *Indian J Med Res.* 1996;103:4–18.
7. Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology and management. *Clin Microbiol Rev.* 2005;18:383–416.
8. Jain VK, Jain D, Kataria H, Shukla A, Arya RK, Mittal D. Melioidosis: a review of orthopedic manifestations, clinical features, diagnosis and management. *Indian J Med Sci.* 2007;61:580–590.
9. Lipika K, Vishal SS, Damodar S, Chakrapani M. Emerging clinico-epidemiological trends in melioidosis: analysis of 95 cases from western coastal India. *Int J Infect Dis.* 2012;16:e491–e497.
10. Schlech 3rd WF, Turchik JB, Westlake Jr RE, Klein GC, Band JD, Weaver RE. Laboratory-acquired infection with *Pseudomonas pseudomallei* (melioidosis). *N Engl J Med.* 1981;305:1133–1135.
11. Green RN, Tuffnell PG. Laboratory acquired melioidosis. *Am J Med.* 1968;44:599–605.
12. Poe RH, Vassallo CL, Domm BM. Melioidosis: the remarkable imitator. *Am Rev Respir Dis.* 1971;104:427–431.
13. Suputtamongkol Y, Chaowagul W, Chetchotisakd P, et al. Risk factors for melioidosis and bacteremic melioidosis. *Clin Infect Dis.* 1999;29:408–413.
14. Kosuwon W, Saengnipanthkul S, Mahaisavariya B, Laupattarakasem W, Kaen K. Musculoskeletal melioidosis. *J Bone Joint Surg Am.* 1993;75:1811–1815.
15. Gopalakrishnan R, Sureshkumar D, Thirunarayan MA, Ramasubramanian V. Melioidosis: an emerging infection in India. *J Assoc Phys India.* 2013;61:612–614.
16. Dance DA. Melioidosis as an emerging global problem. *Acta Trop.* 2000;74:115–119.
17. Dance DA. Melioidosis: the tip of the iceberg? *Clin Microbiol Rev.* 1991;4:52–60.