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Clinical Study
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Non-Caseating Granulomatous Infective Spondylitis: Melioidotic Spondylitis

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Study Design: Retrospective clinical analysis.

Purpose: To delineate the clinical presentation of melioidosis in the spine and to create awareness among healthcare professionals, particularly spine surgeons, regarding the diagnosis and treatment of melioidotic spondylitis.

Overview of Literature: Melioidosis is an emerging disease, particularly in developing countries, associated with a high mortality rate. Its causative pathogen, *Burkholderia pseudomallei*, has been labeled as a bio-terrorism agent.

Methods: We performed a retrospective analysis of patients who were culture positive for *B. pseudomallei*. Assessment of patients was performed using clinical, radiological, and blood parameters. Clinical measures included pain, neurological deficit, and return to work. Radiological measures included plain radiography of the spine and magnetic resonance imaging. Blood tests included erythrocyte sedimentation rate and C-reactive protein levels.

Results: Four patients having melioidosis with spondylitis were evaluated. All of them had diabetes mellitus; three had multiple abscesses which required incision and drainage. Their clinical spectrum was similar to that of tuberculous spondylitis; all had back pain and radiology revealed infective spondylodiscitis with prevertebral and paravertebral collections with psoas abscess. Three patients underwent ultrasound-guided drainage of the psoas abscess and one had aspiration of the subcutaneous abscess. Bacteriological cultures showed presence of *B. pseudomallei*, and histopathology showed non-caseating granulomatous inflammation. All patients were treated with intravenous Ceftazidime for 2 weeks, followed by oral bactrim double strength and Doxycycline for 20 weeks. All patients improved with treatment and were healed at follow up.

Conclusions: Melioidosis presents with a clinical spectrum similar to that of tuberculosis. A diagnosis of melioidotic spondylitis should be considered, particularly in patients with diabetes with neutrophilic leukocytosis and clinical-radiological features suggestive of infective spondylodiscitis. Bacteriological culture and histopathology helps in differentiating the two conditions. Health education for healthcare professionals is important for correctly diagnosing this disease.

Keywords: *Burkholderia pseudomallei*; Melioidosis; Tuberculosis; Spondylitis; Non-caseating granuloma; Antibiotics

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Introduction

Melioidosis is a bacterial disease caused by *Burkholderia pseudomallei*, an intracellular gram-negative pathogen, which is associated with a wide clinical spectrum, from subcutaneous tissue collections to rapidly progressive septicemia [1]. Although several reports describe the multisystem involvement of melioidosis in detail [1-3], few cases of melioidotic spondylitis have been reported [4-6]. Histopathologically, melioidotic spondylitis presents as a non-caseating, granulomatous inflammation that is frequently confused with tuberculous spondylitis. The aim of this study is to delineate the clinical presentation of melioidosis in the spine and to create awareness among health care professionals, particularly spine surgeons, about the diagnosis and treatment of melioidotic spondylitis.

Materials and Methods

This study consisted of a retrospective analysis of patients

Table 1. Clinico-radiological features of patients

Age/Sex	Duration	Clinical presentation	Abscess at other sites	Previous history	Level of spine involved	Radiological features
58/Male	6 mo	Low back ache	Multiple subcutaneous abscesses and abscesses around 11th and 12th ribs	On ATT for 3 mo	L3	Altered signal intensity in L3 vertebral body with normal discs
		Discharging sinuses at the back		Splenectomy 4 yr ago		Thickened psoas muscle with minimal abscess
						Involvement of the lower left ribs (11th and 12th) with extension of the abscess component into the paraspinal region at D9–L3 level
58/Male	8 mo	Mid and low back ache	Splenic abscess	Suspected to have TB elsewhere and was treated with ATT	D12, L1	Altered signal intensity seen involving D12 and L1 vertebrae and intervening intervertebral disc which are hyperintense on STIR sequences and hypointense on T1W
		Pseudo-flexion deformity of the hip				Associated epidural, pre- and para-vertebral abscesses and psoas abscess
65/Male	7 mo	Low back ache		Suspected to have TB elsewhere and was treated with ATT	L5, S1	Extensive altered signal intensity seen in the L5 vertebral body and entire sacrum with involvement of the intervening disc with large paraspinal, prevertebral, paravertebral, abscesses with epidural component. Paravertebral component extends in to the iliopsoas and left pyriformis muscle.
58/Male	2 yr	Low back ache	Retro-peritoneal abscess	Treated with ATT for 9 mo for pulmonary tuberculosis	S3	Multi loculated collection is noted in the left psoas muscle and also along the left iliacus muscle
		Swelling in the lower back		Abscess drained		Lesion was noted at the posterior aspect of the S3 vertebral body

ATT, anti-tubercular treatment; TB, tuberculosis; STIR, short TI inversion recovery.

Table 2. Laboratory parameters and management

Glycoxylated haemoglobin (HbA1c %)	WBC count/ mm^3	Erythrocyte sedimentation rate (mm/hr)	C-reative protein (mg/L)	Intervention	Treatment
10.1	15,800	127	79	Aspiration of sub-cutaneous abscess	Injection ceftazidime 2 g every eighth hourly for 2 weeks, followed by doxycycline 100 mg twice a day and cotrimoxazole DS 960 mg twice a day for 20 weeks
8.9	13,200	77	68.8	Ultrasound guided aspiration and drainage of psoas abscess	Pig tail drainage of the abscess
					Skin traction for the right hip and slow mobilization of the hip
					Injection ceftazidime 2 g every eighth hourly for 2 weeks, followed by doxycycline 100 mg twice a day and cotrimoxazole DS 960 mg twice a day for 20 weeks
9.8	12,000	98	86	CT-guided biopsy of the lesion	Injection ceftazidime 2 g every eighth hourly for 2 weeks, followed by doxycline 100 mg twice a day and cotrimoxazole DS 960 mg twice a day for 20 weeks
8.9	13,800	53	68.2	Ultrasoud-guided drainage of psoas abscess	Pig tail drainage of the psoas abscess
					Injection ceftazidime 2 g every eighth hourly for 2 weeks, followed by doxycline 100 mg twice a day and cotrimoxazole DS 960 mg twice a day for 20 weeks

WBC, white blood cell; DS, double strength; CT, computed tomography.

with culture proven melioidotic spondylitis who were treated at Christian Medical College and Hospital, Vellore in Southern India over a period of 5 years (from January 2009 to December 2014). Their clinical presentation, demographic profile, risk factors, laboratory findings, bacteriological cultures, histopathological reports, and treatment strategies and outcomes were analyzed in detail.

Results

During the study period, 890 patients with tuberculous spondylitis and 210 patients with pyogenic spondylodiscitis were treated in the Department of Orthopaedics. Diagnosis was confirmed by bacteriological cultures with or without histopathological evidence. Four patients (prevalence, 0.36%) with culture proven melioidotic spondylitis were identified. All were males, with a mean age of 54 years (range, 39–65 years), from North-Eastern India, none of them were farmers. All patients presented with fever and back pain along with associated constitutional symptoms, such as loss of weight and appetite. Two of them presented with multiple discharging sinuses; three had multiple abscesses elsewhere (prostate, spleen, and subcutaneous spaces) which had been treated earlier with drainage and anti-tuberculous chemotherapy (empirically for 6 months) with no clinical improvement. None of the patients had any overt neurological deficit. Their clinical and radiological features are described in detail in Table 1.

Blood analysis revealed neutrophilic leukocytosis (>75%), with elevated erythrocyte sedimentation rate (ESR) (mean, 88 mm/hr; reference value, 30–40 mm/hr for adults) and C-reactive protein (CRP) levels (mean, 75.5 mg/L; reference value, <6 mg/L). All patients had uncontrolled diabetes mellitus (HbA1c >9.4) (Table 2). Magnetic resonance imaging of the spine showed paradiscal involvement in two patients (with plain radiograph

revealing disc space narrowing) (Fig. 1A) and vertebral body involvement (central type) in the other two patients. Paravertebral and psoas abscesses were evident in three patients (Fig. 1B, C). All patients were clinically suspected to have active hematogenous infective spondylodiscitis, probably of tuberculous etiology. One patient underwent local aspiration of a subcutaneous abscess, another underwent computed tomography–guided biopsy of the lesion, and the remaining two had ultrasound-guided aspiration and Malecot catheter drainage (pig tail drainage) of the psoas abscess (Tables 1, 2). Tissue and fluid samples were sent for microbiological and histopathological confirmatory tests. Smears stained with dilute carbol fuchsin revealed a typical "safety pin appearance" (Fig. 2), and all cultures showed the presence of *B. pseudomallei* growing as smooth pink colonies in *B. pseudomallei* selective agar, as smooth, opaque white colonies in blood agar (Fig. 3A), or as pink colonies in MacConkey agar (Fig. 3B). The bacterium was sensitive to Ceftazidime and Doxycycline, resistant to Ciprofloxacin and Gentamycin, and biopsy samples revealed non-caseating granulomatous inflammation (Fig. 4).

Patients were treated with intravenous Ceftazidime (2 g every 8 hours for 2 weeks, followed by Doxycycline [100 mg twice a day]) and Cotrimoxazole double strength (960 mg twice a day) for 20 weeks as per the recommended regimen [7,8].

All patients showed symptomatic improvement at follow-up. They were assessed clinically and radiologically, and blood tests were performed to monitor ESR and

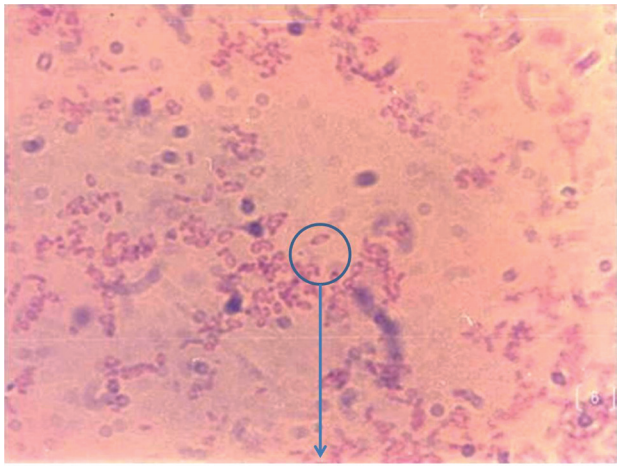

Fig. 2. Dilute carbol fuchsin staining demonstrating *Burkholderia pseudomallei*'s typical "safety pin appearance" (bipolar staining, 512 ×323).

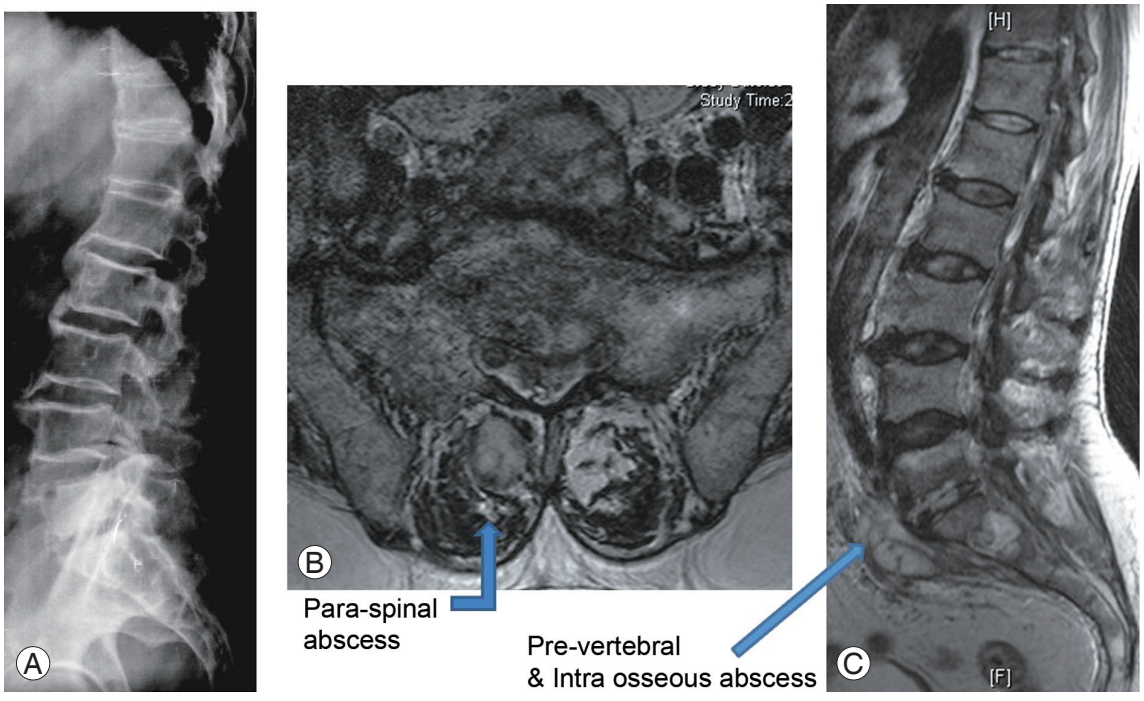

Fig. 1. Radiological findings. **(A)** Lateral view of the lumbosacral spine showing decreased L5–S1 disc space. **(B, C)** T2-weighted magnetic resonance imaging of the axial and sagittal sections revealing L5–S1 infective spondylodiscitis with pre- and paravertebral abscesses.

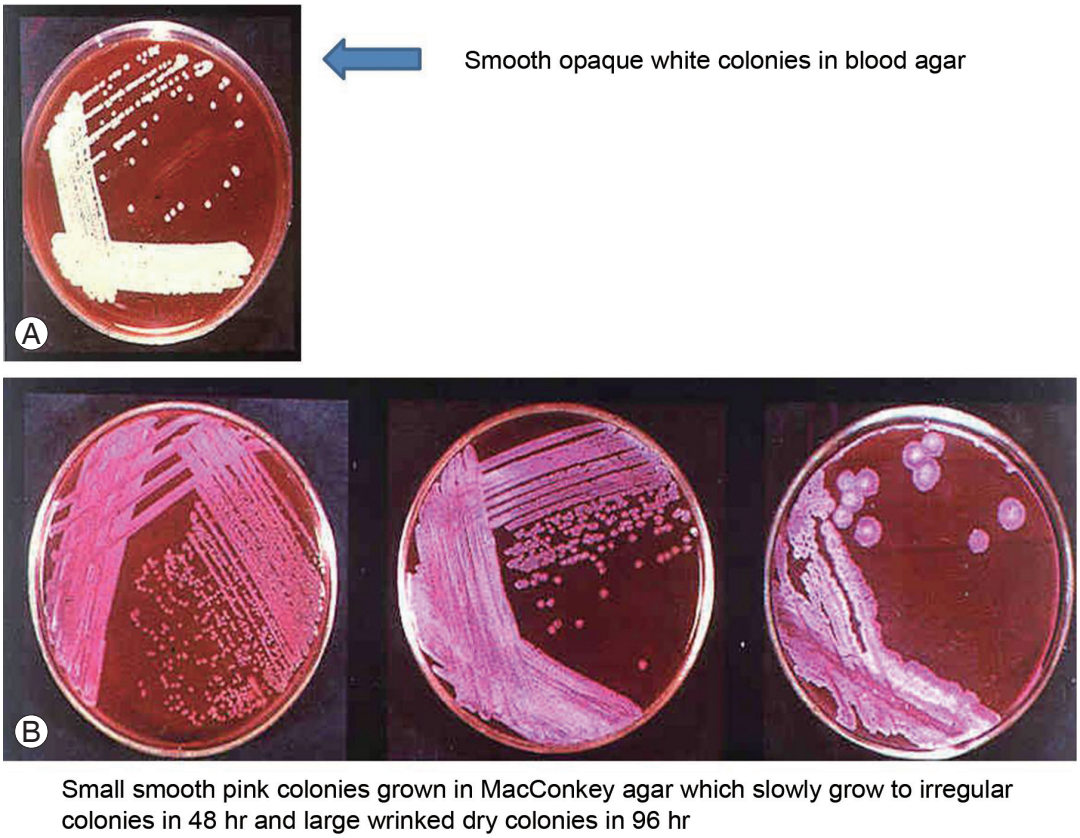

Fig. 3. Bacterial cultures. **(A)** Smooth, white colony growth on blood agar. **(B)** Serial growth as pink colonies on MacConkey agar (24, 48, and 96 hours).

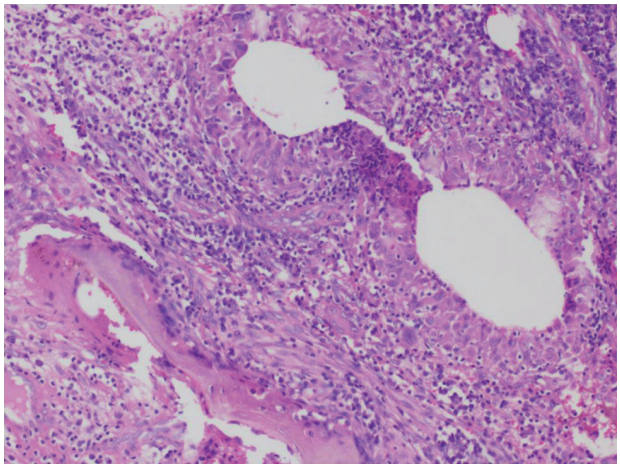

Fig. 4. Histopathology image revealing non-caseous granulomatous inflammation in the intertrabecular spaces (H&E, ×100).

CRP levels. Two patients returned for follow-up; one was disease-free and the other showed residual psoas abscess. The remaining two patients were asymptomatic, as determined via telephonic interview. The average duration of follow up was 2 years.

Discussion

Melioidosis is regarded to be endemic to Northern Australia and Southeast Asia, and is an emerging disease in developing countries like India [9], where it is still underdiagnosed mainly because of the lack of awareness, low index of suspicion, and inadequate laboratory facilities [10].

Melioidotic infection preponderantly occurs in males, usually by inoculation through skin abrasions or by inhalation [7]. There are multiple risk factors associated with the disease, such as diabetes mellitus; intravenous drug abuse; steroid use; rainfall [4]; exposure to contaminated soil [7]; rice farming; hematological malignancies; excessive alcohol intake; and chronic liver, kidney, or respiratory disease. In our study, male gender and uncontrolled diabetes mellitus (HBA1c >8.3) were the only specific risk factors identified.

Melioidosis has already been termed as the "remarkable

Table 3. Comparision of patients with already reported literature

Author	Age (yr)	Sex	Risk factor	Presentation	Radiological feature	Treatment
Kosuwon et al. [13] (1 case)	45	Male	Endemic region (Thailand)	Back pain, kyphosis L1,2	L1, 2 bilateral psoas abscess	Debridement followed by cotrimoxazole, doxycycline and injection kanamycin for 6 months
			Diabetes mellitus			
Wilairatana and Wilairatana [14] (1 case)	52	Male	Endemic region (Thailand)	Back pain, spastic paraplegia	D9 vertebral collapse with D9–10 disc involvement	Anterior debridement and fusion followed by injection ceftazidime 2 g 8th hourly for 4 weeks followed by oral augmentin 750 mg three times a day for 4 months
			Diabetes mellitus			
Subhadrabandhu et al. [15] (4 cases)	43–62	3 Males, 1 Female	Endemic region farmers (3/4)	Back pain, fever (1/4)	Vertebral body destruction with scalloping and narrowing of disc spaces	Anterior decompression and fusion followed by cotrimoxazole, injection ceftazidime/injection chloramphenicol/injection kanamycin
			Diabetes mellitus (2/4)			
Nather et al. [16] (1 case)	71	Male	Nil	Fever, girdle pain radiating to umbilicus	D9–11 posterior elements involved with extensive vertebral osteomyelitis	Radical 2 stage anterior and posterior surgery was done
						Injection piperacillin, vancomycin and clindamycin –Died of septicaemia
Pisuttimarn and Mootsikapun [17] (1 case)	61	Male	Endemic region (Thailand)	Fever, low back pain	Sacrum with psoas abscess	Injection ceftazidime 2 g 8th hourly for 2 weeks followed by oral cotrimoxazole and doxycycline
Our study (4 cases)	58–65	Males	Endemic region (India)	Fever, low back pain	Paradiscal (2/4)	Pig tail drainage of psoas abscess (2/4)
			Uncontrolled diabetes mellitus (HbA1c >9)	All 4 were suspected and treated for tuberculosis	Vertebral body (2/4)	Injection ceftazidime 2 g 8th hourly for 2 weeks followed by oral cotrimoxazole and doxycycline for 20 weeks
					Psoas abscess (4/4)	

imitator" [11] and "mimicker of maladies" [12]. Melioidotic spondylitis is a fairly uncommon, chronic condition and hence poses a special challenge in terms of both diagnosis and treatment. In developing countries, as the incidence of tuberculosis is high, virtually all patients with spondylitis with abscess, discharging sinuses, and elevated ESR and CRP levels are treated along the therapeutic guidelines of tubercular spondylodiscitis. Growth of the bacterium in culture media always remains the "gold standard" method of diagnosis in case of infective spondylitis. Lack of awareness, inadequate laboratory facilities, and high prevalence of tuberculosis are the main reasons for underdiagnosis of melioidotic spondylitis. Table 3 shows a comparative summary of our clinical analysis and data reported in the literature [13-17].

Conclusions

Melioidotic spondylitis presents with a clinical picture similar to that of tuberculosis, with fever and back pain

being the main complaints. Tissue biopsy shows non-caseating granulomas, and bacteriological studies are performed to confirm the disease, which is treatable with appropriate antibiotic therapy.

In regions where tuberculosis is prevalent, melioidotic spondylitis should be considered in the differential diagnosis of patients who do not respond to empirical anti-tubercular treatment. This is of particular importance in patients with uncontrolled diabetes mellitus with suspected infective spondylits.

We advise that healthcare workers and all treating physicians, particularly orthopedic and spinal surgeons, maintain a high index of clinical suspicion in light of the increasing incidence of this potentially fatal disease.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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