

Case Report

Unusual cases of melioidosis infection in cancer patients in North India: Covert peril for oncology care

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ABSTRACT

Melioidosis is a life-threatening, emerging infectious disease caused by the environmental bacterium *Burkholderia pseudomallei*. The disease is called “the Great Mimicker” because it has a wide range of clinical presentations and can be commonly mistaken for tuberculosis, pneumonia, and other pyogenic infections. Early diagnosis of this disease is essential, as the case-fatality rate is very high, up to 30-47%, and may range from 40% to 75% in immunocompromised patients. We presented an interesting case report of two patients from the North India Oncology Center, where oncologists initially confirmed the diagnosis as cancer and later noted melioidosis as the primary infection. Both patients survived after receiving appropriate antimicrobial therapy. Our case report aims to enumerate the clinical presentation and histopathological and microbiological findings along the clinical course of this disease.

Keywords: Cancer, Diagnosis, Melioidosis, Solid tumor, *Burkholderia melioidosis*

INTRODUCTION

Melioidosis is an endemic disease in tropical and subtropical regions of the world and plays an important role in causing community-acquired bacterial sepsis.^[1] In a cancer center, approaching a case with suspicion of melioidosis and its early diagnosis and treatment are crucial. In certain instances, especially in non-endemic areas, oncologists may fail to diagnose melioidosis, which could result in improper or delayed treatment. This is because the disease itself presents with symptoms of pneumonia, cellulitis, and osteomyelitis.^[2] The disease can mimic tumor-like lesions or cancer, and such has been reported in some studies.^[3,4] According to research published in North Australia, clinicians further diagnosed melioidosis in suspected cancer cases.^[3] Similarly, Zhao *et al.*^[4] published a study in which a case of pulmonary melioidosis mirrored bronchogenic carcinoma in radiological investigation.^[4] It is well known that, in addition to cancer, melioidosis can also mimic chronic infections like tuberculosis.^[5] However, the concurrent presentation of malignancy and melioidosis is rarely encountered in routine clinical practice.^[3] It is difficult for oncologists to approach the suspicion of melioidosis in cancer patients until other causes of malignancy and infection have been ruled out.^[4] Herein, we report two unique cases of concurrent *Burkholderia pseudomallei* infection with solid tumor malignancy.

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CASE REPORT

Case 1

A 47-year-old female resident of Jaunpur district, Uttar Pradesh, visited our outpatient department with the chief complaint of a lump in her left breast along with a history of on-and-off fever for the past 6 months. Fever is of low grade and associated with fatigue, myalgia, and pain, especially in the breast lump. There is an occupational history of agriculture in the family. There was no history of cough, breathlessness, skin rashes or skin lesions, or trauma. The tissue sample received in the microbiology laboratory was cultured in Blood agar and MacConkey agar, and a Gram stain was prepared. The sample was also sub-cultured in brain heart infusion broth for enrichment. The culture plates were incubated at 37°C, and reading was done in the next 18-24 hours. Gram staining of the tissue sample revealed plenty of pus cells and occasional epithelial cells with plenty of Gram-negative bacilli (GNB) (bipolar and having a safety pin appearance) [Figure 1].

The culture showed the growth of non-lactose-fermenting colonies in MacConkey agar, which were further identified by an automated identification and susceptibility system

(Vitek-2 BioMérieux, Germany, and MALDI-TOF, Bruker). The minimum inhibitory concentration ($\mu\text{g/mL}$) interpretation for susceptible (S), intermediate (I), and resistant (R) in terms of antibiotic susceptibility was performed using Clinical and Laboratory Standards Institute - M45-A2 guidelines.^[6] The organism was identified as *B. pseudomallei* (99% probability) and the strain was sensitive to piperacillin-tazobactam ($=8 \mu\text{g/mL}$), ceftazidime ($=4 \mu\text{g/mL}$), cefoperzone-sulbactam ($\leq 8 \mu\text{g/mL}$), cefepime ($\leq 1 \mu\text{g/mL}$), aztreonam ($\leq 4 \mu\text{g/mL}$), doripenem, ($<0.25 \mu\text{g/mL}$), imipenem ($\leq 2 \mu\text{g/mL}$), meropenem ($\leq 0.25 \mu\text{g/mL}$), amikacin ($\leq 2 \mu\text{g/mL}$), gentamicin ($\leq 4 \mu\text{g/mL}$), ciprofloxacin ($\leq 0.25 \mu\text{g/mL}$), and levofloxacin ($<0.25 \mu\text{g/mL}$). Based on the clinical symptoms and investigations, the patient was prescribed meropenem in a dose of 500 mg IV TDS as intensive therapy. Counseling was done regarding the compliance with long-term oral intake of antibiotics for the eradication phase of treatment. In the gastro-oncology outpatient department, the patient was monitored for the same oral antimicrobial therapy, and the cancer treatment was continued. She was restarted on the 2nd cycle of chemotherapy, paclitaxel. The patient is currently on follow-up, receiving maintenance adjuvant chemotherapy.

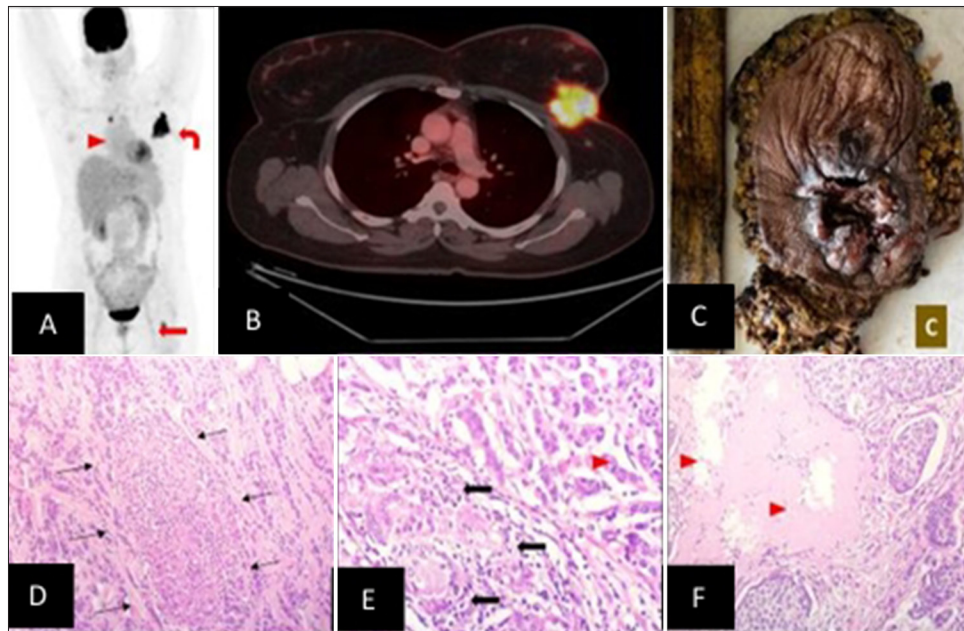


Figure 1: (A) Maximum intensity projection image showing hypermetabolic mass in the left breast region (red curved arrow), metastatic paratracheal node (red arrow head), and left femur lesion (arrow). (B) Axial fused fludeoxyglucose positron emission tomography/computed tomography images showing a hypermetabolic primary left breast lesion (arrow). (C) Gross picture of the mastectomy specimen shows skin ulceration and fibrinosuppurative slough formation. (D) Biopsy from the left breast shows a well-formed granuloma (black arrows) surrounded by the invasive breast carcinoma cells [Hematoxylin and eosin (H&E), $\times 10$]. (E) The granuloma is composed of numerous multinucleated giant cells (black arrows) adjacent to the tumor nests (red arrow heads), (H&E, $\times 40$). (F) Extensive areas of necrosis are seen amidst large tumor nests (Red Triangle depicts as star), (H&E, $\times 20$). Scale Bar of D: $10 \times 200 \mu\text{m}$, E: $20 \times 100 \mu\text{m}$, and F $40 \times 40 \mu\text{m}$

Case 2

A 66-year-old female resident of Bihar came with chief complaints of a left-sided neck swelling for the past month. There was a history of an enlarging, painful mass on the left side of the neck, fever, poor appetite, and an approximate weight loss of 5 kg since the initiation of the chief complaints. The fever was of low grade and associated with fatigue, myalgia, and anorexia. There is no history of cough, breathlessness, skin rashes, skin lesions, or trauma. There was an occupational history of agriculture in the family. On clinical examination, a 2.5 cm × 2.5 cm swelling was palpable in the left region. The mass was firm, mobile, and tender. There was no history of voice change, dysphagia, or breathlessness. A fine-needle aspiration cytology report from a laboratory showed metastatic deposits of adenocarcinoma. A positron emission tomography-computed tomography (PET-CT) was done, and it showed multiple hypermetabolic lesions involving the left supraclavicular and mediastinal regions [Figure 2a-c]. Given the PET-CT findings, a core-needle biopsy of the left supraclavicular node was done.

Histopathological analysis: The left supraclavicular biopsy showed lymph nodal tissue infiltrated by a tumor arranged in sheets and vague glands. The individual cells were round to oval and showed a severe degree of pleomorphism, a high N/C ratio, coarse chromatin, inconspicuous nucleoli, and a moderate amount of cytoplasm. Many well-formed granulomas composed of multinucleate giant cells (arrow), histiocytes, and fibroblasts were noted [Figure 2d]. A final impression of metastatic adenocarcinoma with chronic granulomatous infection was given. Based on histopathological findings, the patients were advised to have four cycles of pemetrexed and carboplatin chemotherapy for 3 weeks. A few months after treatment, the patient presented in the hospital with a history of high-grade fever, weakness, and shortness of breath. Routine laboratory investigations were done, and paired blood culture was collected in automated Bact-Alert bottles and sent to the microbiology lab for further analysis. Blood culture flashed positive for GNB and was subcultured in blood and MacConkey agar and kept in an incubator at 37°C. After 24-48 hours of incubation, blood agar showed smooth, creamy, white colonies at

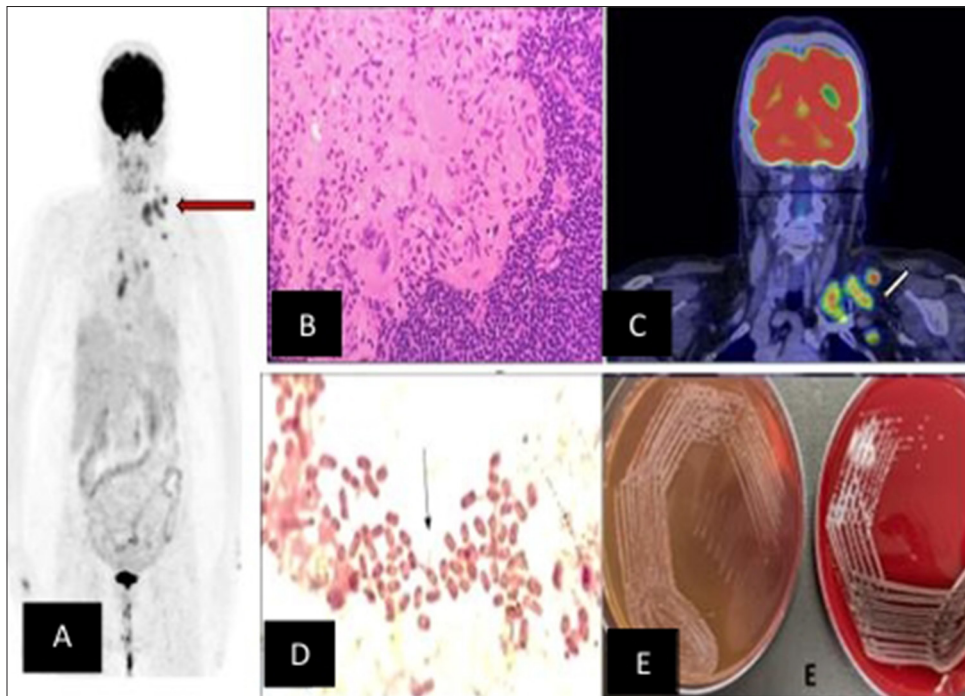


Figure 2: (A) Maximum intensity projection image showing multiple hypermetabolic lesions involving the left supraclavicular and mediastinal region (red arrow). (B) Histopathological examination of the cervical lymph nodes shows many large well-formed granulomas composed of multinucleated giant cells (black arrows), histiocytes, and fibroblasts [Hematoxylin and eosin, ×40]. (C) Contrast-enhanced axial computed tomography (CT) and fused axial fludeoxyglucose positron emission tomography/CT images showing glucose hypermetabolism in multiple enlarged, rounded, enhancing left supraclavicular nodes (arrows). (D) Gram staining of the tissue sample revealed plenty of pus cells and occasional epithelial cells with plenty of gram-negative-bacilli (Bipolar and having a safety pin appearance). (E) In Blood agar: Smooth, creamy, white colonies at 24 hours. May become dry and wrinkled, as shown in the image, often with a purplish hue at 48-72 hours in MacConkey agar: Pink to metallic brown colonies at 24-48 hours.

24 h, which became dry and wrinkled after 48 hours. In MacConkey agar, pink to metallic brown colonies were noted at 24-48 hours [Figure 2e]. Isolated colonies were picked up, and further automated identification and sensitivity testing were done in VITEK-2 (Germany, BioMérieux). Vitek-2 identified the organism as *B. pseudomallei* (99% probability), and the strain was sensitive to cefoperazone-sulbactam (≤ 8 $\mu\text{g/mL}$), piperacillin-tazobactam ($= 8$ $\mu\text{g/mL}$), ceftazidime ($= 4$ $\mu\text{g/mL}$), cefepime (≤ 1 $\mu\text{g/mL}$), aztreonam (≤ 4 $\mu\text{g/mL}$), doripenem (< 0.25 $\mu\text{g/mL}$), imipenem (≤ 2 $\mu\text{g/mL}$), and cotrimoxazole (≤ 20 $\mu\text{g/mL}$) and resistant to ciprofloxacin and levofloxacin. Based on culture findings, the patients were given injections of cefoperazone-sulbactam in a dose of 1.5 mg IV TDS and meropenem (500 mg) IV every 8 hours. After the patient was stable, she was counseled for a long course of antibiotics with cotrimoxazole. The patient was followed up for the negative blood culture report and discharged with advice to follow up after 3 weeks. In the follow-up visit, the patients were advised to restart the cancer treatment, and chemotherapy was restarted with pemetrexed and carboplatin. The patient is currently on follow-up, receiving maintenance adjuvant chemotherapy.

DISCUSSION

B. pseudomallei, a saprophytic Gram-negative soil bacterium, is the causative agent of human melioidosis.^[7] The bacterium can invade and replicate in both phagocytic and non-phagocytic cells. The secretion apparatus type of *Burkholderia* species is a type III secretion system 3, and Bim, A protein found on one pole of the bacteria; this helps to facilitate intracellular spread. On phagocytosis by macrophages, *B. pseudomallei* is able to activate the suppressor of cytokine signaling 3 and cytokine-inducible Src homology 2-containing protein, resulting in a decrease in the gamma interferon signaling response.^[8,9] The interference with host innate immune cells, such as macrophages, could have a profound impact on the innate immune response to bacteria, as well as on the development of the adaptive immune response. The organism can produce a cluster of overlapping chronic manifestations ranging from localized infections to fulminant septicemia, mainly prevented in subtropical and tropical areas such as Northern Australia and Southeast Asia.^[3-5] In a cancer care facility, a correct diagnosis of melioidosis is essential due to its pattern of antibiotic resistance and need for targeted treatment.^[7,8] The disease is typically acquired in the community among Southeast Asian agricultural workers, but there are risk factors such as diabetes mellitus, long-term respiratory and renal disorders, and a number of immunosuppressive diseases like cancer.^[7-9] There are limited data regarding the concurrent presentation of human melioidosis and solid tumor patients.^[10] Our case report aims to add clinical, histopathological, and

microbiological characteristics of uncommon presentations of human melioidosis in different solid organ malignancy patients.

Our cancer patients had community-acquired infections of *B. pseudomallei*, as demonstrated by microbiological culture. That was identified by microbiological culture. Our cases represent a diagnostic and therapeutic challenge in the course of chemotherapy, as the oncologist and pathologist diagnosed solely the cases of breast and neck node metastasis. We aim to present an overview of the histopathological findings to be used as an aid, along with microbiological culture and sensitivity, while establishing the confirmed diagnosis of melioidosis in cancer patients. Histopathology of melioidosis is a necrotizing and/or granulomatous inflammation with abscess formation and the presence of numerous multinucleate giant cells,^[11] which resembles tuberculosis. One of our cases also showed extensive fibrin thrombi in the tissue sections. In addition, immunohistochemistry has previously been studied as a means to improve the diagnosis of melioidosis, but culture remains the gold standard, especially because melioidosis can be easily misdiagnosed as tuberculosis.^[12-15] Early diagnosis and appropriate management are crucial in reducing serious complications leading to high mortality in melioidosis patients. In an oncology setup, it is of prime importance that patients must be ruled out for this disease, as it closely mimics cancer. The full course of antimicrobial therapy must be prescribed to avoid relapse and recurrence.

It is hoped that our experience will encourage oncologists to consider melioidosis as a potential explanation for a cancer patient's presentation, expediting its diagnosis and the initiation of potentially life-saving antimicrobial therapy. The study also emphasizes the importance of thorough diagnostic evaluation and repeated collection of microbiological samples.

CONCLUSIONS

Clinical, radiological, and histopathological features of melioidosis are varied and coexist with malignancy or emerge during chemotherapy. It is important to define the clinical presentation and optimal clinical management of patients with melioidosis and cancer because misdirection significantly delays correct treatment and may increase the risk of serious morbidity and mortality in cancer patients. Thus, there is a crucial need for promoting awareness among oncologists for melioidosis, and it should be considered as a differential diagnosis by oncologists when confronted with an infectious disease in a cancer patient.

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