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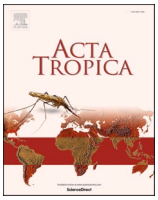

Melioidosis masquerading as malignancy in tropical Australia; lessons for clinicians and implications for clinical management

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ABSTRACT

Melioidosis is a life-threatening, emerging infectious disease caused by the environmental bacterium *Burkholderia pseudomallei*. Melioidosis is hyperendemic in tropical Australia and southeast Asia, however the disease is increasingly encountered beyond these regions. Early diagnosis is essential as the infection has a case-fatality rate of up to 50 %. Melioidosis most commonly involves the lungs, although almost any organ can be affected. Most patients present acutely but an insidious presentation over weeks to months is also well described. We present a case series of 7 patients from tropical Australia whom local clinicians initially believed to have cancer – most commonly lung cancer – only for further investigation to establish a diagnosis of melioidosis. All 7 patients had comorbidities that predisposed them to developing melioidosis and all survived, but their delayed diagnosis resulted in 3 receiving anti-cancer therapies that resulted in significant morbidity. The study emphasises the importance of thorough diagnostic evaluation and repeated collection of microbiological samples. It is hoped that our experience will encourage other clinicians – in the appropriate clinical context – to consider melioidosis as a potential explanation for a patient's presentation, expediting its diagnosis and the initiation of potentially life-saving therapy.

1. Introduction

Melioidosis is an emerging infectious disease which is caused by *Burkholderia pseudomallei*, a Gram-negative bacterium found in the soil and surface water of tropical and subtropical regions. Melioidosis is seen most commonly in southeast Asia and northern Australia, but it is increasingly being reported from other regions around the world and in returning travellers. (Meumann et al., 2023; Dan, 2015) With increasing environmental disruption, a growing global burden of the comorbidities that increase the risk of the disease, and potentially, the effects of climate change, the incidence of melioidosis is anticipated to rise. (Meumann et al., 2023; Fairhead et al., 2022)

Up to 50 % of patients who develop melioidosis will die and even in well-resourced settings about 10 % succumb. (Meumann et al., 2023; Currie et al., 2021; Stewart et al., 2017) Early diagnosis, adequate source control and the prompt prescription of antibiotics with activity against *B. pseudomallei* reduce the risk of death. Pneumonia is the most frequent clinical presentation of melioidosis but almost any organ of the body can be involved. (Currie et al., 2021) Approximately 90 % of patients present acutely, most are bacteraemic and over 20 % of patients have septic shock. However, melioidosis may also present insidiously, with weeks of persistent, low-grade constitutional symptoms. (Currie et al., 2021; Prinsloo et al., 2023; Meumann et al., 2012)

This non-specific presentation means that even in regions where melioidosis is endemic, attending clinicians may consider other diagnoses. As melioidosis most commonly involves the lung, there is the potential for the infection to be mis-diagnosed as a primary or secondary lung cancer if the patient presents with chronic symptoms. (Zhao et al., 2020; Kho et al., 2021; Zaw et al., 2019; Saravu et al., 2012; Wilson et al., 2016) As melioidosis often affects other organs, melioidosis can also be mis-diagnosed as an extrapulmonary or metastatic malignancy. (Liang et al., 2016; Owen et al., 2021)

With urban expansion in Far North Queensland (FNQ), in tropical Australia, the local incidence of melioidosis has more than quadrupled in the last 25 years. (Prinsloo et al., 2023; Smith et al., 2021) There is also a significant local cancer burden which in 2021 had an age-standardised incidence in FNQ of 530/100,000 population. (Queensland Health, 2023) In this case series we present 7 patients

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living in FNQ who were initially believed to have a malignancy only for further investigation to establish the diagnosis of melioidosis. It is hoped that our experience will encourage other clinicians – in the appropriate clinical context – to consider melioidosis as a potential explanation for a patient's presentation, expediting its diagnosis and the initiation of life-saving therapy.

2. Case 1

A 71-year-old female with a history of hazardous alcohol use who had been diagnosed with low-grade lymphoma 2 years previously, presented with 3 weeks of fevers and night sweats. Imaging demonstrated innumerable hypoattenuating masses throughout an enlarged liver and spleen, which were felt to represent evolving lymphoma (Fig. 1). She was commenced on oral prednisolone with plans to commence bendamustine and rituximab 3 days later. However, blood cultures collected on admission to hospital were positive for *B. pseudomallei.* She received 6 weeks of intravenous (IV) meropenem and subsequently oral trimethoprim-sulfamethoxazole (TMP/SMX). She remains on long-term TMP/SMX given her underlying lymphoma, but she is alive and well almost 3 years after her diagnosis of melioidosis (table 1).

3. Case 2

A 57-year-old female presented with generalised seizures after a 2-day history of fever and headache. She was a smoker and had a history of hazardous alcohol use but had no other medical conditions. Brain imaging demonstrated a large right frontal lesion which was suggestive of a malignancy (Fig. 2). Infection remained a differential diagnosis but 5 sets of blood cultures and serology for *B. pseudomallei* were negative.

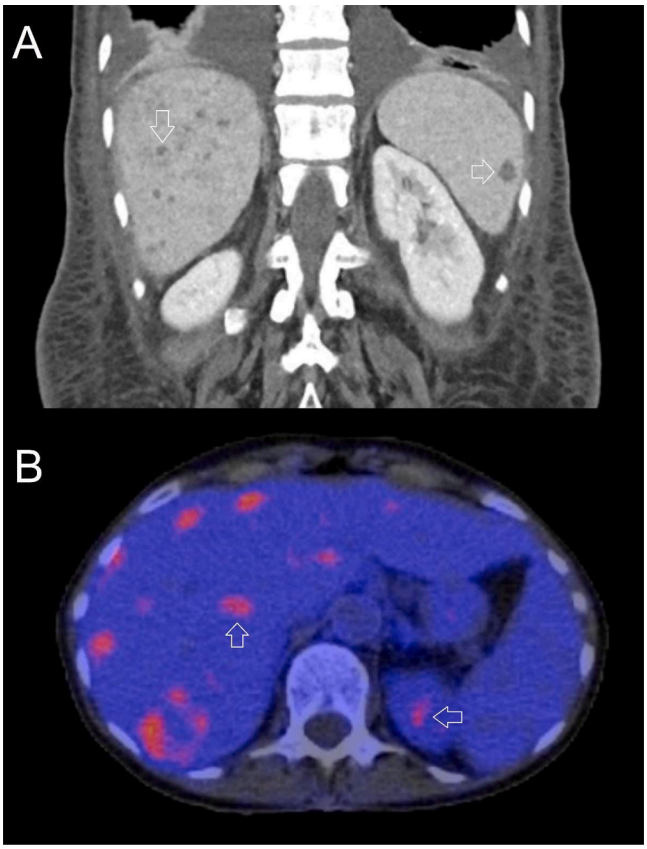

Fig. 1. (Case 1) Panel A: CT of abdomen with contrast (coronal view) demonstrating hepatic and splenic lesions (arrowed). Panel B: PET (axial view) demonstrating hepatosplenomegaly with avid lesions in both organs (arrowed).

Dexamethasone was initiated to reduce brain oedema, but her level of consciousness deteriorated, and she underwent emergency craniotomy. Frozen section histology was reported as a low-grade glioma, but brain tissue cultures were positive for *B. pseudomallei,* and the final histological report (11 days after the frozen section) was of a cerebral abscess with Gram negative bacilli consistent with *B. pseudomallei.* She received 8 weeks of IV meropenem for 8 weeks followed by TMP/SMX for 6 months. She recovered completely and is now back at work 6 years after her initial presentation.

4. Case 3

A 69-year-old female presented with a 3-day history of fevers and diarrhoea, on a background of type 2 diabetes mellitus. Imaging demonstrated a spiculated pulmonary lesion with mediastinal and hilar lymphadenopathy (Fig. 3). She was thought to have metastatic malignancy and an extensive work up – including multiple blood cultures – to exclude infection was negative. Positron emission tomography (PET) imaging was performed to stage the presumed cancer; this demonstrated avidity of the intra-thoracic lesions, but also avidity of the right tonsil, consistent with a diagnosis of metastatic tonsillar cancer. However, a PET-avid lesion was also noted in the left buttock. This lesion was aspirated and grew *B. pseudomallei*; the patient received 4 weeks of IV ceftazidime and three months of TMP/SMX. She remains well, living in the community, 5 years later.

5. Case 4

A 59-year-old male smoker with diabetes mellitus was admitted with a 6-month history of weight loss and cough. Imaging identified a spiculated right upper lobe mass, suspicious for a primary lung malignancy, with bulky mediastinal lymphadenopathy compressing the superior vena cava (SVC) (Fig. 4). A respiratory multidisciplinary team discussion recommended the commencement of dexamethasone to address, what was thought to represent, impending SVC obstruction. In the ensuing days he deteriorated and developed pneumomediastinum, requiring vasopressor support and an intensive care unit admission. Blood cultures collected during his deterioration grew *B. pseudomallei*; the patient received 4 weeks of IV ceftazidime and three months of TMP/SMX. He remains well, living in the community, 7 years later.

6. Case 5

A 66-year-old woman presented with a 12-month history of cough and 7 kg of weight loss. She was a smoker and had chronic obstructive pulmonary disease (COPD). Imaging demonstrated a right hilar mass and lymphadenopathy compressing the right main bronchus (Fig. 5). Bronchoscopy revealed a fistulous connection between the right main bronchus and the mediastinum with – what was thought to be – necrotic tumour within the fistula. The patient was advised it was highly likely that she had incurable lung cancer. However, lung biopsy grew *B. pseudomallei* and she was treated with 12 weeks of intravenous meropenem and, as TMP-STX was not tolerated, amoxycillin-clavulanate as eradication therapy. The fistula resolved with treatment, and she remains well 3 years later.

7. Case 6

A 73-year-old man presented with 2 weeks of fevers, vomiting and abdominal pain on a background of type 2 diabetes mellitus. He was a smoker and had a urostomy following a radical cystoprostatectomy for prostate cancer 9 years previously. Imaging demonstrated an obstructed right kidney and a lung mass (Fig. 6). A conduitoscopy was performed and a nephrostomy placed. There were initial concerns for a malignant process given his history and the new lung lesion, however urine and blood cultures grew *B. pseudomallei*. After 4 weeks of IV meropenem and

Table 1
Presentation of the seven patients and their subsequent clinical course.

Case	Age/ gender	Risk factors for melioidosis	History of occupational or recreational exposure to *B. pseudomallei*	Presentation	Presumed cancer diagnosis	How melioidosis was confirmed	Outcome
1	71 F	Lymphoma and alcohol	No	Weight loss, night sweats, hepatosplenomegaly with focal hypodensities	Progression of known lymphoma	Blood culture	Alive 34 months later
2	57 F	Alcohol	No	Fevers, headache, seizures, frontal lobe lesion	Brain cancer	Culture of brain tissue (after dexamethasone)	Alive 6 years later
3	69 F	DM	No	Fevers and diarrhoea. Lung lesion, tonsillar enlargement, mediastinal lymphadenopathy, and buttock abscess	Lung cancer with metastases	Culture of aspirate of buttock abscess	Alive 5 years later
4	59 M	DM and chronic lung disease	No	Lung mass with mediastinal lymphadenopathy and early SVC obstruction	Lung cancer	Blood culture (after dexamethasone)	Alive 7 years later
5	66 F	DM and chronic lung disease	No	Mediastinal mass with broncho-mediastinal fistula	Lung cancer	Culture of tissue sample from bronchoscopy	Alive 3 years later
6	73 M	DM and chronic kidney disease	No	Ureteric obstruction and hilar lung mass	Lung cancer and/ or urothelial cancer	Urine and blood culture	Alive 7 years later
7	82 M	Chronic lung disease	Keen gardener	Asymptomatic (initially)	Lung cancer	Blood culture (after radiotherapy)	Alive 21 months later

M: male; F: female; SVC: superior vena cava; DM: diabetes mellitus.

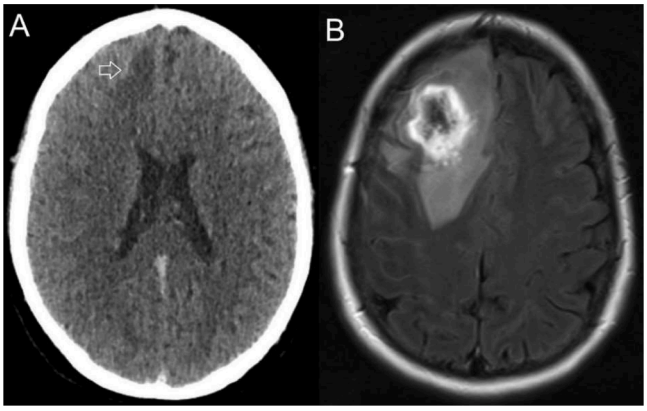

Fig. 2. (Case 2) Panel A: CT brain with contrast (axial view) demonstrating decreased attenuation of the R frontal lobe and ring enhancement (arrowed). Panel B: MRI (axial FLAIR) – performed 7 days later – demonstrating rapid interval growth of the mass in the right frontal lobe with associated vasogenic oedema (these images have been published previously). (Owen et al., 2021).

3 months of TMP-SMX the lung lesion had resolved although the ureteric stricture persisted, and it was necessary to create an ileal conduit 2 years later. He remains well, living in the community, 7 years later.

8. Case 7

An asymptomatic 82-year-old man with a background of COPD was referred to the outpatient's department after a routine chest x-ray identified a left lower lobe pulmonary lesion which was thought to represent a lung cancer (Fig. 7). The lesion and hilar and mediastinal lymph nodes were avid on PET imaging. His-underlying COPD precluded fine needle aspirate and a bronchoscopy with washings was non-diagnostic. His-case was discussed in a thoracic multidisciplinary team meeting where a consensus was reached that lung cancer was the most likely diagnosis; radiotherapy was recommended, and he received 50 Gray in 5 fractions. One month later he developed cough and fever. Repeat imaging demonstrated new pulmonary infiltrates and blood cultures isolated *B. pseudomallei.* He received 4 weeks of IV ceftazidime and 3 months of doxycycline (after not tolerating TMP/SMX). A repeat CT chest 15 months after diagnosis of the melioidosis showed resolution of the left lower lobe lesion and the patient remains well and living in the community 21 months later.

9. Discussion

This case series demonstrates that even in a region where *B. pseudomallei* is endemic and local clinicians are familiar with the disease, melioidosis can be misdiagnosed as cancer with enormous potential ramifications for the patient. While all 7 individuals in this series survived the life-threatening infection in Australia's well-resourced health system, 4 received therapy for the presumed cancer, and in 3

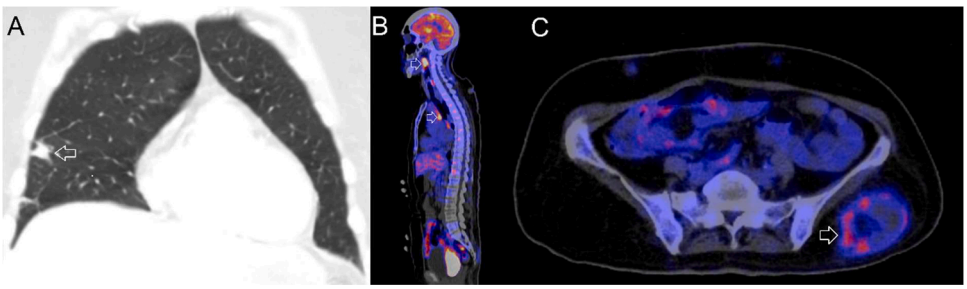

Fig. 3. (Case 3) Panel A: CT chest (coronal view) demonstrating a 10 mm peripheral nodule in the right middle lobe (arrowed).Panel B: Positron emission tomography (sagittal view) demonstrating avidity in the right palatine fossa (arrowed) and mediastinum (arrowed). Panel C: Positron emission tomography (axial view) demonstrating avidity in the left buttock (arrowed).

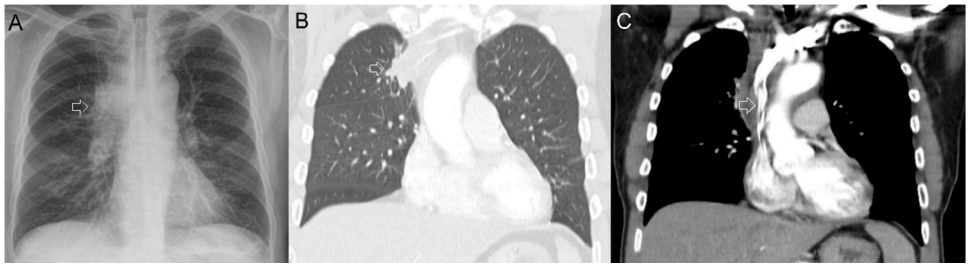

Fig. 4. (Case 4) Panel A: Chest x-ray demonstrating right hilar lymphadenopathy (arrowed), Panel B: CT chest (coronal view) showing right upper lobe mass (arrowed), Panel C: CT chest (coronal view) demonstrating hilar and subcarinal lymphadenopathy and partial obstruction of the superior vena cava (arrowed). These images have been published previously. (Wilson et al., 2016).

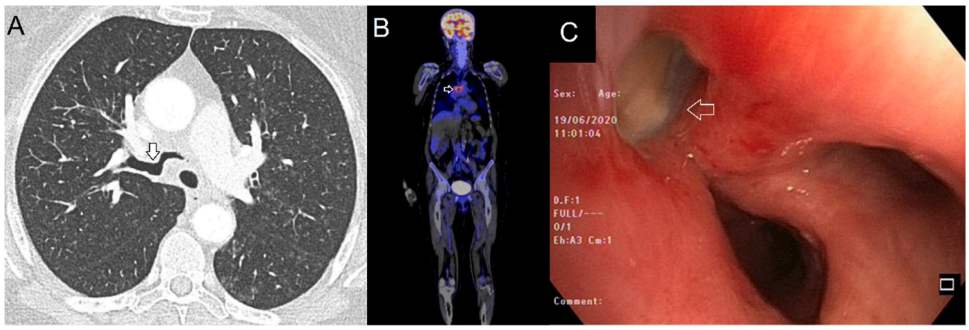

Fig. 5. (Case 5) Panel A: CT chest (axial view) demonstrating bronchus intermedius fistula extending into the mediastinum (arrowed). Panel B: PET (coronal plane) with FDG avidity of hilar and mediastinal lymphadenopathy (arrowed). Panel C: Bronchoscopy demonstrating fistula (arrowed) between bronchus intermedius and mediastinum.

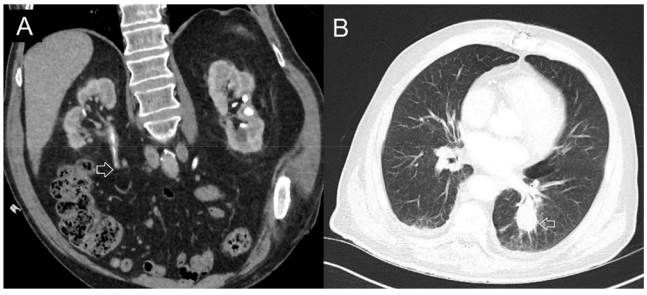

Fig. 6. (Case 6) Panel A: CT abdomen (coronal view) demonstrating obstruction of the right ureter (arrowed). Panel B: CT chest (axial view) demonstrating an irregular mass adjacent to the L hilum (arrowed).

this resulted in significant morbidity.

The cases demonstrate the importance of a high index of suspicion for melioidosis in the appropriate clinical context. Approximately 85 % of patients with melioidosis have classical comorbidities that predispose them to developing the disease. (Currie et al., 2021) These include diabetes mellitus, chronic lung disease, hazardous alcohol use, chronic kidney disease and immunosuppression; indeed, cancer itself is a risk factor for developing melioidosis. It was notable that all the patients in this series had one – and sometimes several – of these comorbidities.

However, the case histories demonstrate that the clinical presentation of melioidosis and cancer can be very similar, and there is significant overlap in the epidemiology of the two conditions in Australia. (Smith et al., 2018) This is, at least partly, explained by the role that obesity, cigarette smoking and hazardous alcohol use play in the development of cancer and – either directly (in the case of alcohol) or indirectly (in the case of obesity and smoking via the classical risk factors of diabetes and chronic lung disease) – in predisposing to melioidosis. (Queensland Health 2023; Hanson et al., 2021) Indeed, the most common presumed malignancy in the series was lung cancer and this diagnosis was considered in many of the cases because the patient was – or had been – a smoker.

It may not be surprising that local clinicians suspected lung cancer as the likely diagnosis in many of the cases, as lung cancer is far more common than melioidosis in the FNQ region. Lung cancer is the most

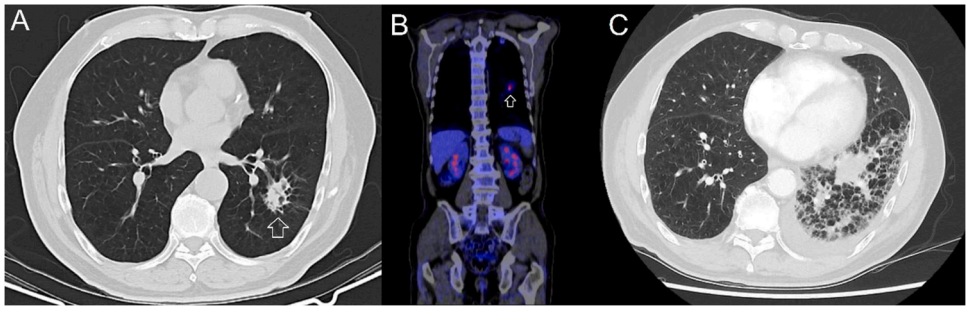

Fig. 7. (Case 7) Panel A: CT chest (axial view) demonstrating spiculated lesion in the left lower lobe (arrowed). Panel B: PET (coronal view) demonstrating avidity of left lower lobe lesion (arrowed). Panel C: CT chest (axial view) demonstrating airspace opacities in the left lower lobe and associated pleural effusion.

common cause of cancer death in FNQ and 3rd most common cause of death in the general population. In FNQ, between 1998 and 2021 there were 259 patients with pulmonary melioidosis, over the same time period there was 3229 diagnoses of lung cancer. (Queensland Health 2023) Australia's recent announcement of a national lung cancer screening program – where from 2025 low dose computed tomography will be employed in high-risk individuals (smokers and ex-smokers) in an effort to detect lung cancer earlier – will inevitably also identify non-malignant nodules. Pulmonary nodules are a recognised manifestation of *B. pseudomallei* infection and several other infectious diseases that are endemic in tropical Australia. (Sim et al., 2022; Sim et al., 2023) As nodules are identified in the national lung cancer screening program it will be important to obtain a tissue diagnosis before initiating inappropriate medical therapies (such as, in this series, corticosteroids), radiotherapy or surgery (lobectomy or pneumonectomy in the case of a pulmonary nodule). (Savelkoel et al., 2023) A tissue diagnosis is also essential in the age of novel targeted cancer treatment. (Ziv et al., 2016)

The series also demonstrates the benefits and risks of using PET scanning during diagnostic evaluation. PET scanning has been used most commonly in the staging and follow up of patients with cancer, however it remains essential to consider the clinical context in the interpretation of any imaging. In this series a PET-avid lung lesion was felt sufficient – after multidisciplinary review – to initiate radiotherapy in case 7 without a tissue diagnosis. Conversely, in case 3, PET imaging identified a clinically unsuspected deep buttock abscess that was able to be drained very simply, establishing the diagnosis of melioidosis.

It is notable that most patients in the series were diagnosed on blood culture which, in many cases, established the unexpected diagnosis of melioidosis. The majority of patients with melioidosis are bacteraemic, and while the importance of blood cultures in the diagnostic evaluation is axiomatic, clinicians unfamiliar with the pathogen should recognise that the median time for *B. pseudomallei* to flag positive in blood cultures is longer (median time to positive: 31 h) than for most other pathogens. (Prinsloo et al., 2023) It is important that the pathogen is not discarded as a contaminant, especially in non-endemic areas where it may be mis-classified as a non-pathogenic environmental bacterium. (Meumann et al., 2023) Of course, not every patient with melioidosis is bacteraemic and the clinical course of cases two, three and five emphasises the importance of tissue biopsy and culture in the appropriate clinical context.

The study also demonstrates the value of enhanced follow up of individuals who survive their melioidosis. (Hanson and Smith, 2019) Although the median age of the cohort was 69 – and all patients had significant comorbidity – access to universal health care in Australia's well-resourced health system is likely to have contributed to the fact that they were alive and well in the community at least 21 months after their diagnosis of melioidosis. Finally, although this report focuses on the experience in tropical Australia, there have been case reports of melioidosis misdiagnosed as cancer from Singapore, Malaysia, India, Taiwan and emphasising that this is an issue that confronts clinicians in many other parts of the world. (Zhao et al., 2020; Kho et al., 2021; Saravu et al., 2012; Liang et al., 2016) As the global incidence of cancer is expected to increase in the next 20 years, particularly in transitioning countries which carry a disproportionate burden of melioidosis, differentiation between melioidosis and malignant disease is likely to be an important clinical consideration in many parts of the world in the future. (Sung et al., 2021)

In summary, we present the cases of 7 patients presenting with melioidosis, that experienced clinicians – working in a region where melioidosis is endemic and is increasing in incidence – initially believed had a diagnosis of cancer. The cases re-emphasise the higher index of suspicion that is necessary in the presence of classical risk factors for melioidosis and the importance of thorough diagnostic evaluation before the initiation of anti-cancer therapy. It is hoped that the case series will provide salutary lessons for clinicians working in endemic regions. More importantly it may assist clinicians unfamiliar with melioidosis who, in an era of growing international travel and migration, may be now more likely encounter patients with this life-threatening, emerging infection.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. The Far North Queensland Human Research Ethics Committee, which provided ethical approval for the study (HREC/18/QCH/91–1261 and HREC/15/QCH/46–977).

Data availability statement

Data cannot be shared publicly because of the Queensland Public Health Act 2005. Data are available from the Far North Queensland Human Research Ethics Committee (contact via email FNQ_HREC@health.qld.gov.au) for researchers who meet the criteria for access to confidential data.

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CRediT authorship contribution statement

Kelly Baker: Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Ty Duncan:** Data curation, Visualization, Writing – review & editing. **Samantha Kung:** Data curation, Writing – review & editing, Validation. **Simon Smith:** Conceptualization, Data curation, Methodology, Supervision, Visualization, Validation, Writing – review & editing. **Josh Hanson:** Conceptualization, Methodology, Supervision, Visualization, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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