Melioidosis and idiopathic pulmonary hemosiderosis: a cast-iron case

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Abstract
Melioidosis is an infection with clinical importance in northern Australia due to the high associated mortality despite appropriate therapy. This report presents a case of acute pulmonary melioidosis on a background remarkable for the absence of typical risk factors for infection, but the presence of a high iron pulmonary microenvironment consequent to idiopathic pulmonary hemosiderosis. In light of recent genetic analysis of *Burkholderia pseudomallei*, we postulate that the patient inadvertently provided a high-substrate environment for the iron-scavenging ability of *B. pseudomallei*’s siderophore associated virulence factors, giving her a unique major risk factor for infection. This highlights the importance of considering individual patient factors in addition to population-wide risk factors in the differential diagnosis of a serious illness, and the value of genetic analysis of clinically significant pathogens.

Case Report

The Australian born, Caucasian woman first attended our North Queensland practice in 1996 (age 28) with hemoptysis and dyspnea requiring hospitalization and a four-unit packed red cell transfusion with her pre-transfusion hemoglobin being 66 g/L (reference 115–160 g/L). On examination, she showed no infective signs or symptoms, and blood panels including a full blood count, renal, and liver function tests were unremarkable.

Further investigations including anti-nuclear, anti-neutrophil cytoplasmic, anti-gliadin and anti-glomerular basement membrane antibodies were negative, as was serology for leptospirosis, legionella, chlamydia and mycoplasma. Urine microscopy was unremarkable, and a chest X-ray demonstrated bilateral parenchymal infiltrates consistent with diffuse alveolar hemorrhage.

Her medical history included mild iron deficiency anemia with a baseline hemoglobin of 104 g/L and a mean cell volume of 78 g/fL (reference 80–100 g/fL) and pelvic endometriosis. Her social history including smoking (greater than 10 pack years) and two to five standard alcoholic drinks per week. She denied illicit substance use.

Treatment of the initial episode consisted of intravenous antibiotic and glucocorticoid therapy, with symptom resolution over 2 weeks. A subsequent transthoracic echocardiogram was normal, and an endoscopy with duodenal biopsy excluded coeliac disease (known to be associated with autoimmune-mediated alveolar hemorrhage).

In the subsequent 15 months, she had two further episodes of unprovoked acute pulmonary hemorrhage requiring transfusions and was commenced on immunosuppressive therapy with chloroquine. A repeat autoimmune screen was negative, and a bronchoscopy with lavage and biopsy in November 1997 demonstrated hemosiderin laden macrophages in the absence of capillaritis consistent with a diagnosis of idiopathic pulmonary hemosiderosis (IPH) [1].

With no further episodes over the following 18 months, her immune suppression was ceased. However, a major hemorrhage in 2001 requiring hospitalization and transfusion led to prophylactic recommencement, which was continued until 2003.

In February 2004, while not on immunosuppression, she developed a febrile illness with productive cough and pleuritic chest pain. There was no recent travel, sick contact or animal exposure history. On admission, she demonstrated a neutrophilia of 23.2 × 10⁹ (reference 4–11 × 10⁹), a C-reactive protein of 264 mg/L (reference < 5 mg/L) and erythrocyte sedimentation rate of 81 mm/h (reference
< 20 mm/hour). Chest X-ray demonstrated dense consolidation in the right middle lobe and intravenous antibiotics were commenced – initially ceftriaxone, then ticarcillin/clavulanic acid and gentamicin after no response. Blood cultures taken on admission were positive for *Burkholderia pseudomallei* after approximately 48 h with an anti- *B. pseudomallei* antibody titre of 320. A diagnosis of melioidosis was made and meropenem with trimethoprim/sulphamethoxazole was commenced. After clinical and biochemical improvement, she was discharged on a 3-month course of trimethoprim/sulphamethoxazole.

Repeat imaging one, 3 and 6 months later, illustrated gradual resolution of her right middle zone consolidation with a residual scar. With a declining anti-*B. pseudomallei* antibody titre. Follow-up chest radiographs and spirometry have shown no evidence of progressive lung disease, and there has been no further episodes of pulmonary hemorrhage.

**Discussion**

We report a case of *B. pseudomallei* infection on a background of IPH itself, a diagnosis derived from her multiple alveolar hemorrhages, consistently negative autoimmune markers, preserved renal function and bronchioalveolar lavage findings. This is consistent with previously discussed IPH diagnostic principles [1].

*Burkholderia pseudomallei* is a gram-negative bacillus endemic throughout northern Australia and southeast Asia. A saprophyte, the incidence of acute melioidosis typically spikes during and immediately post the wet season in tropical areas, and more commonly affects those with a discernible exposure history and documented risk factors such as diabetes mellitus, chronic renal disease, or immunosuppression [2].

Acute melioidosis has a high morbidity and mortality despite optimal antimicrobial and supportive therapies. In a recently reported 10-year case series of 252 patients with a diagnosis of melioidosis confirmed microbiologically in northern Australia, there were 49 deaths, giving a mortality rate of 19% [2].

Genomic analysis of *B. pseudomallei* has revealed multiple drug efflux pumps, beta-lactamases, cephalosporinases, exoproteins (that cause host tissue destruction) as well as siderophores, malleobactin (involved in host iron extraction) and others which upregulate in iron-deficient conditions and have shown a positive correlation with increasing virulence in vivo [3]. Conversely, mutation studies have demonstrated that removal of these iron acquisition and utilization genes results in diminished virulence [4]. Additionally, *B. pseudomallei* has previously been shown to have an enhanced growth pattern in a high-iron culture medium when compared to low-iron conditions, with a related species *B. cenocepacia* (a common pathogen in individuals with cystic fibrosis who also have a high-iron pulmonary microenvironment), having increased aggregation and biofilm production when cultured in a high-iron medium [5].

With this information, we hypothesize that the iron-abundant pulmonary microenvironment of our patient (secondary to her IPH) was a significant factor in her contracting melioidosis. The absence of classical risk factors (including immunosuppression) would have otherwise rendered her an unlikely candidate for this infection; however, by inadvertently providing a substrate that allowed for increased expression of iron-related virulence factors she enabled colonization and ultimately infection with *B. pseudomallei*.

We were able to identify one case in the literature of melioidosis in a patient with IPH; however, this patient had other documented risk factors for infection including indigenous heritage and higher risk environmental exposure.

This case highlights the need to consider both patient and pathogen-specific risk factors for infection when investigating a febrile illness in the undifferentiated patient, and suggests a further uncommon but relevant risk factor for pulmonary melioid infection.

**Disclosure Statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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