

## CASE STUDY

# Melioidosis and sickle cell disease: Description of a rare association

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**Abstract:** Melioidosis and its germ are increasingly reported on the African continent and particularly in Central Africa, probably due to the increased awareness of clinicians and microbiologists and the growing recognition of the organism. It is called "Great Mimicker" because it produces a wide range of clinical characteristics such as would be found in patients living with sickle cell disease (SCD) in particular. However, to date, no publication presents this association between melioidosis and SCD. The authors describe here 3 clinical cases presenting this very rare association between melioidosis and SCD. These are 3 children with SCD (homozygous SS) residing in Lubumbashi in Haut-Katanga province in the Democratic Republic of Congo. One patient presented with sepsis as a clinical form of the disease. All 3 had presented a pulmonary form. Only one patient was treated specifically after the diagnosis of melioidosis; for the other two, this diagnosis was confirmed after their death. Thus the death rate is 66.67%. This article describes, through these 3 clinical cases, a very rare first association between melioidosis and SCD. This association requires research to establish whether, like Thalassemia, SCD can be considered a risk factor for melioidosis. A screening of cases of melioidosis in the general population should allow us to focus on this.

**Keywords:** sickle cell disease, Melioidosis, Africa, children, *Burkholderia pseudomallei*

## 1 Introduction

Melioidosis, an infection caused by *Burkholderia pseudomallei*, is endemic in northern Australia and parts of Southeast Asia<sup>[1]</sup>. The clinical manifestation varies from mild localized infection to fulminant sepsis. Melioidosis and its germ are increasingly reported on the African continent and particularly in Central Africa, possibly due to the increased awareness of clinicians and microbiologists and the growing recognition of the organism<sup>[2]</sup>. *Burkholderia pseudomallei* is a Gram-negative bacillus found in soil. Infection occurs by inoculation or inhala-

tion, especially in patients with sickle cell disease (SCD). The disease has been called the "Great Mimicker" because it produces a wide range of clinical features such as would be found in patients with SCD<sup>[3]</sup>. In fact, in patients living with a SCD, infection is a major determinant of the outcome, particularly in Africa. The Democratic Republic of Congo (DRC) pays the heaviest price for SCD in Africa<sup>[4]</sup>.

Infection is probably the most important cause of death in these patients<sup>[5]</sup>. Hemoglobinopathies including thalassemia major are associated with an increased incidence of melioidosis<sup>[6]</sup>. Could this be the case for people with SCD?

We did not find in the literature descriptions of melioidosis in patients with SCD. Hence the interest of this series of 3 cases of association between melioidosis and SCD observed in Lubumbashi in the province of Haut-Katanga in the DRC.

## 2 Case presentation

### 2.1 Case 1

A 9-year-old boy with SCD known since the age of 3 was admitted with chest pain, physical weakness and fever. He was on a daily treatment of 5 mg of folic acid,

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**Figure 1.** Image showing a right postero-basal alveolar focus in case 1

500 mg of Hydrea and 500 mg of Deferiprone. His history indicates that he had already been transfused 7 times and hospitalized following pneumonia in 2015. Eleven months before this admission, he had suffered a stroke and had been put on a transfusion exchange program. He was of normal weight for his age. The initial blood count showed a hemoglobin level of 5.7 g/dl with normal values for liver and kidney functions. The C-reactive protein was 24 mg/l. The chest x-ray on admission showed the presence of a right postero-basal alveolar focus, a normal aspect of the hilum, a cardio-thoracic index (CTI) corrected in the standards, the whole suggesting a right basal pneumonia (Figure 1). We therefore concluded in an Acute Thoracic Syndrome. Parenteral therapy with ceftriaxone and amikacin was started without success for 10 days for ceftriaxone and 5 days for amikacin. During his stay in hospital, the patient was transfused twice to correct his anemia and at the same time manage his painful crisis.

After 12 days of treatment with persistent fever, a second anteroposterior X-ray reveals an ICT corrected to 0.57, a normal aspect of the islands and a right postero-basal alveolar focus with air bronchogram suggesting a right postero-basal alveolar pneumonitis this time associated uncompensated cardiomegaly (Figure 2).

Because of the intensifying chest pain and 81% desaturation, the patient received opioid analgesics and was placed on oxygen.

On the 16th day of her admission, the chest x-ray revealed worsening of the lesions of right basal bronchopneumonia with low-abundance pleural effusion and barely a peri-hilar infiltrate on the left, concluding in a pejorative radiological course with worsening of bronchopneumonia (Figure 3).

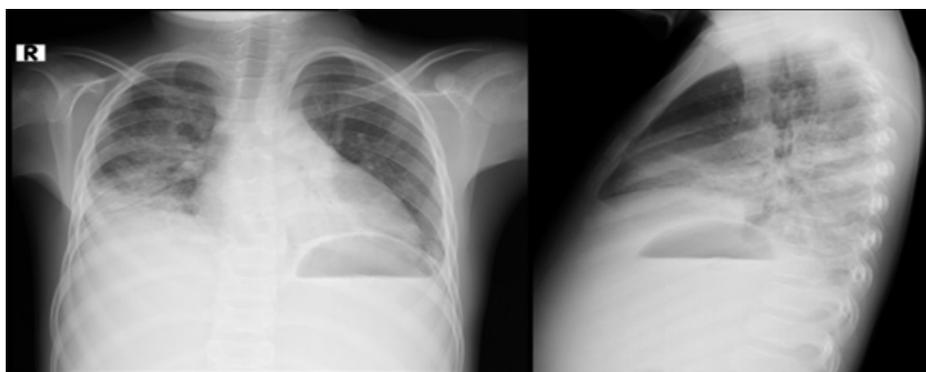
In addition, a thoracic CT scan is performed with the spiral technique without and with iodine injection followed by multi-planar reconstructions revealing a typical alveolar syndrome in the form of parenchymal densification occupying the two lower lobes and partly the lateral and medial segments of the middle lobe. , as well as an aeric bronchogram showing true "lobites". Conclusion: bilateral massive basal pneumonia predominantly on the right, in particular of two lower lobes and the right middle lobe. His repeat exams for acid-fast bacilli (AFB) were microscopically negative, as well as the GeneXpert sputum exam negative.

A blood sample taken on day 3 of hospitalization for culture showed a negative result. However, the aerobic vial of a second sample taken on day 7 of hospitalization was positive. On Gram stain, Gram negative rods with bipolar staining were visualized. Subcultures carried out on agar medium enriched with sheep blood and on Mac Conckey medium incubated at  $35 \pm 2^\circ \text{C}$  made it possible to isolate grayish colonies with a particular intense odor of earth. The API 20NE system (bioMérieux, Marcy l'Étoile, France) identified the isolate as *B. pseudomallei* with the numerical profile 1156577 (99.9% certainty). The antibiotic resistance profile was as follows: resistant Gentamicin, Tobramycin and ampicillin; while Piperacillin,

Treatment with infusion ceftazidime for 21 days followed by oral cotrimoxazole for 2 months combined with folic acid got rid of the fever. Regular clinical improvement was observed with treatment although fever did not decrease until the 17th day after admission. The patient was discharged on the 22nd day. The patient was seen again in consultation three months after his discharge from the hospital. He was asymptomatic and the clinical



**Figure 2.** Image showing a normal aspect of the hilum and a right postero-basal alveolar focus with air bronchogram in case 1



**Figure 3.** Image showing worsening of the lesions of right basal bronchopneumonia with low abundance pleural effusion and on the left barely a perihilar infiltrate in case 1

examination was unremarkable.

## 2.2 Case 2

A 4-year-old boy, SCD known since the age of 8 months, was admitted in April 2018 for fever evolving for 22 days and treated successively with ampicillin, cefotaxime and gentamicin then Tazobactam. He was listless, downcast, and pale upon admission. He complained of pain in his right knee. Physical examination revealed an jaundiced and pale child; lethargic; well fed and well developed with an axillary temperature of 39 ° C; a respiratory rate of 42 cycles per minute, an 84% saturation and a pulse of 137 beats per minute. There was a purulent collection in the lower third of the left arm with fistulization and lameness on walking.

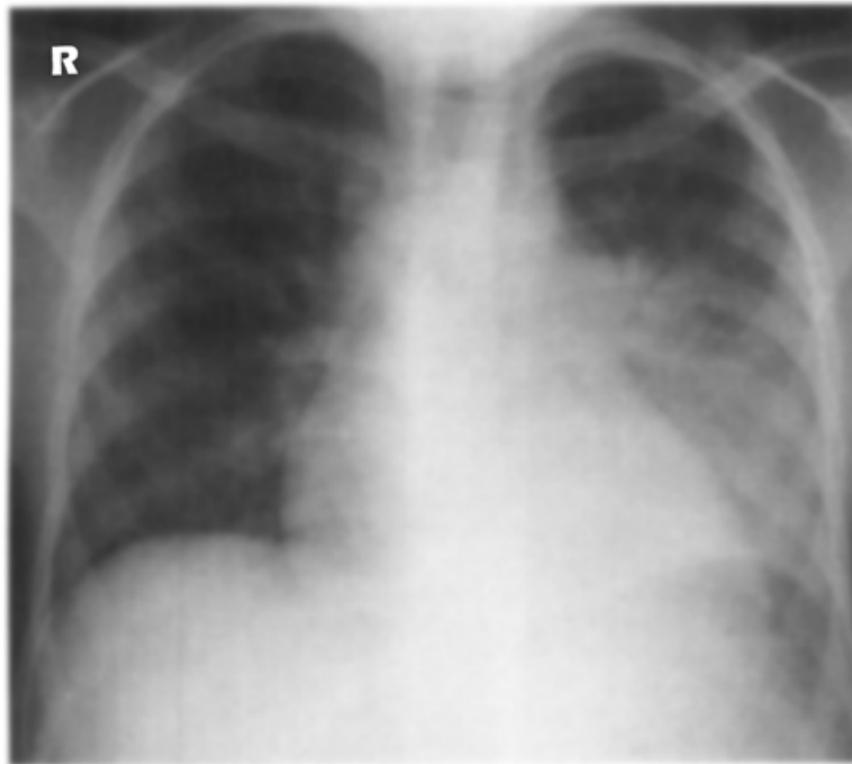
Hemoglobin was 6.9 g/dL, 22% hematocrit, white blood cells were 27,300 per mm<sup>3</sup> (86% polymorphonuclear neutrophils, 13% lymphocytes, 1% monocytes). Chest, lower and upper extremity x-rays were normal. CRP was quantified at 196 mg/L. The pyoculture isolated

on day 3 a *Burkholderia pseudomallei* while the blood culture came back negative.

One week after admission, his clinical condition deteriorated and the patient developed oligo-anuria and died in a picture of multiple organ failure despite treatment with ofloxacin and parenteral lincomycin.

## 2.3 Case 3

An 8-year-old boy had a clinic of cough, fever and chest pain on his left side for 11 days. The physical examination was marked by a temperature of 39.8°C, a respiratory rate of 37 cycles per minute, dullness on percussion and egophony at the base of the left lung and a decrease in vesicular murmur on the left lung. 'auscultation. Hemoglobin was 5.2 g/dl with 9% reticulocyte count. The white blood cell count was 32,000 cells/mm<sup>3</sup> with a differential of 83% neutrophils and 17% lymphocytes. The chest x-ray showed union of the left lower lobe with pleural effusion (Figure 4). Thoracentesis produced a small amount of golden yellow fluid. The puncture fluid



**Figure 4.** Image showing union of the left lower lobe with pleural effusion in case 3

was sent to the laboratory for analysis.

The blood cultures came back negative while that of pleural fluid isolated colonies with an API20NE biochemical profile of 1156576, suggesting *B. pseudomallei* (99% identity). The patient died on the 9th day of hospitalization.

Table 1 presents the clinical, paraclinical, therapeutic and evolutionary characteristics of these 3 patients.

### 3 Discussion

Melioidosis primarily affects people who have direct contact with moist soils and who have an underlying predisposition to infection<sup>[1]</sup>. The clinical features of melioidosis mimic many clinical pictures, leading to frequent misdiagnosis of the disease<sup>[7]</sup>.

The 3 patients included in this series of cases are homozygous SS (SCD) and the culture of the biological specimens isolated *Burkholderia pseudomallei*. In our patients a picture of pneumopathy had been identified. The pulmonary form would be the most common clinical form of melioidosis beyond the 4 forms encountered: pulmonary form, sepsis, localized infections and chronic infections<sup>[8]</sup>. Chest x-ray may show bilateral bronchopneumonia, miliary granulations (0.5-1 cm), multiple small lung abscesses involving the upper lobes, segmental or

lobar infiltrates, and cavitary lesions. Symptoms depend on the route of inoculation, but one form of the disease may progress to another<sup>[9]</sup>. Diagnosis is based on laboratory isolation of *Burkholderia pseudomallei* from sputum, blood, urine, pus, or skin lesions. Blood cultures are usually negative. There are agglutination tests and complement fixation tests<sup>[11]</sup>. In our series, the diagnosis was confirmed once from a blood culture and twice from pus culture.

The delay in diagnosis in our series reflects the reality of medical care in the Democratic Republic of Congo and in Africa, where hospital resources are limited and the capacity to diagnose melioidosis as part of routine laboratory practice does not exist. not<sup>[10]</sup>.

Only case 1 is still alive today. A notion of play in a marshy area was found at home. The environmental study 2 years in the screen isolated positive signals for *Burkholderia pseudomallei* in the vicinity<sup>[2]</sup>. This same case has been under a transfusion exchange program for 11 months and in addition he was transfused twice during his hospital stay. Repeated blood transfusions may be linked to adverse events, for example the build-up of too much iron in the body leading to an increased risk of infection<sup>[11]</sup>. Iron storage does not directly damage cells, but its intracellular renewal contributes to labile intracellular iron pools that generate harmful free radicals<sup>[12]</sup>. This

**Table 1.** General characteristics and results of case investigations

Clinical cases		Case 1	Case 2	Case 3
Identity	Age	9 years	4 years	8 years
	Sex	M	M	M
	Weight	28 kg	12 kg	20 kg
	Months of the year	February	April	March
	Statut Hb	SS	SS	SS
	Symptomatology duration	21 days	27 days	20 days
Symptomatology	Frontal headache	Yes	Yes	No
	Fever	Yes	Yes	Yes
	Subcutaneous-Lesions	Yes	No	Yes
	Arthralgy	Yes	No	Yes
	Edemas	No	No	Yes
	Subcutaneous-Nodules	Yes	Yes	Yes
	Dyspnea	Yes	Yes	Yes
	Cough	Yes	Yes	No
	Pulse			
	Lymphadenopathy	Yes	Yes	Yes
	Hépatomégaly	Yes	Non	Yes
	Pallor	Yes	Yes	Yes
	Dactylitis	No	No	Yes
	Vomiting	No	No	No
Paraclinic	White cells	18500/mm <sup>3</sup>	27300/mm <sup>3</sup>	32000/mm <sup>3</sup>
	Hb	5.7 g/dL	6.9 g/dL	5.2 g/dL
	Neutrophil	78%	86%	83%
	CRP	24	196	92
	Blood culture	Positive	Negative	Negative
	Pyoculture	Not done	Positive	Positive
Treatment	Treatment before culture	Ceftriaxone amikacin	Ofloxacin lincocin	Amoxicillin azithromicin
	Treatment after culture	Ceftazidim then cotrimoxazole		
Evolution of the case		Cured	Dead	Dead

in addition to the infectious susceptibility linked to his SCD status<sup>[13]</sup>.

Treatment of *Burkholderia pseudomallei* is difficult. The drugs traditionally used to treat melioidosis include ceftazidime or Meropenem alone and then a relay with cotrimoxazole<sup>[8]</sup>. Even with adequate antimicrobial treatment, the death rate in melioidosis is around 50%<sup>[14]</sup>. In our series this death rate was 66.67%.

It is known that subjects living with a SCD are susceptible to bacterial infections, secondary to a combination of several susceptibility factors, both genetic and organic, and this from the age of 2 months until the end of their life<sup>[13]</sup>.

#### 4 Conclusion

This article describes, through 3 clinical cases, a first association between melioidosis and SCD. This association requires research to establish whether, like Thalassemia major, another hemoglobinopathy, SCD can be considered as a risk factor for melioidosis. A screening of cases of melioidosis in the general population should allow us to focus on this.

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