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Case presentation: We report four new cases of melioidosis with a case that was complicated by a failure of several organs (case 2) which were observed on Mayotte Island. The last two affected cases came from Madagascar. Burkholderia pseudomallei was isolated from blood cultures, confirming the diagnosis. Prolonged treatment with ceftazidime or Ertapenem intravenously followed by cotrimoxazole alone or combined with oral doxycycline led to complete recovery.

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Melioidosis an Emerging Disease in the Indian Ocean Region: Case Series Study in Mayotte

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Conclusion: Melioidosis poses a potential threat in the Indian Ocean region in general and Mayotte and should be carefully monitored. The high incidences of diabetes and climatologic conditions such as rainy seasons with the occurrence of tropical cyclones make Mayotte a possible setting for melioidosis. It would therefore not be surprising to see a marked increase in the incidence rate of melioidosis in the years to come.

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I. INTRODUCTION

Melioidosis is a bacterial zoonosis in humid tropical areas, caused by a Gram-negative bacillus Burkholderia pseudomallei, an invasive germ, transmitted by inoculation, inhalation or ingestion. Although inhalation is the first route of infection described, it is now well known that inoculation is the most common mode of infection [1]. It was described in 1912 by Whitmore in Burma (Myanmar) [2]. It is a severe, opportunistic infection, difficult to treat, with high mortality. It is an emerging disease in the process of spreading. It mainly affects susceptible persons who are directly in contact with contaminated wet soils. Immunosuppressed elderly persons (e.g., those suffering from diabetes mellitus and/ or alcoholism, chronic kidney and lung disease) are at increased risk of developing infection. It can reach all the organs and especially the lungs. The disease has protean manifestations ranging from localized abscess formation

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to disseminated abscesses, septicemia, shock [3–4]. Ceftazidime or meropenem are the therapeutic choice for treating severe cases of infection and can be given by the IV route for several weeks, followed by oral treatment (up to 20 weeks) with trimethoprim-sulfamethoxazole and doxycycline [5]. Here, we report four new cases of melioidosis that were observed in Mayotte, which is a French overseas department.

Case summary 1

In 2016, 73-year-old Comorian with a history of high blood pressure, chronic renal failure, insulin-requiring diabetes, does not smoke, non-alcoholic. Living in Mayotte for many years, with no notion of recent travel. He consults in the emergency room for fever and chills with an infectious focus on the left on the chest X-ray. The clinical examination found crackles from both bases. The general condition of the patient allows return home with amoxicillin / clavulanic acid. Three days after going to the emergency room, he consults again for persistent fever. The biological assessment shows a moderate inflammatory syndrome with GB 15 G / L with PNN 12.2 G / L, thrombocytopenia at 86 G / L, CRP 222 mg / L, urea 34 and creatinine 369 and HbA1c at 11%. A blood culture taken during its first emergency visit highlights Burkholderia pseudomallei after 6 hours of incubation on the aerobic sample. A chest CT scan showed necrotizing pneumonitis with bilateral effusion and small parenchymal condensation of the focal right upper lobe. Based on the antibiogram, treatment with Ertapeneme (1 g / day) and cotrimoxazole 960 mg (1 tablet / day) for 14 days was started. Apyrexia is achieved on the fifth day of treatment. The control blood cultures will all come back sterile. After two weeks of dual antibiotic therapy, the patient is treated with cotrimoxazole alone for a total of 3 months. A good clinical-biological evolution at the end of the treatment without relapse was observed.

Case summary 2

In March 2018, 54-year-old Comorian woman with type 2 and hypertensive diabetes. Living in Mayotte for many years, with no notion of recent travel, does not smoke, does not drink alcohol. Farmer. For the past month and a half, she had had a deterioration in general condition with weight loss, fever with chills, headache with a dry mouth, tongue, pallor and an imbalance of diabetes. She complains of diffuse abdominal pain, constipation on physical examination. On admission, the

biology found GB 10.5 G / L, PNN 9.19 G / L, thrombocytopenia: 105 giga / L, prothrombin level: 42%, CRP 257mg / L. Cytolysis three times normal, moderate cholestasis without jaundice, HbA1c 13%. Three blood cultures (aerobic Falcon) grow to Burkholderia pseudomallei. The Thoraco-Abdo-pelvic CT scan performed on admission found moderate bilateral pleural effusion, predominantly on the left, and a thin layer of pericardial effusion at the mediastinal window. At the parenchymal level, there were multiple diffuse nodular lesions of central and peripheral distribution, bilaterally and predominantly on the right with bilateral hilo-basal peri-broncho-vascular thickening with left postero-basal parenchymal condensation. There were also multiple hypodense lesions on the hepatic parenchyma evoking micro-abscesses and stable appearance of the intra-splenic abscessed collections and Thrombosis of the splenic vein associated with several lymphadenopathies at the level of the splenic hilum thus confirming the image of the thrombus at level of portal division of the left liver. The brain scan did not find any argument in favor of an abscess. Initially treated with Ceftriaxone then adapted to the results of blood cultures with Ceftazidime (6g / day) plus intravenous Cotrimoxazole (3200mg / day) for 14 days then relay maintenance treatment with cotrimoxazole (960mg) oral (6 tablet / day) and doxycycline (200mg / day). She also benefited from a curative anticoagulation by Lovenox then Rivaroxaban for 3 months. At 6 months of treatment, there was a good clinical-biological and CT evolution with almost complete regression of the pulmonary, hepatic and spleen lesions. No relapse after 3 months of follow-up

Case summary 3

In July 2018, 61-year-old Mahorais, whose only history was a benign prostate enlargement with a first placement of a permanent catheter in Madagascar a month before his hospitalization. Addressed to the emergency room in front of a table of febrile glairo-bloody diarrhea evolving for 3 days, a general examination found fever. Biology finds an inflammatory syndrome (22 G / L of leukocytes, CRP 339mg, a 2N cholestasis without hepatic cytolysis and an increased free bilirubinemia and PSA at 14.88. A vesico-prostatic ultrasound found in the bladder a clot of hematoma measuring 73 mm long transverse axis 54 mm thick and 54 mm high or 113 ml in volume. The prostate was enlarged, homogeneous, without image of a nodule. Cytobacteriological examination of the urine found leukocyturia at 19200 / mm³, red cells 1686 / mm³, as well as Gram-negative bacteria live Put on ceftriaxone and Ofloxacin Cytobacteriological examination of urine and two aerobic blood cultures confirmed the presence of Burkholderia pseudomallei Diagnosis of hemorrhagic shock secondary to massive hematuria within the framework of a septicemia with urinary starting point by

Burkholderia pseudomallei was posed. Passage with the block for clot removal vesical I by the upper route and retropubic adenomectomy. Introduction after antibiogram of Ceftazidime (6g / day) for 14 days with then switch with Doxycycline (300 mg / day) for 3 months. The evolution is quickly favorable both urologically and infectiously. Note that the blood cultures and Cytobacteriological examination of the urine carried out after the treatment returned sterile and an abdominopelvic scanner showed nothing.

Case summary 4

In December 2018, Mahorais, 62, type II diabetes and high blood pressure. After a month's stay in Madagascar, presents to the emergency room three weeks after his return for feverish cough; a hypothesis of right lung disease was raised and treated with amoxicillin / clavulanic acid with return home. Returns to the emergency department two days later for increases in the pulmonary picture with stage IV dyspnea, productive cough and chest pain. The clinical examination is without particularity. Biology GB 14.3G / L, including PNN 10.0G / L, P 407G / L, CRP 295mg / L and HBA1c 9.8%. A Thoraco Abdomino-Pelvic CT scan found at the mediastinal level: infra-centimetric lymphadenopathy at the level of the Baret's compartment and right bronchopulmonary, a bilateral pleural effusion larger on the right. At the parenchyma level, there were several bilateral pulmonary foci, the largest of which was located at the level of the upper right lobe with an aspect of early collection abscess 43 mm in diameter located in the posterior sub pleural. Several other foci of pseudo-nodular appearance are found at the level of the right apex, at the level of the lingula and at the level of the two lower lobes. Abdomino-pelvic no abnormality. Aerobic blood culture returns positive to Burkholderia pseudomallei. The diagnosis of a hypoxemic pneumonia with Burkholderia pseudomallei was confirmed with initiation under meropenem (6 g / day) and cotrimoxazole (960mg) oral (4 tablet / day) for 14 days then relay with Doxycycline (200mg / day) and cotrimoxazole (960mg) even dose for 3 months. Significant improvement at the clinical level with oxygen and biological withdrawal. No relapses were reported after three months of follow-up.

II. DISCUSSION

We report two indigenous cases and two imported cases of melioidosis from Madagascar observed between 2016 and 2018 in Mayotte which is the last French overseas department, located in the Indian Ocean region. Melioidosis is a seasonal condition, the incidence of which increases with each rainy season [6]. In fact, 75 to 81% of cases are detected during the months when rainfall is highest [7]. Hygiene conditions and access to drinking water could be at issue because a study carried out in 2013 in

Thailand shows that ingestion of non-drinking water is clearly criminalized in low-income countries [8]. According to INSEE in 2017, almost a third of the inhabitants of Mayotte did not have access to water in their accommodation. To obtain water, the Mahorais use an outdoor tap shared between several dwellings. Those who do not have them call on "neighbors or relatives". "The others, mainly residents of sheet metal houses, get their water from a fire hydrant, from a well or directly from a river or stream," said INSEE. A review of the literature published in 2017 shows that 13 cases of melioidosis have been documented in the Indian Ocean region since 2004 [9,10,11]. In the Indian Ocean region, most of these cases occurred after a stay in Madagascar [10,12], like our two imported cases. The incidence of melioidosis in Madagascar may be more important than assumed because it is likely that many cases are never diagnosed or treated. The number of cases diagnosed is probably lower than reality, due to the lack of diagnostic means in developing countries, and the ignorance of this pathology by doctors. These recent clinical reports suggest that this infection is endemic in the Indian Ocean region. In our case series, three-quarters of our patients were diabetic. Various studies clearly demonstrate that almost 50% of melioidosis patients have varying degrees of diabetes mellitus. Additionally, *B. pseudomallei*-infected diabetics have impaired IL12P70 production that results in decrement of IFN- γ [13]. It was also found that pulmonary localization was the most frequent with almost 75% of cases. According to the literature, melioidosis is expressed in the majority of cases by pneumonia, regardless of the endemic area [14]. This is often severe and may require the use of intensive care. Pulmonary involvement occurs in the form of pneumonia, lung abscess, pleural effusion or even pleural empyema [15]. Genitourinary disorders with prostatic abscess have also been reported in Australia, while a significant proportion of hepatic or splenic abscesses have been found mainly in Thailand [14,16]. Our patients were treated during the attack phase with either a carbapenem or ceftazidime as monotherapy for at least two weeks and then relayed with trimethoprim sulfamethoxazole or doxycycline alone or both. Study confirms that ceftazidime or meropenem are the therapeutic choice for the treatment of severe cases of infection and can be administered IV for several weeks, followed by oral treatment (up to 20 weeks) with trimethoprim sulfamethoxazole and doxycycline [5].

III. CONCLUSION

Melioidosis poses a potential threat in the Indian Ocean region in general and Mayotte and should be carefully monitored. The high incidences of diabetes and climatologic conditions such as rainy seasons with the occurrence of tropical cyclones make Mayotte a

possible setting for melioidosis. It would therefore not be surprising to see a marked increase in the incidence rate of melioidosis in the years to come. In addition, clinicians examining travelers with severe pneumonia or sepsis returning from subtropical or tropical regions should consider the differential diagnosis of acute melioidosis especially that novel molecular methods of diagnosis (e.g., PCR) are being increasingly implemented for routine diagnosis. Report to the laboratory to avoid accidental contamination on the one hand and on the other hand, it is feared that *B. pseudomallei* will be used as a biological weapon

Key learning points

- *Burkholderia pseudomallei* is the causative agent of melioidosis, which is prevalent throughout Southeast Asia.
- This bacterium is an important bioweapon and bioterrorism risk worldwide.
- The overall fatality rate of septicemia in melioidosis is very high, and bacteria are intrinsically resistant to many antimicrobial agents.
- Melioidosis increasingly affects travelers visiting endemic areas, thereby leading to septicemia.
- Clinicians should consider acute melioidosis as a differential diagnosis.

Top five papers

[1] Allou N, Martinet O, Allyn J, Bouchet B, Jaffar-Bandjee M-C, Galas T, et al. (2017) Emergence of melioidosis in the Indian Ocean region: Two new cases and a literature review. *PLoS Negl Trop Dis* 11(12): e0006018. <https://doi.org/10.1371/journal.pntd.0006018>

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Abreviation

B. pseudomallei: Burkholderia pseudomallei
 CRP: C-REACTIVE PROTEIN
 CT scan: Computerized Tomography
 GB: white blood cells
 HbA1c: glycated hemoglobin
 IV: Intravenous injection
 INSEE: The National Institute of Statistics and Economic Studies
 IL12P70: Interleukin-12, p70

IFN- γ : Interferon-gamma receptor
 PNN: Polynuclear neutrophils
 PSA: Specific Prostate Antigen
 P: Platelets
 PCR: Polymerase Chain Reaction