ACUTE SEPTICAEMIC MELIOIDOSIS A REPORT OF THREE FATAL CASES

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SYNOPSIS

Three fatal cases of acute septicaemic melioidosis in debilitated patients are reported. As acute septicaemic melioidosis is rapidly fatal, early vigorous treatment with appropriate antimicrobial agents is indicated in debilitated patients with septicaemia strongly suggestive of the disease. Clinical features, diagnosis and treatment of the disease are discussed.

INTRODUCTION

Melioidosis is a disease caused by a Gram-negative bacillus, Pseudomonas pseudomallei. It was first described in 1912 by Whitmore and Krishnaswami in post-mortem examinations of Rangoon beggars and morphine addicts (1). Since then numerous cases have been reported from Southeast Asia which is the main endemic area. The first reported case of acute melioidosis in Singapore was by Gilmour in 1931 (2). The disease finally gained worldwide prominence following the involvement of French and United States military forces in the protracted Indochina conflict after World War II (3, 4).

The clinical spectrum of melioidosis is protean. It may present as a subclinical infection detected only by a positive melioidosis haemagglutination titre (5), or it may present as an acute fulminant septicaemia, a subacute infection or a chronic suppurative infection (6, 7). The acute septicaemic form has a very high case fatality rate and it is seldom entertained in the differential diagnosis of acute septicaemic illness in Singapore. The object of this paper in reporting three fatal cases of acute septicaemic melioidosis is to remind us that the disease, though often forgotten, is not gone from our midst.

CASE REPORTS

Case I. A 69 year old unemployed Chinese man was admitted to hospital with a 5-day history of fever, chills and cough productive of mucoid sputum. II months previously he was investigated for palmar hyperkeratosis, clubbing, gynaecomastia and an abnormal chest radiograph showing a round opacity in the left lower zone. Percutaneous transthoracic needle biopsy of the pulmonary lesion was reported as showing a moderately differentiated adenocarcinoma. He was then given a course of palliative radiotherapy.

On clinical examination he was acutely ill and dehydrated. His temperature was 39°C, pulse 100/minute, respiratory rate 25 breaths/minute and blood pressure 150/85 mm Hg. Clubbing, palmar hyperkeratosis, spider naevi and gynaecomastia were noted. Crepitations were heard in both lungs. The remainder of the clinical examination was normal.

Laboratory studies showed the following: haemoglobin 11.5 g/dl, total white blood cell count 10300/cmm with 83% polymorphs, 14% lymphocytes, 2% monocytes and 1% eosinophils, platelets 175000/cmm, erythrocyte sedimentation rate 50 mm in first hour, blood urea 46 mg/dl, serum sodium 132 mmol/l, potassium 4.1 mmol/l, chloride 93 mmol/l, creatinine 1.1 mg/dl, blood sugar 262 mg/dl, plasma calcium 8.2 mg/dl and phosphate 2.9 mg/dl. Urine contained white cells. Arterial blood gas analysis showed pH 7.437, P_aO_2 63.2 mm Hg, P_aCO_2 23 mm Hg and oxygen saturation 91.5%. Sputum smear for acid fast bacilli and sputum culture for pathogens were negative. Chest radiograph showed a large opacity in left lower zone and multiple nodular opacities in right lung.

Initially he was treated for septicaemia with intravenous gentamicin, ampicillin and cloxacillin. He continued to have a swinging fever with daily spikes up to 40°C. On the fourth hospital day, he was given intravenous cefotaxime and hydrocortisone. On the fifth hospital day, Pseudomonas pseudomallei was isolated from his blood culture (Table 1) and he was commenced immediately on intravenous chloramphenicol. However his clinical state deteriorated rapidly and he died on the sixth hospital day.

Case 2. A 51 year old male Chinese labourer was admitted to hospital with a 7-day history of fever and chills. 3 days prior to admission he was noted to be confused, unsteady on his feet and incontinent of urine. He had diabetes mellitus for 4 years and was on oral hypoglycaemics. He consumed alcohol moderately.

Clinical examination showed an acutely ill man dehydrated and prostrated. His temperature was 39.4°C, pulse 100/minute, respirartory rate 25 breaths/minute and blood pressure 170/70 mm Hg. His sensorium was obtunded. A tinge of jaundice was noted and his liver was mildly enlarged, soft and not tender. The other systems were unremarkable.

Laboratory studies showed the following: haemoglobin 15.2 g/dl, total white blood cell count 19700/cmm with 91% polymorphs, 6% lymphocytes, 1% monocytes and 2% eosinophils, platelet 275000/cmm, blood urea 30 mg/dl, serum sodium 126 mmol/l, potassium 4.3 mmol/l, chloride 92 mmol/l, creatinine 2.4 mg/dl, blood sugar 214 mg/dl. Urine contained albumin and white cells. Blood films for malaria parasites were negative. Liver function test parameters were total protein 6.1 g/dl, albumin 2.9 g/dl, bilirubin 3.9 mg/dl, alkaline phosphatase 740 u/l and glutamate pyruvate transaminase 98 u/l. Amoebic antibody was negative. Chest radiograph was normal and electrocardiograph showed sinus tachycardia.

The initial diagnosis was septicaemia with acute liver failure. He was given intravenous fluids, soluble insulin, intravenous ampicillin, cloxacillin, gentamicin and metronidazole. A high colonic washout was also performed. He remained extremely toxic and died 32 hours after admission. Blood culture reported 4 days after his death grew Pseudomonas pseudomallei (Table 1).

Case 3. A 39 year old male Indian driver was admitted to the surgical unit of our hospital with a 7-day history of fever. 5 days prior to admission he developed upper abdominal pain and progressive weakness of the lower limbs. He had no history of alcohol abuse. He had diabetes mellitus controlled on tolbutamide for 7 years. Soon after admission, the attending surgeon excluded an acute surgical abdomen and the patient was transferred to the medical unit for furthur management.

Clinical examination showed a toxic looking man slightly confused and prostrated. His temperature was 41°C, pulse 128/minute, respiratory rate 25 breaths/minute and blood pressure 120/70 mm Hg. A tinge of jaundice was noted. Crepitations were heard in both lungs. His abdomen was distended with tenderness in the right hypochondrium and reduced bowel sounds. The liver was just palpable, soft and not tender. Motor power of the lower limbs was reduced with active movement against gravity but not against resistance (Grade 3). The lower limb reflexes were absent but plantar responses were normal. Sensation to pin prick was normal. The remainder of the examination was unremarkable.

Laboratory studies showed the following: haemoglobin 13.3 g/dl, total white blood cell count 4700/cmm, blood urea 24 mg/dl, serum sodium 124 mmol/l, potassium 3.4 mmol/l, chloride 86 mmol/l, blood sugar 294 mg/dl. Urine contained white cells and granular casts. Arterial blood gas analysis showed pH 7.511, P_aO_2 51.3 mm Hg, P_aCO_2 31.6 mm Hg and oxygen saturation 88.9%. Blood films for malaria parasites were negative. Cerebrospinal fluid pressure and cerebrospinal fluid were normal. Liver function test parameters showed total protein 6.6 g/dl, albumin 3.3 g/dl, bilirubin 2.8 mg/dl, alkaline phosphatase 155 u/l and glutamate oxaloacetate transaminase 111 u/l. Widal-Weil Felix test was negative. Chest radiograph and electrocardiograph were normal.

Initially he was treated for acute cholangitis with intravenous fluids, gentamicin, ampicillin and metronidazole. 24 hours after admission, progressive weakness of his upper limbs was noted. His general condition remained very poor with high spiking fever. On the second hospital day, he was breathless and hypoxaemic, and needed ventilatory assistance. At this point, tests for urine porphobilinogen and porphyrin were positive and he was treated as for acute inter-

TABLE 1
ANTIBIOTIC SENSITIVITY OF THREE ISOLATES OF PSEUDOMONAS PSEUDOMALLEI BY THE DISC METHOD

Antibiotic	Sensitivity		
	Case 1	Case 2	Case 3
Amikacin	R	R	NT
Ampicillin	R	R	R
Carbenicillin	R	R	NT
Cefotaxime	S	S	S
Ceftriaxone	NT	S	S
Cefuroxime	S	R	NT
Cephaloridine	R	R	R
Cephalothin	R	R	NT
Chloramphenicol	S	NT	NT
Co-trimoxazole	R	R	S
Gentamicin	R	R	R
Kanamycin	S	R	NT
Minocycline	S	NT	NT
Netilmicin	R	R	NT
Novobiocin	S	NT	NT
Streptomycin	R	R	NT
Tetracycline	S	S	S
Tobramycin	R	R	NT

S = sensitive; R = resistant; NT = not tested.

TABLE 2
MORTALITY IN ACUTE SEPTICAEMIC MELIOIDOSIS ACCORDING TO VARIOUS AUTHORS

Author	Number treated	Number of deaths	Percent mortality
Rimington (9)	5	5	100
Weber (6)	5	4	80
Thin (10)	3	3	100
Puthucheary (11)	7	6	86
Rode (12)	20	14	70
Total	40	32	80

mittent porphyria with large amounts of intravenous 10% dextrose. Motor power of the upper limbs returned but overall clinical status remained very poor. On the third hospital day, he went into septicaemic shock and he died despite vigorous attempts to resuscitate him. Blood culture reported 3 days after his death grew Pseudomonas pseudomallei (Table 1).

DISCUSSION

Acute septicaemic melioidosis is an uncommon disease even in endemic Singapore. This is a surprising observation as a serological survey in neighbouring Malaysia showed that subclinical infection was common and that 1.9 to 15.8% of selected healthy population groups had positive haemagglutination titres (5). Moreover the causative organism, Pseudomonas pseudomallei, was readily isolated from surface water and soil particularly after heavy rainfall (8). The three fatal cases described here had associated debilitating diseases: Case 1 had bronchogenic carcinoma and possibly diabetes mellitus, Case 2 had diabetes mellitus, and Case 3 had diabetes mellitus and acute intermittent porphyria. Whitmore originally demonstrated acute melioidosis in post-mortem examinations of the 'ill-nourished, neglected wastrels of the town' (7) and subsequent authors reported acute melioidosis in patients with debilitating diseases such as chronic alcoholism, diabetes mellitus, malnutrition, leprosy and cancer (9-12). All these observations support the contention that acute septicaemic melioidosis is more likely in debilitated patients, and subclinical, subacute or chronic melioidosis is more likely in previously healthy individuals. Current thinking is that the bacillus gains entry into the body by penetration of abraded skin or

by inhalation of dust (10, 11, 13), and males are predominantly affected because of a heavier occupational and recreational exposure (13).

The clinical features of acute melioidosis are not specific. In the majority of these cases, the disease develops with sudden high fever, chills, prostration, confusion, headache, cough, vomiting, abdominal pain and occasional profuse watery diarrhoea (6, 9-13). Clinical examination reveals high fever, tachypnoea, confusion, jaundice, hepatosplenomegaly, muscle tenderness, septic arthritis and skin abscesses (6, 9-13). As acute septicaemic melioidosis is rapidly fatal (Table 2), debilitated patients presenting with the aforementioned clinical features may be started promptly and vigorously on appropriate antimicrobial agents against Pseudomonas pseudomallei.

Routine laboratory investigations are generally unhelpful. The leucocyte count may be normal or slightly raised. Chest radiograph may be normal as in our cases. Radiological abnormalities however may occur and include linear atelectasis, nodular shadows due to metastatic lung abscesses and consolidation commonly of the lung bases, sometimes with pleural effusion or cavitation within the consolidation (14).

The definitive diagnosis of acute melioidosis depends solely on isolating Pseudomonas pseudomallei from blood, pus, sputum or urine. However culture results are often delayed due to difficulty in identifying the organism. If the disease is suspected, it is therefore helpful to forewarn the laboratory so that the microbiologist will allow for prolonged incubation of the culture and use of selective medium. After 48-72 hours of culture, colonies of Pseudomonas pseudomallei exhibit a wrinkled appearance and produce a distinctive musty odour (11, 13). Recovery of the bacillus may be improved by using a selective medium described by Ashdown (15). Available purulent secretions when stained by methylene blue, Wayson's or Wright's stain may show the bacillus as rod shaped with a clear centre and darkly staining ends, the overall appearance resembling a closed safety pin (13). Serological tests are not so useful in acute melioidosis. Paired sera to demonstrate a fourfold or greater rise in titre over two weeks are rarely obtained in acute melioidosis because death intervenes within two weeks in the absence of appropriate vigorous therapy. A single low-titre positive serological test does not differentiate between active and past infections. An encouraging recent report that immunoglobulin M — indirect fluorescent antibody test (IgM-IFA test) may be of value in diagnosing clinical melioidosis and monitoring activity of the disease (16) merits further study.

The optimal therapeutic regimen for acute melioidosis has not been established. Often recommendations are based on experience with a few cases and prospective study on treatment is hampered by the scarcity of clinical cases. Isolates of Pseudomonas pseudomallei in our three cases were sensitive in vitro to tetracycline, minocycline, chloramphenicol, novobiocin, cefotaxime and ceftriaxone but were resistant to amikacin, ampicillin, carbenicillin, cephaloridine, gentamicin, netilmicin, streptomycin and tobramycin; variable sensitivity results were noted for cefuroxime, co-trimoxazole and kanamycin (Table 1). Since various authors have reported a consistently high case fatality rate for acute melioidosis (Table 2), prompt treatment with multiple antibiotics and supportive treatment of the underlying debilitating disease are recommended (6, 10-13). One such recommendation (13) consisted of tetracycline 4-6 g/day (80 mg/kg), chloramphenicol 4-6 g/day (80 mg/day) and one of the following: co-trimoxazole (trimethoprim 9 mg/kg, sulphamethoxazole 45 mg/kg), sulfisoxazole 140 mg/kg, kanamycin 30 mg/kg or novobiocin 60 mg/kg; the favoured third drug is either co-trimoxazole or novobiocin. These recommended huge doses are potentially toxic and careful monitoring of the relevant organ system is required. The role of the third generation cephalosporins is not clear but ceftazidine has been used successfully in a patient with multiresistant strain of Pseudomonas pseudomallei (17). Strict isolation of patients is not mandatory but it is prudent to handle all infectious body fluids and pus with due caution. Treatment duration is for a minimum of 30 days but in some cases, prolonged maintenance therapy with co-trimoxazole or tetracycline up to 6-12 months is needed (11, 17).

REFERENCES

1. Whitmore A, Krishnaswami CS: An account of the discovery of a hitherto undescribed infective disease occurring among the population of Rangoon. Ind Med Gaz 1912; 47; 262-7.
2. Gilmour CCB: A case of melioidosis in Singapore. Malayan Med J 1931; 6: 12-3.
3. Rubin HL, Alexander AD, Yager RH: Melioidosis- a military medical problem? Mil Med 1963; 128: 538-42.
4. Sanford JP, Moore WL: Recrudescent melioidosis:. a Southeast Asian legacy. Am Rev Respir Dis 1971; 104: 452-3.
5. Strauss JM, Alexander AD, Rapmund G, Gan E, Dorsey AE: Melioidosis in Malaysia. III. Antibodies to Pseudomonas pseudomallei in the human population. Am J Trop Med Hyg 1969; 18: 703-7.
6. Weber DR, Douglass LE, Brundage WG, Stallkamp TC: Acute varieties of melioidosis occurring in U.S. soldiers in Vietnam. Am J Med 1969; 46: 234-44.
7. Prevatt AL, Hunt JS: Chronic systemic melioidosis. Review of literature and report of case, with a note on visual disturbance due to chloramphenicol. Am J Med 1957; 23: 810-23.
8. Strauss JM, Alexander AD, Rapmund G, Gan E, Dorsey AE: Melioidosis in Malaysia. II. Distribution of Pseudomonas pseudomallei in soil and surface water. Am J Trop Med Hyg 1969; 18: 698-702.
9. Rimington RA: Melioidosis in north Queensland. Med J Aust 1962; 1: 50-3.
10. Thin RNT, Brown M, Stewart JB, Garrett CJ: Melioidosis: A report of ten cases. Q J Med 1970; 39: 115-27.
11. Puthucheary SD, Lin HP, Yap PK: Acute septicaemic melioidosis. A report of seven cases. Trop Geogr Med 1981; 33: 19-22.
12. Rode JW, Webling DD'A: Melioidosis in the Northern Territory of Australia. Med J Aust 1981; 1: 181-4.
13. Sanford JP. Melioidosis and Glanders. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. Harrison's Principles of Internal Medicine. McGraw Hill. 1983: 954-7.
14. Bateson EM, Webling DD'A: The radiological appearances of pulmonary melioidosis: A report on twenty-three cases. Aust Radiol 1981; 25: 239-45.
15. Ashdown LR: An improved screening technique for isolation of Pseudomonas pseudomallei from clinical specimens. Pathology 1979; II: 293-7.
16. Ashdown LR: Relationship and significance of specific immunoglobulin M antibody response in clinical and subclinical melioidosis. J Clin Microbiol 1981; 14: 361-4.
17. So SY, Chau PY, Leung YK, Lam WK, Yu DYC: Successful treatment of melioidosis caused by a multiresistant strain in an immunocompromised host with third generation cephalosporins. Am Rev Respir Dis 1983; 127: 650-4.