INTRODUCTION

Rhodococcus equi, previously known as "Corynebacterium equi", a gram-positive, weakly acid-fast staining coccobacillus, once thought to be exclusively an equine pathogen, is an emerging life-threatening opportunistic pathogen in immunocompromised hosts.

Primarily it causes zoonotic infections affecting horses, cattle, sheep and swine, causing pneumonia, lymphadenitis and pyometra. It is a rare opportunistic human pathogen causing pneumonia and pulmonary abscesses in patients with lymphoreticular malignancies and solid organ transplants (Van Etta et al, 1983). More recently, in the past decade, HIV infection has been associated with R. equi infection (Muntaner et al, 1997). Almost all human infections have occurred in patients who have defects of cell-mediated immunity with or without histories of animal exposure.

R. equi is readily found in soil, especially where domesticated livestock graze (Prescott, 1991). Intestinal carriage in adult herbivores is passive and only represents acquisition from contaminated grass. Exposure to soil contaminated with manure is the most likely route of acquiring infection in both animals and humans. Inhalation of dust particles laden with virulent R. equi is the major route of pneumatic infection, but infections by the oral route (due to ingestion of soil or food) or by direct inoculation due to trauma have also been described (Van Etta et al, 1983). Necrotizing lobar pneumonia is the commonest form of infection caused by R. equi.

Extrapulmonary manifestations described in human beings include subcutaneous nodules,
brain and renal abscesses, lymphadenitis, endophthalmitis and osteomyelitis (Mayor et al., 1995) and fever of unknown origin. Bacteremia and dissemination of infection follow from the primary site of infection which usually is the lung. Numerous complications are related to R. equi infections and the reported mortality is 50-55% in patients infected with HIV and 20-25% in patients with non-HIV associated immunocompromized conditions (Harvey and Sunstrum, 1991).

We report four cases of R. equi infection in immunocompromized hosts seen at the University Hospital, Kuala Lumpur, between November 2003 and February 2005. We believe this is the first report of such infections in Malaysia. This article aims to bring about improved recognition of this easily overlooked pathogen.

**CASE HISTORIES**

The relevant clinical data of the four patients with R. equi infections are summarized in Table 1. All four patients were adults, the youngest being 16 and the oldest, 60 years. There were three males and one female, who was a Thai national.

Fever, cough and signs and symptoms relevant to the respiratory system were the predominant presenting features. Immune system dysfunction was present in all four cases; one had AIDS and the three others had non-HIV associated immunocompromized conditions. All had very low peripheral white cell counts. All four patients were given empirical antimicrobial therapy. Two patients (cases # 3 and 4) were given specific antimicrobials after culture and

**Table 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Underlying illness</th>
<th>Chest X ray</th>
<th>Antimicrobial therapy</th>
<th>Duration of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>M</td>
<td>Cough, fever, lethargy, abdominal swelling, anorexia-2 months. Bilateral coarse crepitations, Pleural effusion R lung, Hb = 8.2 g/l, TWBC = 0.6 x 10⁹/l</td>
<td>Acute lymphatic leukemia</td>
<td>Multiple bilateral patchy opacities. Consolidation, effusion of R. lower lobe</td>
<td>Cefepime- 2 wks Piperacillin-tazobactam</td>
<td>2 months</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>M</td>
<td>Productive cough, greenish sputum, fever 7 days, lethargy, pallor, Hb = 8.7 g/l, TWBC = 0.9 x 10⁹/l</td>
<td>T-cell lymphoblastic leukemia</td>
<td>NA</td>
<td>Piperacillin-tazobactam, Gentamicin, Cefepime</td>
<td>1 week</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>F</td>
<td>Cough, fever, chill, rigors, cachexia, tachypnea. Oral thrush R. inguinal node +ve Hb=12 g/l, TWBC = 1.8 x 10⁹/l</td>
<td>AIDS</td>
<td>Cavitation. Consolidation of R. lower lobe</td>
<td>Ceftriaxone, Fluconazole Vancomycin, Azithromycin HAART</td>
<td>4 weeks</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>M</td>
<td>Cough, fever, pallor, breathlessness. Coarse crepitations Hb=10 g/l, TWBC=0.6x10⁹/l</td>
<td>Old PTB, diabetes, congestive cardiac failure</td>
<td>Consolidation, Fibrosis of L. lower lobe CT scan-necrosis of mediastinal lymph nodes</td>
<td>Azithromycin, Flucloxacillin</td>
<td>5 weeks</td>
</tr>
</tbody>
</table>

NA = not available; R = right; L = left
sensitivity tests were available. R. equi was isolated from the blood cultures of the first three patients and from a bronchoalveolar lavage of the fourth patient. Patients number one, three and four died, but the status of number two was not available at the time of writing this paper.

We were unable to elicit any history of exposure to horses or to contaminated soil, but the first patient lived in a village and tended his garden frequently.

The following is a more detailed report of case number one.

Case # 1

A 60 year old man was admitted to the University Hospital on 18 November 2003 with a history of cough, fever, lethargy, anorexia, loss of weight and abdominal swelling of two months duration. The swelling was not painful. He had been admitted to another hospital one month previously for a biopsy but did not follow-up there. On examination, he was pale, jaundiced, cachexic and dehydrated. His blood pressure was 90/50. His lungs were clear. There was no discernible lymphadenopathy peripherally. A large ill defined hard mass was palpable in the abdomen, about 30 cm by 30 cm which was mildly tender.

A CT scan of the thorax, abdomen and pelvis showed enlarged lymph nodes in the aortopulmonary window, subclavian area and markedly enlarged mesenteric nodes. The lung parenchyma was clear but there was atelectasis at the bases. Ascites were present. Biochemically it was noted that he had a metabolically active lymphoproliferative disorder with a markedly raised lactate dehydrogenase. A bone marrow examination confirmed the diagnosis of acute lymphoblastic leukemia.

On the 26th of November he developed erythema over the left brachial region, fever and crepitations in the lungs. Blood cultures grew Staphylococcus aureus thought to originate from an infected PICC site. He was given cephapime for 10 days.

Following this he again developed bilateral basal crepitations, fever, breathlessness, with poor air entry, especially in the right lower zone. Chest X ray showed multiple bilateral patchy

DISCUSSION

The role of R. equi as a human pathogen was not established until 1967, when the first case report was published of a 29 year old man with plasma cell hepatitis who developed a cavitatory pulmonary lesion after cleaning animal pens at a stockyard (Golub et al, 1967). All three of our patients were immunocompromized with very low white cell counts. Patient number three had AIDS and a CD4 count of zero. Current opinion is that the R. equi infection should be considered an AIDS-defining event (Albrecht, 1997). Therefore, R. equi should form part of the differential diagnosis of cavitary pneumonia in
Patients with HIV infection.

Humans usually acquire infection by inhalation of soil contaminated with the manure of herbivores resulting in pulmonary infections but disease associated with the gastrointestinal tract without pulmonary involvement suggests ingestion of contaminated material as a possible route (Verville et al, 1994). Usually, no history of exposure or contact with farm animals is elicited, as was the case in our four patients. Delay in diagnosis often results because of insidious onset of disease, clinical similarity to mycobacterial and fungal infections, and the indistinguishable morphology of R. equi from normal diphtheroid respiratory flora (Linder, 1997).

**Bacteriology**

R. equi is a soil organism with simple growth requirements. It is cultured easily on ordinary nonselective media when incubated aerobically at 37°C. Large, smooth, irregular, highly mucoid colonies appear within 48 hours. Although R. equi is named for its production of red pigment, cultures less than four days old rarely appear pigmented. After 4-7 days incubation, colonies usually develop a delicate salmon pink color, although they may be nonpigmented or slightly yellow (Scott et al, 1995). It is a facultative, intracellular, non-motile, non-spore forming organism. Gram stain shows pleomorphic gram-positive rods varying from coccoid to long, curved, and clubbed forms (Fig 2). The organism may be inconsistently acid-fast with Ziehl-Neelsen staining, depending on the age of culture and growth media. R. equi is non-fermenting (distinguishing it from pathogenic corynebacteria), gelatinase-negative, catalase-positive, usually urease-positive and oxidase-negative (Verville et al, 1994). Also helpful in identifying R. equi is synergistic hemolysis (resembling the CAMP test), displayed by cross-streaking on sheep-blood agar with a number of other bacteria, including Arachanobacterium haemolyticum and Staphylococcus aureus (Fig 3). In the modern microbiology laboratory, practical identification of R. equi is most easily accomplished by the application of a commercially available panel of biochemical tests (API Coryne, bioMerieux, Marcy-Etoile, France; Remel RapiD CB Plus System, Lenexa, KS, USA) to isolates which have the typical colony characteristics and Gram-stain morphology (Verville et al, 1994).

**Virulence**

The ability of R. equi to remain inside macrophages, grow and ultimately destroy the macrophages, is the property most closely associated with virulence in both the human and animal host (Hondalus and Mosser, 1994). Electron microscopic examination of cultured equine macrophages showed that organisms evaded killing by preventing phagosome-lysosome fusion, thus multiplying in and eventually killing the phagocytes (Zink et al, 1987). Soluble cytotoxic
substances were found to be associated with virulent phenotypes of the organism but these have not been characterized yet. Strains of R. equi, irrespective of virulence, produce cholesterol oxidase, which is responsible for the organism’s participation in synergistic hemolytic reactions with other bacteria, such as S. aureus. S. aureus was isolated together with R. equi from the blood of patient number one and from the bronchoalveolar lavage of patient number four. Whether the synergistic hemolytic reaction seen in vitro plays any role in vivo in the pathogenesis of the infection is yet to be elucidated. Experiments using cultured mouse macrophages with phagocytosed R. equi suggest a role for cholesterol oxidase in macrophage destruction in infections (Linder, 1997).

In vitro, R. equi is usually susceptible to erythromycin, ciprofloxacin, vancomycin, aminoglycosides, rifampin, imipenem and meropenem. The intracellular survival of the organism has led to recommendations that R. equi infections be treated with lipophilic antibiotics that penetrate cells. Combined antimicrobial therapy involving parental glycopeptide plus imipenem for at least three weeks, followed by an oral combination of rifampin, plus either macrolides or tetracycline has been recommended (Linder, 1997). Most authors recommend therapy be continued for a minimum of two months due to the frequency of relapses following shorter courses (Verville et al., 1994). However, host-immune competence may be the most important consideration in determining duration of therapy.

R. equi is a unique opportunistic pathogen in humans and an intact cell-mediated immunity appears to have a primary role in protection against infections. Recent investigations have shown that T-cell subsets, specifically functional CD4+ lymphocytes are necessary to effect complete clearance of a R. equi challenge in immunodeficient mice (Kanaly et al., 1996).

In summary, R. equi infection is an uncommon opportunistic infection in immunocompromized individuals. A high index of suspicion is required to diagnose pulmonary infections. The practice of regarding coryneform organisms in sputum Gram stains and cultures as contaminants may contribute to a significant number of missed diagnoses (Verville et al., 1994).

REFERENCES


Kanaly ST, Hines SA, Palmer GH. Transfer of a CD4+ Th 1 cell line to nude mice effects clearance of Rhodococcus equi from the lung. Infect Immun 1996; 64: 1126-32.


