Pneumonia caused by *Moraxella catarrhalis* in haematopoietic stem cell transplant patients. Report of two cases and review of the literature

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Abstract: *Moraxella catarrhalis* is a gram negative diplococcus that causes a variety of upper and lower respiratory tract infections. Patients with malignant, hematological disorders treated with intensive cytotoxic chemotherapy, and recipients of various forms of haematopoietic stem cell transplant receiving immunosuppressive agents are at high risk of developing severe infections and septic complications. Early detection of the organism and prompt treatment with appropriate antibiotics provide both resolution of the infection and prevention of further consequences. Two patients with haematopoietic stem cell transplant who developed pneumonia caused by *M. catarrhalis* at King Faisal Specialist Hospital and Research Centre in Riyadh are reported and the literature is reviewed. To our knowledge, these are the first case reports of *M. catarrhalis* pneumonia in haematopoietic stem cell transplant patients.

Key Words: *Moraxella catarrhalis, Acute myeloid leukemia, Graft versus host disease, Stem cell transplant, Umbilical cord blood transplant.*

Introduction

In spite of the availability of antimicrobial agents, pneumonia constitutes the sixth most common cause of death and the number one cause of death from infection [1]. Pneumonia can be particularly life-threatening in the elderly, patients with pre-existing cardiac or pulmonary conditions, in immunocompromised individuals, and in pregnant women [1].

Infections are the most common cause of morbidity and mortality in patients with malignant disorders, and in haematopoietic stem cell transplant (SCT) recipients, despite the use of infection prophylaxis, growth factors, and newer antimicrobial agents [2,3]. The main risk factors for development of infection in patients with malignant disorders include: uncontrolled malignancy, cytotoxic chemotherapy, immunosuppressive treatment, and immunological deficits, e.g. hypogammaglobulinaemia and T-cell depletion [4]. In this category of patients, the risk of infection is directly proportional to the intensity and duration of cytotoxic chemotherapy and immunosuppressive treatment [4].

Case Reports

Case 1: A 17 years old Saudi female was diagnosed to have acute myeloid leukaemia (AML), M6 type, at King Faisal Specialist Hospital and Research Centre (KFSH&RC) in February 2005. She presented with: fever, fatigue, mucosal bleeding, anaemia, thrombocytopenia, normal leucocytic count, few blasts on the blood film and 40% blasts in the bone marrow but no palpable external lymphadenopathy or abdominal organomegaly. After receiving an ICE (idarubicin, cytozar and etoposide) induction course of chemotherapy, she achieved the first complete remission of her leukaemia. Thereafter, she received a consolidation course of chemotherapy composed of high dose cytosine arabinoside. On 22/5/2005, she received a non-myeloablative, allogeneic, peripheral blood SCT. The conditioning protocol consisted of: fludarabine and one session of total body irradiation. She was given prophylactic antibiotic therapy consisting of bactrim, penicillin and acyclovir. In addition she received prophylaxis for graft versus host disease (GVHD) in the form of cyclosporine-A. The post-SCT course was complicated by acute GVHD of the colon, grade II, treated with steroids, cyclosporine-A, and tacrolimus; Two episodes of CMV infections were treated with intravenous (IV) ganciclovir and reduced donor chimerism was managed with donor lymphocyte infusions. On 27/11/2006, the patient was readmitted with a two week history of low grade pyrexia and productive cough with yellowish sputum. Physical examination revealed reduced inspiratory volume with coarse crackles over the mid and lower lung fields bilaterally. Sputum culture grew beta-lactamase positive *M. catarrhalis* sensitive to certriaxone, ceftazidime, cefatoxime, and cefuroxime, but resistant to ampicillin and penicillin. Ziehl Neelsen stain and acid fast bacillus culture of the sputum were negative. Fungal cultures and aspergillus galactomannan test were also negative. Cytomegalovirus antigen test and shell vial were negative. Chest X ray (CXR) showed bilateral pulmonary infiltrates, more prominent on the left. Computerized tomography (CT) scan of the chest showed nodular infiltration involving the left lower lobe and the lateral segment of the right lower lobe (Figure 1). The patient was treated with IV ceftriaxone 2 grams per day for 5 days. She then received oral cefuroxime 500 mg twice daily for 10 more days. Following discharge, she had routine follow up at the SCT clinic. On 18/12/2006, chest CT revealed complete resolution of nodular

pulmonary lesions. The patient was last seen at SCT clinic on 16/1/2007. She remained totally asymptomatic and physical examination confirmed her lung sounds were clear. Complete blood count (CBC) showed WBC: 7.74 x 10^9/L, HB: 148 g/L, PLT: 247 x 10^9/L. The patient continued on tacrolimus and a tapered dose of prednisone in addition to prophylactic penicillin, bactrim and acyclovir.

Case 2: A 50 year old Saudi male was diagnosed to have AML, M4 type, at KFSH&RC in early April, 2005. He presented with: recurrent perianal abscesses, elevated WBC count of 41 x 10^9/L with myeloblasts on blood film, anemia, thrombocytopenia, and 80% blast cells on bone marrow biopsy, but no external, palpable lymphadenopathy and no palpable, abdominal organomegaly. Initially he received ICE induction chemotherapy but his leukemia was refractory to this so he was then given an FA (fludarabine and cytosine arabinoside) salvage course of chemotherapy which resulted in his first complete remission of leukemia. After controlling his AML, the patient was prepared for umbilical cord blood transplant (UCBT) since he had no compatible sibling donor. He received a pre-treatment protocol of IV busuphan and fludarabine. He was given prophylactic antibiotics consisting of bactrim, acyclovir, and penicillin as well as GVHD prophylaxis of IV methylprednisolone and cyclosporine-A. On 31/8/2005, the patient received an UCBT. Post-procedure, the patient developed a number of complications including: *Klebsiella pneumoniae* bacteremia and septic shock which were treated with IV meropenem and gentamicin. His fungal lung infection was treated with liposomal amphotericin-B (amBisome) and voriconazole. His prolonged pancytopenia and delayed recovery of blood counts were managed with growth factor and granulocyte transfusions. On 6/12/2005, the patient was discharged from the SCT unit on cyclosporine-A. The chimerism study showed no engraftment, so treatment was continued with supportive measures [growth factors, packed red cell and platelet transfusions] for the low blood counts. In October2006, the patient was found to have a relapse of his AML. On 23/12/2006, he presented to the SCT clinic with a one week history of: fever, sore throat, and productive cough with yellow sputum. Physical examination revealed reduced inspiratory volume with crackles over middle and lower lung fields bilaterally. CXR showed radiological evidence of bronchopneumonia. Blood cultures were negative but sputum cultures revealed growth of beta-lactamase, positive *M. catarrhalis* sensitive to ceforuxime, ceftazidime, cefotaxime and erythromycin, but resistant to penicillin and ampicillin. The patient received a five day course of IV ceftriaxone (two grams per day) at the oncology male treatment area. His treatement then was changed to oral cefuroxime 500 mg twice daily for one more week. Two weeks later, the patient was evaluated at the outpatient clinic. He was asymptomatic and physical examination showed his chest was clear. Repeat CXR showed nearly complete resolution of the previous bronchopneumonic shadows. Thereafter, the patient remained clinically stable till he traveled to the USA in late January, 2007 for a second alternate donor SCT.

Discussion

Moraxella (*Branhamella*) *catarrhalis* (formerly called *Neisseria* or *Micrococcus catarrhalis*) is a gram negative, anaerobic diplococcus frequently found as a commensal of the upper respiratory tract [5-8]. The organism was discovered and described in some detail more than a century ago [9]. However, *M. catarrhalis* has emerged as a human pathogen in the last decade [7,9]. Recently, *M. catarrhalis* is considered to be the third most common and most important cause of bronchopulmonary infections after *Haemophilus influenzae* and *Streptococcus pneumoniae* [10,11]. Risk factors for the development of *M. catarrhalis* infections and bacteremia include: advancced age; underlying chronic lung disorder e.g. bronchial asthma, chronic obstructive airway disease, alveolitis, and pulmonary fibrosis; pneumoconiosis and congenital lung disease; sickle cell disease and immunocompromised individuals e.g. HIV-positive patients, or those with agammaglobulinaemia, granulocytopenia and acute leukemia [5-17]. *M. catarrhalis* is linked to a variety of infections including upper and lower respiratory tract infections, bacteremia, septic complications, endocarditis, meningitis, and brain abscess in addition to wound infections [5-9,11-14,16-18]. Invasive infection due to *M. catarrhalis* may occur in immunocompromised individuals but is uncommon [5,6,8,11,18]. *M. catarrhalis* can lead to community acquired as well as nosocomial infections [9,13,16,19]. *M. catarrhalis* can be isolated from blood, nasopharyngeal secretions, sputum, tracheal secretions, bronchoalveolar lavage, wound swabs, and tissue cultures e.g. endocardium [5,8,12-18,20,21]. Both of these patients were severely immunocompromized. Both had AML and were treated with two different forms of SCT. They had received cytotoxic chemotherapy and various immunosuppressive agents. Both infections were community acquired.

The isolated organisms were cultured from sputum while blood cultures were negative in both patients. The lung infection in the initial patient was invasive and rather severe although the patient was not neutropenic at the time of the infection. Bronchopneumonia occurred during a period of neutropenia and after the relapse of AML in the second patient.

The first reported case of beta-lactamase production by *M. catarrhalis* was in 1976 [11]. Since that time, there has been a dramatic increase in the frequency of beta-lactamse production by this organism [11]. Today, 90% or more of the strains of *M. catarrhalis* are beta-lactamase producers [8-11,16,22]. Consequently when *M. catarrhalis* is considered to be the causative organism, the choice of an empiric antimicrobial therapy should be a beta-lactamase resistant antibiotic [23]. The strains of *M. catarrhalis* are resistant to benzylpenicillin, ampicillin, amoxicillin and lincomycin and are usually susceptible to certain cephalosporins, macrolides, tetracyclines, and fluoroquinolones in addition to the combination of trimethoprim-sulfamethoxazole [8-10,15,19,24]. Ceftriaxone has highly favorable pharmacokinetics which allow once daily dosing regimens to be employed even in the most severe infections associated with cancer therapy [25]. The overall mortality related to bacteremic pneumonia due to *M. catarrhalis* is about 13.3% despite the underlying disease [15]. Bacteremic pneumonia due to *M. catarrhalis* requires prompt treatment to prevent the development of serious organ complications such as endocarditis [18]. However, appropriate antimicrobial therapy can lead to clinical and microbiological cure in nearly all patients infected with this organism [13]. In these two patients, both isolates were beta-lactamase producers. Both were treated with IV ceftriaxone followed by oral cefuroxime. Obtaining necessary cultures and other required testing as well as early institution of appropriate antimicrobial therapy led not only to the resolution of pulmonary infiltrations but also to the prevention of further complications.

Haematopoietic SCT is associated with pulmonary opportunistic infections and immune mediated responses that include idiopathic pneumonia syndrome and brochiolitis obliterans [26]. Pulmonary complications are the most common cause of death in SCT recipients. Unfortunately, the majority of these complications are not diagnosed antemortem [27]. As a consequence of underdiagnosis, SCT recipients may not receive appropriate therapy for a potentially treatable pulmonary complication [27]. Autopsy findings in recipients of allogeneic SCT and UCBT have shown that infectious complications are the causes of death in approximately 50% of deceased patients [27]. The dose-reduced conditioning regimens utilized in non-myeloablative SCT are associated with lower rates of pulmonary complications [26]. The use of steroid therapy in SCT has been shown to be a leading risk factor for infectious processes [28]. Recipients of allogeneic haematopoietic SCT have prolonged immunodeficiency that may extend beyond the first year post-SCT [29]. Depletion of T-cell used in mismatched SCT reduces the incidence of GVHD in graft recipients, but T-cell deficiency in these already extensively T-cell-depleted patients may be an additional risk factor for infectious complications [30]. The reconstitution of immunity in SCT recipients is often delayed in adults, patients with extensive GVHD. and in T-cell depleted grafts [29]. *However, the full reconstitution of the immune system in a recipient of hematopoietic SCT is one of the hallmarks of a successful graft [31].*

The first patient was expected to have a lower rate of infectious complications since she had received a nonmyeloablative allogeneic SCT. However, the development of GVHD and the use of various immunosuppressive agents predisposed this patient to an invasive lung infection despite having normal neutrophilic counts. The second patient had received an UCBT since he encountered serious complications before the autologous recovery of his blood counts and had not had a successful graft. His immunity continued to be depressed due to a relapse of his leukemia and since he was neutropenic at the time of the bronchopneumonia.

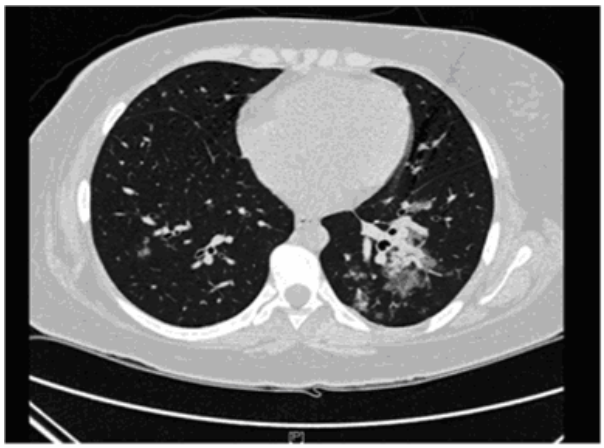

Figure 1: CT scan of chest showing bilateral nodular pulmonary infiltration more prominent on the left side

Conclusion

M. catarrhalis can cause severe and invasive infections in immunocompromised individuals particularly patients with acute leukemia and

recipients of haematopoietic SCT who have been subjected to intensive cytotoxic chemotherapy and various immunosuppressive agents. Infections caused by this organism should be treated promptly in order to prevent sepsis and further complications.

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