Case Report

Mycoplasma Pneumonia Associated with Severe Autoimmune Hemolytic Anemia

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ABSTRACT

Mycoplasma pneumonia is an uncommon cause of autoimmune hemolytic anemia (AIHA). It is usually mild and self-limiting. Rarely, it is severe necessitating steroid therapy. We present a case of severe autoimmune hemolytic anemia (AIHA) caused by *Mycoplasma pneumoniae* that required steroids, intravenous immunoglobulin, plasmapheresis, and cyclophosphamide. The mechanism of action of each line of treatment has been discussed.

KEY WORDS: autoimmune hemolytic anemia, cyclophosphamide, intravenous immunoglobulin, *Mycoplasma pneumoniae*, plasmapheresis, steroids

INTRODUCTION

Pneumonia caused by *Mycoplasma pneumoniae* is usually benign and self-limited illness. Only one patient out of every 15 to 30 infected with *Mycoplasma pneumoniae* develops clinical pneumonia, and only one patient in 50 with pneumonia requires hospitalization[1]. Fatalities or near-fatalities have been reported rarely and is generally from a respiratory embarrassment[1]. We present a healthy female who developed a life-threatening autoimmune hemolytic anemia complicating Mycoplasma pneumonia.

CASE REPORT

A 24-year-old female was admitted with productive cough for a week, and fever for two days. She had also abdominal pain, vomiting and red urine. She was previously healthy and was not using any drugs. On examination she was pale and jaundiced. The blood pressure was 120/80 mm Hg, pulse 130/minute, respiratory rate 24 breaths/minute, and the temperature was 38.5˚ C. There were bilateral basal crackles in the chest, mostly on the left side. She had mild epigastric tenderness but no guarding. The abdomen was soft and lax. There was no organomegaly and no palpable lymph nodes. Her cardiac examination apart from tachycardia was normal.

On admission, her hemoglobin was 87 grams/liter with a mean corpuscular volume 136.2, white cell count was 25.3 x 10^9/L, of which 63.3% neutrophils, 11.3% monocytes and. platelets 589 x 10^9/L. Peripheral blood film showed rouleux formation with marked agglutination. Total bilirubin 89.8 UMol/liter (normal 0-17), of which 29.4 direct (normal 0-5), creatine kinase 652U/liter (normal 21-232), aspartae transaminase 77 U/liter (normal 30-65), and alanine transaminse was normal. The urea, creatinine, electrolytes, amylase, prothrombin time, activated partial thromboplastin time were normal. Haptoglobin was reduced and there was free hemoglobin in the urine. Cold agglutinin titer > 1:512 (normal < 1:64). Erythrocyte sedimentation rate was 180, and reticulocyte count was 2%. Lactate dehydrogenase was 776 U/liter (normal 100-190). Direct Coombs' test was strongly positive. Chest X-ray showed infiltrations in the left base. Blood and urine cultures were all negative. Ultrasound abdomen was normal. Immunoglobulin electrophoresis showed increased alpha-one globulin. Bone marrow biopsy showed erythroid hyperplasia with decreased iron stores, and increased megakaryocytes. The antinuclear antibody test was negative. The complement fixation test for *Mycoplasma pneumoniae* was positive for IgM at 60 IU/ml, and IgG 61 IU/ml. Two weeks later, IgG became 200 IU/ml. Virology study for Epstein-Barr virus, adenovirus and influenza virus were all negative.

The patient was prescribed erythromycin 500 mg intravenously every six hourly, cefotaxime two grams eight hourly, hydrocortisone 100 mg six hourly, iron tablets, and folic acid 10 mg twice daily. She was kept in a warm room and all her fluids were warmed before being given. Blood transfusion could not be given because of incompatibility due to presence of antibodies. Next day her hemoglobin dropped to 72 grams/liter, and reticulocyte count increased to 6%. Hydrocortisone was stopped and she was started on methylprednisolone one gram per day, and intravenous immunoglobulin two grams/kg body

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weight. The hemoglobin dropped further and reached 53 grams/liter, and the reticulocyte count increased to 10%. Cyclophosphamide was given at a dose of 750 mg intravenously. On the third day the hemoglobin reached 33 grams/liter, and reticulocyte count increased to 13.3%. As she was critically ill, plasmapheresis was started. During the first three days she could not tolerate the least compatible washed red blood cells. Only on the fourth day could blood transfusion be given safely. Her condition gradually improved, and she was kept on tapering dose of steroids. The antibiotics were continued for a total of three weeks. The patient was discharged with a hemoglobin of 127 grams/liter. Three months after discharge there was no detectable antibodies in patient's serum.

She was followed for one year without any medication and her last hemoglobin was 130 grams/liter.

DISCUSSION

Mycoplasma pneumonia accounts for 22.8% of mild respiratory tract infections that can be managed without hospitalization[2], and 5% of hospitalized patients with chest infections[3]. Antibodies (IgM) to I antigen on erythrocyte membranes appear during infection and produce cold agglutination in about 60% of patients. Hemolysis is usually clinically not significant, but occasionally may be severe. Our patient had a combination of warm and cold agglutinin AIHA evidenced by direct Coombs' test, presence of cold agglutinins (IgM), and IgG antibodies. Cold agglutinins are produced during the course of certain infections, such as mycoplasma pneumonia and infectious mononucleosis[4]. Much less commonly, cold agglutinins are associated with other viral diseases. In most cases with post infectious cold agglutinins, the antibody titer is low and little hemolysis is seen. The peak titer usually occurs two to three weeks after onset of infection and disappears in two to three months.

The cold agglutinins are usually IgM, and the destruction of erythrocytes is primarily complement-mediated. This process is relatively inefficient in the absence of exposure to cold.

Mycoplasma pneumoniae produces peroxidase, which alters the I-antigen locus of erythrocytes. This altered antigen initiates antibody production. In cold temperature, the complement is fixed in this reaction[5]. The Coombs' test is often positive in the presence of this antibody, and intravascular hemolysis is always associated with a high cold agglutinin titer (1:500 or more)[5,6], as seen in our patient. The cold agglutinin titer appears in seven to 10 days, reaches its peak in four weeks gradually falls to a lower level in another three to four weeks, and then becomes negative in four months[2].

Hemolytic anemia can occur without a reticulocytic response, and such patients may have severe anemia[7]. In a study of 109 patients with AIHA 20% had initial reticulocyte response below 4%. Seventy-five percent of such patients had erythroid hyperplasia of the bone marrow[8]. Thus in most cases, the poor reticulocyte response at presentation may be due to a lag in marrow response to hemolytic anemia, which was seen in our patient.

There are generally two ways to explain the inappropriate reticulocyte response: direct and indirect marrow suppression. In direct bone marrow suppression, the marrow will not respond appropriately, if it is damaged or suppressed; for example, during aplastic crisis caused by sickle cells[9], or as a consequence of chemotherapy in chronic lymphocytic leukemia[10]. In the indirect bone marrow suppression most clinical situations are caused by reduction in plasma iron since it limits erythrocyte production. The most common causes are iron deficiency, infection, inflammation, malignancy, or erythropoietin deficiency. Other nutrients are also important, such as folate.

The most effective therapy for cold agglutinin hemolysis is avoidance of cold. It includes keeping the patient, particularly the extremities and the ears, warm. The transfused blood should be warmed to 37° C by an efficient "in line" blood warmers[11].

Reduction of antibody production in warm agglutinin AIHA is achieved by steroids and cytotoxic drugs, with limited effect in cold agglutinin disease. Patients with warm agglutinin AIHA have 60-70% response to prednisone at 1 mg/Kg body weight[12]. Cytotoxic drugs such as cyclophosphamide and azathioprine have been used successfully in daily and pulse therapy doses[12]. Cyclosporine has been used in some resistant cases. Vincristine has been used also.

Intravenous immunoglobulin may reduce immune activity by interacting with Fc antibodies. It may also increase the number of T suppressor cells. It may also accelerate fractional catabolism of IgG by increasing plasma concentration of IgG[13]. Plasmapheresis is used mainly to remove antibodies from plasma mainly IgM, leading to a reduction of rate of hemolysis. It is relatively short lived, as the half-life for replacement of protein is five days[14].

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