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A Rare Clinical Association Of Mycoplasma Pneumoniae Infection With Severe Autoimmune Hemolytic Anemia And Pulmonary Embolism: Case Report And Review Of Literature

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Abstract:
Autoimmune hemolytic anemia (AIHA) is a known complication of various infections, the link between Mycoplasma infection and AIHA is relatively rare. It mainly causes disease of varied severity of illness from asymptomatic or upper respiratory infection to severe pneumonia. About 25% of Mycoplasma infections are associated with an extrapulmonary complication at variable time. Hemolytic anemia associated with M. pneumoniae infection has been most commonly attributed to IgM cold agglutinins. Cold agglutinin syndrome often results in mild subclinical hemolysis and remain unrecognized. Fatal and severe hemolysis is very rare and often associated with significant lower respiratory tract involvement. Pulmonary embolism is an extremely rare complication associated with Mycoplasma infection and can cause fatal outcome if not timely detected and intervened. We report a case of severe cold agglutinin mediated autoimmune hemolytic anemia complicated with pulmonary embolism induced by M. pneumoniae infection in a 17-year old female and successful recovery.

Keywords: *Mycoplasma pneumoniae, Autoimmune hemolytic anaemia, Pulmonary embolism.*

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I. Introduction:

Mycoplasma is the smallest living-free organism in the nature. It is an important and common cause of respiratory infections. It mainly causes disease of varied severity of illness from asymptomatic or upper respiratory infection to severe pneumonia. About 25% of Mycoplasma infections are associated with an extrapulmonary complication at variable time. Common extrapulmonary sites involved are central nervous system (CNS), cardiac, dermatologic, gastrointestinal musculoskeletal, and hematological1-3. The different mechanisms by which M. pneumoniae causes extra-pulmonary complications are cytokine mediated effects, autoimmunity or immune complexes, and vasculitis or thrombosis. Hematological complications involve thrombocytopenia, thrombotic thrombocytopenic purpura, hemophagocytosis, and hemolytic anemia.4 Hemolytic anemia associated with M. pneumoniae infection has been most commonly attributed to IgM cold agglutinins, whereby IgM autoantibodies attach to the antigen I on red blood cells causing mild hemolysis and rarely severe hemolytic anemia5. M. pneumoniae can also cause warm autoimmune hemolytic anemia, characterized by warm-reacting IgM antibodies, however it's a relatively rare complication with an incidence ranging from 6-13%.6 On rare occasions, M. pneumoniae can be complicated by combined IgM cold agglutinins and IgG warm agglutinins hemolytic anemia.7 Association of pulmonary embolism in Mycoplasma induced AIHA is extremely rare and can cause fatal outcome if not timely detected and intervened.8

Here we report a case of severe cold agglutinin mediated autoimmune hemolytic anemia complicated with pulmonary embolism induced by M. pneumoniae infection in a 17 year old female.

II. Case Report:

A 17 years old female from Hooghly district, West Bengal, India with no co-morbidities presented to the emergency dept. with severe shortness of breath. She had intermittent fever and productive cough for 1 week which was associated with generalized weakness. There was no significant past medical or surgical history. She

had outside reports showing Hb -3.4gm%, TLC-16100/µL, Platelet -3 lakh/µL with normal iron profile and stool for OBT was negative. She had menarche at the age of 13 years with normal cycle and normal menstrual blood loss. Family history was not contributory to the present illness.

On examination- she had severe pallor, coarse crepitations on left side of chest. She was severely tachypnic with respiratory rate of 30 to 35/min. SpO2 was 82% in room air and ABG showed PO2 of 62 mmHg. Heart Rate was-128/min, blood pressure-100/60. She was started on NIV with titrated FiO2 targeting SPO2 of 94-96%. Her chest X ray showed non homogenous opacities of pneumonitic changes on left lung field. She was empirically started with Inj. Meropenem and Inj. Teicoplanin considering her clinical condition and she was shifted to ICU for further management

We planned for 2-unit blood transfusion. Blood bank informed that they found severe auto agglutinating blood sample. We provisionally diagnosed it as a case of autoimmune hemolytic anemia with LRTI. We planned to transfuse best matched packed RBC while keeping the patient warm and slowly transfusing under close observation to avoid possible hemolysis. One unit PRBC was prewarmed to room temperature and slowly transfused over 4 hours without any complications.

Her 2D Echo showed good biventricular systolic function with LVEF- 60%, PASP- 40 mm Hg, IVC-14 mm and a thin film of pericardial effusion. CRP was 23 mg/L. Procalcitonin-0.39 ng/ml. USG whole abdomen showed hepatosplenomegaly.

Next day she was put on intermittent NIV and O2 through face mask. She was still tachypnic and tachycardic. Blood report showed Hb- 5 gm%, TLC- 13100/ µL, Transferrin saturation -20 %, Ferritin- 169 ng/ml, Vit B12-169 pg/ml, Folate- 7.5 ng/ml, TSH- 3.3 µIU/ml, Reticulocyte count was very high- 17.62 %. Bilirubin-0.8mg/dl. Blood for APLA (antiphospholipid antibody) was sent. She was transfused with another unit of PRBC with proper precaution. Direct Coombs test came as strongly positive (4+). Her extended coombs test showed strong positivity for c3d (4+) and cold agglutinin titre was 1:1024. So, she was diagnosed as cold agglutinin syndrome. Respiratory panel came positive for mycoplasma pneumoniae and Adenovirus. So, it was obvious that her cold agglutinin syndrome was attributed to Mycoplasma pneumoniae infection. Inj. Doxycycline 100mg IV twice daily was added and planned to continue for 10 days. Inj. Meropenem and Teicoplanin was de-escalated to Inj. Ceftriaxone 2gm once daily. It was planned to decide on steroid or Rituximab if anti-infective measures fail.

Her O2 requirement was decreased to face mask first then to nasal canula but she persistently remained tachypnic and tachycardic. She had episodes of fever around 100°F till day 5. Repeat 2D Echo and ECG done to rule out viral myocarditis. Hs-TROP I was normal- 0.11pg/ml, NT-PRO-BNP was 127pg/ml. APLA test came as negative. Her D-DIMER came as very high- 6772.4 ng/ml. CT pulmonary angiography with high-resolution cuts was planned. HRCT showed left lower lobe consolidation with synpneumonic effusion. USG quantification showed only 200ml of pleural fluid. CTPA showed pulmonary embolism with obstructed right descending artery. Inj. Enoxaparin 60 mg S/C twice daily was started as therapeutic dose. For tachycardia tablet Ivabradine was added.

She became afebrile from day 6. She was requiring O2 at 1 lit/min through nasal canula. Her Hb increased to 7.6 gm%. Total 4 units PRBCs was transfused. Dyselectrolytemia was corrected. She was off O2 from day 8. Her chest X ray got improved with clearing of previous pneumonitic patches. Her tachycardia got settled. She was shifted to general ward.

She was completed with 10 days of Inj. Doxycycline. She was shifted to oral anticoagulant Epixaban 2.5 mg twice daily from injectable enoxaparin. Her Hb increased to 10.4 gm%. She was discharged in stable condition on day 11 with the advice of cardiology follow up for anticoagulant course.

Figure no 1: showing highly positive Direct Coombs test (DCT) and extended DCT showing high positivity to C3d.

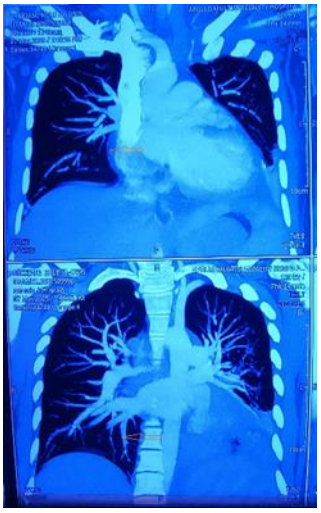

Figure no 2: CTPA showing pulmonary embolism with obstructed right descending artery

III. Discussion:

Autoimmune hemolytic anemia consists of warm and cold antibodies that are directed against antigen on red blood cell surface. These antibodies may be primary or secondary to any underlying cause like infections, malignancy, etc. Cold agglutinin disease is rare contributing 15% of autoimmune hemolytic anemia with incidence of 1 per million every year.9 Cold agglutinin titre is frequently observed during Mycoplasma infection. About 50% of patients infected with Mycoplasma have cold agglutinin.10 In our patients the cold agglutinin titre was very high 1:1024.

Cold agglutinin syndrome often results in mild subclinical hemolysis and remain unrecognized. Fatal and severe hemolysis is very rare and often associated with significant lower respiratory tract involvement. Maryam Alasfour et al. reported a case of severe cold agglutinin mediated autoimmune hemolytic anemia induced by M. pneumoniae infection in a 72-year-old which lead to fatal outcome due to progressive hemolysis and cardiogenic shock.8 In our case we could manage her timely and discharged her in stable condition.

Classical laboratory features are similar to any form of hemolytic anemia. Elevated lactate dehydrogenase and bilirubin levels with increased reticulocyte count were common in cold agglutinin hemolytic anemia. Our patient had hemoglobin level of 3.4 gm% with very high reticulocyte count 17.62%.

Mycoplasma culture was rarely used for routine diagnosis because of many limitations like nature of organism, incubation period, expensive and specialized growth media, etc. Therefore, diagnosis is usually confirmed by serological test or polymerase chain reaction gene amplification technique. In our patient, diagnosis was based on positive PCR testing and Coomb test in the presence of cold agglutinin antibody similar to other cases reported.1

Mycoplasma pneumoniae-associated cold antibody hemolytic anemia is usually self–limiting, and most patients recover with conservative treatment. Keeping the patient warm and treatment of underlying condition are the mainstay of treatment. Antibiotics is generally recommended but probably play a limited role in the treatment of hemolysis. Theoretically, a faster clearance of the pathogen by antibiotic treatment could limit the production of cold agglutinins and their hemolytic effect.11 In our case we started antimicrobial therapy directed to Mycoplasma immediately after PCR positivity and observed successful recovery.

In AIHA, blood transfusion can aggravate hemolysis, so this should be used cautiously. If blood transfusion was needed as life-saving measure in case of severe hemolysis or cardiorespiratory compromise, risk of transfusion-related hemolysis may be reduced by keeping blood and patient warm.9 We transfused best matched PRBC considering the critical Hb% value and possible risk of hemodynamic instability.

Most appropriate pharmacotherapy for Cold Agglutinin hemolytic anaemia has remained an area of clinical research. A favourable response to steroid is present in available few case reports. In a study by Swiecicki et al., around 40% of patients had favourable response to steroid containing regimen.9 Other literature showed doubtful response with Steroid specifically in cold agglutinin hemolysis12.

In our patient we started antimicrobial therapy directed to Mycoplasma. We planned to start steroid if primary treatment fails. Our patient responded remarkably with antibiotic only that's why we didn't start steroid therapy. Few literatures advocated use of Rituximab or Azathioprime with favourable response.9 We didn't try in our patient as our patient improved gradually with antimicrobial treatment.

Pulmonary embolism is an extremely rare complication associated with Mycoplasma infection. Very few case reports are only available. It is unsure if thromboembolism occurs secondary to M. pneumoniae infection or due to venous stasis in critically ill patients. Cold agglutinin induced hemolysis was thought to cause a

hypercoagulable state resulting in widespread thromboembolism. Yue Lu MD et al. reported a case of 65 years of female with fatal outcome who had massive PE detected on postmortem following M. pneumoniae associated AIHA.13 A case series recommends that anticoagulant prophylaxis and investigation for thromboembolism should be considered in life- threatening cases.14 We were vigilant in our case and did CTPA at appropriate time and started therapeutic anticoagulant therapy.

IV. Conclusion:

By reporting this case, we aim to raise awareness among clinicians regarding the potential hematological complications associated with M. pneumoniae infection. Timely recognition of these complications can facilitate early intervention, appropriate treatment, and improved patient outcomes. We need further research works to know the pharmacotherapy more precisely and the role of steroid in M. pneumoniae induced auto immune hemolytic anaemia.

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