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Case Report

MANAGEMENT OF PNEUMONIA WITH MULTILOCULATED LEFT PLEURAL EFFUSION CAUSED BY EXTENDED SPECTRUM BETA-LACTAMASES PRODUCING *KLEBSIELLA PNEUMONIAE*

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ABSTRACT

Increase in the mortality and morbidity in pleural infection is a concern worldwide due to increasing resistant Gram negative pathogens like *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Klebsiella species.* Rise of pneumonia due to *K. pneumoniae,* is more likely observed in alcoholics, diabetics, hospitalized and patients receiving mechanical ventilation. In the present study, we discuss a case of a 59 year old male patient with pulmonary effusion infected with extended spectrum beta-lactamases (ESBL) producing *K. pneumoniae* with co-morbidities of uncontrolled Type II diabetes mellitus (DM), hypertension and coronary artery disease (CAD), treated with a newer antibiotic adjuvant entity: Elores (ceftriaxone/sulbactam/disodium edetate) and recovered well.

KEYWORDS: Gram negative pathogens, beta-lactamases, Elores.

INTRODUCTION

The incidence of pleural infection continues to rise worldwide. Pleural infections significantly increase the morbidity and mortality. Reported mortality rate in adults is up to 20%. The accumulation of fluid in the pleural space is a common manifestation of a wide range of diseases.[1]

The bacteria isolated from infected pleural effusion vary significantly between community and hospital-acquired infections. In India, microbial causes of pleural infections are mainly caused by Gram-negative pathogens. Isolation of aerobic Gram-negative bacteria from pleural fluid cultures range from 84.54% to 95.6%.[2] Common Gram-negative organisms identified in pleural infections are *Acinetobacter spp., Klebsiella spp and Pseudomonas aeruginosa*.[3] *Klebsiella pneumoniae* is the predominant bacterium associated with Lower Respiratory Tract Infections (LRTI) in the developing nations like India.[4] Pneumonia due to *K.pneumoniae* is more common in alcoholics, diabetics, hospitalized and patients on prolonged mechanical ventilation.[5] Diabetes mellitus is a major risk factor for *K. pneumoniae* infection and relates to more pulmonary complications than non-diabetic.[6]

Local evolution of Multi-Drug Resistant (MDR) bacteria due to persistent exposure of multiple antibiotics combined with horizontal gene transfer leads to rapid and widespread of resistant genomes like Extended-Spectrum β-lactamases (ESBLs). The prevalence of various beta-lactamases in the Gram-negative bacteria is alarmingly high, with 8 to 80% of ESBL production.[2, 7] *K. pneumoniae* and *Escherichia coli* remain the major ESBL-producing organisms isolated worldwide.[7]

The isolation of aerobic Gram-negative bacteria or multiple pathogens from pleural fluid is associated with poor prognosis and requires a more aggressive broad spectrum antimicrobial chemotherapy.[2, 8] Moreover, increasing resistance to beta lactam group of antibiotics with/without beta lactamase inhibitor combination, has created a therapeutic challenge in treating MDR ESBL producing organisms due to production of

latest generation of beta lactamase enzymes which are not neutralized by tazobactam and clavulanic acid. Hence, a need of a newer antibiotic with a novel approach against ESBL producing pathogens in pleural infections is highlighted.

Here, we are presenting a case of pneumonia with multiloculated left pleural effusion caused by ESBL producing *Klebsiella pneumoniae* in patient with uncontrolled Type-2 diabetics treated effectively with an Antibiotic Adjuvant Entity: Elores.

CASE REPORT

A 59 years male patient, known case of hypertension, uncontrolled Type II DM, old CVA, CAD was admitted in a private hospital with chief complaints of left side chest pain, cough, fever and breathlessness since 2-3 days, treated for CAD with minor improvements. Patient was referred to our hospital for further management. On general examination patient was conscious oriented but general condition was poor and dyspnoeic. His blood pressure was 140/80 mmHg, temperature 98.40° F, pulse rate 102/min, respiratory rate 24/min and SPO_2 98% and random blood sugar level on glucometer was 310 mg/dL. On systemic examination CVS S1S2 were normal, respiratory system showed decreased air entry left side with creps, while abdominal was soft and CNS was non remarkable. Patient was investigated. Haematological report showed deranged values for haemoglobin 9.7 g/dL(low), total leukocyte count (TLC) 16.9 $x10^3/mm^3$ (high), platelet count 4.98 x $10^3/mm^3$ (high), erythrocyte sedimentation rate (ESR) 35 mm/h (high) and serum creatinine 1.68 mg/dL (high). Chest X ray and High-resolution computed tomography (HRCT) scan of chest showed left lower zone collapsed/consolidation associated with multiloculated left pleural effusion and minimal right pleural thickening. Left upper lobe and right lung surfaces were lined with fibrotic bands. Contrast-enhanced computed tomography (CECT) was done to rule out empyema. Based on the clinical and lab findings, medicine, chest and diabetologist opinion was taken and followed. Ultrasonography (USG) guided pleural aspiration was done and sample sent for culture and sensitivity.

Patient was empirically put on intravenous piperacillin-tazobactam 4.5 g TDS, levofloxacin 750 mg along with insulin infusion, nebulisation and other supportive measures. Laboratory reports of pleural effusion showed Glucose: 08 g/dL, Protien: 2.44 g/dL, Albumin: 0.4 g/dL, Adenosine Deaminase (ADA): 70.15 g/dL, TLC: 3000µl, Neutrophils: 90 and lymphocytes: 10. Culture sensitivity report showed ESBL producing *Klebsiella pneumoniae,* resistant to piperacillin-tazobactam, Meropenem and Imipenem-cilastatin, but sensitive for Elores (Ceftriaxone/Sulbactam/Disodium edetate). Patients general condition deteriorated even after 3 days of antimicrobial therapy, with haemoglobin 9.4 g/dL, TLC $10.9x10^3/mm^3$, ESR 48 mm/h, platelet count $5.48x10^3/mm^3$ and serum creatinine 1.66 mg/dL were not improved.

Based on the sensitivity and biochemical parameters, antibiotic therapy with Piperacillin-tazobactam and levofloxacin was stopped and Elores 3g BID with 90 minutes infusion was initiated along with other supportive treatment. Elores treatment was continued for 7 days. Patient condition gradually improved, chest X ray on the 7th day after Elores treatment showed gross resolution and improvement. Patient was discharged from the hospital on oral treatment with follow up advised after 7 days. Patient responded well to the treatment.

DISCUSSION

Pleural infections are associated with significant morbidity and mortality. *Klebsiella pneumoniae* is the predominant bacterium associated with lower respiratory tract infections in India, especially in patients with diabetic, hospitalized and receiving mechanical ventilation.[4] The rising incidence and prevalence of *K. pneumoniae* can be attributed to increased resistant mechanism to antibiotics: hyperproduction of ESBL enzymes, porin-deficient mutant development, hyperactivity of efflux pump and delay in appropriate antimicrobial treatment.[9]

Furthermore, with increasing prevalence and resistance to expanded spectrum cephalosporins, ESBL producing pathogens create a major therapeutic challenge in clinical setups. *Klebsiella pneumoniae* and *Escherichia coli* remain the major ESBL-producing organisms isolated worldwide. The percentage of ESBL producing organisms ranging from 4% to 83% in India.[2]

In patients with diabetes, pulmonary complications are relatively more as compared to non-diabetics. Disturbances in

acquired immunity, alteration in the function of capillary endothelium and the rigidity of red blood cells may affect the hosts' ability to combat infections.[10] Diabetes mellitus is known as a major risk factor for *K. pneumoniae* infection.[10, 11]

Pleural effusions can be either free flowing or loculated. Loculation of pleural fluid develop next to the occurrence of visceral-to-parietal adhesions, blocking fluid from falling to the dependent portion of the pleural cavity thereby leading to development of loculations in any part of the pleural cavity. In the present case, patient presented with left lower zone collapse/ consolidation associated with multiloculated left pleural effusion and minimal right pleural thickening. Diagnosis by HRCT and/or CECT is performed to rule out empyema, as treatment for empyema requires chest tube drainage in addition to antibiotic therapy.[12]

Patients with suspected pleural infection should receive appropriate broad spectrum antibiotic therapy from the time of first review based on local prescribing guidelines, resistance patterns and culture sensitivity report.[13]

In the present case patient was empirically put on intravenous piperacillin-tazobactam 4.5 g TDS, levofloxacin 750mg (based on hospital antibiogram) along with insulin infusion, nebulisation and other supportive measures. USG guided pleural aspiration was done, culture and sensitivity reports showed ESBL producing *K.pnemoniae,* resistant to piperacillin-tazobactam with sensitivity for Elores. Based on the clinical radiological and laboratory findings patient was diagnosed as Type II diabetic, pneumonia with multiloculated left pleural effusion caused by ESBL producing *K. pneumoniae*. Post 3 days of empiric therapy the antibiotic was switched to Elores 1.5g B.D dose with 90 minutes infusion on the basis of culture and sensitivity report.

Elores is an Antibiotic Adjuvant Entity with a novel combination of Ceftriaxone/Sulbactam/ Disodium edetate, can combat antimicrobial resistance produced by bacteria. The reason for increased susceptibility of Elores is synergistic activity of ceftriaxone, sulbactam and disodium edetate, which makes more susceptible it towards ESBLs and MBLs producing organisms.

In an *in-vitro* study done on *K.pnemoniae* strains collected from North India, Elores showed a significant susceptibility against ESBLs and MBLs.[14] This is because of Elores activity against down regulation of ESBL/MBL producing genes, increased bacterial cell permeability, down regulation of efflux pump over expression and ability to break bacterial biofilms.[15]

Phase-III clinical trial on Elores reported clinical cure rate of 91.30% (42/46) and 97.05% (33/34) in LRTI patients.[16] Sahu *et al*., reported 82% sensitive and intermediate sensitive to ESBL producing clincal strains of *K. pneumoniae* majority isolates from sputum, urine, tissue and pus.[15]

CONCLUSION

Rise in the incidence of pleural infection worldwide by multi-drug resistant ESBL producing *K. pneumoniae* can be attributed to the higher efficacy of the pathogen to transfer resistance factors from one bacterium to other. Patients with co-morbidities like diabetes, increase the chances for pulmonary complications. Early recognition and diagnosis with prompt broad spectrum antibiotic improves the condition of patient. We have presented here a case of MDR ESBL producing *K. pneumoniae* in Type II diabetic patient treated with a newer antibiotic adjuvant entity: Elores, which showed promising results, both in safety and efficacy. Elores could be considered as an effective solution for treating Gram negative ESBL producing pathogens where first line of antibiotics fail to respond.

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