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Case Report
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Therapeutic Drug Monitoring Guided Polymyxin Treatment in a Rare Case of Lipoid Pneumonia

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Abstract

Exogenous lipoid pneumonia caused by diesel siphonage is a rare condition. Here, we report a case of severe pneumonia, septicemia, and sepsis following diesel siphonage. The patient was treated with ventilator support, corticosteroids, extracorporeal membrane oxygenation, therapeutic lung lavage, and antimicrobials. With therapeutic drug monitoring guiding dosage optimization, polymyxin B was used as an essential chemotherapy to successfully treat multi-drug resistant Gram-negative bacterial infections. The patient recovered well following effective clinical interventions. Overall, therapeutic drug monitoring is beneficial for safely optimizing polymyxin B dosing to maximize efficacy and minimize adverse events.

Keywords: Exogenous lipoid pneumonia; Polymyxin B; Therapeutic drug monitoring; Dosage optimization

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Introduction

Exogenous Lipoid Pneumonia (ELP) is a rare and challenging form of pneumonia caused by the aspiration or inhalation of fatty substances such as diesel, gasoline, and paraffin oil [1]. Common symptoms of ELP include cough, fever, dyspnea, acute and chronic pulmonary inflammatory reactions, and local pulmonary fibrosis [2,3]. ELP may be complicated by bacterial infection [4], making rational antimicrobial treatment essential. However, there are no established guidelines for the treatment of ELP or for antimicrobial therapy targeting secondary bacterial infections. Here, we report the treatment of a patient with ELP caused by diesel siphonage, where Therapeutic Drug Monitoring (TDM) was applied to adjust polymyxin therapy to combat nosocomial Multi-Drug Resistant (MDR) bacterial infection.

Case Presentation

A 39-year-old truck driver presented to the Emergency Department of Pingshan People's Hospital on July 4th, 2023, after siphoning diesel (Figure 1). He reported experiencing reflexive vomiting twice immediately after the incident. He had no history of chronic diseases such as hypertension, diabetes, coronary heart disease, or infectious diseases such as tuberculosis and hepatitis. In the Emergency Department, he underwent gastric lavage once. Subsequently, he exhibited restlessness and confusion. A chest Computed Tomography (CT) scan revealed uneven transmittance in the middle lobe of the right lung and the lower lobes of both lungs, multiple small nodules in both lungs, incomplete inhalation, and mild inflammation (Figure 2A). The diagnoses considered were aspiration pneumonia, organic solvent poisoning (diesel), and acute respiratory distress syndrome. Tracheal intubation and mechanical ventilation (FIO_2 100%, PEEP 16 cm H_2O) were initiated immediately, followed by fiberoptic bronchoalveolar lavage, continuous blood purification, and hemoperfusion. Methylprednisolone (anti-inflammatory), norepinephrine (vasoactive agent), and imipenem-cilastatin (antibiotic) were administered. After his condition was temporarily stabilized by correcting acid-base imbalance, maintaining electrolyte balance, and providing analgesia and sedation, he was transferred to the Intensive Care Unit (ICU).

On July 4th, bedside X-rays in the ICU revealed worsening pneumonia in both lungs. On the

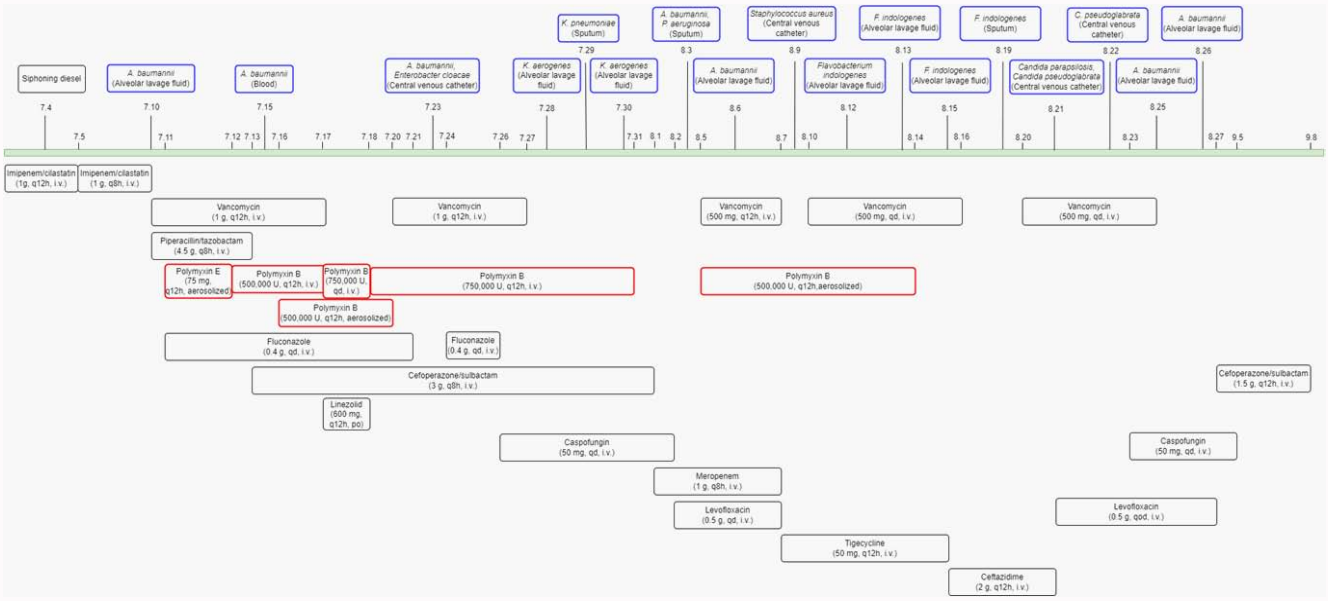

Figure 1: History of infections and antimicrobial therapy in the patient. Blue boxes indicate bacteria and fungi identified from the patient, and red boxes indicate the use of polymyxin B.

morning of July 5th, a blood gas test indicated a pH of 7.10, a PCO2 of 61.1 mm/Hg, a PO2 of 97 mm/Hg, an LAC of 6.0 mmol/L, and an Arterial Blood Gas (ABE) of -13.4 mmol/L. The White Blood Cell (WBC) count was 15.22 × 109/L, with neutrophils at 92.3%, and C-reactive protein (CRP) at 100.76 mg/L. Prothrombin TIME (PT) was 16.7 seconds, activated Partial Thromboplastin Time (aPTT) exceeded 180 seconds, and Thrombin Time (TT) exceeded 240 seconds. The patient was transferred to the ICU at Shenzhen People's Hospital the same day. Despite receiving mechanical ventilation, adequate sedation and analgesia, prone position ventilation, NO inhalation, and other treatments, the patient showed little improvement. On July 8th, the oxygenation index was 130 mmHg, and Acute Respiratory Distress Syndrome (ARDS) was diagnosed. Consequently, Venovenous Extracorporeal Membrane Oxygenation (VV-ECMO) was initiated and continued until July 24th. The patient suffered from recurrent MDR bacterial and fungal infections which included *Acinetobacter baumannii*, *Klebsiella aerogenes*, *Pseudomonas aeruginosa, Chryseobacterium indologenes, Staphylococcus aureus,* and *Candida parapsilosis*, leading to pneumonia and septicemia (Figure 1). Bacterial infections were treated at varying times with a range of antibiotics including intravenous and aerosolized polymyxin B (Figure 1). All polymyxin B MICs of relevant organisms were in the susceptible range [5]. Therapeutic Drug Monitoring (TDM) using liquid chromatography-tandem mass spectrometry (LC MS/MS) [6] was performed to monitor plasma concentrations of polymyxin B and guide the rational use of this last-line antibiotic. Polymyxin B (500,000 units (U) 12-hourly) was administered via an intravenous infusion over 2 h from July 12th to 17th. On July 17th, the average steady-state plasma concentration (Css, avg) of polymyxin B was 0.96 mg/L (Cmax, 1.54 mg/L), well below the recommended target Css, avg of 2 mg/L (Figure 2B) [7]. On July 18th, the dose of polymyxin B was increased to 750,000 U 12-hourly, and on July 21st, a Css, avg of 2.46 mg/L (Cmax, 4.92 mg/L) was reported. Beginning July 18th, significant decreases in IL-6, C-Reactive Protein (CRP), and procalcitonin (PCT) were observed, suggesting that the dosage of polymyxin B had been effectively optimized (Figure 2C). On July 19th, multiple exudates and consolidations were observed in both lungs, along with several small lymph nodes in bilateral hilar and mediastinal areas, and bilateral pleural effusion was greater than before (Figure 2A). On July 29th, a CT scan indicated interstitial inflammation and partial consolidation in both lungs, with no obvious absorption compared to the previous images, characteristic of ELP (Figure 2A). On August 29th, interstitial inflammation and partial consolidation were still present in both lungs, with slightly more absorption observed in the upper lung lesions compared to before (Figure 2A). Rehabilitation continued throughout the treatment process, including joint mobility training, transfer training, gait and walking exercises, among others. By early September, he was lucid, the spontaneous circulation was stable, and his liver function, platelets, coagulation, serum creatinine, and urine volume were all normal. His muscle strength had recovered, the ventilator was removed, and infection was under control. The patient was transferred to the Rehabilitation Department on September 8th, 2023.

Discussion

ELP is a rare pulmonary inflammatory disease that typically results from the aspiration or inhalation of fat-containing substances, manifesting in two forms: acute and chronic ELP [8]. Chronic ELP, caused by long-term exposure to lipid substances, is often confused with bacterial pneumonia and pulmonary tuberculosis due to the lack of specific clinical manifestations. Acute ELP usually arises from accidental inhalation of a large quantity of lipid material over a short period, as observed in the patient reported here. This form of ELP can trigger a severe inflammatory response and ARDS [9,10]. Currently, there are no evidence-based guidelines for ELP treatment. Common interventions include ventilator-assisted ventilation, extracorporeal membrane oxygenation, supportive treatment, corticosteroids, antibiotics, and therapeutic lung lavage [11]. These treatments were essential in managing this patient. Additionally, given the patient's progression to ARDS, ECMO was employed as a crucial therapy. Superimposed secondary bacterial infections were the main treatment obstacle for this patient. For two months following diesel

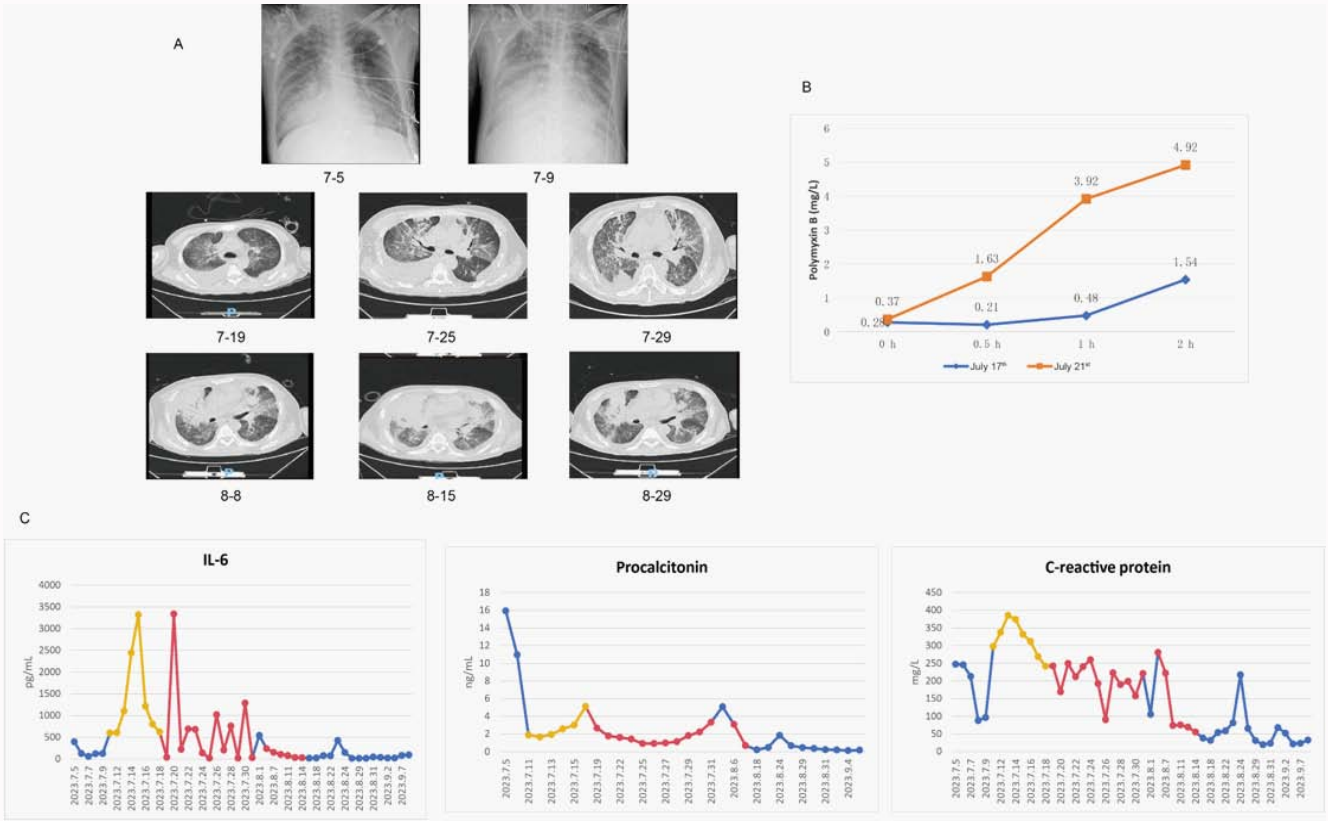

Figure 2: Clinical observations of bacterial infection in the patient. (A) Serial chest radiographs at ICU admission (7-5); after commencement of ECMO and before commencement of polymyxin B therapy (7-9); after the polymyxin B dose was increased (7-19); after cessation of ECMO (7-25, 7-29, 8-8, 8-15, and 8-29). (B) Polymyxin B concentrations in plasma across the 2 h infusion time before (July 17th) and after (July 21st) dose optimization. Peak concentrations occurred at the end of the infusion [8]. (C) Clinical indicators evaluating the patient's systemic inflammation: IL-6 (normal <7 pg/mL); procalcitonin (normal <0.05 ng/mL); C-reactive protein (normal <5 mg/L). The gold and red dots indicate measurements taken during polymyxin B treatment, with the gold dots taken before the dose of polymyxin B was increased and the red dots taken after the dose of polymyxin B was increased. Blue dots indicate measurements taken in the absence of polymyxin B treatment.

siphonage, he experienced repeated infections with MDR bacteria and fungi, with per persistent infections from Gram-negative bacteria presenting the major treatment challenge. These infections were treated with multiple antibiotics, including polymyxin B (Figure 1). The polymyxins (polymyxin B and colistin), which retain excellent antimicrobial activity against numerous problematic Gram-negative pathogens [12,13], are generally considered a last resort for Gram-negative bacterial infections. The therapeutic window for polymyxin treatment is extremely narrow, as the threshold concentrations for antibacterial efficacy and nephrotoxicity overlap [7]. Therefore, TDM is highly recommended for polymyxin optimization.

The recommended therapeutic target concentration for polymyxin B to effectively treat A. baumannii, P. aeruginosa, and Enterobacteriaceae is a Css, avg of 2 mg/L [7]. In this 65 kg patient with normal renal function, TDM indicated that the initial dosing regimen of 500,000 U administered every 12 h achieved a Css, avg of only 0.96 mg/L, and no improvement in the patient's condition was seen. The initial dosing regimen was chosen based on the product information, which recommended a dose of 500,000-1,000,000 U/day administered q12h (Shanghai Pharma No.1 Biochemical & Pharmaceutical CO., LTD., Shanghai, China). Therefore, the initial dosing regimen used that maximum recommended dose of the pharmaceutical product. Increasing the dose to 750,000 U every 12 h achieved a Css, avg of 2.46 mg/L, after which notable improvements in the patient's condition were observed. Nephrotoxicity, which occurs in up to ~30% of patients following intravenous administration of polymyxin B [14-16], could not be assessed because acute kidney injury was diagnosed on July 12th, prior to the commencement of intravenous polymyxin B, and Continuous Renal Replacement Therapy (CRRT) was initiated on July 13th.No neurotoxicity or skin pigmentation was observed during polymyxin treatment. Aerosolized polymyxin B was also used for this patient to treat Gram-negative bacterial lung infections. However, TDM for aerosolized polymyxin B using bronchoalveolar lavage fluid could not be conducted due to the large amount of diesel mixed in with the lung fluid. Therefore, the efficacy of aerosolized polymyxin B could not be evaluated in this patient. The treatment of this lipoid pneumonia patient can be divided into three phases: the initial phase (July 4th – July 10th), the repeated nosocomial infection phase (July 11th – August 26th), and the recovery phase (August 27th – September 8th). Antimicrobials were administered based on clinical microbiology laboratory tests and inflammatory biomarkers, with doses determined according to pharmacy instructions and disease treatment guidelines. Vancomycin doses were adjusted using TDM, while the doses of imipenem/cilastatin and cefoperazone/sulbactam were optimized using inflammatory biomarkers and other clinical indicators such as renal function.

In conclusion, MDR bacterial infection was the main obstacle in the treatment of this lipoid pneumonia patient. Timely TDM should

be conducted to optimize antimicrobial dosing regimens. For patients who experience repeated infections, inflammatory biomarkers are prompt and sensitive measurements to evaluate the dose-efficacy relationship of polymyxin B.

Acknowledgments

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