Managing clozapine-induced neutropenic fever: A case report

Regis G. Rosa, Maria D. Rosa, Alcina J. S. Barros

ABSTRACT

Introduction: Clozapine is an atypical antipsychotic, which is associated with an increased risk of neutropenia. Given that the signs and symptoms of infection in neutropenic patients are often subtle or absent because of the lack of an appropriate inflammatory response, fever may constitute the sole indicator of a serious underlying infection. Unfortunately, data about management of patients with neutropenic fever secondary to clozapine are scarce. Consequently, the entire management of this syndrome is based on extrapolation of data from the experience with cancer patients with neutropenia secondary to cytotoxic chemotherapy.

Case Report: Herein, we describe the management of a neutropenic fever case complicated with septic shock and acute respiratory failure in an 57-year-old Caucasian female with the diagnosis of schizophrenia and type-2 diabetes mellitus, who was being treated with clozapine. The patient rapidly developed cardiorespiratory collapse requiring mechanical ventilation and vasoactive drugs few minutes after arrival at hospital. Profound neutropenia (absolute neutrophil count 60 cells/mm³) and lobar pneumonia were diagnosed. Broad-spectrum antimicrobial therapy with piperacillin-tazobactam plus vancomycin and supportive intensive care were promptly implemented. The clozapine-induced neutropenia was managed with filgrastim. *Pseudomonas aeruginosa* was isolated from the tracheal aspirate and blood cultures. After a total length of hospital stay of 44 days, the patient was discharged home.

Conclusion: Neutropenic fever is a serious complication of clozapine treatment. Prompt administration of empiric broad-spectrum antibiotics and supportive care are required to avoid the high levels of mortality associated with this syndrome.

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Keywords: Clozapine, Critical care, Febrile neutropenia, Neutropenic fever, Septic, Shock

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INTRODUCTION

Neutropenia is the most feared adverse effect of clozapine, an antipsychotic dibenzodiazepine, primarily because its occurrence is known to predispose patients to severe infections [1]. The estimated incidence of clozapine-induced neutropenia ranges from 0.5–2.0% of patients treated with this medication, with the majority of cases occurring within the first three months after the start of treatment [2]. Although the exact mechanism of neutrophil toxicity is unknown, some evidence suggests immunologically mediated reactions may play a role [3].

Neutropenic fever (NF) is a syndrome characterized by fever in the presence of neutropenia (absolute neutrophil count < 500 cells/mm³) [4]. NF constitutes a medical emergency that requires the prompt administration of empirical broad-spectrum antimicrobials to prevent the characteristically high probability of mortality, which may reach values of approximately 10% in specialized centers [5,6]. The classical signs and symptoms of infection are often subtle or absent because an appropriate inflammatory response is missing due to granulocytopenia [7], underscoring the importance of early assessment and appropriate management of patients with NF. Among factors related to NF treatment, microbiologically effective initial antibiotics, time to antibiotic administration, and restoration of tissue perfusion play important roles in reducing mortality [8–10]. Herein, we describe the management of a NF episode complicated with septic shock in a 57-year-old Caucasian female with refractory schizophrenia after four weeks of treatment with clozapine.

CASE REPORT

A 57-year-old Caucasian female who had been diagnosed with paranoid schizophrenia since the age of 20 and type 2 diabetes mellitus since the age of 45 was admitted to a tertiary referral hospital due to fever (axillary temperature 38.9°C), sinus tachycardia (heart rate 110 bpm), malaise, and dehydration. She had a history of recent hospitalization due to refractory psychosis in which her antipsychotic treatment was switched from risperidone to clozapine. Clozapine treatment had been titrated up to a dosage of 400 mg orally per day starting four weeks before the hospitalization recounted here, and the routine white blood cell counts had been normal at the second and third weeks of treatment.

At the current hospitalization, the patient rapidly developed cardiorespiratory collapse requiring mechanical ventilation and continuous infusion of norepinephrine despite initial oxygen administration and fluid challenge with 1 L of crystalloid. She also presented oliguria (urine output < 0.5 mL/kg/h) and signs of poor peripheral perfusion (cold extremities, cyanosis, and capillary refill time > 2 s). The complete blood cell count demonstrated leukopenia (total leukocyte count 410 cells/mm³) and profound neutropenia (absolute neutrophil count 60 cells/mm³) with no abnormalities in hemoglobin or platelet counts. Initial C-reactive protein was elevated (96 mg/L) as was serum creatinine and BUN (3.5 mg/dL and 62 mg/dL, respectively). There were no abnormalities in serum electrolytes or liver function tests. The initial chest X-ray showed a lobar consolidation in the upper-right pulmonary lobe. After obtaining two samples of blood cultures and quantitative tracheal aspirate, the patient was treated according to current guidelines for the management of NF with 4.5 g piperacillin-tazobactam administered intravenously over

a 4 h period every 8 h, plus 1.0 g vancomycin administered intravenously every 12 h [4, 11–13]. The time between emergency arrival and antibiotic administration was 50 min. Acute respiratory failure was managed through a lung-protective mechanical ventilation strategy with low tidal volumes (6 ml per kilogram of ideal body weight) [14]. Restoration of tissue perfusion was performed with vasopressors, inotropes, and intravenous fluids according to established early goal-directed therapy for septic shock [15]. The clozapine-induced neutropenia was treated by subcutaneously administering 5 mg/kg/day of Filgrastim, a granulocyte colony-stimulating factor. After implementing these measures, septic shock progressively improved and the vasopressor dose was gradually reduced. Peripheral perfusion and diuresis substantially improved without the need for hemodialysis. *Pseudomonas aeruginosa* was isolated from the tracheal aspirate and blood cultures. The isolated bacteria was sensitive to piperacillin-tazobactam and carbapenems, and resistant to cefepime, fluoroquinolones, and aminoglycosides. After results of the antimicrobial susceptibility tests, vancomycin treatment was suspended given that there was no evidence of infection by gram-positive bacteria. After the fifth day of treatment, neutrophil counts began to increase, and reached values above 500 cells/mm³ after the eighth day. The antimicrobial treatment with piperacillin-tazobactam was maintained for 14 days, and the patient was extubated on the tenth day. The patient stayed 13 days in the ICU and 44 days in the hospital. Upon discharge, the patient was using quetiapine for the treatment of schizophrenia with good control of psychotic symptoms.

DISCUSSION

The present case report describes the successful management of a severe case of NF complicated with septic shock. Probably, the profound neutropenia caused by clozapine followed by a high virulent bacterial infection (*Pseudomonas aeruginosa*) contributed to the complicated course of NF. Successful management in this situation is noteworthy as the expected mortality rate for neutropenic patients with septic shock has been reported to be quite high at 35–50% [16,17].

According to current guidelines, patients with NF should be treated initially with empiric intravenous therapy, comprising β -lactam antibiotic monotherapy with antipseudomonal activity (i.e. ceftazidime, cefepime, piperacillin/tazobactam, meropenem, or imipenem) within 1 hour from onset of neutropenic sepsis [4,18]. This recommended regimen reflects the principle of broad-spectrum initial therapy that focuses primarily on aerobic gram-negative bacteria such as *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* spp., and *Enterobacter* spp., and aerobic gram-positive bacteria such as methicillin-susceptible staphylococci and viridans streptococci. The addition of vancomycin to the initial

regimen, which aims to combat resistant gram-positive bacteria (i.e. methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*), is indicated in cases of hemodynamic instability, suspected catheter-related infection, pneumonia, or infection of the skin and soft tissue. Our patient was treated initially with the combination of piperacillin-tazobactam and vancomycin due to the presence of hemodynamic instability and pneumonia. Glycopeptide was discontinued as soon as the initial cultures ensured the absence of infection by gram-positive bacteria. Filgrastin, a colony-stimulating factor, was used in this case as means to decrease the duration of clozapine-induced neutropenia. Its presumed efficacy is based on case reports [19–20] and studies in cancer patients under cytotoxic chemotherapy [21]. Given that protective mechanical ventilation and appropriate restoration of tissue through fluid challenge and vasopressor are two measures associated with better outcomes in critically ill patients, they likely played important roles in the positive outcome reported here [18].

CONCLUSION

In summary, patients with clozapine-induced neutropenia are at risk for severe infections. The timely administration of appropriate antimicrobials as well as rapid tissue-perfusion restoration are of paramount importance to avoid unfavorable outcomes in this context.

Author Contributions

Regis G. Rosa – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Maria D. Rosa – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Alcina J. S. Barros – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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