CASE REPORT

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Empyema in a Patient with Schizophrenia Using Clozapine: A Case Report

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ABSTRACT

Schizophrenia is associated with a high risk of thoracic infections and pneumonia. The use of atypical antipsychotics clozapine may also increase the risk of pulmonary infection. However, psychotic patients are less likely to report physical symptoms, and these dangerous conditions may go undetected. In this case report, we present 47-year-old woman with schizophrenia who had been using clozapine and did not complain of respiratory symptoms. After admission, she was diagnosed with *streptococcus intermedius* empyema. Although empyema has a high mortality rate, thanks to the timely admission and proper diagnosis, the patient recovered after 3 weeks of medical and surgical treatment.

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INTRODUCTION

An empyema refers to a collection of pus within the pleural cavity, from an adjacent pneumonia, direct inoculation, or other sources.[1] Aspiration of organism develops into pneumonia, and parapneumonic effusion occurs.[2] After 10-21 days without treatment in a complicated parapneumonic effusion, it eventually develops into the empyema stage.[2] The symptoms of empyema are similar to those of pneumonia, and early detection helps prevent disease progression.[1,2] Aspiration, immunocompromise, malignancy, alcoholism, diabetes, gastroesophageal reflux disease, and poor oral hygiene are predisposing factors for empyema.[1] *Streptococcus intermedius* is an anaerobic bacterium that is relatively common in empyema, and aspiration from oral secretions may act as an important risk factor for pulmonary infection.[3,4] However, the causative microorganism is identified in approximately half of all cases, and *S. intermedius* may be overlooked as part of the normal flora.[4] The incidence of empyema is increasing, with approximately 60,000 cases diagnosed each year in the United States.[5] Treatment of pleural empyema includes antibiotic therapy, chest tube drainage, intrapleural fibrinolysis, and surgery.[2] The mortality rate of empyema is 20%,[1] and a large number of premature deaths in schizophrenia are caused by respiratory diseases.[5] Therefore, treatment based on timely detection is important. However, psychotic patients are less likely to report physical symptoms[6] and serious infection may have an insidious onset, making early detection challenging.[2]

Due to an unhealthy lifestyle and poor self-care, patients with schizophrenia are vulnerable to diseases, including respiratory disease.[7] The risk of pneumonia in schizophrenia is 3 times higher than that in the general population.[7] Clozapine may increase infection risk possibly by interfering with immunological defenses.[8] Moreover, literature suggests that clozapine and pneumonia have strong bidirectional associations.[8] There is little published information on the rarer adverse effects, may be severe and potentially life threatening, of clozapine, especially lung disease.[9] This case report presents a rare case of empyema in a patient with schizophrenia taking clozapine and discusses the clinical implications of the case.

CASE PRESENTATION

A 47-year-old woman with schizophrenia using clozapine was admitted to the psychiatric department with complaints of nausea, poor oral intake, and weight loss. Since her diagnosis of schizophrenia 8 years ago, the patient was hospitalized in the psychiatric department 8 times in addition to undergoing outpatient treatment. As treatment-resistant schizophrenia, she has been taking clozapine since 2 years ago. Positive symptoms were relatively well managed; however, the negative symptoms persisted. Due to her negative symptoms such as social withdrawal and poor self-care, hygiene care, including oral hygiene, was not performed well. The patient

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continued to complain of sedation and sialorrhea, which is frequently observed with clozapine use. Because of these uncomfortable adverse reactions, electroconvulsive therapy (ECT) was performed shortly after using clozapine. Psychotic symptoms improved with ECT, but maintenance ECT was not implemented because of the patient's refusal to undergo it. Six months after her last hospitalization, she took 100 mg clozapine and maintained an outpatient follow-up. While taking clozapine, she complained of sialorrhea and sedation and spent a lot of time lying down without personal hygiene. About 2 weeks before admission, she complained of nausea and poor oral intake and had a weight loss of 6 kg in 2 weeks.

At the time of admission, her blood pressure was 105/70 mmHg; pulse rate, 74 bpm; respiratory rate, 20 breaths/min; body temperature, 36.7°C; and oxygen saturation was 96% in room air. Initial blood analysis revealed a mild leukocytosis (11.61 × 10^9/L; reference, 4-10 × 10^9/L) with 75.2% neutrophils. Hemoglobin (8.7 g/dL; reference, 12-16 g/dL), total iron-binding capacity (138 μg/dL; reference, 215-535 μg/dL), iron (12 μg/dL; reference, 60-180 μg/dL), and albumin (2.5 g/dL; reference, 3.5-5.2 g/dL) levels were decreased. Elevated procalcitonin 0.171 ng/mL (0.171 ng/mL; reference, <0.046), erythrocyte sedimentation rate (85 mm/h; reference, 0-20 mm/h), and serum C-reactive protein (CRP, 22.11 mg/dL; reference, <0.5) were consistent with inflammatory response. Electrocardiogram was normal.

Chest radiography revealed a massive amount of right-sided pleural effusion. A chest computed tomography (CT) scan with contrast demonstrated a large amount of fluid collection with diffuse pleural thickening and atelectasis of the right lung (Figure 1). From the day after admission, intravenous piperacillin/tazobactam (4.5 g every 6 hours) was used empirically. There were no gastrointestinal bleeding findings on dynamic CT with contrast. Blood and sputum cultures were negative for *Mycobacterium tuberculosis* and non-tuberculous mycobacteria. Polymerase chain reaction for adenovirus, influenza virus A/B, *Mycoplasma pneumoniae*, and *Legionella pneumoniae* were all negative. *S. intermedius* was identified in the pleural fluid. Chronic inflammation with fibrosis was observed on pleural biopsy. The patient was finally diagnosed with *S. intermedius* empyema. The patient was transferred to the Department of Respiratory Medicine. A 16 French chest tube was inserted for drainage of the pleural space. Based on the discretion of the physician and the results of the antibiotic susceptibility test, intravenous ampicillin/sulbactam (3 g every 6 hours) was administered for 3 weeks. With intrapleural fibrinolysis, drainage was successfully performed, but right hydropneumothorax and segmental atelectasis in the right lung were confirmed. Therefore, the patient was referred for thoracic surgery, and decortication through thoracotomy was performed.

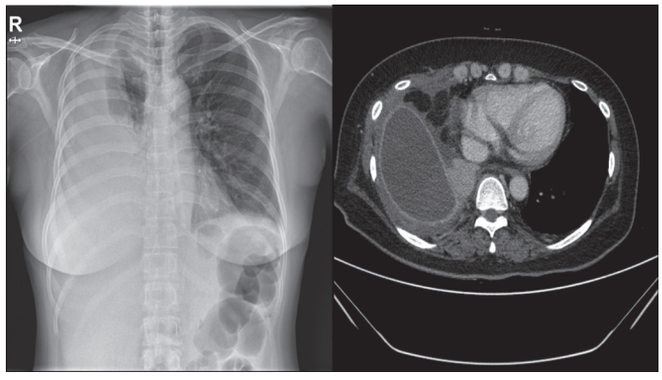

Figure 1. Chest radiograph and chest computed tomography (CT) scan on admission.

Clozapine was discontinued during respiratory medical treatment, and the patient's psychotic symptoms worsened. After surgical intervention, she was transferred to a psychiatric department again for psychotic symptom control and antipsychotic medication changes. The total positive and negative syndrome scale (PANSS) score was 120 (positive scale, 26; negative scale, 28; and general psychopathology scale, 66). Aripiprazole was administered via a long-acting injection, and amisulpride was added to the drug regime. After 3 weeks, the total PANSS score slightly decreased to 111 (positive scale, 25; negative scale, 25; and general psychopathology scale, 61). C-reactive protein decreased to 4.38 mg/dL, and other laboratory tests were within the normal range. Follow-up chest radiography and chest CT scan after a month of decortication showed decreased right pleural effusion and pleural thickening (Figure 2). The patient's food intake gradually increased, and nausea symptoms were not observed. Informed consent was obtained from the patient to report her case in this case study.

MAIN POINTS

- In schizophrenia, psychotic symptoms, lack of self-care, and unhealthy lifestyles may contribute to infection risk.
- Psychotic symptoms can make it difficult for patients with schizophrenia to recognize and express their medical conditions.
- Clozapine may be particularly associated with the risk of pneumonia.
- Clinical suspicion of pulmonary infection in patients with schizophrenia taking clozapine is important.

DISCUSSION

Empyema is characterized by fever, cough, dyspnea, and chest pain.[1,2] The onset of empyema may be insidious, with patients appearing chronically ill with weight loss and anemia.[1] In this case, a 47-year-old female patient with thoracic empyema presented with nausea, poor oral intake, and weight loss without respiratory symptoms.[1,5]

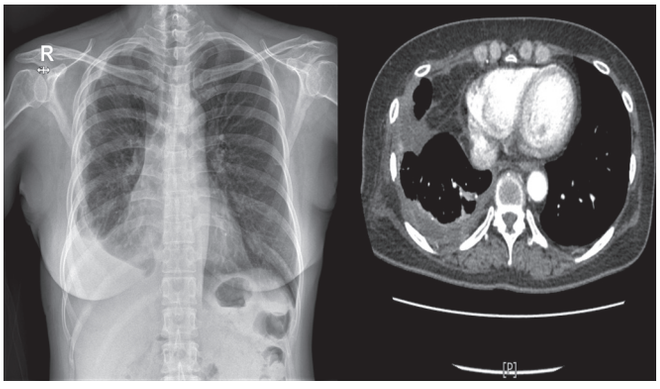

Figure 2. Chest radiograph and chest computed tomography (CT) scan after decortication.

Bacterial pneumonia with parapneumonic effusion is the most common precursor, and parapneumonic effusion occurs in 20%-40% of 1 million pneumonia patients hospitalized in the United States each year.[1] Furthermore, under the current COVID-19 pandemic, COVID-19 infection may enhance clozapine toxicity and increase the risk of pneumonia.[10]

Previous studies have suggested that schizophrenia and second-generation antipsychotics increase the risk of developing respiratory infections.[11] Although the mechanism for this has not yet been clearly elucidated, it can be assumed that various factors may have an effect. Lack of self-care, especially poor oral hygiene, and unhealthy lifestyles such as smoking, drinking alcohol, malnutrition, and a high rate of comorbidity in patients with schizophrenia may be associated with empyema.[5] Pleural empyema is easily caused by the aspiration of mixed bacterial flora and other materials from the oropharyngeal cavity and even from the upper gastrointestinal tract.[5] Patients with schizophrenia are at a higher risk of developing swallowing difficulty, leading to aspiration pneumonia.[12] Patients with schizophrenia were reported to have a 2.4-fold higher incidence of pleural empyema than a control group.[5] Patients with schizophrenia who have respiratory infections may have poorer clinical outcomes.[13] However, psychotic symptoms in patients with schizophrenia can make the recognition and expression of medical conditions difficult. Thus, thoracic infection increases morbidity and mortality in patients with schizophrenia and threaten the health of these patients.[14]

Clozapine is the most effective antipsychotics used for treatment-resistant schizophrenia.[9] Clozapine is known to carry higher risks of pneumonia and lethality during pneumonia.[15] Clozapine has complex immune system effects possibly increasing pneumonia risk.[16] Antipsychotics have immunoregulatory and anti-inflammatory effects; however, clozapine may have inflammatory effects.[17] Clozapine can modulate the cytokine network[18,19] and directly influences the plasma levels of several cytokines that resemble an inflammatory reaction.[17] Systemic inflammations can increase clozapine level.[8] Also, clozapine can cause inflammation and may increase the risk of infection possibly by interfering with immunological defenses.[8] Pneumonia may be associated with clozapine intoxication, and the clozapine, by interfering with immunological mechanisms, may increase the risk of pneumonia. Clozapine has a high affinity for muscarinic receptors that may contribute to hypersalivation and its high affinity for histamine 1 receptor may contribute to sedation.[15] Clozapine is prone to cause side effects, such as agranulocytosis, sialorrhea, impairment of swallowing function, and increases the risk of aspiration pneumonia.[11] Furthermore, sedation secondary to antihistamine effects in the central nervous system may also contribute to the risk of developing aspiration pneumonia.[20] The possibility of reducing oropharyngeal peristalsis due to clozapine and its proinflammatory properties also increase the susceptibility to pneumonia.[21,22] It has been suggested that clozapine may be more commonly associated with pneumonia than other antipsychotic medications.[11] This result may be attributed to clozapine's strong anticholinergic effect.[23,24] *S. intermedius* belongs to the *Streptococcus anginosus* group and is an important causative pathogen of bacterial pneumonia, pulmonary abscess, and empyema.[4] *S. intermedius* is an anaerobe that forms the normal flora of the oropharyngeal, urogenital, and gastrointestinal tracts.[3] It has been reported that aspiration of oral secretions is an important mechanism in empyema associated with pneumonia caused by *S. intermedius*.[3,4] However, anaerobic species are particularly difficult to culture, and *S. intermedius* can potentially be neglected as part of the normal flora.[1,4]

Among previously published cases, cases of severe respiratory disease in patients with schizophrenia taking clozapine are exceedingly rare. In our case, the patient had no predisposing factors. While taking clozapine, the patient had adverse drug reactions which can interfere with swallowing, increasing the potential for aspiration. Previous findings suggest that empyema is associated with an increased risk of aspiration. The identification of *S. intermedius* supports our hypothesis. Fortunately, the patient in this case was successfully treated with combined medical and surgical treatment. In our case, the most probable hypothesis is the same as above, clozapine could be one of the possible causes, but the possibility that hidden malignancy, which can contribute to the development of empyema, or the occurrence of trauma or surgery could not be completely excluded. Nevertheless, especially in patients with schizophrenia using clozapine, even if they do not complain of typical respiratory symptoms or have no underlying disease, close evaluation is necessary. This case highlights the importance of clinical suspicion of respiratory infection in schizophrenia with clozapine use. Therefore, patients taking clozapine should be evaluated for the drug-related

adverse reactions such as sialorrhea and sedation, and the clozapine dose adjustment or alternative therapy may be required accordingly. In addition, possible preventive measures through regular imaging examination, oral hygiene management, and a healthy lifestyle may be helpful. Furthermore, clinicians must be prepared to prevent, detect, and manage potentially life-threatening events associated with clozapine. Early recognition of serious side effects may allow for better therapeutic management.

CONCLUSION

In the present case, empyema occurred after clozapine use in a patient with schizophrenia without comorbidities. In addition, since the patient did not complain of typical respiratory symptoms, unnoticed aspiration pneumonia may have progressed to chronic inflammation and empyema. Psychotic patients are less likely to perceive or report physical symptoms, and serious infection may have an insidious onset, making early detection challenging. Since early diagnosis and treatment are important, clinicians should be suspicious of pulmonary infection in patients with schizophrenia under clozapine use, and take appropriate preventive measures.

Informed Consent: Informed consent was obtained from the patient for this case report.

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