Case Report
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Pulmonary Embolism during a Retrial of Low-dose Clozapine

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Pulmonary emboli (PE) are increasingly recognized as an adverse effect of clozapine. However, little is known about the characteristics or mechanisms of clozapine-associated PE. We present a case of a 34-year-old with treatment-refractory schizophrenia who developed rhabdomyolysis during his first clozapine trial. During re-trial on a lower dose than his initial trial, the patient developed chest pain that he attributed to "pacemakers." The pleuritic description and associated tachycardia prompted medical workup and the patient was ultimately diagnosed with a clozapine-associated PE. The patient's only risk factors for PE were obesity and tobacco use, while his hypercoagulability workup was unrevealing. Clozapine use was continued at a lower dose following these adverse effects given inefficacy of other agents in managing the patient's psychotic symptoms. The patient experienced significant relief of psychotic symptoms with continued clozapine therapy and a course of electroconvulsive therapy. The patient's presentation was unusual in that it occurred during a retrial of clozapine, after the initial trial was stopped when he developed rhabdomyolysis. This case demonstrates the importance of maintaining vigilance for PE in patients on clozapine as well as not dismissing somatic complaints in patients experiencing psychosis. Additionally, given his history rhabdomyolysis, an uncommon adverse effect of clozapine, the development of a second uncommon adverse effect (PE) raises the question of whether these events may be associated.

KEY WORDS: Clozapine; Pulmonary embolism; Thromboembolism.

INTRODUCTION

Pulmonary embolism (PE) is a common and potentially fatal form of venous thromboembolism in which the pulmonary artery or one of its branches is obstructed. Known risk factors include inherited or acquired hypercoagulability syndromes, trauma, immobilization, malignancies, obesity, and tobacco use [1-3].

Clozapine, an atypical antipsychotic used in treatment-resistant schizophrenia, has been increasingly associated with PEs [4-8]. PE has been found to be the most common medical cause of death during clozapine use and the second most common cause of death overall, following suicide [9,10]. Mortality rates of PEs as a clozapine-associated complication are estimated at 27–36% [10,11]. However, little is known about the characteristics or mechanisms of clozapine-associated PE. We present the case of a patient who developed recurrent adverse effects of clozapine, including a PE during a clozapine retrial. The patient provided verbal permission to share his case and efforts have been made to avoid identifiers to maintain patient confidentiality.

CASE

A 34-year-old African American male with treatment-refractory schizophrenia, homicidal behavior, cannabis and tobacco use, and obesity (body mass index of 34) was admitted to a state inpatient psychiatric facility for management of hallucinations and delusions that a "cyber gang" had implanted "pacemakers" in his body to cause him pain and control his mind. His family history was significant for schizophrenia in his mother and maternal aunt, as well as bipolar disorder in his sister. He had no

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known history of cardiovascular disease or thromboembolic events.

On admission, the patient began a treatment course of electroconvulsive therapy (ECT) in combination with clozapine therapy. This combination of treatments resulted in significant relief of psychotic symptoms. However, he soon developed myalgia and was found to have acute creatine kinase elevation (3,127 U/L). The patient was diagnosed with rhabdomyolysis. His symptoms and elevated creatine kinase resolved upon clozapine discontinuation and supportive care. However, he decompensated psychiatrically after cessation of clozapine, even despite continued ECT. Multiple trials of other antipsychotics, including risperidone, olanzapine, aripiprazole, and pimavanserin, led to only marginal improvement. Thus, clozapine was retried and cautiously titrated to 200 mg oral nightly. However, the patient's creatine kinase rose once again (maximum of 1,968 U/L), prompting taper of clozapine to 100 mg.

Approximately one month later, the patient subsequently developed chest pain that he attributed to "pacemakers." The pleuritic description of the pain and tachycardia prompted chest computed tomography angiography, which demonstrated an acute subsegmental PE. Hypercoagulability workup was negative, including protein C, protein S, factor II, factor IV, and homocysteine. Laboratory data revealed an elevated D-dimer at 2.75 μg/ml, erythrocyte sedimentation rate at 60 mm/hr, C-reactive protein at 93 mg/dl, and creatine kinase at 452 U/L. Electrogardiogram demonstrated sinus tachycardia and troponin level was not elevated. Absolute neutrophil count was measured at 4,400 /mm^3. Clozapine plasma level was 268 ng/ml. Given his negative hypercoagulability work-up and the temporal relation to clozapine re-trial, his PE was determined to most likely be secondary to clozapine.

The patient was treated appropriately for his PE with anticoagulation and made a full recovery without decline in his physical function. He underwent weekly maintenance treatment course of ECT in combination with cautiously continued clozapine therapy and experienced marked improvement in psychosis. He was discharged from the inpatient psychiatric facility after a three-month hospitalization.

DISCUSSION

While our case had several typical features of clozapine-associated PEs described in the literature, our case also has several atypical and novel features. Our case was typical in that 87% of reported clozapine-associated PE occurred within six months of drug initiation [11]. Furthermore, based on the current literature, most patients who experienced a clozapine-induced PE are male, with a mean age of 43.2 years, without risk factors for PE, and prescribed a mean clozapine dosage of 281.4 mg daily, with a variable duration spanning days to years [10]. Our case also demonstrates the dose-independent characteristic of clozapine-associated PE.

Our case was unusual in that the patient developed PE during a retrial and in the setting of a prior rare complication, specifically rhabdomyolysis. There is one report of thromboembolism and rhabdomyolysis occurring in a patient taking risperidone and mirtazapine [12]. To our knowledge, this is the first described case of a patient developing these two adverse effects associated with clozapine, though it is unclear if these conditions were related. Cloapine-associated rhabdomyolysis may be correlated with the development of clozapine-associated PE, possibly through shared risk factors or pathophysiological mechanisms. Future work is needed to clarify this. Our case is also unique as it is one of only a handful of reported cases that describes the continued use of clozapine following PE [1].

The specific pathogenesis of clozapine-associated PE has not been fully elucidated and is likely multifactorial [11]. Possible underlying mechanisms include platelet dysfunction [2,3,13], immunomodulatory and proinflammatory effects, and metabolic syndrome associated with antipsychotic drugs [14]. Because of clozapine's strong affinity for $5HT_{2a}$ receptors (at least 10 times stronger than for D2 receptors), $5HT_{2a}$-induced platelet aggregation leading to thromboembolism has also been hypothesized [6,15]. In addition, clozapine often leads to sedation as a side effect, which may contribute to immobility and venous stasis [10]. Our patient also underwent a treatment course of ECT prior to his PE, which could have also contributed to immobility and increased risk of PE. Although ECT may increase the risks of PE, this is a very rare side effect and the benefits of continuing ECT were felt to outweigh the risks given the patient's intractable psychosis

leading to homicidality. The only other identified risk factors for PE in our patient were obesity and a remote history of smoking.

Our case is important in that it reminds clinicians that, in addition to monitoring for more "classic" complications of clozapine such as agranulocytosis, prescribers should remain vigilant to detect atypical adverse effects when prescribing clozapine, especially in the medically ill and during re-trials. This case also demonstrates the importance of not dismissing somatic complaints in patients who are psychotic, as the patient's chest pain due to "pacemakers" could have easily been mistakenly overlooked.

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■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

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