**CLINICAL VIGNETTE**

# Malignant Catatonia Secondary to Clozapine Withdrawal: A Psychiatric Emergency

Jaye Anthony Estrada, MD, MPH and Kathleen Yip, MD

***Case***

A 46-year-old female with schizoaffective disorder and recent robotic renal cell carcinoma resection presented to the emergency department (ED) with passive suicidal ideation and increasing abdominal pain over the past day. Three days prior she had left partial nephrectomy for a left upper pole renal cell carcinoma. She had an uncomplicated initial postoperative course until the day of ED presentation.

On arrival, her vitals were 99.2°F, blood pressure of 144/85, heart rate 120 and respiratory rate of 27. She was alert and oriented to person, place, time and situation. Given her passive suicidal ideation, psychiatry was consulted while the patient was undergoing concurrent evaluation of abdominal pain. She had only mild tenderness to palpation at the site of the incision. On psychiatry's arrival they noted that the patient was altered and unresponsive with a Glasgow Coma Scale of 3, a heart rate of 130 and an increased respiratory rate in the 30s.

Resuscitation and a broad workup were initiated, including computed tomography imaging of the head, chest, abdomen and pelvis, which showed only a fluid collection at the site of the nephrectomy. While in the radiology suite, staff noticed that she suddenly became responsive and asked for water. She continued to be tachycardic to the 140s, hypertensive, tachypneic, and became febrile, prompting empiric antibiotics covering possible intra-abdominal infection and meningitis, while she underwent further evaluation and admission to the intensive care unit (ICU).

While in the ICU, the patient was noted to be saying words repetitively, laughing inappropriately to the situation, engaging in unusual postures, mutism and not responding to commands. Due to concern for catatonia, she received lorazepam, which caused significant improvement in her symptoms. Collateral information from her sister later revealed that the patient had stopped taking her chronic medications including clozapine three days before her surgery and had not resumed them after her surgery. She had no prior history of catatonia. Given this new information, the patient was restarted on clozapine. She rapidly reconstituted to her baseline mental status and her vitals normalized.

***Discussion***

*What is Catatonia?*

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), defines catatonia as a clinical presentation that is dominated by three or more of the following symptoms: stupor, catalepsy, waxy flexibility, mutism, negativism, posturing, mannerisms, stereotypy, agitation not influenced by external stimuli, grimacing, echolalia and echopraxia.[1] Immobility and mutism are the most common signs.[2] In catatonia, patients maintain full physical capacity despite their impaired movements. Though despite their full capacity, when this motor dysregulation occurs, movements are unable to be started or stopped which can lead to frozen postures or bizarre repetitive movements.

Catatonia can be subdivided into several forms, but is generally classified as retarded catatonia, excited catatonia and malignant catatonia. Retarded catatonia is what we classically view as catatonic and characterized by movement inhibition and mutism. Excited catatonia or "Bell's mania" is described as increased agitation, restlessness and repetitive stereotypic movements.[3] It can often be associated with delirium. Malignant catatonia is characterized by acute onset of fever, autonomic instability (i.e., hypo- or hypertension, tachycardia, tachypnea, diaphoresis) as well as typical symptoms of catatonia.[4] Elevation in creatine kinase and leukocytosis as well as low serum iron can also be seen.[5] Secondary complications from catatonia typically result from prolonged immobility which includes malnutrition, pressure ulcers, aspiration pneumonia and pulmonary emboli from deep vein thrombosis. Overall, mortality from malignant catatonia has been estimated from 10 to 20%.[6]

*Etiology and Pathophysiology of Catatonia*

Causes of malignant catatonia are wide-ranging, but can include psychiatric mood and psychotic disorders, neurologic disorders such as seizure and multiple sclerosis, infectious such as viral encephalitis and malaria, metabolic such as uremia, pharmacologic such as benzodiazepine withdrawal and toxin-mediated such as toxic epidermal necrolysis.[5,7] It is thought that 20% of catatonias are due to a medical cause.[5] With regards to psychiatric conditions, it is often misperceived that catatonia is tied closest to schizophrenia, but one study, reported nearly half of the patients admitted to a psychiatric ward for catatonia were due to mood disorders.[8]

The exact pathophysiology of malignant catatonia is unknown, though there have been several theories. Some center around the dopamine-GABA feedback loops in the mesostriatal-mesocorticolimbic systems and the hypothalamus.[9] One theory follows the restitutive hypothesis which states that the brain will self-regulate to prevent psychosis and restore homeostasis.[9] In psychosis, there is a hyperdopaminergic state in mesolimbic systems which will cause the brain to downregulate dopamine receptors in the mesolimbic area and elsewhere in the brain.[9] In particular, the mesostriatal system, which involves $GABA_A$ feedback from the nucleus accumbens through to the pars reticulata of the substantia nigra and the hypothalamic dopamine system, may also be downregulated. The nucleus accumbens has been connected to the initiation of motor activity. If this region becomes too hypodopaminergic while psychosis is continuing, this can lead to motor symptoms of catatonia.[4,9] Hyperthermia in malignant catatonia may be due to the role of dopamine in thermoregulation in the hypothalamus.[4] Dopamine has been shown to help reduce core body temperature, thus a hypodopaminergic state could help lead to excessive temperatures. Dysfunction with GABAergic transmission has been extrapolated due to the reversal of symptoms with benzodiazepines. Lorazepam has been effective in 60-80% of all patients with catatonia.[10]

*What is Clozapine-Withdrawal Malignant Catatonia?*

Clozapine was initially identified in 1959, but it was not until the late 1980s when studies showed its superior effect on both positive and negative symptoms of treatment-refractory schizophrenia as compared to chlorpromazine.[11,12] Clozapine has also been shown to reduce the risk of recurrent suicidal behaviors in patients with schizophrenia.[11]

Prescriptions in the United States are closely monitored through the Clozapine Risk Evaluation and Mitigation Strategy (REMS) program in which every patient is monitored and every prescriber must be registered.[13] The careful monitoring stems from 17 Finnish patients who developed agranulocytosis in the mid-1970s, eight of whom died.[12] Given the fear of agranulocytosis, patients must receive weekly CBC monitoring of absolute neutrophil counts for the first six months, every two weeks for the next six months, then every four weeks indefinitely. Besides agranulocytosis, myocarditis, venous thromboembolism, seizures and gastrointestinal hypomotility are other major, life-threatening adverse effects.[11]

Abrupt discontinuation of clozapine has been associated with increased anxiety, insomnia, motor restlessness or mute withdrawal, psychotic symptoms, tardive dyskinesia, altered consciousness, confusion, nausea and diaphoresis. Rapid withdrawal of clozapine symptoms has been attributed to "cholinergic overdrive" given its strong anticholinergic action.[14]

In addition to these cholinergic overdrive symptoms, clozapine withdrawal has also been associated with withdrawal catatonia. Like benzodiazepines, clozapine has been associated with increased GABA activity. Clozapine has been shown to increase GABA levels through effects on receptors located on GABA interneurons as well as act as an agonist at $GABA_B$ receptors. GABA receptor downregulation is thought to occur with long-term clozapine use. If clozapine is abruptly discontinued, a state of GABA hypoactivity resulting in a catatonic episode can occur.[15] Given the unique receptor profile of clozapine, it is not surprising that clozapine was the only antipsychotic reported to cause withdrawal catatonia within a 2-week period following discontinuation, with most occurring within seven days.[15] Autonomic symptoms were present in at least half of the cases.

*Treatment*

There is no consensus or concrete guidelines for the treatment of malignant catatonia. Generally, intravenous lorazepam is recommended and if/when patients do not respond, then electroconvulsive therapy (ECT) should be considered.[16] In the unique situation of malignant catatonia secondary to clozapine withdrawal, it is recommended that clozapine be restarted as soon as possible. Even with the re-initiation of clozapine or ECT, response time in one study ranged from two days to several months.[15]

***Summary***

The patient in our case exhibited multiple signs of malignant catatonia secondary to clozapine withdrawal including the onset of her symptoms within 5-6 days after the abrupt discontinuation of medication, autonomic dysregulation with fever, hypertension and tachycardia, stupor, mutism and echolalia. The patient's rapid improvement with lorazepam and clozapine re-initiation confirmed the diagnosis.

Clozapine withdrawal catatonia has been shown to respond favorably to re-initiation of clozapine in addition to the use of benzodiazepines and ECT. This case highlights the consequences of abruptly stopping clozapine. Clinicians should urge patients to maintain daily compliance due to the high morbidity and mortality of malignant catatonia and discuss with a psychiatrist should a patient need to stop this medication for any reason.

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