

Neuroleptic malignant syndrome induced by extended-release injectable aripiprazole: A case report

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SUMMARY

Neuroleptic malignant syndrome is a rare but potentially fatal condition associated with the use of medications that affect the central dopaminergic system. It is characterized by symptoms such as hyperthermia, muscular rigidity, confusion, and autonomic instability. This case report presents a female patient diagnosed with schizophrenia who was initially treated with zuclopenthixol depot but could not tolerate its side effects. Therefore, her treatment was switched to long-acting injectable aripiprazole. Fifteen days after the administration of long-acting injectable aripiprazole, she presented to the emergency department with classic symptoms of neuroleptic malignant syndrome including fever, muscular rigidity, altered consciousness, hypertension, and hypersalivation. The clinical course of the case is described, and the findings are discussed in light of the existing literature.

Key words: Neuroleptic malignant syndrome, Aripiprazole, Extended-release injection, Antipsychotic drugs

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a rare but life-threatening condition, typically associated with the use of medications that affect central dopaminergic neurotransmission (1). The majority of NMS cases are linked to antipsychotic drugs; however, it has also been reported in association with other medications such as lithium, antidepressants, and metoclopramide (2). According to various reports, NMS develops in approximately 0.02% to 3% of patients exposed to an antipsychotic agent (3).

The risk of NMS has been reported to be higher with typical antipsychotic drugs, particularly those with high potency. Atypical antipsychotics are considered less likely to induce NMS due to their relatively lower dopamine D2 receptor blockade. This also applies to aripiprazole, which is a partial D2 agonist and thus does not exert full blockade effects (4). However, it has been noted that more case data are needed to accurately determine the true incidence of NMS associated with atypical

antipsychotics (5). There are very few reported cases in the literature concerning NMS associated with the long-acting injectable (LAI) form of aripiprazole (6,7). As publications related to NMS cases associated with long-acting atypical antipsychotics increase, the resulting data will contribute to a more accurate clinical approach for this patient population. This report aims to contribute to the literature by presenting a case of NMS associated with the use of the long-acting form of the atypical antipsychotic aripiprazole.

CASE

A 62-year-old female patient was reported to have been under follow-up with a diagnosis of schizophrenia. She presented to the emergency department of our hospital with symptoms including fever, altered mental status, tremors, hypersalivation, and palpitations. On physical examination, she was unresponsive to verbal stimuli, exhibited rigidity particularly in the upper extremities, and showed coarse tremors in the distal parts of the extremities. Her body temperature was recorded at

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39.6 °C, blood pressure at 145/95 mm Hg, and heart rate at 145 bpm. Laboratory investigations revealed a leukocyte count of 11,490/mm³ (reference range: 4,000–10,000), neutrophil count of 9,640/mm³ (reference range: 2,000–8,000), CK level of 3,120 U/L (reference range: 0–175), aspartate aminotransferase (AST) level of 81 U/L (reference range: 13–40), and alanine aminotransferase (ALT) level of 45 U/L (reference range: 10–45). Although the patient had no prior history of renal failure, her blood urea nitrogen was 64 mg/dL (reference range: 20–50) and creatinine was 1.4 mg/dL (reference range: 0.5–1.1). Cranial computed tomography (CT) revealed no signal changes in the cerebral or cerebellar parenchyma that would suggest acute or subacute ischemia or infarction. Thoracic CT showed a consolidated area in the right lung associated with minimal inflammation.

The patient had a history of schizophrenia for approximately 20 years, with four prior hospitalizations, the most recent of which occurred about five years ago due to non-adherence to treatment. She had previously used oral forms of antipsychotics such as aripiprazole, paliperidone, olanzapine, and haloperidol. For the past year, she had been receiving intramuscular zuclopenthixol decanoate at a dose of 200 mg every two weeks. It was reported that her medication had been changed approximately 15 days earlier due to side effects such as emotional blunting, apathy, and rigidity in the extremities, and that she had been administered 400 mg of long-acting injectable aripiprazole. It was reported that the oral form of aripiprazole was not reintroduced, as the patient had previously used and tolerated it. It was reported that for approximately two days prior to admission, she had experienced loss of appetite, difficulty walking, and somnolence. With the onset of fever and altered consciousness, she presented to the emergency department. In the emergency department, she was evaluated by psychiatry, neurology, and anesthesiology and reanimation specialists. A diagnosis of NMS induced by aripiprazole LAI was primarily considered. It was decided to monitor the patient in the intensive care unit (ICU).

The patient was followed in the ICU for 7 days, during which she received supportive care inclu-

Table 1. Changes in the patient's laboratory parameters

	Reference range	Emergency department	Intensive care day 3	Intensive care day 7
White blood cell count (mm ³)	4000-10000	11490	6140	7500
Neutrophile count (mm ³)	2000-8000	9640	4950	5200
Creatinine kinase (U/L)	0-175	3120	788	153
Aspartate aminotransferase (IU/L)	13-40	81	46	40
Alanine aminotransferase (IU/L)	10-45	45	45	43
Urea (mg/dl)	20-50	64	43	36
Creatinine (mg/dl)	0.5-1.1	1.4	0.4	0.5

ding bromocriptine at a dose of 10 mg/day. Her symptoms gradually subsided. She was subsequently transferred to the neurology ward, where she was monitored for an additional 5 days. Her level of consciousness returned, and although limb rigidity had improved, it persisted to some extent. Laboratory parameters gradually approached normal ranges (Table 1). CSF analysis did not reveal any findings suggestive of infection or systemic disease.

At a follow-up visit approximately one month after discharge, the patient's rigidity had resolved, and her general condition was stable. Paliperidone was initiated at 3 mg/day, as she had previously used it without adverse effects. The dose was increased to 6 mg/day after 15 days. Her positive psychotic symptoms were under control, and apathy and emotional blunting had partially improved. Her CK level, measured one month after discharge, was 151 U/L. The patient has been maintained on paliperidone monotherapy at 6 mg/day for approximately one year and remains in remission.

DISCUSSION

In this case report, we present a case of NMS that developed following a switch from zuclopenthixol, a typical depot antipsychotic, to aripiprazole LAI. Regardless of the dose and route of administration, every antipsychotic drug has the potential to induce NMS. However, it has been suggested that the type of antipsychotic used, along with certain individual or environmental risk factors, may predispose individuals to the development of NMS. Factors such as high-dose antipsychotic use, rapid dose escalation, intravenous administration, and polypharma-

cy have been reported to increase the risk of NMS (8).

In this case, the initiation of long-acting aripiprazole only 15 days after discontinuation of depot zuclopenthixol may have resulted in a clinically relevant pharmacodynamic interaction. Given the long elimination half-life of zuclopenthixol (approximately 19 days), plasma concentrations may still have been present at meaningful levels, thereby modifying the impact of aripiprazole's partial agonist properties (9). The prior exposure to depot zuclopenthixol, a potent D2 receptor antagonist, could have led to receptor supersensitivity. Under such conditions, the partial agonist activity of aripiprazole may provide insufficient dopaminergic stimulation, paradoxically resulting in impaired dopaminergic signaling. Owing to its submaximal intrinsic activity, aripiprazole may be unable to adequately activate hypersensitive receptors and, in this context, may functionally act as a dopamine antagonist. This interpretation aligns with the dopaminergic hypofunction hypothesis in the pathogenesis of NMS (10). Accordingly, this case underscores the importance of carefully planning antipsychotic switching strategies, taking into account drug half-lives and pharmacodynamic properties.

Long-acting injectable antipsychotics (LAI-APs) are a valuable option for maintenance treatment of schizophrenia due to their effectiveness in preventing relapse (11). Nevertheless, LAI-APs remain underutilized in many countries due to various concerns, including pain, needle phobia, and cost (12). Additionally, there are concerns that LAI-APs may be associated with serious adverse effects such as NMS, tardive dyskinesia, and cardiovascular events, and may lead to longer-lasting symptoms compared to oral antipsychotics (OAPs) (11,13). This may be attributed to the relatively higher doses used in LAI-APs and their slower elimination from the body compared to OAPs.

Whether LAI-APs are associated with a higher risk of NMS compared to OAPs remains a matter of debate. A case-control study utilizing healthcare records identified LAIs as a potential risk factor for NMS (14). Another case-control study using elec-

tronic health record data found that the risk varied depending on the type of LAI used (15). Studies based on adverse event reporting databases have suggested that LAI use does not increase the risk of NMS (16,17). In Japan, a study using data from a spontaneous adverse event reporting database reported fewer cases of NMS among patients using LAI aripiprazole and LAI paliperidone compared to those using their oral equivalents (11). The risk of NMS associated specifically with LAI-SGAs remains unclear, as there are very few reports exploring the association between NMS and these newer agents compared to LAI first-generation antipsychotics (LAI-FGAs). Therefore, additional case reports and systematic reviews are needed to better understand the relationship between LAI-SGAs and NMS.

NMS has been reported to occur relatively early in the course of both LAI and oral SGA antipsychotic treatment (11). In a study from Japan using data from a spontaneous adverse event reporting system, NMS symptoms were found to emerge approximately three weeks after the administration of LAI aripiprazole (11). In previous case reports of aripiprazole LAI-induced NMS, symptoms were reported to develop on day 30 in one case and on day 40 in another (18,19). In a case characterized by malignant CK elevation and subclinical NMS symptoms, onset occurred three days following LAI aripiprazole administration (6). In our case, symptoms began on day 15, which partially overlaps with the timeframes reported in previous case studies.

Since NMS tends to occur during the relatively early phases of antipsychotic treatment, tolerability assessment becomes particularly important to prevent NMS associated with LAI antipsychotics. In our case, it was learned that oral aripiprazole was not reinitiated because the patient had previously tolerated it. However, it remains unclear how long the patient had taken oral aripiprazole and whether it was used consistently. When treatment with LAI-SGAs is planned, tolerability should be assessed with oral SGAs for more than one month, and careful monitoring for the emergence of NMS, especially during the early phase of LAI-AP administration is recommended (11).

The biological basis of NMS remains unknown. Antipsychotic drugs exert their effects through dopamine D2 receptor blockade, and this blockade has been proposed to play a role in the pathophysiology of the syndrome (3). Furthermore, the potential cytotoxicity and genotoxicity of aripiprazole have been studied in MKN45 and NIH3T3 cells, which are related to cancer cell lines. Aripiprazole was identified as a potentially potent cytotoxic agent (20). Therefore, it is not surprising that aripiprazole may lead to elevated CK levels due to cellular breakdown (6). These findings appear to have some relevance to the pathogenesis of neuroleptic malignant syndrome, although they have not yet been thoroughly investigated.

Advanced age, comorbid medical conditions, psychological or physical stress, prolonged exposure to high temperatures, dehydration, and electrolyte imbalances have been proposed as contributing factors to the development of NMS (8). Upon the patient's initial presentation to the emergency department, elevated levels of urea and creatinine were noted. Muscle rigidity and rhabdomyolysis observed in NMS lead to the release of myoglobin from muscle cells. Myoglobin exerts toxic effects on renal tubules, potentially resulting in acute kidney injury. In our case, the markedly elevated CK level (3,120 U/L) supports this mechanism. In addition, the patient's insufficient fluid intake and possible dehydration may have impaired renal perfusion, contributing both to transient elevations in renal function tests and to increased susceptibility to NMS. Dehydration and electrolyte imbalances are recognized risk factors for NMS. During intensive care follow-up, renal function tests rapidly normalized with appropriate fluid therapy, indicating that the renal impairment was not permanent and was most likely secondary to rhabdomyolysis and/or dehydration.

The clinical course of NMS is heterogeneous. There are four primary symptom clusters associated with NMS: hyperthermia, muscular rigidity, altered mental status, and autonomic instability (1,8). However, in the early stages of NMS, muscular rigidity may not be sufficiently developed, and CK levels can remain within normal limits (1,8). It has been reported that cases associated with atypical antipsychotics may present atypically, potential-

ly leading to missed diagnoses in the absence of classic features (1). Nevertheless, despite receiving an atypical antipsychotic, our patient exhibited symptoms from all four major clusters, and her CK level was markedly elevated. These findings are consistent with the Levenson criteria and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic standards (21,22). Differential diagnoses were systematically evaluated. First, infectious causes presenting with fever and altered mental status (pneumonia, sepsis, meningitis, encephalitis) were investigated and ruled out. Cranial CT revealed no evidence of acute or subacute ischemia or hemorrhage, and magnetic resonance imaging was deemed unnecessary. Cerebrospinal fluid analysis was normal, showing no cell elevation or protein/glucose imbalance indicative of infection. Blood cultures were negative. Although chest CT demonstrated a minimal consolidation area in the right lung, this finding was not sufficient to account for the patient's clinical presentation (rigidity, marked elevation of creatine kinase). Moreover, C-reactive protein and procalcitonin levels were mildly to moderately elevated, but not at levels consistent with sepsis or severe pneumonia.

Metabolic disorders and withdrawal syndromes were also considered; however, electrolyte values, thyroid function tests, and blood glucose levels were all within normal ranges. Malignant hyperthermia was excluded based on clinical history and the absence of relevant pharmacologic triggers. In light of these data, given the temporal relationship with antipsychotic administration, the presence of typical NMS features, and the exclusion of alternative diagnoses through laboratory and imaging studies, a diagnosis of NMS was established in this case.

Mortality rates associated with neuroleptic malignant syndrome (NMS) have reportedly declined over the years (23). However, despite appropriate treatment, a mortality rate of approximately 10% still persists (1). In a study utilizing data from a spontaneous adverse event reporting database in Japan, it was reported that 34 out of 260 NMS cases linked to oral aripiprazole use (13.1%) resulted in death (11). In contrast, no fatalities were reported among 15 cases associated with aripiprazole LAI

use in the same study. Nonetheless, another case report described a 40-year-old female patient who had been receiving aripiprazole LAI and presented without early rigidity. In that case, a delayed diagnosis was followed by a rapid deterioration involving acute renal failure, cardiovascular instability, and malignant arrhythmia, ultimately resulting in death (19). Known risk factors for NMS-related mortality include advanced age, infections, respiratory failure, renal failure, and cardiac failure (1). In our case, the patient's symptoms were typical of NMS, which facilitated early diagnosis and prompt initiation of treatment in the ICU. Renal function normalized rapidly, cardiac function remained preserved, and symptoms regressed significantly with supportive therapy.

NMS is reported to be twice as common in males compared to females. While it can affect individuals of all ages, the risk is considered higher among males under 40 years of age (1). Our patient, by contrast, was a relatively older woman. Despite her age, gender, and the use of antipsychotic was “atypical”, the clinical presentation was “typical” for NMS. In conclusion, it should be emphasized that NMS can occur at any age and in association with any antipsychotic medication.

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