CHEST

A Woman in Her 60s With Fever and Altered Mental Status in a Psychiatric Hospital

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A woman in her 60s with a history of hepatitis C with cirrhosis and major depressive disorder with psychotic features was admitted to the inpatient psychiatric unit for suicidal ideation. She was initially treated with a combination of sertraline and paliperidone. The paliperidone was subsequently changed to risperidone and ultimately to olanzapine. She developed worsening mental status and was then treated for catatonia with benzodiazepines. Over 2 days, her mental status continued to worsen and she developed fever and tachycardia. She was transferred to the ICU and endotracheally intubated for inability to protect her airway. She was started on lactulose via orogastric tube but showed no improvement in her mental status after 2 days despite having two or three bowel movements per day. CHEST 2016; 150(6):e171-e174

Physical Examination Findings

Vital signs were as follows: temperature, 38.1°C; pulse, 125 beats/min; BP, 155/80 mm Hg; respiratory rate, 24 breaths/min; oxygen saturation, 100% while on volume control at 6 cm^3/kg; fraction of inspired oxygen, 0.4; and positive end-expiratory pressure, 5. She opened her eyes in response to sound but did not follow commands and did not require sedation to tolerate an endotracheal tube. Her pupils were sluggishly reactive and her sclera were icteric. Her chest had symmetric expansion with inspiration and was clear to auscultation throughout. Her cardiac examination results were normal. She had no abdominal distention or evidence of ascites. Her liver was not palpable and there were no facial grimacing in response to palpation. All extremities were rigid and without clonus. Hyporeflexia was present throughout.

Laboratory Findings

A complete blood count produced normal results except for a hemoglobin concentration of 10.8 g/dL. The results of a comprehensive metabolic panel were normal except for a bicarbonate level of 18 mM and an albumin level of 2.7 g/dL. The serum ammonia level was 94 μM. Urinalysis results were normal, and a chest radiograph demonstrated appropriate placement of the endotracheal and orogastric tubes and no other abnormalities. Creatine kinase peaked at 348 International Units/L (upper limit of normal, 240 International Units/L). Cerebrospinal fluid analysis revealed a hemorrhagic tap with 36,026 RBCs/μL, 22 WBCs/μL, protein at 84 g/dL, and glucose at 93 g/dL. Extensive microbiologic studies of the cerebrospinal fluid, serum, and respiratory secretions produced negative results. Brain magnetic resonance imaging with angiography indicated no pathology, including encephalitis or hemorrhage, and an EEG was consistent only with encephalopathy.

What is the diagnosis?

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Diagnosis: Neuroleptic malignant syndrome

Discussion

Neuroleptic malignant syndrome (NMS) is a potentially lethal condition that can go unrecognized in the ICU. Its features can be variable and include altered mental status, fever, and autonomic instability, which are also present in many conditions commonly encountered in the ICU. Although the syndrome's early association with first-generation antipsychotic medication use gave rise to its name, observational studies have since demonstrated that NMS is associated with additional classes of medications (Table 1). These include second-generation, or "atypical," antipsychotics, antiemetics, and even the cessation of dopaminergic agents used in the treatment of Parkinson's disease. The common feature linking each of these medications to NMS is a reduction in dopaminergic signaling, suggesting a potential key mechanistic feature of NMS. This is further substantiated by the observation that a "loss of function" allele of the dopamine D_2 receptor gene is more common in patients with NMS than in those who do not develop the syndrome. Thus, early recognition of NMS and prompt avoidance of risk factors is an important component of effective management.

Previous estimates suggest that NMS occurs in one of every 10,000 patients treated with antipsychotic medications, although misdiagnosis may underestimate the true incidence rate. An increase in the number of available antipsychotic medications combined with a rapid rise in their off-label indications has resulted in a dramatic increase in their use since the mid-1990s. Indeed, more than 50 million prescriptions for atypical antipsychotic medications were issued in the United States in 2011 alone. This pattern of use is particularly evident in ICUs as physicians have recently increased the focus on the negative consequences of delirium, including increased mortality and long-term cognitive effects. As such, while there is little evidence indicating that antipsychotics improve patient outcomes in delirium, survey data suggest that 40% of ICU physicians prescribe typical and 10% prescribe atypical antipsychotics for sedation. Thus, critically ill patients are frequently exposed to antipsychotics and commonly have conditions whose symptoms may mask NMS, potentially leading to underrecognition.

TABLE 1] Medications Associated With NMS

Medication Class	Examples
Typical/first-generation antipsychotics	Haloperidol Fluphenazine Perphenazine Chlorpromazine Thioridazine
Atypical/second-generation antipsychotics	Olanzapine Ziprasidone Risperidone Clozapine Quetiapine Aripiprazole Paliperidone
Antiemetics	Metoclopramide Promethazine Prochlorperazine Droperidol
Dopaminergic agents (cessation associated with NMS)	Levodopa

NMS = neuroleptic malignant syndrome.

The older definition of NMS as described in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) was based on strict diagnostic criteria. Specifically, it required that a patient exhibit rigidity and hyperthermia in the setting of antipsychotic use *and* two or more minor features including the following: dysautonomia, evidence of muscle injury, tremor, and changes in the level of consciousness, among others. No alternative explanation could be present for these features. However, as our understanding of NMS has improved, it is recognized that NMS can be present with a variety of combinations of these signs or symptoms. Conversely, isolated hyperthermia, rigidity, or dysautonomia has also been described with antipsychotic medication use but does not always progress to NMS. Therefore, the definition of NMS in the more recent edition of the DSM (DSM-V) has been changed and now allows the diagnosis to be made with any combination of these classic signs or symptoms if they occur during exposure to medications with known associations with NMS and have no alternative medical or psychiatric cause (Table 2).

When assessing a patient with fever and/or encephalopathy in the ICU, it is important to keep NMS high on the list of possible diagnoses and to investigate for additional signs to confirm this diagnosis. Although not completely specific, generalized rigidity is present in more than 80% of patients with NMS and is an uncommon finding in other conditions treated in the ICU. Its presence can narrow the differential diagnosis to a few possibilities including CNS infection, malignant hyperthermia, cocaine intoxication, malignant catatonia, intrathecal baclofen withdrawal, and serotonin syndrome. Because of frequent concomitant use of