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Case Report

Acute pulmonary embolism in a patient with neuroleptic malignant syndrome

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ABSTRACT

Neuroleptic malignant syndrome (NMS) is a life-threatening complication seen in psychiatric patients exposed to antipsychotic medications. NMS is associated with medication with dopamine antagonist action. The typical tetrad of symptoms of NMS includes fever, muscle rigidity, altered mental status and autonomic dysfunction. Acute pulmonary embolism is one of the major complications seen in patients diagnosed with neuroleptic malignant symptoms. Here we present a case report of a 64 years old female with a history of psychiatric illness, presented with fever, rigidity and altered mental status and diagnosed to have NMS. Later her condition was complicated by pulmonary embolism. She was treated with bromocriptine and heparin infusion and improved symptomatically.

Keywords: NMS, Antipsychotics, Acute pulmonary embolism

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a life-threatening adverse reaction to neuroleptic drugs. It is characterized by fever, altered mental status, muscle rigidity, and autonomic dysfunction.[1] It has been associated with virtually all neuroleptics, including newer atypical antipsychotics, as well as a variety of other medications that affect central dopaminergic neurotransmission.[2] Psychiatric patients taking conventional antipsychotic drugs or clozapine, under physical restraint or suffering from severe catatonia or NMS seem to have an increased risk to develop deep venous thrombosis and pulmonary embolism which are potentially life-threatening events.[3]

We present a 64 years old female diagnosed with NMS, later complicated by pulmonary embolism.

CASE REPORT

A 64 years old female with history of psychiatric illness for 20 years on regular psychiatric medications was admitted to the hospital with altered mental status in form of drowsiness, disorientation and difficulty in walking of 3 weeks duration. On examination she had temperature of 99^0F, tachycardia (pulse rate: 102/min), blood pressure was 140/80 mmHg, respiratory rate was 22/min and oxygen saturation were 98% in room air. She also had rigidity of all 4 limbs. The rest of the systemic examination was normal. She has a past medication history of quetiapine 50 mg daily, risperidone 8mg daily and haloperidol 20 mg daily for 1 year.

She had haemoglobin of 10.9 g/dL, white blood count 12700, platelet 303000, CRP:65.5. Serum sodium was 132 and potassium was 3.6. Serum creatinine was 1.72 and blood urea was 48. SGOT was 186 and SGPT was 66. Serum bilirubin, total protein, serum albumin and alkaline phosphatase were normal. Her creatinine phosphokinase was 7617. Her TSH was 1.71, anti-TPO-47 U/mL, vitamin B12>200 pg/mL and reticulocyte count were 0.70. ANA was 7 AU/mL, P-ANCA: 2.07 U/mL, C-ANCA: 0.92 U/mL, Anti-ds DNA antibody: 9.08 IU/mL and procalcitonin was 0.51 ng/mL. Direct coomb test was weakly positive. MRI brain showed age related chronic ischemic changes and age related cerebral and cerebellar

parenchymal atrophy. EEG showed Dys-III triphasic waves. Ultrasonography abdomen showed mild hepatomegaly with fatty infiltration.

In view of fever, muscle rigidity, altered sensorium, past history of neuroleptic medications and elevated creatine phosphokinase values, the case fits to the criteria of NMS. So, the medications like quetiapine, risperidone and haloperidol were discontinued immediately. She was started on Bromocriptine 2.5 mg thrice daily and dose was increased to 5 mg thrice daily later. The urine analysis showed growth of E. coli. She was started on IV Amoxicillin and clavulanic acid, then escalated to IV Meropenem according to sensitivity. She was also treated with IV fluids and other supportive treatments.

On third day, she was oriented, communicating normally. Fourth day, she developed chest pain, tachypnea and desaturation (SPO_2:91%). Her blood pressure was normal. Chest X-ray and arterial blood gas analysis shows pH:7.46, pCO_2:30.6 mmHg, pO_2:61 mmHg and $cHCO_3$:21.2 mmol/L. ECHO showed old inferior wall Myocardial infarction and normal RV and LV systolic function with ejection fraction of 61%. D-dimer was requested and it was 1.13 mg/dL. CT pulmonary angiogram showed right pulmonary artery partial thrombosis (Figure 1).

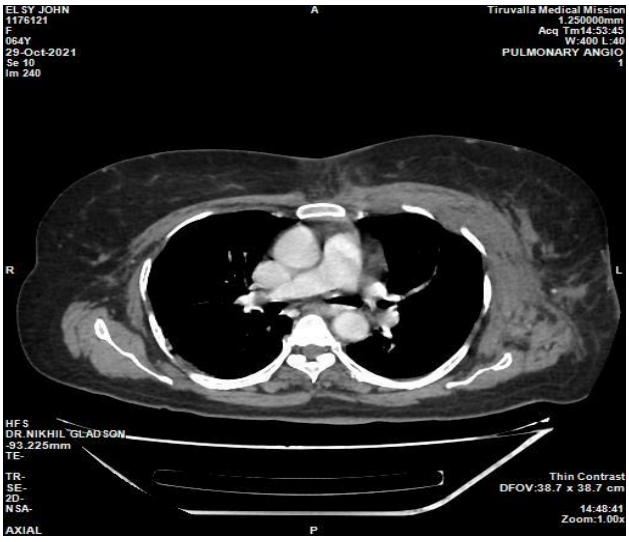

Figure 1: CT pulmonary angiogram of right pulmonary artery partial thrombosis.

She was started on heparin infusion. After 1-week, oral anticoagulation (Rivaroxaban) was started. After 2 weeks of admission, her vital became stable, CPK level return to normal and acute kidney injury resolved. She was discharged from hospital without any further complications.

DISCUSSION

NMS is a rare and fatal complication of neuroleptic drugs. It has classically been characterized by the presence of triad of fever, muscle rigidity and altered mental status and common laboratory findings of NMS include elevated creatine kinase level and leukocytosis.[1]

Once symptoms appear, progression can be rapid and can reach peak intensity in as little as 3 days. Muscle rigidity is the most frequently described motor sign. Other additional extrapyramidal motor findings have been reported including tremor, chorea, akinesia, and dystonic movements including opisthotonus, trismus, blepharospasm, and oculogyric crisis. Other symptoms that have been associated with NMS include dysphagia, dyspnoea, abnormal reflexes, mutism, and seizures.[2] The presentation may be heterogeneous and this is reflected in the current DSM IV criteria (Table 1).[1,2]

Table 1: DSM-IV criteria.

S. no	Diagnostic and statistical manual of mental disorders (Fourth edition (DSM-IV)) research criteria for NMS
A	**Development of severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication.**
B	**Two (or more) of the following:**
	Diaphoresis
	Dysphagia
	Tremor
	Incontinence
	Changes in level of consciousness ranging from confusion to coma.
	Mutism
	Tachycardia
	Elevated or labile blood pressure
	Leukocytosis
	Laboratory evidence of muscle injury (e.g., elevated creatinine phosphokinase)
C	**The symptoms in criteria A and B are due to another substance or a neurological or other general medical condition.**
D	**The symptoms in criteria A and B are not better accounted for by a mental disorder.**

The exact pathophysiology of NMS is unknown. It has been suggested that marked and sudden reduction in central dopaminergic activity resulting from D2 receptor blockade within the nigrostriatal, hypothalamic, mesolimbic and mesocortical pathways. Dopamine's normal role of central thermoregulation is interfered by dopaminergic receptor antagonism of neuroleptics. Heat is produced from serotonin stimulation in the hypothalamus, and dopamine inhibits this process. Dopaminergic blockade therefore leads to less inhibition of serotonin stimulation and contributes to the hyperthermia seen in NMS.[1]

All classes of D2 dopamine receptor antagonists have been associated with NMS. This Includes not only typical and atypical neuroleptics used in the treatment of psychosis, but also neuroleptic drugs such as prochlorperazine,

droperidol, and promethazine, used as antiemetics, anesthetics, and sedatives. Haloperidol has been implicated in nearly half of the reported cases and is the sole precipitating agent in a significant number of cases.[4]

Complications of NMS may include myoglobinuric renal failure, cardiac and respiratory failure, aspiration pneumonia, pulmonary embolism, disseminated intravascular coagulation, and persistent long term cognitive sequelae caused by hypoxia and prolonged hyperthermia.[5]

Majority of patients with acute pulmonary embolism presented with dyspnoea, tachycardia, hypoxia, pleuritic chest pain, syncope or hypotension. In case of massive pulmonary embolism hypotension or shock would be the major symptoms, which usually results from right heart failure. In less severe cases, patients are often hemodynamically stable. But signs of right heart strain, dysfunction or myocardial injury can be seen on echocardiogram or by laboratory biomarkers. CT pulmonary angiography is considered the gold standard of diagnosis for acute pulmonary embolism.[6]

Antipsychotic medications are a known risk for venous thromboembolism (VTE). Immobilization, surgery, leg fracture, pregnancy and cancers are well known risk factors of venous thromboembolism. Immobilization and physical restraint were the most provoking factors for the VTE in a patient using antipsychotic medications.[7]

Several underlying mechanisms have been proposed to explain the association between antipsychotic drugs and VTE. Sedation induced by antipsychotic drugs can increase venous stasis. Hypercoagulability via an enhanced aggregation of platelets with conventional antipsychotics or via hyperprolactinemia in an indirect pathway are also the possible causes. Another hypothesis is the increased levels of lupus anticoagulant and anticardiolipin antibodies induced by conventional antipsychotic agents and clozapine.[3] Dehydration, fever and rhabdomyolysis can each lead to a systemic hypercoagulable state and altered mental status. NMS is associated with high mortality rate due to these cardiovascular, respiratory and renal complications.[8]

As far as concern about the management of NMS, the causative agent must be withdrawn immediately. Hydration, serial monitoring and correction of electrolyte abnormalities, initiation of cooling measures and several dopaminergic drugs, including bromocriptine and amantadine can be reverse symptoms in NMS. Dantrolene, a muscle relaxant agent is also useful in the treatment of hypothermia and rigidity seen in NMS.[9]

As acute pulmonary embolism (PE) is a significant cause of death among hospitalized patients with risk factors, early diagnosis and treatment are necessary to prevent complications. Cardiopulmonary support should be initiated first via oxygen supplementation and inotropic support if needed. Anticoagulation should be initiated as soon as pulmonary embolism is diagnosed unless the patient has a strong contraindication. Pulmonary artery reperfusion is the next target of treatment. Systemic thrombolysis is indicated for high-risk Pulmonary embolism (PE) with hemodynamic instability. If thrombolysis is contraindicated, surgical embolectomy should be considered. Intermediate risk patient with elevated lab values and have evidence of right ventricular dysfunction on CT or echocardiography can be considered for thrombolysis /reperfusion. Patient with intermediate-low risk PE should usually be admitted to hospital for short period for anticoagulation treatment.[6,10]

CONCLUSION

NMS is a life-threatening condition seen in patients with psychiatric illness. It is a rare adverse reaction seen in patients using antipsychotic medication with dopamine antagonistic action.

Acute pulmonary embolism is a highly morbid condition, which enhances the mortality rate of patients with NMS. The main risk factor for pulmonary embolism in these patients is immobility. In a patient with NMS, it can either due to direct sedative effect of antipsychotics or due to the state of hypercoagulability seen in NMS. In acute pulmonary embolism without hemodynamic instability anticoagulation only is enough to prevent complications.

The causes of pulmonary embolism in NMS are multifactorial-fever, dehydration, restricted mobility and psychiatric illness.

It needs further studies and research to confirm causes of acute pulmonary embolism in patients with NMS.

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