

CASE REPORT

Haloperidol-related neutropenia

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ABSTRACT

Phenothiazines like antipsychotics have been known to cause neutropenia, but this has been reported very rarely with haloperidol. A 20-year-old male patient admitted to emergency service (emergency room) with shortness of breath, chest pain, and anger. He was diagnosed with pneumonia and prescribed moxifloxacin. After 2 days with antibiotic, he readmitted. Left lung pneumothorax was detected, and thorax computerized tomography was requested. However, he opposed and beaten one of the hospital officials. The diagnosis of manic episode due to antibiotic moxifloxacin was considered. The tube thoracostomy had to be done, and antibiotic therapy was stopped. Haloperidol 10 mg/day and biperiden 4 mg/day injections were administered because he continued to resist medical interventions. After haloperidol, his leukocyte count decreased. He responded well to filgrastim (Neupogen) and blood transfusions, so a drug-related cause of neutropenia has been suspected. He was switched from haloperidol to quetiapine 300 mg twice a day. His white blood cell count returned to normal levels.

Key words: Agranulocytosis, antipsychotic, haloperidol, neutropenia

INTRODUCTION

Antipsychotics, mood stabilizers, antidepressants, benzodiazepines, barbiturates, hypnotics, antithyroid drugs some antibiotics and nonsteroidal anti-inflammatory drugs have been reported to cause agranulocytosis and neutropenia. Phenothiazines like antipsychotics and its derivatives have been known to cause neutropenia, but this side effect has been reported very rarely with haloperidol.^[1,2] Following is a newly diagnosed patient with bipolar affective disorder who later developed neutropenia which has thought to be related to haloperidol and afterward his continuation therapy with quetiapine.

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CASE REPORT


A 20-year-old male, single, Caucasian patient admitted to an emergency room (ER) with shortness of breath, chest pain, and anger. We could not get the information about physical examination and laboratory workup done in that emergency service. He was diagnosed with pneumonia and prescribed moxifloxacin.

After 2 days with antibiotic therapy, the patient complained of difficulty in breathing and readmitted at September 28, 2017. He had respiratory tachypnea, and his vital signs were as follows: oxygen saturation: 92%, blood pressure: 140/70 mmHg, and pulse: 130/min. On physical examination, no breathing sounds could be heard on the left lung with auscultation. He had uncontrolled fast speech and aggressive behaviors. In the first whole blood count we could reach, the white blood cell (WBC) count was 6900 and the neutrophil count was 2710.

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Left lung pneumothorax was detected on chest X-ray, and thorax computerized tomography (CT) was requested for detailed evaluation. However, he opposed and beaten one of the hospital officials, so the patient was referred to a mental health hospital.

The patient had never consulted to a psychiatrist before. There was no physical disease or psychiatric disorder mentioned in the patient's family history. He was a real estate agent, living with his mother and father. He was smoking but did not have any alcohol or substance abuse. In his psychiatric evaluation in the mental health hospital, the diagnosis of manic episode due to antibiotic moxifloxacin was considered and olanzapine was recommended. For the treatment of pneumothorax and psychiatric disorder together, he was transferred to our general hospital and has never used olanzapine.

He was hospitalized in thoracic surgery inpatient clinic. The tube thoracostomy had to be done, but it could not be performed because of aggressive behaviors due to mania. Although local anesthesia was preferred, he could only let this procedure with deep sedation in the operating room. Postoperative chest X-ray showed that the left lung was expansive, and there was 400-cc drainage from the chest tube with minimal air leak. The pleural fluid culture was negative. His purified protein derivative, *Mycobacterium* DNA, and QuantiFERON tests were negative. With consultation of infectious diseases, antibiotic therapy was stopped.

His thorax CT showed cystic air spaces in the left hemithorax and subcutaneous emphysema emerged after thoracostomy. Despite the vital values and breathing had returned to normal limits, a psychiatric consultation was requested due to continuing psychomotor agitation. In the psychiatric evaluation, the patient was agitated and hostile. At the same time, he was swearing and pointing his pain at the region of the chest tube. He was alert and fully oriented.

His appearance was congruent with his chronological age. His speech was very fast with flight of ideas. His thought content had grandiose themes. His mood was dysphoric and his affect was irritable. He had decreased need to sleep.

There were visual hallucinations and unorganized delusions. A brain magnetic resonance imaging (MRI) scan was performed due to the presence of psychopathology after a medical condition with acute onset within 1 week and with an atypical course. The brain MRI was normal. He was refusing to take oral psychiatric pills, and his central venous catheter could only be placed under sedation in the operating room. He was given paracetamol and codeine for his pain. Haloperidol 10 mg/day and biperiden 4 mg/day intramuscular injection were administered to the patient who continued to resist the medical team and medical interventions. The 2nd day after haloperidol, his leukocyte count was 4100 and it continued to be low on subsequent days. The hematology consultation was requested on the fact that the patient's daily hemograms had fallen. Peripheral blood smear done on the 3rd day was neutropenic with monocytes and activated lymphocytes which raised a suspicion of *Cytomegalovirus* (CMV) or Epstein-Barr virus (EBV). He was ordered 30 units of filgrastim (Neupogen) with blood transfusions and he responded well, so a drug-related cause of neutropenia has been suspected. Three days after the second filgrastim (Neupogen) dose, bone marrow aspiration biopsy was done. Flow cytometry and karyotyping had been applied. WBC and neutrophil counts demonstrated in Figures 1 and 2, respectively. The peaks in the figures correlated with the dates when filgrastim (Neupogen) was given and/or transfusion has been done.

It has been thought that neutropenia in this patient was related to peripheral destruction because bone marrow progenitors were normal. From laboratory tests, *Brucella* agglutination (wright), toxoplasma IgG, venereal disease research laboratory, anti-HIV, anti-HCV antibodies, and

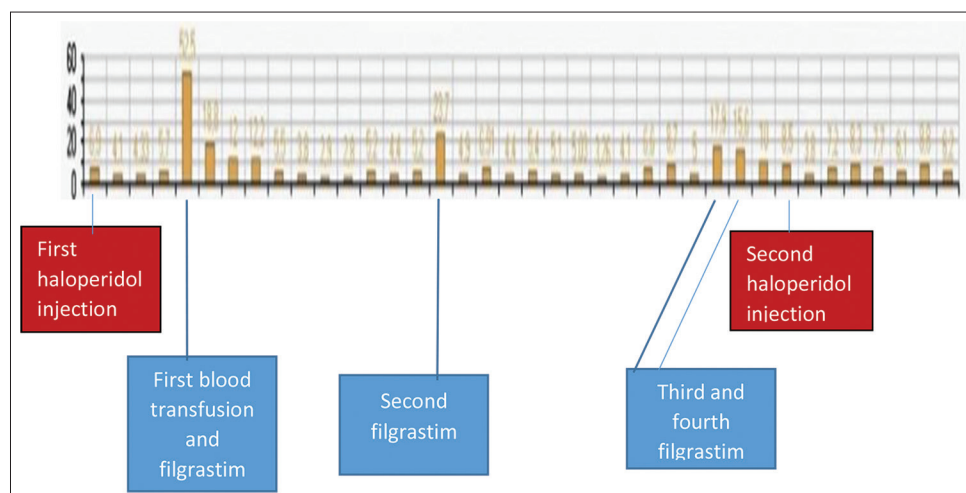


Figure 1: White blood cell in chronological order

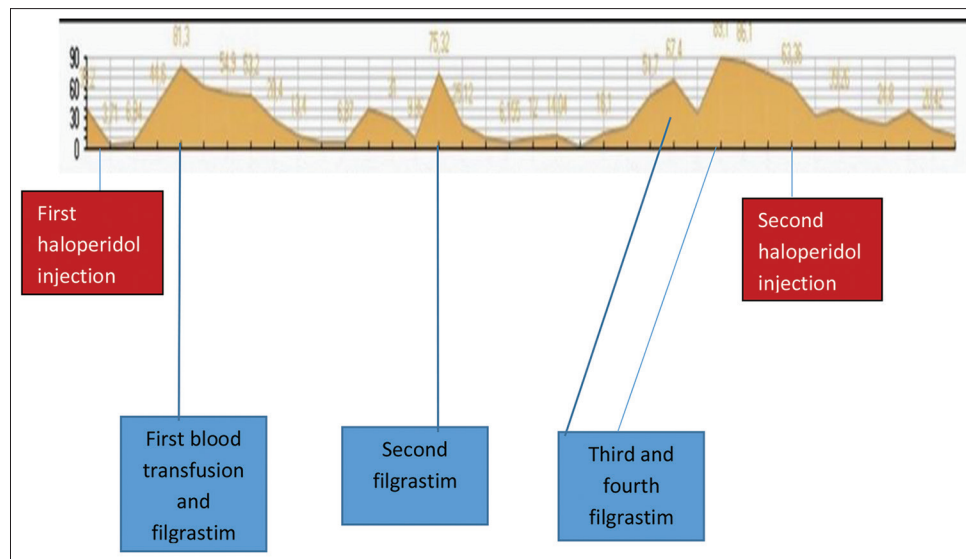


Figure 2: Percentage of neutrophils in chronological order

HBsAg were negative. For suspicion of CMV and EBV infections, antibodies were analyzed CMV IgM–, CMV IgG+, viral-capsid antigen (VCA) IgM–, and VCA IgG+. Acute CMV and EBV infections were excluded, and a drug-related cause has been suspected.

Moxifloxacin, paracetamol–codeine combination, haloperidol, and biperiden were among the medications he had been given. Moxifloxacin has been reported to cause agranulocytosis^[3,4] in some cases but also inversely been used widely with beta-lactam antibiotics to prevent infections in patients with leukemia and neutropenic fever. In our patient, moxifloxacin was removed from his drug therapy on the 3rd day. Leukocyte count did not change after moxifloxacin discontinuation.

Agranulocytosis cases related to paracetamol have been reported in the French literature but none from Turkey.^[5-7] Codeine which is found in a low dose in combination has not been associated with agranulocytosis widely.^[8] The paracetamol and codeine combination continued as needed in the 1st week of treatment, but haloperidol and biperiden persisted to be given.

Biperiden has not been associated with neutropenia. The hematology consultant has noted that haloperidol may be related to agranulocytosis (rare), anemia, decrease in red cell count, leukocytosis, leukopenia, and ordered some transfusions beside filgrastim (Neupogen) also asked for change in psychiatric treatment.

The patient was switched from haloperidol to quetiapine 300 mg twice a day. Neutropenia was corrected with filgrastim (Neupogen), his WBC count returned to normal levels by treatment with quetiapine, and the patient was discharged. One month later, he was brought to

ER with agitation, overvalued ideas of grandiosity, and attempt to harm hospital officials. Emergency medicine doctor had given a haloperidol and biperiden injection again to calm down him. Attending psychiatrist learned that he quitted quetiapine. This time he was not using moxifloxacin. His neutrophil count decreased again after haloperidol injection. The diagnosis of bipolar affective disorder, manic episode was made for this patient. He was transferred to a mental health hospital for inpatient stay with a warning note for the physicians to avoid haloperidol in that patient.

DISCUSSION

There has been some suspicion about drug-induced neutropenia to have an immunological background. Recovery and rebound leukocytosis may occur upon withdrawal of the offending drug.

Moxifloxacin reported to induce psychosis and hallucinations^[9] of our patient did not resolve spontaneously with discontinuation of it. Even if more than 1-month period had been passed without moxifloxacin, hypomanic symptoms continued. Lithium has beneficial effects on mania and leukopenia, but we did not add lithium to treatment of this patient because he was still in acute manic episode. However, in order for lithium to reach an effective serum concentration, time is needed. Lithium would be more effective in maintenance treatment besides and he was reluctant to use any medication. If we had prescribed lithium due to increase in the number of medications, his drug adherence would be even poorer. This was his first manic episode, and there are discrepancies in guidelines about using lithium in the first episode without knowing if another episode will occur again and when it will be.

Although there is the greatest risk of agranulocytosis with clozapine from antipsychotics, haloperidol may be blamed for neutropenia very rarely. In the literature, it is mentioned that African, Arabian, and Jewish minority groups have a high risk of chronic low leukocyte count which is called benign ethnic neutropenia. In addition, elderly patients are more susceptible to neutropenia, but our patient does not carry these risk factors.

According to the Naranjo Adverse Drug Reaction Probability Scale, the score is 6 which means probable.^[10] In the literature, haloperidol-induced neutropenia cases are scarce and there is usually usage of additional antipsychotics too,^[2,11,12] and we could reach only one case report of neutropenia with solely haloperidol.^[2]

The patients should be told to tell their doctor about the high fever and painful sore throats as soon as possible. Routine hemogram monitoring is not required as it is with clozapine in the follow-up of haloperidol treatment, but it is useful to ask for blood count during routine controls in patients who use haloperidol so that this rare side effect is not missed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not

be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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