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## CLINICAL VIGNETTE

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# Anemia Associated with an Atypical Antipsychotic

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### *Case Presentation*

A 92-year-old woman with no significant prior medical history presented to the emergency department after several days of not eating, along with disturbing behaviors. She was brought in by her two daughters, who stated that she had exhibited a long history of odd behaviors that were noteworthy for verbal and physical abuse to them. The patient's daughters also mentioned that this behavior worsened over the preceding several months, with increasing paranoid thoughts, including complaints of other people stealing from her. About ten days before coming to the hospital, she stopped eating. The daughters denied any significant memory problems.

The patient denied any significant medical history, and had not seen a doctor for many years, until a prior recent visit to a new primary care physician a few days before the hospitalization. She was taking no medications at the time of admission. She immigrated to the United States about sixty years ago, and worked mostly as a housekeeper until age 84.

Initial evaluation in the hospital revealed an elderly, thin woman who did not appear acutely ill, and had no abnormal physical findings. Mental status evaluation found her to be partially oriented, and speaking tangentially, interrupting her interlocutors. She also exhibited signs of paranoia, with preserved memory.

Abnormal findings from initial diagnostic studies included hypophosphatemia, hypokalemia, and acute kidney insufficiency with a creatinine of 2.4 mg/dl. Other laboratory tests, including complete blood count, with hemoglobin of 10.1 g/dl, white blood cell count of 6.79 per mm<sup>3</sup> and platelets of 419 per mm<sup>3</sup>. Head CT without contrast did not find hemorrhage or mass effect, but did reveal chronic microvascular ischemic changes.

The admitting team obtained a psychiatry consult, and based on the available evidence, they gave her a diagnosis of "mood disorder, not otherwise specified". They recommended giving a low dose of an antipsychotic to help with her paranoid thoughts and disorganization, as well as an antidepressant to help with depressive symptoms like her poor appetite. The team-initiated treatment with olanzapine at 2.5 mg at night, and escitalopram at 5 mg daily. Within two to three days, her mood improved, and she was eating regularly. With the help of her improved oral intake and intravenous fluids, her electrolyte disturbances and renal function improved as well.

After a week in the hospital, she was discharged to a nursing facility for skilled rehabilitation with physical and occupational therapy. At her initial evaluation there, her physical exam was unremarkable, and her mental status showed her to be pleasant, with no signs of paranoia or depressed mood. Her only abnormal finding on the initial evaluation was a hemoglobin of 7.5 g/dl with MCV of 94, a significant drop from the initial hospital laboratory testing. Her white blood cell count was 5.3 per mm<sup>3</sup>, with 222 platelets per mm<sup>3</sup>. Two days later, her hemoglobin dropped to 7.0 g/dl, with 4.4 white cells per mm<sup>3</sup>, and 324 platelets per mm<sup>3</sup>. The patient showed no new physical symptoms, and had no evidence of gastrointestinal bleeding.

Anemia evaluation did not reveal any obvious causes. Iron studies with ferritin of 150, TIBC of 129, and serum iron of 27 showed it to be unlikely that iron deficiency was the cause of such an acute drop in hemoglobin. Folate, B12, and reticulocyte counts and bilirubin were normal.

Having ruled out iron and other nutritional deficiencies, as well as hemolysis, as likely causes, we looked at new medications as the next most likely possibility. Neuroleptics are known to cause bone marrow disorders, so we stopped the olanzapine. Three days after stopping olanzapine, her hemoglobin improved to 8.2. However, this also coincided with a return to aggressive behaviors and paranoia. After a discussion with her daughters, we introduced risperidone at 0.25 mg, given at night. Her behaviors and hemoglobin remained stable after four days and she was discharged home to the care of her two daughters.

### *Discussion*

Medications can be associated with different varieties of blood dyscrasias, affecting all cell lines. Drugs can cause anemia through different mechanisms. They can either affect the bone marrow directly, or they can cause hemolysis. Drugs can also be toxic to other cell lines in the marrow, leading to leukopenia or thrombocytopenia. Agranulocytosis, a life-threatening variety of drug-induced leukopenia, is an absence of circulating granular leukocytes. Blood dyscrasias due to medication side effects account for a small percentage of adverse drug reactions with one or two cases with serious hematological toxicity per year per 100,000 patients.<sup>1</sup> Most blood dyscrasias due to medications resolve after removing the offending drug.

Drug-induced aplastic anemia may not resolve on withdrawal of the drug.<sup>2</sup> Aplastic anemia is a life-threatening disorder associated with bone marrow failure leading to pancytopenia. In aplastic anemia, the hemoglobin level falls less quickly than with hemolysis, because the erythrocyte half-life in blood is around 120 days.

Drug-induced hemolytic anemia is often an acute process, with symptom onset within an hour of receiving the drug. Symptoms include severe pallor, fatigue, jaundice, or dark urine. Drug-induced hemolysis can be due to oxidative hemolysis from glucose 6-phosphate dehydrogenase (G6PD) deficiency; more common in persons of African, Asian, and Mediterranean descent. People with this disorder can suffer from oxidative stress leading to hemolysis. Some of the neurotoxicity of antipsychotics may be due to lipid peroxidation, which is a type of oxidative stress.<sup>3</sup> Hemolysis may also be due to autoimmune mechanisms, thrombotic microangiopathy, or methemoglobinemia.

Antipsychotic drugs are associated with a variety of adverse reactions, including neurologic like extrapyramidal reactions, metabolic changes leading to weight gain and diabetes mellitus, and hematologic reactions. Neutropenia and agranulocytosis are the most significant blood dyscrasias associated with this class of medications. Agranulocytosis can be life-threatening and require urgent treatment. Clozapine is well-known to cause agranulocytosis, with about 1% of patients developing the condition.<sup>4</sup> Due to this, in the United States, regulations require strict monitoring for neutropenia. Other antipsychotics are also associated with neutropenia and agranulocytosis. Reports of leukocytosis or neutropenia occur in up to 4 percent of patients receiving risperidone.<sup>5</sup> Placebo-controlled trials on quetiapine, report the incidence of neutrophil counts below 1000/mm<sup>3</sup> was 0.3%.<sup>6</sup>

Though reports of neutropenia, agranulocytosis, and thrombocytopenia are well-documented with antipsychotics, reports of anemia are not associated with this class of medication. A Pubmed search on October 28, 2020 associating “antipsychotics” or “neuroleptics” with “anemia” did not identify any published reports of anemia. However, package inserts for risperidone and quetiapine both report that anemia was observed in the clinical trial evaluation of these drugs.<sup>5,6</sup> The package insert for olanzapine only reports anemia during animal trials of the drug.<sup>7</sup>

### Case Conclusion

The temporal relationship between the addition of olanzapine in this patient and the development of a normocytic anemia and the subsequent rapid improvement in hemoglobin upon the withdrawal of the drug, raise strong suspicions that the anemia was drug-induced. The absence of nutritional deficiencies and a lack of evidence of bleeding also support this hypothesis.

If olanzapine was a major or sole cause of the patient’s anemia, the mechanism is unclear. Because the anemia developed over

the course of a few days, an aplastic anemia seems unlikely. Similarly, an acute hemolytic reaction would probably have been associated with a reticulocyte response and hyperbilirubinemia, and clinical signs such as fever, which were absent.

Even though the evidence for a drug-induced anemia is not incontrovertible in this patient’s case, it highlights the importance of considering medication side effects when assessing new and serious problems in older adults. Drug reactions in older persons are common, and a simple measure like the removal of a potentially offending medication can be a low-cost, simple intervention that could lead to better outcomes for our patients.

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