The patient is a black woman in her early 30s, who has no medical conditions but who has been diagnosed with schizophrenia, undifferentiated type. She presented to the clinic in May 2003 with refractory psychotic symptoms of thought disorganization, thought blocking, paranoia, religious preoccupation, and intermittent auditory hallucinations.

On admission to the clinic, her medications were clozapine (300 mg); risperidone (4 mg); lamotrigine (100 mg); and citalopram (80 mg). Her clozapine level was 360 ng/mL and norclozapine 208 ng/mL. Blood counts were within normal limits.

Over the next 5 years, the patient continued to complain about sedation and weight gain. Clozapine was tapered by 25-mg doses to a dose of 150 mg. Because of ongoing refractory psychotic symptoms, she was maintained on clozapine 150 mg.

In November 2009, clozapine was further tapered to 75 mg, with plans to eventually discontinue. During this period, she underwent bimonthly monitoring. In November 2009, her absolute neutrophil count (ANC) dropped to 1.8 K/uL, with white blood cell count (WBC) of 4 K/uL. Clozapine was discontinued in January as lab values fluctuated between low normal and below normal.

Risk-benefit analysis of clozapine termination was discussed with patient. Two weeks later, despite clozapine discontinuation, her WBC count dropped to 3.2 K/uL with ANC 1.2 K/uL. She went on daily monitoring, and a hemato-oncology evaluation was performed. Bone marrow aspiration biopsy was negative, and her low blood values were determined to be medication-induced.

One month after discontinuation of clozapine (February), low blood counts persisted, with values of WBC 3.1 K/uL and ANC 1.2 K/uL. There was mild elevation in values in March (8 weeks later), but that was transient. In April (12 weeks later), because of ongoing low WBC/ANC values, the treatment team considered risperidone as a contributor to ongoing granulocytopenia. Risperidone was tapered from 4 mg to 3.5 mg. After further decrease of risperidone to 3 mg in June, blood work returned to normal, with WBC 5.7 K/uL and ANC 2.7 K/uL.
Late-onset Neutropenia

DISCUSSION
Second-generation antipsychotics are effective in the treatment of schizophrenia. Clozapine is an atypical antipsychotic agent that has been found effective in the treatment of treatment-resistant schizophrenia. However, clozapine has been associated with the development of agranulocytosis, a hematologic condition characterized by decrease in leukocytes and granulocyte counts.

Granulocytopenia is an abnormally low concentration of granulocytes in the blood. Closely related terms include agranulocytosis (no granulocytes at all) and neutropenia (deficiency of neutrophil granulocytes). Neutropenia is defined by a neutrophil count of less than 2 K/uL, and agranulocytosis by ANC of less than 0.5 K/uL. This is usually associated with leukopenia as defined by WBC of less than 3.5 K/uL.1

Neutropenia is a sign of impending agranulocytosis in patients who take clozapine and can lead to discontinuation of the drug. Patients with agranulocytosis remain at risk for infection and possible death. The cumulative incidence of agranulocytosis is 0.80% after 1 year and 0.91% after 1.5 years.2 Recently, clozapine national registry has suggested that incidence is as low as 0.38%.3

Current stringent monitoring requirements have helped minimize the adverse effects of agranulocytosis in clozapine-treated patients. True prevalence of hematologic adverse reactions in second-generation antipsychotics other than clozapine is difficult to estimate. Isolated case reports have associated these medications with induction of leukopenia or agranulocytosis. However, alterations in WBC counts during treatment with other second-generation antipsychotics have not been systematically investigated.

The occurrence of neutropenia, which can lead to agranulocytosis, is a substantial hazard in administration of clozapine. Our case demonstrates a sudden development of neutropenia in a patient treated and maintained on clozapine for many years. Along with a sudden drop of WBC less than 3.5 K/uL, ANC also dropped to less than 1.5 K/uL, and continued to do so despite discontinuation of clozapine (see Figure, page 531). Interestingly, the ANC level never went less than 0.5 K/uL, and the patient did not manifest any physical symptoms.

Various factors, including age, race, gender, and genetics play an important role in induction neutropenia. Women and the elderly have been found to be at higher risk for clozapine-induced blood dyscrasias.2 It has been established that the risk for clozapine-induced agranulocytosis is greatest during the first 3 months of treatment,2 with 70% of cases occurring within in 6 to 18 weeks.4 Although the risk is reduced after 6 months and decreases over time, clozapine-induced agranulocytosis continues to pose a risk after years of exposure. In our case, the patient was a 30-year-old woman, and she was maintained on clozapine for more than 5 years with routine blood work monitoring.

Two cases of delayed-onset clozapine-induced agranulocytosis after 4 and 11 years of treatment have been reported.5,6 These reports postulate that agranulocytosis may be caused by a permanent change in maturation of blood cells, leading to myelodysplastic syndrome. Clozapine-induced agranulocytosis could be caused by immunologic or toxic effects on bone marrow. Reports indicate that clozapine accelerates the normal process of cell death in neutrophils. There may be a decreased proliferation of isolated lymphocytes induced by clozapine’s metabolite norclozapine.

It has been suggested that clozapine can induce two distinct types of neutropenia. The first is mild-to-moderate neutropenia (> 1.5 K/uL) in which recovery is rapid (2 to 8 days) after clozapine discontinuation. The second type is agranulocytosis, which is more severe and has an incidence of 0.78%. Agranulocytosis develops despite discontinuation of clozapine after neutrophil count drops to less than 1.5 K/uL, and generally lasts for 14 to 21 days.7

Our patient may have had mild-to-moderate neutropenia; however, blood counts failed to return to normal after discontinuation of the drug.

Guidelines for use of clozapine are based on normative WBC/ANC values in white population. Other population groups, particularly blacks of African or West Indian origin, have idiosyncratically low WBC values (0.9 to 4.2 K/uL), a phenomenon called benign ethnic neutropenia.8,9 Our patient, who is black, always had low normal...
blood counts; however, sudden onset of neutropenia could not be explained on the basis of ethnicity.

Literature has highlighted three case reports of either neutropenia or agranulocytosis with risperidone. In one case, reversible neutropenia during an upper respiratory infection possibly involved risperidone; rechallenge in the same patient was safely documented. Also, there is one case report of augmentation with risperidone on a clozapine patient, resulting in agranulocytosis.

Risperidone and clozapine are both partially metabolized by hepatic microsomal P450 2D6 system. Consequently, it is possible that risperidone could be a second-degree offender because it increases clozapine levels and risk for neutropenia and agranulocytosis. We do not have clozapine levels to compare before risperidone was added to the medication regimen. However, agranulocytosis with clozapine exposure is suggested to have an immunemediated mechanism, implying that it would be independent of plasma concentration of clozapine. Moreover, return of WBC/ANC levels to normal after lowering the dose of risperidone is highly suggestive of risperidone as the cause for neutropenia.

Researchers in a study who compared incidence of neutropenia and agranulocytosis concluded that second-generation atypical antipsychotics other than clozapine can induce neutropenia. This rarely progresses to agranulocytosis and is short-lasting.

Currently, there are no guidelines for hematologic monitoring for atypical antipsychotics other than clozapine. Current clozapine guidelines require WBC/ANC monitoring for the first 4 weeks but do not indicate long-term monitoring after termination of treatment. This case highlights the risk for blood dyscrasias with atypical antipsychotics. Nevertheless, clinicians need to be cognizant of late-onset neutropenia and cumulative effects of other psychotropic medications on bone marrow.

REFERENCES