

## CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

### Hematology Quiz – Case 58

A 68-year-old lady presented to the emergency department because of neutropenia. She denied fever or other symptoms prior to her admission. She suffered from a chronic schizophrenic disorder and resided permanently in a psychiatric clinic. During the last two months a slow decline of the white blood cells, especially the neutrophils, had been noted on regular blood tests. Apart from her psychiatric disorder, treated with clozapine for the last two months, her medical history was also notable for hypothyroidism and arterial hypertension, treated with levothyroxine and furosemide, respectively.

On examination, she was febrile to 38 °C without rigor, with a heart rate of 107 bpm. The remainder of the examination was unremarkable. Her initial complete blood count was as follows: Ht: 34.8%; Hb: 11.9 g/dL; MCV: 84.1 fL; WBC:  $0.97 \times 10^9/L$  (neutrophils 0/ $\mu L$ , lymphocytes 890/ $\mu L$ ); PLTs:  $332 \times 10^9/L$ . Examination of a peripheral blood smear confirmed the complete absence of neutrophils, without any other quantitative or qualitative abnormalities. The remainder of her blood tests was remarkable for the following: LDH: 268 IU/L (normal range: 115–221 IU/L); folic acid: 10.8 ng/mL (normal range: 5.4–18 ng/mL); vitamin B<sub>12</sub>: 164 pg/mL (normal range: 279–996 pg/mL); TSH: 9.8 mU/L (normal range: 0.34–4.25 mU/L). She also tested negative for HIV.

A bone marrow aspiration was performed; bone marrow smears were examined (figures 1 to 6), and immunophenotyping of the bone marrow cells was carried out.

Bone marrow smears showed complete absence of the

myeloid cells. Flow cytometry revealed that the myeloid cells comprised 7.6% of the nucleated cells and were negative for CD10 and CD16 which are expressed in metamyelocytes and mature neutrophils.

On consideration that the agranulocytosis might be drug-induced, clozapine was immediately discontinued. During her hospitalization, the patient received broad spectrum antibiotics, although the blood and urine cultures obtained were sterile. Eventually, two weeks later, the patient's absolute neutrophil count raised to 100/ $\mu L$ . Although, G-CSF was not administered from the beginning, it was administered at that point to help the absolute neutrophil count raising rapidly to normal. G-CSF treatment in nonchemotherapy drug-induced neutropenia has been associated with less antibiotic use and faster recovery, but its efficacy is not fully proven in nonchemotherapy drug-induced neutropenia with granulocyte count  $<0.1 \times 10^9/L$  and symptoms of infection.

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2018, 35(2):282–283

**A. Halioti,  
S. Hatzidavid,  
M. Tambaki,  
E. Cholongitas,  
N.A. Viniou,  
P. Diamantopoulos**

*First Department of Internal Medicine,  
"Laiko" General Hospital, National  
and Kapodistrian University of Athens,  
Athens, Greece*

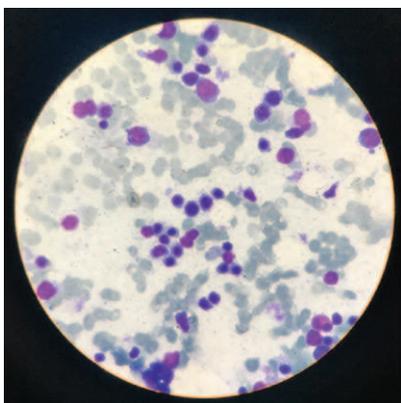


Figure 1

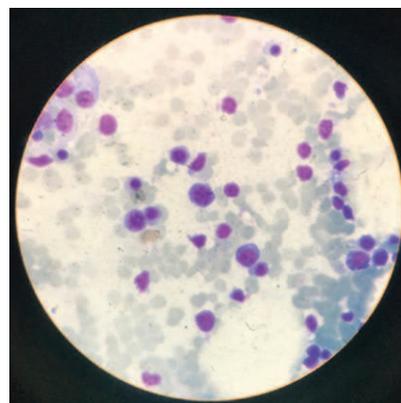


Figure 2

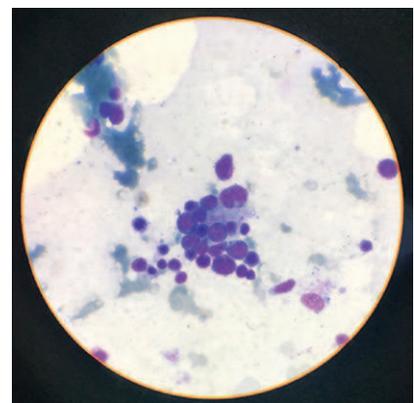


Figure 3

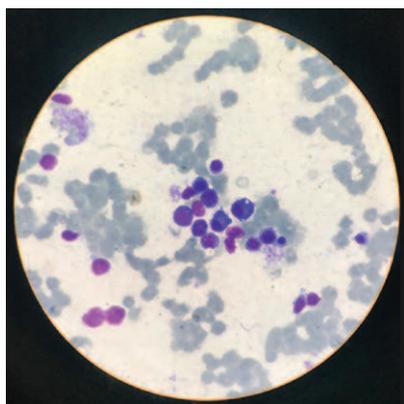


Figure 4

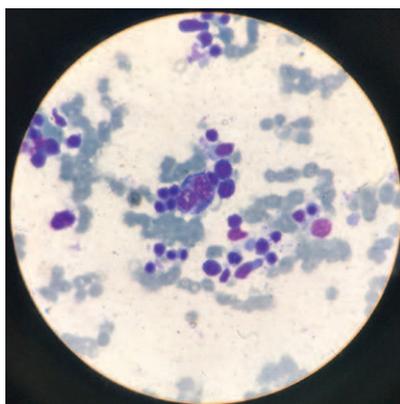


Figure 5

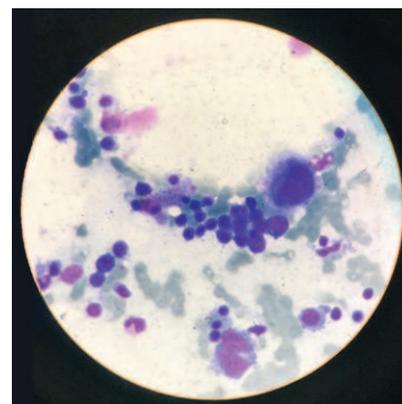


Figure 6

### Comment

Clozapine, classified as a second generation (atypical) antipsychotic drug, is the treatment of choice for schizophrenic patients who fail to respond to other antipsychotic medications, and is also used to eliminate the suicidal behavior in patients with schizophrenia. Its clinical effects are mediated through blocking specific receptors (serotonergic, adrenergic, cholinergic, dopaminergic, histaminic) in neuronal tracts of the brain. Clozapine is notably related with severe neutropenia, the most serious adverse effect of the drug, occurring rarely (0.38% of all clozapine treated patients), and usually reported in the first 18 months after treatment initiation. The pathogenesis of this adverse outcome is not fully understood yet; an immunological mechanism may exist. Genetic aberrations in human leukocyte antigen genes and genes associated with apoptosis and ubiquitination may be important components of clozapine-induced agranulocytosis. Measures recommended to reduce the incidence of clozapine induced-neutropenia and subsequent life-threatening infections are: (a) Avoidance of clozapine if the initial absolute neutrophil count (ANC) of the patient is below  $1.5 \times 10^9/L$ , (b) regular monitoring of the patient's ANC during treatment, and immediate treatment discontinuation if  $ANC < 1.0 \times 10^9/L$ , (c) informing the patient about the first signs of an infection while on clozapine.

Rechallenge with clozapine after the resolution of an initial neutropenic episode may be feasible in selected patients following careful consideration of the risks and benefits. In a recent report of 19 cases of rechallenge, one third of the patients re-exposed to the drug developed a second hematologic adverse reaction that was less severe and prolonged compared to the first episode in 83% of the cases. Concurrent use of lithium and G-CSF with clozapine may be useful to reduce the risk of agranulocytosis.

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### Corresponding author:

P. Diamantopoulos, First Department of Internal Medicine, "Laiko" General Hospital, National and Kapodistrian University of Athens, Athens, Greece  
e-mail: pandiamantopoulos@gmail.com

*Diagnosis: Clozapine induced agranulocytosis*