Drug induced agranulocytosis is a severe hematological complication, with an incidence in Europe of 2.4 - 15.4 cases per million inhabitants per year, that may complicate with sepsis and septic shock in two thirds of patients. Drugs that are known to induce agranulocytosis include colchicine, sulfasalazine, NSAIDs and tamoxifen (1). The negative prognostic factors for agranulocytosis are age (over 65), sepsis or septic shock, renal failure and neutrophiles less than 100/mm3 (1). With a proper treatment (broad-spectrum antibiotics, antifungal and hematopoietic growth factors) mortality is less than 5% (1). The impact of hematopoietic growth factors (granulocyte colony stimulating factors - G-CSF and granulocyte macrophage colony stimulating factor - GM-CSF) in reducing mortality is unknown; however, their use decreases the duration of agranulocytosis, antibiotic therapy duration and hospitalization. The duration of neutropenia in symptomatic or asymptomatic patients is influenced by the administration of hematopoietic growth factors, if the neutrophil count is less than 100/mm3, but not if the neutrophil count is greater than or equal to 100/mm3 (2). Drugs causing agranulocytosis should be discontinued and remain permanently contraindicated (3).

We present the case of a 54 year old patient with breast cancer treated with tamoxifen, with a concomitant diagnosis of reactive rheumatoid arthritis for which she received daily sulfasalazine, daily Colchicine and NSAIDs as required. Two months after initiation of the treatment for osteo-articular pathology, the patient presented with agranulocytosis.

Key words: breast cancer, rheumatoid arthritis, agranulocytosis, tamoxifen, colchicines, sulfasalazine.

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Drug induced agranulocytosis

Citric citrulline peptide (CCP) antibody determination was performed and showed a markedly increased value (> 320U/ml than normal value <7 U/ml). All these findings led to the diagnosis of moderately active seropositive rheumatoid arthritis. Treatment with sulfasalazine 500mg was initiated, with titration up to 2g/day, associated with colchicine 1mg/day and meloxicam 10mg/day (with proton pump inhibitors if necessary, for gastric protection).

Two months after the initiation of anti-inflammatory treatment for osteo-articular pathology, the patient was admitted to the Hematology Clinic of Cluj-Napoca with leukopenia with agranulocytosis (WBC= 1500/mm³, neutrophils 0%). The rest of the blood count was normal. Medulograma described smears with areas of fatty tissue and megakaryocytes in all stages of differentiation, with some areas of the marrow with lower cellularity and many crushed cells (nuclei free), with normoblasts in all stages of differentiation, together with frequent lymphocytes and some plasma cells, with no evidence of mature granulocytic series, as all elements were blasts. The conclusion of the medulogram was agranulocytosis, bone marrow without signs of metastatic invasion.

The case was interpreted as drug-induced agranulocytosis. Antirheumatic therapy and hormone therapy with tamoxifen were discontinued and granulocyte growth factor (0.5MU/kg/e/day, 3 days) was administrated, associated with antibiotic, antifungal, and corticosteroid therapy with hematologic improvement (WBC =71040/mm³). Control blood counts performed after 3 weeks were normal (neutrophils=7170/mm³, hemoglobin=14g/dl, platelets=304.000/mm³) and the administration of Tamoxifen 20mg/day was resumed.

Several mechanisms of developing drug-induced agranulocytosis have been described: immune-mediated mechanism (drug acting inducing formation of antibody antineutrophil), accelerated neutrophil apoptosis, mediated destruction by complement inhibition granulopoiesis and direct toxic effect of the drug on myeloid precursors (4). Agranulocytosis described in our patient was more likely caused by the administration of sulfasalazine and colchicine; it is a rare but potentially life-threatening occurrence (5). In a report performed by the FDA (U.S. Food and Drug Administration) between 2004 and 2011 on drug side effects, sulfasalazine adverse effects were reported in 1434, of which 35 were agranulocytosis (0.64%) and 33 neutropenia (0.61%) (6). Mortality reported with sulfasalazine-induced agranulocytosis varies between 6% and 20% and depends on the duration of neutropenia (5). Agranulocytosis postsulfasalazine appears after one to three months after starting therapy. Medulograma describe bone marrow hypoplasia or aplasia, usually limited to myeloid series but may be accompanied by erythroid hypoplasia series. In a review of 62 cases of sulfasalazine - induced agranulocytosis, 6.5% of patients died. Granulocyte recovery occurs in one to two weeks after drug discontinuation and reaches normal values in 1-3 weeks (7).

In the report effectuated by FDA, regarding colchicine, 876 colchicine-adverse effects were described, of which 7 (0.16%) were represented by leukopenia(8). The effect of colchicine-induced leucopenia may be increased with concurrent or recent therapy with drugs that cause blood dyscrasias and drugs that produce bone marrow suppression. These drugs are defined as drugs that cause unpredictable myelotoxicity, which occurs in a minority of patients and are not dose dependent or bone marrow suppression predictable dose. These agents include NSAIDs and sulfasalazine that the patient uses to control joint manifestations in rheumatoid arthritis.

The report conducted by the FDA on tamoxifen described 3282 adverse effects, of which 19 (0.24%) were leukopenias (9). In the presented case, post-tamoxifen agranulocytosis is less likely, given that the patient received hormone therapy for a period of two years and eight months, and she had no modified blood counts during follow-up visits.

Sulfasalazine and colchicine remain permanently contraindicated for this patient.

References