Case Report

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Severe Pancytopenia Induced by Methotrexate in a Rheumatoid Arthritis Patient

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Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting approximately 1% of the global population, with a higher prevalence in women. Methotrexate (MTX), a disease-modifying antirheumatic drug (DMARD), is commonly used in RA treatment. However, improper or unsupervised use can lead to severe hematological toxicities, including pancytopenia. A 74-year-old female patient with RA presented with fever, oral ulcers, weakness, and difficulty swallowing. Physical examination revealed ecchymotic skin lesions and candidal plaques in the oral cavity. Laboratory results indicated severe pancytopenia (WBC: 1.1×10^9/L, RBC: 2.75 x 1012/L, PLT: 9×10^9/L). Methotrexate intoxication was suspected. The patient received supportive treatment, including folate supplementation, Filgrastim for neutropenia, platelet apheresis, and erythrocyte transfusion. Scattergram analysis revealed marked alterations in neutrophil and eosinophil populations. Following treatment, hematological parameters normalized, but neutrophil volume changes persisted, suggesting a prolonged bone marrow effect of MTX. This case highlights the importance of routine complete blood count monitoring, including scattergram analysis, in RA patients receiving DMARD therapy. Laboratories should consider adjusting CBC measurement protocols in cases of suspected drug-induced pancytopenia to enhance diagnostic accuracy and early detection of hematological toxicity.

Keywords: Methotrexate toxicity, pancytopenia, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease with a global prevalence of approximately 1%, and its prevalence increases with age. It is generally seen three to five times more frequently in women than in men, usually between the ages of 40 and 50. One of the treatment options is Methotrexate, which belongs to the group of disease-modifying antirheumatic drugs (DMARDs) (1).

Methotrexate is a folate antimetabolite that inhibits DNA synthesis, repair, and cellular replication. Methotrexate works by binding to and inhibiting dihydrofolate reductase, leading to reduced formation of reduced folate and inhibition of thymidylate synthase. This results in the inhibition of purine and thymidylic acid synthesis, thereby affecting DNA synthesis, repair, and cellular replication. Actively proliferative tissues are more sensitive to the effects of methotrexate (2).

In this case, a patient diagnosed with RA was initially started on Methotrexate therapy, which was later discontinued by the Rheumatology department. However, the patient continued to take and use her medications unsupervised for approximately 7 months, 2 tablets per day. As a result, the patient developed mouth ulcers, skin lesions, and pancytopenia. This case highlights the necessity of considering alternative modifying agents or medications for geriatric patients who may not be able to take Methotrexate regularly and appropriately, or who cannot be monitored consistently. Additionally, in similar cases, it is emphasized that laboratory values, especially scattergram analyses of complete blood counts, should be used to assess the relationship with disease management.

Eosinophil elevation in rheumatoid arthritis is a very rare but documented condition. It remains controversial whether this increase is related to treatment independently of rheumatoid arthritis or if it is associated with the inflammatory processes caused by the disease (3). Additionally, there is literature indicating that the extent of eosinophilia may be a marker for the severity of rheumatoid arthritis, and that this change in value might be caused by disease-modifying antirheumatic drugs (4-9).

Rheumatoid arthritis is an incurable disease (1). In order to prevent the progression of the disease, disease-modifying drugs are used and efforts are made to prevent progression. Disease-modifying drugs for the disease are abbreviated as DMARDs and consist of Hydroxychloroquine, Sulfasalazine, Gold salts, D-penicillamine, Azathioprine, Cyclophosphamide, Methotrexate, Leflunomide, Tumor necrosis factor-α blockers, Anakinra Abatacept, and Rituximab. The most commonly used of these is Methotrexate (10).

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Case Report

A 74-year-old female patient presented to our hospital's emergency department with complaints of fever, widespread painful plaques in the mouth, oral intake disorder, weakness, and difficulty swallowing. During the patient's physical examination, prominent ecchymotic lesions on the body, widespread candidal plaques on the oral mucosa, areas of necrosis intermittently, and cryptic lesions on the tonsils were observed.

During the otolaryngologist's examination, crusting secondary to bleeding was observed at the nasal vestibules, while the nasal mucosa appeared normal. In the evaluation of the oral cavity, poor oral hygiene, aphthous ulcerative lesions on the bilateral buccal mucosa, and mucosal ulcerative aphthous lesions on the uvula and posterior oropharyngeal wall were observed. In the laryngeal evaluation, a yellowish plaque (suspected candidiasis) was noted on the laryngeal mucosa, while the bilateral vocal cords appeared normal and mobile.In addition, the patient's past history revealed that she had hypertension and asthma.

Due to the inability to measure the patient's complete blood count values, the presumptive (unconfirmed) diagnosis of the disease was communicated to the laboratory. A new sample was collected and analyzed in the laboratory using the reticulocyte mode on the device (Beckman Coulter DXH-800) by changing its routine working mode.

White Blood Cells: 1.1 (10^9/L), Neutrophils: 0.1 (10^9/L), Lymphocytes: 0.54 (10^9/L), Eosinophils: 0.51 (10^9/L), Monocytes: 0.01 (10^9/L), Hemoglobin: 8.7 g/dL, Hematocrit: 24.6%, Platelets: 9 (10^9/L) were detected (Figure-1 and Table-1). In the peripheral smear examination, no atypical cells or blasts were observed, and leukopenia was noted. Platelet levels were consistent with the blood count.

Current findings were found to be compatible with intoxication due to uncontrolled methotrexate use. Other tests performed for the etiology of pancytopenia include Total Protein; 46 g/L (66-83), Albumin; 25 g/L (35-52), Urea; 69 mg/dL (12-50), Uric Acid; 4.96 mg/dL (2,6-6), AST; 10 U/L (5-40), ALT; 11 U/L (5-40), Total Bilirubin; 1.38 mg/dL (0,1-1,2), Direct Bilirubin; 0.40 mg/dL (0-0,3), Calcium; 7.5 mg/dL (8,8-10,6), Magnesium; 1.57 mg/dL (1,7-2,6), Phosphorus; 2.01 mg/dL(2,4-4,5), CRP; 333 mg/L (0-8), Erythrocyte sedimentation rate; 78 mm/h (0-30), Procalcitonin; 0.84 µg/L (0-0,1), vitamin B12; 351 ng/L (125-505), Folate; 8,66 µg/L (3,1-19,9)

The patient's radiological examinations revealed a normal chest X-ray. The patient, who had a fever and neutropenia, was started on Meropenem 3x1 g and Vancomycin 2x1 g with a preliminary diagnosis of febrile neutropenia. Methotrexate was discontinued and Folbiol 2x1 was initiated. Filgrastim 30 mIU (1×1 SC) was initiated with frequent hemogram monitoring. Due to the risk of bleeding, platelet apheresis was administered for thrombocytopenia, and erythrocyte suspension was infused for symptomatic anemia. On follow-up, platelet count was 58 (10^9/L), hemoglobin was 11 g/dL, and hematocrit was 32%.

Leukopenia improved during daily follow-ups after two days of Filgrastim. The patient, who had no fever after admission, had Meropenem and Vancomycin discontinued on the 3rd day, and the treatment was narrowed to Ciprofloxacin. The patient's laboratory values were found to be normal on the 5th day.

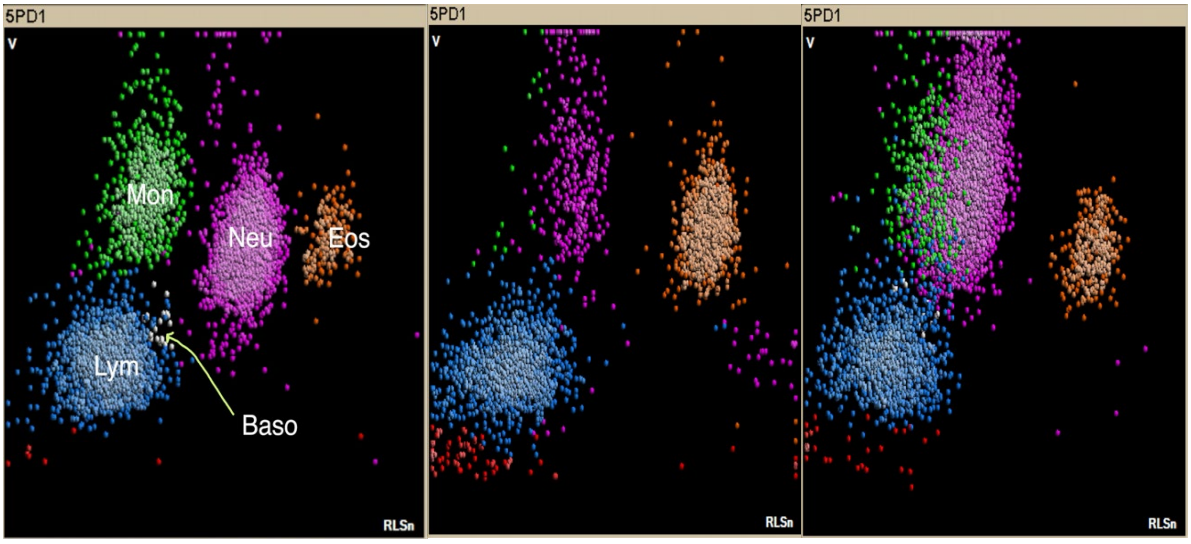

Figure 1. A-Scattergram of a normal patient B- Scattergram of at admission C-Scattergram of after treatment

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Table 1: Complete blood count parameters at admission and after treatment

Parameter	At Admission	After Treatment	After Treatment 10th Day	Reference Value	Unit
WBC	1.1	9.5	9.2	3.6-11	10^9/L
RBC	2.75	3.66	3.77	3.8-5.3	10^{12}/L
HGB	8.7	11.2	11.5	11.7-16	g /dL
HCT	24.6	33.1	33.5	35-47	%
MCV	89.6	90.5	88.8	75.3-95.3	fL
MCH	31.7	30.6	30.6	24.3-33.2	pg
MCHC	35.3	33.8	34.5	32-36	g/dL
PLT	9	58	310	150-450	10^9/L
MPV	8.0	8.7	8.0	7-11.2	fL
PCT	0.05	0.17	0.25	0.1-0.5	mg/dL
PDW	18	18.8	18	8-18	fL
NEU#	0.14	6.58	5.5	1.9-8.2	10^9/L
LYM#	0.54	1.96	2.69	1.0-3.2	10^9/L
MON#	0.01	0.47	0.66	0.2-0.9	10^9/L
EOS#	0.51	0.38	0.32	0-0.5	10^9/L
BAS#	0.001	0.03	0.04	0-0.1	10^9/L
NEU%	12.76	68.89	59.77	40-75	%
LYM%	51.30	20.54	29.17	16-45.9	%
MON%	0.56	4.96	7.13	4.5-12.5	%
EOS%	35.35	5.29	3.46	0.5-7.0	%
BAS%	0.03	0.32	0.47	0.2-1.5	%
RDW-CV	14.3	14.9	15.2	12.3-17.7	%
RDW-SD	44.6	46.4	46.4	37-54	fL

Discussion

Hematologic toxicities associated with methotrexate use include, though rarely, anemia, leukopenia, or thrombocytopenia, which may occur without significant reductions in other cell lines, or the more rarely seen condition of pancytopenia may accompany them. To prevent these complications, the American College of Rheumatology (ACR) guidelines recommend monitoring and routine peripheral complete blood counts(11).

When comparing the two-dimensional scattergram of our patient's admission to the hospital (5PD1-RLSn) with the scattergram of a patient with normal complete blood count parameters, we observe that the levels of monocytes and basophils are completely erased (Green-White Dots), the levels of neutrophils are significantly reduced (Pink Dots), and the levels of eosinophils and lymphocytes are increased (Blue-Orange Dots). In the laser scattering method, the laser is directed to the cells passing through the flow system and the low-angle signal represents the cell volume information, the medium-angle and high-angle signal represents the cell nucleus information and the cytoplasm information. The obtained data is displayed in a 2- or 3-dimensional diagram of WBC subgroups. The system creates these images by instantaneously measuring cell volume (Y-axis) and the light loss calculated according to the axis (X-axis).

The hematological differential parameter changes at the time of the patient's admission indicate that eosinophils have increased both in percentage and cell volume, while neutrophils have an increased cell volume but are significantly reduced in number. The post-treatment scattergram changes are observed in Figure-1C. Although the hemogram diff image is quite similar to that of a healthy patient, neutrophils are still larger in volume. These cell changes suggest that methotrexate affects the bone marrow, creating aberrant lines in the granulocyte series, and likely extends the half-lives of these lines (eosinophil lifespan 8-18 hours), indicating that although the total WBC has normalized, cell-based volume corrections have not yet occurred. Detailed analyses with flow cytometry, examining the clusters of differentiation (CD16, CD49, CD69, etc.) of granulocyte series cell lines, could contribute to explaining the pathophysiology of this effect.

Conclucion

In conclusion, the severity of the pancytopenic state at admission suggests that laboratories performing CBC measurements could enhance accuracy by modifying their procedures in similar cases.We believe that in systemic

diseases like rheumatoid arthritis, if disease-modifying antirheumatic drugs (DMARDs) are used, it is important to routinely include scattergram analysis in hemogram follow-ups to detect possible side effects, especially intoxication, at an early stage.

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