

A Case of Inflammatory Arthritis and Methotrexate Use in a Patient with Myelodysplasia

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Myelodysplastic syndromes (MDS) are hematopoietic stem cell abnormalities of differentiation and maturation. These disorders are characterized by normal or hypercellular bone marrow, peripheral blood cytopenias, and possible transformation to acute myelogenous leukemia (AML). Myelodysplasia is associated with a number of rheumatologic diseases and occurs with a high prevalence in the geriatric population. This disorder may be preceded by a paraneoplastic inflammatory joint disease, or it may appear after the onset of a number of rheumatologic diseases.

Therapeutic options for elderly patients with connective tissue diseases and myelodysplasia are limited. Methotrexate is frequently used as a second-line, disease-modifying agent for treatment of rheumatologic diseases. This medication offers an option for significant improvement in functional outcomes and quality of life for elderly patients. The beneficial effects of methotrexate must be balanced against such untoward effects as immunosuppression. The toxicities of methotrexate are more likely to occur in elderly patients; in patients with renal dysfunction, hepatic dysfunction, or folate deficiency; and in patients who are also taking antifolate agents, protein-bound drugs other than methotrexate, or nonsteroidal anti-inflammatory drugs (NSAIDs).

Review of the literature suggests a possible association between methotrexate use and development of secondary myelodysplasia. This article describes the development of myelodysplasia in a patient with rheumatoid arthritis who was previously treated with methotrexate. The pathology, diagnosis, and treatment of MDS as well as the pharmacology and toxicities of methotrexate are also discussed.

CASE PRESENTATION

History

A 72-year-old woman presents to the geriatric medicine clinic for initial evaluation of generalized arthralgias and arthritis. The patient describes progressive dif-

ficulty with swollen, painful joints over the past month. One year before her current presentation, the patient was examined by a rheumatologist, who made a diagnosis of psoriatic arthritis based on presumed psoriasis that appeared on the patient's elbows, the presence of symmetric polyarthritis, and the absence of rheumatoid factor. The patient's arthralgias and arthritis were refractory to therapy with NSAIDs, and methotrexate was initiated. The patient took oral methotrexate 7.5 mg/week for 4 months, but the medication was discontinued 2 months before her current presentation to the geriatric medicine clinic due to a herpes zoster exacerbation. Three days before her evaluation at the geriatric medicine clinic, she presented to the university hospital emergency department where she was found to have a urinary tract infection. She was discharged home from the emergency department with a 3-day oral course of double-strength trimethoprim-sulfamethoxazole (1 tablet taken twice daily).

At current presentation, the patient denies fever, headache, vision changes, dyspnea, and abdominal pain. She has lost 5 lb in 2 months and has experienced chills and increased urinary frequency. Medications on presentation include folic acid, 1 mg daily; acetaminophen/hydrocodone, one half tablet every 4 hours as needed; conjugated estrogen, 0.625 mg daily; prednisone, 5 mg daily; vitamin E, 400 IU daily; and lorazepam, 1 mg 3 times daily. The patient takes all of these medications orally.

Physical Examination

The patient appears cushingoid and weighs 162 lb. Her temperature is 98.7°F; blood pressure, 112/70 mm Hg; heart rate, 100 bpm; and respiratory rate,

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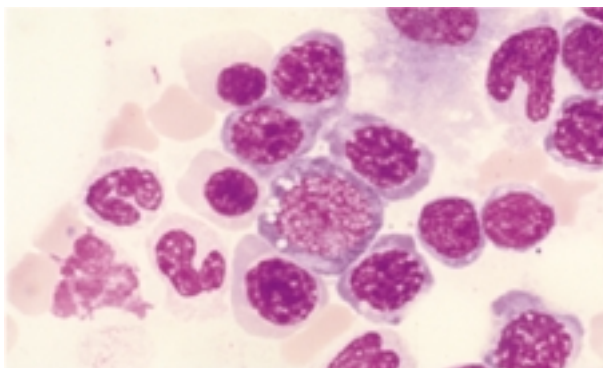


Figure 1. Wright's stain of the case patient's bone marrow shows numerous blasts with abnormal and asynchronous maturation. Note the erythroblast (center) with loosely packed chromatin and vacuoles in the cytoplasm. Original magnification $\times 100$ using oil immersion lens.

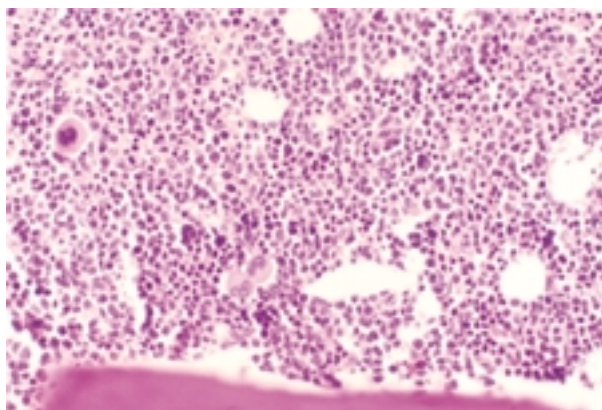


Figure 2. Hematoxylin-eosin stain demonstrates the case patient's bone marrow to be hypercellular with cells that contain multiple nuclei. Original magnification $\times 10$.

16 breaths/min. Warmth, tenderness, and synovitis involving the wrists, metacarpophalangeal joints, ankles bilaterally, left proximal interphalangeal joint, and the right great toe are noted. She is also tender over the C7 spinous process and both shoulders. Well-healed zosteriform lesions are present on the right cystiform angle. The remaining findings on physical examination are unremarkable.

Laboratory Evaluation

Serum chemistry findings are sodium, 133 mEq/L; potassium, 4.5 mEq/L; and glucose, 102 mg/dL. The leukocyte count is $11.4 \times 10^3/\mu\text{L}$, with 12% segmented neutrophils, 3% band cells, 30% lymphocytes, 35% monocytes, 7% metamyelocytes, 1% myelocytes, 1% blasts, and 11% atypical lymphocytes. The erythrocyte count is $2.59 \times 10^6/\mu\text{L}$; hemoglobin is 9 g/dL; mean corpuscular volume is 102 fL; and the platelet count is $180 \times 10^3/\mu\text{L}$. Liver and thyroid function test results are unremarkable. Urinalysis reveals specific gravity, 1.027; pH, 5.5; protein, 1+; blood, 3+; and 3–10 erythrocytes and 0–5 leukocytes per high-power field. Results of urine culture are unremarkable. Mild diffuse osteopenia without evidence of erosive arthropathy is noted on radiographs of the hands.

Diagnosis

The patient is evaluated as an outpatient and receives rheumatology and hematology-oncology consultations. Based on her symmetric polyarthritis, the rheumatologic diagnosis is revised to rheumatoid arthritis. The patient undergoes bone marrow biopsy and aspiration that reveal 30% blasts with normal cytogenet-

ic characteristics. Flow cytometry of the bone marrow aspirate shows atypical immature myeloid cells with low-density CD45 and non-homogeneous expression of CD33 and CD13, with a distribution of CD34 densities. The bone marrow biopsy is hypercellular with preserved architecture (**Figures 1 and 2**). These bone marrow study findings are consistent with a diagnosis of refractory anemia with excess blasts in transformation.

Treatment

The patient's synovitis improves with oral prednisone, 5 mg twice daily, and a left trochanteric bursa injection of 40 mg methylprednisolone acetate and 10 mL of 1% lidocaine. Her complete blood count findings remain unchanged, and she does not require transfusions. She is monitored with serial laboratory tests and physical examination and is observed to be doing well with supportive care for the myelodysplasia.

DISCUSSION

Myelodysplastic Syndrome

Pathology. MDS designates a group of disorders that primarily affect persons older than 50 years, although a few cases have been observed in children.¹ These disorders represent abnormalities that affect trilineage cell populations. Clonal disorders result from disruptions that occur within a pluripotent stem cell. It is estimated that 15% to 20% of cases of MDS will terminate in AML. MDS is manifested by ineffective hematopoiesis, normal or hypercellular bone marrow, and peripheral blood cytopenias.

Both primary and secondary MDS occur. Secondary MDS is commonly attributed to exposure to ionizing radiation or intensive therapies with alkylating agents.²

Table 1. The Most Common Karyotypic Abnormalities Associated with Myelodysplasia

Chromosome 5 (5q- or 5-)
Chromosome 7 (7-)
Trisomy 8
Trisomy 13
Reciprocal translocations involving chromosomes 13,3,1

Adapted with permission from Jandl JH: Hematopoietic malignancies. In *Blood: Textbook of Hematology*, 2nd ed. Boston: Little Brown, 1996: 830–839.

The case presented here highlights the possible association of low-dose (7.5 mg/week) methotrexate exposure and the development of MDS in an elderly patient.

Several chromosomal abnormalities exist in patients with MDS. The most commonly described aberrations of karyotypes are shown in **Table 1**. Patients who present with or subsequently develop complex chromosomal aberrations, as well as patients with monosomy 7, are at high risk for transformation to AML.

Diagnosis. The diagnosis of MDS is based on morphologic, cytochemical, and immunocytochemical studies. MDS is classified according to the French-American-British (FAB) system. The FAB system is based on morphologic features of blasts present in MDS (**Table 2**). The percentage of blasts in the bone marrow is recognized as the most important diagnostic factor of MDS. Refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML) are based on bone marrow morphologies more than peripheral blood morphologies.

Another diagnostic tool used to determine the natural history of myelodysplasia was developed by the International Myelodysplastic Syndrome Risk Analysis Workshop. This tool is a scoring system that is based on the percentage of bone marrow blasts, cytogenetic features, and cytopenias.³ Also, cytochemical and immunocytochemical stains are useful to enhance the diagnosis of MDS. For example, Sudan black B fat stains or peroxidase stains confirm a myeloid origin for blast cells. Additionally, immunocytochemical studies are useful to identify the origin of lineage for blasts and other cell types seen in MDS.

Treatment. Treatment for myelodysplasia in elderly patients is largely supportive and requires close monitoring by a hematologist-oncologist. Stem cell trans-

Table 2. French-American-British Classification of Myelodysplastic Syndromes

MDS Subtype	Frequency of Blasts, Blood	Frequency of Blasts, Marrow	Median Survival (months)
RA	< 1%	< 5%	50
RARS	< 1%	< 5%	51
RAEB	< 5%	5%–20%	11
RAEB-T	> 5%	20%–30%	5
CMML	< 5%*	5%–20%	11

CMML = chronic myelomonocytic leukemia; MDS = myelodysplastic syndrome; RA = refractory anemia; RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; RARS = refractory anemia with ringed sideroblasts.

* Together with > 100,000/mL monocytes in peripheral blood.

plantation is the only therapy for potential cure. Transplantation is most successful when performed in a patient who is younger than 55 years, has an allogeneic transplantation source, and has low disease burden. Anemia is the most common problem in MDS. The majority of patients with MDS eventually succumb to complications of infections.

Erythrocyte transfusions are an integral part of supportive care for MDS. Folate and cobalamin, irrespective of serum assay results, are frequently administered. This practice is occasionally noted to result in improved complete blood count values. Administration of pyridoxine is also observed to temporarily improve blood counts and thus diminish transfusion requirements. However, sustained benefit from pyridoxine therapy is rare.

Growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), erythropoietin, and interleukin-3 are used alone or in combination with cytarabine to increase blood counts. However, peripheral blood and bone marrow myeloblasts have been reported to increase as a result of treatment with G-CSF and GM-CSF, and the progression to AML with this type of therapy is also noted to increase.⁴ The response rate to erythropoietin is high in patients with less-severe anemias and low in patients with more-severe anemias.

Cytarabine is used in a dose of 15 mg/m² per day for the treatment of MDS. Small trials using 5-aza-2'-deoxycytidine and amifostine have shown promise as therapeutic options for elderly patients with MDS.⁵ However, the risks from aggressive chemotherapy for MDS, especially in older persons, frequently outweigh

the benefits. Aggressive chemotherapy (ie, with 5-aza-2'-deoxycytidine and amifostine) can induce a brief complete remission and may be considered for those who fail cytarabine therapy.

Arthritides associated with myelodysplasia. Several paraneoplastic manifestations relating to rheumatologic diseases that precede myelodysplasia have been described. These include acute monoarthritis, symmetric seronegative or seropositive arthritis, seronegative oligoarthritis, systemic and cutaneous vasculitis, polymyalgia rheumatica-like syndrome, systemic lupus erythematosus-like syndrome, rheumatoid arthritis-like syndrome, peripheral neuropathies, adhesive capsulitis, and relapsing polychondritis.⁶ Also, preexisting rheumatoid arthritis, Sjögren's syndrome, and mixed connective tissue disease have known associations with myelodysplasia as well as other malignancies.^{7,8-11}

Methotrexate

Pharmacology. Methotrexate and its historical precursor, aminopterin, are folic acid analogues that inhibit DNA and RNA synthesis by various mechanisms of action; inhibition of dihydrofolate reductase is a well-known action of methotrexate. Similarly, trimethoprim inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase, whereas sulfamethoxazole blocks the synthesis of dihydropterotic acid from para-aminobenzoic acid and pteridine.¹² Thymidine synthesis is in turn interrupted by inhibition of dihydrofolate reductase. The derivatives of methotrexate, including polyglutamyl derivatives, are even more potent than their parent drug at inhibiting enzymes that are useful to folic acid pathways.¹³ Purine synthesis and pyrimidine synthesis are also impaired by methotrexate and its derivatives.

The antirheumatic properties of methotrexate can be understood by examining the various pharmacologic mechanisms of the drug that exert anti-inflammatory, immunosuppressive, and cytotoxic effects. In addition to the inhibition of dihydrofolate reductase, methotrexate inhibits several distal enzymes, the most crucial of which is aminoimidazole-carboxamide-ribotide-transformylase (AICAR-transformylase). Inhibition of AICAR-transformylase results in the accumulation of AICAR, which impedes the function of several cell types that are necessary to produce the inflammation of rheumatoid arthritis. Also, methotrexate has been shown to diminish the production of interleukin (IL)-1 and leukotriene B₄, inhibit lymphocyte proliferation, reduce levels of $\gamma\delta$ T cells as well as double-negative cells

(CD4⁻, CD8⁻), and decrease serum levels of immunoglobulins M and A and rheumatoid factor.

Disease-modifying antirheumatic drugs are commonly used in the general patient population at doses of 5 to 25 mg/week; at these doses, methotrexate and its metabolites circulate, primarily bound to albumin. Oral methotrexate in this dose range is absorbed in a dose-dependent manner,¹³ and subcutaneous methotrexate is well-distributed. However, scant literature is available on the methotrexate dose ranges needed to achieve anti-inflammatory benefits in the geriatric population.

Toxicities. Methotrexate is metabolized via polyglutamylation to 7-hydroxymethotrexate and other metabolites in the liver. Methotrexate-polyglutamates are known to linger in the intracellular compartment for prolonged periods.¹³ The elimination of methotrexate from the body occurs by both renal and biliary routes. Notably, the toxicity of methotrexate is dependent on the rate of drug clearance by renal mechanisms. Patients with renal and hepatic dysfunction are more susceptible to serious toxicities from methotrexate use. The physician is advised to cautiously monitor for drug interactions between methotrexate and other drugs (**Table 3**), particularly when methotrexate is used in conjunction with other potentially nephrotoxic drugs.

Adverse effects accompany long-term use of methotrexate, and numerous toxicities result from the folate-deficient state created by methotrexate use. Folinic acid (leucovorin) reduces toxicities of methotrexate but alters its efficacy, whereas folic acid reduces toxicities without altering the efficacy of methotrexate. In addition to effects on immunity and wound healing, a number of adverse effects to the central nervous, cardiovascular, pulmonary, gastrointestinal, hepatic, musculoskeletal, integumentary, genitourinary, and hematologic systems have been documented.¹⁴ The most commonly cited neoplastic disorders are leukemia, lymphomas, and lung malignancies.^{13,15} Serial laboratory studies are necessary to monitor for toxicities. Complete blood count, liver function, urinalysis, and renal function tests are routinely monitored in patients who receive methotrexate. Also, chest radiographs are obtained at baseline and then repeated periodically. The association of methotrexate use with secondary myelodysplasia is beginning to be recognized.⁷

SUMMARY

Myelodysplasia occurs with a high prevalence among persons older than age 50 years. This disorder

Table 3. Possible Interactions Between Methotrexate and Other Medications

Drug category	Effect	Examples
Antifolates	May result in severe folate deficiency	Trimethoprim-sulfamethoxazole
Protein-bound drugs other than MTX	May displace MTX and increase its toxicity	Salicylates, certain antibiotics
NSAIDs	Substantially alter renal clearance mechanisms (especially important in patients with renal insufficiency and in the elderly)	Ibuprofen, naproxen

MTX = methotrexate; NSAIDs = nonsteroidal anti-inflammatory drugs.

may present as paraneoplastic inflammatory joint diseases and/or follow the onset of a connective tissue disease. Similarly, new-onset rheumatoid arthritis occurs in 75% of patients older than age 60 years. Methotrexate is frequently used as a disease-modifying treatment for rheumatoid arthritis and other rheumatologic diseases. Although methotrexate significantly improves the quality of life for patients who are debilitated by rheumatologic disorders, the use of this drug requires vigilance for adverse drug events, especially in elderly patients, patients with renal or hepatic dysfunction or folate deficiency, and patients who are also receiving protein-bound drugs and/or NSAIDs. Because methotrexate use may be accompanied by an increased relative risk of developing MDS, the association between use of this drug and the development of myelodysplasia warrants further investigation. **HP**

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