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Case Report

Severe bone marrow suppression accompanied by pulmonary infection and suspected acute cholecystitis associated with leflunomide and low-dose methotrexate combination therapy: a case study

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Abstract: A 65-year-old woman developed hyperpyrexia, mouth ulcers, coughing, expectoration with blood-stained sputum, right upper quadrant tenderness, and suppurative tonsillitis after receiving 6 weeks of combination treatment with leflunomide, celecoxib, and low-dose methotrexate for active rheumatoid arthritis. On admission, routine blood tests showed agranulocytopenia, severe thrombocytopenia, and a further decrease in hemoglobin concentration compared with relatively normal values for platelet and white cell counts and a slightly reduced hemoglobin concentration 45 days previously. Chest radiography revealed inflammation in both lungs and Murphy sign was positive. Severe bone marrow suppression accompanied by pulmonary infection and acute cholecystitis associated with leflunomide and low-dose methotrexate combination therapy was highly suspected. The patient's complications gradually resolved over 6 weeks of symptomatic treatment. This case highlights that, especially at the beginning of treatment, bone marrow suppression associated with methotrexate and leflunomide combination therapy for anti-rheumatic purpose can be very serious, even when administered in standard doses. Monitoring of blood counts during low-dose methotrexate and leflunomide combination therapy should be mandatory every 2 weeks, especially during the first 3 months of treatment. When blood counts decline rapidly, therapy with methotrexate and leflunomide should be stopped immediately.

Keywords: Methotrexate, leflunomide, severe bone marrow suppression, acute attack of chronic cholecystitis, pulmonary infection

Introduction

Methotrexate (MTX) and leflunomide (LEF) are both effective first-line disease-modifying anti-rheumatic drugs (DMARDs) that are used to treat active rheumatoid arthritis (RA). The potentially complementary mechanisms of action of these two effective DMARDs provide a rationale for their use in combination therapy in patients whose condition is no longer responsive to MTX alone [1].

In general, low-dose MTX and LEF combination therapy is safe and well tolerated in patients with RA, its adverse events being comparable to those of monotherapy and other non-biological DMARDs treatments [2]. The most commonly reported adverse events associated with MTX and LEF, namely nausea, alopecia, diarrhea, alopecia, nausea, rash, and increases in plasma liver enzyme concentrations, are generally mild to moderate and resolve without complications [3]. However, serious adverse drug reactions (ADRs) such as liver disease [4], pancytopenia [5, 6], severe leukopenia [7], opportunistic infections [5, 6], and toxic epidermal necrolysis [8] can necessitate discontinuation of therapy and hospitalization, and may be fatal [9]. Herein we described the first case, to our knowledge, of a 65-year-old woman with RA who developed severe bone marrow suppression accompanied by pulmonary infection, acute attack of chronic cholecystitis, and hemorrhage from the digestive tract associated with low-dose MTX and LEF combination therapy.

Table 1. Original laboratory data collected during the first hospitalization

Measurement	Value	Reference range
Hematological panel		
White blood cells (× 10^9/L)	7.46	3.50~9.50
Neutrophilic granulocyte (%)	75.0	50.0~70.0
Red blood cells (× 10^{12}/L)	3.13	3.8~5.1
Hemoglobin concentration (g/L)	86	115~150
Platelets (× 10^9/L)	328	100~350
Serum chemistry results		
Aspartate aminotransferase (U/L)	18	13~35
Alanine aminotransferase (U/L)	16	3~35
Albumin (g/L)	32.4	36.0~51.0
Blood urea nitrogen (mmol/L)	12.67	2.4~8.2
Creatinine (μmol/L)	99.1	31.8~91.0
Uric acid (μmol/L)	462.6	90~420
Erythrocyte sedimentation rate (mm/H)	160.2	0~20
C-reactive protein (mg/L)	52.9	0.0~6.0
Globulin (g/L)	35.8	25.0~35.0
Total complement (U/mL)	62	23~46
Rheumatoid factor (IU/mL)	46.9	0.0~20.0
Immunoglobulin g (g/L)	20.80	8.00~16.00
Antinuclear antibodies	Positive	Negative
Antikeratin antibodies	Positive	Negative
Anti-RA33 antibody (U/mL)	38	<25
Glucose-6-phosphate isomerase (mg/L)	2.1	<0.4
Anti-CCP antibody (U/mL)	25	<46

Ethical approval

No ethical approval was required for this case report.

Case report

A 65-year-old woman was admitted to the Third Affiliated Hospital of Sun Yat-sen University, China because of 4 years of swelling and pain in the metacarpophalangeal, knee, proximal and distal interphalangeal, ankle, and wrist joints bilaterally and 3 days of fever, chills, coughing, and expectoration. The results of laboratory examinations on the first day of admission, including blood counts, liver or renal function, and serum chemistry, are shown in **Table 1**. She gave a history of hemorrhage from the upper digestive tract and pulmonary infection 49 days prior to this admission. Color Doppler ultrasound on the first day of admission revealed chronic cholecystitis with multiple cholecystolithiasis. A chest X-ray film (**Figure 1A**) showed no meaningful results. She was diagnosed as having active RA on evaluation of radiologic, physical, and laboratory examinations. After 2 weeks of symptomatic treatment, including anti-infective and anti-inflammatory agents and anti-rheumatoid therapy, her condition improved and she was discharged with a white blood cell (WBC) count of 6.43 × 10^9/L, hemoglobin concentration of 83 g/L, and platelet count of 320 × 10^9/L. On discharge, oral combination therapy for RA comprising LEF (20 mg/day), MTX (10 mg/week), celecoxib (0.2 g/day), and methylprednisolone (8 mg/day) was continued. Pantoprazole (40 mg/day), teprenone (50 mg, 3 times daily), and calcium carbonate and vitamin D_3 (600 mg + 125 IU/day) were also prescribed orally as adjuvant therapies to inhibit gastric acid secretion, provide gastric mucosal protection, and prevent methylprednisolone-associated osteoporosis, respectively.

Thirty days later the patient was hospitalized again because of 3 days of pyrexia, pharyngeal pain, coughing, right upper quadrant tenderness, and expectoration of blood-stained sputum. Physical examination at the emergency department showed a body temperature of 39.5°C, third-degree tonsillar swelling with overlying pus, positive Murphy sign, and 0.5 × 1 cm mouth ulcers in both cheeks.

The day after this admission, laboratory examinations revealed pronounced decreases in platelet count (10 × 10^9/L), WBC count (0.48 × 10^9/L with a neutrophil count of 0.04 × 10^9/L), and hemoglobin concentration (53 g/L) compared with results during the first hospitalization. On the second day after hospitalization, abnormal serum biochemistry results included aspartate transaminase 79 U/L, alanine aminotransferase 288 U/L, C-reactive protein 208.8 mg/L, erythrocyte sedimentation rate 145 mm/h, blood urea nitrogen 10.8 mmol/L, uric acid 501 μmol/L, and serum creatinine 158 μmol/L. A fecal occult blood test was positive. Unlike the chest radiograph (**Figure 1A**)

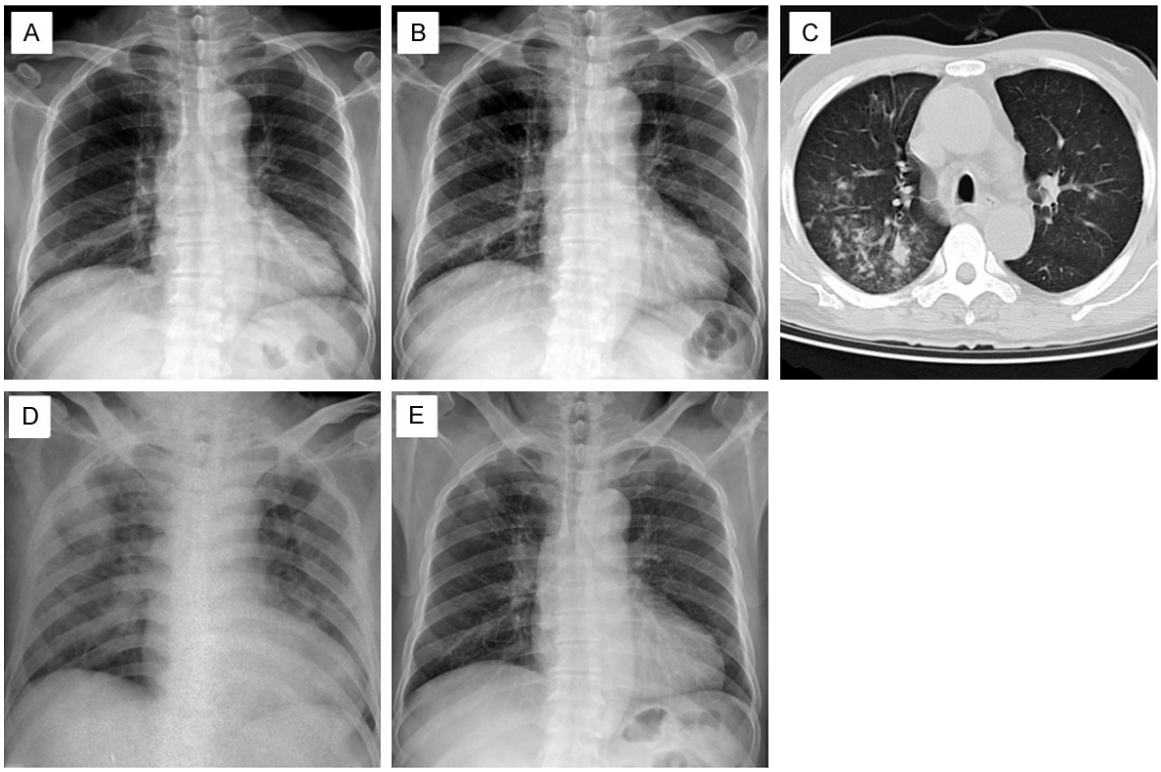

Figure 1. Changes in evidence of inflammation on chest imaging. A. Normal chest radiograph obtained 1 week before initiation of methotrexate and leflunomide combination therapy. B. Chest radiograph obtained on the day of the second admission, 5 weeks after commencing methotrexate and leflunomide combination therapy, showing mild inflammation in both lungs. C. Computed tomography of the chest obtained on the third day of the second admission, showing more inflammation in both lungs than was noted in the chest radiograph on the day of admission, with nodules and seepage in the right lung. D. Chest radiograph obtained 10 days after admission, showing more pronounced evidence of inflammation in both lungs than was present in the previous chest radiograph. E. Chest radiograph obtained after 4 weeks of symptomatic treatment, showing significant resolution of inflammation in both lungs.

obtained before initiation of MTX and LEF combination therapy during the first hospitalization, a chest radiograph (**Figure 1B**) taken the day after the second admission revealed mild inflammation in both lungs that was more marked on the right. Severe bone marrow suppression accompanied by pulmonary infection, acute attack of chronic cholecystitis, and hemorrhage from the digestive tract associated with MTX and LEF combination therapy was highly suspected. MTX, LEF, and celecoxib were stopped, the last because of possible liver or renal toxicity. Intravenous imipenem and cilastatin (1 g 3 times daily) and vancomycin (0.5 g 3 times daily) were prescribed to control the pulmonary infection. Reduced glutathione was also administered intravenously (1.2 g/day) to provide liver protection. Iodine glycerin was applied locally to relieve mouth ulcer pain and the dosage of pantoprazole was increased to 40 mg every 12 h for 3 days. Other intensive supportive therapies included parenteral nutrition, transfusion of red cells and platelets, and administration of recombinant human granulocyte colony-stimulating factor (300 μg/day injection) to increase the leukocyte count. Computed tomography of the chest (**Figure 1C**) obtained on the third day after admission and a chest radiograph (**Figure 1D**) obtained 10 days after admission showed increasingly severe evidence of inflammation. Therefore, from the tenth day after admission intravenous voriconazole (400 mg, twice daily on the first day, followed by 200 mg every 12 h) was added to the anti-infection protocol because of possible combined fungal infection in both lungs (**Figure 1C** and **1D**). The patient's complications resolved gradually after 6 weeks of comprehensive treatment. She was discharged with a normal blood count, a body temperature of 36.8°C,

negative fecal occult blood test, healed mouth ulcers, normal liver function, and improved chest radiograph (**Figure 1E**) together with resolution of other symptoms. A Chinese patent medicine, tripterigium wilfordii glycosides (20 mg, 3 times daily, oral), and oral methylprednisolone (8 mg/day) in combination with hydroxychloroquine sulfate (200 mg, twice daily, oral) were substituted for the LEF/MTX/celecoxib combination therapy. Routine blood tests were normal at 2-week and 1-month follow-up visits.

Discussion

The Naranjo ADR Probability Scale [10] was used to assess this case. First, the timing is appropriate because the abnormal symptoms occurred after MTX and LEF combination therapy had been instituted (score 2). Second, bone marrow suppression has been recorded in association with both MTX and LEF [5-7] (score 1). Third, discontinuation of MTX and LEF/celecoxib combination therapy and the use of symptomatic treatment resulted in marked improvement of our patient's condition, supporting the contention that an ADR had occurred (score 2). Fourth, none of the other agents administered concomitantly are documented as causing such reactions (score 2). The main ADRs attributed to celecoxib are gastrointestinal damage [11], cutaneous eruptions or anaphylaxis [12, 13], thromboembolic events [14], cholestatic hepatitis, and renal injury [15, 16]; hematologic toxicity associated with celecoxib has not been reported thus far. Nevertheless, the patient did have a history of hemorrhage from the upper digestive tract and celecoxib may have exacerbated this symptom. Methylprednisolone can stimulate the hematopoietic function of bone marrow, increasing the number of circulating reticulocytes, neutrophils, and platelets, and can, therefore, be used to treat aplastic anemia [17] and immune thrombocytopenic purpura [18]. Moreover, the other agents administered as adjuvant therapies are relatively safe and free of adverse effects of the type experienced by our patient and were, therefore, unlikely to be contributing factors. Finally, because routine blood tests were unremarkable before the initiation of MTX and LEF combination therapy and during the first week of treatment, the likelihood of hematologic disease is minimal (score 1). Thus, the total Naranjo ADR Probability Scale score of 8 for this case of severe bone marrow suppression accompanied by pulmonary infection after low-dose MTX and LEF combination therapy suggests a probable ADR.

The mechanisms by which a serious ADR occurred in our patient may have been as follows. First, MTX and LEF may depress bone marrow function synergistically because LEF reportedly inhibits pyrimidine synthesis in lymphocytes and MTX can interfere with the synthesis of tetrahydrofolic acid, pyrimidines, and purines, further reducing the activity of immunocompetent and other rapidly dividing cells [5, 19]. Thus, this combination may carry a greater risk than monotherapy [5]. Second, both the active metabolite of LEF (A771726) and celecoxib have high protein binding rates (99% and 97%, respectively) and may displace MTX, with its lower protein binding rate (50%), from plasma proteins, thus increasing its hematologic toxicity. This possibility may have been exacerbated by the patient's hypoproteinemia and renal insufficiency [5, 6, 20]. Third, genetic factors may have contributed to a predisposition to pulmonary infection, tolerability of the medications, risk of adverse events, and elimination of MTX [21, 22]. Finally, it is possible that MTX and LEF combination therapy without folic acid supplementation has greater hematologic toxicity [23].

Conclusions

Clinicians should consider the possibility of severe bone marrow suppression and subsequent or accompanying serious complications, such as pulmonary infection or other opportunistic infections, and hemorrhage from the digestive tract, when prescribing low-dose MTX and LEF combination therapy for RA. Regular monitoring of blood counts is strongly recommended to detect any bone marrow suppression, especially during the first 3 months of treatment. Supplementary folic acid should also be prescribed because it decreases hematologic toxicity and other adverse reactions of MTX with very little loss of efficacy [22]. When blood counts decline rapidly, therapy with MTX and LEF should be stopped immediately. Furthermore, combined MTX and LEF may be inappropriate in patients with a history of pulmonary disease or hemorrhage from the digestive tract.

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This patient gave written informed consent for publication of details of his case.

Disclosure of conflict of interest

None.

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