Leukemoid Reaction after Methotrexate-Induced Pancytopenia in a Patient undergoing Continuous Ambulatory Peritoneal Dialysis

Chiao-Ying Sun, MD; Hou-Chang Lin, MD; Yung-Chih Chen, MD; Chi-Ren Tsai, MD; Mai-Szu Wu, MD

Methotrexate has been used as an important alternative therapy in the treatment of various rheumatic diseases. Life threatening marrow suppression in end-stage renal disease patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis has been reported. A 33-year-old woman with systemic lupus erythematosus undergoing chronic peritoneal dialysis developed severe mucositis and pancytopenia after low-dose methotrexate treatment for arthritis. The leukocyte count recovered after methotrexate was withdrawn but a leukemoid blood picture developed during her recovery. No evidence of leukemia was found on bone marrow biopsy. The leukocyte count gradually returned to normal with conservative therapy. *(Chang Gung Med J 2006;29:513-7)*

Key words: leukemoid reaction, methotrexate, systemic lupus erythematosus, continuous ambulatory peritoneal dialysis.

Leukocytosis exceeding 50,000/mL is referred to as a leukemoid reaction and is characterized by a significant increase in early neutrophil precursors in the peripheral blood. The differential count has a marked "left shift," evidenced by the presence of myelocytes and metamyelocytes, and increased numbers of band forms in the peripheral blood. Promyelocytes and myeloblasts may occasionally be found in peripheral blood in severe reactions. Proliferation of all the normal myeloid elements is observed in the bone marrow in leukemoid reactions, in contrast to acute leukemia, in which the immature elements predominate.[1] A leukemoid reaction has been reported in association with a variety of infections,[2] intoxications,[3] malignant diseases,[4] hemorrhage and sudden hemolysis.[5] The exact mechanism of a leukemoid reaction is not clear. A genetic defect[6] or abnormal cytokine production[7,8] might be the cause of the extremely high leukocyte count.

Methotrexate is used in many malignant and autoimmune diseases. Bone marrow suppression with pancytopenia is one of the major complications of methotrexate therapy.[9] The blood count usually recovers slowly from the nadir within 1-2 weeks after cessation of methotrexate. A leukemoid reaction after this complication had never been reported in the literature.

We had a patient with underlying systemic lupus erythematosus (SLE) who was undergoing regular continuous ambulatory peritoneal dialysis (CAPD). She received a small dose methotrexate to treat intractable arthritis. Pancytopenia developed after 4 weeks of therapy. A severe leukemoid reaction appeared unexpectedly after cessation of methotrexate therapy. This case report suggests that methotrexate might be associated with this unusual hematolog-

From the Division of Nephrology, Chang Gung Memorial Hospital, Keelung.
Received: Jul. 20, 2004; Accepted: Oct. 5, 2005
Correspondence to: Dr. Mai-Szu Wu, Division of Nephrology, Chang Gung Memorial Hospital. 222, Maijin Rd., Anle Chiu, Keelung, Taiwan 204, R.O.C. Tel.: 886-2-24313131 ext. 2501; Fax: 886-2-24335342; E-mail: maxwu1@cgmh.org.tw

ical complication in patients with end-stage renal disease (ESRD) undergoing peritoneal dialysis.

CASE REPORT

The patient, a 33-year-old woman, had ESRD due to lupus nephritis and had received CAPD for 5 years. She had taken low-dose prednisolone and hydroxychloroquine for intermittent arthritis.

Arthralgia, tenderness and swelling of the bilateral hand joints appeared 3 months prior to this admission. Daily prednisolone 30 mg, hydroxychloroquine 400 mg and meloxican 15 mg failed to resolve the arthralgia after one month. Methotrexate 5 mg was given weekly for arthritis 4 weeks before admission. The dose was increased to 7.5 mg per week 2 weeks later due to poor response. In the meantime, the prednisolone was adjusted to a daily dose of 10 mg, the same as her previous maintenance dose. She routinely took folic acid 5 mg daily according to nutrition recommendations for CAPD patients, and this was continued during the methotrexate treatment. The patient came to our emergency department because of a sudden onset of mucositis, tachycardia, general weakness and chest discomfort after 4 weeks of low-dose methotrexate therapy. Respiratory distress, an anemic appearance and leg edema were noted. Laboratory findings revealed pancytopenia with a leukocyte count of 1500/mL, a hemoglobin level of 6.4 g/dL and a platelet count of 1.42 x 10^5/mL (Table 1). Serology studies indicated normal complement and auto-antibody levels (C3: 121 mg/dL; C4: 34.1 mg/dL, and anti-dsDNA < 40 IU/mL). The serological findings suggested the pancytopenia was not likely a lupus manifestation. The maintenance dose of prednisolone was maintained because there was no evidence of SLE flare.

There was no fever during the hospitalization. Blood, urine, sputum and dialysate cultures grew no microorganism. There were no clinical signs or symptoms which suggested active infection during hospitalization.

After admission, methotrexate therapy was discontinued due to a possible bone marrow suppressive effect. Vitamin B12 and folate levels indicated there was no vitamin deficiency (vitamin B12 level: 1390 pg/mL, folate level: 735 ng/ml). The leukocyte count continued to decrease to a level of 600/mL with prominent lymphocytes (80%) 5 days later (Table 1). A low reticulocyte count (< 1%) further indicated bone marrow suppression. The leukocyte count increased to 4,100/mL 1 week after cessation of methotrexate. It increased rapidly afterwards up to a maximum of 61,800/mL with myeloid series hyperplasia on the 15th day of hospitalization (Table 1). A bone marrow study revealed no evidence of malignancy except for remarkable myeloid hyperplasia

Table 1. Serial Complete Blood Cell Counts

Cell count/date	7/26	7/29	7/31	8/2	8/4	8/7	8/9	8/12	8/14	8/16	8/19	8/22
WBC 1000/mL	1.5	0.9	0.6	4.1	19.1	49.7	61.8	43.6	28.1	18.7	13.3	11.2
RBC million/mL	2.13	2.76	2.57	2.92	2.47	2.55	2.45	2.35	2.86	2.71	2.57	2.38
Hemoglobin g/dL	6.4	8.4	7.8	8.8	7.6	7.8	7.6	7.1	8.8	8.3	8	7.7
Hematocrit %	18.7	23.3	21.7	24.7	21.3	21.9	21.1	20.4	24.6	23.4	22.6	21.7
Platelets 1000/mL	142	78	64	105	162	363	384	325	243	187	161	121
Atypical lymphocytes %	0	0	0	2.5	0	0.5	0	0.5	0	0	0	0
Blasts %	0	0	0	5	3	0	0	0	0	0	0	0
Promyelocytes %	0	0	0	14.5	2	0	0.5	0	0	0	0	0
Myelocytes %	0	0	0	8	5	1	7	0	0	0	0	0
Meta-myelocytes %	0	0	0	2	29	8.5	4.5	0	0	0	0	0
Bands %	0	0	0	1.5	6	5	1.5	2	0.5	0	0	0
Segmented %	64	40	15	23.5	32	69.5	77.5	81.5	85	89	87	81
Lymphocytes %	35	55	80	21	11	8	3.5	8	7.5	4	9	10
Monocytes %	1	2	4	22	11	7	5	8	7	7	4	9
Eosinophils %	0	2	1	0	1	0.5	0.5	0	0	0	0	0
Basophils %	0	1	0	0	0	0	0	0	0	0	0	0

Abbreviations: WBC: white blood cells; RBC: red blood cells.

(Fig. 1). Over the next 2 weeks the leukocyte count gradually returned to 11,200/mL with conservative therapy.

DISCUSSION

Methotrexate has been used as an important alternative therapy in the treatment of various rheumatic diseases.[10] Accumulative evidence suggests that methotrexate in a low weekly dose might be an effective and safe therapy in SLE patients who are steroid-dependent or resistant.[11] The prevalence of hematologic toxicity, including leukopenia, thrombocytopenia, megaloblastic anemia, and pancytopenia, is estimated to be 3% in methotrexate-treated rheumatoid arthritis patients.[12] Severe, and at times fatal, pancytopenia has been reported in 1 to 4% of these patients.[9,13] This adverse effect is more likely to occur in patients with renal insufficiency.[14]

Low-dose methotrexate therapy can cause life threatening marrow suppression in ESRD patients undergoing chronic hemodialysis or CAPD.[9,13] Methotrexate is poorly cleared by hemodialysis and even less so by peritoneal dialysis.[14] Currently the most promising strategy to decrease or prevent methotrexate toxicity is concomitant prescription of folic acid or folinic acid.[15] However in this case, concurrent folic acid supplementation did not prevent hematological toxicity from methotrexate. Even low-dose methotrexate should be avoided in CAPD patients.

In this report, we described a SLE patient under CAPD. She developed pancytopenia, apparently caused by methotrexate toxicity. A leukemoid reaction appeared subsequently during the recovery phase. We believe that methotrexate toxicity was associated with these hematologic abnormalities as demonstrated by the clinical course and bone marrow biopsy. This profile of hematologic adverse effects associated with methotrexate toxicity has not been reported previously. The mechanisms of leukemoid reaction are not understood thoroughly. A leukemoid reaction might come from overproduction or decreased degradation of hematogenic cells. Overproduction has been reported in patients with trisomy 21, malignancy and inflammatory processes.[6-8] Defective removal or destruction of hematogenic cells is also thought to play an important role in the leukemoid process.[6-8]

A leukemoid reaction is a lymphoproliferative disorder. Methotrexate has an oncogenic potential even in low weekly doses in a subset of patients with rheumatoid arthritis.[16] It was conjectured that there is a correlation between hematologic malignancies, especially lymphoma, and the use of methotrexate.[16,17] From these reports, we speculate that the leukemoid reaction after the use of methotrexate in this patient might be a part of the spectrum of methotrexate related lymphoproliferative disorders.

Inflammatory processes are common in individuals with chronic renal failure. The possible causes include an increased incidence of infection, the uremic mileu, elevated inflammatory cytokines, and the presence of widespread arteriosclerosis. Inflammation is reported to be a strong predictor of mortality in dialysis patients.[18,19] Human peritoneal mesothelial cells from uremic patients more readily release interleukin (IL-8) on stimulation with IL-1 than

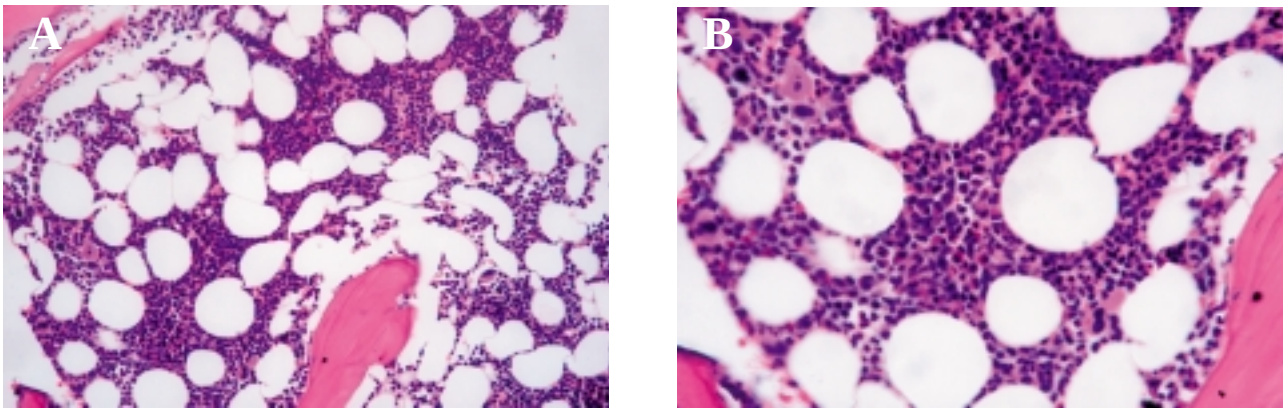

Fig. 1 Bone marrow biopsy showing myeloid hyperplasia (Wright-Giemsa stain, Ax100, Bx200).

those from healthy individuals.[20] IL-6 release is enhanced by chronic peritoneal dialysis treatment.[20] Several studies suggested that unregulated inflammatory cytokine production due to malignancy, chronic infection or congenital genetic defects could induce a leukemoid reaction in humans. IL-1, IL-6, granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor were reported to involve in the formation of a leukemoid reaction.[6-8] The inflammatory cytokines stimulated by a chronic inflammatory state due to uremia or the dialysis process might have played important roles in the leukemoid reaction in our patient.

In conclusion, we reported an unusual methotrexate associated hematological complication in a patient with ESRD undergoing peritoneal dialysis. Methotrexate, even low doses, should be avoided in patients with renal failure. The putative roles of inflammatory cytokines in the leukemoid reaction in uremic patients need further studies to elucidate.

REFERENCES

1. Hilts SV, Shaw CC. Leukemoid blood reactions. N Engl J Med 1953;249:434-8.
2. Twomey JJ, Levell BS. Leukemoid reactions to tuberculosis. Arch Intern Med 1965;116:21-8.
3. Gursoy M. Haznedaroglu IC, Celik I. Sayinalp N, Ozcebe OI, Dundar SV. Agranulocytosis, plasmacytosis, and thrombocytosis followed by a leukemoid reaction due to acute acetaminophen toxicity. Ann Pharmacother 1996;30:762-5.
4. Ferrer A, Cervantes F, Hernandez-Boluda JC, Alvarez A, Montserrat E. Leukemoid reaction preceding the diagnosis of colorectal carcinoma by four years. Haematologica 1999;84:671-2.
5. Marinella MA. Extreme leukemoid reaction associated with retroperitoneal hemorrhage. Arch Intern Med 1998;158:300-1.
6. Seibel NL, Sommer A, Miser J. Transient neonatal leukemoid reactions in mosaic trisomy 21. J Pediatr 1984;104:251-4.
7. Chen YM, Whang-Peng J, Liu JM, Chao Y, Lai CR, Wang SY, Perng RP. Leukemoid reaction resulting from multiple cytokine production in metastatic mucoepidermoid carcinoma with central necrosis. Jpn J Clin Oncol 1995;25:168-72.
8. Melhem MF, Meisler AI, Saito R, Finley GG, Hockman HR, Koski RA. Cytokines in inflammatory malignant fibrous histiocytoma presenting with leukemoid reaction. Blood 1993;82:2038-44.
9. Williams HJ, Willkens RF, Samuelson CO Jr, Alarcon GS, Guttadauria M, Yarboro CH, Polisson RP, Weiner SR, Luggen ME, Billingsley LM, Dahl SL, Egger MJ, Reading JC, Ward JR. Comparison of low-dose oral pulse methotrexate and placebo in the treatment of rheumatoid arthritis: a controlled clinical trial. Arthritis Rheum 1985;28:721-30.
10. Willkens RF, Watson MA. Methotrexate: a prospective of its use in the treatment of rheumatic diseases. J Lab Clin Med 1982;100:314-21.
11. Sato EI. Methotrexate therapy in systemic lupus erythematosus. Lupus 2001;10:162-4.
12. Weinblatt ME. Toxicity of low dose methotrexate in rheumatoid arthritis. J Rheumatol Suppl 1985;12:35-9.
13. Hanrahan PS, Scrivens GA, Russell AS. Prospective long term follow-up of methotrexate therapy in rheumatoid arthritis: toxicity, efficacy and radiological progression. Br J Rheumatol 1989;28:147-53.
14. Gutierrez-Urena S. Molina JF. Garcia CO. Cuellar ML. Espinoza LR. Pancytopenia secondary to methotrexate therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:272-6.
15. van Ede AE, Laan RF, Blom HJ, De Abreu RA, van de Putte LB. Methotrexate in rheumatoid arthritis: an update with focus on mechanisms involved in toxicity. Semin Arthritis Rheum 1998;27:277-92.
16. Gono T, Shimojima Y, Hoshi K, Yamamoto K, Tokuda T, Shikama N, Matsuda M, Ikeda S. Malignant lymphoma associated with rheumatoid arthritis, developing shortly after initiation of oral methotrexate. Intern Med 2004;43:135-8.
17. Ebeo CT, Girish MR, Byrd RP, Roy TM, Mehta JB. Methotrexate-induced pulmonary lymphoma. Chest 2003;123:2150-3.
18. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int 1999;55:648-58.
19. Qureshi AR, Alvestrand A, Divino-Filho JC, Gutierrez A, Heimburger O, Lindholm B, Bergstrom J. Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol 2002;13 suppl 1:28-36.
20. Plum J, Fleisch MC, Razeghi P, Fussholler A, Lordnejad MR, Grabensee B. Influence of uremia on cell viability and cytokine release of human peritoneal mesothelial cells. Kidney Blood Press Res 2002;25:195-201.

腹膜透析病患於 Methotrexate 引發之全血球缺乏症後併發類白血病反應

孫樵隱 林厚昌 陳勇志 蔡啓仁 吳麥斯

Methotrexate 爲風濕免疫疾病重要的治療藥物。Methotrexate 於末期腎病進行血液透析或腹膜透析病患常引發嚴重的骨髓抑制。本文報告一位 33 歲系統性紅斑性狼瘡進行腹膜透析之女性病患於接受低劑量 Methotrexate 治療關節炎後發生嚴重的口角炎及全血球缺乏症。白血球數在停用 Methotrexate 之後即逐漸上升並發生類白血病反應，骨髓切片亦證實非白血病。病患在保守性治療之後白血球數逐漸恢復正常。文中我們描述一罕見 Methotrexate 相關之血液併發症，並討論類白血病反應可能之發生機轉。(長庚醫誌 2006;29:513-7)

關鍵字：類白血病反應，Methotrexate，系統性紅斑性狼瘡，腹膜透析。

長庚紀念醫院 基隆院區 腎臟科
受文日期：民國93年7月20日；接受刊載：民國94年10月5日
索取抽印本處：吳麥斯醫師，長庚紀念醫院 腎臟科。基隆市204安樂區麥金路222號。Tel.: (02)24313131轉2501; Fax: (02)24335342; E-Mail: maxwu1@cgmh.org.tw