Case Reports

Two rare cases of methotrexate-induced pneumonitis and pleurisy in patients with gestational trophoblastic neoplasms

D. Zhang, *M.D.*; **Z. Ding,** *M.D.*; **J. Qian,** *Ph.D.*; **X. Xie,** *M.D.*; **Y. Wang,** *Ph.D.*

Department of Gynecologic Oncology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou (China)

Summary

Background: Pneumonitis is a serious and unpredictable side-effect of treatment with methotrexate (MTX) that may result in a life-threatening outcome. Pulmonary toxicity of methotrexate in patients with a gestational trophoblastic neoplasm (GTN) has rarely been reported before. *Case Reports:* For the first time two cases of methotrexate-induced pneumonitis and pleurisy in GTN patients of Chinese ethnicity are presented. Two patients were both categorized as the low-risk group, and underwent a single regimen therapy of methotrexate. Their symptoms, such as fever, chest pain, acute nonproductive cough, dyspnea and hypoxemia did not respond to antibiotics immediately. Treatment with corticosteroids may be helpful. *Conclusion:* Awareness of pneumonitis and pleurisy, potentially life-threatening complications of MTX, is very necessary and important to early recognition and treatment.

Key words: Methotrexate; Pneumonitis; Pleurisy; Gestational trophoblastic neoplasm.

Introduction

Methotrexate (MTX) is a folate antagonist used for several chronic inflammatory and neoplastic conditions, as well as for a gestational trophoblastic neoplasm (GTN). Pneumonitis is a serious and unpredictable side-effect of treatment with methotrexate (MTX) which may be life-threatening [1, 2]. Pulmonary toxicity occurs in 0.5% to 14% of patients receiving low-dose MTX [3]. Rheumatoid arthritis (RA) is the most frequent underlying disease [4, 5]. To our knowledge, methotrexate pneumonitis and pleurisy in patients with a GTN have rarely been reported before, only one case report of respiratory failure due to pneumocystis carinii (PCP) following methotrexate therapy for GTN was presented in 2005 [2]. For the first time two cases of GTN patients of Chinese ethnicity who developed pneumonitis and pleurisy following single-regimen therapy with methotrexate are presented.

Case Reports

Case 1

A 47-year-old woman presenting with amenorrhea (for 55 days) and an elevated β-hCG level of 40.642 mIU/ml, who had undergone suction evacuation of the uterus on July 1, 2005, was diagnosed with hydatidiform mole. The β-hCG level decreased in the first three weeks, but unfortunately rose again and then remained at 830-1000 mIU/ml in the following four weeks. Pulmonary nodular shadows (0.5 cm in diameter) were found by pulmonary computed tomography (CT). Hepatic ultrasonography (US), cranial CT and chest X-ray were normal. The diagnosis of a gestational trophoblastic neoplasm with FIGO Stage III and a WHO score of 2 was confirmed. The methotrexate-citrovorum factor rescue (MTX-CF) protocol (methotrexate 1.0 mg/kg IM every other day for four doses with leucovorin 0.1 mg/kg 24 hours after each dose of methotrexate) was initiated on August 21, 2005. After two courses of MTX chemotherapy (total dosage 500 mg), the patient had chest pain, fever (38.8°C), cough, and pharyngalgia. The peripheral leucocyte count was 7.1×10^9/l, neutrophilic granulocytes were 79% and eosinophilia was 0.3%; chest radiography was rejected by the patient. Clindamycin (1.8 g/day IV) was prescribed. Two days later her symptoms disappeared and hCG levels decreased to less than 5 mIU/ml. The patient underwent the third MTX course on September 20, 2005. On the sixth day of the third course the patient merely presented fever (38.4°C), without chest pain or cough. The practitioner prescribed levofloxacin (400 mg/day IV). Her body temperature was normal on the seventh day, but in the early dawn of the eighth day the patient felt sharp chest pains, especially beneath the arch of the ribs, and shortness of breath. It was even hard for her to lie down. Clinical examination revealed that her blood pressure was 125/80 mmHg, heart rate 90 beats per minute and respiratory rate at 30 per minute with a temperature of 37.5°C. Dyspnea was relieved after a few moments, but the chest pain continued. The peripheral blood cell count, urine routine, hepatic function and renal function were normal. Pulmonary CT revealed bilateral pleurisy and diminished pulmonary lesions compared to the previous scan. Cefuroxime (1.5 g IV/day) was prescribed and oxygen therapy was given. The symptoms were alleviated five days later. The following two courses of chemotherapy were switched to actinomycin-D (Act-D) for a 5-day course (10 ug/kg/day × 5 days) because of the above-mentioned symptoms caused by MTX. No chest pain, dyspnea, fever or cough occurred after switching to the Act-D course.

Case 2

A 42-year-old woman presenting with amenorrhea (for 58 days) and elevated β-hCG levels (> 10000 mIU/ml), had undergone suction evacuation of the uterus on Feburary 2, 2007. She was pathologically diagnosed as having hydatidiform mole. The

Revised manuscript accepted for publication February 11, 2008

Fig. 1A

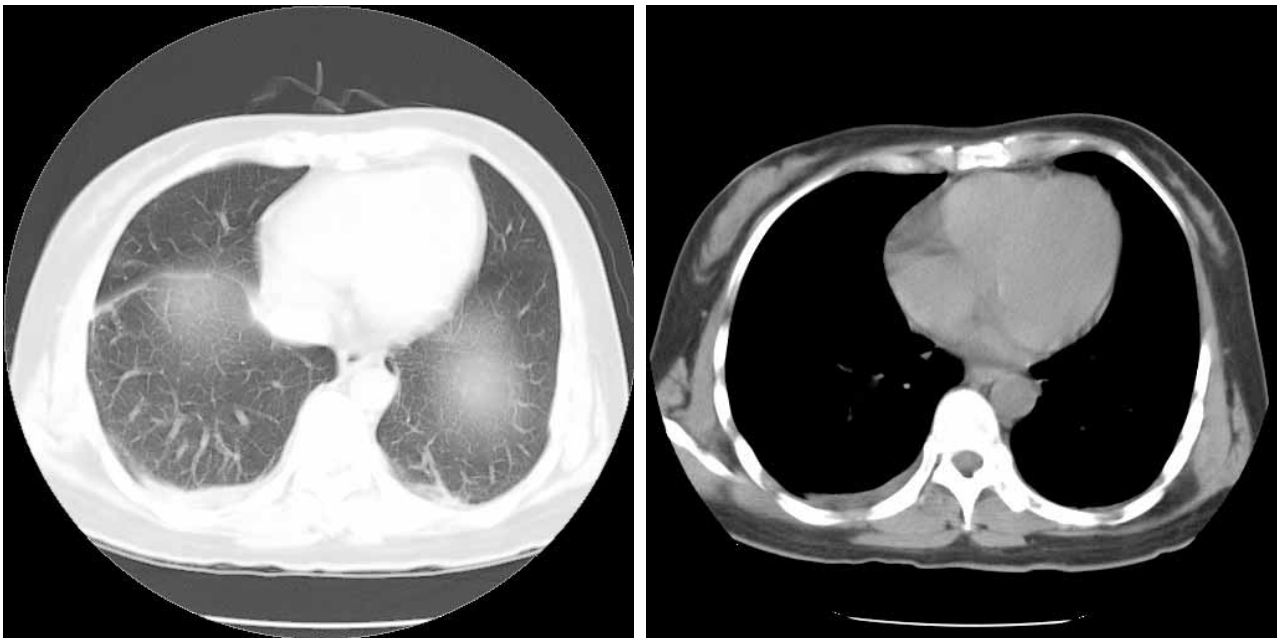

Fig. 1B

Figure 1. — Pulmonary CT showing "bilateral pleurisy with right pleural effusion".

β-hCG level decreased in the first three weeks, but rose again in the fourth week and kept rising to 936 mIU/Ml in the fifth week. A 2.5 cm lesion was found by uterine US, while chest X-ray, pulmonary CT, hepatic US and cranial CT were normal. The diagnosis of GTN was made and FIGO stage/WHO score I:1 were confirmed. A single regimen therapy of MTX (0.4 mg/kg daily for 5 days IM) was initiated on March 11, 2007. HCG declined to 3 mIU/ml after two courses of MTX chemotherapy. On the last two days of the fourth course of MTX therapy (total dosage 440 mg), the patient presented with fever (37.8°C), and levofloxacin (400 mg/d IV) was prescribed. On the sixth day when the fourth course finished, the temperature declined to normal, but she complained of chest and back pain. Auscultation revealed moist rale and pleural rale. The white blood cell count was 5.0×10^9/l, and C-reactive protein was 20.0 mg/l. Pulmonary CT revealed bilateral pleurisy with right pleural effusion (Figure 1 A/B). The practitioner prescribed prednisone (15 mg daily). The symptoms were alleviated a few days later and the patient was discharged (the prednisone was decreased gradually over seven days).

Discussion

Pneumonitis is a serious and unpredictable side-effect of treatment with MTX that may result in life-threatening complications [1]. To our knowledge, MTX pneumonitis and pleurisy in patients with GTN has rarely been reported before. There was only one case report of respiratory failure due to PCP following MTX therapy for GTN by French doctors in 2005 [2]. MTX pneumonitis has not been reported in GTN patients of Chinese ethnicity.

We report two cases of MTX-induced pneumonitis and pleurisy in Chinese patients with GTN, aged 42 and 47, respectively, who had no history of interstitial lung disease before chemotherapy. They were both categorized as the low-risk group, and underwent single regimen therapy of methotrexate: one MTX-CP protocol, and the other the 5-day MTX protocol. Total dosage was 440 mg and 500 mg, respectively, when pulmonary symptoms such as fever, chest pain, acute nonproductive cough, dyspnea and hypoxemia appeared. Their symptoms did not respond to antibiotics immediately, but were alleviated several days later. The first patient's pulmonary function clearly improved after the treatment of corticosteroids. Based on the symptoms and clinical examinations, we considered the diagnosis of interstitial pneumonitis and pleurisy induced by MTX.

MTX is a folate antagonist used in several chronic inflammatory and neoplastic conditions. Pulmonary toxicity occurs in 0.5% to 14% of patients receiving low-dose MTX [3]. Manifestations of pulmonary toxicity are protean and include parenchymal inflammation, pneumonia, airway hyper-reactivity, air trapping and possibly neoplasm. Rheumatoid arthritis (RA) was the most frequent underlying disease [4, 5]. There were also case reports of MTX pneumonitis in psoriatic patients [6] and acute lymphoblastic leukemia [7], causing acute respiratory failure and fatal results. Most patients present subacute symptoms over several weeks, which include dyspnea, dry cough, fever, and bibasilar crackles. The chest radiograph is normal in a small number of cases, but more commonly reveals bilateral interstitial or mixed, interstitial and alveolar infiltrates with a predilection for the basis. CT scans demonstrate ground-glass opacities, interstitial infiltrates, septal lines or widespread consoli-

dation. Pulmonary function studies reveal a restrictive ventilatory defect and/or impaired gas exchange [4-7]. Bronchoalveolar lavage (BAL) may be helpful in ruling out an infectious etiology and in supporting the diagnosis of MTX-induced pneumonitis. Cellular interstitial infiltrates, granulomas, fibrosis, atypical epithelial cells, and diffuse alveolar damage (DAD) are the main histologic features. Lung biopsy reveals cellular interstitial infiltrates, granulomas or a diffuse alveolar damage pattern accompanied by perivascular inflammation [8]. These clinical and pathological findings are not specific to MTX pneumonitis but can also be seen in other drug-induced lung toxicities. The pathogenesis of MTX pueumonitis is still uncertain. It is believed to be related to hypersensity and direct toxicity of MTX.

Once MTX-induced pneumonitis (MIP) is suspected, MTX should be withdrawn. Corticosteroids may accelerate resolution and are recommended in severe or fulminant cases. Cyclophosphamide may successfully cure some cases of interstitial pneumonia resistant to steroids [9]. The prognosis of MIP is usually favorable, but occasionally the outcome may be fatal.

Gynecologists, as well as the managers of GTN patients receiving MTX, should be aware of this potentially life-threatening complication. The prompt evaluation of new pulmonary symptoms in patients receiving MTX is important in the early recognition of this drug-induced complication. It is also important that all patients receiving MTX be educated concerning this potential adverse reaction and instructed to contact their physicians when significant new pulmonary symptoms develop while undergoing therapy. If MTX pneumonitis is suspected, MTX should be discontinued, supportive measures instituted, and careful examination for different causes of respiratory distress conducted.

References

[1] Zisman D.A., McCune W.J., Tino G., Lynch J.P. 3rd.: "Drug-induced pneumonitis: the role of methotrexate". *Sarcoidosis Vasc. Diffuse Lung Dis*., 2001, *18,* 243.
[2] Christophe B., Leila A., Christophe S., Jean-Sebastien A., Jean-louis R., Yann L.: "Respiratory failure due to Pneumocystis carinii following methotrexate therapy for gestational trophoblastic disease". *Br. J. Obstet. Gynecol.,* 2005, *112,* 382.
[3] Cannon G.W.: "Methotrexate pulmonary toxicity". *Rheum. Dis. Clin. North Am.,* 1997, *23,* 917.
[4] Imokawa S., Colby T.V., Leslie K.O., Helmers R.A.: "Methotrexate pneumonitis review of the literature and histopathological findings in nine patients". *Eur. Respir. J.,* 2000, *15,* 373.
[5] Shimizu Y., Tsukagoshi H., Nemoto T., Honma M., Nojima Y., Mori M.: "Effect of methotrexate on pulmonary function in patients with rheumatoid arthritis: a prospective study". *Rheumatol. Int.,* 2002, *22,* 204.
[6] Mazokopakis E., Katsogridakis K., Koutsopoulos A., Voloudaki A., Froudarakis M., Kritikos H. et al.: "Fatal methotrexate-induced pneumonitis in a psoriatic patient". *Mil. Med.,* 2004, *169*, 298.
[7] Tatsumoto C., Kawakami K., Nagayama J., Kawano H.: "Methotrexate-induced interstitial pneumonitis in a child with acute lymphoblastic leukemia". *Rinsho. Ketsueki.,* 2004, *45,* 1100.
[8] Cho I., Mori S., Imamura F., Kiyofuji C., Sugimoto M.: "Methotrexate pneumonia lacking dyspnea and radiographic interstitial patterns during treatment for early rheumatoid arthritis: bronchoalveolar lavage and transbronchial lung biopsy in a differential diagnosis". *Mod. Rheumatol.,* 2007, *17*, 256.
[9] Ozawa Y., Ida M., Suda T., Katou M., Enomoto N., Fujii M. *et al.*: "A case of subacute idiopathic interstitial pneumonia resistant to steroids, successfully treated with cyclophosphamide". *Nihon. Kokyuki. Gakkai. Zasshi*., 2004, *42,* 945.

Address reprint requests to:
Z. DING, M.D.
Department of Gynecologic Oncology
Women's Hospital, School of Medicine
Zhejiang University, Xueshi Rd #2,
310006 Hangzhou (China)
e-mail: dingzm@zju.edu.cn