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## Spontaneous Pneumothorax in a Patient with Osteosarcoma During Treatment with Methotrexate

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**Abstract:** Methotrexate is a commonly prescribed antineoplastic and immune modulating compound that has gained wide acceptance in the management of rheumatoid arthritis, psoriasis, sarcoidosis and a number of neoplastic disorders. High dose methotrexate with folinic acid rescue is widely used to treat osteosarcoma, which predominantly afflicts children. Although generally considered safe and easy to use, methotrexate has been associated with a number of adverse reactions. Serious toxicity may affect the lungs, liver and bone marrow. Pulmonary complications of methotrexate may be classified as inflammatory, infectious and possibly neoplastic. We describe a patient with osteosarcoma who presented with leg pain and subsequently developed a spontaneous pneumothorax during treatment with Methotrexate.

**Key words:** Methotrexate, Osteosarcoma, Spontaneous Pneumothorax

### INTRODUCTION

Methotrexate is an analogue of the vitamin folic acid that inhibits cellular proliferation by inducing an acute intracellular deficiency of certain folate coenzymes (Cronstein, 1996; Lynch and McCune, 1997). The molecular formula of methotrexate was first described in 1946. Since that time, the compound has gained widespread use as an antineoplastic agent and in the treatment of rheumatoid arthritis, psoriasis and other chronic inflammatory conditions. A number of adverse effects may result from the use of methotrexate. Serious toxicity may affect the lungs, liver and bone marrow (Cronstein, 1996; Imokawa *et al.*, 2000). Methotrexate is a commonly prescribed antineoplastic and immune modulating compound that has gained wide acceptance in the management of rheumatoid arthritis, psoriasis, sarcoidosis and a number of neoplastic disorders. Although generally considered safe and easy to use, methotrexate has been associated with a number of adverse reactions. Pulmonary toxicity has been well-described and may take a variety of forms (Lateef *et al.*, 2005). Pulmonary complications of methotrexate may be classified as inflammatory, infectious and possibly neoplastic (Conaghan *et al.*, 1995). The administration of methotrexate doses  $\geq 1000$  mg m<sup>-2</sup> combined with

leucovorin (LV) rescue is defined as high-dose methotrexate (HDMTX). HDMTX is an important component of treatment for a variety of malignancies, including Acute Lymphoblastic Leukemia (ALL), lymphoma, osteosarcoma, breast carcinoma and head and neck carcinoma (Widemann *et al.*, 2004). Osteosarcoma is a rare disease generally affecting children and adolescents and the most common primary bone malignancy in children and young adolescents; approximately 10-20% of patients have metastases at the time of diagnosis. Many studies have addressed the efficacy, clinical and pathological response and pharmacokinetics of methotrexate in these patients. HDMTX intravenous infusions followed by folinic acid (LV) rescue are frequently used in the treatment of osteosarcoma and response is generally correlated with methotrexate dose (Comandone *et al.*, 2005; Daw *et al.*, 2006). Spontaneous Pneumothorax in patients who received methotrexate is rare, in this research we report Spontaneous Pneumothorax in a patient with osteosarcoma During Treatment with Methotrexate.

### PATIENT

A 15-year-old male was admitted due to a chronic pain and swelling of distal of left thigh. He had suffered

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from these problems for two months. On admission, the patient was not ill and had a temperature of 37.2°C. No lymphadenopathy was detected. Heart sounds were normal. His lungs were clear on auscultation. The abdomen was normal. Hepatomegaly and splenomegaly were not detected. There was no skin rash. A 10×12 cm mass with swelling and tenderness was located on distal of left thigh. Laboratory studies showed a white blood count of 3200 mm<sup>-3</sup>, haemoglobin of 11.5 g dL<sup>-1</sup> and a platelet count of 244,000 mm<sup>-3</sup>. Alkaline phosphates was 1088 IU L<sup>-1</sup>. Erythrocyte Sedimentation Rate (ESR) was 64 mm at 1 h. Chest X-ray demonstrated a normal pattern. A whole body bone scan showed bone sarcoma in left femur without metastasis to distant skeletal bone. MRI showed a mass in mid shaft of femur with bone destruction and bone marrow involvement compatible with osteogenic sarcoma. An open biopsy was done that showed proliferating spindle-shaped cells that was consistent with osteosarcoma. Thereby he was under treatment with cisplatin and adriamidine. Three weeks after first chemotherapy he was treated with Methotrexate and leukoverin. After one day, he complained from dyspnea that was occurred abruptly. A chest X-ray was done. In X-ray, right sided pneumothorax was demonstrated (Fig. 1). Thus, a chest tube was inserted in right side. The patient's recovery was uneventful and he was discharged. Follow-up after 6 months showed the patient to be in a stable condition without any respiratory symptoms.



Fig. 1: Posteroanterior upright chest radiograph revealing a large pneumothorax of the right lung

## DISCUSSION

MTX carries a significant risk of pulmonary toxicity. Toxicity includes acute pneumonitis, pulmonary fibrosis and opportunistic infections such as *Pneumocystis carinii* and a high rate of herpes zoster (Gotsman *et al.*, 2001). Pulmonary complications of methotrexate may be classified as inflammatory, infectious and possibly neoplastic (Conaghan *et al.*, 1995). Hypersensitivity pneumonitis is the most common pulmonary toxicity associated with the use of methotrexate (Hilliquin *et al.*, 1996). A number of other pulmonary conditions have been associated with methotrexate use, including (Rosenow *et al.*, 1992):

- Bronchiolitis obliterans with organizing pneumonia (BOOP)
- Acute lung injury with noncardiogenic pulmonary edema
- Pulmonary fibrosis (which may be rapidly progressive)
- Bronchitis with airways hyperreactivity

Features of MTX-induced pulmonary injury are variable and included diffuse parenchymal opacification, reticular opacities and centrilobular nodules. The precise mechanisms by which methotrexate results in pulmonary injury are unknown. Most researchers suggest that methotrexate pneumonitis is a form of hypersensitivity lung disease because there is typically fever, eosinophilia, an increase in CD4+T cells in bronchoalveolar lavage fluid and a mononuclear cell infiltration of the lungs with granulomatous inflammation. Pulmonary toxicity has occurred following both low and high doses and by a variety of routes of administration, suggesting that some side effects may result from idiosyncratic mechanisms unrelated to folate antagonism. None of the proposed mechanisms accounts for the observation that pulmonary toxicity may remit despite continued therapy and may not occur upon rechallenge (Cronstein, 1996; Lynch and McCune, 1997).

A small number of case studies describe patients with pulmonary nodules, developing pneumothorax after the initiation or augmentation of methotrexate treatment (Steeghs *et al.*, 2005). But our patient had not any pulmonary nodules before initiation of methotrexate also no definitive relationship could be established. In summary, the mechanisms of methotrexate pulmonary toxicity are unresolved and may be multiple. To our knowledge, this is the first described case of a neoplastic patient with spontaneous pneumothorax during treatment with methotrexate. Methotrexate may have initiated the

pulmonary disease and causing pneumothorax in patients without any pulmonary risk factor as nodule or cavitations. Therefore, pneumothorax should be considered, even in patients treated with low-dose methotrexate.

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