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Methotrexate-induced pericarditis and pericardial effusion; first reported case

LN Forbat, BW Hancock, AH Gershlick

Summary

We report a case of methotrexate-induced pericarditis and pericardial effusion in a 22-year-old pregnant woman. These complications have not previously been described as isolated phenomena associated with methotrexate therapy.

Keywords: pericarditis, pericardial effusion, methotrexate, toxicity

Introduction

Methotrexate is used in different schedules in oncology and commonly in low dose oral regimens in rheumatology. The recognised features of methotrexate toxicity are shown in the box. Pericarditis and pericardial effusion have not previously been described as isolated phenomena, whereas pneumonitis and/or pleurisy are complications which occur idiosyncratically¹ in patients treated with methotrexate^{2,3} and are reported to occur in 5–12% of treated patients.^{1,4} In cyclical regimens used in oncology, pleural/pulmonary complications are very rare; however, in patients with persistent gestational trophoblastic disease receiving low-dose intramuscular repeated-course schedules, over 20% of patients may be affected.⁵ Steroids are not usually used to treat methotrexate lung; however, they may be of therapeutic value in some patients.¹ Occasionally the symptoms may be so severe and intractable that a change in cytotoxic therapy is required. We report a case of pericarditis and pericardial effusion leading to symptoms of breathlessness.

Case report

A 22-year-old woman presented with a molar pregnancy. Beta-human chorionic gonadotrophin (BHCG) levels were 6295 IU/l (normal <7) and a complete hydatidiform mole was removed at dilatation and curettage. Post-operatively BHCG levels fell to 3720 IU/l; however two months later a computed tomography (CT) scan showed a single pulmonary nodule and her BHCG levels remained elevated. She was treated with intramuscular methotrexate and folinic acid rescue.⁶ Nine courses were given over a 16-week period (total methotrexate dose 1.8 g). In month two she presented with pleuritic chest pains of the left and anterior chest. She was otherwise well and had no cough, sputum, or fever. On examination the only abnormality was a pleural rub at the left base. Methotrexate-associated pleurisy and pneumonitis was diagnosed. She was advised to ensure adequate hydration and symptoms responded to treatment with naproxen. BHCG levels remained normal during this episode. Two months after treatment she had recurrence of her symptoms of pleuritic chest pain and was also breathless on exertion. She remained afebrile and on clinical examination there were no abnormal signs. Chest X-ray showed cardiomegaly and echocardiogram revealed a large pericardial effusion (5 cm depth posteriorly and 2 cm anteriorly) without evidence of impaired myocardial function at rest. ECG, full blood count (eosinophil count $0.1 \times 10^9 \text{ l}^{-1}$), urea, electrolytes and liver function were normal. Erythrocyte sedimentation rate was 18 mm/h. Pericardial aspiration was performed and 650 ml of clear fluid was drained. Cytology revealed abundant lymphocytes, reactive mesothelial cells and scattered eosinophils, but no malignant cells. Biochemistry of the aspirate was consistent with an inflammatory exudate; glucose 4.7 mmol/l (serum 5.2), albumin 28g/l, total protein 49 g/l. Bacterial cultures including tuberculosis were negative, as were serial viral titres and an auto-antibody screen. Her symptoms of breathlessness resolved and there has been no recurrence after 18 months.

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Features of methotrexate toxicity

Acute: mild nausea/vomiting, diarrhoea, ulcerative stomatitis, conjunctivitis, pleurisy, marrow suppression
Chronic: skin rashes, cirrhosis/acute liver atrophy, nephropathy, defective oogenesis/spermatogenesis, osteoporosis, CNS: various effects following intrathecal treatment

Discussion

This is the first reported case of methotrexate-induced pericarditis and pericardial effusion. The syndrome of methotrexate pleural toxicity is invariably of pleuritic pain with normal chest X-ray and ventilation/perfusion scan. X-Ray changes if present are non-specific and diagnosis may require bronchoscopy and lavage^{3,7} or lung biopsy.⁷ The differential diagnosis is infection, pulmonary infarction and tumour-related complications. Pleural effusions after methotrexate therapy are most likely to be due to cancer; in this case the fluid should be drained and therapy changed. This patient had methotrexate chemotherapy followed by two episodes of pleurisy, the second being associated with pericarditis and a large pericar-

dial effusion. As in the majority of cases with pleural toxicity there was no peripheral eosinophilia; however, eosinophils were present in the pericardial fluid. An unrecognised viral infection or a reaction to an unsuspected allergen remains a possible cause; however, we believe that the pericardial effusion was most likely a complication of methotrexate chemotherapy and that, as with methotrexate pneumonitis, this is likely to be an immune-mediated serositis.⁷ The possibility of pericarditis and significant pericardial effusion should be considered as a potentially severe complication of methotrexate therapy. The regular use of echocardiography could provide information on the incidence of isolated asymptomatic pericardial effusion and that concomitant with methotrexate pneumonitis/pleurisy.

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The association of hereditary neuropathies and heritable skeletal disorders

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Summary

We describe two patients with associations of hereditary neuropathies and heritable skeletal disorders not previously reported. The first patient had Marfan's syndrome and hereditary motor and sensory neuropathy Type 1. The second patient had Ehlers-Danlos syndrome, Klippel-Feil syndrome and tomaculous neuropathy.

Keywords: hereditary neuropathy, heritable skeletal disorders, Marfan's syndrome, Ehlers-Danlos syndrome, Klippel-Feil syndrome

There are occasional reports of the association between a peripheral neuropathy and Marfan's syndrome, Ehlers-Danlos syndrome, or Klippel-Feil syndrome.¹⁻⁵ We report two patients with associations not previously described.

Patients

Case 1

A 19-year-old man presented with progressive difficulty in walking. He had no sensory symptoms. He was of thin build. His paternal grandmother, father and sister were said to

have a similar build. On examination, he had bilateral pes cavus and decreased tendon reflexes. He also had arachnodactyly, a high arched palate and bilateral lens dislocations. A diagnosis of Marfan's syndrome and a probable hereditary neuropathy was made.

Echocardiography showed mitral valve prolapse. Nerve conduction studies showed marked slowing of motor conduction velocity in the median nerve (15 m/s; lower limit of normal 48 m/s) and absence of sensory action potentials (median, ulnar, radial and sural). Electromyographic examination showed neuropathic changes in tibialis anterior. The findings thus showed a severe demyelinating and degenerating neuropathy consistent with hereditary motor and sensory neuropathy Type I.

Other family members were not available for clinical or electrophysiological examination.

Case 2

A 16-year-old boy presented with tingling in the distribution of the median nerve in the right hand. He had previously complained of tingling in the little finger of the left hand which was subsiding. On examination, he had blunting to pin prick sensation in the right median

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