CLINICAL RESEARCH

Avascular necrosis of bone caused by combination chemotherapy without corticosteroids

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Abstract

Avascular necrosis of bone is sometimes a complication of cancer chemotherapy that includes corticosteroids but generally occurs at a single site. A patient with testicular teratoma who received chemotherapy that did not include steroids developed avascular necrosis of the left femoral head, left scaphoid, and both medial femoral condyles. Symptoms were relieved with anti-inflammatory drugs and physiotherapy.

This case indicates that avascular necrosis may be caused by cancer chemotherapy that does not include steroids.

Introduction

Avascular necrosis of bone is a rare complication of cancer chemotherapy. In most reported cases the patients have had Hodgkin's disease and have been treated with several drugs including corticosteroids; the commonest site of disease is the femoral head.[1] Avascular necrosis at multiple sites has not been previously reported as a complication of combination chemotherapy. We report a case of avascular necrosis at four sites in a patient receiving chemotherapy for a testicular teratoma who at no stage received corticosteroids or radiotherapy to any of the affected areas.

Case report

A previously well 22 year old white man presented in 1978 with a four month history of left testicular swelling. Orchidectomy was performed, and histological examination showed the tumour to be a poorly differentiated embryonal carcinoma. α Fetoprotein and human chorionic gonadotrophin concentrations were normal. A chest radiograph showed multiple pulmonary deposits, but a lymphogram and a computed tomogram of the abdomen were normal. Ten days after operation chemotherapy was started with vinblastine 0·3 mg/kg (days 1 and 2) and bleomycin 15 mg/m^2 (days 1 and 4); this was repeated every three weeks. The pulmonary lesions resolved completely. After a total dose of 312 mg bleomycin and 36 mg vinblastine he developed painful effusions of both knees. Radiographs of both knees were normal. Serum urate concentration, antistreptolysin O titre, and erythrocyte sedimentation rate were not raised, and Rose-Waaler and rheumatoid slide latex tests yielded negative results. The effusions were attributed to the chemotherapy, which was therefore changed to vincristine 2 mg, actinomycin D 0·6 mg/m^2, and cyclophosphamide 750 mg/m^2 on day 1 every three weeks for six cycles. The effusions slowly subsided.

Eleven months after orchidectomy his knee effusions returned, and radiographs showed periostitis of the medial aspects of both femurs. His symptoms subsided spontaneously. Sixteen months after orchidectomy the tumour recurred in the left lung and the mediastinum. He was treated with cisplatin 20 mg/m^2 on days 1-5, vinblastine 0·2 mg/kg on days 1 and 2, and bleomycin 15 mg on days 2, 9, and 16.

After four cycles of treatment the disease was stable and the residual lung deposits were excised. Histological examination showed mature teratoma in mediastinal lymph nodes and no viable tumour in the lung deposits. His mediastinum was therefore irradiated. During the course of the irradiation he complained of a painful left hip and left wrist and further pain in both knees. An isotope bone scan showed increased uptake at these sites, and radiographs showed the characteristic appearance of avascular necrosis of both medial femoral condyles and the left femoral head and a cystic lesion in the left scaphoid. He gained symptomatic relief from anti-inflammatory agents and physiotherapy, but it was a further year before he could walk without the support of a stick.

Discussion

Avascular necrosis in an adult usually occurs at a single site and is most often associated with trauma to the femoral or humoral head. Its occurrence at several sites has been associated with disease processes leading to impairment of local bone circulation such as decompression sickness, Gaucher's disease, sickle cell anaemia, collagen vascular disease, and ionising radiation. Avascular necrosis at both single and multiple sites

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has also been associated with corticosteroid treatment, the femoral head being the site usually affected. This complication of steroid treatment may occur even when the drugs are given for conditions in which vasculitis does not occur—for example, to prevent rejection of renal allografts.[2]

Ihde and De Vita were the first to report the association of combination chemotherapy containing corticosteroids with the development of osteonecrosis in patients with malignant lymphoma.[1] Thorne *et al* found those affected to be most commonly men, with Hodgkin's disease the most common underlying lymphoma and the femoral head the usual site of the osteonecrosis.[3] The total dose of steroids varied from 1·4 g to 18·95 g. Timothy *et al* showed that radiological changes preceded symptoms by six to 21 months.[4]

There are only two previous reports of avascular necrosis occurring with cancer chemotherapy that did not include corticosteroids. Ihde and De Vita mentioned in discussion a 15 year old boy with Burkitt's lymphoma who received cyclophosphamide alone and developed necrosis of the tibial tubercle,[1] and Obrist *et al* reported on a patient with necrosis in the head of the humerus after treatment with cyclophosphamide, methotrexate, and fluorouracil for breast carcinoma.[5]

In our patient the initial signs were of bilateral knee effusions associated with periostitis. Though these might have been a manifestation of hypertrophic pulmonary osteoarthropathy, there were no lung lesions at this time and no finger clubbing. He subsequently developed symptoms and signs of osteonecrosis in the left femoral head, both medial femoral condyles, and the left scaphoid. Bleomycin and vinblastine are the most likely causes of the osteonecrosis because of the chronology of events. This case shows that avascular necrosis can be caused by cancer chemotherapy that does not include steroids.

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Erythrocyte choline concentrations and cluster headache

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Abstract

Erythrocyte choline concentrations were measured in patients with cluster headache and age related control subjects. Concentrations were significantly reduced in the patients with headache both during a cluster period and between clusters, being 58% and 55% of the control value, respectively. After two weeks' treatment with lithium, choline concentrations in the patients with cluster headache increased to 78 times the control value (mean 369·2 μmol/l (3840 μg/100 ml) compared with 4·7 μmol/l (49 μg/100 ml)).

The presence of depressed erythrocyte choline concentrations during and between cluster attacks indicates that this may be a predisposing condition which results in a cluster attack only when associated with a trigger factor.

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Introduction

For 10 years lithium has been known to be beneficial in cluster headache,[1] patients with both episodic and chronic forms showing a high degree of improvement.[2-4] The aetiology of cluster headache and the way in which lithium produces its effect are, however, unknown. Some insight into the mode of action of lithium has emerged from studies on manic depressive patients, where it has been found that administration of lithium greatly increases erythrocyte choline concentrations.[5,6] The major part of this effect may be accounted for by the inhibitory action of lithium on choline transport that occurs in human erythrocytes, preventing outward transport of choline.[7,8] In addition, choline concentrations in patients not receiving lithium are significantly different from those of controls in depression, Gilles de la Tourette's syndrome, and dementia.[6,9-12] In view of these observations we have measured choline concentrations in erythrocytes and plasma of patients with cluster headache (a readily definable and homogeneous population) and compared them with those in age matched controls to establish whether abnormal choline concentrations also occur in this condition.

Subjects and methods

Patients with cluster headache were divided into three groups—those who were between cluster periods (quiescent group), those who were experiencing a cluster period but were not receiving lithium (acute group), and those who were receiving lithium (lithium group). Patients studied satisfied the following criteria: they suffered severe unilateral head or facial pain occurring in bouts lasting 30 minutes to two hours and associated with ipsilateral lacrimation and rhinorrhoea and recurring once or more daily for weeks or months. Clusters were separated by intervals of complete freedom from pain for at least three months. Patients suffering from chronic cluster headache or