■ CASE REPORT

Metastatic adenocarcinoma after intramedullary fixation of a tibial fracture

A REPORT OF TWO CASES

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We present two cases of metastatic lung cancer which occurred at the site of a previously united tibial fracture. Both patients were treated with a locked intramedullary nail. The patients presented with metastases at the site of their initial fracture approximately 16 and 13 months after injury respectively.

We discuss this unusual presentation and review the relevant literature. We are unaware of any previous reports of a metastatic tumour occurring at the site of an orthopaedic implant used to stabilise a non-pathological fracture. These cases demonstrate the similar clinical presentation of infection and malignancy: a diagnosis which should always be considered in such patients.

Metastatic spread from a primary adenocarcinoma of the lung to the tibia is extremely rare. Rarer still is spread to the site of a previously treated tibial fracture. The exact mechanism of metastasis to the skeleton is not fully understood. Current evidence supports a role for both the seeding hypothesis¹ and the anatomically orientated mechanical theory² and suggests that the microanatomy of the medullary canal may function as a point of integration between these two theories.³ We present two cases of metastatic lung cancer occurring at the site of a previously united fracture of the tibia. We are not aware of any report in the literature which describes the development of a metastatic tumour at the site of a previous non-pathological fracture.

Case reports

Case 1. A 61-year-old retired nurse was admitted with a closed displaced fracture of the right tibia which she sustained in a fall. Examination revealed an isolated injury with no evidence of compartment syndrome or associated neurovascular injury. Radiographs (Fig. 1) showed a displaced spiral fracture at the junction of the middle and distal thirds of the tibia and a fracture of the proximal fibula. Her medical history included type 2 diabetes mellitus, hypertension and hypothyroidism following treatment for a solitary toxic adenoma of the thyroid eight years earlier. She had no respiratory symptoms or weight loss. Pre-operative assessment including a full blood count, renal function, liver function tests and bone profile, was normal. She smoked

between 10 and 15 cigarettes per day. She underwent fixation of the tibial fracture with a reamed locked intramedullary Expert tibial nail (Synthes GmbH, Solothurn, Switzerland) and made an uncomplicated recovery. Five months later her fracture was clinically and radiologically united (Fig. 2). She remained symptom-free for about 16 months when she developed pain and swelling of the right calf and difficulty walking. Inflammatory markers showed a slightly raised plasma viscosity of 2.01 and a CRP of 11.5 mg/l. Radiographs showed periosteal reaction at the lateral border of the original fracture site with evidence of local bony destruction (Fig. 3). Open biopsy revealed a poorly differentiated metastatic adenocarcinoma with immunohistochemistry strongly suggestive of a lung primary. Subsequent investigations including a CT scan of the chest, abdomen and pelvis, and a technetium-99m bone scan confirmed a mass of 3 cm in diameter in the right lung with multiple small pulmonary nodules, spread to the liver and bony metastases in the sternum, spine, ribs and right elbow. She is currently undergoing palliative radiotherapy to the sites of bony metastasis and palliative chemotherapy is being considered.

Case 2. A 65-year-old man sustained a closed, comminuted spiral fracture at the junction of the middle and distal thirds of the right tibia and fibula in a fall in April 1997, which was fixed 48 hours later using a Grosse & Kempf locked intramedullary nail (Stryker Orthopaedics, Mahwah, New Jersey) (Fig. 4). He made an uncomplicated recovery.

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Fig. 1

Case 1. Initial anteroposterior and lateral radiographs showing a displaced spiral fracture at the junction of the middle and distal thirds of the right tibia and a proximal fracture of the fibula.

Fig. 2

Case 1. Five months after surgery, anteroposterior and lateral radiographs showing that the fracture has radiologically healed.

At 12 weeks post-operation he complained of further pain and swelling in the leg which required him to continue to mobilise partial weight-bearing. There was radiological evidence of delayed union. The symptoms settled and seven months after the initial injury, radiographs showed sound bony union (Fig. 5). One year after the injury the intramedullary nail was removed.

At surgery there was a membrane of tissue surrounding the nail but no macroscopic evidence of infection. Microbiological analysis revealed a few coagulase-negative staphylococci on culture. Histological analysis of the membrane revealed inflammatory tissue with no atypical features. He developed a discharging sinus from the site of

Fig. 3

Case 1. At 16 months after the original index procedure. Radiograph showing a periosteal reaction at the lateral border of the original fracture site with evidence of local bony destruction.

Fig. 4

Case 2. Immediate post-operative anteroposterior and lateral radiographs showing successful reduction of the fracture.

removal of the proximal locking screw, from which *Staphylococcus aureus* was cultured. This was initially treated with oral antibiotics but failed to settle and excision of the sinus and local debridement was performed. Histological analysis of the tissue revealed inflammatory reaction only.

The sinus recurred and a MR scan showed a large mass proximally around the site of insertion of the tibial nail which was felt to represent an inflammatory mass. He was treated with a six-week course of benzylpenicillin and flucloxacillin. Six weeks later a further MR scan (Fig. 6)

Fig. 5

Case 2. Seven months after surgery, anteroposterior and lateral radiographs reveal radiological union of the fracture.

Fig. 6

Case 2. Sagittal view of an MR scan showing an enlarging inflammatory mass in the proximal tibia.

showed some persistent swelling and he underwent formal exploration. A large area of the anterior cortex of the proximal tibia was found to have been eroded with gross inflammatory change throughout the adjacent soft tissues. Histological examination confirmed a moderately differentiated metastatic deposit of adenocarcinoma. Immunohistochemical analysis did not suggest a tumour of the prostate. A chest x-ray was normal but CT scans showed a small hilar lesion consistent with a primary lung tumour. He was treated with palliative radiotherapy and chemotherapy.

Discussion

The first case of primary malignancy associated with an orthopaedic implant was reported by McDougall in 1956.⁴ Since then, a further 29 cases have been reported, the majority of which were associated with joint replacements.⁵ There are only nine reports of malignancy after internal fixation of a fracture,^{4,6-13} and only one after intramedullary nailing.¹³ Three types of primary malignancy were seen in these reports; sarcomas, malignant fibrous histiocytomas and tumours of haemopoietic tissue. Metastatic tumours may develop adjacent to implants used to stabilise pathological fractures, because of direct spread or dissemination during surgery. Previous reports have reviewed the epidemiological, *in vitro* and *in vivo* evidence of the carcinogenic properties of metals and metallic implants.^{5,14} This case report is the first to report the development of a metastatic tumour at the site of an orthopaedic implant used to stabilise a non-pathological fracture.

Research has shown the importance of the formation of blood vessels in neoplasms both as a predictor of malignant potential and in the metastatic pathway.¹⁵ It is thought that patients with a primary tumour can harbour dormant micrometastases¹⁶ which can remain undetected years after

the primary tumour has been treated, until exogenous factors trigger growth and a clinical relapse. Investigation of these micrometastases has shown that, at a cellular level, growth occurs at a similar rate to that of the primary tumour.¹⁷ The difference lies in the rate of apoptosis. In rapidly cycling cells, an increased rate of apoptosis is known to occur. These cells can be rescued by growth factor stimulation,¹⁸ such as that required for angiogenesis. This in turn, increases the haematogenous delivery of such factors to the site of metastasis, resulting in rapid growth of the malignant cells. *In vitro* studies have demonstrated an increased rate of metastasis in the presence of angiogenic molecules.¹⁹ Cytokines are important effector molecules in the repair and remodelling of skeletal tissue.²⁰ Thus, at a fracture site, neo-vascularisation occurs in a cytokine-rich environment to stimulate cell growth and division and matrix formation: an ideal environment to rescue malignant cells from apoptosis.

The cases presented here may have occurred for one of two reasons. First, metastatic cells may have seeded the tibia prior to the injury. Tissue damage during insertion and subsequent removal of the nail in the second patient provided a favourable intercellular environment to save the metastatic cells from cell death, resulting in rapid tumour growth. Secondly, the tibia may have been free from tumour at the time of injury. Up-regulation of vascular endothelial adhesion molecules at the site of the fracture may have increased the probability of tumour seeding. Vascular endothelial adhesion molecules are an important method of recruiting leucocytes to an inflammatory focus *in vivo*, and are also important in the metastatic pathway.²¹ It has been shown that the timing of a secondary wound is important in the development of viral-induced wound tumours in chicks.²² This may explain why rapid growth did not occur at the frac-

ture or at the site of the initial surgery. In any case, the orthopaedic injury and fixation probably influenced the site of distant spread in these patients.

Injury and inflammation have been associated with tumour formation.²³ Tumour involvement of surgical wounds after laparoscopy of patients with abdominal malignancy is well-documented.²⁴ These are the first reported clinical cases of metastatic tumour involving a surgical site distant to the primary and in association with an orthopaedic implant. As with the first report of implant-associated malignancy in 1956,⁴ these cases demonstrate the similar clinical presentation of infection and malignancy: a diagnosis which should always be considered in such patients.

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