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Prolonged fever and heterotopic ossification in a C4 tetraplegic patient. Case report

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Prolonged fever is an uncommon diagnostic problem in a spinal cord injury patient. The underlying causes include recurrent infections, thromboembolic phenomena and central fever. We report a case of heterotopic ossification in a traumatic C4 tetraplegic patient presenting as prolonged fever of 3 months' duration. Treatment with oral indomethacin led to prompt resolution of the fever and acute manifestations of heterotopic ossification. The efficacy of indomethacin in the treatment of heterotopic ossification in spinal cord injury needs to be further confirmed in larger studies.

Keywords: fever; heterotopic ossification; tetraplegia; indomethacin; bone scan

Introduction

Fever is a common diagnostic problem in patients with spinal cord injuries. The incidence of fever, infection or both during hospitalisation has been reported to be about 67% in a spinal referral unit.[1] Point prevalence of fever has been reported to be 10.8% in another study.[2] The commonest causes of fever are infections, especially of the urinary tract and soft tissues, and thromboembolic complications.[3] Rarer causes include heterotopic ossification (HO), and central fever.[4,5]

Heterotopic ossification is the formation of bone in abnormal anatomic locations, usually around a neurologically affected joint. It is a frequent complication in spinal cord injury, the incidence ranging from 16 to 53%.[6] If left untreated, it may eventually lead to joint ankylosis, and adversely affect mobility, self care and functional independence.

Although fever has been documented to be associated with HO, prolonged fever is unusual. We report a case of prolonged fever due to heterotopic ossification in a C4 tetraplegic patient.

Case report

A 40-year-old Malay man was admitted to the neurosurgical department following a road traffic accident. He suffered a fracture of the right lateral process of the C4 vertebra with bony fragments in the spinal canal adjacent to the laminae of C7 and T1, as well as a fracture of the T1 transverse process. Magnetic resonance imaging showed cord oedema at C4 level.

Initial examination revealed that the neurological level of injury was incomplete below C4, complete below C5 on the left and complete below C4 on the right. There was no sensation to touch or pinprick below C5 bilaterally. Intravenous methylprednisolone was commenced within 8 h of injury, and given hourly for 24 h.

The patient developed respiratory distress with hypoxemia (PO2 of 55 mm Hg) secondary to a chest infection on the third day of admission and was intubated and ventilated. He also had a fever which settled with a 10-day course of antibiotics. In the second week of admission, the patient started to spike a fever again. Clinically, the lungs were clear and the abdomen was soft and non-tender, and the liver was felt 2 cm beneath the costal margin. A small, clean, shallow pressure ulcer in the sacral area was also noted.

The total white count was 13 600 dL^{-1}, with 88% neutrophilia. Blood cultures and urine microscopic examination were normal. Although endotracheal tube cultures grew pseudomonas aeruginosa, the chest radiograph was normal. Liver function tests showed hypoalbuminemia (serum albumin 32 $g L^{-1}$), mildly raised transaminases (SGPT 47 $U L^{-1}$, SGOT 50 UL^{-1}) and a raised alkaline phosphatase (173 UL^{-1}). Ultrasound of the hepatobiliary system was unremarkable. He was reviewed by the infectious disease physician who was of the opinion that there was no evidence of significant infection and antibiotics were not needed.

The patient continued to have daily fever for the next 3 months, reaching as high as 39 degrees celsius (Figure 1). During this period, repeated clinical examination was unremarkable and he remained well constitutionally. Investigations related to looking for a focus of infection were negative and ultrasound doppler of the lower limbs revealed no deep vein thrombosis. A white cell scan was not performed.

The patient was transferred to the rehabilitation medicine department at 14 weeks post injury. On examination, there was low grade fever and the neurological status was essentially unchanged. There was spasticity of all limbs measuring 1+ on the modified Ashworth scale. Stiffness and limitation of range of movements in both shoulder and hip joints were detected. There was also redness, tenderness and warmth in both shoulders, anteriorly and laterally.

Radiological examination of the shoulders revealed periarticular soft tissue calcification, with periosteal reaction in

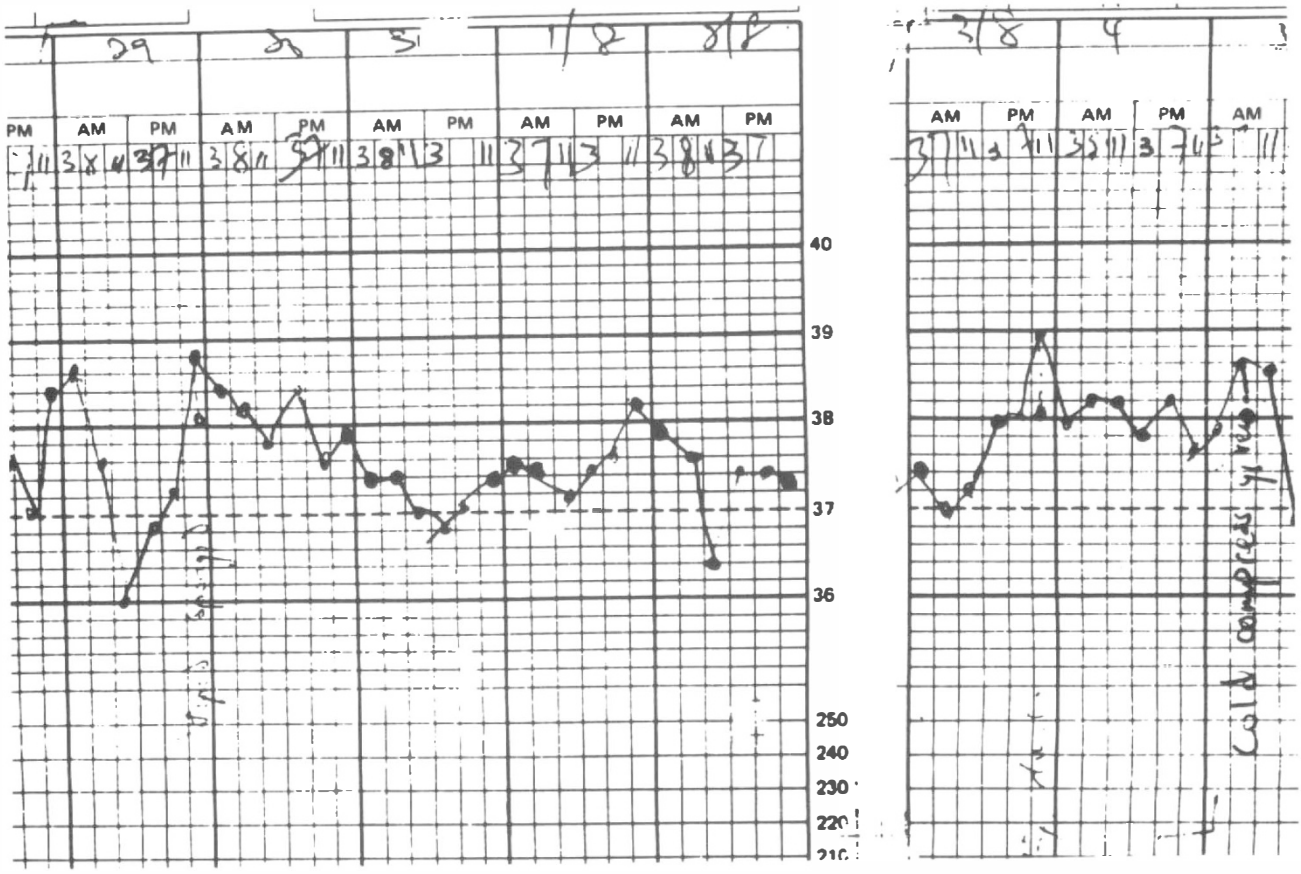

Figure 1 Typical pattern of daily fever in the patient

the upper humerus bilaterally (Figure 2). Periarticular ossification of both hips and knees was also present (Figure 3). The erythrocyte sedimentation rate was 115 mm h^{-1} and serum alkaline phosphatase was 110 U L^{-1}. A diagnosis of heterotopic ossification was made and the patient was started on oral indomethacin, 25 mg thrice daily in addition to a regime of gentle joint mobilisation.

The fever settled remarkably after 4 days of indomethacin (see Figure 4). Reduction in tenderness and warmth of the shoulder joints was noted at 2 weeks. Joint range of motion, however, remained the same. Bone scan done at this stage showed increased tracer uptake at the following sites, suggestive of extensive HO: right shoulder, left shoulder, right hip, left hip and the medial condyle of the right femur. Throughout his stay, the patient remained afebrile except for a bout of fever at 3 months post rehabilitation, attributed to urinary tract infection. Five months into rehabilitation, neurological and functional improvements were noted. The motor level had improved to complete below C5 on the right and complete below C7 on the left. There was also mild increase in range of motion of both shoulders and hips. Repeat bone scans at this stage revealed reduction in uptake over both shoulders, right hip and knee indicative of maturation of ectopic bone. Radiographs of the shoulders also showed increasing ossification (Figures 5 + 6). Repeat serum alkaline phospatase level was normal at 95 U L^{-1}. Indomethacin was stopped at this stage in view of the evidence of maturity of bone.

By discharge, the patient was able to sit upright and feed and groom with minimal supervision. He was also able to propel himself in an electric wheelchair on level ground, and was able to learn to control his environment through adapted switches via an infrared environmental control.

Discussion

Heterotopic ossification (HO) in spinal cord injury occurs commonly within the first 4 months of injury.[7] Common presentations include swelling, warmth, erythema and tenderness of involved joints. A systemic febrile reaction is known to coexist with HO, and Stover has reported that 'low grade fever in the more extensive cases may persist for a couple of weeks'.[7] Prolonged and persistent fever for 3 months, commencing as early as 2 weeks post injury, is rare.

We believe that the prolonged fever in this case report is due to HO for the following reasons. Firstly, clinical and radiological features of HO were present with the fever. Secondly, there was a temporal relationship between the resolution of fever with improvement in tenderness of the joints, and indomethacin treatment. Moreover, no active source of infection was found after careful clinical examination and investigations. Finally, other causes of fever could not be elucidated including thromboembolism and drug fever. Central fever was not considered here as it is essentially a diagnosis of exclusion.

The mechanism and pathophysiology of HO is not known. Several proteins however have been isolated

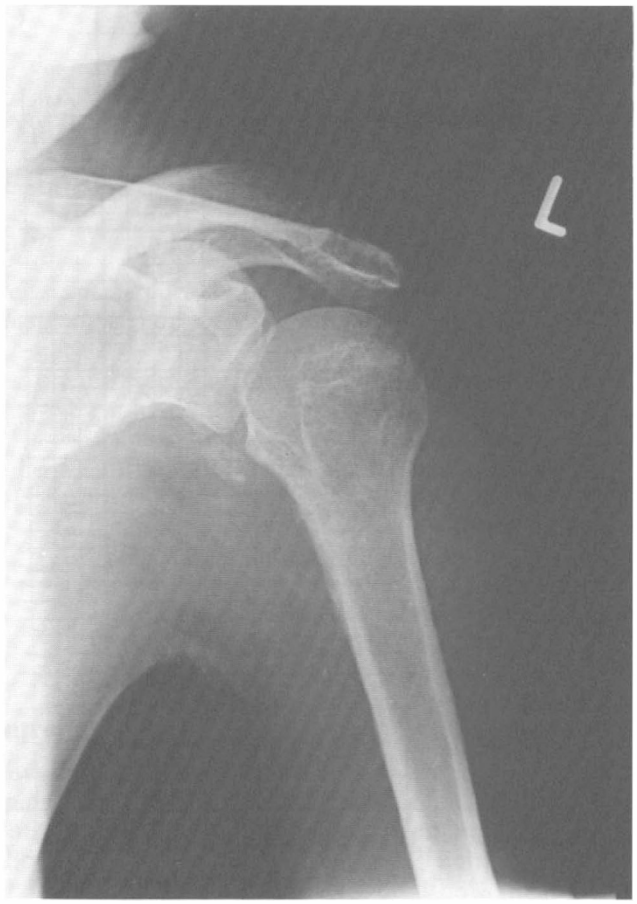

Figure 2 Radiograph of the left shoulder showing early periarticular ossification

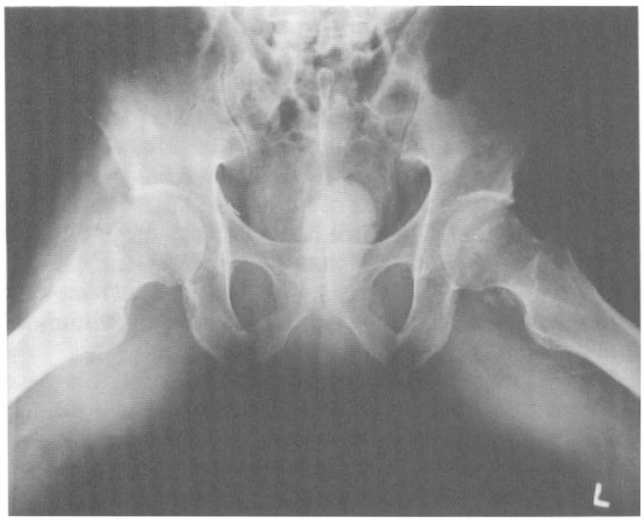

Figure 3 Radiograph of both hips showing bilateral periarticular ossification

and implicated in the aetiology. One of these is bone morphogenic protein (BMP) which has been shown to promote ectopic osteoinduction experimentally by inducing differentiation of undifferentiated mesenchymal cells.[8] Other proteins include osteogenin and osteoinductive factor.[9] Prostaglandins and like substances have also been postulated to be involved in the triggering of local bone remodelling in trauma and experimentally induced ectopic ossification in soft tissues and in the differentiation of preosteoblast cells.[10,11]

The mechanism of fever due to HO is just as unclear. It is possible that mediators involved in the process of HO include endogenous pyrogens that trigger the febrile response.

Although indomethacin has been shown to be effective in the prophylaxis of HO after total hip arthroplasty and following excision of ectopic bone via the inhibition of prostaglandins and differentiation of mesenchymal cells into osteogenic cells, its role in the prevention and treatment of HO in spinal cord injury is still to be determined conclusively.[12,13] Although there was resolution of fever and improvement in tenderness, warmth and swelling in this patient with the institution of indomethacin, there appeared to be little alteration in the natural history and course of heterotopic ossification. Its benefit seems to be in preventing the inflammatory reaction rather than interfering with the process of ossification once the inflammatory reaction has started. The subsidence in fever could also have been contributed to by the antipyretic activity of indomethacin, presumably by suppressing the synthesis of prostaglandins in the hypothalamus, involved in mediating the pyretic effect of endogenous pyrogens.[14]

Sodium etidronate, a biphosphonate, is the drug used most extensively in the treatment of spinal cord injury (SCI) related HO. It acts by inhibiting osteoid mineralisation, binding calcium phosphate and preventing hydroxyapatite crystallisation. Given prophylactically in SCI patients, it has been shown to retard the progression and final severity of HO. The overall incidence of HO in both treated and untreated patients were however similar.[15] This drug was not used for the patient in this case report as it was not available locally. Whether it will inhibit fever due to HO is not known.

Early diagnosis and recognition of HO is important so that appropriate treatment can be started and complications prevented. To this end, radionuclide bone scan is the most sensitive diagnostic tool and has been reported to precede clinical manifestations by up to 6 weeks.[16] More recently, ultrasound has also been found to be useful especially in situations where deep vein thrombosis is a differential diagnosis.[17]

Apart from the use of disodium etidronate in the treatment of established HO, careful regular stretching of involved joints to maintain range of motion is also important. Although controversial, repeated forceful manipulation of joints has also been advocated.[18] Surgical resection of matured ectopic bone should be contemplated in cases where there is significant functional limitation of joint mobility.[19] Recurrence of HO after resection though is a major concern. In this respect, it is interesting to note that the combination of indomethacin and disodium etidronate has been shown to be effective in the prevention of recurrence of HO

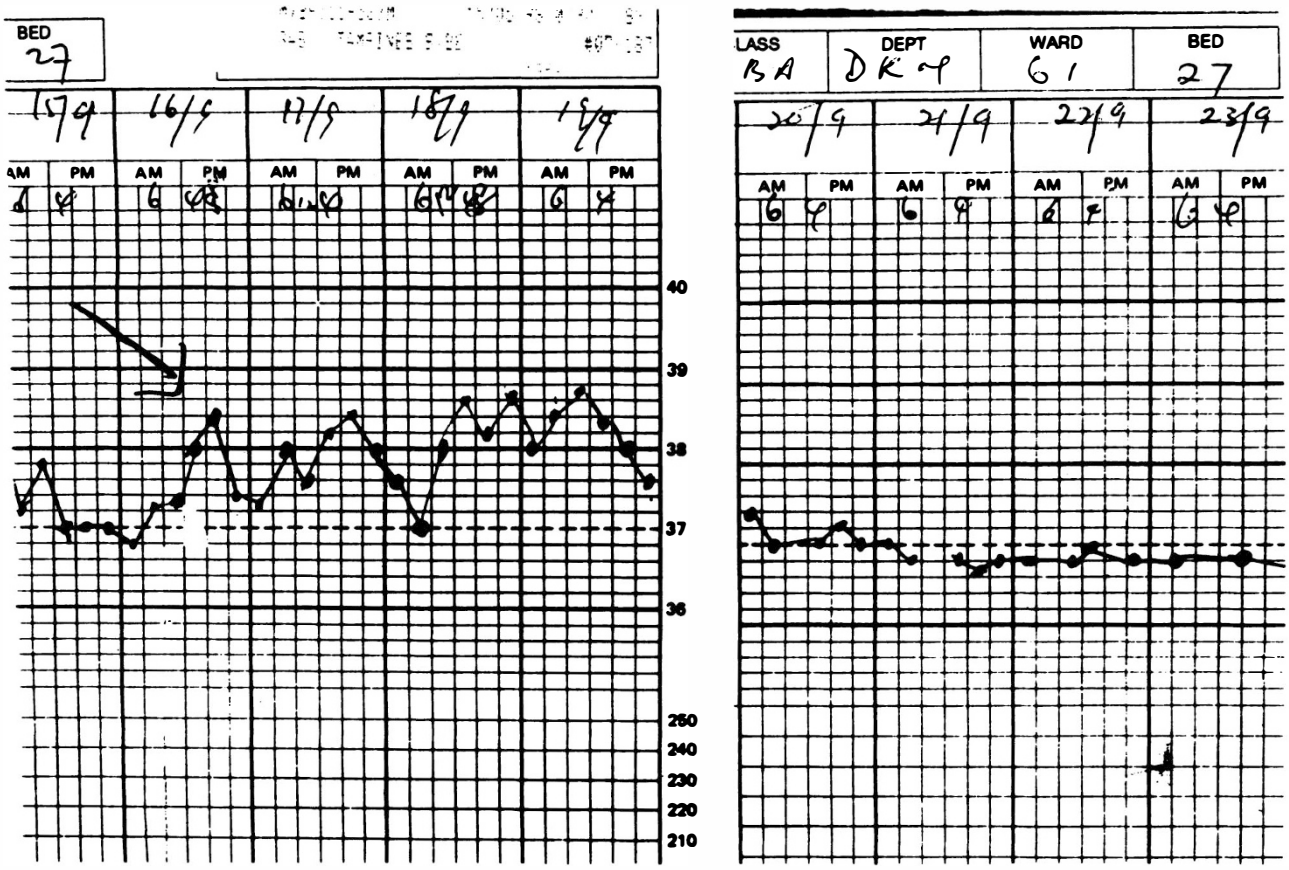

Figure 4 Dramatic settling of fever 3 days after starting indomethacin treatment. (Arrow indicates date of starting indomethacin)

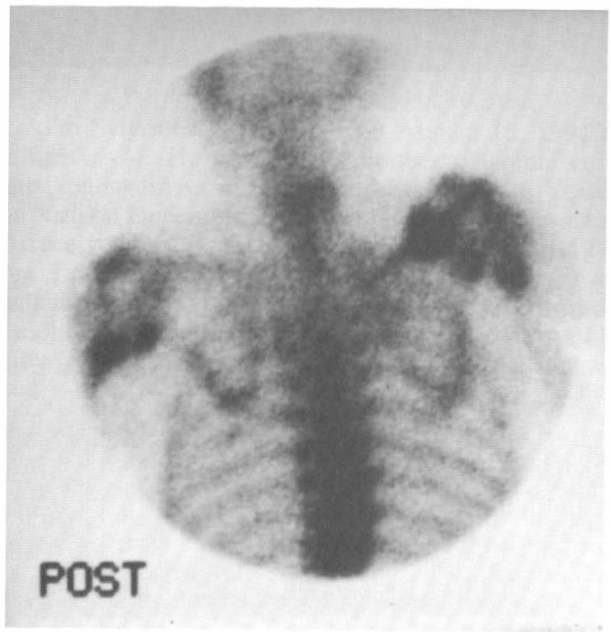

Figure 5 Bone scan of the patient showing increased uptake in both shoulders

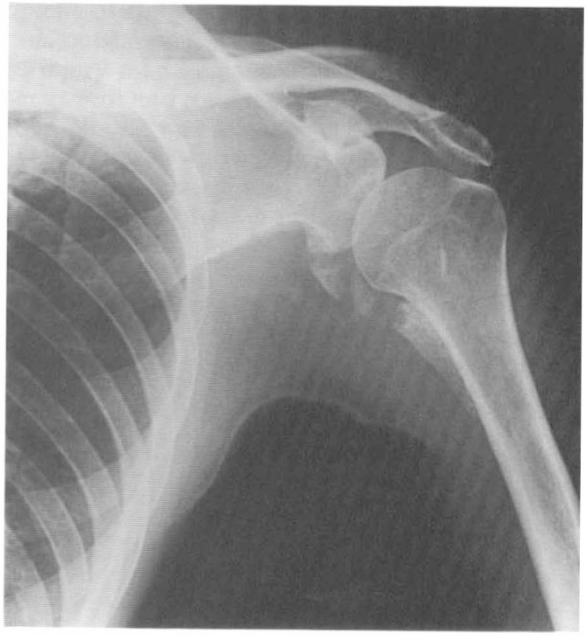

Figure 6 Radiograph of left shoulder at 8 months post injury showing increasing maturity of ossification

after surgical resection in two spinal cord injured patients.[20]

Conclusions

Fever is often a diagnostic problem in the spinal cord injured. Clinicians managing these patients should be cognisant of the association of prolonged fever with HO especially in the absence of infection and thromboembolism. Early diagnosis via radionuclide bone scan is recommended where possible. In view of the effectiveness of indomethacin in the reduction of fever and acute manifestations of HO, trials of its value in the prevention and treatment of HO in SCI patients are being planned.

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