Heterotopic Ossification Complicating Long-term Sedation

SIR—Heterotopic ossification is the formation of mature trabecular bone in periartricular soft tissues [1]. This syndrome is seen most commonly following neurological disorders (spinal trauma, head injury, long-term coma), tetanus, severe burns or hip surgery. The common sites of periartricular ossification are proximal joints and limbs. Localized swelling, warmth, redness and limited range of motion are typically the earliest manifestations, occasionally requiring differentiation from septic arthritis or deep venous thrombosis [2, 3]. In the intensive care unit, critically ill patients admitted for respiratory failure frequently need sedation to facilitate mechanical ventilation [4]. The duration and depth of sedation required leads to prolonged immobilization, increasing the risk of morbidity by delaying return of the mobile state. Although sedation is commonly used in ventilated patients, there is, however, little information in the literature of the adverse effects and potential complications of the prolonged administration of high doses of sedative and analgesic drugs [5, 6]. To our knowledge, there is no previous report of heterotopic ossification complicating prolonged sedation without neuromuscular blockade. We report five cases of heterotopic ossification presenting as acute arthritis following long-term sedation in patients undergoing mechanical ventilation.

Five patients (see Table I) were admitted to the intensive care unit for acute respiratory distress complicating pneumococcal pneumonia (case 1), thoracic (case 5) or abdominal surgery (case 2), or both (cases 3 and 4). All patients received sedation by continuous i.v. infusion of benzodiazepines and opioids (mean duration 21 days) and prolonged mechanical ventilation (mean duration 38 days) without neuromuscular blockade. While still in the intensive care unit, all five patients developed features of acute arthritis, including heat, swelling, redness or limited joint motion involving the shoulders (two cases), elbows (two cases), hips (two cases) and knees (three cases). Radiographs showed characteristic changes of early heterotopic ossification (soft-tissue swelling and amorphous calcifications around an otherwise normal joint), while bone scan revealed heterotopic ossification in 11 unsuspected sites. Because of preventive anticoagulant therapy, synovial fluid aspiration of the affected joints was not performed. Subsequent radiographs and computed tomographic (CT) scans demonstrated progression of the flocculent calcifications to well-organized heterotopic bone (Fig. 1).

The clinical and radiographic findings in our patients are typical of heterotopic ossification, a well-documented potential complication of paralysis following spinal cord lesion or brain injury. Its pathogenesis is still unclear, but multiple factors, including local trauma, vascular stasis, immobilization and tissue hypoxia, contribute to periartricular soft tissue metaplasia [7]. In the intensive care unit, these risk factors may converge in ventilated patients receiving long-term sedation. Although we did not use any neuromuscular blocking agents in our patients, they were kept in a completely bedridden state with functional immobility for at least 11 days. Thus, we believe that deep continuous sedation may lead to a prolonged immobilization, allowing the development of heterotopic ossification, in the absence of any anatomical central nervous system lesion or chemical paralysis.

Increasing use of sedation in the intensive care unit, together with improvements in critical care leading to increased survival after acute respiratory failure, may result in a greater prevalence of heterotopic ossification in heavily sedated patients. Rheumatologists and critical care physicians should be aware of this potential complication and should be alert to its presentation so that early diagnosis can be made and appropriate treatment initiated to minimize limitation of joint motion and prevent ankylosis.

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<table>
<thead>
<tr>
<th>Patient</th>
<th>Sedation (days)</th>
<th>Mechanical ventilation (days)</th>
<th>Based on clinical signs</th>
<th>Sites of heterotopic ossification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (39/M)</td>
<td>23</td>
<td>52</td>
<td>Shoulders, elbows, right hip</td>
<td>Shoulders, elbows, right hip, right knee</td>
</tr>
<tr>
<td>2 (37/F)</td>
<td>11</td>
<td>28</td>
<td>Left knee</td>
<td>Hips, knees, left shoulder</td>
</tr>
<tr>
<td>3 (65/M)</td>
<td>27</td>
<td>55</td>
<td>Left elbow</td>
<td>Left elbow, right knee</td>
</tr>
<tr>
<td>4 (49/M)</td>
<td>12</td>
<td>22</td>
<td>Right shoulder, right hip, right knee</td>
<td>Shoulders, right elbow, hips, right knee</td>
</tr>
<tr>
<td>5 (36/M)</td>
<td>24</td>
<td>33</td>
<td>Knees</td>
<td>Hips, knees</td>
</tr>
</tbody>
</table>

TABLE I
Characteristics of patients with heterotopic ossification following long-term sedation
LETTERS TO THE EDITOR


Scurvy, Osteoporosis and Megaloblastic Anaemia Due to Alleged Food Intolerance

Sir—Adult scurvy may present to the rheumatologist with ‘pseudovasculitic’ lower limb purpura [1], haemarthrosis [1, 2], femoral head destruction [2, 3] or nerve entrapment due to haematoma [4]. We report a case of spinal osteoporotic fracture associated with scurvy.

A 71-yr-old Caucasian woman presented with acute thoracic pain and extensive bruising over the arms, legs and feet [1]. Her calves were purple, tense and swollen due to s.c. and i.m. haemorrhage. Laboratory studies revealed a haemoglobin of 6.9 g/dl, mean corpuscular volume (MCV) 122 fl, white cell count 5.1×10⁹/l, platelets 92×10⁹/l, prothrombin time 13 s (control 13 s), kaolin cephalin clotting time (KCCT) 36 s (control 33 s), B12 405 ng/l (170–700), serum folic acid 1.8 μg/l (2–14). Thoracic spine X-ray showed a crush fracture of T9 and gross osteopenia. Isotope bone scan confirmed increased uptake only at the site of the fracture. Bone marrow biopsy revealed a megaloblastic picture.

The patient had attended a private allergy clinic 5 yr previously for advice about severe headaches which she believed were caused by an allergy to vitamin C. Despite advice to the contrary, she had restricted her diet to dairy produce, meat, fish and cereals. The serious consequences of this diet were explained and she began to eat fruit and vegetables supplemented with folic acid and vitamin C. Within 1 week, her skin and muscle haemorrhages had cleared. Six weeks later, the haemoglobin level was 14.3 g/dl, MCV 101 fl, white cell count 6.8×10⁹/l and platelets 189×10⁹/l. The patient was well and eating a normal diet without headaches or symptoms of allergy.

Although this woman had an early menopause at the age of 43, it is likely that scurvy contributed to the development of osteoporosis. Ascorbic acid is an essential co-factor for the biosynthesis of collagen since it is a specific requirement for prolylhydroxylase and lysylhydroxylase [5]. Hydroxyproline is essential for the stability of the collagen helix, whilst the formation of inter- and intra-chain cross-links between hydroxylsyl and lysyl residues is necessary to form a stable connective tissue matrix. Spinal osteoporosis

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Fig. 1.—Three-dimensional CT scan of the pelvis (patient 4) showing large bilateral heterotopic ossification posterior to the hip joints (curved arrows).