Chronic non-bacterial osteomyelitis coexistent with familial Mediterranean fever

Sirs,

Chronic non-bacterial osteomyelitis (CNO) is a rare condition that manifests with sterile destructive osteomyelitis accompanying with fever, local bone pain, and swelling. Clinical spectrum varies from single to multifocal lesions. The metaphyseal plates of long bones, vertebrae, and clavicles are commonly involved. Laboratory investigations for infectious and malignant diseases are negative (1). There is no diagnostic test, although modest elevation in acute phase reactants, and absence of autoantibodies are typical (2).

Familial Mediterranean fever (FMF) is an autosomal recessive inherited disorder which results due to Mediterranean fever gene (MEFV) mutation and characterised by recurrent febrile serositis attacks (3). We herein report two CNO cases coexisting with FMF.

Case 1. An 11-year-old boy referred to our clinic with persistent swelling at medial region of right clavicle, relapsing fever and concomitant osteomyelitis attacks. Physical examination showed swelling and tenderness on medial portion of right clavicle; mildly elevated acute phase reactants, leukocytosis and anaemia were detected. X-ray showed clavicular expansion, whole body radionuclid and magnetic resonance (MRI) scans were compatible with osteomyelitis (Fig. 1A-B). Microbiological tests were negative and the histopathological examination revealed chronic osteomyelitis. MEFV gene analysis revealed M694V/E148Q compound heterozygous mutation. Diagnoses of CNO and FMF were thus confirmed. The patient was treated with colchicine and naproxen, and all symptoms regressed within six months.

Case 2. A 13-year-old boy was admitted to our clinic with fever, swelling and warmth on left shoulder when 8-year-old. In his past medical history, he had recurrent fever attacks and had been hospitalised with pericardial effusion. Osteomyelitis was diagnosed in left humerus. MEFV gene analysis revealed M680I/M694V compound heterozygocity and he was diagnosed as FMF. Clinical wellness was achieved with colchicine. After 4.5 years, he appeared with similar symptoms at the right shoulder following a colchicine-free period for several months. Mild anaemia and elavated acute phase reactants were detected. MRI revealed osteomyelitis, and millimetric abscesses in deltoid muscle (Fig. 1C). After debridement, antibiotics, naproxen and colchicine were started. Bone biopsy revealed chronic osteomyelitis. The diagnosis was attained as CNO in the case of FMF. One month later, arthritis developed in the left knee and methotrexate was added. Symptoms resolved within six months.

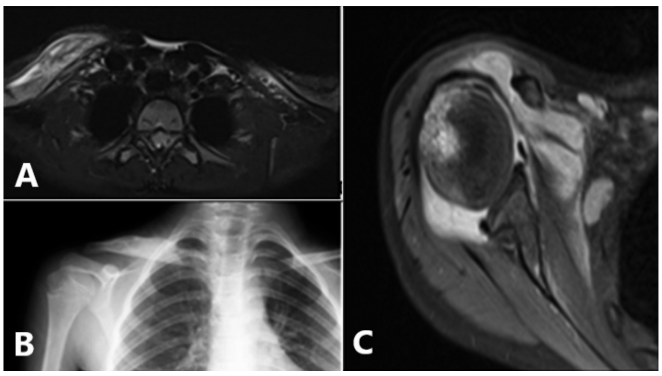

Fig. 1. Radiographic images of cases; magnetic resonance image (MRI) and direct radiography of clavicle osteomyelitis of case 1, and MRI of right shoulder of case 2, respectively. **1A**. Expansion and sclerosis of medial portion of right clavicle, **1B**. Expansion at medial region of right clavicle, **1C**. Osteomyelitis at right humerus head, increased fluid at joint space, milimetric abscesses on deltoid muscle.

CNO has associations with certain inflammatory disorders including palmoplantar pustulosis, psoriasis vulgaris and inflammatory bowel disease (2). On the other hand, there are well defined associations between FMF and inflammatory diseases (3).

There is no proven evidence about the link between FMF and CNO; however, anecdotal reports emphasised the presence of MEFV mutations and colchicine response in CNO cases. Moussa *et al*. described seven paediatric CNO patients. One of these patients who had FMF with M694V heterozygous mutation suffered from arthritis and back pain. She had been on colchicine therapy, and naproxen, methotrexate, and pamidronate had been administered to the patient sequentially to achieve clinical response (4). Another patient, a 14-year-old female with multifocal bone lesions, was diagnosed as having CNO. The patient had E148Q-P369S-R408Q heterozygous mutations. Naproxen therapy failed, but colchicine addition provided nearly excellent suppression of the disease activity (5). In the present study, case 2 was in remission with colchicine therapy after diagnosis of FMF. When he stopped taking colchicine, CNO symptoms recurred. Recently, Babaoglu *et al*. reported an FMF patient who had CNO, and who had well responded to Anakinra (6).

The first line therapy in CNO is non-steroidal anti-inflammatory drugs (NSAIDs). In NSAIDs resistant cases corticosteroids, disease-modifying antirheumatic drugs, bisphosphonates and biologics could be used (7, 8). In our cases, NSAIDs, colchicine and methotrexate were highly effective in controlling disease activity.

In conclusion, clinicians should investigate FMF signs in patients with CNO. Conversely, when osteomyelitis is diagnosed in an FMF patient, CNO should be kept in mind in the differential diagnosis.

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