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Chronic recurrent osteomyelitis with clavicular involvement in children: diagnostic value of different imaging techniques and therapy with non-steroidal anti-inflammatory drugs

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Abstract Chronic recurrent, uni- or multifocal osteomyelitis (CRMO), an inflammatory disorder of unknown origin, involves mk:/night/arul/4310946m.3dultiple osseous sites and may affect the clavicle. We report on 6 children with clavicular involvement out of 11 children suffering from CRMO. The major clinical symptoms were local swelling and pain. Five children had hyperostosis of the clavicle and synovitis of adjacent joints. Histology showed chronic osteomyelitis with a predominance of lymphocytes in the inflammatory infiltrates. Cultures of biopsy tissue specimens were sterile. The patients were followed for at least 3.5 years. Three patients had up to six relapses. The most effective diagnostic tools to define CRMO were standard X-ray and bone scan in combination with biopsy and cultures. In our patients CT and MRI were misleading as they suggested the presence of malignancy. However, the sensitivity of MRI to detect involvement of bone, adjacent joints and soft tissues were better in comparison to X-ray or bone scan. Non-steroidal anti-inflammatory drugs were effective in reducing pain, swelling and limitation of motion. Reconstructive surgery was not indicated in any case. The long-term outcome of growth and function of affected bones was excellent.

Conclusion Diagnosis of chronic osteomyelitis of the clavicle should be made by history and physical examination and be confirmed by standard X-ray, bone scan and open biopsy. In contrast MRI and CT can provide data on the involvement of adjacent joints, soft tissue and muscles especially in the early process of disease, but do not add information relevant to the patient's management. Treatment with non-steroidal anti-inflammatory drugs is rapidly beneficial in most patients.

Key words Chronic recurrent multifocal osteomyelitis · SAPHO syndrome · Diagnostic imaging · Non-steroidal anti-inflammatory drugs

Abbreviations *CRMO* chronic recurrent multifocal osteomyelitis · *NSAID* non-steroidal anti-inflammatory drugs · SAPHO syndrome Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis

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Introduction

The clavicle is a rare site of osteomyelitis. Only about 1% –5% of paediatric patients with osteitis have a clavicular lesion [11, 29, 37, 39]. Bacterial osteomyelitis of the clavicle usually results from contiguous spread of an infection due to surgical procedures of the head and neck [25] or due to central intravenous catheter procedures of the subclavian vein [24, 26]. *Staphylococcus aureus*, *Coccidioides immitis*, *Pseudomonas aeroginosa*, *Mycobacterium tuberculosis*, *Streptococcus* and *Rochalimaea henselae* have been isolated from clavicular osteomyelitic lesions [12, 40]. Since 1972 [13] several reports have been published on chronic recurrent multifocal osteomyelitis (CRMO), an inflammatory lesion of bone without a known infectious cause affecting preferably the metaphyses of the long bones of children and adolescents [7, 12, 16, 32]. In contrast to septic osteomyelitis these lesions are roentgenographically characterized as hyperostotic and osteosclerotic in addition to osteolytic. Chronic sclerosing osteomyelitis of the clavicle has been demonstrated to be a manifestation of CRMO [4, 20]. There is a multitude of labels for this disease: ''chronic sclerosing osteomyelitis'' [20], ''condensing osteitis'' [2, 27], ''sclerosis and hyperostosis'' [20] and ''pustulotic arthroosteitis'' [17]. Histologically, there are subperiosteal bone formation, signs of chronic inflammation with infiltration of leucocytes, in very early lesions granulocytes, later on mainly lymphocytes or monocytes [3, 19, 34]. Auto-immune or infectious causes have been suggested [13]. In children pustulosis palmoplantaris was associated with CRMO initially in 1978 [4]. To date, approximately 120 children with CRMO have been reported, approximately 60 of whom had clavicular involvement [1–4, 7–10, 13, 15–21, 28, 30–33, 38]. In adults an analogous clinical entity including Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis has been described as SAPHO syndrome [23]. CRMO has been regarded as the paediatric subset of SAPHO syndrome [22]. A highly similar disorder with a genetic background was identified in mice [6].

We present six children with non-bacterial, sclerosing osteomyelitis of the clavicle. The aim of the present study was to evaluate the contribution of modern imaging techniques to diagnosis, to monitor growth of the affected bones, and to evaluate the therapeutic effect of non-steroidal anti-inflammatory drugs (NSAID).

Table 1 Clinical characteristics of six patients with chronic osteomyelitis of the clavicle (*P* pain, *S* swelling, *I* impairment of motion, *AC* acromioclavicular joint, *SC* sternoclavicular joint, *A* ankle joint)

Patient No.	1	2	3	4	5	6
Sex	F	F	F	F	F	M
Age at onset (years)	12	9	12	9	10	15
Symptoms	P,S,I	P,S,I	P,S,I	P,S	P,S,I	P,S
No. of lesions	2	2	2	1	1	1
Arthritis	SC,A	AC,A	none	SC	SC	SC
Plantar pustulosis	No	No	Yes	No	No	No
Biopsy/needle aspiration	Yes	Yes	Yes	Yes	Yes	No
Treatment with NSAID	Yes	Yes	Yes	Yes	Yes	Yes
No. of relapses after biopsy	6	0	1	0	6	0
Follow up in years	4	4	3.5	4	3.5	3.5

Table 2 Diagnostic findings of six patients with chronic osteomyelitis of the clavicle (*l* left, *r* right, *med* medial, *lat* lateral, *dist* distal, *N* normal, *Pos* positive, *Neg* negative. *N.D.* not done).

Patient No.	1	2	3	4	5	6
Localization						
Clavicle	l, med	l, lat	l, med	r, med	l, med	r, med
Tibia	r, dist	l, dist	N	N	N	N
ESR in mm/h	30	25	20	33	20	12
CRP in mg/l	Neg	85	Neg	Neg	Neg	Neg
WBC/µl	9,300	7,700	5,600	9,300	N.D.	12,900
HLA B27	Neg	Neg	Neg	Pos	Neg	Pos
X-ray	Type of bony changes of the clavicle and ankle					
sclerotic	⊕	⊕	⊕	⊕	⊕	∅
lytic	⊕	⊕	⊕	∅	∅	∅
hyperostotic	⊕	⊕	⊕	⊕	⊕	∅
Bone scan	^{99m}Tc MDP uptake					
	⊕	⊕	⊕	∅	N.D.	N.D.
MRI, (Pat. 4:CT)						
''Soft tissue tumour''	⊕	⊕	⊕	⊕	N.D.	⊕
Histology	Type of predominant white cells in osteitis					
granulocytic	⊕				N.D.	N.D.
lymphocytic		⊕	⊕	⊕	N.D.	N.D.
Microbiology of biopsy material	Neg	Neg	Neg	Neg	Neg	N.D.

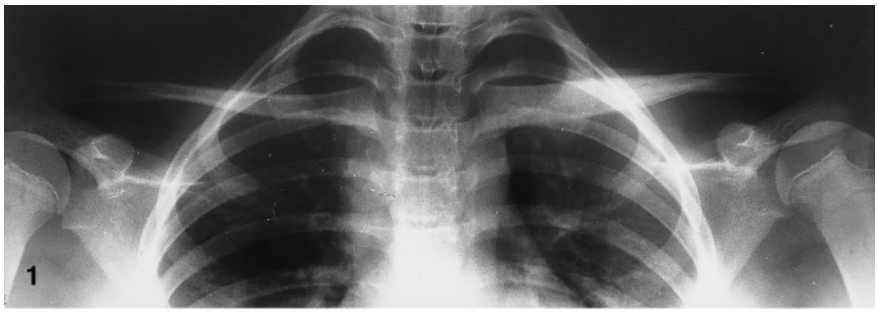

Fig. 1 Standard X-ray of the upper thorax of patient 1 showing hyperostosis of the medial aspect of the left clavicle. There is no involvement of sternum or contralateral side

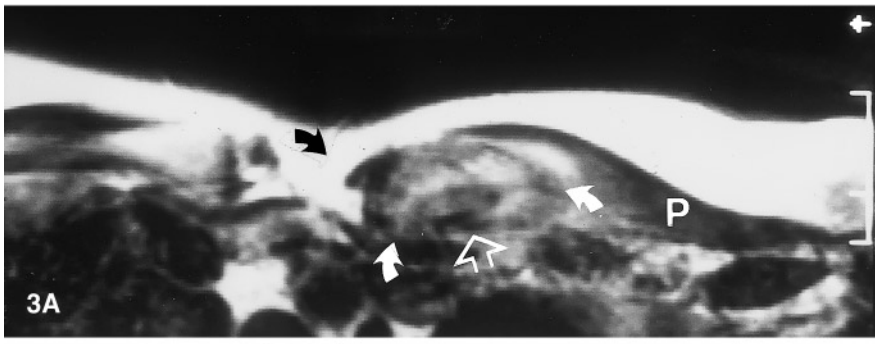

Fig. 2 Standard X-ray of the distal lower leg of patient 1 showing mainly sclerosing lesions with central osteolytic area of the distal left tibia

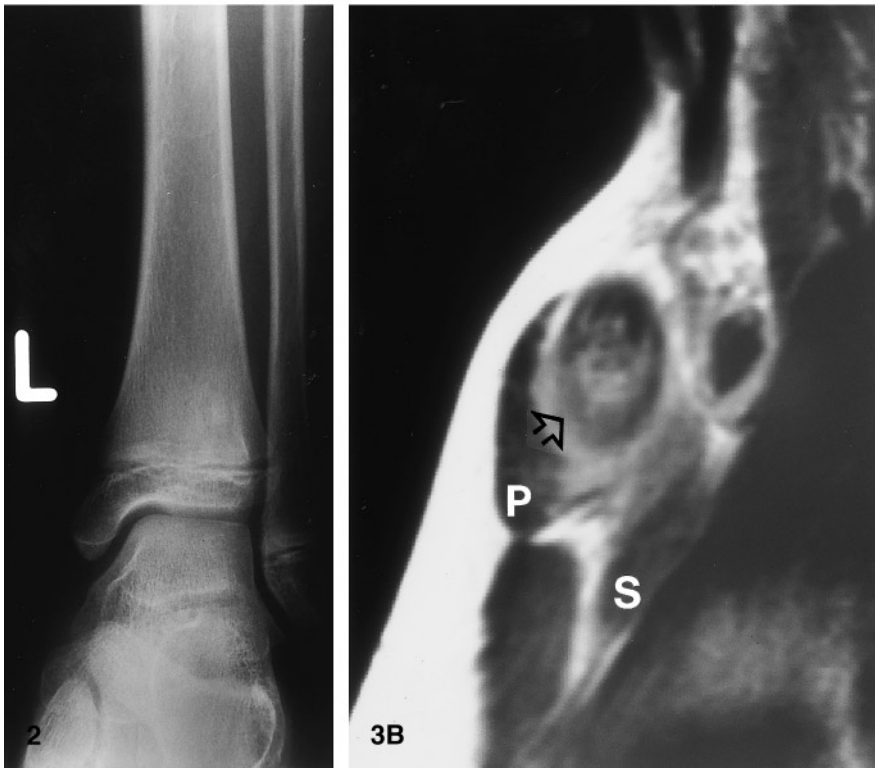

Fig. 3 A Transverse T1-weighted image (SE 460/20) of the sternoclavicular joints of patient 1 after administration of gadolinium-DTPA (dose 0.2 mmol/kg body weight): The medial end of the left clavicle is enlarged. The compacta/spongiosa structure is destroyed with barely recognizable remnants of the compacta (*open arrow*). The clavicle is surrounded by an inhomogeneously contrasted soft tissue "tumour" (*curved white arrows*) which cannot be distinguished from the major pectoral muscle (*P*). Arthritis of the left sternoclavicular joint is demonstrated by the uptake of gadolinium-DTPA (*black arrow*). **B** Sagittal T1-weighted image (SE 460/20) of the medial end of the left clavicle of patient 1 after administration of gadolinium-DTPA i.v. (dose 0.2 mmol/kg body weight): the compacta at the lower margin of the clavicle is destroyed. The clavicle is surrounded by an inhomogeneously contrasted soft tissue "tumour" (*open arrow*) which only in part reveals a sharp border to the surrounding tissue. Hence the major pectoral (*P*) and subclavian muscle (*S*) are involved in the process of inflammation demonstrated by an inhomogeneous uptake of gadolinium-DTPA

Results

We report six children, five girls and one boy, 9–15 years of age (median: 11.2 years) who presented with pain and swelling of either one end of the clavicle, four of them with impairment of shoulder movement. Two patients had a second lesion in the distal tibia with pain, swelling and impairment of motion of the ankle joint. Patients were followed according to a predetermined protocol including history, physical examination (Table 1), standard X-ray (Fig. 1, 2) and modern imaging modalities including bone scan, CT or MRI (Table 2) for at least 3.5 years. In four patients MRI indicated a swelling of the sternal or acromial tip of the clavicle, a destruction of the compacta and a bone marrow oedema of the clavicle in T1-weighted images even when X-rays or bone scan were unremarkable (patients 4, 6). These lesions revealed an inhomogeneous, hyperintense signal in the T2-weighted images. After i.v. administration of

gadolinium-DTPA, a marked, but inhomogeneous, signal enhancement of the lesions could be noted in the T1-weighted images both in the bone lesions and in the adjacent soft tissue "tumour" (Fig. 3, 4). The soft tissue infiltration involved the compacta and the adjacent soft tissue and muscles, including the pectoral muscle. In addition, CT in one patient revealed a tissue mass adjacent to the clavicle. Therefore differential diagnosis included malignant tumours infiltrating the clavicle or the metaphyses/epiphyses of the tibia. Synovitis of the sterno- or acromioclavicular joints with gadolinium-DTPA enhancement of the synovia was noted in two of four patients (Fig. 3A).

To exclude malignancy, four patients underwent open biopsy and one patient had needle aspiration (patient 5). In patient 6 biopsy was refused. Histology in all lesions showed non-specific granulomatous osteomyelitis with a predominant lymphocytic cell infiltrate and a bone forming periostitis (Fig. 5). Cultures from all biopsies were negative. In our patients the diagnosis of chronic osteomyelitis of the clavicle was made 1–5 months after the occurrence of first symptoms except patient 5 (12 months) and within 10 days after the first presentation at our institution.

Five children were treated successfully with the NSAID naproxen (15 mg/kg/day) after diagnosis was made. Swelling and pain were markedly reduced already after the 1st week of therapy. Naproxen was equally effective in the treatment of frequent relapses in patients 1 and 5 at the same dosage. After open biopsy on the left clavicle, patient 3 improved without further treatment. Three years later treatment with naproxen improved manifestations of a relapse on both medial aspects of the clavicles in this patient. No side-effects of treatment were noted.

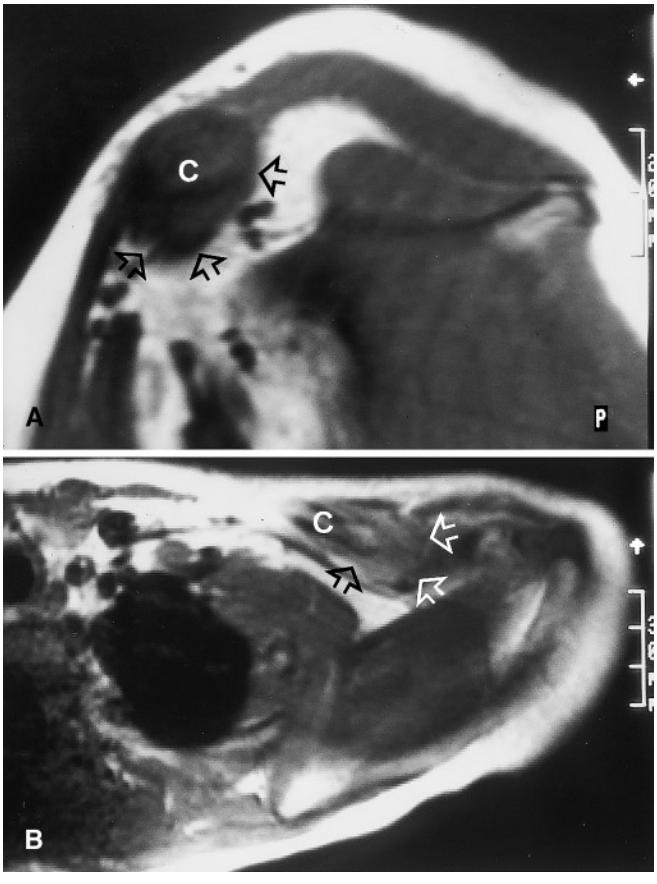

Fig. 4 A Sagittal T1-weighted image (SE 550/20) of the lateral end of the left clavicle of patient 2: the enlarged clavicle (*C*) shows thinning of the upper and dorsal compacta and partial destruction of the compacta at the lower margin. Behind and under the clavicle a soft tissue mass is present (*open arrows*). **B** Transverse T1-weighted image (SE 460/20) of the lateral end of the left clavicle of patient 2 after administration of gadolinium-DTPA i.v. (0.2 mmol/kg body weight): the clavicle is visualized only in part (*C*). The lateral end of the clavicle is surrounded by a soft tissue mass (*open arrows*) which takes up gadolinium-DTPA inhomogeneously

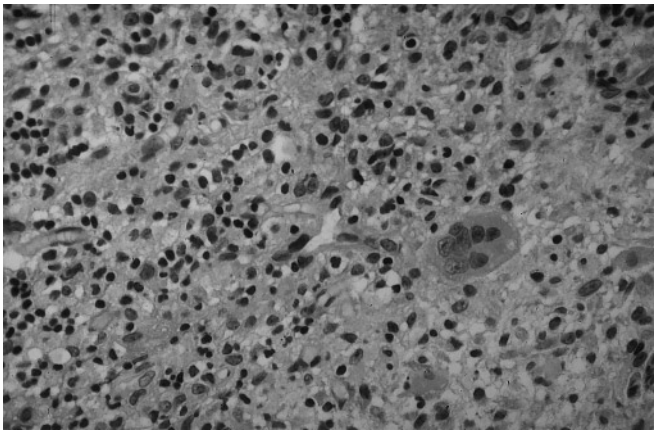

Fig. 5 Histological section of a tissue biopsy taken from the clavicle of patient 2 (Haematoxylineosin staining, magnification 1,000*): osteomyelitis of the clavicle showing a predominant mononuclear and lymphocytic infiltration of the osteolytic lesion. A multinucleated giant cell is present

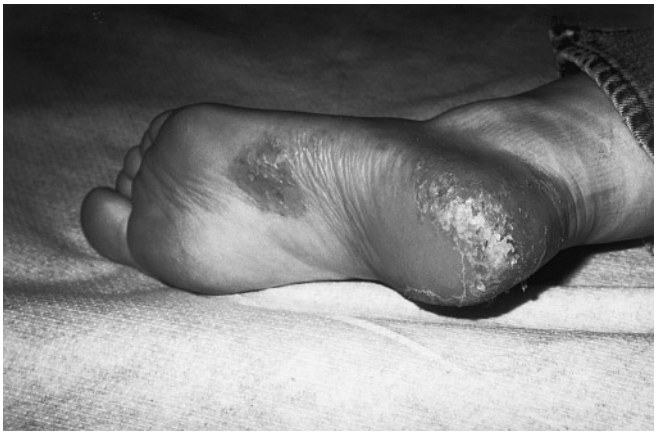

Fig. 6 Plantar pustulosis of patient 3 with chronic osteomyelitis of the clavicle. Initially vesiculation with watery fluid inside the vesicles and erythema were noted. Later erupted pustules were drying and scaling. Walking was painful. Healing of this lesion was prolonged for months. Topical ointment was applied

After 3.5 years of follow up, growth of the shoulder girdle and lower legs was unimpaired in all children. The function of shoulder joints and shoulder girdle was normal. Standard X-ray examination showed consolidation of bone with no lytic residues, minor local hyperostosis and symmetrical growth of the clavicles in five patients. There was no hint for a persistent inflammation affecting the adjacent joints, soft tissue or muscles. The clinical outcome after open biopsy was excellent. Although all five girls were in puberty (PH 3–5) there were no cosmetic complaints.

Discussion

Imaging techniques

There are extensive data on standard X-ray and bone scan examinations of the various bone lesions of CRMO/SAPHO syndrome including the clavicular lesions [2, 32]. However, there is only limited data on modern imaging including CT and MRI. To date, lesions of the femur, the spine and the clavicle have been described [34, 38]. A lower signal intensity of bone in the T1-weighted image and an uptake of gadolinium-DTPA were noted [34, 38]. However, in contrast to our patients involvement of adjacent soft tissue and muscles around the clavicle, which might lead to the erroneous diagnosis of malignancy has not been described so far. Differential diagnosis of CRMO includes osteosarcoma, Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, leukaemia and Langerhans cell histiocytosis [35].

In acute osteomyelitis MRI can recognize a low signal intensity defect within the marrow fat on T1-weighted images early in disease, corresponding to bone marrow oedema before changes are noted in X-ray or bone scan [36]. MRI is highly sensitive for alterations in water content of bone marrow which are found in acute inflammatory processes, e.g. osteomyelitis. An increased water content results in longer T1 and T2 relaxation times. The superior anatomical resolution of MRI provides a significant diagnostic advantage over radionuclide techniques. In chronic osteomyelitis not only destruction of the compacta of bone, but also a significant soft tissue inflammation and arthritis of adjacent joints may be present. MRI can easily assess the extent of this inflammatory process. If acute osteomyelitis progresses into the surrounding tissue a marked, inhomogeneous uptake of gadolinium-DTPA without sharp borders evolving into the adjacent tissue can be noted [36]. In our cases however, the extent of inflammation of adjacent soft tissue resembled a tumour mass surrounding the bony lesion. Due to this soft tissue "tumour" interpretation of MRI/CT favoured malignancy and not chronic inflammation. In two cases the amount of gadolinium-DTPA uptake into the tumour mass and into the adjacent muscles was identical demonstrating an inflammatory process extending even further (Fig. 3b). In CRMO a possible inflammation of soft tissue, joints or entheses prior to an incipient bone lesion has not been discussed so far. Interestingly the early signs of relapse in our patients were pain and soft tissue swelling, however by X-ray, hyperostotic bone lesions were unchanged compared to the latter. If soft tissue inflammation is the primary event in CRMO this might be another possible explanation for the discrepancies found between MRI, bone scan and X-ray.

Therapy

There are reports on aggressive surgical treatment for chronic osteomyelitis of the clavicle resulting in mutilating tissue defects [1, 9, 14]. In our patients such interventions could be avoided. Patients were advised to limit physical exercise or sports especially with stress to the shoulder girdle in the 1st year after biopsy. Fractures of the clavicle were not seen under this regimen.

Most patients suffering from CRMO have only slightly elevated inflammation parameters. If laboratory data suggest a highly inflammatory process and multifocal bacterial osteomyelitis cannot be excluded, intravenous antibiotic treatment should be started immediately after biopsy (patient 2). However antibiotic treatment should be discontinued if biopsy tissue is sterile and the histological examination is characteristic for CRMO. Long-term antibiotic courses have been recommended previously [9], but are ineffective in CRMO [4, 7, 16]. If clinical symptoms and radiographic imaging are typical, it may be more appropriate to treat the patient with NSAID, but not with antibiotics [11, 16]. In our patients treatment with NSAID rapidly reduced pain, swelling and limitation of motion within a few days both when diagnosis was made for the first time and in case of relapse. The mechanism of action may be due to inhibition of the cyclooxygenase I and II pathways and consequently inhibition of prostaglandin biosynthesis. Other non-prostaglandin processes may be blocked by high anti-inflammatory doses of NSAID including interference with enzymes, synthesis of proteoglycans by chondrocytes, transmembrane ion fluxes, cell–cell binding or lymphocyte function [5].

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