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Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome in childhood: a report of ten cases and review of the literature

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Abstract Chronic recurrent multifocal osteomyelitis is a rare chronic inflammatory musculoskeletal process observed in children and young adults. Recently, the acronym SAPHO syndrome (for **s**ynovitis, **a**cne, **p**ustulosis, **h**yperostosis, **o**steitis) was coined to emphasise the association between osteo-articular inflammations and different skin abnormalities which are aseptic and filled with neutrophils. In adults, chronic recurrent multifocal osteomyelitis is now a classical manifestation of SAPHO syndrome. Chronic skin disorders were seen in eight of ten children on follow-up at the University Children's Hospitals in Bern and Zurich and in 61 of 260 paediatric cases reported in the literature. The different skin lesions were palmoplantar pustulosis ($n = 40$), non-palmoplantar pustulosis ($n = 6$), psoriasis vulgaris ($n = 16$) or severe acne ($n = 4$). More rarely Sweet syndrome ($n = 2$) or pyoderma gangrenosum ($n = 1$) were reported.

Conclusion The synovitis, acne, pustulosis, hyperostosis, osteitis syndrome is pertinent even in paediatrics since skin involvement is frequent.

Key words Acne · Ankylosing spondylitis · Arthritis · Chronic recurrent multifocal osteomyelitis · Osteomyelitis · SAPHO syndrome · Skin diseases

Abbreviations *CRMO* chronic recurrent multifocal osteomyelitis · *SAPHO* synovitis, acne, pustulosis, hyperostosis, osteitis

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a rather rare chronic inflammatory musculoskeletal process of children and young adults first reported in 1972 by Giedion et al. [23]. The disease is characterised by multiple sites of osteo-articular involvement, periodic exacerbations and remissions and a failure to isolate pathogens from affected areas [7]. More recently, Chamot et al. [14] coined the acronym synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. This acronym emphasises and publicises the association between osteo-articular inflammations and different skin abnormalities (characterised pathologically by neutrophilic pseudo-abscesses) including palmoplantar or other forms of pustulosis, severe acne or psoriasis. In adults, CRMO is now a classical manifestation of SAPHO syndrome [3, 4, 8, 23, 42, 43, 44, 46, 66, 79, 88].

Little is known, however, of the possible concomitant presence of chronic musculoskeletal inflammation and

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chronic skin disorders in childhood. To answer this question, we analysed the records of the patients with CRMO on follow-up at the University Children's Hospitals in Bern and Zurich. Furthermore, we reviewed all paediatric cases of CRMO reported in the literature to date.

Patients and methods

Between 1983 and 1998, nine paediatric cases (five girls and four boys) of CRMO were investigated at the Department of Paediatrics, University of Bern, Switzerland. Case 1 has already been published in part elsewhere [9]. One more female case was investigated in 1993 at the Department of Paediatrics, University of Zurich, Switzerland. The ages at onset ranged from 2.9 to 13.5 years (Tables 1 and 2). Five out of the ten patients did not originate from Switzerland (Albania, Italy, Libya, Russia, and Yugoslavia, respectively). Three patients had a history of sinusitis, one of a dental abscess and one of a trauma preceding the onset of symptoms. Only osseous lesions confirmed either on plain radiographs or bone scans were included in the analysis.

Results

The patients presented with complaints of pain, tenderness and swelling at one ($n = 6$) or more bone sites ($n = 4$). On examination the patients appeared moderately systematically ill with temperature higher than 38.5 °C only in one of them. The ESR was >20 mm/h (range 21–120 mm/h, median 33 mm/h) in nine of the ten patients. The typical radiological feature was a slight osteolysis, with a lamellar periosteal reaction, suggesting osteomyelitis and a distinct increase in activity on bone scans at affected sites. Bacterial cultures of biopsy specimens obtained from nine patients were negative for both aerobic and anaerobic pathogens in eight patients. Moderate growth of coagulase-positive staphylococci was noted from a bone biopsy in a female patient (Table 1, case 3) with clinical and radiological evidence of multiple foci. The response of this patient to antibiotics was poor and subsequently new foci developed. On follow-up during 0.4 to 4.0 years (median 3.1 years) the patients developed further bone foci. Furthermore, articular involvement was noted on follow-up in eight and enthesitis in four patients (Tables 1 and 2). The bone involvement was multifocal in all but two patients (Table 1, cases 7 and 9), whose clinical course was characterised by several recurrences, leading to radiologically detectable local hyperostosis. Case 8 is worthy of mention because of the presence of spine lesions resembling ankylosing spondyloarthropathy.

Skin involvement was noted in eight patients (Tables 1 and 2) and was diagnosed by morphological appearance but without histopathological examination. In two female patients, palmoplantar pustulosis preceded the musculoskeletal processes by 3 months and 8 years, respectively, and in one male patient psoriasis vulgaris preceded it by 2 years. In five further patients (three boys and two girls) skin disorders such as psoriasis vulgaris ($n = 1$), palmoplantar pustulosis ($n = 1$) or other forms of pustulosis ($n = 3$; trunk in two cases, trunk and head in one case) were observed 0.1 to 4.9 years (median 0.2 years) after the onset of the musculoskeletal processes. None of the ten patients had first degree relatives affected by seronegative spondyloarthropathy. The histocompatibility antigen HLA B27 was negative in the seven patients who underwent this examination (Tables 1, 2).

Discussion

Review of the literature

A computerised search of the database of the United States National Library of Medicine was performed to identify the publications dealing with paediatric cases of CRMO. The query terms osteomyelitis, chronic recurrent multifocal osteomyelitis, CRMO, SAPHO and all child were used. Pertinent secondary references found in these articles were also reviewed. The mentioned methodology revealed that at least 260 patients aged 18 years or less with CRMO (i.e. a clinical course of at least 3 months) were published between 1972 and 1998 in English, French, German and Italian. For the purposes of the current analysis, only radiologically confirmed bone lesions (by means of conventional X-rays or scintigraphy) were considered [1, 2, 5–7, 10, 13, 15–18, 20–22, 24–41, 46, 47–51, 53, 55–58, 60–65, 67, 69–78, 81, 82–88, 90–94].

The χ^2-test and the Mann–Whitney test were used to compare the results obtained in patients with and without skin involvement and also in those who tested positive or negative for the antigen HLA B27. $P < 0.05$ was accepted to indicate statistical significance.

In the 260 patients, the average age at onset of the disease was 10 years; 81% of cases occurred in females (Table 3). The sex ratio, age at onset and the number of bone lesions were similar in 199 patients without and in 61 with skin involvement (Table 3). The most affected bone sites included the metaphyses of tubular bones, the flat bones and the spine. The location of the bone lesions was similar in 199 patients without and in 61 with skin involvement with the exception of the ulna, which was more frequently affected ($P < 0.05$) in patients without skin involvement (Table 4). The histocompatibility antigen HLA B27 was positive in 5 of the 57 patients who underwent this examination. This antigen was more prevalent in patients with skin involvement than in those without ($P < 0.05$; Table 3). An involvement of the axial skeleton (spine, ribs, pelvis, sternum and clavicle) was observed in four of the five (80%) patients with a positive antigen HLA B27 and in 46 of the 52 (85%) who tested negative for this antigen.

Pustulosis, psoriasis, acne conglobata, Sweet syndrome and pyoderma gangrenosum were observed in the 61 patients with skin involvement (Table 5).

Table 1 Clinical characteristics of ten paediatric patients (six girls and four boys) with CRMO treated in the Departments of Paediatrics, Universities of Bern and Zurich, Switzerland

Case Gender	1[a] Female	2 Male	3 Female	4 Male	5 Female	6 Female	7 Female	8 Male	9 Male	10 Female
Age at onset (years)	12	7.0	2.9	13	10	10	7.8	14	10	3.0
Skin lesion	Pustulosis Palmoplantaris	Pustulosis Trunk and head (capillitium)	Pustulosis Palmoplantaris	Pustulosis Trunk	None	Psoriasis Vulgaris	None	Pustulosis Trunk	Psoriasis Vulgaris	Pustulosis Palmo-plantaris
Bone lesions										
Mandibule	+	+	–	–	–	–	+	–	–	+ (Bilateral)
Clavicle	–	–	+	–	–	–	–	–	+	+
Spine	–	–	–	–	–	Cervical Thoracic	–	Lumbar	–	Cervical Thoracic
Pelvis	Ilium, ischium, sacrum	Pubis	–	Ilium	–	–	–	–	–	–
Long bones	Distal tibia and fibula (bilateral) Distal femur	Distal and proximal tibia and femur	Ulna (bilateral), humerus, tibia diaphysis (Bilateral)	–	Proximal and distal tibia	Proximal tibia (bilateral)	–	–	–	–
Foot	–	–	Calcaneus and talus	Calcaneus	Calcaneus and talus	–	–	Calcaneus	–	–
Further bones	–	–	Rib	–	–	Frontal bone		–	–	–
Arthritis										
Ileosacral joint	+	–	–	+	–	–	–	+ (Bilateral)	–	–
Hip	–	+	+	–	–	+	–	+	+	+
Ankle	–	–	+ (Bilateral)	–	–	+ (Bilateral)	–	+	–	–
Further joints	–	Knee, shoulder	–	–	–	Knee (bilateral), sternoclavicular, costovertebral, and sternocostal joints	–	Cervical spine, sternoclavi-cular joint	–	–
Enthesitis	Achilles tendon, acromion, clavicle	–	–	Achilles tendon	–	Major trochanter, patella (bilateral), pes anserinus, tarsus (bilateral)	–	Spine	–	–
HLA antigen B27	Negative	Negative	Not assessed	Negative	Not assessed	Negative	Negative	Negative	Negative	Not assessed

[a] Case 1 has been published [9]

Table 2 Characteristics of ten paediatric patients (six girls and four boys) with CRMO (Departments of Paediatrics, Universities of Bern and Zurich, Switzerland)

Parameter	*N*
Musculoskeletal involvement	10
Age at onset (years, median and range)	11 (2.9–14)
Bone involvement	10
Articular involvement	8
Enthesitis	4
Skin involvement	8
Age at onset (years, median and range)	11 (3.0–15)
Palmoplantar pustulosis	3
Other forms of pustulosis (trunk, $n = 2$; trunk and head, $n = 1$)	3
Psoriasis vulgaris	2
HLA B27 positive	0/7

General review

The term CRMO describes a distinct clinical-radiological-pathological entity for which no cause is known [3, 4, 7, 8, 14, 23, 24, 42–45, 66, 79, 89]. Clinically the disease is characterised by the insidious onset of local pain and swelling in affected bones and joints (usually multifocal and symmetrical) and enthesitis. Sometimes fever and elevated ESR are observed. The course is one of intermittent periods of exacerbation and remission. The present report and review of the literature indicate that in childhood, CRMO is found in patients with a median age of 10 years and occurs twice as frequently in females as in males. In childhood the disease most commonly affects the extremities (most often the proximal and distal metaphyses of the tibia and femur). Other sites of involvement include the spine, clavicle, pelvis and ribs. More rarely the disease affects the jaw, scapula and sternum. In adults, however, the anterior chest wall is the most distinctive localisation [3, 4, 8, 14, 23, 42–45, 66, 79, 89].

Radiologically, lesions in the long bones are often symmetrical and metaphyseal. The appearance is that of osteomyelitis with metaphyseal lucency, with or without bordering sclerosis. Bone scintigraphy demonstrates increased uptake at the involved sites. Magnetic resonance imaging scans are highly sensitive, provide data on the involvement of adjacent joints and soft tissue and are helpful in disease monitoring [8, 13, 14, 40, 50, 62, 79, 86, 89, 90, 93]. The histopathology of bone lesions is variable. Early lesions are characterised by the presence of neutrophils and are reported as pseudo-abscesses. Chronic lesions demonstrate a predominance of lymphocytes with the occasional presence of plasma cells and histiocytes. Non-caseating granulomatous foci occasionally co-exist [4, 6, 8, 44, 45]. Most cultures are negative for bacteria, fungi and *Mycobacteria*. Rarely, coagulase-positive staphylococci (as in one of our cases) or, more frequently, coagulase-negative staphylococci or *Propionibacterium acnes* grow. The pathogenic role of these germs is questionable. They have traditionally been considered contaminants in view of the lack of response to appropriate antibiotics. It has also been suggested that SAPHO results from hitherto unrecognised micro-organisms of low virulence [13, 20, 24, 34, 48, 51, 57, 60, 65, 76, 91]. If a responsible micro-organism exists, it might be detectable in the near future by molecular technologies. The present analysis and a recent review suggests that CRMO can be diagnosed if the following criteria are fulfilled: (1) a disease course of 3 months or more, (2) bioptical evidence of chronic bone inflammation with exclusion of other diseases and (3) failure to cultivate a micro-organism [81].

In a large proportion of the children with CRMO presented in this report and those reviewed in the paediatric literature, the skeletal manifestations were associated with different chronic skin disorders, such as palmoplantar pustulosis (which is considered by some dermatologists as a variant of psoriasis vulgaris) [58], non palmoplantar pustulosis, psoriasis vulgaris or severe acne [5, 7, 9, 13, 16, 20, 25, 28, 31–33, 35–37, 46, 48, 49, 51, 57, 64–66, 69, 70–72, 74, 77, 86, 88, 93]. Sweet syndrome [56] or pyoderma gangrenosum [86] were less frequently reported. Despite major clinical differences, all the mentioned skin conditions share the common denominator of being aseptic lesions filled with neutrophils at some stage during the course of their development [3, 4, 8, 14, 23, 42–45, 66, 79, 89].

Table 3 Characteristics of 260 paediatric patients with CRMO reported in the literature

	All patients	Patients without skin involvement	Patients with skin involvement
Number of patients	260	199	61
Gender[a]			
Female	181*	143	38
Male	42	29	13
Age at onset (years, median and interquartile range)	10 (8.0–12)	10 (8.0–11)	11 (9.0–13)
Number of bone lesions (median and interquartile range)	3 (2–5)	3 (2–5)	3 (2–5)
HLA B27 antigen positive[a]	5/57	0/26	5/31**

[a] Information not available for some patients
*$P < 0.05$ versus males
**$P < 0.05$ versus patients without skin involvement

Table 4 Osseous lesions and iliosacral arthritis in 260 paediatric patients with CRMO reported in the literature

Localisation	All patients (n = 260)	Patients without skin involvement (n = 199)	Patients with skin involvement (n = 61)
Extremities	664	544	120
Tibia	250	203	47
Femur	136	118	18
Foot	88	72	16
Fibula	61	46	15
Radius	34	28	6
Humerus	32	21	11
Hand	31	25	6
Ulna*	31	30	1
Spine	108	79	29
Cervical	5	3	2
Thoracic	56	38	18
Lumbosacral	18	13	5
Exact localisation unknown	29	25	4
Clavicle	89	67	22
Pelvis	49	37	12
Ribs	32	19	12
Jaw	13	7	6
Sternum	12	8	4
Scapula	8	7	1
Skull	5	3	2
Other osseous lesions[a]	10	6	4
Iliosacral joint	24	17	7

[a] Localisation unknown
*$P < 0.05$ versus patients without skin involvement

Table 5 Skin lesions in patients with CRMO

Lesion	Literature	Present study
Palmoplantar pustulosis	37/61[a]	3/10
Generalised pustulosis	1/61	–
Other forms of pustulosis	2/61	3
Psoriasis vulgaris	14/61	2
Acne conglobata	4/61	–
Sweet syndrome	2/61	–
Pyoderma gangrenosum	1/61	–

[a] Three of the 37 patients were reported to have psoriasis pustulosa. According to the recent literature [58], palmoplantar pustulosis and psoriasis pustulosa do not represent different entities

Underreporting and the occasional appearance of skin lesions many years after onset of osteo-articular lesions likely account for the higher prevalence of skin lesions in our own cases (80%) as compared with those reported in the paediatric literature (23%). The age at disease onset and the skeletal sites of predilection were similar in patients with and without skin involvement. Surprisingly, the ulna was more frequently affected in the cases without skin involvement. In addition, the antigen HLA B27 was more prevalent in patients with skin involvement than in those without.

In 1987 the unifying acronym SAPHO syndrome was proposed to designate patients suffering from apparently sterile inflammatory arthro-osteitis, often associated with the aforementioned skin conditions [3, 4, 8, 14, 23, 42–45, 66, 79, 89]. The results of the present study suggest that the acronym SAPHO is worthy of consideration even in childhood.

So far it is impossible to have a full understanding of the pathophysiology of SAPHO syndrome [3, 4, 8, 13, 22, 41, 42, 45, 46, 65, 78, 87]. Spread of cutaneous infection seems unlikely as the cause of SAPHO syndrome because classical pathogens are not cultured in most patients. However, occasionally organisms may be cultured, as discussed above [3, 4, 8, 13, 22, 41, 42, 45, 46, 65, 78, 87]. The mechanisms explaining the link between skin and osteo-articular lesions remain incompletely understood. Some hypotheses relate this syndrome to an auto-immune response triggered by a micro-organism. The molecular mimicry hypothesis suggests that a fragment from a micro-organism mimics a molecule in a bone or joint, then the immune system mistakenly attacks normal osteo-articular tissue. The immune complex hypothesis suggests that a fragment from a micro-organism, coupled with an immunoglobulin, is deposited in a bone or joint and activates a sterile inflammation. Finally, according to the immune barrier breakdown hypothesis, a skin infection breaks down a barrier between immune cells and superficial skin tissues. Consequently, normal skin antigens are exposed to the immune system and epitopes in bones or joints resembling skin antigens become subject to an immunological cross-reaction resulting in inflammatory sequelae [8, 51, 53]. It is worthy of mention, however, that none of these hypotheses provides an explanation when osteo-articular lesions precede skin lesions.

The antigen HLA B27 contributes to the development of ankylosing spondyloarthropathy, Reiter syndrome, reactive arthritis and enteropathic arthropathies [11, 68]. The results of the present study and review of the literature provide some information on the possible association between the antigen HLA B27 and SAPHO syndrome in childhood. In fact, the prevalence of this antigen appears identical (9%) in paediatric patients with CRMO and in the general European population [11]. Surprisingly, the mentioned antigen was rather frequent (16%) in paediatric patients with the concurrent occurrence of bone and skin lesions [14]. In adults with SAPHO syndrome, the prevalence of the antigen HLA B27 is rather high, varying between 15% and 30%. It has even been suggested [23, 42, 45] that the majority of adult patients with SAPHO syndrome satisfies the accepted diagnostic criteria for the spondyloarthropathies [19]. In the experimental animal a chromosomal mutation is linked to a disease resembling CRMO in humans. These data argue against an association between SAPHO syndrome and HLA B27 [12].

More than 60 paediatric patients with both CRMO and different skin abnormalities sharing the peculiarity of being lesions filled with neutrophils at some stage during the course of their development (mostly pustulosis, psoriasis vulgaris or severe acne) have been so far documented in 74 reports [1, 2, 5–7, 10, 13, 15–18, 20–22, 25–41, 46, 47–51, 53, 55–58, 60–65, 67, 69–78, 81,

82–88, 90–94]. Yet, with few exceptions [5, 25, 28, 33, 35, 36, 49, 61, 71, 74], the acronym SAPHO has so far been used only in reports including both children and adults [14, 17, 88]. The present report and review of the literature demonstrates that in childhood, the skeletal manifestations are almost identical in CRMO with skin involvement and in those without. It is therefore concluded that the use of the unifying acronym SAPHO syndrome is justified both in adulthood as well as in childhood.

Recognition of SAPHO syndrome is important to avoid prolonged antibiotic treatment of osteo-articular lesions and unnecessary invasive procedures. Our data and a very recent analysis of no more than 214 paediatric patients with CRMO help to provide a picture of SAPHO syndrome and enable a differentiation from other diseases such as primary bone tumours, metastases, Langerhans cell histiocytosis and classical bacterial osteomyelitis. The following features are characteristic of SAPHO syndrome: (1) local bone pain with gradual onset, (2) multifocal lesions, especially in tubular long bones and spine, (3) failure to cultivate an infectious organism, (4) a protracted course for years with exacerbations and improvement with anti-inflammmatory drugs and (5) skin conditions sharing the common denominator of being filled with neutrophils, mostly palmoplantar pustulosis, non palmoplantar pustulosis, psoriasis vulgaris or severe acne [81].

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