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Chronic Recurrent Multifocal Osteomyelitis (CRMO) and Synovitis Acne Pustulosis Hyperostosis Osteitis (SAPHO) Syndrome – Two Presentations of the Same Disease?

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ABSTRACT The two most common entities among generally rare but under-diagnosed autoinflammatory bone disorders are chronic recurrent multifocal osteomyelitis (CRMO) and synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Due to their similarities, many authors consider CRMO to be a subtype of SAPHO syndrome. The aim of this study was to compare clinical, laboratory, and imaging features and outcomes of patients with CRMO and SAPHO. The analysis of the data from 6 children with CRMO (four girls and two boys, age 3.5-14 years) and of 6 children (6 boys, age 13.5-17.5 years) with SAPHO syndrome was performed. The initiating symptoms in all patients with CRMO were bone pain with multifocal bone lesions. There were no skin manifestations. Five out of six patients achieved control with nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, while one patient required disease-modifying antirheumatic drugs (DMARDs). The initiating symptom in five patients with SAPHO syndrome were severe acne, while in one patient acne occurred two years after the disease onset. Two patients typically developed inflamed sternoclavicular joints and sternum, while the others showed changes affecting other skeletal regions. Three patients achieved control with NSAIDs and corticosteroids, the others required DMARDs and TNFα inhibitors. In comparison with patients with CRMO, patients with SAPHO suffered more frequent and longer lasting exacerbations. In conclusion, CRMO and SAPHO syndrome have an array of common characteristics, but also a number of differences. Nevertheless, further investigation into the etiopathogenesis is required to establish a definite relationship between CRMO and SAPHO.

KEY WORDS: SAPHO syndrome, CRMO, acne conglobata

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INTRODUCTION

Autoinflammatory bone disorders are a group of diseases characterized by a nonspecific inflammatory reaction whose trigger is most likely the inappropriate activation of the innate immune system (1-4). This group of disorders includes SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), chronic recurrent multifocal osteomyelitis (CRMO), Majeed syndrome, deficiency of the interleukin-1-receptor antagonist (DIRA), pyogenic arthritis, pyoderma gangrenosum, and acne syndrome (PAPA) and cherubism. Among the above, SAPHO syndrome and CRMO are the most common (2). While the genetics for DIRA, PAPA, and Majeed syndrome are well defined, the genetics behind SAPHO syndrome and CRMO are still unclear (1). Increased levels of IL1β, IL6, IL12, and TNFα as well as decreased levels of IL10 have been observed, pointing toward dysregulation of these pathways and an imbalance between proinflammatory and anti-inflammatory cytokines (3,4).

Due to the uncertain cause and similar features, a certain number of authors support the hypothesis that CRMO is a pediatric form of the SAPHO syndrome (5-7). Whether this is true or CRMO is a separate entity is yet to be determined.

The main characteristic of the SAPHO syndrome is osteitis, which may or may not be followed by a spectrum of skin lesions (8,9). The syndrome has a chronic character with periods of remissions and exacerbations (5). SAPHO syndrome can occur at any age, with the prevalence of <1/10000 in Caucasians (5,10–13). The anterior chest wall is the most frequently affected site. The spine is affected less often, lesions can rarely be found in the long bones and the mandible (14,15). Uncommonly, only the manubriosternal junction is affected, resulting in diagnostic doubts in relation to the other causes of chest pain, especially concerning the cardiac pathology (16). Arthritis is found in more than 90% of the patients, with a preference for the axial skeleton (9). Skin manifestations in the form of neutrophilic dermatoses (acne conglobata, acne fulminans, palmoplantar pustulosis, hidradenitis suppurativa, pustular psoriasis, and rarely pyoderma gangrenosum and Sweet's syndrome) (14) can occur before, concurrently, or after the onset of osteomuscular symptoms. However, the disease can advance without any skin manifestations (12,17).

CRMO is an autoinflammatory disorder causing a sterile inflammation of the bone (18). Because of its nonspecific clinical and diagnostic findings, incompletely understood pathophysiology and the lack of recognition, the diagnosis is often late (19,20). CRMO affects children of the median age of 10 years (21-24). Initial presentation is usually bone pain varying from mild to intense. The most commonly affected areas are the metaphysis of the long bones, pelvis, vertebral bodies, and clavicles (1,25). However, lesions can affect any bone in the body, including the neurocranium (26,27). CRMO can also affect the skin, lungs, gastrointestinal system, and eyes (1,2). Due to the relapsing and remitting character of the disease, impairment and bone deformation can occur (3). Luckily, whole-body magnetic resonance imaging (MRI) has shown a great success in detecting bone changes and is recommended at the onset of a disease as well as during the follow-up (19,28,29).

PATIENTS AND METHODS

A retrospective medical records review of all patients suffering from SAPHO syndrome or CRMO aged

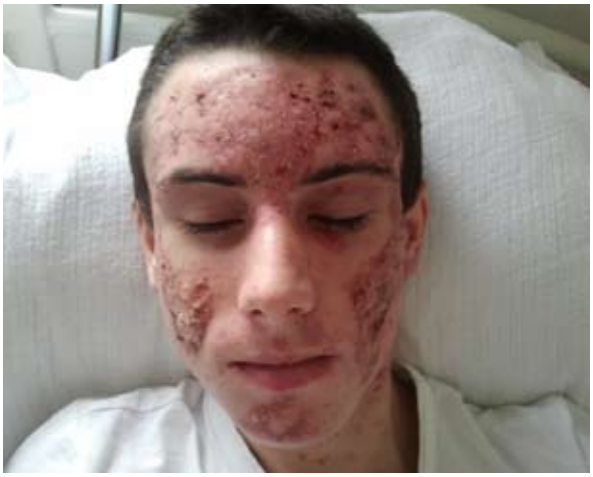

Figure 1. Acne conglobata on the face of patient 1 with SAPHO syndrome.

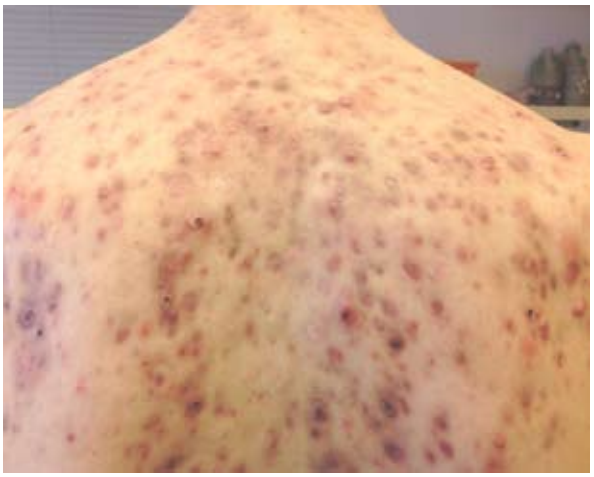

Figure 2. Acne conglobata on the back of the patient 2 with SAPHO syndrome.

Table 1. Clinical and laboratory features of patients with SAPHO syndrome and CRMO

Patient	1	2	3	4	5	6	7	8	9	10	11	12
Disease	SAPHO	SAPHO	SAPHO	SAPHO	SAPHO	SAPHO	CRMO	CRMO	CRMO	CRMO	CRMO	CRMO
Sex	Male	Male	Male	Male	Male	Male	Female	Female	Female	Female	Male	Male
Age/years	17.5	15.5	16.0	16.5	17.0	13.5	4.5	3.5	8.0	9.0	7.0	14.0
Initiating symptom	Acne conglobata	Pain in the chest wall	Acne conglobata	Acne conglobata	Acne conglobata	Acne conglobata	Pain and edema of the right leg	Severed walk and hypotrophy of lower extremities	Pain in the lumbar vertebra	Edema and pain in the right clavicle (sternal end)	Back and abdominal pain	Pain in the right lower leg
Location of lesions	SI joints, sternum, SC joints	SI joints, sternum, vertebra, left AMC joint	Maxilla, Mandible	SI joint, vertebra, ribs	Pelvis, ribs, SC joints, sternum	SI joints	Distal part of the right tibia, metatarsal bone	Long bones of the extremities, vertebra, ribs, clavicle	Vertebra, pelvis	Right clavicle and SC joint, rib	Vertebra (Th8-Th11, L4), right shoulder	Middle thirds of both tibias
Lesions	Erosion, lytic lesion, edema	Erosion, sclerosis, edema, vertebral (Andersson) lesion	Lytic lesion	Inflammation osteoporosis	Erosion, edema	Erosion	Sclerosis, lytic lesion, hyperostosis	Sclerosis, lytic lesion, osteoporosis	Inflammation lytic lesion	Erosion, hyperostosis	Sclerosis, osteoporosis, edema	Hyperostosis
Inflammation of the long bones	/	/	/	/	/	/	Yes	Yes	/	Yes	/	Yes
CRP/mg/L	104.0	41.7	50.0	79.5	93.1	26.5	11.5	11.0	48.0	0.5	134.5	3.3
ESR/mm/h	80.0	31.0	50.0	37.0	63.0	74.0	60.0	25.2	98.0	28.0	100.0	11.0
High fever	Intermittent	/	/	/	Yes	/	Intermittent	Intermittent	Yes	/	Intermittent	/
Skin manifestation	Acne conglobate, PG	Acne conglobata	Acne conglobata	Acne conglobata	Acne conglobata	Acne conglobata	/	/	/	/	/	/
Therapy	NSAID, MTX, Sulfasalazine, Isotretinoin	NSAID, MTX, Sulfasalazine, Isotretinoin, CS, TNF inhibitor	NSAID, Isotretinoin	NSAID, CS, Isotretinoin	NSAID, CS, MTX, Isotretinoin,	NSAID, CS, Isotretinoin	NSAID, azithromycin	NSAID, CS	NSAID, CS	NSAID, sulfasalazine	NSAID	NSAID, azithromycin

AMC: acromioclavicular; CS: corticosteroids; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drugs; PG: *Pyoderma gangrenosum*; SI: sacroiliac; SC: sternoclavicular

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Figure 3. A technetium 99m (Tc-99m) bone scan showing intensive tracer uptake at the sternoclavicular joints and sternum, which represent a typical "bull's head" sign in patient 1 with SAPHO syndrome.

1-18 years, dating from 2006 to 2016, was performed at the Division of Paediatric Immunology and Rheumatology, Department of Paediatrics, of the University Hospital Centre Zagreb. The following data were collected and analysed: sex, age, date of diagnosis, clinical data, laboratory testing, diagnostic results, and therapy. The approval of the ethics committee was obtained before the data was collected.

RESULTS

Patients with SAPHO syndrome

Six patients were diagnosed with SAPHO syndrome, all boys, with the median age of 16 years (13.5-17.5) at the disease onset. All patients presented with skin manifestations – acne conglobata (Figure 1 and Figure 2) – with one patient also having pyoderma gangrenosum. Five patients had skin manifestations as the initiating symptom, while in one patient acne appeared two years after the appearance of osteomuscular symptoms, with skeletal pain as the initiating symptom (Table 1). Only two patients had increased body temperature (patients 1 and 5). Five patients experienced lumbosacral pain extending to the hips, and three of them also had a typical pain in the anterior chest wall. In addition, patient 1 felt pain in the left knee, patient 4 in the left shoulder, and patient 5 in the right leg and cramps in both legs. Laboratory results for every patient showed increased inflammatory markers (Table 1).

All patients underwent plain radiography and most underwent MRI. The chest wall was affected in four out of six patients. There were no lesions of the long bones. A technetium 99m (Tc-99m) bone scan showed increased tracer uptake in the anterior costal wall (ACW) in three patients (patients 1, 2, and 5), but only two had a typical "bull's head sign" (patients 1 and 5) (Figure 3). Other affected locations were the sacroiliac joints (patients 1, 2, 5, 6), knees (patients 1, 5), foot (patient 5), and hand (patient 1). Patient 3 had an increased tracer uptake only in the right maxilla and mandible.

Due to acne conglobata as the first symptom in five patients, three patients (patients 1, 4, and 5) were initially treated with antibiotics (mostly azithromycin and clindamycin), but all unsuccessfully. Because of the osteoarticular symptoms in all patients, NSAIDs were introduced as the first-line therapy, but without a satisfying effect in all but one patient (patient 3). Subsequently, patient 1 received DMARDs – sulfasalazine and later methotrexate. Patients 2 and 5 were treated with corticosteroids and DMARDs; however, patient 2 eventually needed TNFα inhibitors (etanercept). Patients 4 and 6 were treated with corticosteroids. All patients were also treated with isotretinoin (Table 1). Under prescribed therapy, all patients achieved disease control.

Patients with CRMO

Six patients were diagnosed with CRMO: four girls and two boys, of median age 7.5 (3.15-14) at the disease onset (Table 1). The initiating symptom in five patients was bone pain: patients 7 and 12 presented with pain in the right leg, while patients 9 and 11 experienced pain in the back accompanied with high fever. Patient 10 presented with pain in the right sternoclavicular joint. Patient 8 had impaired walking capacity and hypotrophy of lower extremities as initiating symptoms (Table 1). All patients had multifocal inflammatory bone lesions, three of them had dominating lesions in the lower extremities (tubular bones), two in the axial skeleton, and one in the clavicle. Only patient 8 had symmetric lesions. No of patients with CRMO had skin manifestations or inflammatory bowel syndrome. Increased inflammatory markers (CRP, ESR) were noted in four patients, followed by increased body temperature (Table 1).

Plain radiography was performed, followed by scintigraphy and MRI in most patients. In patient 7, radiography showed lesions of the right tibia and of the third metatarsal bone, while scintigraphy showed increased tracer uptake in these areas as well as in the right mandible, creating a multifocal image. Patient 8 had multiple lesions of the long bones of the extremities, spine, ribs, and clavicle, with scintigraphy showing a symmetrical multifocal increased tracer

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uptake in the long bones of the extremities. MRI and scintigraphy confirmed changes in Th12 and L3 in patient 9. In patient 10, lesions of the right clavicle, sternoclavicular joint and first rib were detected with radiography. Inflammatory changes of the vertebra and right shoulder in patient 11 were confirmed with radiography, MRI, and scintigraphy, while scintigraphy showed increased tracer uptake in both tibias in patient 12 (Table 1).

All patients were treated with NSAIDs. Patients 9 and 11 were treated with antibiotics (ceftriaxone or amoxicillin with clavulanic acid) because of elevated inflammatory markers and fever, but without any effect. Patients 7 and 12 were simultaneously treated with azithromycin due to its anti-inflammatory effect, followed by vitamin D3, calcium, and physical therapy, alongside NSAIDs, which led to remission. Due to the inefficacy of NSAIDs in patients 8 and 9, disease control was achieved only after introduction of corticosteroids. Patient 10 achieved disease control after the introduction of sulfasalazine alongside NSAID, while NSAIDs were sufficient in patient 11 (Table 1). In the end, disease control was achieved in all patients.

DISCUSSION

SAPHO syndrome

The aim of our study was to analyze and compare clinical, laboratory, and imaging features as well as the outcomes of patients with CRMO and SAPHO syndrome.

The first sign of the SAPHO syndrome is usually oscillating, progressive, palpatory skeletal pain (5). Our findings were different, as 5 out of 6 patients (83%) had skin lesions as the first symptom (Table 1), while only one patient had skeletal pain as the initiating symptom. Skeletal pain occurred after 2 months or up to 4 years later in 4 patients. Lumbosacral pain occurred in five patients (83%), and anterior chest wall pain in three (50%). In a study conducted by Li *et al.*, all of 164 patients reported pain in the ACW, and 67.6% presented with pain in the lumbosacral region (11).

Studies have shown that skin manifestations (neutrophil dermatoses) (5) appear in a range from 2/3 (12) to 94.5% of patients (11). They usually develop two years prior or after the osteomuscular symptoms (5,9,30). In comparison, all of our patients had skin manifestations, occurring in five patients as the first symptom, whereas in one patient they manifested two years after the first osteoarticular symptom. The association of noninfectious osteitis and skin changes is often critical for the diagnosis (14,31). While all our patients had skin manifestations, unfortunately, patients without them were probably left undiagnosed or recognized as some other disease (probably juvenile spondyloarthritis).

Four out of six patients had lesions in the chest wall, which is its most common location. The second most common location is the spine, primarily affecting the thoracic segment, which was observed in two of our patients (14). Five patients showed symptoms of sacroiliitis, which was then followed by osteosclerosis of the iliac bone, typical for SAPHO syndrome (8,9).

Only two of our patients presented a typical "bull's head sign" on the skeletal scintigraphy, pathognomonic for the syndrome, which are findings similar to those of Fu *et al.* where only 22.9% of patients had this sign, suggesting its lack of sensitivity (32,33).

Due to the similarities between SAPHO syndrome and osteomyelitis, the hypothesis that *Propionibacterium acnes* cases the syndrome, but also because of severe acne, patients are often treated with antibiotics (34,35). Studies have shown that this treatment is effective only in a low percentage of cases. Moreover, the symptoms would reoccur by the end of the therapy (36,37). In our study, three patients were treated with antibiotics (mostly azithromycin and clindamycin) with no improvement in skin status.

All of our patients were treated with isotretinoin because of its high potency against severe acne (35).

Our patients were treated with NSAIDs due to the osteoarticular symptoms, but NSAIDs were a sufficient treatment only in one patient. Corticosteroids and DMARDs were used as the second line of therapy (5,14). They were effective in four of our patients, while one patient (patient 2) did not achieve sufficient control of the disease. In a survey conducted by Li *et al.*, 49.0% of patients considered DMARDs effective, while 81.2% of patients reported a decrease of pain under corticosteroid therapy (11). The disease was progressing in patient 2, so a TNFα inhibitor (etanercept) was introduced because of its positive rapid effect on patients with refractory SAPHO syndrome and therapy-resistant acne conglobate (38-41).

CRMO

The first symptom at the disease onset is usually bone pain, which agrees with our findings, in which 5 out of 6 patients experienced pain as the initiating symptom, and one patient had walking disability and muscle hypertrophy (1). CRMO lesions are most often positioned on the clavicle, tibia, femur, fibula, and pelvis (3,23,24,42). A lesion on the distal part of the tibia was confirmed by radiography in patient 7, extending to the epiphyseal plate, which is a very common location and type of lesion for CRMO (1,42).

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Three of our patients in the lower extremities (tubular bones) and two patients had dominating lesions in the axial skeleton. Two out of six patients had lesions in the clavicle, which is one of the most commonly affected sites (43).

In cohort studies, 70-99% of patients had multifocal lesions, which is in agreement with our study (44). All of our patients had multifocal lesions, which were symmetric in only one patient. The main goal of whole-body imaging is to recognize the multifocal and bilateral patterns characteristic for CRMO and to diminish the need for biopsy (19,28,29). Unfortunately, the highly recommended whole-body MRI was not available in Croatia during our retrospective study.

Patients 9 and 11 were treated with antibiotics (mostly ceftriaxone and amoxicillin with clavulanic acid) due to the high inflammatory markers and fever but without any effect, which corresponded to other studies (45). While all patients were treated with NSAIDs, patient 7 and 12 were treated simultaneously with azithromycin because of its potential anti-inflammatory and immunomodulatory effect (46). Unfortunately, due to the simultaneous treatment with NSAID, we cannot assess whether azithromycin had any effect. Only patient 11 had a satisfactory response to NSAIDs. Corticosteroids were introduced into therapy in patients 8 and 9, which is a great choice in patients with exacerbations nonreactive to NSAIDs (2,3,22). Patient 10 was successfully treated with sulfasalazine alongside NSAIDs.

SAPHO syndrome and CRMO comparison

Whether SAPHO syndrome and CRMO are distinct diseases or different manifestations of the same syndrome has not yet been answered with certainty. Considering the fact that CRMO usually affects children and SAPHO syndrome usually affects adolescents and adults, some researchers believe CRMO is a pediatric form of SAPHO syndrome (5,6). Our patients with CRMO were aged between 3.5 and 14.0 years, while patients suffering from SAPHO syndrome were between 13.5 and 17.5 years, which supports the proposed age preferences of these diseases (2). However, there have been records of pediatric patients with SAPHO syndrome (6,47) and adults with CRMO (48) which, on the other hand, supports the hypothesis of the two distinct pathologies with different manifestations regardless of age. Both SAPHO syndrome and CRMO have a marked female predominance, which was in agreement with our results regarding patients with CRMO (four girls and two boys). However, all our patients with SAPHO syndrome were male, differing from recent literature and increasing the distinction between our two groups (Table 1) (9,11,19,49).

There are a number of similarities between the diseases. The lesions are osteodestructive, later osteoprolific, and followed by osteitis and hyperostosis. The bone biopsy is conclusive with inflammation and usually shows a sterile culture. Skin changes and IBD are associated with both diseases. However, SAPHO syndrome has lesions on the axial skeleton, while CRMO has them on the lower extremities near the metaphysis of the long bones (50). Notably, some studies describe CRMO and SAPHO syndrome as one disease, which impedes an objective comparison (5,7). The number of patients for this study was limited and therefore comparison with larger studies is more difficult.

Both groups in this study had almost identical symptoms followed by increased inflammatory markers, occasionally increased body temperature, and sterile cultures (Table 1). However, some discrepancies were observed. Patients suffering from SAPHO syndrome had lesions on the axial skeleton and acne conglobate, while patients with CRMO had multifocal lesions mostly positioned on the tubular bones, without skin manifestations. Furthermore, five out of six patients with CRMO achieved control with NSAIDs and corticosteroids, whereas patients with SAPHO syndrome suffered longer and more frequent exacerbations and needed DMARDs and TNFα inhibitors to achieve control (Table 1).

The retrospective form of the study, small sample size, and differences in age and sex between the two groups of patients presented a limitation in executing our study.

CONCLUSION

There are a number of shared elements between CRMO and SAPHO syndrome, but we found a number of differences such as sex predominance, skin manifestation, bone lesion location, and progression of the disease. The occurrence of CRMO predominantly during childhood and SAPHO syndrome in adolescence is consistent with past studies. At this stage, it is not possible to establish with certainty whether SAPHO syndrome and CRMO are the same disease. This question will be answered with certainty only when the inconclusive etiopathogenesis of these two most frequent autoinflammatory bone disorders is revealed.

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