

SAPHO Syndrome

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Abstract

The acronym SAPHO stands for morbid alterations of the osteoarticular system: synovitis; acne; pustulosis), often psoriatic, mainly palmo-plantar, hyperostosis); as well as osteitis. As described by Kahn et al. in 1994, three diagnostic criteria characterize SAPHO syndrome: 1) multifocal osteomyelitis with or without skin manifestations; 2) sterile acute or chronic joint inflammation associated with either pustular psoriasis or palmo-plantar pustulosis, or acne, or hidradenitis; 3) sterile osteitis in the presence of one of the skin manifestations. According to Kahn, one of criteria is sufficient for the diagnosis of SAPHO. The syndrome is often chronic and eventually self-healing, though never septic or malignant, it is clinically heterogeneous, covering several diseases. Definite diagnosis can be hard to establish. For each case, clinical, radiological and histopathological signs need to be taken into account. The causes of SAPHO syndrome are hardly known, common genetic factors are still unclear, apart from a few exceptions. Incidence and prevalence for SAPHO syndrome are still unknown, no data are available, prevalence of CRMO (chronic recurrent multifocal osteomyelitis, one of the frequent manifestation of SAPHO) is estimated at 0.04% in Germany. Diagnosis confirmation relies on RMI, scintigraphy or histopathology. Multidisciplinary follow-up is required. Surgical operation is exceptional. Treatment by non-steroid anti-inflammatory drugs is symptomatic. Treatment of CRMO (Chronic recurrent multifocal osteomyelitis, one of the frequent feature of SAPHO) with antibiotics is not effective. Calcitonin or diphosphonates may have been proposed owing to their osteotropic effects. Very recently by analogy with spondylarthropathies, a treatment with TNF-inhibitors was successfully proposed in some cases. We recommend applying the following treatment: combination of anti-inflammatory and immunomodulating drugs (Azithromycin) and hormonal osteotropic drugs (calcitonin).

Keywords

SAPHO syndrome, chronic recurrent multifocal osteomyelitis, pustulo-psoriatic hyperostotic spondylarthritis, palmo-plantar pustulosis, pustular psoriasis, acne conglobata, acne fulminans, primary chronic osteomyelitis, "skibo" disease, inflammatory anterior wall syndrome, lympho plasma cellular osteomyelitis, sclerosing osteomyelitis, sympathetic arthritis, osteitis, sterno-costo-clavicular hyperostosis, macrolide, azythromycin, calcitonin, diphosphonate, multifocal recurrent periostitis, bone marrow edema.

Nomenclature

SAPHO syndrome is characterized by the osteoarticular and dermatological symptoms that were compiled by French rheumatologists after a national survey carried out in 1987 (1). The acronym "SAPHO" stands for morbid alterations of the osteoarticular system:

- **S**ynovitis;
- **A**cne (acne conglobata or fulminans);
- **P**ustulosis on the skin, often psoriatic, mainly on the palms of hands and on the soles of feet (palmo-plantar pustulosis), as well as
- **H**yperostosis;
- **O**steitis.

More than fifty terms (2) referring to affections that may be observed in SAPHO syndrome have been used in the literature. However, these terms do not reflect the wide spectrum of diseases characterizing SAPHO syndrome. Most of them are isolated observations only partially overlapping the syndrome. "Pustulotic arthroosteitis" (3-5) described in Japan and "acquired hyperostosis syndrome" (3,6) familiar to German radiologists are clinically heterogeneous and not sufficiently delineated.

Definition

SAPHO syndrome is a "skibo" (contraction of skin-bone) disease, that is a disease combining osseous and articular manifestations associated with skin manifestations (7).

As described by Kahn *et al.* in 1994 (8), three diagnostic criteria characterize SAPHO syndrome:

- 1) multifocal osteitis with or without skin manifestations;
- 2) sterile acute or chronic joint inflammation associated with either pustules or psoriasis of palms and soles, or acne, or hidradenitis;
- 3) sterile osteitis in the presence of one of the skin manifestations mentioned bellow.

According to Kahn, one of criteria is sufficient for the diagnosis of SAPHO.

The skin disorder associated to these criteria is the pustular kind of:

- psoriasis (pustular psoriasis, palmo-plantar pustulosis) or
- acne (acne conglobata, acne fulminans or follicular occlusion triad) (9).

The syndrome is often chronic and eventually self-healing, though never septic or malignant (2,8,10-20).

Differential diagnosis – classification of SAPHO syndrome

Classification

Since 1986, our team discovered and documented two new diseases belonging to SAPHO syndrome as nosologic entities (15):

- Pustulo-psoriatic hyperostotic spondylarthritis (PPHS) described in 1985/86 (21) and
- chronic recurrent multifocal osteomyelitis of the adult age "the adult CRMO" (22) described in 1997.

PPHS combines symptoms of the third diagnostic criterion mentioned by Kahn *et al.* with some of the second. The adult CRMO is a new group within CRMO since the disease had been only observed in children so far. It enlarges the first SAPHO criteria group to an independent entity.

SAPHO syndrome is clinically heterogeneous, covering several diseases. Definite diagnosis can be hard to establish. For each case, clinical, radiological and histopathological signs need to be taken into account.

Differential diagnosis of CRMO

- acute (septic) osteomyelitis and possibly polyosteomyelitis
- Langerhans cell histiocytosis
- benign or malignant bone tumors (e.g. Ewing's sarcoma)
- chronic polyarthritis (23), especially juvenile idiopathic arthritis (24)
- ankylosing spondylitis (25).

Differential diagnosis of PPHS

- psoriatic spondylarthritis
- ankylosing spondylitis (Bechterew's disease)
- primarily chronic osteomyelites

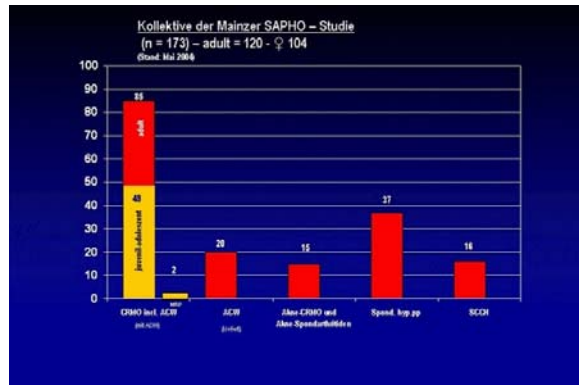
We consider "multifocal recurrent periostitis" as a variant of CRMO (26).

Only acne fulminans may lead to pseudo-septic symptoms. Usually high fever, leukocytosis, cultural evidence of pus germs, significantly increased CRP as well as destructive arthritis are exclusion criteria of SAPHO syndrome.

Clinical manifestations

The following clinical description relies on our follow-up of a SAPHO cohort (n=173), with mention of the frequency for each manifestation (cf. table 1). The two independent entities that mainly determine the syndrome are CRMO and PPHS.

Table 1: Follow-up of a SAPHO cohort (n=173), with mention of the frequency for each manifestation



ACW: anterior chest wall
MRP: multifocal recurrent periostitis

CRMO

CRMO was long believed to be a rare benign inflammatory bone disease. It was thought to occur only in children and adolescents (19,28-38) and to often affect females. SAPHO syndrome in childhood is similar to juvenile CRMO (20,22,39).

Up to now, we have followed up 85 cases (49% of our cohort) affected by CRMO. Disease course can be subacute, chronic or relapsing. Lesions in characteristic areas, *i.e.* anterior thoracic wall, lamellar bones, pelvis, spinal cord are observed, as well as a new form of chronic arthritis (22). The histopathology of the bone marrow is pathognomonic with lympho plasma cellular inflammation. Study of the biopsy does not show any proliferation of purulent bacteria (40-43). The number of inflamed areas affecting the bones and joints decreases with increasing manifestation age. In general, in half cases, patients are affected by an anterior chest wall (ACW) syndrome with inflammation of the sternum and neighbouring joints (14,43,44). The common pelvis type is particularly painful with coxofemoral lesion that is both a painful and handicapping inflammation of the hip joint (46). In children, joints near metaphyseal bone marrow lesions are also often inflamed. Sympathetic arthritis however is not chronically destructive and mainly occurs at the lamellar bones of legs (23,46).

In adults, osteomyelitis affects the diaphyses of lamellar bones, especially of the thigh (femur) (22).

Primary chronic osteomyelitis of the clavicle is very characteristic and can occur as a unifocal lesion (42,47).

The axial type of CRMO affects one or several vertebrae like in sterile spondylitis (25,43,48-51),

secondarily sometimes also the discs (spondylodiscitis) (52,53). That is why it can be mistaken as ankylosing spondylitis (20), all the more since sacroiliitis is relatively frequent (54-57). Jawbones may also be affected, painfully disfiguring the face with swellings. This type of lesion can be unifocal (35, 70).

Palmo-plantar pustulosis seldom occurs in children and adolescents (30%), but is more frequent in adults (up to more than 70%). Pustular acne (puberty acne especially in males) as well as psoriasis vulgaris, familial type are quite rare (14,22,58-60). Isolated cases of neutrophil dermatosis have been described ([Pyoderma gangrenosum](#), [Sweet syndrome](#)) with CRMO cases (61,62).

Para osseous and perivertebral inflammatory oedema in soft tissues lead to complications. Spondylitis can cause a fracture (25,64,65).

Cases associated with pulmonary diseases (65), dyserythropoetic anemia (66), Takayasu disease (34,25), borreliosis (42) and with Behçet disease (67) have been described.

Pustulo-psoriatic hyperostotic spondylarthritiden (PPHS) (21)

It is an HLA-B27 negative spondylarthropathy of the adult age (68). It is characterized by inflammation of the connective tissue near bones. It consists of the triad:

- sterno-costo-clavicular hyperostosis with fibroostitis costo-clavicular and painful ossifying periostitis, often affecting one side only and complicated by stenosis of the neighbouring subclavian vein (69);
- productive spondylopathy (ossifying lesions of the spine with syndesmophytes or parasyndesmophytes) (68);
- palmo-plantar pustulosis (psoriatic), sometimes manifesting on the hands. It may be associated with arthrides and sacroiliitis (14). PPHS was reported in 37 patients (21%) of our cohort.

In general, CRMO occurs in half and PPHS in a quarter of all SAPHO cases. The type of dermatosis present in both CRMO and PPHS is very similar. Pathogenically however (and apparently also etiologically), these entities are totally different.

Imperfect forms of CRMO and PPHS

The remaining quarter of SAPHO syndrome is composed of three clinical pictures that are difficult to delineate. They are considered as imperfect forms of CRMO and PPHS (see table 1):

- the anterior chest wall syndrome is an undifferentiated form of CRMO;

- the syndrome of the "sterno-costo-clavicular hyperostosis" (SCCH) is an undifferentiated form of PPHS;
 - cases affected by acne conglobata or acne fulminans show different lesions of the skeleton. Acne-spondylarthritis was already known (70); a new form, acne-CRMO, needs to be mentioned; its course may be dramatic during puberty (27,42).

Enteropathic variant

An enteropathic variant is also observed within SAPHO syndrome: it is combined with a chronic inflammatory bowel disease (IBD) (Crohn's disease or ulcerative colitis) (10,14,71,72), presenting analogies with enteropathic spondylarthritides (73). We observed 5 such cases, 9% of the cohort. Four of them presented CRMO, Crohn's disease and palmo-plantar pustulosis.

To sum-up, the main clinical pictures of SAPHO are:

- CRMO in children, in adolescents
 - CRMO in adults
 - Inflammatory anterior thoracic wall syndrome
 - Acne-CRMO
 - Triad: CRMO + Crohn + palmo-plantar pustulosis
 - Recurrent multifocal periostitis
 - Pustulo-psoriatic hyperostotic spondylarthritis
 - Sterno-costo-clavicular hyperostosis
 - Acne-spondylarthritis
-

Etiology

The causes of SAPHO syndrome are hardly known. Due to the various clinical pictures, SAPHO cannot be caused by a single factor. However, it cannot be excluded that cutaneous lesions common to all patients are an etiologic component (15). Common genetic factors are still unclear, apart from a few exceptions (60,58). For PPHS, there is no genetic explanation, all the more since HLA-B27 antigen is not more prevalent than in average. Pathogenesis is clearly of an enthesopathic nature and can be attributed to an immunopathologic phenomenon. No infectious agent has been found in sterile osteomyelitis of CRMO. An interesting hypothesis has been put forward by our team: since in several cases, anaerobic, hypovirulent germs normally located on the skin were found, *Propionibacterium acnes* may play an important role (74-76), as a potential antigenic trigger. Thus under special circumstances, these germs

may trigger moderate inflammation of the bone marrow, typically immunological with lympho plasmacellular infiltrates, inducing a sclerosing and hyperostosing reaction that may lead to the picture of sclerosing osteomyelitis. This morphogenetic process underlies CRMO (77) and characterizes this primarily chronic osteomyelitis as a reactive osteomyelitis (22). Adequate serology does not exist.

A "cmo-mouse" (chronic multifocal osteomyelitis) has been known for 10 years as an experimental animal model in CRMO. This study tends to show that hereditary factors contribute to the onset of CRMO (77). The department of Medical Genetics of the University – Pediatric Clinic Munich (Mrs. Dr Jansson) is working on it (58). Familial cases of CRMO rarely occur.

Prevalence

Incidence and prevalence for SAPHO syndrome are still unknown, no data are available.

PPHS is rare and it took us 20 years to collect 37 cases.

For CRMO, however, we have certain clues. Due to better knowledge, diagnosis of CRMO is more frequently established, suggesting that its rarity is only apparent. Its frequency is close to that of some collagenoses, like scleroderma. Taking these data into account, prevalence of CRMO is estimated at 0.04% and therefore the number of CRMO cases (children, adolescents and adults) in Germany (80 million inhabitants) should be 15,000. This number shows that CRMO is not a "very rare" disease. Incidence is of course unknown.

Diagnosis

Criteria for SAPHO syndrome were defined by Kahn *et al.* (2,8,11,12) (cf. definition).

SAPHO must be suspected when a patient is affected by a pustular skin disease associated with rheumatic pains. If examination shows that the pains are caused by a sterile inflammation of bones or joints, the hypothesis tends to be confirmed. It is worth noting that palmoplantar psoriasis is not always present.

Diagnosis can be established after evidence of sterile inflammation of the bone marrow revealed by typical MRI sequences (49-51,74) and showing inflammatory bone marrow oedema at characteristic bony areas (sternum, clavicle, metaphyses of lamellar bones, pelvis bones, vertebrae, calcaneus, lower jaw, etc...) (80,81). Finally the histopathologic with sterile evidence of a plasma-cell sclerotic process and infiltration of non-infectious inflammatory cells (lymphocytes and plasma cells) (41-43,61,74) precise the diagnosis CRMO.

The process is not always multifocal. Though rare, unifocal bone lesions may be observed most often at the collar bone (42,30) or lower jaw (55).

Lab tests

The results of lab tests are uncharacteristic, with variable signs of inflammation with low activity. For differential diagnosis, it must be noted : C-reactive protein whose increase is highly inferior to that of sedimentation rate and the absence of leukocytosis.

Disease course

The many variants of SAPHO syndrome may have different courses.

Only adults are affected by PPHS, its course is constant and chronic. Disease can only develop after puberty apparently. Healing occurs only after the active phase is over, this phase may last several decades. Even though the patient is cured, he may have some sequellae partially handicapping.

CRMO was considered to be recurrent and relapsing as its name implies. However this is not always the case. Patients with subacute courses have been reported, this means that they totally recover after the first phase of the disease. When CRMO is recurrent, remission periods last between some months and several years (39) (20 years maximum), but 1 month and a half in average.

Some chronic cases have also been reported. Disease course is uneven, that is with ups and downs but no remission. Relying on our experience, patients with the longest lifespan are those who developed CRMO in late childhood but did not heal at the end of puberty (39). Courses between 2 years and a half and 20 years have been reported (32). In some cases with serious motility handicaps, especially for the pelvis type due to coxitis (46), bad prognosis needs to be mentioned. In rare cases, epiphysitic retardation with growth differences (37) can occur. Surveillance is absolutely required for the spondylitic type due to the risk of lesion of the spinal cord (82,83).

The youngest child in our cohort developed CRMO at 3 years. Manifestations reach a peak in women in their late 20's. In the oldest patients that were followed-up, CRMO was developed in one in his/her sixties and in the other in his/her seventies. It is hard to assess successful therapy since no reliable statistic data (32-34,82-85) on spontaneous CRMO cases are available. Relying on our observations, disease lasts between 2 and 20 years, 4-5 in average.

Visceral complications occasionally occur in soft tissues surrounding the bones affected (clavicle,

vertebras, pelvis). The area is inflammatory, edematous and fibrotic (86).

These complications are the following (15,20,25,38,87,88):

- angiostenosis (subclavia in osteitis of the clavicle, pelvis veins due to retroperitoneal fibrosis in osteitis of the iliac bone)
- vasculitis (aortitis between spondylitis and sternal osteitis)
- neural irritations (plexus neuritis in spondylitis of the lower cervical vertebrae, intercostal neuralgia)
- pleurisy and pericarditis in upper thorax osteitis.
- CRMO may be complicated by IBD (ulcerative colitis, Crohn's disease) (73).

Long-term follow-up of CRMO patients undergoing treatment often requires another skeleton scintigraphy. In any case, MRI is required every six months for surveillance. Lab tests are not of utmost importance for surveillance, except when complications due to treatment occur.

Therapy

No specific drug exists for SAPHO syndrome. It is mainly composed of non steroid anti-inflammatory drugs or sulfamides such as sulfasalazine (2,10,85). Dosage should be adapted to each case taking into account the side effects. Corticoids must be prescribed only very rarely and are only indicated in urgent cases and for a limited time period. Some trials were carried out with various immunomodulating treatments, among them anti-alpha-TNF (89). In most cases, treatment with methotrexate is given (31). Success is hard to assess because of lack of strict control. Up to now, treatment for SAPHO has been symptomatic only.

Follow-up of patients with SAPHO absolutely requires an inter-disciplinary cooperation. Surgery is necessary in only very few cases, e.g. in the area of the spine. Surgical treatment of spondylitis is nowadays considered as a professional mistake. Spontaneous metaphyseal fractures of the lamellar bones happen only in rare cases (40,12), but they heal spontaneously with conservative orthopedic treatment.

Treatment of pustular skin disease, usually of psoriatic type, should be taken in charge of by dermatologists. This is also the case for the serious forms of acne, which favourably respond to retinoids administered *per os* or cutaneously. Acne fulminans can become a medical emergency.

All the patients with SAPHO must benefit from rehabilitation from a physiotherapist.

Antibiotics did not turn out to be a success for the treatment of CRMO. It is considered to be too constraining and risky for the patients.

Macrolides are an exception (98). Due to the great success of azithromycin in the treatment of CRMO, we assumed that the macrolide have anti-inflammatory and even immunomodulating effects (90). This clinical postulate has proven to be right in the meantime experimentally as well as clinically (46), so that we recommend a long-term therapy with azithromycin (or clarithromycin in case of intolerance) as the first-line treatment of CRMO.

At the same time, we discovered a hormonal treatment of CRMO by calcitonin. This hormone stabilizes the bone mass, has an osteotropic effect, acts as an antagonist, stimulates the inhibition of osteoclasts (for it reduces bone resorption) and also stimulates osteoblasts. Finally, it is effective against bone inflammation. In several cases, pain was eradicated and the altered functions were recovered thanks to only a few months of treatment with calcitonin (74).

In adults, subcutaneous injections of calcitonin of 100 units are administered 4 times a week.

In children, calcitonin also proved to be beneficial, it was very well tolerated. They received a nasal spray with half of the dose (20). More recently and for refractory cases, calcitonin was replaced by diphosphonates whose effect is theoretically comparable. These are administered either *per os* (one tablet of alendronate⁷⁰ once a week) or pamidronat infusion. Patients responded well to these treatments (91-94).

For 6 years, we have been combining both treatment principles (20,90), combination of anti-inflammatory and immunomodulating drugs with hormonal osteotropic effects. It is a long-term treatment, alternating the 2 types of drugs. Twenty adults and 26 children have received this treatment. It gave good and even excellent results, with very few side effects. In most cases, MRI confirmed success. Few risks are associated with this treatment and we recommend applying it experimentally to patients with SAPHO. A multicenter study is absolutely needed to assess this treatment in SAPHO.

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