Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: review and update

Shuang Liu, Mingwei Tang, Yihan Cao and Chen Li

Abstract: Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a spectrum of heterogeneous diseases characterized by osteoarticular and dermatological manifestations. Osteitis and hyperostosis are core clinical manifestations in SAPHO syndrome, typically affecting multiple areas and possibly progressing to irreversible osteoarticular damage. Most patients with SAPHO have cutaneous involvement, mainly manifested as palmoplantar pustulosis and severe acne. Systemic manifestations are uncommon but occasionally reported. Epidemiological studies suggest the annual prevalence of SAPHO syndrome varies from 0.00144 in 100,000 in Japanese individuals to fewer than 1 in 10,000 in White individuals. The precise etiopathogenesis of SAPHO remains unclear, but it is generally considered an autoinflammatory syndrome that may be related to various etiologies, such as immune dysfunction, infection and genetic predisposition. Owing to the relapsing-remitting disease course, the goal of management is to improve clinical symptoms and prevent disease progression. Various treatments, including nonsteroidal anti-inflammatory drugs, conventional disease-modifying antirheumatic drugs, bisphosphonates, biologics, and antibiotics, are promising options for alleviating the disease.

Keywords: diagnosis, etiology, imaging, SAPHO syndrome, treatment

Received: 7 November 2019; revised manuscript accepted: 23 February 2020.
Therapeutic Advances in Musculoskeletal Disease 12

Immune inflammation. The potential inflammation of Th17 and regulatory T (Treg) cells in patients with SAPHO, which may be related to the depletion of natural killer (NK) cells and an imbalance of Th17 and regulatory T (Treg) cells in patients with SAPHO, which may be related to immune inflammation. The potential inflammation-mediated pathogenesis was further supported by the response to biologics targeting TNF-α, IL-1, and the IL-17–IL-23 axis. In addition, several studies have isolated Propionibacterium acnes, Staphylococcus aureus, Haemophilus parainfluenzae, and actinomycetes in SAPHO osteitis lesions, among which P. acnes was the most common species. The interaction between transcription factor Forkhead Box O1 (FoxO1), P. acnes, NLRP3-inflammasome, and IL-1β may play a role in the development of osteitis. The genetic susceptibility of SAPHO syndrome remains to be investigated. Family aggregation of SAPHO syndrome has been reported. Certain single nucleotide polymorphisms (MDM2 T309G, p53 G72C, rs6908425 T>C in CDKAL1) were found to be associated with SAPHO syndrome. Mutation in the NCSTN subunit of γ-secretase was identified in a patient with sporadic SAPHO with the manifestation of hidradenitis suppurativa. Some genes on chromosomes 1 and 18 (LPIN2, PSTPIP2, and NOD2) were also found to be associated with conditions similar to SAPHO syndrome but not in SAPHO syndrome itself. The connection between SAPHO syndrome and certain human leukocyte antigens (HLAs; including HLA-A26, HLA-B27, HLA-B39, and HLA-B61) has been controversial. The potential etiologies of SAPHO syndrome are summarized in Table 1.

Clinical manifestations

Osteitis and hyperostosis are the core clinical manifestations in SAPHO syndrome, which typically affect multiple areas and may progress into irreversible bone and joint damage. The most commonly affected area is the anterior chest wall (ACW), followed by the axial skeleton (including the spine and the sacroiliac joints), the long bones of the extremities, the irregular bones (such as mandible), and the peripheral joints. ACW involvement, which occurs in 65–90% of patients, is highly characteristic of SAPHO syndrome. More specifically, the typical affected structures of the ACW include the sternocostal joints, the sternoclavicular joints and the costoclavicular ligament. The surrounding soft tissue can become reddish and swollen, leading to the compression of nearby structures. Approximately 32–52% of patients have axial involvement, which manifests as pain in the spine or gluteal region. This group of patients usually presents with more serious clinical manifestations and requires more aggressive treatment. Peripheral bone and joint involvement is common in patients with SAPHO, which occur in 65.8–82.9% of patients.

Most patients with SAPHO have cutaneous involvement, mainly manifested as palmpoplantar pustulosis (PPP) and severe acne (SA), which are shown in Figure 1. PPP, which is recognized as a special type of psoriasis, is characterized by chronic, recurrent, sterile, small pustules and vesicles. Among the 354 Chinese patients in the cohort, 94.6% reported skin involvement, of whom 91.9% had PPP, 14.3% had SA, and 15.8% had psoriasis vulgaris. Skin manifestations can occur at any stage of the disease or be absent. A majority of the patients (over 70%) develop both cutaneous and osteoarticular symptoms within 2 years, although longer intervals have been reported.

Systemic manifestations such as fever and elevation of inflammatory markers are uncommon but occasionally reported. Other extra-articular manifestations include inflammatory bowel disease, pulmonary involvement, venous thrombosis (most commonly affecting the subclavian vein), dura mater hypertrophy, and uveitis.

Diagnosis

The most widely applied diagnostic criteria were proposed by Benhamou and colleagues in 1988, who established the diagnosis of SAPHO syndrome on the basis of clinical manifestations and radiological examinations, including bone, articular or skin manifestations. Another commonly used diagnostic criterion was proposed in 1994 and revised in 2003 by Kahn and Kahn, who established the diagnosis of SAPHO syndrome mainly on the basis of clinical symptoms. The diagnostic criteria are summarized in Table 2.
Currently, no specific clinical features or laboratory findings have been verified to confirm the diagnosis of SAPHO syndrome. Based mostly on clinical and radiological manifestations, the diagnosis of SAPHO syndrome is, to some extent, a diagnosis of exclusion. However, for patients without the typical pattern of skin lesions and osteoarticular involvement (e.g., with long/flat bone involvement), the diagnosis remains challenging.

**Differential diagnosis**

Considering the complexity of manifestations of SAPHO syndrome, other inflammatory, infectious, and neoplastic etiologies should be considered. For example, Sonozaki syndrome [or pustulotic arthro-osteoiteis (PAO)], which belongs to the group of psoriatic arthritis, includes PPP as well as arthro-osteitis, which typically involves the sternoclavicular joint.51,52 Considering the overlaps with other clinical entities, patients with SAPHO syndrome should be distinguished from patients with other osteoarticular diseases, with or without skin manifestations, and other systematic autoinflammatory diseases (Table 3).

**Disease evaluation**

A comprehensive evaluation is important for the diagnosis and management of SAPHO syndrome. As shown in Figure 2 and Table 4, the disease shows unique patterns of vertebral involvement by multiple imaging techniques,53 yet manifestations may vary with the age of onset, the affected regions, and the course of disease. A series of inflammatory markers and bone metabolites have been found to be useful in quantifying the inflammatory status of SAPHO syndrome. In addition, patient-reported outcomes (PROs) have been widely used in the

---

**Table 1. Potential etiologies of SAPHO syndrome.**

| Potential etiologies     | Evidence                                                                 | References                                      |
|--------------------------|--------------------------------------------------------------------------|------------------------------------------------|
| **Immune dysfunction**   | Elevation of a series of proinflammatory cytokines (TNF-α, IL-1, IL-8, IL-17, IL-18) | Hurtado-Nedelec and colleagues12; Berthelot and colleagues13 |
|                          | Involvement of the IL-23/Th17 axis                                       | Firinu and colleagues14; Wendling and colleagues15 |
|                          | Elevation of RANKL in the active group of patients                       | Zhang and colleagues16                          |
|                          | Depletion of NK cells and an imbalance of Th17/Treg cells                | Xu and colleagues17                             |
|                          | Generally good response to biologics                                     | Daoussis and colleagues18                       |
| **Infection**            | Certain bacterial species (Propionibacterium acnes, Staphylococcus aureus, Haemophilus parainfluenzae, and actinomycetes) were isolated in SAPHO lesions. | Rozin10; Colina and colleagues19                |
|                          | Interaction between FoxO1, P. acnes, NLRP3-inflammasomes and IL-1β       | Berthelot and colleagues13                      |
| **Genetic susceptibility**| Family aggregation                                                       | Gonzalez and colleagues20; Kurc and colleagues21; Huaux and colleagues22,23; Dumolard and colleagues24 |
|                          | Certain single nucleotide polymorphisms (MDM2 T309G, p53 G72C, rs6908425 T>C in CDKAL1) were found to be associated with SAPHO syndrome. | Assmann and colleagues25; Li and colleagues26 |
|                          | Mutation in the NCSTN subunit of γ-secretase was identified in a patient with sporadic SAPHO and hidradenitis suppurativa. | Li and colleagues27                             |
|                          | Possible connection with HLA (HLA-39, HLA-61)                           | De Souza and colleagues31; Khanna and El-Khoury32; Thakur and colleagues33 |

FoxO1, Forkhead Box 01; HLA, human leukocyte antigen; IL, interleukin; NK, natural killer; RANKL, receptor activator nuclear factor kappa-B ligand; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; Th, helper T cell; TNF, tumor necrosis factor; Treg, regulatory T cell.
evaluation of a variety of chronic diseases, including SAPHO syndrome, which better reflect the functional impairment of the disease.

**Imaging assessment**

**X-ray and computed tomography**

Conventional X-ray and computed tomography (CT) scans are classical choices to assess bone hypertrophy and osteitis. X-ray imaging can detect osteoarticular changes in the long bones at relatively late stages, with characteristic manifestations including irregular bone morphology, cortical thickening, increased density of the medullary cavity with or without low-density destruction areas. However, the low sensitivity of X-ray to detect lesions at early stages, especially those in the ACW, may lead to delayed diagnosis.

The high density and spatial resolution of a CT scan facilitates its use in detecting osteoarticular...
lesions that are difficult to observe on X-ray. The ability to clearly reveal bone hyperplasia at the attachment point of the costoclavicular ligament at an early stage makes CT an important diagnostic tool for SAPHO syndrome. The whole-spine CT can clearly demonstrate the distinct characteristics of spinal lesions, in which the location of vertebral corner and ‘kissing’ involvement pattern are indicative of SAPHO syndrome.55

Magnetic resonance imaging
With an advantage over CT in assessing early and active disease, magnetic resonance imaging (MRI) can be employed as a guide for treatment and follow up. Bone marrow edema shown on MRI suggests an active disease state, presenting as a low signal on T1WI, a high signal on T2WI and short-T1 inversion recovery images, and marked enhancement on enhanced scans.37

Whole-body bone scintigraphy
Whole-body bone scintigraphy (WBBS) has the advantages of demonstrating multifocal osteoarticular lesions at the same time and finding clinically insidious lesions.53 The typical ‘bull’s head’ pattern on WBBS, that is, the high uptake of the ‘sternocostoclavicular’ joint and the sternal angle is highly specific for SAPHO syndrome.58 The bull’s head sign is especially important for the diagnosis of patients with nontypical SAPHO who have atypical cutaneous lesions or lack cutaneous manifestations.59 Based on WBBS manifestations, the osteoarticular involvement in SAPHO syndrome can be categorized into three distinct patterns, that is, the spinal type, the costal type and the sternoclavicular type.64 However, both active and chronic lesions manifest as high uptake areas on WBBS, which means WBBS cannot determine the disease activity of lesions.

Positron emission tomography/CT
Positron emission tomography (PET)/CT can demonstrate the location and distribution of inflammation in osteoarticular lesions.60 The typical PET/CT findings of SAPHO syndrome are multiple skeletal lesions in the ACW or spine with low to moderate 18F-FDG uptake and concurrent osteolysis and osteosclerosis.61 In addition, PET/CT serves as an important diagnostic tool to differentiate benign lesions from bone metastasis.62,63 However, the ability of PET/CT to determine disease activity in SAPHO syndrome requires further investigation.

Laboratory tests
Elevation of nonspecific inflammatory markers [e.g. erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] can be seen in the active phase of the disease.8,65 During the improvement and relapse periods, serum amyloid A appeared to show higher sensitivity than CRP.66 An anomaly of proinflammatory and anti-inflammatory cytokine expression was observed in active SAPHO patients, presenting as higher levels of serum TNF-α, IL-6, IL-8, and IL-17A levels.12,16 Raised immunoglobulin (Ig)G4 levels are reported in 23% of patients with SAPHO and are associated with higher disease activity.57 Abnormal levels of bone metabolites may also occur, manifesting as an increase in the osteoclast marker β-isolated C-terminal peptide (β-CTX) and a decrease in the osteoblast marker osteocalcin.68

Table 3. Differential diagnosis of SAPHO syndrome.

| Symptoms of SAPHO syndrome | Alternative diagnoses                                                                 |
|----------------------------|---------------------------------------------------------------------------------------|
| Synovitis                  | Rheumatoid arthritis, spondyloarthritis                                                |
| Acne                       | PAPA syndrome, Behçet’s disease                                                        |
| Pustulosis                 | Pustular psoriasis, psoriasis arthritis, Sneddon–Wilkinson syndrome, Sonozaki syndrome (pustulotic arthro-osteitis) |
| Hyperostosis               | Diffuse idiopathic skeletal hyperostosis                                               |
| Osteitis                   | Chronic bacterial osteomyelitis, Ewing sarcoma, osteosarcoma, metastatic tumors, Paget’s disease, deficiency in interleukin-1 receptor antagonist syndrome |

PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis.
An increased RANKL level and RANKL/osteoprotegerin (OPG) ratio are seen in patients with active SAPHO. The frequency of HLA-B27 was not significantly higher than that in the normal population. Potential laboratory markers of SAPHO syndrome are summarized in Table 5.

**Patient-reported outcomes**

Studies based on PROs on SAPHO syndrome are limited. A nationwide patient survey in Germany showed a high impact of SAPHO syndrome on patients’ general health and quality of life, mainly due to musculoskeletal symptoms. Further investigation is needed to explore the usefulness of PROs to reflect the treatment efficacy of drugs and the functional status of patients.

**Figure 2.** Characteristic radiological manifestations of SAPHO syndrome. CT revealed bone cortical destruction and osteosclerosis of bilateral sternoclavicular joints, and swelling of the surrounding soft tissues (a). Whole spinal CT showed bone destruction in multiple vertebrae (b). MRI demonstrated multiple patchy, short T1 and long T2 (d) signals of lumbar vertebrae. WBBS showed increased radioactivity in the left sternoclavicular joint, the left first anterior rib, the second and fourth lumbar vertebrae, and the right iliac joint (e). PET/CT showed bone destruction and increased glucose metabolism in left clavicle bone (f) and vertebra (g).

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SAPHO, synovitis, acne, pustulosis, hyperostosis and osteitis; WBBS, whole-body bone scintigraphy.

**Treatment**

**Strategy**

To date, most studies on the treatment of SAPHO syndrome are case reports, case series, or observational cohorts. Evidence based on randomized clinical trials is still lacking. As a result, no consensus has been reached on the treatment of SAPHO syndrome.

The first and primary goal of treatment is the improvement of clinical symptoms, including ostealgia and skin rash. Second, treatment should take effect in slowing the progression of joint involvement and the regression of articular function, thereby improving patients’ quality of life in the long term. Table 6 summarizes the current treatment options on SAPHO syndrome.
Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally regarded as first-line medications for pain relief and symptom control of SAPHO syndrome. NSAIDs work quickly and remarkably for patients at the diagnostic stage of disease. However, NSAID monotherapy has shown limited effects in patients with extensive osteomyelitis.92 The gastrointestinal side effects of NSAIDs should be taken into consideration.

Disease-modifying antirheumatic drugs

Conventional disease-modifying antirheumatic drugs (cDMARDs) are usually recommended as second-line options, and the responses to cDMARDs vary among different patients. For patients with peripheral joint involvement and relatively low levels of axial spine joint involvement, the administration of methotrexate (MTX) could be effective.72–74 Improvement of peripheral osteoarticular symptoms and pleural effusions could occur within several weeks to months. However, the efficacy of MTX for the treatment of osteitis, osteomyelitis or enthesitis is uncertain. Other cDMARDs, including sulfasalazine, hydroxychloroquine, leflunomide, thalidomide, and colchicine, have been reported to be beneficial in SAPHO syndrome based on case reports or case series.7,40,93 Further evidence is needed to determine the efficacy of these agents.

Corticosteroids

Systematic or intra-articular corticosteroids work quickly but transiently.94 Relapses tend to occur when treating cutaneous lesions and appear to be even more serious than before.95 Taking adverse effects into consideration, corticosteroids are preferably used as a bridge treatment in moderate doses and for a short term.

Bisphosphonates

Bisphosphonates consistently inhibit osteoclast activity and exert anti-inflammatory effects.96

---

**Table 4. Imaging techniques used in SAPHO syndrome.**

| Imaging techniques | Typical findings | Advantages | Disadvantages | References |
|--------------------|------------------|------------|---------------|------------|
| *X-ray*            | Irregular bone morphology, cortical thickening, increased density of the medullary cavity | Economic and classical tools to detect osteoarticular changes in the long bones | Low sensitivity in detecting early lesions | Earwaker and Cotten36; Dihlmann and Dihlmann37; Fritz and colleagues54 |
| *CT*               | Bone hyperplasia and bone bridge formation at the attachment point of the costoclavicular ligament | High density and spatial resolution; the ability to detect osteoarticular changes at early stages | Low sensitivity in detecting soft tissue; ionizing radiation | Xu and colleagues55; Suzuki and colleagues56 |
| *MRI*             | Bone marrow edema (low signal on T1WI sequence, a high signal on T2WI and short-T1 inversion recovery sequence, and marked enhancement) | Higher specificity in active inflammation in bone and soft tissue | Low sensitivity in detecting structural bone changes | Depasquale and colleagues37 |
| *WBBS*           | ‘Bull’s head’ pattern (high uptake of the ‘sternocostoclavicular’ joint and the sternal angle) | Demonstrating multifocal osteoarticular lesions at the same time; facilitating the diagnosis of patients with nonclassical SAPHO | Inability to determine the activity of lesions | Carr57; Schaub and colleagues58; Duan and colleagues59 |
| *PET/CT*         | Multiple skeletal lesions in the ACW or spine with low to moderate 18F-FDG uptake and concurrent osteolysis and osteosclerosis | Demonstrating the location and distribution of inflammation; facilitating the differential diagnosis from bone metastasis | Uncertain ability to determine disease activity; expensive | Kohlfuerst and colleagues60; Sun and colleagues61; Patel and colleagues62; Takeuchi and colleagues63 |

ACW, anterior chest wall; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; WBBS, whole-body bone scintigraphy.
The use of intravenous bisphosphonates (especially pamidronate) for SAPHO syndrome has been reported, demonstrating partial or full remission of both ostealgia and cutaneous lesions.29,78

**Targeted drugs**

Use of anti-TNF-α biologics has been frequently reported. Previous reports of the treatment of SAPHO syndrome with infliximab,79 adalimumab,75,80 and etanercept87 have proved the effectiveness of these treatments for osteoarticular and cutaneous lesions. However, during anti-TNF-α therapy, some patients develop new paradoxical skin lesions, which present as psoriasiform scaly plaques or pustular lesions.98,99

Other less commonly used biologics, such as anakinra,89 ustekinumab,15 secukinumab,15,85 and apremilast,91 have also shown beneficial effects in some patients. Although administration of tocilizumab, an anti-IL-6 agent, showed efficacy to some extent, aggravation or development of lesions were quite common. Existing observations indicate that tocilizumab may not be an ideal option for SAPHO syndrome, and it should be considered with caution.86–88

Tofacitinib, a small-molecule nonspecific JAK 1 and JAK 3 inhibitor, was used to treat a patient refractory to SAPHO and demonstrated amelioration in terms of clinical symptoms, inflammatory parameters, and MRI.90

**Antibiotics**

Since infection by *P. acnes* is thought to be a possible pathogenetic trigger of SAPHO syndrome, especially for patients with SA,13 antibiotics have also been considered for treatment. Tetracyclines,29 clindamycin,100 and azithromycin29 have been reported to be successful in treating some cases of acne but show little efficacy against other symptoms. Skin involvement in SAPHO syndrome mainly manifests as PPP, in which condition antibiotics show an effect that is curative but not as dramatic as that in the treatment of acne.

**Prognosis**

SAPHO syndrome is a chronic disease that typically follows a relapsing–remitting disease course.101 Some patients undergo one or two attacks with eventual spontaneous resolution. Others experience a prolonged and sometimes disabling evolution with the appearance of new cutaneous or osteoarticular manifestations. The prognosis of SAPHO syndrome is generally good.40,102 However, for patients with pathological fractures in the vertebral bodies or clavicle, the prognosis is not optimistic.103

**Conclusion**

SAPHO syndrome is a chronic inflammatory disorder characterized by osteoarticular and dermatological involvement. Osteitis and hyperostosis...
Table 6. Treatment on SAPHO syndrome.

| Categories | Drugs | Research type | Response evaluated by radiology | Decrease In inflammatory markers | Response for osteoarticular symptoms | Response for cutaneous symptoms |
|------------|-------|---------------|---------------------------------|-------------------------------|-------------------------------------|---------------------------------|
| NSAIDs     |       |               |                                 | N/A                           | + (new-onset cutaneous lesion)      | N/A (new-onset cutaneous lesion) |
| Corticosteroids |      |               |                                 | N/A                           | +                                   | N/A                             |
| DMARDs     |       |               |                                 | N/A                           | +                                  | N/A                             |
| Antibiotics |       |               |                                 | N/A                           | +                                  | N/A                             |
| Biophosphonate |     |               |                                 | N/A                           | +                                  | N/A                             |
| TNF-α inhibitor |     |               |                                 | N/A                           | +                                  | N/A                             |
| IL-17/12 inhibitor |     |               |                                 | N/A                           | +                                  | N/A                             |
| IL-6 inhibitor |     |               |                                 | N/A                           | +                                  | N/A                             |
| JAK inhibitor |     |               |                                 | N/A                           | +                                  | N/A                             |
| PDE-4 inhibitor |     |               |                                 | N/A                           | +                                  | N/A                             |

+ general improvement without specifying certain symptoms; −, no improvement; ±, contradictory results reported by previous studies.

DMARD, disease-modifying antirheumatic drug; IL, interleukin; MRI, magnetic resonance imaging; N/A, not available/applicable; NSAID, nonsteroidal anti-inflammatory drug; PDE-4, phosphodiesterase type 4; PPP, palmoplantar pustulosis; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; TNF, tumor necrosis factor.
are considered the core clinical manifestations, which mainly affect the axial skeleton with characteristic involvement of the ACW. A wide spectrum of neutrophilic dermatoses is associated with the disease, with PPP and SA most commonly observed. The pathogenesis remains unclear, yet SAPHO syndrome is considered an autoinflammatory disorder related to a variety of genetic and environmental factors and immune dysregulation. Diagnosis is still challenging due to the clinical heterogeneity of the disease. A comprehensive evaluation including imaging and laboratory examinations is important for early diagnosis and treatment. A variety of therapeutic options, including bisphosphonates and targeted drugs, have been proposed to alleviate symptoms and prevent disease progression.

Acknowledgement
Shuang Liu and Mingwei Tang contributed equally to this manuscript.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the CAMS Initiative for Innovative Medicine (grant number 2017-I2M-3-001), the Capital Medical Research and Development Fund (grant number 2016-4-40112), and the National Key Research and Development Program of China (grant number 2016YFC0901500).

Conflict of interest statement
The authors declare that there is no conflict of interest.

Clinical trial registration
Not applicable.

ORCID iD
Chen Li https://orcid.org/0000-0002-3191-4003

References
1. Chamot AM, Benhamou CL, Kahn MF, et al. Acne-pustulosis-hyperostosis-osteitis syndrome: Results of a national survey. 85 cases. Rev Rhum Mal Osteoartic 1987; 54: 187–196.
2. Rukavina I. SAPHO syndrome: a review. J Child Orthop 2015; 9: 19–27.
3. Jelusic M, Cekada N, Frkovic M, et al. Chronic recurrent multifocal osteomyelitis (CRMO) and synovitis acne pustulosis hyperostosis osteitis (SAPHO) syndrome - two presentations of the same disease? Acta Dermato-Venereol Croat 2018; 26: 212–219.
4. Kubaszewski L, Wojdasiewicz P, Rozek M, et al. Syndromes with chronic non-bacterial osteomyelitis in the spine. Reumatologia 2015; 53: 328–336.
5. Sugase T, Akimoto T, Kanazawa H, et al. Sterno-costoclavicular hyperostosis: an insufficiently recognized clinical entity. Clin Med Insights Arthritis Musculoskelet Disord 2017; 10: 1175944117702877.
6. Constantinou CA, Fragoulis GE and Nikiphorou E. Hidradenitis suppurativa: infection, autoimmunity, or both? Ther Adv Musculoskelet Dis 2019; 11: 1759720x19895488.
7. Nguyen MT, Borchers A, Selmi C, et al. The SAPHO syndrome. Semin Arthritis Rheum 2012; 42: 254–265.
8. Cao Y, Li C, Xu W, et al. Spinal and sacroiliac involvement in SAPHO syndrome: a single center study of a cohort of 354 patients. Semin Arthritis Rheum 2019; 48: 990–996.
9. Li C, Zuo Y, Wu N, et al. Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: a single centre study of a cohort of 164 patients. Rheumatology (Oxford) 2016; 55: 1023–1030.
10. Rozin AP. SAPHO syndrome: is a range of pathogen-associated rheumatic diseases extended? Arthritis Res Ther 2009; 11: 131.
11. Golla A, Jansson A, Ramser J, et al. Chronic recurrent multifocal osteomyelitis (CRMO): evidence for a susceptibility gene located on chromosome 18q21.3–18q22. Eur J Hum Genet 2002; 10: 217–221.
12. Hurtado-Nedelec M, Chollet-Martin S, Nicaise-Roland P, et al. Characterization of the immune response in the synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome. Rheumatology (Oxford) 2008; 47: 1160–1167.
13. Berthelot JM, Corvec S and Hayem G. SAPHO, autophagy, IL-1, FoxO1, and Propionibacterium (cutibacterium) acnes. Joint Bone Spine 2018; 85: 171–176.
14. Firinu D, Barca MP, Lorrai MM, et al. TH17 cells are increased in the peripheral blood of patients with SAPHO syndrome. Autoimmunity 2014; 47: 389–394.
15. Wendling D, Aubin F, Verhoveen F, et al. IL-23/Th17 targeted therapies in SAPHO syndrome. A case series. Joint Bone Spine 2017; 84: 733–735.
16. Zhang S, Li C, Zhang S, et al. Serum levels of proinflammatory, anti-inflammatory cytokines, and RANKL/OPG in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. Mod Rheumatol 2019; 29: 523–530.

17. Xu D, Liu X, Lu C, et al. Reduction of peripheral natural killer cells in patients with SAPHO syndrome. Clin Exp Rheumatol 2019; 37: 12–18.

18. Daoussis D, Konstantopoulos G, Kranitis P, et al. Biologics in SAPHO syndrome: A systematic review. Semin Arthritis Rheum 2019; 48: 618–625.

19. Colina M, Lo Monaco A, Khodeir M, et al. Propionibacterium acnes and SAPHO syndrome: a case report and literature review. Clin Exp Rheumatol 2007; 25: 457–460.

20. Gonzalez T, Gantes M, Bustabad S, et al. Acne fulminans associated with arthritis in monozygotic twins. J Rheumatol 1985; 12: 389–391.

21. Kurc D, De Saint-Pere R, Madoule P, et al. Chronic osteitis and arthritis of palmoplantar pustulosis. A familial form of B-27 negative spondylarthropathy. Rev Med Interne 1987; 8: 79–84.

22. Huaux JP, Esselinckx W, Rombouts JJ, et al. Pustulotic arthroosteitis and chronic recurrent multifocal osteomyelitis in children. Report of three cases. J Rheumatol 1988; 15: 95–100.

23. Dumolard A, Gaudin P, Juvin R, et al. SAPHO syndrome or psoriatic arthritis? A familial case study. Rheumatology (Oxford) 1999; 38: 463–467.

24. Ferguson PJ, Lokuta MA, El-Shanti HI, et al. Neutrophil dysfunction in a family with a SAPHO syndrome-like phenotype. Arthritis Rheum 2008; 58: 3264–3269.

25. Assmann G, Wagner AD, Monika M, et al. Single-nucleotide polymorphisms p53 G72C and Mdm2 T309G in patients with psoriasis, psoriatic arthritis, and SAPHO syndrome. Rheumatol Int 2010; 30: 1273–1276.

26. Li N, Ma J, Li K, et al. Different Contributions of CDKAL1, KIF21B, and LRRK2/MUC19 polymorphisms to SAPHO syndrome, rheumatoid arthritis, ankylosing spondylitis, and seronegative spondyloarthritis. Genet Test Mol Biomarkers 2017; 21: 122–126.

27. Li C, Xu H and Wang B. Is SAPHO syndrome linked to PASH syndrome and hidradenitis suppurativa by nicastrin mutation? A case report. J Rheumatol 2018; 45: 1605–1607.

28. Hurtado-Nedelec M, Chollet-Martin S, Chapeton D, et al. Genetic susceptibility factors in a cohort of 38 patients with SAPHO syndrome: a study of PSTPIP2, NOD2, and LPIN2 genes. J Rheumatol 2010; 37: 401–409.

29. Ajuhani F, Tournadre A, Tatar Z, et al. The SAPHO syndrome: a single-center study of 41 adult patients. J Rheumatol 2015; 42: 329–334.

30. Brandsen RE, Dekel S, Yaron M, et al. SAPHO syndrome. Dermatology 1993; 186: 176–180.

31. De Souza A, Solomon GE and Strober BE. SAPHO syndrome associated with hidradenitis suppurativa successfully treated with infliximab and methotrexate. Bull NYU Hosp Jt Dis 2011; 69: 185–187.

32. Khanna L and El-Khoury GY. SAPHO syndrome—a pictorial assay. Iowa Orthop J 2012; 32: 189–195.

33. Thakur U, Blacksin M, Beeke K, et al. Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) and chronic recurrent multifocal osteomyelitis (CRMO): role of imaging in diagnosis. Radiography 2012; 18: 221–224.

34. Li C, Cao Y and Zhang W. Clinical heterogeneity of SAPHO syndrome: challenge of diagnosis. Mod Rheumatol 2018; 28: 432–434.

35. Boutin RD and Resnick D. The SAPHO syndrome: an evolving concept for unifying several idiopathic disorders of bone and skin. AJR Am J Roentgenol 1998; 170: 585–591.

36. Earwaker JW and Cotten A. SAPHO: syndrome or concept? Imaging findings. Skeletal Radiol 2003; 32: 311–327.

37. Depasquale R, Kumar N, Lalam RK, et al. SAPHO: What radiologists should know. Clin Radiol 2012; 67: 195–206.

38. Dihlmann W and Dihlmann SW. Acquired hyperostosis syndrome: spectrum of manifestations at the sternocostoclavicular region. Radiologic evaluation of 34 cases. Clin Rheumatol 1991; 10: 250–263.

39. Navarini AA, Burden AD, Capon F, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol 2017; 31: 1792–1799.

40. Hayem G, Bouchaud-Chabot A, Benali K, et al. SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999; 29: 159–171.

41. Sonozaki H, Mitsui H, Miyanaga Y, et al. Clinical features of 53 cases with pustulotic arthro-osteitis. Ann Rheum Dis 1981; 40: 547–553.
42. Kahn MF, Bouvier M, Palazzo E, et al. Sternoclavicular pustulotic osteitis (SAPHO). 20-year interval between skin and bone lesions. *J Rheumatol* 1991; 18: 1104–1108.

43. Naves JE, Cabre E, Manosa M, et al. A systematic review of SAPHO syndrome and inflammatory bowel disease association. *Dig Dis Sci* 2013; 58: 2138–2147.

44. Li C, Liu S, Sui X, et al. Pulmonary high-resolution computed tomography findings in patients with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome. *PLoS One* 2018; 13: e0206858.

45. Carranco-Medina TE, Hidalgo-Calleja C, Calero-Paniagua I, et al. Thrombotic manifestations in SAPHO syndrome. Review of the literature. *Reumatol Clin* 2015; 11: 108–111.

46. Shiraishi W, Hayashi S, Iwanaga Y, et al. A case of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome presenting with hypertrophic pachymeningitis. *J Neurol Sci* 2015; 349: 229–231.

47. Przepiera-Bedzak H, Fischer K and Brzosko M. Extra-articular symptoms in constellation with selected serum cytokines and disease activity in spondyloarthritis. *Mediators Inflamm* 2016; 2016: 7617954.

48. Benhamou CL, Chamot AM and Kahn MF. Synovitis-acne-pustulosis hyperostosis-osteomyelitis syndrome (SAPHO). A new syndrome among the spondyloarthropathies? *Clin Exp Rheumatol* 1988; 6: 109–112.

49. Kahn MF and Khan MA. The SAPHO syndrome. *Baillieres Clin Rheumatol* 1994; 8: 333–362.

50. Kahn MF. Proposed classification criteria of SAPHO syndrome. *American college of rheumatology 67th Annual Scientific Meeting*, October, 2003.

51. Brzezinska-Wcislo L, Bergler-Czop B and Lis-Swiety A. Sonozaki syndrome: case report and review of literature. *Rheumatol Int* 2012; 32: 473–477.

52. Kose R, Senturk T, Sargin G, et al. Pustulotic arthro-ostitis (sonozaki syndrome): a case report and review of literature. *Eurasian J Med* 2018; 50: 53–55.

53. McGauvran AM, Kotsenas AL, Diehn FE, et al. SAPHO syndrome: imaging findings of vertebral involvement. *AJNR Am J Neuroradiol* 2016; 37: 1567–1572.

54. Fritz J, Tzaribatchev N, Claussen CD, et al. Chronic recurrent multifocal osteomyelitis: comparison of whole-body MR imaging with radiography and correlation with clinical and laboratory data. *Radiology* 2009; 252: 842–851.

55. Xu W, Li C, Zhao X, et al. Whole-spine computed tomography findings in SAPHO syndrome. *J Rheumatol* 2017; 44: 648–654.

56. Suzuki M, Kanazawa H, Shinozaki T, et al. Radiologists need to be aware of secondary central venous stenosis in patients with SAPHO syndrome. *Eur Radiol* 2017; 27: 4532–4537.

57. Carr F. The ‘hidden’ SAPHO syndrome. *BMJ Case Rep* 2014; 2013201665.

58. Schaub S, Sirkis HM and Kay J. Imaging for synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome. *Rheum Dis Clin North Am* 2016; 42: 695–710.

59. Duan N, Chen X, Liu Y, et al. Multimodal imaging findings of SAPHO syndrome with no skin lesions: a report of three cases and review of the literature. *Exp Ther Med* 2012; 12: 2665–2670.

60. Kohlfuerst S, Igerc I and Lind P. FDG PET helpful for diagnosing SAPHO syndrome. *Clin Nucl Med* 2003; 28: 838–839.

61. Sun X, Li C, Cao Y, et al. F-18 FDG PET/CT in 26 patients with SAPHO syndrome: a new vision of clinical and bone scintigraphy correlation. *J Orthop Surg Res* 2018; 13: 120.

62. Patel CN, Smith JT, Rankine JJ, et al. F-18 FDG PET/CT can help differentiate SAPHO syndrome from suspected metastatic bone disease. *Clin Nucl Med* 2009; 34: 254–257.

63. Takeuchi K, Matsusita M and Takagishi K. A case of SAPHO (synovitis-acne-pustulosis-hyperostosis-osteomyelitis) syndrome in which [18F] fluorodeoxyglucose positron emission tomography was useful for differentiating from multiple metastatic bone tumors. *Mod Rheumatol* 2007; 17: 67–71.

64. Cao Y, Li C, Yang Q, et al. Three patterns of osteoarticular involvement in SAPHO syndrome: a cluster analysis based on whole body bone scintigraphy of 157 patients. *Rheumatology (Oxford)* 2019; 58: 1047–1055.

65. Przepiera-Bedzak H, Fischer K and Brzosko M. Serum levels of angiogenic cytokines in psoriatic arthritis and SAPHO syndrome. *Pol Arch Med Wewn* 2013; 123: 297–302.

66. Wekell P, Bjornsdottr H, Bjorkman L, et al. Neutrophils from patients with SAPHO syndrome show no signs of aberrant NADPH oxidase-dependent production of intracellular reactive oxygen species. *Rheumatology (Oxford)* 2016; 55: 1489–1498.

67. Li C, Xiang Y, Wu X, et al. Serum IgG4 elevation in SAPHO syndrome: does it unmask
a disease activity marker? Clin Exp Rheumatol. 2020; 38(1): 35–41.

68. Chen L, Zhang S, Liu J, et al. Association between disease activity and osteocalcin, β-isomerized C-terminal telopeptides in SAPHO syndrome. Chin J Rheumatol 2016; 20: 304–307.

69. Witt M, Meier J, Hammitzsch A, et al. Disease burden, disease manifestations and current treatment regimen of the SAPHO syndrome in Germany: results from a nationwide patient survey. Semin Arthritis Rheum 2014; 43: 745–750.

70. Su CF, Shen YC, Liao HT, et al. SAPHO syndrome with enthesopathy. BMJ Case Rep 2019; 12: e225929.

71. Wang L, Li C, Yu M, et al. Long-term remarkable remission of SAPHO syndrome in response to short-term systemic corticosteroids treatment in an immunoglobulin E elevated patient: a case report. Medicine (Baltimore) 2019; 98: e16045.

72. Vekic DA, Woods J, Lin P, et al. SAPHO syndrome associated with hidradenitis suppurativa and pyoderma gangrenosum successfully treated with adalimumab and methotrexate: a case report and review of the literature. Int J Dermatol 2018; 57: 10–18.

73. Akcaboy M, Bakkaloglu-Ezgu SA, Buyukkaragoz B, et al. Successful treatment of a childhood synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome with subcutaneous methotrexate: a case report. Turk J Pediatr 2017; 59: 184–188.

74. Hasegawa S, Yabe H, Kaneko N, et al. Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome with significant bilateral pleural effusions. Intern Med 2017; 56: 2779–2783.

75. Genovese G, Caorsi R, Moltrasio C, et al. Successful treatment of co-existent SAPHO syndrome and hidradenitis suppurativa with adalimumab and methotrexate. J Eur Acad Dermatol Venereol 2019; 33(Suppl. 6): 40–41.

76. Delattre E, Guillot X, Godfrin-Valnet M, et al. SAPHO syndrome treatment with intravenous pamidronate. Retrospective study of 22 patients. Joint Bone Spine 2014; 81: 456–458.

77. Liu S, Li C, Tang MW, et al. Improvement of lymphangioleiomyomatosis following successful tofacitinib treatment for refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome. Chin Med J (Engl) 2019; 132: 2378–2379.

78. Zwaenepoel T and Vlam K. SAPHO: treatment options including bisphosphonates. Semin Arthritis Rheum 2016; 46: 168–173.

79. Fruehauf J, Cierny-Modre B, Lel SC, et al. Response to infliximab in SAPHO syndrome. BMJ Case Rep 2009; 2009: bcr1020081145.

80. Garconvich S, Amelia R, Magarelli N, et al. Long-term treatment of severe SAPHO syndrome with adalimumab: case report and a review of the literature. Am J Clin Dermatol 2012; 13: 55–59.

81. Zhang L and Gao Z. Etanercept in the treatment of refractory SAPHO syndrome. Am J Clin Exp Immunol 2016; 5: 62–66.

82. Vilar-Alejo J, Dehesa L, del Rey PDLR, et al. SAPHO syndrome with unusual cutaneous manifestations treated successfully with etanercept. Acta Derm Venereol 2010; 90: 531–532.

83. Zhang LL, Zhao JX and Liu XY. Successful treatment of SAPHO syndrome with severe spinal disorder using entercept: a case study. Rheumatol Int 2012; 32: 1963–1965.

84. Kamata Y and Minota S. Successful treatment of a patient with SAPHO syndrome with certolizumab pegol. Rheumatol Int 2015; 35: 1607–1608.

85. Assmann G, Bittenbring T, Wagner AD, et al. Impact of interleukin 17 blocking agent on clinical outcome in sapho patients. Annals of the Rheumatic Diseases 2019; 78: 875–876.

86. Fujita S, Kosaka N, Mito T, et al. Development of aseptic subcutaneous abscess after tocilizumab therapy in a patient with SAPHO syndrome complicated by amyloid A amyloidosis. Int J Rheum Dis 2015; 18: 476–479.

87. Sato H, Wada Y, Hasegawa E, et al. Adult-onset chronic recurrent multifocal osteomyelitis with high intensity of muscles detected by magnetic resonance imaging, successfully controlled with tocilizumab. Intern Med 2017; 56: 2353–2360.

88. Sun XC, Liu S, Li C, et al. Failure of tocilizumab in treating two patients with refractory SAPHO syndrome: a case report. J Int Med Res 2018; 46: 5309–5315.

89. Wendling D, Prati C and Aubin F. Anakinra treatment of SAPHO syndrome: short-term results of an open study. Ann Rheum Dis 2012; 71: 1098–1100.

90. Yang Q, Zhao Y, Li C, et al. Case report: successful treatment of refractory SAPHO syndrome with the JAK inhibitor tofacitinib. Medicine (Baltimore) 2018; 97: e11149.

91. Adamo S, Nilsson J, Krebs A, et al. Successful treatment of SAPHO syndrome with apremilast. Br J Dermatol 2018; 179: 959–962.
92. Hofmann SR, Kapplusch F, Girschick HJ, et al. Chronic recurrent multifocal osteomyelitis (CRMO): presentation, pathogenesis, and treatment. *Curr Osteoporos Rep* 2017; 15: 542–554.

93. Scarpato S and Tirri E. Successful treatment of SAPHO syndrome with leflunomide. Report of two cases. *Clin Exp Rheumatol* 2005; 23: 731.

94. Jung J, Molinger M, Kohn D, et al. Intraarticular glucocorticosteroid injection into sternocostoclavicular joints in patients with SAPHO syndrome. *Semin Arthritis Rheum* 2012; 42: 266–270.

95. Firinu D, Garcia-Larsen V, Manconi PE, et al. SAPHO syndrome: current developments and approaches to clinical treatment. *Curr Rheumatol Rep* 2016; 18: 35.

96. Amital H, Applbaum YH, Aamar S, et al. SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. *Rheumatology (Oxford)* 2004; 43: 658–661.

97. Saez-Martín LC, Gomez-Castro S, Roman-Curto C, et al. Etanercept in the treatment of SAPHO syndrome. *Int J Dermatol* 2015; 54: e206–e208.

98. Li C, Wu X, Cao Y, et al. Paradoxical skin lesions induced by anti-TNF-alpha agents in SAPHO syndrome. *Clin Rheumatol* 2019; 38: 53–61.

99. Campbell JA, Kodama SS, Gupta D, et al. Case series of psoriasis associated with tumor necrosis factor-alpha inhibitors in children with chronic recurrent multifocal osteomyelitis. *J AAD Case Rep* 2018; 4: 767–771.

100. Assmann G, Kueck O, Kirchhoff T, et al. Efficacy of antibiotic therapy for SAPHO syndrome is lost after its discontinuation: an interventional study. *Arthritis Res Ther* 2009; 11: R140.

101. Colina M, Govoni M, Orzincolo C, et al. Clinical and radiologic evolution of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a single center study of a cohort of 71 subjects. *Arthritis Rheum* 2009; 61: 813–821.

102. Maugars Y, Berthelot JM, Duclos XM, et al. SAPHO syndrome: a followup study of 19 cases with special emphasis on enthesis involvement. *J Rheumatol* 1995; 22: 2135–2141.

103. Li Y, Liu G, Zhao Y, et al. SAPHO syndrome with pathological fractures of vertebral bodies: a case report. *BMC Musculoskelet Disord* 2019; 20: 27.