SAPHO syndrome: meet you treat you

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Abstract
SAPHO syndrome is a rare autoimmune disease, people to its understanding is not very clear, but the study found that the actual prevalence is not low, as previously reported data show, so that for the disease of clinical misdiagnosis of misdiagnosis and delayed diagnosis of the situation is very serious In this review, we summarized the diagnosis and treatment status and research progress of SAPHO syndrome, so as to help medical workers better identify and treat SAPHO syndrome in clinical practice.

Keywords: SAPHO syndrome, Etiology, Clinical and Imaging Features, Diagnosis, Treatment

SAPHO syndrome is a rare chronic immune-mediated disease named after the first letter of each disease of synovitis acne pustulosis and osteitis Windom et al. [8] first reported the correlation between musculoskeletal symptoms and the appearance of acne in 1961. Since then, different experts have defined the disease by different names, such as pustular osteoarthritis, sternocostal clavicular hyperostoplasia, acne-related joint disease and chronic recurrent multifocal osteomyelitis (CRMO) [9]1987, Chamot The concept of SAPHO syndrome was first proposed by et al. [10] and gradually accepted. In 1994, Magrey and Khan [11] proposed diagnostic criteria for SAPHO syndrome after a large number of studies. Epidemiology: Current reports on disease prevalence are limited. In 1994 Khan [11] reported a prevalence of 1 in 10,000 caucasians, and Schilling estimated the prevalence in Germany to be somewhere between systemic lupus erythematosus and scleroderma, providing a figure of 0.04% (i.e. 40/100,000) [12]. A national questionnaire survey in Japan in 2001 showed that the annual prevalence of SAPHO syndrome was 0.00144/100,000 [67], but the epidemiological data from China are not clear.

Pathogenesis
Etiology of SAPHO syndrome is not clear According to previous articles, there are several hypotheses that are the most popular one is that SAPHO syndrome is caused by a low-virulent pathogen or an autoimmune response triggered by a viral or bacterial pathogen, such as propionibacterium acnes [13] Propionibacterium acnes can activate complement and induce IL-1 Il-8 and tnf-a have strong immunomodulatory activity [14] in Japan, a series of reports have observed that they are significantly associated with tonsillitis, sinusitis and odontogenic infection [62] another hypothesis is that SAPHO syndrome is associated with serum-negative joint disease, especially PsA [15,16] genetic studies have found that LPIN2 NOD2 and PSTPIP1 mutations can affect the clinical course of SAPHO syndrome by regulating the production of PMN IL-8 under bacterial stimulation, which has achieved certain results in animal experiments [24], HLA-B27 -39 and -61 alleles are more common in PATIENTS with SAPHO syndrome, and their role needs further research [25]. Some scholars also believe that it may be an autoinflammatory disease caused by exposure of genetically susceptible individuals to infectious agents Induction of IL-23/ Th17 axis and activation of neutrophils seem to play a key role [23], Yuxiu Sun (Sun Y) et al. first studied the plasma proteome profile of SAPHO patients and found that complement system inhibitors such as CFH and C4BP were up-regulated in SAPHO syndrome, which may play an important role in the pathogenesis of SAPHO syndrome [51]. It is speculated that no single genetic variation can explain all the complex manifestations of this disease, and the following six pathways are suggested: osteoclast differentiation pathway phagosomal pathway Fc Epsilon RI pathway Rap1 pathway Fc γ pathway R-mediated phagocytosis pathway and bacterial invasion of epithelial cells, and the changes in these pathways are the causes of this disease [53], which need further study.

Clinical Manifestations
SAPHO syndrome has the same clinical characteristics as other diseases such as infectious discitis serum-negative SpA and psoriatic arthritis (PsA) [1] most patients develop musculoskeletal disorders such as pain, tenderness and swelling or limited range of motion related to the bone site, most commonly the anterior chest wall and spine in adults [15,47]. At the same time, the prevalence of bone loss or osteoporosis in SAPHO patients is much higher than that in the general population [58]. The most common skin injuries are palm-plantar impetigo (PPP) and acne
PPP is a chronic and recurrent skin disease, which is considered to be a special type of psoriasis, characterized by 2-4 mm pale yellow sterile intradermal pustules on the palms and planter soles. Erythema and hyperkeratosis are pathologic manifestations of diffuse perivascular neutrophil infiltration [29]. The most common clinical complications include hypothyroidism, diabetes sjogren’s syndrome, antiphospholipid syndrome, metabolic syndrome, depression, etc. [49].

**Laboratory Examination**

Serological examination of SAPHO syndrome is currently considered non-specific, but elevated ESR CRP may occur during the onset [27]. RF ANA and human leukocyte antigen B-27 (HLA-B27) are mostly negative, while serum IL1 IL-8, IL-18, TNF-α and Th17 are present [23] with the continuous progress of research, serum markers such as serum amyloid a-1 (SAA1) against Sp17 autoantibodies may become the characteristic biomarkers of SAPHO syndrome patients [59,66], which require further study and observation of the effects of examination: Radiographic findings may differ at different stages of the disease. In the early stage, osteitis presents as focal osteosclerosis with erosive changes in the bone cortex and edematous thickening of adjacent soft tissues. Subsequently, osteosclerosis (diffuse osteosclerosis with increased bone volume) and synovitis develop [30]. Osteoarthritis has been reported in over 90% of SAPHO cases (sternoclavicular region, 65 90%); The spine, 32.52%; The pelvis, 13 52%; Long bone, 30%; Mandible,11%) [50]. Radiographs may show bone dilatation sclerosis and osteolysis periosteum reaction or new bone formation at attachment points, although early changes are generally not clearly identified on X-ray [19]. CT can show joint erosion osteosclerosis and hyperosteogenesis around joint space changes. MR imaging can show edema and associated soft tissue inflammation in active lesions, and can best observe the earliest inflammatory changes. It can also be used to assess the extent and activity of lesions with the added advantage of avoiding radiation exposure [30,45,46,55,62]. Whole body bone scintigraphy (WBBS) [2,31] can reveal classic scintiticocephalic signs in patients, with the stalk sterna representing the upper skull and the inflamed sternoclavicular joint corresponding to the Angle, contributing to the diagnosis of disease. WBBS provides an additional advantage: it often examines unknown bone sites involved, since clinical symptoms do not necessarily correlate with skeletal changes Helps physicians and patients understand the likely manifestations and complications of the natural course of their disease to avoid unnecessary diagnostic procedures, PET/CT is very useful in the detection of malignant tumors, helping to rule out metastatic disease in difficult cases, assessing the affected site of SAPHO syndrome, monitoring disease activity, and providing new evidence for the hypothesis that the disease may be associated with focal inflammation such as tarsitis and sinüsitis, with the disadvantage of being expensive [64,65].

**Diagnosis**

At present, the most widely used diagnostic criteria were formulated by Benhamou et al. [22] in 1988. A diagnosis can be made if at least one of the following four criteria is met: combined acne/explosive acne or suppurative eccinitis with osteoarticular symptoms; Palmoplantar pustulosis with osteoarthropathy; Hypertrophy of bone (anterior chest wall/limbs or spine) with or without skin diseases; The exclusion criteria for chronic recurrent multifocal myeloiditis (medial or peripheral) with or without dermatosis: 1. Sepsis osteomyelitis; 2. Infectious chest wall arthritis; 3. Infectious palmoplantar pustulosis; 4. Dyskeratosis of palmar and plantar skin; 5 diffuse idiopathic hypertrophy; In 1994, Magrey and Khan [23] proposed another diagnostic criterion for SAPHO syndrome based on pathological examination: sternocostal clavicular hypertrophy, combined with one of the following three: 1. Osteoarthritis and/or osteoarthritis with palmoplantar pustulosis; 2.1. Osteoarthritis and/or arthritis with severe acne; 3. Aseptic osteitis complicated with characteristic skin lesions, such as palmoplantar impetigo, psoriasis, acne, eccrine and other skin diseases, were revised in the American Annual Meeting of rheumatology in 2003. Any one of the following 5 conditions can be diagnosed: bone and (or) joint disease accompanied by palmoplantar impetigo; Bone and/or joint disease with severe acne; Isolated aseptic hypertrophy or osteitis in adults (except propionibacterium acnes); Chronic recurrent multifocal osteomyelitis in children 5. Bone and joint involvement associated with chronic bowel disease meets one of the five conditions and excludes infectious arthritis bone tumor non-inflammatory bone injury can confirm SAPHO syndrome main differential diagnosis: These include infectious osteomyelitis osteosarcoma ewing’s sarcoma bone metastasis cosinophilic granuloma Paget’s disease infectious discitis sternoclavicular osteoarthritis clavicular compression osteitis and medial clavicle epiphysis necrosis [17,18] 5. Treatment: Traditional therapies non-steroidal anti-inflammatory drugs (NSAIDs) are usually used as first-line treatment for pain relief or at the diagnostic stage [48], but in most cases they are insufficient second-line drugs including steroid bisphosphonates antibiotics and disease-improving antirheumatic drugs (DMARDs) [19,29] Intraarticular or systemic corticosteroids can be used short-term in most patients [3] to help improve symptoms, but long-term use leads to well-known complications bisphosphonates, especially pamidronates, have sustained and rapid efficacy against bone inflammation [4] and can not only participate in bone remodeling, but also inhibit IL-1β Secretion of IL-6 and TNF-α in treatment of osteoporosis [12,19,58] some patients have partial or complete sustained remission over time [4-7] when the skin biopsy pathogen propionibacterium acnes is positive, antibiotic treatment is better [23,61]. Schilling recommended azithromycin, which has both anti-inflammatory and immunomodulatory effects [12], and clindamycin and tetracycline have also been reported to have achieved some efficacy [33,34] macrolides or neoquinolones effectively inhibit the production of various inflammatory cytokines, such as interleukin-1,-6,-8, and tumor necrosis factor -α. [35,36] traditional disease-improving antirheumatic drugs (cdmards) usually include methotrexate (MTX), including sulfopridine hydroxyclooroquine Leflunomide azathiprine thalidomide and colocine, which have been reported to be beneficial for SAPHO syndrome [56,57] patients with no improvement in clinical symptoms or laboratory indicators after long-term treatment with nsaid with any of the following drugs were defined as refractory SAPHO syndrome.
With the deepening of the understanding of SAPHO syndrome, while improving inflammatory markers and patient quality of life, providing an important treatment option for patients with refractory SAPHO [26,60]. Surgical treatment can be considered in the case of malformation loss of function, increased pain and failure of conservative treatment, but it should be noted that surgical treatment may not prevent recurrence of the disease [32,54].

Research on SAPHO syndrome continues unabated. There are no known clinical or laboratory markers that reliably measure disease activity in response to treatment, OMERACT presented at the 2020 SIG(Organization Association) meeting The CNO/SAPHO Working Group conducted a series of discussions and efforts aimed at developing a core domain set (CDS) for CNO and SAPHO that includes new treatment options for SAPHO syndrome, especially in patients who do not respond well to conventional DMARDs and biologics [20-22,38,39]. Tofacitinib, an oral Janus kinase inhibitor, has been shown to relieve nail lesions and PPP in patients with SAPHO syndrome, while improving inflammatory markers and patient quality of life, providing an important treatment option for patients with refractory SAPHO [26,60]. Surgical treatment can be considered in the case of malformation loss of function, increased pain and failure of conservative treatment, but it should be noted that surgical treatment may not prevent recurrence of the disease [32,54].

Summary

With the deepening of the understanding of SAPHO syndrome, more and more patients will be able to receive more timely treatment. At the same time, it is helpful to determine the true prevalence of SAPHO and establish more comprehensive data information, which requires the joint efforts of rheumatology, radiology, orthopedic dermatology and other disciplines.

References


