

World Journal of *Clinical Cases*

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Contents

Semimonthly Volume 8 Number 19 October 6, 2020

OPINION REVIEW

- 4280 Role of monoclonal antibody drugs in the treatment of COVID-19
Ucciferri C, Vecchiet J, Falasca K

MINIREVIEWS

- 4286 Review of simulation model for education of point-of-care ultrasound using easy-to-make tools
Shin KC, Ha YR, Lee SJ, Ahn JH
- 4303 Liver injury in COVID-19: A minireview
Zhao JN, Fan Y, Wu SD

ORIGINAL ARTICLE

Case Control Study

- 4311 Transanal minimally invasive surgery vs endoscopic mucosal resection for rectal benign tumors and rectal carcinoids: A retrospective analysis
Shen JM, Zhao JY, Ye T, Gong LF, Wang HP, Chen WJ, Cai YK
- 4320 Impact of *mTOR* gene polymorphisms and gene-tea interaction on susceptibility to tuberculosis
Wang M, Ma SJ, Wu XY, Zhang X, Abesig J, Xiao ZH, Huang X, Yan HP, Wang J, Chen MS, Tan HZ

Retrospective Cohort Study

- 4331 Establishment and validation of a nomogram to predict the risk of ovarian metastasis in gastric cancer: Based on a large cohort
Li SQ, Zhang KC, Li JY, Liang WQ, Gao YH, Qiao Z, Xi HQ, Chen L

Retrospective Study

- 4342 Predictive factors for early clinical response in community-onset *Escherichia coli* urinary tract infection and effects of initial antibiotic treatment on early clinical response
Kim YJ, Lee JM, Lee JH
- 4349 Managing acute appendicitis during the COVID-19 pandemic in Jiaying, China
Zhou Y, Cen LS
- 4360 Clinical application of combined detection of SARS-CoV-2-specific antibody and nucleic acid
Meng QB, Peng JJ, Wei X, Yang JY, Li PC, Qu ZW, Xiong YF, Wu GJ, Hu ZM, Yu JC, Su W
- 4370 Prolonged prothrombin time at admission predicts poor clinical outcome in COVID-19 patients
Wang L, He WB, Yu XM, Hu DL, Jiang H

- 4380** Percutaneous radiofrequency ablation is superior to hepatic resection in patients with small hepatocellular carcinoma

Zhang YH, Su B, Sun P, Li RM, Peng XC, Cai J

- 4388** Clinical study on the surgical treatment of atypical Lisfranc joint complex injury

Li X, Jia LS, Li A, Xie X, Cui J, Li GL

- 4400** Application of medial column classification in treatment of intra-articular calcaneal fractures

Zheng G, Xia F, Yang S, Cui J

Clinical Trials Study

- 4410** Optimal hang time of enteral formula at standard room temperature and high temperature

Lakananurak N, Nalinthassanai N, Suansawang W, Panarat P

META-ANALYSIS

- 4416** Meta-analysis reveals an association between acute pancreatitis and the risk of pancreatic cancer

Liu J, Wang Y, Yu Y

SCIENTOMETRICS

- 4431** Global analysis of daily new COVID-19 cases reveals many static-phase countries including the United States potentially with unstoppable epidemic

Long C, Fu XM, Fu ZF

CASE REPORT

- 4443** Left atrial appendage aneurysm: A case report

Belov DV, Moskalev VI, Garbuzenko DV, Arefyev NO

- 4450** Twenty-year survival after iterative surgery for metastatic renal cell carcinoma: A case report and review of literature

De Raffele E, Mirarchi M, Casadei R, Ricci C, Brunocilla E, Minni F

- 4466** Primary rhabdomyosarcoma: An extremely rare and aggressive variant of male breast cancer

Satală CB, Jung I, Bara TJ, Simu P, Simu I, Vlad M, Szodorai R, Gurzu S

- 4475** Bladder stones in a closed diverticulum caused by *Schistosoma mansoni*: A case report

Alkhamees MA

- 4481** Cutaneous ciliated cyst on the anterior neck in young women: A case report

Kim YH, Lee J

- 4488** Extremely rare case of successful treatment of metastatic ovarian undifferentiated carcinoma with high-dose combination cytotoxic chemotherapy: A case report

Kim HB, Lee HJ, Hong R, Park SG

- 4494** Acute amnesia during pregnancy due to bilateral fornix infarction: A case report
Cho MJ, Shin DI, Han MK, Yum KS
- 4499** Ascaris-mimicking common bile duct stone: A case report
Choi SY, Jo HE, Lee YN, Lee JE, Lee MH, Lim S, Yi BH
- 4505** Eight-year follow-up of locally advanced lymphoepithelioma-like carcinoma at upper urinary tract: A case report
Yang CH, Weng WC, Lin YS, Huang LH, Lu CH, Hsu CY, Ou YC, Tung MC
- 4512** Spontaneous resolution of idiopathic intestinal obstruction after pneumonia: A case report
Zhang BQ, Dai XY, Ye QY, Chang L, Wang ZW, Li XQ, Li YN
- 4521** Successful pregnancy after protective hemodialysis for chronic kidney disease: A case report
Wang ML, He YD, Yang HX, Chen Q
- 4527** Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report
Li B, Li GW, Xue L, Chen YY
- 4535** Percutaneous fixation of neonatal humeral physeal fracture: A case report and review of the literature
Tan W, Wang FH, Yao JH, Wu WP, Li YB, Ji YL, Qian YP
- 4544** Severe fundus lesions induced by ocular jellyfish stings: A case report
Zheng XY, Cheng DJ, Lian LH, Zhang RT, Yu XY
- 4550** Application of ozonated water for treatment of gastro-thoracic fistula after comprehensive esophageal squamous cell carcinoma therapy: A case report
Wu DD, Hao KN, Chen XJ, Li XM, He XF
- 4558** Germinomas of the basal ganglia and thalamus: Four case reports
Huang ZC, Dong Q, Song EP, Chen ZJ, Zhang JH, Hou B, Lu ZQ, Qin F
- 4565** Gastrointestinal bleeding caused by jejunal angiosarcoma: A case report
Hui YY, Zhu LP, Yang B, Zhang ZY, Zhang YJ, Chen X, Wang BM
- 4572** High expression of squamous cell carcinoma antigen in poorly differentiated adenocarcinoma of the stomach: A case report
Wang L, Huang L, Xi L, Zhang SC, Zhang JX
- 4579** Therapy-related acute promyelocytic leukemia with FMS-like tyrosine kinase 3-internal tandem duplication mutation in solitary bone plasmacytoma: A case report
Hong LL, Sheng XF, Zhuang HF
- 4588** Metastasis of esophageal squamous cell carcinoma to the thyroid gland with widespread nodal involvement: A case report
Zhang X, Gu X, Li JG, Hu XJ

- 4595** Severe hyperlipemia-induced pseudoerythrocytosis - Implication for misdiagnosis and blood transfusion: A case report and literature review
Zhao XC, Ju B, Wei N, Ding J, Meng FJ, Zhao HG
- 4603** Novel brachytherapy drainage tube loaded with double 125I strands for hilar cholangiocarcinoma: A case report
Lei QY, Jiao DC, Han XW
- 4609** Resorption of upwardly displaced lumbar disk herniation after nonsurgical treatment: A case report
Wang Y, Liao SC, Dai GG, Jiang L
- 4615** Primary hepatic myelolipoma: A case report and review of the literature
Li KY, Wei AL, Li A
- 4624** Endoscopic palliative resection of a giant 26-cm esophageal tumor: A case report
Li Y, Guo LJ, Ma YC, Ye LS, Hu B
- 4633** Solitary hepatic lymphangioma mimicking liver malignancy: A case report and literature review
Long X, Zhang L, Cheng Q, Chen Q, Chen XP
- 4644** Intraosseous venous malformation of the maxilla after enucleation of a hemophilic pseudotumor: A case report
Cai X, Yu JJ, Tian H, Shan ZF, Liu XY, Jia J
- 4652** Intravesically instilled gemcitabine-induced lung injury in a patient with invasive urothelial carcinoma: A case report
Zhou XM, Wu C, Gu X
- 4660** Bochdalek hernia masquerading as severe acute pancreatitis during the third trimester of pregnancy: A case report
Zou YZ, Yang JP, Zhou XJ, Li K, Li XM, Song CH
- 4667** Localized primary gastric amyloidosis: Three case reports
Liu XM, Di LJ, Zhu JX, Wu XL, Li HP, Wu HC, Tuo BG
- 4676** Displacement of peritoneal end of a shunt tube to pleural cavity: A case report
Liu J, Guo M
- 4681** Parathyroid adenoma combined with a rib tumor as the primary disease: A case report
Han L, Zhu XF

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Peer-reviewer of *World Journal of Clinical Cases*, Prof. Adrián Ángel Inchauspe, obtained his MD in 1986 from La Plata National University (Argentina), where he remained as Professor of Surgery. Study abroad, at the Aachen and Tübingen Universities in Germany in 1991, led to his certification in laparoscopic surgery, and at the Louis Pasteur University in Strasbourg France, led to his being awarded the Argentine National Invention Award in 1998 for his graduate work in tele-surgery. He currently serves as teacher in the Argentine Acupuncture Society, as Invited Foreigner Professor at the China National Academy of Sciences and Hainan Medical University, and as editorial member and reviewer for many internationally renowned journals. (L-Editor: Filipodia)

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Rapid remission of refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome in response to the Janus kinase inhibitor tofacitinib: A case report

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Abstract

BACKGROUND

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disease for which clinical treatment has not been standardized. Janus kinase (JAK) inhibitors represent a novel therapeutic option for rheumatoid arthritis, psoriatic arthritis, and some other autoinflammatory diseases. However, the clinical utility of JAK inhibitors in treating SAPHO syndrome has not been thoroughly investigated. In this study, we describe a patient with SAPHO syndrome who failed to respond to conventional treatment but demonstrated a remarkable and rapid response to the JAK inhibitor tofacitinib.

CASE SUMMARY

A 62-year-old female patient presented with swelling and pain at the sternoclavicular joints, back pain that limited her activities, arthralgia in the right knee, and cutaneous lesions. Her symptoms were unresponsive to nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, Tripterygium wilfordii hook f, and bisphosphonates. SAPHO syndrome was diagnosed in accordance with dermatological and osteoarticular manifestations and abnormal inflammatory factors. Multiple image studies have illustrated bone lesions and pathological fractures of vertebral bodies. Oral treatment with tofacitinib at 5 mg twice daily with methotrexate and bisphosphonates was initiated. The patient reported that her pain symptoms were relieved after 3 d and her cutaneous lesions were reduced after 4 wk of treatment. Vertebral lesions were improved

Checklist (2016).

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after 6 mo on tofacitinib. No serious adverse effects were noted.

CONCLUSION

JAK inhibitor therapy may be a promising strategy to treat SAPHO syndrome.

Key Words: Inflammation; Janus kinase inhibitor; Synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome; Case report

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Core Tip: Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare autoinflammatory disease for which clinical treatment has not been standardized. We describe a patient with SAPHO syndrome who failed to respond to conventional treatment but demonstrated a remarkable and rapid response to the Janus kinase inhibitor tofacitinib. This case highlights that Janus kinase inhibitor therapy may be a promising strategy to treat SAPHO syndrome.

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INTRODUCTION

Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, a rare disease with an estimated prevalence of 0.00144/100000^[1], is characterized by a constellation of clinical features including dermatological disorders and inflammatory osteoarticular lesions. It was named by Chamot *et al*^[2] in 1987^[3]. However, there is no evidence-based treatment recommendation for SAPHO. Current goals of treatment are to relieve clinical symptoms, control inflammation, and enhance the quality of wellbeing of the patient.

This report describes a patient with SAPHO syndrome who presented with palmoplantar pustules, swelling and pain at the sternoclavicular joints, back pain, and arthralgia in the right knee. These clinical features failed to respond to conventional treatment, but remitted after use of the Janus kinase (JAK) inhibitor tofacitinib.

CASE PRESENTATION

Chief complaints

A 62-year-old female patient presented to the Rheumatology Department of our hospital complaining of Swelling and tenderness in the right knee, severe tenderness in the lower back, and cutaneous lesions.

History of present illness

The patient presented with lower back and left side hip pain and palmoplantar pustules in March 2014. Blood analysis showed an erythrocyte sedimentation rate (ESR) of 89 mm/h (reference range, 0-20 mm/h) and C-reactive protein (CRP) at 8.78 mg/L (reference range, 0-10.00mg/L). Complete blood count and measures of liver and renal function were all within the normal range. Rheumatoid factor, anti-cyclic citrullinated peptide antibody, human leukocyte antigen B27, and antinuclear antibodies were all negative. Magnetic resonance imaging (MRI) scans of her lumbar spine demonstrated multiple vertebral lesions (L1 and L2 vertebral bodies and surrounding soft tissue). With empirical administration of nonsteroidal anti-inflammatory drugs (NSAIDs), the above symptoms were partially relieved. Swelling and pain at the sternoclavicular joints was completely relieved after using NSAIDs.

Swelling and tenderness in the right knee was evident and more severe tenderness with limited movement arose in the lower back in August 2018. The patient was

diagnosed with SAPHO syndrome. She had been suffering from recurrent pustules on the palms of her hands and lateral of her crus for 5 years prior to admission. There was no history of similar symptoms in her family.

History of past illness

At age 30, she was diagnosed with viral encephalitis, with sequelae including speech difficulties and paroxysmal hand tremors. She also had a history of hypertension for the past 5 years.

Physical examination

The patient's temperature was 36.8 °C, heart rate was 80 bpm, respiratory rate was 16 breaths per min, blood pressure was 120/80 mmHg, and oxygen saturation in room air was 99%. Swelling and tenderness was evident in the right knee and tenderness with limited movement in the lower back. A pustule-like rash was found on the palm and flank of both legs.

Laboratory examinations

Blood analysis showed an ESR of 90 mm/h (reference range, 0–20 mm/h), CRP at 9.85 mg/L (reference range, 0–10.00 mg/L), complement C3 at 1.26 g/L (reference range, 0.79–1.52 g/L), complement C4 at 0.37 g/L (reference range, 0.16–0.38 g/L), and immunoglobulin G at 17.30 g/L (reference range, 7.51–15.60 g/L). A complete blood count, electrolytes, and liver and renal function were all within the normal range. Rheumatoid factor, anti-cyclic citrullinated peptide antibody, human leukocyte antigen B27, antinuclear antibodies, extractable nuclear antigen and anti-double stranded DNA antibodies were all negative. Serum proinflammatory cytokine levels were significantly elevated: Tumor necrosis factor alpha (TNF- α) 16.9 pg/mL (reference range, \leq 8.1 pg/mL), interleukin 1-beta (IL-1 β) 6.4 pg/mL (reference range, $<$ 5 pg/mL), IL-6 2.98 pg/mL (reference range, \leq 3.4 pg/mL), IL-8 32.0 pg/mL (reference range, $<$ 62 pg/mL), and IL-10 $<$ 5.0 pg/mL (reference range, \leq 9.1 pg/mL). In addition, there was vitamin D deficiency, β -collagen degradation products, and bone-derived alkaline phosphatase redundancy. Hepatitis A, B, and C serologies were negative. No evidence of tumor or tuberculosis was found.

Imaging examinations

Sternoclavicular joints lesions and sacroiliac joints with bone hyperplasia were revealed by computerized tomography (Figure 1A and B). MRI obtained on various segments of the spine indicated end plate inflammation at the C6/7 and abnormal signal intensity at C5, T2 and T3, which suggested bone marrow edema (Figure 1D-G). MRI scans of the thoracic and lumbar spine demonstrated multiple vertebral lesions and pathological fractures (T10 and L1 vertebral bodies), and end plate inflammation at T10/11, T12/L1 and L5/S1 (Figure 1H-J).

FINAL DIAGNOSIS

A diagnosis of SAPHO syndrome was made, in accordance with the diagnostic criteria proposed in 2012^[4].

TREATMENT

Treatment with NSAIDs and methotrexate (MTX) (10 mg/wk) was initiated. Pain in the right knee and lower back remitted. Swelling and tenderness in the left elbow appeared 1 mo later. Therefore, tripterygium wilfordii hook f (TwHF) (10 mg 3 times/d) was initiated together with NSAIDs and MTX. After 3 mo, all symptoms were improved and ESR was reduced to 42 mm/h. Treatment with MTX (10 mg/wk) and TwHF (20 mg 2 times/d) with bisphosphonates was initiated. Unfortunately, symptoms in the left elbow recurred 1 mo later, and pain in the left side of the waist at night was aggravated. Meanwhile, serum ESR and CRP levels increased to 78 mm/h and 10.15 mg/L, respectively (Figures 2 and 3). Serum proinflammatory cytokine levels were significantly increased: TNF- α 21.7 pg/mL, IL-1 β 26.5 pg/mL, IL-6 3.39 pg/mL, IL-8 37.0 pg/mL, and IL-10 5.0 pg/mL (Figure 3). Note that the palmoplantar pustules recurred throughout the course of the disease. It should be mentioned that during the course of the disease, the patient also took leflunomide for 3 d, and then

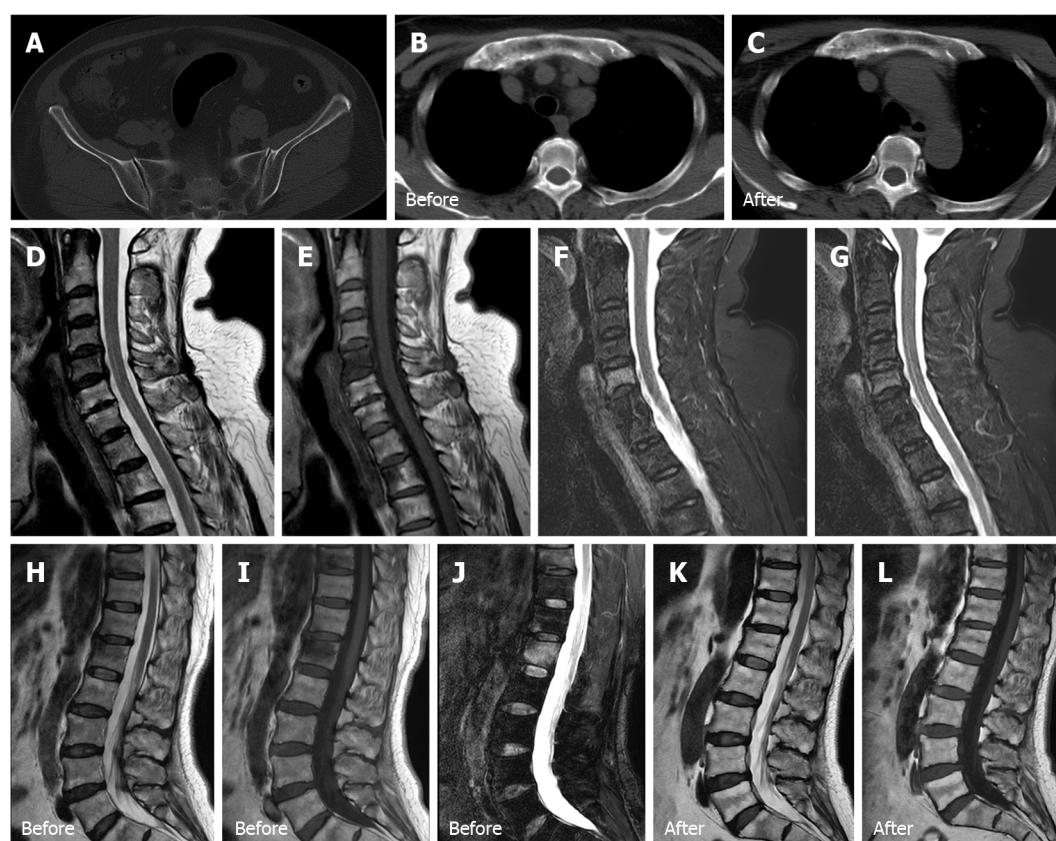


Figure 1 Imaging before and after treatment. A: Computed tomography scans of the sacroiliac joints revealed bone hyperplasia, and osteosclerosis; B and C: Computed tomography scans of the sternoclavicular joints revealed hyperostosis and lesions; D-G: Magnetic resonance imaging scans of the cervical and thoracic spine showed a herniated disc at C4/5 and C5/6, abnormal signal intensity at C5, T2 and T3, and end-plate inflammation at C6/7; H-J: Magnetic resonance imaging scans of the thoracic and lumbar spine: multiple vertebral bone marrow edema and mild pathological fractures (T10 and L1 vertebral bodies), end-plate inflammation (T10/11, T12/L1 and L5/S1) and paravertebral ossification; K and L: End-plate inflammation in L5/S1 and paravertebral ossification, no other obvious abnormality.

stopped due to a significant increase in blood pressure.

Tofacitinib, a small-molecule inhibitor of JAKs, was administered at 5 mg twice daily together with MTX (10 mg/wk) and bisphosphonates.

OUTCOME AND FOLLOW-UP

After 3 d of using tofacitinib, the patient reported that the pain was remarkably relieved and the palmoplantar pustules healed after 4 wk. ESR, CRP, IL-1 β and TNF- α levels decreased to normal or near-normal ranges after 6 mo on tofacitinib (Figure 3). Bone marrow edema on T10 and L1 vertebral bodies disappeared, no pathological fractures were found, and end-plate inflammation improved (Figure 1K and L). Bone hypertrophy of the sternoclavicular joint was not improved (Figure 1C). The patient developed an upper respiratory infection at week 12 which improved after 3 d of self-medication. No other adverse effects including anemia, leukopenia, liver function impairment, or kidney function impairment were noted. The patient was very satisfied with the treatment.

DISCUSSION

SAPHO syndrome is an auto-inflammatory disease with significant cutaneous and musculoskeletal inflammation. The etiology is unknown and may be related to genetic, infective and immune factors.

The diagnostic criteria have been revised three times. The original diagnostic criteria in 1994 emphasized aseptic inflammation of bone and joint with characteristic skin manifestations, but it was important to note the pathologic and pathological evidence of the disease. However, subsequent studies have proved that the prognosis of

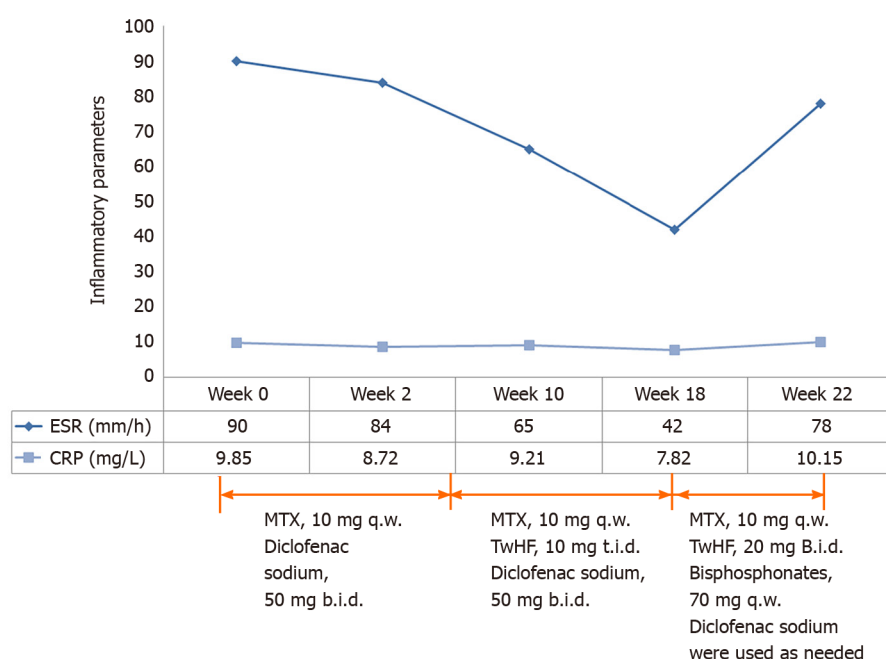


Figure 2 Dosage, frequency, duration of different treatments and levels of serum inflammatory parameters before initiation of tofacitinib treatment. ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; MTX: Methotrexate, TwHF: Tripterygium wilfordii hook f; t.i.d.: Three times per day; b.i.d.: Twice per day; q.w.: Once per week.

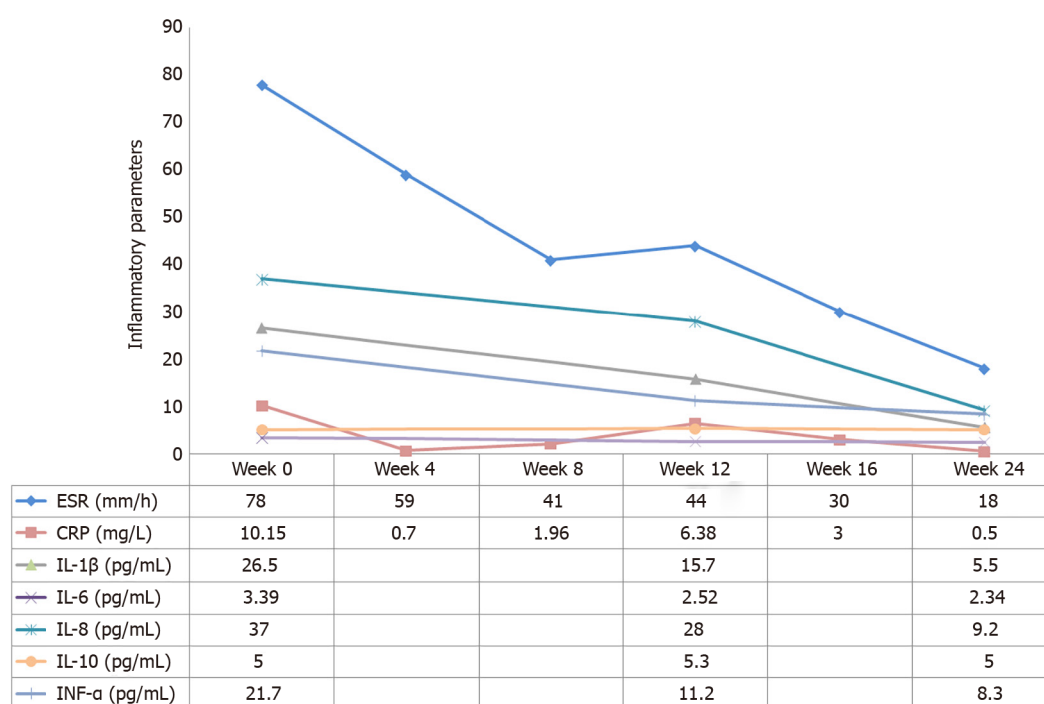


Figure 3 Levels of serum inflammatory parameters after initiation of tofacitinib treatment. IL: Interleukin; TNF: Tumor necrosis factor.

SAPHO syndrome is relatively good, so invasive operations are no longer recommended. The following revisions were made at the ACR annual meeting in 2003, which emphasize that SAPHO can be diagnosed as long as characteristic rashes (palmar plantar pustules and severe acne) are accompanied by joint symptoms. Bone biopsy or imaging evaluation were performed only in patients without rash. However, the revised criteria required the exclusion of infectious osteomyelitis, bone tumors, and non-inflammatory densification changes. As of 2012, the criteria emphasized the imaging approaches. SAPHO can be diagnosed with evidence of bone hypertrophy in

the anterior chest wall, extremities, and spine, as well as a characteristic rash. Invasive examination is no longer recommended and clinical symptoms such as the typical rash and characteristic imaging features are emphasized in diagnosis.

SAPHO has following clinical characteristics: A characteristic skin rash, predominantly axial bone involvement, especially the sternoclavicular joint, followed by the spine and sacroiliac joint. Some patients have peripheral joint involvement. Inflammatory indicators and bone destruction indicators are elevated, and imaging evidence of bone hypertrophy and disc inflammation can be found. The course of SAPHO is prolonged and recurring. The first subacute attack may be completely cured, and the disability rate is low. The patient followed in this study demonstrated most of the clinical manifestations described above, and the diagnosis of SAPHO was clear after exclusion of infection, tuberculosis, tumor and other diseases.

Due to its rarity, treatment has not been standardized and is mostly based on case reports, case series, expert judgment, and learning from RA, psoriatic arthritis, for the purpose of controlling the pain and the inflammatory process. In general, NSAIDs and analgesics can be regarded as first-line treatments for pain relief^[5]. Short-term use of glucocorticoids may be necessary. Some reports have shown that disease-modifying antirheumatic drugs (DMARDs) are beneficial to patients and can be used chronically^[6]. However, the efficacy of anti-inflammatory treatment on skin and joint symptoms remains controversial. Antibiotics are effective in some patients, especially those with skin lesions^[7]. Bisphosphonates have been used as a third-line treatment for SAPHO syndrome due to their ability to inhibit bone resorption and relieve joint symptoms^[8]. As a result, we started patient treatment with methotrexate and diclofenac, gradually adding TwHF and bisphosphonates. Unfortunately, the patient did not respond well to these drugs, particularly the skin rashes. The pathogenesis of SAPHO syndrome remains unclear, however several similarities to auto-inflammatory diseases have been found. Genetic studies have associated SAPHO syndrome with mutations in lipin 2, nucleotide-binding oligomerization domain-containing protein 2, and proline-serine-threonine phosphatase-interacting protein 1^[8]. As has been demonstrated in some studies, propionibacterium acne can be found in joint fluid and bone biopsy specimens of SAPHO patients, which may contribute to the onset of disease by causing abnormal activation of innate immunity and cellular immunity. The levels of IL-1, IL-8, IL-17, IL-18, and Th17 in the peripheral blood of SAPHO patients are increased^[5,9,10]. The expression of TNF- α in peripheral blood and bone tissue is increased, and the level of IL-10 in peripheral blood is decreased, leading to auto-inflammation^[11]. Immune cells are activated by numerous cytokines to produce more cytokines through different pathways, which can make the inflammatory response a cascade of amplification.

In recent years targeted therapies against biological agents such as TNF- α ^[12], anti-IL-1^[13] and IL-23 or IL-17^[14] have proved to be effective treatments for the majority of patients with refractory SAPHO^[5]. However, drug hypersensitivity, treatment failure or paradoxical effects of these inhibitors are frequently observed in clinical practice^[15,16]. Despite the lack of systematic evidence and practical guidelines, many studies have shown that simultaneous use of DMARD, particularly MTX, has improved efficacy and reduced secondary failure of biotherapy due to anti-drug antibodies. Therefore, considering the increase of TNF- α and IL-1 levels suggested in the auxiliary examination, we recommended biological agents to the patient. However, in consideration of the severe allergy to previous drug injections such as penicillin, the patient refused the use of biological agents.

Common biological agents exert an inhibitory effect outside the cell and target single cytokines. JAKs are important intracellular signaling mediators, transmitting signals from receptors for cytokines, interleukins, interferons and colony-stimulating factors to signal transducer and activator of transcription (STAT) by phosphorylation. Then phosphorylated STAT translocates into the nucleus to activate gene transcription. The JAK family consists of four members: JAK1, JAK2, JAK3, and TYK2. Different cytokines signal through different JAK combinations; blocking the JAKs can block the action of a number of cytokines directly or indirectly, including γ -chain cytokines, IL-1, IL-6, IL-7, IL-12, IL-15, IL-17, IL-22, IL-23, and TNF- α (Figure 4). As a result, JAK inhibitors are emerging therapies that are demonstrating efficacy for the treatment of inflammatory diseases that act through cytokine production^[17-21].

Recently, JAK inhibitors showed great efficacy in the treatment of RA in the phase III clinical trial of the global ORAL series^[22], and of psoriatic arthritis in the clinical trial of the OPAL series^[23-25]. Inspired by the treatment guidelines for RA^[26], treatment with tofacitinib, a small-molecule inhibitor of JAKs, was undertaken in the present study. The patient was informed of the possible adverse effects of using JAK inhibitors, such as increased risk of infection, anemia, leucopenia, cancer and cardiovascular

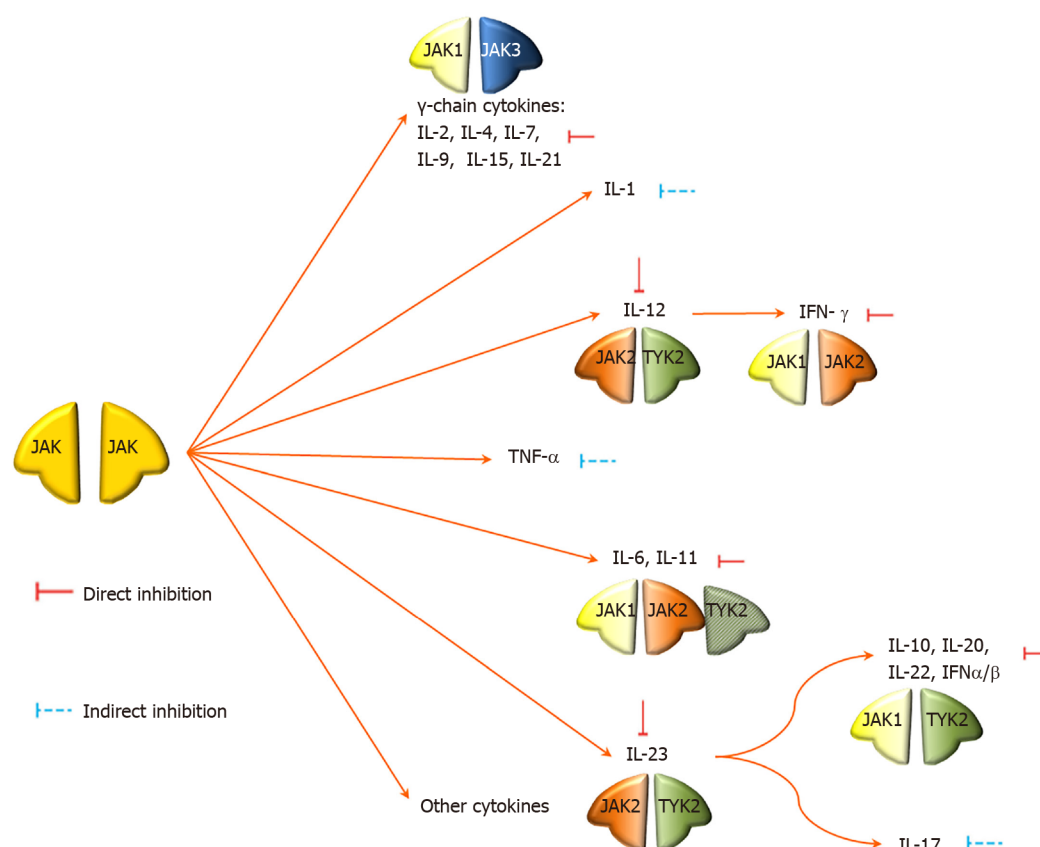


Figure 4 The mechanism of action of Janus kinases. JAK: Janus kinase; IL: Interleukin.

disease^[22]. Although adverse reactions did not arise in this patient, biological indicator measures and precautions should be taken when using JAK inhibitors, based on their biological functions.

CONCLUSION

To the best of our knowledge, SAPHO is rare and easily misdiagnosed. Typical rashes and imaging features are helpful in diagnosis. Traditional DMARDs use is effective to half of the patients, and TNF- α antagonists and IL-1 antagonists have been shown to be effective against refractory SAPHO. The JAK inhibitor Tofacitinib has been shown to be effective in patients with poor response to traditional agents and those unable to tolerate traditional drugs or biological agents; Tofacitinib has a rapid onset, good efficacy and few adverse effects.

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