Chinese Medical Journal®

Improvement of lymphangioleiomyomatosis following successful tofacitinib treatment for refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome

Shuang Liu[1], Chen Li[2], Ming-Wei Tang[1], Wen-Shuai Xu[3], Ke-Qi Chen[3], Xin Sui[4], Xin-Lun Tian[3], Kai-Feng Xu[3]

[1]School of Clinical Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100005, China;
[2]Department of Traditional Chinese Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing 100730, China;
[3]Department of Respiratory and Critical Care Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing 100730, China;
[4]Department of Radiology, Chinese Academy of Medical Sciences & Peking Union Medical College Hospital, Beijing 100730, China.

To the Editor: Lymphangioleiomyomatosis (LAM) is a rare multi-systemic disease that predominantly affects women and is associated with cystic lung destruction, chylous fluid accumulation, and abdominal tumors.[1] The lung function of LAM patients declines at two to four or more times faster rates than the typical age-related decline. Although the mammalian target of rapamycin (mTOR) inhibitor has shown certain benefits for patients with LAM, treatment options remain limited.[2] Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a spectrum of heterogeneous diseases characterized by osteoarticular and dermatological manifestations. Non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs, bisphosphonates, and intra-articular steroids are frequently prescribed but are often insufficient to control disease progression. Biological agents, which may be administered in refractory cases, have recently shown promising clinical utility. Janus kinase (JAK) and downstream effectors signal transducer of activation (STAT) proteins are important intra-cellular signaling molecules for type I and II cytokines, and recent evidence suggested the efficacy of JAK inhibitors in the treatment of autoimmune diseases.[3] Moreover, tofacitinib, a small-molecule selective JAK inhibitor, showed good efficacy in the treatment of refractory SAPHO syndrome.[4] Here, we presented a patient with SAPHO syndrome complicated with LAM whose arthralgia and pulmonary function both improved after tofacitinib treatment.

A 29-year-old female patient presented with progressive polyarthralgia and elevated serum inflammatory parameters in May 2016 and was diagnosed with SAPHO syndrome. Later, enhanced computed tomography (CT) revealed diffusely distributed round, regular, thin-walled cysts in the lung and cystic lesions along the lymphatic vessels in the posterior mediastinum and the retroperitoneal region. The vascular endothelial growth factor D (VEGF-D) was 1776 pg/mL (reference range: <800 pg/mL). She was diagnosed with LAM [Figure 1A] according to the 2017 American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline of LAM.[1] After sequential administration of NSAIDs, glucocorticoids, and interleukin (IL)-6 inhibitors, there was no substantial amelioration of symptomatic, laboratory, or imaging parameters. Inspired by the efficacy observed in other rheumatologic disorders, as well as for a previous SAPHO case, treatment with tofacitinib was considered. Because this JAK inhibitor acts upstream of the mTOR pathway, it is hypothesized that administration of tofacitinib may have some therapeutic effect for LAM. Tofacitinib was tentatively administered at 5 mg orally twice daily. Three weeks later on hospital discharge, the patient reported a marked improvement of symptoms. Inflammatory markers decreased to nearly normal ranges [Figure 1B]. The disease activity index also declined [Figure 1C]. After 16 weeks of tofacitinib treatment, MRI showed obvious amelioration of the bone marrow edema in the sacroiliac and sternoclavicular regions. Regarding LAM, her pulmonary function test showed an obstructive defect over time. Nonetheless, an improvement in the forced expiratory volume in 1 s, forced vital capacity, and diffusing capacity for carbon monoxide (DLCO) was observed after tofacitinib administration [Figure 1D]. The patient tolerated the medicine well and had no adverse effects. Her VEGF-D level remained stable (1931 pg/mL).

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000441

Shuang Liu and Chen Li contributed equally to this work.

Correspondence to: Dr. Xin-Lun Tian, Department of Respiratory and Critical Care Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, #1 Shuaifuyuan, Wangfujing, Beijing 100730, China
E-Mail: xinlun_t@sina.com

Chinese Medical Journal 2019;132(19)

Received: 10-06-2019 **Edited by:** Xin Chen

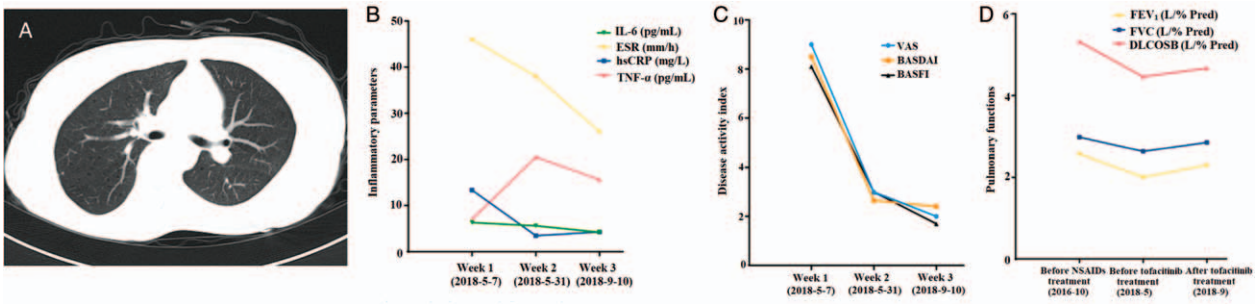

Figure 1: Radiological and laboratory findings for a 29-year-old female patient with synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome complicated with lymphangioleiomyomatosis. (A) Pulmonary high-resolution CT in October 2016 (at initial diagnosis) showed diffusely distributed round cysts in the lung. (B) Serum inflammatory parameters decreased after tofacitinib treatment. (C) The disease activity index decreased after tofacitinib treatment. (D) Pulmonary function changed during the disease course. BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; CT: Computed tomography; DLCOSB: Diffusing capacity for carbon monoxide, single breath; ESR: Erythrocyte sedimentation rate (reference range: 0–20 mm/h); FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; hsCRP: High sensitivity C-reactive protein (reference range: 0–3.00 mg/L); IL-6: Interleukin-6 (reference range: 0–5.9 pg/mL); NSAIDs: Non-steroidal anti-inflammatory drugs; Pred: Predicted value; TNF-α: Tumor necrosis factor-alpha (reference range: 0–8.1 pg/mL); VAS: Visual analogue scale.

Our case indicated that a JAK inhibitor may play a therapeutic role in both SAPHO and LAM. The JAK-STAT pathway has a crucial function in intra-cellular signaling of type I and type II cytokines. Therefore, inhibiting JAK will eventually block the action of pathological cytokines.[3] Moreover, as downstream mediators, JAK inhibitors have the potential to exert greater anti-inflammatory activity than do biologics that target only one cytokine. Tofacitinib, which selectively suppresses JAK1 and JAK3, may block signals of several essential cytokines involved in the transcription of genes responsible for inflammation and immune regulation. Furthermore, a previous study reported crosstalk between JAK and the *phosphoinositide* 3-*kinase*/protein *kinase* B/mTOR signaling pathway, suggesting a potential therapeutic benefit of targeting molecules in this pathway.[5]

In the initial stage of the clinical course, the patient lacked respiratory symptoms but showed typical radiological changes and elevated VEGF-D levels. To avoid invasive techniques, histopathological confirmation was not performed. However, the patient was under serial monitoring, and the later reduction in pulmonary function supported the diagnosis of LAM. One major limitation of this case was that lung function indicators might overestimate the therapeutic effect of JAK inhibitors. In the early stage, lung function might be underestimated due to the restriction of thoracic mobility caused by thoracic pain owing to SAPHO syndrome. Regardless, the improvement in DLCO and stabilization of chest CT also supported the benefit of JAK inhibitors for LAM. Common adverse effects of JAK inhibitors include increased risk of infection and myelosuppression.[3] As for this patient, no obvious toxicity was reported during the 16 weeks of tofacitinib treatment, though its long-term safety still needs further investigation.

In conclusion, this case provided a valuable experience of the clinical utility of tofacitinib in preventing LAM progression and in controlling osteoarticular and cutaneous manifestations of SAPHO syndrome. In the future, clinical trials on a larger scale should be carried out to elucidate the efficacy of JAK inhibitors for LAM and SAPHO syndrome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that the names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

References

1. Gupta N, Finlay GA, Kotloff RM, Strange C, Wilson KC, Young LR, *et al*. Lymphangioleiomyomatosis diagnosis and management: high-resolution chest computed tomography, transbronchial lung biopsy, and pleural disease management. An Official American Thoracic Society/Japanese Respiratory Society Clinical Practice Guideline. Am J Respir Crit Care Med 2017;196:1337–1348. doi: 10.1164/rccm.201709-1965ST.
2. Xu KF, Tian X, Yang Y, Zhang H. Rapamycin for lymphangioleiomyomatosis: optimal timing and optimal dosage. Thorax 2018;73:308–310. doi: 10.1136/thoraxjnl-2017-211135.
3. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov 2017;16:843–862. doi: 10.1038/nrd.2017.201.
4. Yang Q, Zhao Y, Li C, Luo Y, Hao W, Zhang W. Case report: successful treatment of refractory SAPHO syndrome with the JAK inhibitor tofacitinib. Medicine 2018;97:e11149. doi: 10.1097/md.0000000000011149.
5. Bousoik E, Montazeri Aliabadi H. Do we know jack" about JAK? A closer look at JAK/STAT signaling pathway. Front Oncol 2018;8:287. doi: 10.3389/fonc.2018.00287.

How to cite this article: Liu S, Li C, Tang MW, Xu WS, Chen KQ, Sui X, Tian XL, Xu KF. Improvement of lymphangioleiomyomatosis following successful tofacitinib treatment for refractory synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome. Chin Med J 2019;132:2378–2379. doi: 10.1097/CM9.0000000000000441