

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This article is an interesting piece of work which may be a valuable source of knowledge for dermatologists and for all clinicians who in your practice can meet problems of Morbihan diseases. For this reason I recommend this case report for publication in this journal.

ANSWER: Thanks for your positive comment. The language has been further polished carefully.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1. without depression under pressure:non pitting 2.what about acne in PMH?
3.what about other causes of local lymphedema

ANSWER: Thank you for raising these valuable questions. The language has been further polished carefully.

1.As for Question 1, we have replaced "without depression under pressure" with "non-pitting" in the manuscript.

2.As for Question 2, firstly, the patient had no history of acne. Secondly, the patient doesn't present the clinical manifestation of acne, including comedos, papula, pustules or else. It has also been mentioned in the discussion of the manuscript that Morbihan's disease is a rare disease, and the specific potential cause of the disease is unclear. Some scholars previously believed that Morbihan's disease is a rare complication of acne or rosacea, but some patients have no history of acne or rosacea. At present, more researchers tend to think that Morbihan's disease is an independent disease (See reference below).

References: Jerković Gulin S, Ljubojević Hadžavdić S.Morbihan Disease - An Old and Rare Entity Still Difficult to Treat.Acta Dermatovenerol Croat 2020;28(2):118-119[PMID: 32876040]

3.As for Question 3, lymphedema on the face generally present inflammatory diseases including recurrent erysipelas, acne and rosacea, with progressive damage of lymphatic vessels and pathologically visible lymphatic fluid accumulating in the reticular dermis and subcutaneous tissue, manifesting intermittent or continuous edema, but not accompanied by erythema. In this case, there was no representation of erysipelas, acne, rosacea. The facial skin lesions were erythematous edema without lymph fluid accumulation histopathologically, so we suggested that lymphedema caused by other reasons was not considered.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: I read this paper with interest. This article reported a case of Morbihan disease which is a rare disease without standard treatment. Existing treatments for Morbihan disease have shortcomings such as long medication cycle, disease recurrence after drug withdrawal and many side effects. This patient was treated with total glucosides of paeony with good effect and no adverse reactions. Although this article is well written overall, it has some issues. Major 1. The authors should discuss the common side effects of peony and the

possible problems with peony in this case. 2. Please describe the reason why you chose peony instead of MTX or LEF for this case. Minor 1. I can understand what “With endowment can eliminate dermatomyositis” means. Please explain.

ANSWER: Thank you for raising these valuable questions. The language has been polished again.

Concerning Major 1. The adverse reactions of total glucosides of paeony are rare, and the reported adverse reactions are only mild diarrhea. According to the literature, diarrhea is the most likely adverse reaction of total glucosides of paeony in the treatment of Morbihan's disease. The corresponding content has been supplemented in the manuscript. For Major 2, Ammontrexate and leflunomide can be used to treat inflammatory and immune diseases, but the biggest adverse reaction is damage of liver function^[1, 2, 3, 4, 5]. Total glucoside of peony has anti-inflammatory and immunomodulative effects, with few adverse reactions and prominent liver protection effect^[6, 7], so it is selected to treat Morbihan disease.

References:

- [1] Cameiro SC, Cassia FF, Lamy F, et al. Methotrexate and liver function: a study of 13 psoriasis cases treated with different cumulative dosages[J]. *J Eur Acad Dermatol Venereol*, 2008, 22(1):25-29. [PMID: 18181969 DOI: 10.1111/j.1468-3083.2007.02322.x]
- [2] Moreno-Otero R, Garcia-Buey L, Garcia-Sanchez A, et al. Autoimmune hepatitis after long-term methotrexate therapy for rheumatoid arthritis[J]. *Curr Drug Saf*, 2011, 6(3):197-200. [PMID: 22122395 DOI: 10.2174/157488611797579221]
- [3] Lin F, Wang Q, Yu W, et al. Clinical analysis of Chinese limb osteosarcoma patients treated by two combinations of methotrexate, cisplatin, doxorubicin and ifosfamide[J]. *Asia Pac J Clin Oncol*, 2011, 7(3): 270-275. [PMID: 21884438 DOI: 10.1111/j.1743-7563.2011.01406.x]
- [4] FDA. FDA Drug Safety Communication: New boxed warning for severe liver injury with arthritis drug Arava (leflunomide) [EB/OL]. (2010-07-13) [2010-08-20]. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandproviders/ucm218679.html>.
- [5] Van Roon EN, Jansen TL, Houtman NM, et al. Leflunomide for the treatment of rheumatoid arthritis in clinical practice: incidence and severity of hepatotoxicity[J]. *Drug Saf*, 2004, 27(5):345-52 [PMID: 15061688 DOI: 10.2165/00002018-200427050-00006]
- [6] Xiang N, Li XM, Zhang MJ, Zhao DB, Zhu P, Zuo XX, Yang M, Su Y, Li ZG, Chen Z, Li XP. Total glucosides of paeony can reduce the hepatotoxicity caused by Methotrexate and Leflunomide combination treatment of active rheumatoid arthritis. *Int. Immunopharm* 2015; 28(1):802-807 [PMID: 26292180 DOI: 10.1016/j.intimp.2015.08.008].
- [7] Zheng LY, Pan JQ, Lv JH. Effects of total glucosides of paeony on enhancing insulin sensitivity and antagonizing nonalcoholic fatty liver in rats. *Zhongguo Zhong Yao Za Zhi*. 2008; 33(20):2385 - 90 [PMID: 19157135]

Minor 1: This sentence means that dermatomyositis is excluded, and the expression of this sentence has been amended in the manuscript.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a simple case report of a patient which was diagnosed with Morbihan disease, a rare disease with only a few cases reported in the literature. The patient failed conventional therapy with prednisone and was then treated with an Eastern Chinese Medicine herbal extract "glucoside of paeonis" with good effect. Patient remained symptom free for one year without any side effects. I think its straight forward and considering the rarity of this disease and the frequent failure of therapy and/or the side effects of the only effective therapy with oral prednisone, the paper is worthwhile publishing.

ANSWER: We appreciate your positive comment very much.

Reviewer #5:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: I read with a great interest the article titled "Successful treatment of Morbihan disease with total glucosides of paeony : A case report" by Zhou et colleagues. I have some revisions to suggest. A. Convincing evidence is the most important in the case report. So, 1) high quality microphotos (including low-power and high-power views) should be added. 2) the results of TB-PCR, silver stain and/or PAS stain (to assess the granulomas) B. Many descriptions for the Morbihan disease were repeated in the DISCUSSION and CONCLUSION sections. It should be placed in the INTRODUCTION section. C. Descriptions for the total glucosides of paeony were repeated in the DISCUSSION and CONCLUSION sections. It should be placed in the INTRODUCTION section. Its possible action mechanisms in this Morbihan disease could be discussed in the DISCUSSION section with literature reviews.

ANSWER: We appreciate your positive comment very much. The language has been further polished carefully. In regard to question A.1) High quality photomicrographs (including low-power and high-power views) have been added as Figure 2A, 2B and 2C in the revised version of manuscript as required. A.2) Silver staining and PAS staining results have been supplemented as Figure 2F and 2G in the revised version of manuscript as requested. Due to the limitation of experimental conditions, TB-PCR experiment cannot currently be carried out in our hospital. Instead, acid-fast staining experiment results (See Figure 2E) are used to make up for the deficiency of experimental results without TB-PCR.

B. The repeated description of Morbihan disease in the discussion and conclusion has been deleted or adjusted in the revised version of manuscript as suggested.

C. The repeated description of total glucosides of paeony in the discussion and conclusion have been deleted or adjusted in the revised version of manuscript as required. The possible mechanism of total glucosides of paeony in Morbihan disease has been supplemented and discussed in the manuscript.

Reviewer #6:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: case report was designed very well. Current literature and case is very well summarized

ANSWER: We appreciate your positive comment very much. The language has been further polished carefully.