Dear Editor and Reviewers

Thank you very much for your kind consideration for publication of our manuscript, entitled "***Majocchi's Granuloma Caused by Trichophyton Rubrum After Facial Injection with Hyaluronic Acid: A Case Report***". On behalf of my co-authors, we would like to express our great appreciation to you and the reviewers.

The comments were all valuable and were very helpful for revising and improving our paper. According to the comments and suggestions of the reviewer and the editor, we have revised the manuscript and have responded, point by point, to the comments, as listed below. Revised portions are marked in light grey in the paper.

I would like to re-submit this revised manuscript to ***World Journal of Clinical Cases*** and hope that it is now acceptable for publication.

Looking forward to hearing from you!

With kindest regards,

Yours sincerely,

Corresponding author.

Replies to Reviewer and Editor

First, we thank both reviewer and the editor again for their careful review and valuable comments. The comments are all helpful for revising and improving our manuscript.

INSTRUCTIONS FOR SUBMITTING YOUR REVISION

* Editorial Office's comments:

(1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Answer: Many thanks for your careful review. We will upload the approved grant application forms copy of the approval documents to WJCC.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Answer: Many thanks for your careful review. According to the comments, we have provided the original figure documents using PowerPoint and we have made sure that all graphs, arrows, and text portions can be reprocessed by the editor. The original figure documents have been submitted together with our revised manuscript.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references.

Answer: Thank you for your careful review. We have added the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references according to the comments of the editor.

REVIEWER COMMENTS

*** Reviewer #1: Comments to the Author**

This is a very interesting case report with regard to Majocchi's Granuloma caused by *Trichophyton rubrum* after facial injection with Hyaluronic Acid. Nevertheless, several issues have been raised and modifications are required.

(1) The introduction section is too short. Epidemiological data with regard to relevant complications should be added.

Answer: Many thanks for your careful review and thank you for the suggestion. The HA fillers represent an alternative treatment option for the aging face, particularly for facial lines. HA fillers may cause early and immediate adverse reactions, such as needle marks or pinpoint bleeding, erythema or redness, swelling and edema, pain, tenderness, as well as and ecchymosis, which occur in 0.05% to 2% of the cases[1]. Delayed adverse reactions, including hypersensitivity and granulomatous reaction, are reported to occur in up to 0.6% of the cases[2]. Among the complications, the risk of infection is increased because of by improper disinfection of the patient's skin, unqualified incorrect injection techniques, decreased general immunity, and the presence of pathogens[3]. We have revised our manuscript and added the epidemiological information in the introduction of the manuscript. We revised this part from line 73 to 85 in the manuscript.

(2) Apart from histology did you perform any additional laboratory or imaging diagnostic modality?

Answer: Many thanks for your careful review and comments. Besides the most important histological examination (from line 115 to line 119) and mycology examination (from line 124 to line 138) in the manuscript. The patient also did regular tests: blood examinations and the results revealed leukocyte count of 4×10^9/L, hemoglobin level of 110 g/L, and platelet count of 170×10^9/L. There were no abnormal results in the renal and hepatic function tests. Tests for hepatitis B, hepatitis C, HIV, cytomegalovirus and Epstein-Barr virus were negative. We have added the results from line 112 to line 115 in this revised manuscript.

To date, the difficulty in the study of Majocchi's granuloma from an infection lies in the accurate diagnosis of the organism and the identification of susceptibility to antifungal testing *in vitro*, which are important to guide the effective treatment of Majocchi's granuloma disease caused by pathogens. Histological examination has revealed diffuse multinucleated giant cells as well as infiltration of lymphocytes and neutrophils into the dermis. The pathological findings of the skin biopsy included acanthosis and papilloma by HE staining (Figure 2A) and dermal granuloma and cytoplasmic branched septate hyphae by periodic acid-Schiff (PAS) staining (Figure 2B), which proven helpful to establish the diagnosis. However, in order to confirm the pathogens for deciding on the treatment, we did mycology examinations by doing morphology and molecular biological identification, which indicated that this Majocchi's granuloma was caused by *Trichophyton rubrum*.

(3) Treatment should be further discussed. In the discussion section, parallel evaluation with recent studies' evidence is totally missing. Diagnostic as well as therapeutic approach should be analyzed.

Ansewer: Thank you for the insightful suggestion. We also think that the parallel evaluation with recent studies' evidence might make sense to the discussion part. And it could also rich the article by analyzing the diagnostic as well as therapeutic approach. And we revised this part from line 175 to line 193 in the manuscript.

Systemic treatment of *Trichophyton rubrum* infection mainly includes allylamines, azoles, polyenes and hydroxypyridones. In general, terbinafine (250 mg/day), as a representative allylamine antifungal agent, is the preferred systemic antifungal drug for the treatment of MG and is used in 40.8% of cases. When the infectious agent cannot be isolated, terbinafine should be the first-choice treatment because organisms resistant to itraconazole or griseofulvin have been reported to be responsive to terbinafine. Wang et al presented two cases of MG with different clinical features. Both patients had satisfactory relief after treatment with terbinafine[4]. Su et al also successfully treated a case of *Trichophyton rubrum* infection characterized by Majocchi's granuloma and deeper dermatophytosis by giving the patient oral

terbinafine 250 mg/day, and the patient's skin lesion disappeared[5]. However, terbinafine-resistant strains have been found in cases of drug-resistant dermatophyte infection, including *Trichophyton rubrum* infection, in recent years[6-8]. Other systemic antifungal drugs to treat dermatophyte infections include itraconazole, griseofulvin, ketoconazole, voriconazole, and posaconazole[9-13]. Gupta et al found that two pulses of oral itraconazole therapy appeared to be effective in the treatment of Majocchi's granuloma[14]. In the case we reported here, the patient was unresponsive to terbinafine and was successfully treated with itraconazole, which should indicate the need for doctors to select treatment agents by performing *in vitro* antifungal susceptibility testing.

Because we identified that *Trichophyton rubrum* caused this serious Majocchi's granuloma, we treated the patient with terbinafine 250 mg/day for 2 months. However, the painful papules, nodules and abscesses on her face were still present. Then, we adjusted the treatment to itraconazole 400 mg/day for 8 weeks based on the *in vitro* antifungal susceptibility testing results.

(4) Newly published manuscripts should be included.

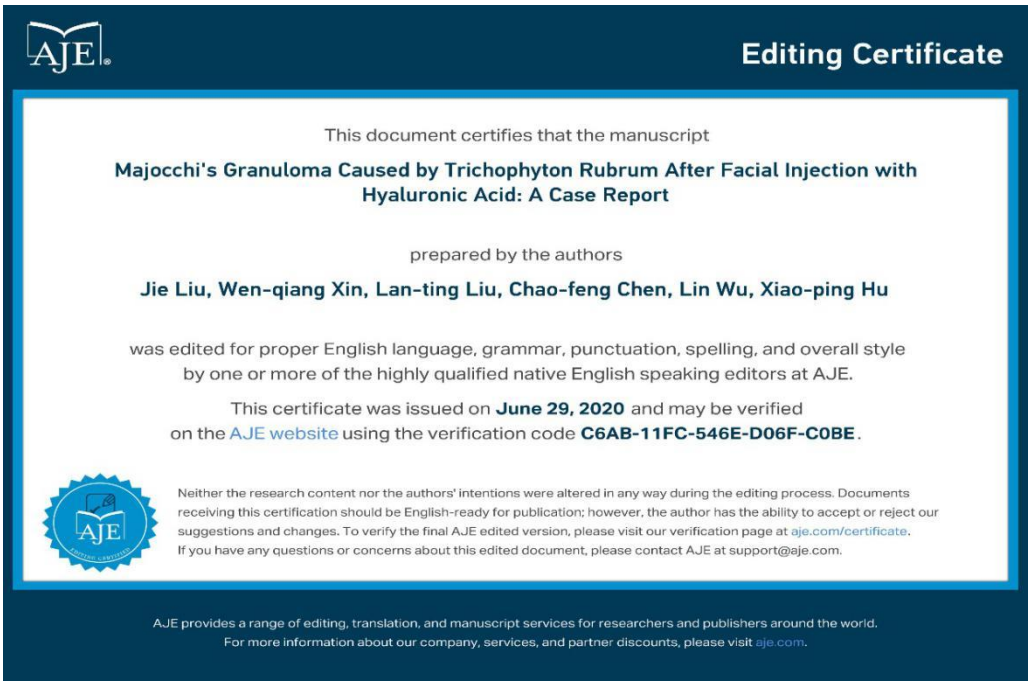
Response: Many thanks for your careful review and positive comments. Thanks for reminding again, we have added new published manuscripts including reference 2, 6, 9, 10, 11.

(5) Grammatical errors should be corrected throughout the Text.

Response: Thank you for the suggestion. We have asked a native English speaker to read through the manuscript, with linguistic errors corrected as well as a certificate of this language revision submitted together with our revised manuscript.

(6) Figures' quality is acceptable.

Response: Thank you for reviewing the manuscript and the positive comments.



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