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Dear Editors of *World Journal of Dermatology*,

We are grateful to the reviewers and editors for the constructive critiques of our manuscript entitled "local hyperthermia cleared multiple cutaneous warts on a nephrotic syndrome patient" submitted to *World Journal of Dermatology*. After carefully reviewing the comments, we revised our manuscript and answered the questions.

Thank you very much for your hard work on our manuscript. We believe that concerns have been adequately addressed, and sincerely hope that the reviewers and editors find our manuscript worthy of being published in this highly regarded journal.

Sincerely yours,

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Our responses to the critiques and concerns are provided below.

1. Response to reviewer 1 (reviewer code: 00646537)
  - Comment: Interesting article. The results look good, but you would need to add a bit on the limitation of any study related to viral warts, which is the natural tendency of wart to resolve spontaneously (although the immunosuppression in this case is an important factor).
  - Response: Thank you for your kindly instruction. I added the spontaneous regress tendency limitation to the discussion part of the case report as follows:  
Common warts have a tendency to regress spontaneously: 23% cases

within 2 months, 30% within 3 months and 65% to 78% within 2 years, however, warts are less likely to resolve in adults and in immunosuppressed patients [1]

2. Response to reviewer 2 (reviewer code: 00646561)

- Comment: Authors have present a novel case of multiple HPV warts treated with local hyperthermia. Figures are of interest. However, in the discussion authors should explain why the treatment in one local area (knee) has an impact over different no-near areas (nose) and provide a plausible hypothesis.

- Response: thank you for your kindly advice, and I raised some possible mechanisms that our team have been researching in the discussion part as follows:

In our previous studies, we found that above fever range hyperthermia could increase influx of Langerhans cells to draining lymph node and could induce the IFN-induced antiviral activity and apoptosis of keratinocytes. These phenomenon suggest hyperthermia may help to setup an immune specific response against HPV infected keratinocytes, which could explain a single target treatment clears other untreated lesions.

3. Response to reviewer 3 (reviewer code: 00646460)

- Comment: This is an interesting clinical report regarding the treatment of multiple viral warts with local hyperthermia therapy. The authors proposed that local hyperthermia could induce the IFN-induced antiviral activity and apoptosis of keratinocytes. Could the authors explain how local hyperthermia could induce resolution of warts at non-treated sites?

- Response: thanks for the kindly advice. In the final part of the case report, I put some possible mechanisms that we have been working on.

4. Response to reviewer 4 (reviewer code: 00646517)

- Comment: I suggest amend the last sentence of the discussion: Local hyperthermia could induce the IFN-induced antiviral activity and apoptosis of keratinocytes. This seems to me inconclude. What do you think, with a title "Local hyperthermia cleared multiple cutaneous warts"

- Response: thank you for your constructive comment. I adjusted the order of the conclusion part and make it more pertinent.

5. Response to reviewer 5 (reviewer code: 00646464)

- Comment: Interesting clinical report. Concerning to viral warts, it is mandatory to warn about the tendency of spontaneous resolution, despite prednisone intake of the patient. Furthermore, the explanation shall encompass not directly heated lesion.

- Response: thank you for the constructive critique. I added the spontaneous limitation of the common warts and raised some possible mechanisms that could explain the resolution of the non-treated lesions.

6. Response to reviewer 6 (reviewer code: 00646535)

- Comment: Interesting method and point of view from Chinese authors,

especially that one treated area induces benefic effects on multiple lesions. There are some other studies regarding this option for warts treatment. Every new information related to this subject is very valuable, as long as there is no perfect way to cure the warts, especially in immunosuppressed patients. Could be added the information from other studies such as: One stone, two birds: managing multiple common warts on hands and face by local hyperthermia. Hu L, Qi R, Hong Y, Huo W, Chen HD, Gao XH. *Dermatol Ther.* 2015 Jan-Feb;28(1):32-5. doi: 10.1111/dth.12178. Epub 2014 Oct 16 Successful clearance of facial common warts by local hyperthermia: report of two cases. Ma Y, Huo W, Hong YX, Chen HD, Gao XH. *Dermatol Ther.* 2012 Jul-Aug;25(4):386-8. doi: 10.1111/j.1529-8019.2012.01470.x.

- Response: thank you for the kindly comment.

- 1 **Sterling JC**, Handfield-Jones S, Hudson PM. Guidelines for the management of cutaneous warts. *Br J Dermatol* 2001; 144: 4-11 [PMID: 11167676 DOI: 10.1046/j.1365-2133.2001.04066.x]