

DERMATOLOGIC THERAPY

Volume 32, Number 4
July/August 2019



Official journal of the
World Health Academy




Editor-in-Chief
Torello Lotti, MD
Professor and Chairman
of Dermatology
University of Rome
"G. Marconi", Rome, Italy

Deputy Editor
Katlein França, MD, PhD
University of Miami
Miller School of Medicine
Miami, USA

WILEY

SPECIAL ISSUE ARTICLE

Local hyperthermia cleared multifarious viral warts in a patient with Cushing's syndrome

Ming-Han Mu | Yi-Ning Wang  | Yu Huang | Xue-Li Niu | Hong-Duo Chen |
Xing-Hua Gao  | Rui-Qun Qi

Department of dermatology, NHC/Ministry of Education/Liaoning Province Key Laboratory of Immunodermatology (China Medical University) The First Hospital of China Medical University, No. 155 Nanjing Bei Street, Heping District, Shenyang, Liaoning, P.R. China

Correspondence

Xing-Hua Gao and Rui-Qun Qi, Ministry of Education Key Laboratory of Immunodermatology (China Medical University), The First Hospital of China Medical University, No. 155 Nanjing Bei Street, Heping District, Shenyang, Liaoning 110001, P.R. China. Emails: gaobarry@hotmail.com; xiaoqiliumin@163.com

Funding information

National Natural Science Foundation of China, Grant/Award Numbers: 81673070, 81872538

Abstract

A female Cushing's syndrome patient had been suffering from extensive viral warts for months. She was diagnosed with flat warts, common warts and plantar warts. The plantar warts on her right foot were initially treated using local hyperthermia at 44°C for 30 min according to a defined protocol, followed by treatment targeting a common wart on her left thumb. In response to hyperthermia, the flat warts on her eyelid dissipated within 12 weeks, and when combined with a 1 week administration of imiquimod, the common warts and plantar warts completely disappeared within 8 weeks. There were no signs of recurrence and during this treatment her Cushing's syndrome was alleviated. This pioneer trial suggests that local hyperthermia may serve as an effective mean for treating multiple cutaneous warts under the conditions of a systemic immunocompromised disease.

KEYWORDS

Cushing's syndrome, human papilloma virus, hyperthermia, warts

1 | INTRODUCTION

Cutaneous viral warts are highly prevalent lesions resulting from the human papilloma virus (HPV). Currently, treatment of multiple warts remains a persistent challenge as conventional treatments, including ablative, keratolytic, or cytotoxic agents, may cause pain, blistering, burning sensations, local irritation, itching, bleeding, secondary infection, scar, or ulceration, as well as high recurrence rates (Lipke, 2006a, 2006b). We had previously conducted a series of preliminary studies treating warts with local hyperthermia and established that this approach was feasible, safe, and effective for cutaneous viral warts.

Notably, in a number of immune-compromised patients, warts have been successfully treated with use of local hyperthermia. In specific, extensive genital warts complicated with diabetes mellitus (Huo, Li, Qi, et al., 2013) or pregnancy (Huo et al., 2014), and common warts in a patient with systemic lupus erythematosus (SLE) (Ren, Huo, Qi, et al., 2015) were effectively treated with hyperthermia. Here, we report a case recently treated for recalcitrant and multifarious warts associated with Cushing's syndrome. Cushing's syndrome involves a

collection of signs and symptoms including high blood pressure, abdominal obesity, and weak bones due to prolonged exposure to cortisol (Broersen, Jha, Biermasz, Pereira, & Dekkers, 2018; Nieman & Ilias, 2005; Pivonello et al., 2016). The impairment of immune function associated with active Cushing's syndrome is responsible for the susceptibility to infections in these patients (Fareau & Vassilopoulos-Sellin, 2007; Pivonello, De Martino, De Leo, et al., 2007).

2 | CASE PRESENTATION

A 32-year-old female was referred to our outpatient clinic. She noticed some rough warty papules on her right foot, right eyelid and left thumb that had been present over the past 2 years. No other obvious symptoms associated with these warts were present. Based on their clinical appearance, they were diagnosed as plantar warts, flat warts and common warts. When treated at a Canadian hospital over the previous year she was advised to use a "corn plaster" but her condition deteriorated. Subsequent cryotherapy administered at approximately weekly intervals for 3 months also proved ineffective. Physical examination at our clinic revealed several fleshy, skin-colored or dark-

Ming-Han Mu and Yi-Ning Wang authors contributed equally to this work.

gray papules in the sole, toe, and heel of the right foot and one on the left thumb. There were also some small glossy papules on her right eyelid. The lesion size on her eyelid was approximately 0.1×0.1 cm on average (Figure 1a), while the other lesions ranged from approximately 0.4×0.5 cm to 3.0×1.0 cm (Figure 1b,c).

In this patient we used a patented hyperthermia device with a light source from a tungsten-halogen lamp (Patent No. ZL200720185403.3, China Medical University, China; Figure 2). A confluent plaque on her right toe was initially chosen as the target lesion, which occurred first (Figure 1b). The target lesion was subjected to local hyperthermia at 44°C , once a day for 3 consecutive days and another 2 days a week later, with each treatment lasting for 30 min. After the first 5 days' treatment the therapeutic regimen was adjusted to once a week. Upon 2-month follow-up, her upper eyelid lesions increased in size and showed an enhanced degree of redness. A month later the lesion on her left eyelid disappeared. The remaining lesions became more dehydrated and hyperpigmented, with no obvious decrease in size (Figure 1d-f). The target lesion was then changed to her left thumb (Figure 1f) and subjected to hyperthermia as described above. An administration of imiquimod once a day for 10 days was then applied simultaneously to her hand and foot. The lesion on her left thumb, as well as all other lesions, completely disappeared within a month

(Figure 1g-i). No obvious adverse sensations or effects occurred during the treatment. A timeline of the treatment protocol and recovery is presented in Figure 3.

During the treatment, the patient was hospitalized for unexplained obesity and diagnosed with hypercortisolism resulting from a left adenoma. A left adrenalectomy was performed and hydrocortisone at an initial dose of 600 mg was administered followed by a gradual maintenance dose of 20 mg/day. During this medication regimen, no changes were experienced in her lesions until the lesion on her left eyelid disappeared.

3 | DISCUSSION

It has been well established that immunosuppressed patients, such as in SLE, are more susceptible to HPV (Gao et al., 2009). In part, this immunosuppression is associated with taking high doses of corticosteroids (Ren et al., 2015). More endogenous glucocorticoids is excreted in Cushing patients, and a study demonstrated that their absolute lymphocyte count was significantly lower than that of controls (Tatsi et al., 2017). Glucocorticoids can regulate adaptive immunity through their capacity to inhibit lymphocyte activation and promote

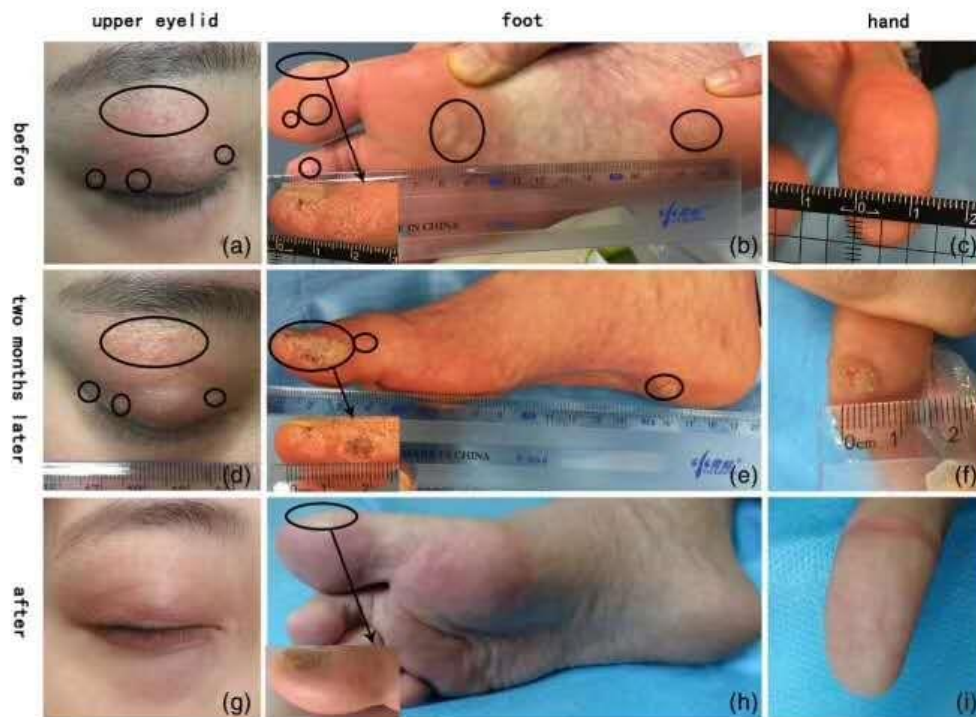


FIGURE 1 Extensive viral warts in a 32-year-old woman with Cushing's disease. Warty lesions before treatment (a-c). Two months after treatment (d-f), the lesions on her upper eyelid became larger and reddish, the remaining lesions became a little drier and hyperpigmented, then we changed the target lesion to her left thumb (f). Complete resolution of all the warty lesions after treatment (g-i)



FIGURE 2 Local hyperthermia device (on the left is the old device and on the right is the new version). The yellow light source of the treatment head provides heat, and the infrared point monitors the real-time temperature (the red number in the upper part of the display). The host will adjust the real-time temperature of the treatment target to the set temperature (yellow number in the lower part of the display), based on the temperature feedback of the infrared point. The new device can provide more precise treatment temperature, with a smart touch-screen console that sets temperature and treatment time for different patients and treatment sites.

lymphocyte apoptosis. At high concentrations, glucocorticoids also inhibit the production of B cells and T cells, and suppress signals that are mediated by pattern recognition receptors (PRRs) and cytokine receptors, thus the risk of infection might be increased (Cain & Cidowski, 2017). Physicochemical methods (such as cryotherapy, carbon dioxide laser) and cytotoxic drugs tend to cause secondary infection, as well as high recurrence rates in these immunosuppressed patients. In contrast to the effects resulting from these traditional methods, heat therapy has been shown to be effective, with tolerable degrees of burning sensations, few severe side effects and low recurrence rates (Li, Zhang, Hong, et al., 2012). Moreover, with this approach extensive cutaneous warts can be removed with the treatment of a single target lesion, thus reductions in multiple scarring and a more effective healing process can be achieved.

The present case indicates that hyperthermia offers a new option for the treatment of warts in Cushing patients when other therapies

fail or are not applicable. Moreover, this approach is typically effective in the treatment of non-targeted lesions. However, in clinical cases where responses fail to meet expectations, local hyperthermia may be combined local application of conventional therapies. Such conditions may be related to different types of HPV-stereotypes, which remain to be tested.

The exact mechanisms of wart clearance are still unclear. Hyperthermia may stimulate cytotoxic and/or apoptotic effects, which may then facilitate the elimination of HPV-infected tissue (Gerner, Cress, Stickney, Holmes, & Culver, 1980; Kampinga, 2006; Roti Roti, Wright, & VanderWaal, 1997).

There exist some limitations of this report which should be noted. The most salient being that this is not a controlled study and represents results from only a single subject. A randomized controlled trial will be required to validate the efficacy of local hyperthermia. Nonetheless, this study serves as an important foundation for the

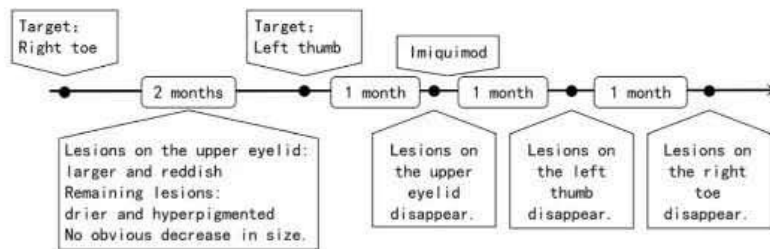


FIGURE 3 The timeline of treatment and recovery

development of a new method in treating multifarious warts of Cushing patients.

ACKNOWLEDGMENT

Written informed consent was obtained from the patient for submission and publication of this case report and accompanying images. Ming-Han Mu and Yi-Ning Wang contributed equally to this work.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING INFORMATION

This work was partly supported by National Natural Science Foundation of China (81673070).

ORCID

Yi-Ning Wang  <https://orcid.org/0000-0003-4116-3554>

Xing-Hua Gao  <https://orcid.org/0000-0001-8809-8564>

REFERENCES

- Broersen, L. H. A., Jha, M., Biermasz, N. R., Pereira, A. M., & Dekkers, O. M. (2018). Effectiveness of medical treatment for Cushing's syndrome: A systematic review and meta-analysis. *Pituitary*, 21(6), 631–641.
- Cain, D. W., & Cidlowski, J. A. (2017). Immune regulation by glucocorticoids. *Nature Reviews Immunology*, 17(4), 233–247.
- Fareau, G. G., & Vassilopoulou-Sellin, R. (2007). Hypercortisolemia and infection. *Infectious Disease Clinics of North America*, 21, 639–657.
- Gao, X. H., Gao, D., Sun, X. P., Huo, W., Hong, Y. X., Li, X. D., et al. (2009). Non-ablative controlled local hyperthermia for common warts. *Chinese Medical Journal*, 122, 2061–2063.
- Gemer, E. W., Cress, A. E., Stickney, D. G., Holmes, D. K., & Culver, P. S. (1980). Factors regulating membrane permeability alter thermal resistance. *Annals of the New York Academy of Sciences*, 335, 215–233.
- Huo, W., Di, Z. H., Xiao, B. H., Qi, R. Q., Weiland, M., & Gao, X. H. (2014). Clearance of genital warts in pregnant women by mild local hyperthermia: A pilot report. *Dermatologic Therapy*, 27, 109–112.
- Huo, W., Li, G. H., Qi, R. Q., Zhang, L., Yan, X. X., Chen, H. D., & Gao, X. H. (2013). Clinical and immunologic results of local hyperthermia at 44 degrees C for extensive genital warts in patients with diabetes mellitus[J]. *International Journal of Hyperthermia*, 29(1), 17–20.
- Kampinga, H. H. (2006). Cell biological effects of hyperthermia alone or combined with radiation or drugs: A short introduction to newcomers in the field. *International Journal of Hyperthermia*, 22, 191–196.
- Li, X., Zhang, C., Hong, Y., Zhang, D., Wei, H., Chen, H. D., & Gao, X. H. (2012). Local hyperthermia treatment of extensive viral warts in Darier disease: A case report and literature review. *International Journal of Hyperthermia*, 28(5), 451.
- Lipke, M. M. (2006a). An armamentarium of wart treatments. *Clinical Medicine & Research*, 4, 273–293.
- Lipke, M. M. (2006b). An armamentarium of wart treatments. *Clinical Medicine & Research*, 4, 273–293.
- Nieman, L. K., & Ilias, I. (2005). Evaluation and treatment of Cushing's syndrome. *The American Journal of Medicine*, 118(12), 1340–1346.
- Pivonello, R., De Martino, M. C., De Leo, M., Tauchmanová, L., Faggiano, A., Lombardi, G., & Colao, A. (2007). Cushing's syndrome: Aftermath of the cure. *Arquivos Brasileiros de Endocrinologia e Metabologia*, 51, 1381–1391.
- Pivonello, R., Isidori, A. M., De Martino, M. C., Newell-Price, J., Biller, B. M., & Colao, A. (2016). Complications of Cushing's syndrome: State of the art. *The Lancet Diabetes and Endocrinology*, 4(7), 611–629.
- Ren, Y., Huo, W., Qi, R. Q., Hu, L., & Gao, X. H. (2015). Intensive local thermotherapy cleared extensive viral warts in a patient with systemic lupus erythematosus. *International Journal of Hyperthermia*, 31(1), 5–7.
- Roti Roti, J. L., Wright, W. D., & VanderWaal, R. (1997). The nuclear matrix: A target for heat shock effects and a determinant for stress response. *Critical Reviews in Eukaryotic Gene Expression*, 7, 343–360.
- Tatsi, C., Boden, R., Sinai, N., Keil, M., Lyssikatos, C., Belyavskaya, E., ... Lodish, M. B. (2017). Decreased lymphocytes and increased risk for infection are common in endogenous pediatric Cushing syndrome. *Pediatric Research*, 83, 431–437. <https://doi.org/10.1038/pr.2017.278>

How to cite this article: Mu M-H, Wang Y-N, Huang Y, et al. Local hyperthermia cleared multifarious viral warts in a patient with Cushing's syndrome. *Dermatologic Therapy*. 2019:e12815. <https://doi.org/10.1111/dth.12815>