6. Ruocco E, Ruocco V, Lo Schiavo A, Brunetti G, Wolf R. Viruses and pemphigus: an intriguing never-ending story. Dermatology 2014;229:310-315.
7. Vassileva S, Drenovska K, Manuelyan K. Autoimmune blistering dermatoses as systemic diseases. Clin Dermatol 2014;32:364-375.
8. Stern JN, Keskin DB, Barteneva N, Zuniga J, Yunis EJ, Ahmed AR. Possible role of natural killer cells in pemphigus vulgaris-preliminary observations. Clin Exp Immunol 2008; 152:472-481.
9. Miracco C, Pietronudo F, Mourmouras V, Pellegrino M, Onorati M, Mastrogiulio MG, et al. Possible implication of local immune response in Darier's disease: an immunohistochemical characterization of lesional inflammatory infiltrate. Mediators Inflamm 2010;2010:350304.
10. Wehner R, Dietze K, Bachmann M, Schmitz M. The bidirectional crosstalk between human dendritic cells and natural killer cells. J Innate Immun 2011;3:258-263.

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Factors Determining Treatment Response to Cryotherapy for Foot Warts

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Dear Editor:

Different clinical and biologic factors, such as disease duration, infection site, and lesion size, are associated with the treatment response to cryotherapy of cutaneous warts[1-3]. However, published data on the predictive factors of cryotherapy in the treatment of cutaneous warts showed inconsistent results[3,4]. In addition, the majority of previous studies have not controlled for confounding variables[1-4], or have included warts located in different anatomical sites[1,2]. Thus, we aimed to investigate the factors affecting the treatment response to cryotherapy in foot warts using multivariable analysis.

We reviewed the medical records of patients having foot warts and who started cryotherapy at the SMG-SNU Boramae Medical Center from February 2016 through January 2018. All patients were followed until we confirmed that their warts completely disappeared, until they were lost to follow-up, or until February 2, 2018 (date of scheduled data extraction), whichever arrived earlier. Age, sex, disease duration, infection site (toe, sole, and periungual), number of lesions, the maximum diameter of lesions, and recurrent status (primary infection vs. re-infection) were obtained from the medical records of the initial visits. Treatment intervals, the number of cryotherapy sessions, and treatment outcomes (cleared vs. persistent) were obtained. A patient with clearance was considered a patient who no longer had visible warts and had sustained normal skin color and skin lines for at least 4 weeks after the last cryotherapy. A responder was defined as a patient having complete clearance of warts within after 6 cryotherapy sessions[5]. The study protocol was approved by the Institutional Review Board of the SMG-SNU Boramae Medical Center (approval number: 30-2017-30) and the requirement for informed consent was waived.

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Table 1. Demographic and clinical characteristics of patients

Variable	All patients (n=89)
Age (yr)	12.0 (9.0~24.0)
Sex	
Male	62 (69.7)
Female	27 (30.3)
Duration (mo)	6.5 (2.0~21.0)
Infection site	
Toe*	34 (38.2)
Sole	50 (56.2)
Periungual†	5 (5.6)
Lesion number	2.0 (1.0~3.0)
Lesion size	
<1 cm	63 (70.8)
≥1 cm	26 (29.2)
Recurrent status	
Primary infection	64 (71.9)
Re-infection	25 (28.1)
N of treatment	4.0 (2.0~9.0)
Treatment intervals	
≤3 weeks	49 (55.1)
>3 weeks	40 (44.9)

Values are presented as median (interquartile range) or number (%). *Whole part of toes including web spaces, except perionychium. †Wart involving the perionychium.

The liquid nitrogen was delivered by cryo-spray until a halo of frozen tissue appeared around the wart, and this was maintained for 10 seconds. Warts were treated with a triple freeze-thaw cycle, with complete thawing of the frozen tissue between the cycles. Before cryotherapy, warts were pared to remove the hyperkeratotic skin without bleeding.

Logistic regression analyses were used to evaluate associations between predictive factors and treatment response. Predictive factors showing univariable associations with treatment response ($p<0.20$) were included in a multivariable logistic regression model.

A total of 89 patients were identified who received cryotherapy for foot warts (Table 1). At the time of database extraction, patients had been followed for a median of 109 days (range, 10~630 days). A total of 47 patients (52.8%) achieved complete clearance within 6 cryotherapy sessions (responders). As shown in Table 2, the univariable logistic regression analysis revealed that male sex, longer disease duration, higher lesion number, larger size (≥1 cm), and longer treatment intervals (>3 weeks) were associated with lower treatment response (Table 2). The mean treatment intervals were 16.4 days in a shorter interval group (mean treatment interval ≤3 weeks) and 33.0 days in the longer interval group (mean treatment in-

Table 2. Univariable and multivariable analysis of treatment response to cryotherapy in foot warts (n=89)

Variable	Univariable analysis				Multivariable analysis	
	Response (n=47)*	Non-response (n=42)	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (yr)	11.0 (8.5~24.0)	16.5 (10.0~24.0)	0.962 (0.917~1.008)	0.107	1.018 (0.953~1.089)	0.592
Sex						
Female	19 (40.4)	8 (19.0)	Reference		Reference	
Male	28 (59.6)	34 (81.0)	0.347 (0.132~0.911)	0.032	0.494 (0.137~1.779)	0.281
Duration (mo)	5.0 (1.0~8.5)	12.0 (6.0~24.0)	0.963 (0.935~0.992)	0.013	0.980 (0.946~1.016)	0.271
Infection site						
Toe†	22 (46.8)	12 (28.6)	Reference		Reference	
Sole	23 (48.9)	27 (64.3)	0.465 (0.190~1.139)	0.094	0.530 (0.155~1.811)	0.311
Periungual‡	2 (4.3)	3 (7.1)	0.364 (0.053~2.487)	0.302	0.308 (0.027~3.556)	0.345
Lesion number	1.0 (1.0~2.0)	3.0 (2.0~6.0)	0.561 (0.400~0.788)	0.001	0.631 (0.451~0.883)	0.007
Lesion size						
<1 cm	41 (87.2)	22 (52.4)	Reference		Reference	
≥1 cm	6 (12.8)	20 (47.6)	0.161 (0.056~0.460)	0.001	0.570 (0.132~2.462)	0.452
Recurrent status						
Primary infection	33 (70.2)	31 (73.8)	Reference		-	
Re-infection	14 (29.8)	11 (26.2)	1.196 (0.472~3.029)	0.706	-	
Treatment intervals						
≤3 weeks	35 (74.5)	14 (33.3)	Reference		Reference	
>3 weeks	12 (25.5)	28 (66.7)	0.171 (0.069~0.429)	<0.001	0.161 (0.050~0.517)	0.002

Values are presented as median (interquartile range), OR (95% CI), or number (%). OR: odds ratio, CI: confidence interval. *Treatment response was defined as complete clearance of warts within 6 sessions. †Whole part of toes including web spaces, except perionychium. ‡Wart involving the perionychium.

terval >3 weeks). There were no significant differences in treatment response according to age, infection site, and recurrent status.

In the multivariable logistic regression analysis, two variables (lesion number, and treatment intervals) remained significantly associated with treatment response (Table 2). A higher number of lesions was significantly associated with lower treatment response (odds ratio [OR] per one lesion-increase, 0.631; 95% confidence interval [CI], 0.451~0.883; $p=0.007$). Additionally, the longer interval group showed lower treatment response compared with the shorter interval group (OR, 0.161; 95% CI, 0.050~0.517; $p=0.002$) (Table 2). However, age, sex, disease duration, infection site, and lesion size were no longer significantly associated with lower treatment response after adjusting for covariates.

We found that longer treatment intervals led to a poor clinical outcome. The associations between treatment intervals and clearance after cryotherapy remain unclear, with conflicting results from previous studies[4,6]. However, previous studies included both hand and foot warts and did not compare >3 week and ≤3 week intervals. Furthermore, the retrospective analysis did not use multivariable analyses to adjust for covariates[4]. We found that several variables were not significantly associated with the treatment response in the multivariable analysis despite significant associations in univariable analyses.

In this study, higher number of warts was associated with a lower clearance rate. Human papillomavirus infections are normally controlled by an intact cell-mediated and humoral immune system[7]. Therefore, patients with cell-mediated immunodeficiency are at increased risk of developing extensive, persistent, and recurrent warts[8]. Similarly, a higher number of warts might indicate lower immunity against warts.

We found that sex, disease duration, and lesion size were not associated with treatment response to cryotherapy. These findings are contrary to those of previous studies[2,3]. Ahmed et al.[2] found that warts that had been present for 6 months or less had a greater chance of clearing (84%) within 3 months than warts that had been present for more than 6 months (39%). Berth-Jones and Hutchinson[3] also reported that the disease duration and lesion size were significant predictors of response. This discrepancy could be partly explained by differences in the statistical methods used as previous studies did not adjust for confounding factors. We found disease duration and lesion size were associated with treatment response using univariable analyses, whereas these associations were no longer significant after adjusting for covariates.

Our study had several limitations. Similar to other retrospective chart review studies, there is a possibility that unmeasured confounding factors were present in our series. However, there were no missing data on independent variables in this study because we had started to document all the above-mentioned variables of patients with cutaneous warts at the initial visit as of February 2016, and we adjusted for covariates in our analysis contrary to previous studies[1-3,9,10]. In addition, we only included patients with foot warts in our cohort; therefore, our results may not be generalizable to all cutaneous warts.

Despite these limitations, our results suggested an effective treatment strategy for cryotherapy of foot warts. Clinicians could consider aggressive cryotherapy from the beginning of the treatment of foot warts if a patient has many lesions. In addition, if the treatment response to cryotherapy is unsatisfactory, clinicians could consider reducing the treatment interval to improve the treatment response.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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REFERENCES

1. Kim KJ, Song KH, Lee CJ. Cryotherpy of warts with liquid nitrogen. Korean J Dermatol 1993;31:495-501.
2. Ahmed I, Agarwal S, Ilchyshyn A, Charles-Holmes S, Berth-Jones J. Liquid nitrogen cryotherapy of common warts: cryospray vs. cotton wool bud. Br J Dermatol 2001;144:1006-1009.
3. Berth-Jones J, Hutchinson PE. Modern treatment of warts: cure rates at 3 and 6 months. Br J Dermatol 1992;127:262-265.
4. Youn SH, Kwon IH, Park EJ, Kim KH, Kim KJ. A two-week interval is better than a three-week interval for reducing the recurrence rate of hand-foot viral warts after cryotherapy: a retrospective review of 560 hand-foot viral warts patients. Ann Dermatol 2010;23:53-60.
5. Sterling JC, Gibbs S, Haque Hussain SS, Mohd Mustapa MF, Handfield-Jones SE. British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. Br J Dermatol 2014;171:696-712.
6. Bourke JF, Berth-Jones J, Hutchinson PE. Cryotherapy of

common viral warts at intervals of 1, 2 and 3 weeks. Br J Dermatol 1995;132:433-436.
7. Kienzler JL, Lemoine MT, Orth G, Jibard N, Blanc D, Laurent R, et al. Humoral and cell-mediated immunity to human papillomavirus type 1 (HPV-1) in human warts. Br J Dermatol 1983;108:665-672.
8. Sri JC, Dubina MI, Kao GF, Rady PL, Tyring SK, Gaspari AA. Generalized verrucosis: a review of the associated diseases, evaluation, and treatments. J Am Acad Dermatol 2012;66:292-311.
9. Bruggink SC, Gussekloo J, Berger MY, Zaaijer K, Assendelft WJ, de Waal MW, et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. CMAJ 2010;182:1624-1630.
10. Cockayne S, Hewitt C, Hicks K, Jayakody S, Kang'ombe AR, Stamuli E, et al. Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. BMJ 2011;342:d3271.

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Differences among Dermoscopic Findings in Riehl's Melanosis of the Cheek and Neck

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Dear Editor:

Riehl's melanosis is a pigmented dermatosis that presents as bilateral, symmetrical, grayish-purplish-brown reticulated hyperpigmentation on the face and neck[1]. The etiology of Riehl's melanosis remains largely unknown, but it is believed to be associated with contact dermatitis or photo-contact dermatitis caused by ingredients from certain cosmetics[2]. The diagnosis of Riehl's melanosis may be difficult because the diagnostic criteria have not been clearly established. Recently, dermoscopy has been widely used for the accurate diagnosis of pigmented skin lesions. Wang and Xu[3] explained that pseudonetwork and grey dots/granules were the most suggestive dermoscopic features of Riehl's melanosis on the face. However, the face and neck have different skin characteristics, and skin lesions of Riehl's melanosis can also be found on the lateral side of the neck in some patients.

In this retrospective study, we compared dermoscopic findings of the face and neck in patients with Riehl's melanosis seen at the Department of Dermatology of Kyung Hee Medical Center (Seoul, Korea) from June 2014 to April 2017. The Ethics Committee of Kyung Hee Medical Center approved the study (approval number: KHMC IRB 2019-06-021). All patients were previously diagnosed with Riehl's melanosis and we reviewed clinical charts and obtained baseline clinical images and dermoscopic images. We have included only those patients who had dermoscopic images of both the face and neck. Digital dermoscopic images of the lesions were obtained using a Dermlite DL3 with polarized light (3Gen Inc., San Juan Capistrano, CA, USA) (10-fold magnification) mounted on a Canon EOS 350D camera (Canon Corp., Tokyo, Japan).

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