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Assessment of Response to Intralesional Vitamin D in Treatment of Warts

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Abstract

The human papillomavirus (HPV) causes the common, transient cutaneous condition known as warts. It is infectious, disfiguring, and occasionally benignly koebnerizes. Immunotherapy, which stimulates the immune system, is the most frequent treatment for warts. Even though vitamin D impacts cell proliferation and differentiation, the vitamin D injections effect on wart therapy is unknown. Vitamin D increases the synthesis of antimicrobial peptides, including lymphopiotin and cathelecidin, by upregulating VDRs on immune cells and keratinocytes of the skin. A deficiency in vitamin D may increase the HPV infection incidence by raising the host's susceptibility to HPV penetration and decreasing its capacity to remove the virus.

Keywords : Warts; Treatment; Immunotherapyand Vitamin D.

1. Introduction

Cutaneous warts are benign epidermal tumors caused by human papillomaviruses (HPVs). It is associated with significant physical and psychological discomfort, thus warrants quick intervention**[1]**.Several conventional treatments are available with variable response. Topical and systemic immunotherapy has acquired a prominent place in the treatment of warts due to the fact that it is non-destructive, user-friendly, and yields promising outcomes **[2]**. Immunotherapy would augment the host response against the causative agent, resulting in resolution without any physical changes or scarring**[3]**.

Human papillomavirus (HPV)

HPVs are a group of dsDNA viruses that belong to the Papillomaviridae family. They form warts by infecting keratinocytes and inducing hyperplasia and hyperkeratosis **[1]**.

More than 200 HPV genotypes have been classified.They cause both genital and cutaneous warts **[4]**. Most HPV types trigger specific wart types and show a predilection for certain anatomical sites. Common warts, flat warts, and plantar warts are examples of extragenital cutaneous warts. HPV types 1, 2, 4, and 7 cause the majority of planter and common warts, whereas types 3, 10, 27, and 41 produce plane warts.**[5]**.

HPV infection has a critical role in common dermatologic and sexually transmitted diseases, as well as in some of the most frequent cancers worldwide **[6]**.

Epidemiology and course of infection

Human papillomavirus can be spread by direct skin-to-skin contact **[7]**. It has been demonstrated that having family members with cutaneous warts significantly increases the likelihood of obtaining warts. Other less important risk factors for the transmission of warts are swimming pools, floors of public showers, classrooms, and locker room environment **[8]**.

Immune response against HPV

The host's immunological response determines the development of an HPV infection. Within two years, 90 percent of the infection will be cleared by the host's immune system. Two years after the initial infection, the presence of the same kind of HPV DNA is described as persistence **[9]**.

Throughout its entire life cycle, HPV possesses exceptional immune evasion skills. Throughout the infection phase, neither viremia nor virus-induced cytolysis occur; hence, the immune system preserves its resistance to HPV. Moreover, the HPV replication strategy delays the creation of the most immunogenic proteins (L1 and L2), initiating their expression just prior to shedding **[10, 11]**.

The special role played by intact immune system in HPV infection can be seen in immunosuppressed patients or in individuals with primary immunodeficiency.HPV-caused warts are the most prevalent cutaneous condition among organ transplant patients**[12]**, with resolution of recalcitrant warts once their immune status has improved **[13].**

Clinical presentation and histology

Human papillomavirus-associated warts are subdivided on anatomical and morphological grounds into:

- Common wart (Verruca vulgaris)
- Plantar wart (Verruca plantaris), wart on the sole of the foot.

- Plane (Verruca plana) or flat wart
- Genital wart (Condylomaaccuminatum) **[14]**.

Common warts are characterized histologically by parakeratosis, acanthosis, papillomatosis, and big, inflated cells in the stratum spinosum. However, plane warts lack papillomatosis. Papillomaviruses can be discovered by immunohistochemical techniques in stratum granulosum and stratum corneum **[1]**.

Treatment Modalities For Warts
Generaltreatmentconsiderations

No therapy: Given the high probability of spontaneous remission of extragenital warts, a "wait and see" strategy may be appropriate in some cases, especially in youngsters **[1]**.

The objective of therapy should always be complete wart eradication without future scarring and as little pain as feasible **[15, 16]**.

Destructive methods

The goal of destructive treatments is to remove or destroy the wart, not the HP infection. Cryotherapy, curettage, surgical excision, and lasers are all physical means of tissue death. Alternatively, chemical treatments such as keratolytic agents (lactic or salicylic acid) and caustic agents may be utilized (silver nitrate or monochloroacetic acid) **[1]**.

In most situations, harmful treatments remove ill keratinocytes and surrounding cells without discrimination, resulting in a larger lesion **[17]**.

Immunotherapy

Immunotherapy is the use of drugs to stimulate or inhibit the immune system in order to treat certain diseases. Various immunotherapy treatments, such as topical and intralesional therapies, have been utilized to treat viral warts. Topical immunotherapies include squaric acid dibutylester, diphenylcyclopropenone, and imiquimod. Candida, MMR (mumps, measles, rubella), tuberculin purified protein derivative, and bacillus calmette-guerin vaccines are included in intralesional immunotherapy. It is envisaged that these therapies will stimulate the cellular immune system to increase HPV identification and clearance, with clearance rates varying by modality **[18]**.

Vitamin D in wart treatment

Long considered to influence the immune response, vitamin D and its active metabolite 1,25 dihydroxyvitamin D (1,25(OH)2D3). VDRs in dendritic cells (DCs), macrophages, and activated T and B lymphocytes; the ability of DCs, macrophages, and activated T and B lymphocytes to express CYP27B1, the enzyme that produces 1,25(OH)2D3; and the ability of 1,25(OH)2D3 to influence the function and proliferation of these cells have been reported previously **[19]**.

Immune function and Vitamin D Level

The majority of specialists concur that vitamin D deficiency occurs at levels less than 20 ng/mL (50 nmol/L); insufficiency, 21–29 ng/ml (50 to 75 nmol/L); the recommended level, more than 32 ng/mL (80 nmol/L); and the highest limit, 100 ng/mL (250 nmol/L)**[20]**.

In their pilot study, **Ojaimi et al. (2013)** recommended levels more than 40 ng/ml to maintain adequate innate immune effects, as significant reductions of proinflammatory cytokines and increased TLR expression upon stimulation were only observed in participants who reached these levels and were lost upon reduction of vitamin D levels back less than 100 nmol/L **[21]**.

The role of vitamin D with respect to adaptive immunity

Vitamin D reduces T-cell activation and proliferation, particularly T helper-1 cells, which generate IFN-gamma and contribute to macrophage activation **[22]**. In addition, it induces a T helper-2 response by regulating the release of other cytokines, causing T-cells to produce more IL-4, IL-5, and IL-10 **[22, 23]**.

Vitamin D Regulation of the Innate Immune System in the Epidermis

Epithelia are crucial for the activation of the innate immune response, the body's first line of defense against invading pathogens. These cells are the most prevalent known to express CYP27B1. The prototypical cell is the epidermal keratinocyte, which has been demonstrated to express CYP27B1 at a very high level. In addition, keratinocytes have the enzyme CYP27A1, which allows them to generate 1,25(OH)2D3 from endogenous vitamin D3 sources **[24]**.Cathelicidin and CD14 expression is also rapidly induced by 1,25(OH)2D3 in human epidermal keratinocytes **[25]**.

Keratinocytes treated with 1,25(OH)2D3 are significantly more efficient than untreated keratinocytes at killing Staphylococcus aureus. TLR2 is expressed when the epidermis is damaged; its co-receptors include CD14 and cathelicidin**[26]**. The absence of this in mice lacking the CYP27B1 enzyme. Unlike macrophages, topically given 1,25(OH)2D3 promotes TLR2 expression in keratinocytes, hence boosting the innate immune response via

a feed-forward loop. Moreover, damage increases the expression of 1,25(OH)2D3-generating enzyme CYP27B1 TNF-alpha and IFN-gamma have both been demonstrated to promote 1,25(OH)2D3 synthesis **[26]**.

Using siRNA technology, 1,25(OH)2D3's ability to induce the creation of cathelicidin and CD14 in human keratinocytes is considerably decreased**[25]**.

Vitamin D receptors (VDR)

VDR, along with steroid, thyroid hormone, and retinoid receptors, is a ligand-dependent transcription factor that belongs to the nuclear receptor superfamily **[23]**. The active form of vitamin D induces the formation of the antimicrobial peptide cathelicidin upon binding to VDR **[19]**. Prior investigations have demonstrated that stimulation of 1-alpha(OH)ase and VDR increases TLR activation **[27-29]**.

2. Conclusion

The intralesional injection of vitamin D is a safe and cost-effective therapy for several types of cutaneous warts.

Vitamin D ability to impact the proliferation and differentiation of epidermal cells as well as the creation of cytokines adds to its efficacy as a warts therapy. Numerous studies have shown that the overexpression of VDR in the skin promotes antimicrobial peptide production **[30]**.

References

[1] D.Abeck.Extragenital cutaneous warts - clinical presentation, diagnosis and treatment. J Dtsch Dermatol Ges.vol.**17**(6),pp. 613-634,2019.

[2] D.M.Thappa, and M.J. Chiramel. Evolving role of immunotherapy in the treatment of refractory warts. Indian Dermatol Online J.vol.**7**(5),pp. 364-370,2016.

[3] S.Sinha, V. Relhan, and V.K. Garg, Immunomodulators in warts: Unexplored or ineffective? Indian J Dermatol.vol. **60**(2),pp. p. 118-29,2015.

[4] G.K.Hogendoorn. Morphological characteristics and human papillomavirus genotype predict the treatment response in cutaneous warts. Br J Dermatol.vol.**178**(1),pp. 253-260,2018.

[5] E.M.de Villiers. Classification of papillomaviruses. Virology.vol.**324**(1),pp. 17-27,2004.

[6] P.Brianti, E. De Flammineis, and S.R. Mercuri, Review of HPV-related diseases and cancers. New Microbiol.vol.**40**(2),pp. 80-85,2017.

[7] S.Jablonska. Cutaneous warts. Clin Dermatol.vol.**15**(3),pp. 309-19,1997.

[8] S.C.Bruggink. Warts transmitted in families and schools: a prospective cohort. Pediatrics, 2013. **131**(5): p. 928-34.

[9] S.Shanmugasundaram, and J. You, Targeting Persistent Human Papillomavirus Infection. Viruses, vol. **9**(8),2017.

[10] J.Doorbar, et al., The biology and life-cycle of human papillomaviruses. Vaccine,vol.**30 Suppl 5**, pp. F55-70,2012.

[11] E.Deligeoroglou, et al., HPV infection: immunological aspects and their utility in future therapy. Infect Dis Obstet Gynecol,pp. 540850,2013.

[12] S.Piaserico, et al., Cutaneous viral infections in organ transplant patients. G Ital Dermatol Venereol, vol.**149**(4), pp. 409-15,2014.

[13] D.Maor, et al., Recalcitrant hyperkeratotic verrucae in a renal transplant recipient clearing with cessation of immunosuppression. JAAD Case Rep, vol.**4**(5), pp. 471-473, 2018.

[14] J.C.Sterling,et al., British Association of Dermatologists' guidelines for the management of cutaneous warts 2014. Br J Dermatol, vol.**171**(4): pp. 696-712, 2014.

[15] V.Meineke, et al., Verrucae vulgares in children: successful simulated X-ray treatment (a suggestion-based therapy). Dermatology, vol. **204**(4),pp. 287-9,2002.

[16] D.M.Ewin, Treatment of HPV with hypnosis--psychodynamic considerations of psychoneuroimmunology: a brief communication. Int J Clin Exp Hypn, vol. **59**(4),pp. 392-8,2011.

[17] C.Boull,. and D. Groth, Update: treatment of cutaneous viral warts in children. Pediatr Dermatol, vol.**28**(3), pp. 217-29,2011.

[18] K.R.Soenjoyo, et al., Treatment of cutaneous viral warts in children: A review. Dermatol Ther, vol. **33**(6): pp. e14034,2020.

[19] D.D.Bikle, D.Vitamin and immune function: understanding common pathways. Curr Osteoporos Rep,vol.**7**(2): pp. 58-63,2009.

[20] B.W.Hollis, , Assessment and interpretation of circulating 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in the clinical environment. Endocrinol Metab Clin North Am, pp.**39**(2), pp. 271-86, 2010.

[21] S.Ojaimi, , et al., Vitamin D deficiency impacts on expression of toll-like receptor-2 and cytokine profile: a pilot study. J Transl Med. vol. **11**: pp. 176.,2013.

[22] M.F.Holick, D.Vitamin: extraskeletal health. Endocrinol Metab Clin North Am. vol. **39**(2), pp. 381-400,2010.

[23] J.Reichrath, D.Vitamin and the skin: an ancient friend, revisited. Exp Dermatol, vol.**16**(7),pp. 618-25.2007.

[24] B.K.Lehmann, Querings, and J. Reichrath, Vitamin D and skin: new aspects for dermatology. Exp Dermatol, vol.**13 Suppl 4**,pp. 11-5.2004.

[25] J.Schauber, et al., Histone acetylation in keratinocytes enables control of the expression of cathelicidin and CD14 by 1,25-dihydroxyvitamin D3. J Invest Dermatol,vol.**128**(4), pp. 816-24,2008.

[26] J.Schauber, et al., Injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. J Clin Invest, vol.**117**(3),pp. 803-11,2007.

[27] N.M.Maalouf, The noncalciotropic actions of vitamin D: recent clinical developments. Curr Opin Nephrol Hypertens, vol. **17**(4): pp. 408-15,2008.

[28] J.S Adams, et al., Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J Immunol, vol.**182**(7),pp. 4289-95,2009.

[29] P.T.Liu,, et al., Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science, vol.**311**(5768),pp. 1770-3,2006.

[30] N.Elsayed Ghaly, et al., Efficacy and safety of intralesional injection of vitamin D(3) versus tuberculin PPD in the treatment of plantar warts: A comparative controlled study. J Cosmet Dermatol, vol.**20**(4): pp. 1231-1240.,2021.