



Management of condyloma acuminatum

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Condyloma acuminatum, raised lesions that develop on skin and mucous membranes after infection with certain-type human papillomavirus (HPV), such as type 6 and type 11, is a bothersome disease, especially of which occurs in the anogenital area (also called as anogenital warts).¹ This disease interferes the infected-individuals not only from the recognition of body image but also produces a significant impairment of sexual function and psychosocial distress. Although there are many traditional therapies available, including topical medications (trichloroacetic acid, podophyllotoxin 0.5% solution [Condyline, Takeda Pharmaceutical Company Ltd; Warticon solution, Stiefel Laboratories Ltd], imiquimod, or other immunomodulators), surgical treatment (cryotherapy, electrosurgery, carbon dioxide-CO₂ laser, and Er:YAG laser), surgical excision, and foreskin removal on the management of condyloma acuminatum,²⁻⁶ due to potential limitations of every therapy, no single therapy could achieve the complete cure status, and of the most importance, it is nearly impossible to prevent the recurrence furthermore, contributing to the exacerbation of the disease burden.² The recent vaccination has provided a highly effective prevention for HPV type 6 and type 11-related condyloma acuminatum,¹ but there is no doubt that many individuals, especially adolescents, have been suffering from this common sexually transmitted disease. We are glad to learn a therapy using the combination of photo-sensitizers and photodynamic therapy (PDT), such as 5-aminolevulinic acid-photodynamic therapy (ALA-PDT), in the management of condyloma acuminatum in this May issue of the *Journal of the Chinese Medical Association*, although the authors did not pay much attention to this therapy.⁷ In contrast, the authors focused on the immune response after therapy.⁷ In fact, this strategy is critical and worthy of discussion.

As shown above, the cause of condyloma acuminatum is HPV. Therefore, the clearance of virus might be one of the most key steps to cure the disease and avoid the recurrence. Although it is

well-known that the rapid progress in the development of direct-acting antivirals is a milestone in the management of various kinds of virus-related diseases and provides >95% of cure rates, such as hepatitis C virus in recent years, the much higher cost of treatment is not always affordable to patients.⁸ Therefore, restoration of the healthy environment, reactivation of immune system, or activation of the immune system of subjects is often considered as the most important step in the prevention and management of virus-related diseases.⁹⁻¹¹

All anti-foreigner, such as malignant cells, virus, parasites, bacteria, and others need the help of the host immune systems, and recently, an understanding of the process of immune check-point inhibition with blocking antibodies that target cytotoxic T-lymphocyte antigen-4 (CTLA-4) and the programmed cell death protein 1 (PD-1) pathway (PD-1/programmed death-ligand 1 [PD-L1]) opens the new vision in the management of these troublesome diseases.¹² The authors studied 24 patients with condyloma acuminatum treated before and after ALA-PDT and found that the expression of PD-1 and PD-L1 was markedly upregulated in the condyloma acuminatum lesions before ALA-PDT; however, it was dramatically downregulated after ALA-PDT, and in addition, M2-like macrophage amount was significantly higher in the condyloma acuminatum before ALA-PDT than that after ALA-PDT.⁷ All hinted that patients infected with condyloma acuminatum might have an immune-suppressed status, at least at the lesion site. The question is raised why the immune response will be changed after ALA-PDT for condyloma acuminatum.

To respond to this, the mechanism of PDT should be introduced. First, the success of PDT therapy requires at least three simultaneously presented components, including a nontoxic photosensitizer absorbing light and exciting along with electron transfer, which involves series of photochemical reactions and produces conversion of reactive singlet oxygen to highly reactive oxygen species (ROS), and PDT effect involves three main mechanism, such as cell death (such as tumor cells or virus-infected cells) via ROS-mediated apoptosis or necrosis, cell-associated vasculature damage, and an initiation of immune response against cells.¹³ PDT-induced apoptosis includes intrinsic/mitochondria-mediated apoptosis and extrinsic/death receptor-mediated apoptosis, and the former involves an increased permeability of mitochondrial inner membrane, an activation of mitochondrial apoptotic death and the latter involves tumor necrosis factor pathway.¹³ That is to say, PDT can directly destroy cells and results in cell death (condyloma acuminatum).

Second, PDT generates highly cytotoxic ROS and results in irreversible damages in endothelial cells and the vascular

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basement membranes, contributing to microvascular destruction, vessel occlusion, hemorrhage, and prevention of the blood vessel formation.¹⁴ Since angiogenesis is a critical step for cell or tissue survival, destruction of microvascular system might lead to cell death.

Third, PDT results in activation of both local and systemic inflammatory responses,¹³ because PDT-induced cell death generates a strong and acute inflammatory response locally, similar to the wound healing.¹⁵ To maintain homeostasis, the host should secrete proinflammatory mediators causing activation of complement and accumulation of various kinds of inflammatory cells and/or immune cells in the treated disease sites to attack diseased cells. In the current study, the authors only focused on the components of macrophages, and explored the expression of some macrophage-related mediators, such as interleukin-10, transforming growth factor beta, PD-1, and PD-L1.⁷ Although it is limited as shown by readers,¹⁶ it is welcome to see more studies to open our vision in the management of infectious skin diseases and malignant disease, which could be applied by PDT, since the combination of the photosensitizers and PDT is widely used in the dermatology field.

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