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LETTER TO THE EDITOR

WILEY

Plasmacytoid dendritic cell and type I interferons as possible explanation for clearance of longstanding warts during COVID-19 in a transplant patient, reply to Erkayman et al

Dear Editor,

We recently read with interest the article entitled "Clearance of longstanding treatment-resistant warts during COVID-19 in a transplant recipient" by Erkayman et al.[1] The authors report on a 49-year-old man, known to have had renal transplantation and maintained on immunosuppressive therapy, who had a longstanding resistant warts regressing during the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The authors speculated on possible mechanism leading to wart regression including the immunological response against SARS-CoV-2.[1] Here, we want to complement the authors by highlighting the potential critical role of plasmacytoid dendritic cells (pDCs) and their product, the type I interferons (IFN-Is), as an explanation of wart regression during SARS-CoV-2 Infection.

Being a specialized DC population with plasma cell morphology, pDCs express CD4, HLA-DR, blood-derived dendritic cell antigen-2, CD123, and Toll-like receptor (TLR)7 and TLR9 in endosomal compartments.[2-5] Upon activation via TLR7/TLR9 sensing of viral- or self-nucleic acids, pDCs produce massive quantities of IFN-Is, which mainly provide viral resistance by controlling viral replication in addition to linking the innate and adaptive immune responses by controlling the function of other immune cells. While normally absent from skin, pDCs contribute to the pathogenesis of multiple infectious (especially viral), inflammatory, and neoplastic diseases.[2,3] Actually, evidence has demonstrated that coronaviruses, including SARS-Cov-2, are linked to pDC's antiviral activity.[4,5] It is now established that SARS-CoV-2 is an efficient pDC stimulator leading to potent IFN induction, chiefly IFN-Is.[4] In addition to controlling SARS-CoV-2 infection in the mild/moderate cases of infection, activated pDCs and IFN-Is have been shown to be recruited to different tissues including the skin where they may contribute to skin manifestations of SARS-CoV-2 such as chilblain-like changes.[5]

Human papilloma virus (HPV) causes benign and malignant mucocutaneous skin lesions.[3] Though the epithelial-located HPV generally evades the host immune system though unclear mechanisms, HPV-related warts occasionally regress in association with acute local inflammation, a process also described with molluscum contagiosum virus (MCV).[3] Recently, we and others have shown that the regression of both types of virally induced skin lesions is mediated through a central role played by pDC recruitment and IFN-I production. Comparing inflamed to non-inflamed warts, we showed that pDCs were present consistently and abundantly in all inflamed warts and were in an active state (demonstrated indirectly by intense expression of MxA, a surrogate marker of IFN-I tissue expression) in most inflamed wart lesions.[3] This was comparable to pDC established role in other cutaneous viral infections such as MCV.[3] This pDC role against warts is further supported by the known effectiveness of intralesional IFN-alfa (endogenous counterpart produced by pDCs) and imiquimod (topical immunomodulator and potent pDC activator by TLR-7 agonism) in treating warts.[2,3]

In summary, SARS-CoV-2 infection probably led to systemic activation of pDCs (contrasting with imiquimod's local cutaneous activation) with secondary potent IFN I-mediated immune response resulting in wart regression. Further supporting this is that the temporary immune boost only lasted during the SARS-CoV-2 infection. Upon its resolution, warts regrew.[1]

KEYWORDS

interferon, plasmacytoid dendritic cell, SARS-CoV-2, warts

DISCLOSURE

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