Clinical, immunologic and genetic characterization of Colombian patients with cutaneous recalcitrant warts

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ABSTRACT

Inborn errors of innate and intrinsic immunity are monogenic diseases that result in predisposition to a whole spectrum of infectious diseases (for example, viruses). Cutaneous warts caused by Human Papillomavirus (HPV) infection has an incidence that range from ~10% in the general population. These lesions are relatively common and most warts regress spontaneously. However, in some individuals, these warts persist for > 2 years without response to conventional therapy (cryotherapy, salicylic acid or bleomycin), and they are called recalcitrant warts (RW). Host defense against HPV relies on intact and functioning cellular immunity including T cell, natural killer cell cytotoxicity and intrinsic immunity. Therefore, in patients in whom warts are recalcitrant, concern for immune defects is raised.

RW have been documented in patients with a few inborn errors of immunity, either in combination with broad infectious phenotypes (combined immunodeficiencies), and HIV+ and transplanted patients. On the another hand, is well documented that patients with Epidermodysplasia Verruciformis present a specific genetic predisposition to beta-HPV infection, but only very few is known about genetic susceptibility to recalcitrant warts and to our knowledge there is not studies searching for monogenic defects associated with RW. Therefore, we hypothesized that susceptibility to RW due to HPV viruses in otherwise healthy individuals, might be due to underlying genetic defects in intrinsic and innate immunity.

Aim: To identify the clinical characteristics and characterize the immunological and genetic defects responsible for susceptibility to cutaneous recalcitrant warts (RW) of Colombian patients with cutaneous recalcitrant warts.

Methodology: All patients included are HIV negative and present recalcitrant warts (RW). We reviewed medical records, including history of HPV infection, pharmacological treatments, and genetic defects. We also draw a pedigree, obtain blood samples, perform immunophenotyping and Whole Exome Sequencing (WES) in patients and relatives using in silico tools for predict the possible impact of the variants on the patients in terms of conservation, selective pressure in the affected gene, variants allelic frequency, impact in the mature protein and previously association with HPV activity. According to genetic findings (gene candidates and affected pathways), we perform functional assays to investigate the correspondence between genotype and phenotype. The patient's immunological characterization will be done through peripheral blood count, measurement of subpopulations of T, B and NK lymphocytes and monocytes and functional test on peripheral blood mononuclear cells.

Preliminary results: Up to date, we have collected 9 patients ages 9 to 15 years old (3 males and 6 females) belonging to 9 families that fulfilled the inclusion criteria. Five patients have a family history of cervix HPV infections and others. We draw the pedigrees and perform WES in 4 patients, and we are performing the analyzes. In addition, phenotyping of peripheral blood leucocytes subpopulations has revealed normal percentage and numbers of T cells, B cells, NK cells and monocytes in one patient.

Expected results: Our study will allow us to understand the clinical and immunological characteristics of patients with recalcitrant cutaneous warts and to dissect the genetic bases of the disease.

Conclusions: Our findings have partially allowed the identification and characterization of patients with RW. We will continue performing exome sequencing analysis

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with the objective of associating the clinical phenotype of patients with their genotype. This will permit in the future to determine a possible genetic origin of this disease.

Key words: *Verruga, Verruca, Verrucae, Warts, Resistant, Recalcitrant, WES, HPV.*

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