Plantar warts in twins after successful bone marrow transplantation for severe combined immunodeficiency

Plantarwarzen bei eineiigen Zwillingsschwestern nach erfolgreicher Knochenmarktransplantation wegen schwerer kombinierter Immundefizienz

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Summary
Nine-year-old twin sisters presented with long-standing severe plantar warts following bone marrow transplantation for severe combined immunodeficiency (SCID). Combination therapy with keratolysis, cidofovir and water-filtered infrared coagulation (WIRA) led to complete clearance after 8 months of therapy. This dermatologic problem and the treatment of SCID including gene therapy are discussed.

Keywords
HPV – Plantar warts – Severe combined immunodeficiency

Zusammenfassung
Wir berichten über 9-jährige Zwillingsschwestern, bei denen hartnäckige Plantarwarzen nach erfolgreicher Knochenmarktransplantation wegen schwerer kombinierter Immundefizienz aufgetreten waren. Kombinationstherapien mit Keratolyse, Cidofovir und wasser-gefilterter Infrarot-Koagulation (WIRA) führten nach 8 Monaten zu einer kompletten Heilung. Dieser Bericht und die aktuellen Behandlungsoptionen des SCID-Syndroms inklusive der Gentherapie werden diskutiert.

Schlüsselwörter
HPV – Schwere kombinierte Immundefizienz – Warzen

Introduction
Cutaneous warts cause significant morbidity and are frequently observed in immunosuppressed individuals [1]. Current treatments include cryotherapy, curettage, electrocautery, laser, surgery, topical virucidal agents (podophyllin, cidofovir, lactalbumin-oleic acid), antimitotic drugs (5-fluorouracil, bleomycin) and immunostimulants (interferon-α and imiquimod) [2–8]. We describe the case of 9-year-old twin sisters who presented with severe plantar warts following bone marrow transplantation for severe combined immunodeficiency.

Case Report
The 9-year-old twin sisters had a 5-year history of plantar warts causing significant pain upon walking. They have been treated with repeated surgical procedures and topical virucidal agents without success. Their past medical history was remarkable for severe combined immune deficiency (SCID) syndrome caused by JAK-3 deficiency diagnosed soon after birth [9, 10]. Immunological investigations revealed a T-cell deficiency, absent NK cells, and low numbers of B-cells (T-B+NK-phenotype). The girls received allogeneic stem cell transplantation at the age of 1 year; the donor was the mother providing mobilized peripheral blood stem cells (PBSC) for twin #1 and bone marrow for twin #2. Once the children had obtained normal blood counts in the post-transplant period, the lymphocyte subpopulations were within the normal age-adjusted range, except for decreased numbers of mature B-cells [10]. Therefore, intravenous immunoglobulin (IVIG) substitution was administered every four weeks. An attempt to discontinue IVIG failed with re-occurrence of infections (pneumonia, and pyoderma) in both twins.

Physical examination revealed multiple, extensive, confluent warts with an exophytic and endophytic growth pattern and black dots (thrombosed blood vessels) on the soles and toes (Figure 1 and 2). Biopsies for papillomavirus typing were not taken.

A multi-step treatment approach was initiated. Initially, salicylic acid tape was used to cover the affected areas for three days with subsequent curettage of the debris following topical lidocaine-prilocaine anesthesia (Figure 2a, b). After removal of the debris, topical imiquimod 5 % cream was applied for three consecutive nights per week for 4 months without success. At week 16, the patients received cidofovir gel, a broad virustatic drug, applied to the warty areas five days a week for 4 weeks that led to a partial regression. At this point irradiation with infrared light (50–100 J/cm^2) was performed twice weekly for 5 weeks. With repetitive application of salicylic acid tape and surgical removal in combination with cidofovir gel and water-filtered infrared-A radiation (WIRA), the recalcitrant warts resolved after 8 months of therapy (Figure 1b, 2c). No adverse events were reported. One year following completion of therapy, no recurrence has been observed.

Discussion
The viral pathogenesis of warts was first suspected by *G. Ciuffo* in 1907 [11],

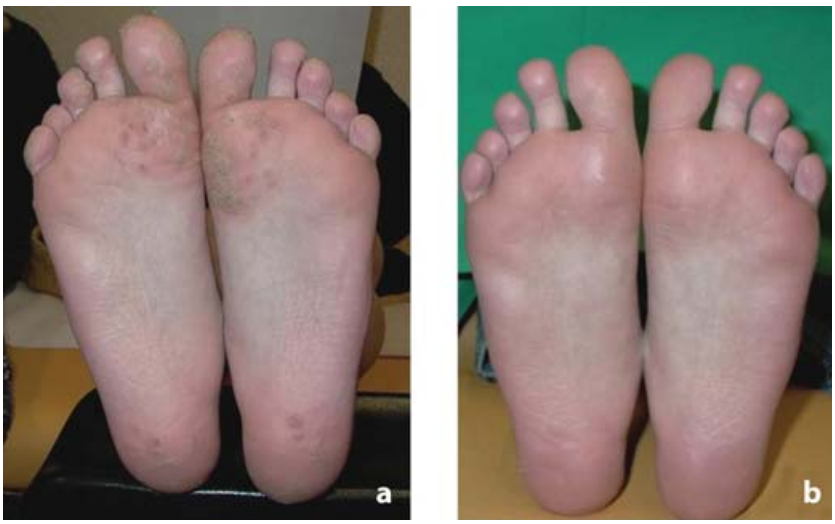

Figure 1: (a) Multiple confluent ingrowing warts and black dots (thrombosed blood vessels) are present on the toes, metatarsal pads and heels. Note that the affected areas are usually exposed to the body weight explaining the endophytic growth pattern. (b) After 8 months the soles are free of warts.
Abbildung 1: (a) Multiple konfluierende Plantarwarzen und „black dots" (thrombosierte Blutgefäße) an den Zehen, dem Fußballen und der Ferse. Man beachte, dass die Läsionen an den durch das Körpergewicht belasteten Stellen vorhanden sind, was das endophytische Wachstumsmuster erklärt. (b) Nach 8 Monaten waren die Fußsohlen warzenfrei.

while human papillomavirus (HPV) has since been identified as their cause [3]. Papillomaviruses are small DNA viruses that spread by direct or indirect contact (microtrauma). Plantar warts are frequently caused by HPV types-1 and –2 that are commonly acquired from swimming pools or shower-room floors where a rough surface causes abrasion of the epithelial barrier to permit HPV infection of keratinocytes [1]. Their endophytic growth is caused by pressure inflicted by the body weight. Warts have a variable clinical morphology with plantar warts presenting as large hyperkeratotic plaques or deep mosaic proliferations (myrmecia) [12]. The diagnosis of warts is usually based on clinical examination but can be confirmed by histology [3].

The prevalence of HPV infection in patients with immunodeficiency is as high as 40–60 %. Whereas 65 % of warts in children resolve spontaneously within 2–3 years, warts in the immunosuppressed population tend to be clinically atypical, extensive and persistent. Immunocompromised individuals are unable to mount adequate T-helper 1 (Th1) cell-mediated immune (CMI) response and are therefore highly susceptible to HPV infection. In our patients the warts first appeared three years after successful HLA-identical hematopoietic stem cell transplantation (HSCT), ie. at a time when immunological recovery had taken place.

SCID (X-linked severe combined immunodeficiency) is a lethal condition caused by mutations in the gene encoding the common γ (γc) chain. The γc-chain is an essential component of most interleukin (IL-)receptors (e.g. IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21). In particular the IL-7- and IL-15-receptors are necessary for the development of T-cells and natural killer cells [13]. Without the γc-chain, there is a complete absence of mature T- and natural killer cells, whereas B cells are usually present in normal or increased numbers. SCID predisposes patients to life-threatening infections and is usually fatal during the first year of life unless transplantation of hematopoietic stem cells restores T-cell function [14]. HLA-identical HSCT confers a 90 % chance of disease-free survival over the first 10–20 years of life. In contrast, haploidentical HSCT is associated with an overall 75 % survival rate at 5 years and a significant risk of graft-versus-host disease (GVHD) [15].

Possible therapeutic alternatives based on gene transfer of the γc gene into autologous hematopoietic precursor cells (retroviral vectors) have recently been developed. In the clinical study of Fischer et al. treatment of infants with lethal SCID by HSCT has demonstrated a rapid correction of immunodeficiency with a normal phenotype (naive/memory) and intact function of T cells and a normal percentage of „recent thymic emigrants" [16]. However, the two youngest patients transplanted with genetically corrected cells developed a leukemia-like lymphocytic proliferation 2–3 years after transplantation [17]. An oligoclonal lymphopoiesis was detected with 50–100 integration events in the patients' T cells. Interestingly, in both affected patients an integration in the LMO-2- and Evi-1-gene has occurred [18]. These genes are important protooncogenes, which are supposed to have caused the lymphocytic proliferation in cooperation with the transgene (γc-chain) and the LTR enhancer. Interestingly, overexpression of the γc-chain and alteration of the JAK-STAT-pathway have not been demonstrated in these children. This serious adverse event has prompted the initiation of numerous safety investigations of insertional mutagenesis to evaluate the effects of dose, vectors, and random insertion in order to devise ways to safely transfer genes in future human trials. One such strategy is the creation of self-inactivating vectors [19, 20].

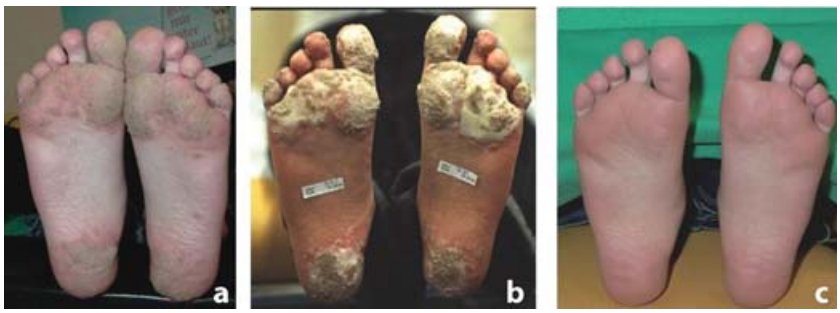

Figure 2: (a) More extensive sheets of warts (myrmecia) on the weight-bearing areas of the feet. (b) Demarcated debris following three days of salicylic acid tape 40 %. (c) At the end of therapy, no warts were present.
Abbildung 2: (a) Ausgeprägtere Warzenbeete (Myrmezien) an den gewichttragenden Stellen der Füße. (b) Abgestorbenes Gewebe nach dreitägiger Behandlung mit 40 % Salicylsäurepflaster. (c) Am Ende der Therapie waren keine Warzen mehr vorhanden.

Recently, the proliferation of non-malignant hematopoietic cells has been demonstrated in mice following insertional mutagenesis [21]. However, the insertion into the LMO-2 locus has only been found in 1 of 1300 analyzed integration sites. In 157 publications representing 5436 mice, 6 publications reported the development of malignant tumors (in two cases leukemias) following the transfer of active genes such as CD40L, TPO, Δ4Notch-Ligand, FLT3-Ligand, MDR-1 and ΔLNGFR. Two months after the transplantation of ΔLNGFR-transduced stem cells, the recipient mice developed an acute myeloid leukemia [22]. In 5 additional studies the γc-chain was retrovirally transferred into 55 X-SCID-mice. After 7–47 months of follow-up, no adverse events have been reported. Likewise in others studies involving 46 macaques, 21 baboons and 12 dogs, no adverse events were reported within 3 years of follow-up. Unlike the babies, the mice had stem-cell transplantation in the adult age and received total body radiation. These studies convincingly showed that one integration is not enough for the development of an acute leukemia; other cofactors must be considered for example the interference in signaling through the expression of truncated cell receptors (ΔLNGFR) [23]. In addition, the high multiplicity of infection, the young age as well as the strong selective pressure of engrafted hematopoietic cells may predispose for leukemia.

Severe chronic HPV disease including epidermodyslasia verruciformis has emerged several years after successful HSCT in some patients with SCID syndrome [24]. Often refractory to standard treatments, a variety of therapeutic attempts has been made to treat warts in the immunosuppressed. Treatment should be performed in a stepwise algorithm which takes into consideration clinical guidelines, efficacy, patient acceptance and costs. Effective treatments include topical keratolytic agents such as salicylic acid or cytotoxic drugs (e.g. 5-fluorouracil, intralesional bleomycin and nitric acid) [25]. According to a recent meta-analysis in the *Journal*, the combination of 5-fluorouracil and salicylic acid seems effective and cost-efficient [26].

Recently, one double-blind study reported the effectiveness of topical alpha-lactalbumin-oleic acid [27], although this drug is currently not available. Recent progress has been achieved using immune response modifiers such as topical imiquimod that acts through stimulation of the innate and adaptive immune system by Toll-like receptors [2, 4]. The H2-blocker cimetidine has also been reported to have immunomodulatory properties and was reported to be effective in an open-label trial [28]. Ablation by CO_2-laser [8] or pulsed-dye laser therapy [7], cryotherapy [3] and surgery have been commonly used. Photodynamic therapy [6] and water-filtered infrared coagulation (WIRA) [29] represent recent developments in the therapy of complicated warts that seem to act by thermic coagulation and potentially increased antigen presentation. Larger studies are needed to document the role of these treatments in the care for patients with warts. Cidofovir is a broad virustatic drug that has been successfully used as a 1.5 % gel containing methylparaben, propylparaben, hydroxy cellulose and propylene glycol to treat recurrent condyloma [30]. However, particular attention should be paid to renal function, since one bone marrow transplant patient with chronic renal insufficiency developed acute renal failure upon treatment of condyloma with topical cidofovir [31]. In addition to these limitations, the costs for therapy are very high and treatment should therefore be reserved for recalcitrant cases.

We report the successful combination treatment (keratolysis, cidofovir and WIRA) of recalcitrant plantar warts in identical twins with the SCID syndrome that occurred following immunological reconstitution. <<<

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