Case Report

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Abstract: Epidermodysplasia verruciformis (EV) is a rare genodermatosis caused by β-human papillomaviruses (HPV) in immunodeficient patients. EV is characterized by flat warts and pityriasis-like lesions and might be isolated or syndromic, associated with some other infectious manifestations. We report here three patients from 2 independent families with syndromic EV for 2 of them. By whole exome sequencing, we found that patients carry new homozygous variants in *STK4*, both leading to a premature stop codon. STK4 deficiency causes a combined immunodeficiency characterized by a broad infectious susceptibility to bacteria, viruses and fungi. Auto-immune manifestations were also reported. Deep immunophenotyping revealed multiple cytopenia in the three affected patients, in particular deep $CD4^+$ T cells deficiency. We report here the fourth and the fifth cases of syndromic EV due to STK4 deficiency.

Keywords: Epidermodysplasia verruciformis; human papillomavirus; STK4 deficiency; CD4+ T cells

1. Introduction

Epidermodysplasia verruciformis (EV) is a genodermatosis characterized by ppityriasis versicolor and flat wart-like lesions. EV is a rare disease, with around 500 cases reported so far, and is the consequence of β-papillomavirus (β-HPV) infection [1, 2]. Patients with EV, after decades, have a high risk of developing actinic keratosis and non-melanoma skin cancer (NMSC), particularly cutaneous squamous cell carcinoma (cSCC), cSCC *in situ* (Bowen's disease) and, to a lesser extent basal cell carcinoma (BCC). NMSC typically occurs in lesions exposed to the sun [3]. EV can be isolated or syndromic, including additional clinical features, mainly infectious [3]. Since the forties,

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it has been hypothesized that EV might also be a genetic disease [4]. In 2002, *EVER1* and *EVER2* have been identified as the two first genes underlying isolated EV [5]. More recently, CIB1 deficiency was reported in patients with isolated EV and as a new partner of EVER1 and EVER2 [6]. EVER1, EVER2 and CIB1 deficiencies are believed to result in a keratinocyte intrinsic deficiency, underlying exquisite susceptibility to β-HPVs [6]. In contrast, syndromic EV have been associated with T cell deficiencies, sharing $CD4^+$ T cell lymphopenia [7,8]. These etiologies of atypical EV include loss-of-function (LOF) mutations of *RHOH* [9], *STK4* [10,11,12], *CORO1A* [13], FLT3LG [14], TRAC [15], *DCLRE1C (encoding the Artemis protein)* [16], *DOCK8* [17,18], *RASGRP1* [19], *LCK* [20], *TPP2* [21] and *ITK* [22]. Here we report 2 novel cases of STK4 deficiency associated with atypical EV.

2. Clinical Reports

2.1. Clinical Phenotypes and Genotypes

2.1.1. Family 1

From birth to 10 years old, the proband (P1) clinical history was unremarkable. He received all childhood vaccines (BCG, MMR, diphteria, tetanus, poliovirus, and HBV) without any complications. However, at the age of 10, he presented recurrent apyretic diarrhea episodes, with no pathogen identified. At the age of 12 years old, P1 growth curve presented a negative deviation from the norm. He had no cardiac clinical symptoms and no electrocardiogram or echocardiographic abnormalities.

P1 was also admitted to pediatrics consultation for generalized flat warts and pityriasis versicolor-like skin lesions, that progressed from the age of 6 years old (Figure 1A). The lesions were initially localized on the face and then generalized to the neck, trunk, arms and the back.

The histology analysis showed hyperkeratosis and parakeratosis, mild acanthosis, and the presence of koïlocytes, keratinocytes with pale-stained cytoplasm in the upper epidermis associated with high levels of intranuclear viral replication (Figure 1B). All together these observations suggested a diagnosis of epidermodysplasia verruciformis. The genotyping of HPV by PCR confirmed the diagnosis, with the identification of HPV5 in a punch biopsy of a lesion from his right arm.

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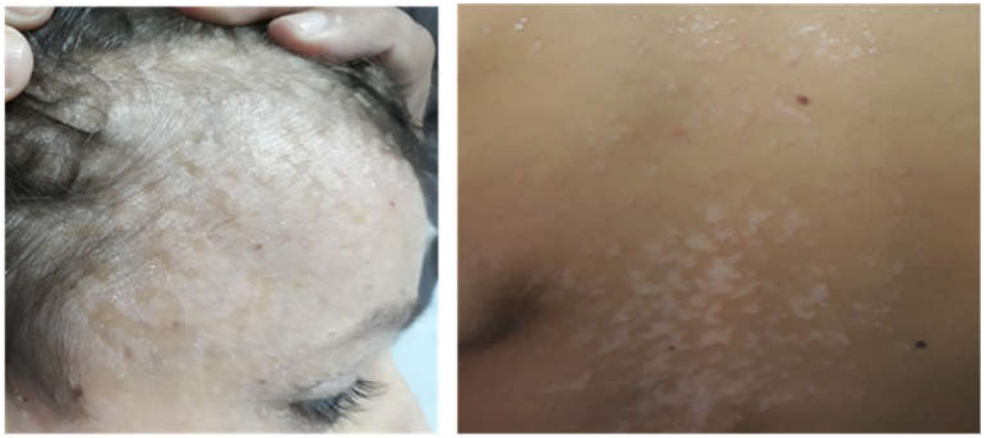

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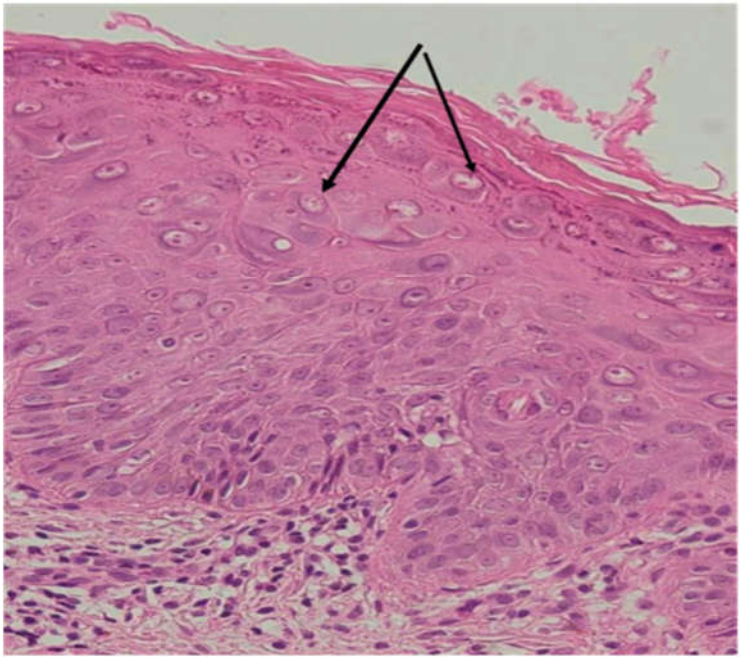

Figure 1. A. Pictures of the lesions on the face and the back of P1. B. Histological study of Punch skin biopsy showed hyperkeratosis and parakeratosis, mild acanthosis, and the presence of koilocytes, keratinocytes with pale-stained cytoplasm in the upper epidermis associated with high levels of intranuclear viral replication. The cytoplasm of the affected cells stains pale blue which is pathognomonic of epidermodysplasia verruciformis lesions without any sign of malignancy (Arrows).

His 16 years old sister (P2) did not develop EV, or any HPV-related skin disease but she presented recurrent low respiratory tract infections since the age of 3 years old with no pathogen identified. She also received all childhood vaccines (BCG, MMR, diphteria, tetanus, poliovirus, and HBV) without any complication and her growth curve presented a deviation from the norm too.

No secondary immunodeficiency was noted in both sibling and no auto-immune manifestation was reported so far. In term of treatment, both siblings have been treated with intravenous immunoglobulins substitution, and antibiotic prophylaxis against opportunistic infections (Trimethoprim/Sulfamethoxazole). In addition, P1 had a treatment with imiquimod application on the skin and skin protection from UV radiation and the skin lesions improved.

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2.1.2. Family 2

An 8 years old girl (P3) from consanguineous marriage parents, presented in pediatric consultation for profuse pityriasis versicolor-like skin lesions the upper and lower limbs, in the trunk and at the face (Figure 2A). These lesions have been evolving since the age of 3 years old. Skin histology of a lesion was typical of EV lesions (Figure 2B).

By PCR on a lesion from the right forearm of the patient, we identified HPV8 confirming the EV diagnosis. She had also recurrent respiratory infections and diarrhea, with stature weight repercussion, from the age of 3 years old. She didn't have secondary immunodeficiency (HIV, diabetes, immune suppressor treatment) or any familial history of primary immunodeficiency or similar lesions. She received all childhood vaccines (BCG, MMR, diphteria, tetanus, poliovirus, and HBV) without any complications. She had no cardiac clinical symptoms and no electrocardiogram or echocardiographic abnormalities. No auto-immune symptom was reported so far.

In term of treatment, she has been treated with intravenous immunoglobulins substitution, and antibiotic prophylaxis against opportunistic infections (Trimethoprim/Sulfamethoxazole). In addition, P3 had a treatment with imiquimod application on the skin and skin protection from UV radiation and the clinical conditions improved.

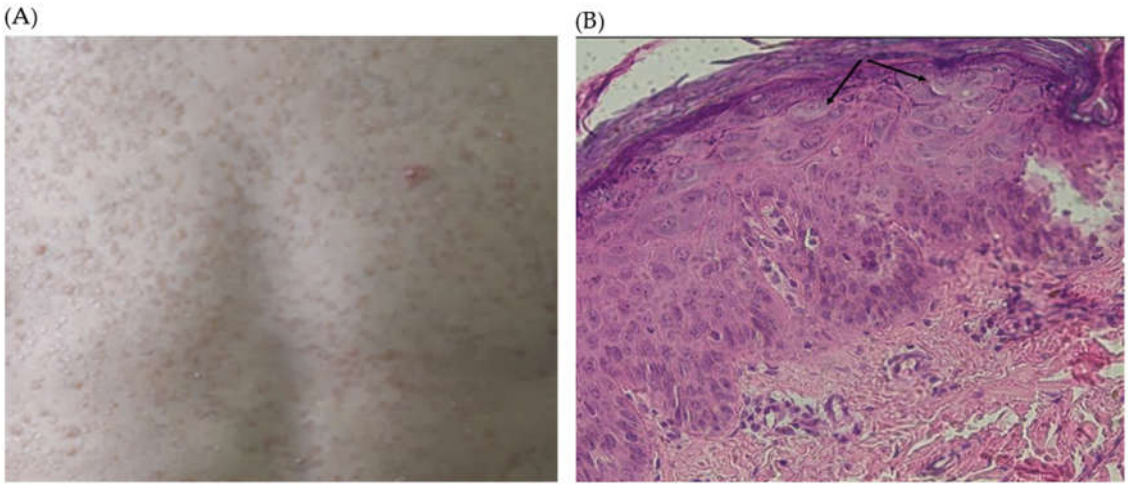

Figure 2. A. Pictures of the lesions on the face and the hand of P3. B. Histological study of Punch skin biopsy showed hyperkeratosis and parakeratosis, mild acanthosis, and the presence of koilocytes, keratinocytes with pale-stained cytoplasm in the upper epidermis associated with high levels of intranuclear viral replication. The cytoplasm of the affected cells stains pale blue which is pathognomonic of epidermodysplasia verruciformis lesions without any sign of malignancy (Arrows).

2.1.3. Genotype

The consanguinity of parents and the clinical history of the 3 patients suggested an inborn error of immunity. To test this hypothesis, we performed genetic investigations in P1 and P3 by combining a deep sequencing array (using a custom-designed Illumina SNP array) with the 407 genes involved in inborn errors of immunity [23] and also whole exome sequencing. In both P1 and P3, we identified 2 predicted LOF homozygous variants in STK4, an essential splice site (c.1305+1G>A) in P1 and a premature stop codon (c.750G>A, p.W250*) in P3. We did not find any other candidate variants in other genes related syndromic EV. The familial segregation confirmed that P1, P2 and P3 were homozygous for their respective allele and their parents and healthy sibling were heterozygous (Figures 3A and B), suggesting that *STK4* was the disease-causing gene in these 2 families.

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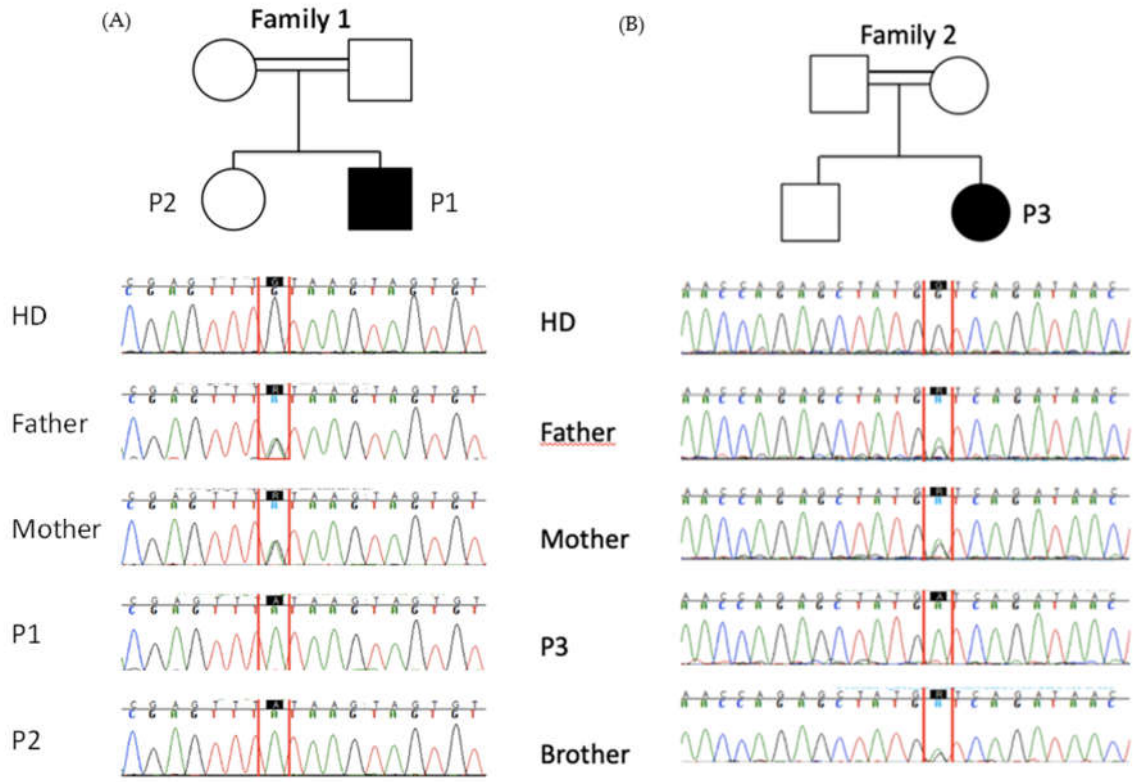

Figure 3. Pedigrees and familial segregation done by Sanger sequencing of STK4 variants in family 1 (panel A) and family 2 (panel B).

2.2. Immunological Phenotype

We then performed immunological analyses in both clinical and research laboratories. In clinical laboratory, P1 and P3 had a profound lymphopenia, with a decreased T, B and NK cell counts as compared with normal range. In addition, P3 had also neutropenia. In contrast, P2, P1's sister, had a normal count on T, B and NK, with the exception of a mild CD4+ T cells lymphopenia. The HLA-DR expression was found normal on CD19+ and CD14+ cells in both siblings. In contrast, the immunoglobulin levels were normal in P1, and P2, with a slight hypogammaglobulinemia observed P2. As for P3, there was a slight hypergammglobulinemia and Hyper Ig E (Tables 1 and 2).

Table 1. Lymphocyte subpopulations count.

Lymphocyte subpopulations (N/mm3)	P1 (12 years)	P2 (8 years)	P3 (6 years)	Normal range (age matched)
T cells				
CD3+	771	2990	1489	1200-2600
CD4+	253	470	243	650-1500
CD8+	450	2330	1057	404-826
B cells				
CD19+	128	430	131	270-860
NK cells				
CD16+/CD56+	74	110	123	100-480

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Table 2. Immunoglobulin levels.

Immunoglobulin levels (g/L)	P1 (12 years)	P2 (8 years)	P3 (6 years)	Normal range (age matched)
IgG	11.62	5.17	17,3	6,10-16,16
IgM	0.49	0.46	2,09	0,22-2,40
IgA	1.99	3.21	2,17	0,84-4,99
IgE (UI/mL)	10	5.18	175,68	<100

A deeper immunophenotyping has been done using CyTOF method (Figure 4). The proportion of NK, CD3+, Treg and gamma-delta T cells in P1, P2 and P3, are in the normal range of healthy donors (Figure 4A). However, we observed a strong reduction of CD4+ T cells, proportion in T lymphocytes, an absence of MAIT cells, and a higher proportion of CD8+ T cells, leading to an inverted CD4/CD8 ratio. In addition, the proportion of recent thymic emigrant cell, as well as naïve CD4 and CD8 T cells, are strongly decreased. In contrast, memory CD4 and CD8 subsets are in the normal range, or even increased in term of proportion (Figure 4B). The B cell compartment is also showing some major differences, such as a decrease of memory B cells and an increase of ABC subset (Figure 4C). Altogether, these immunological results are similar to the ones previously reported in patients with STK4 deficiency.

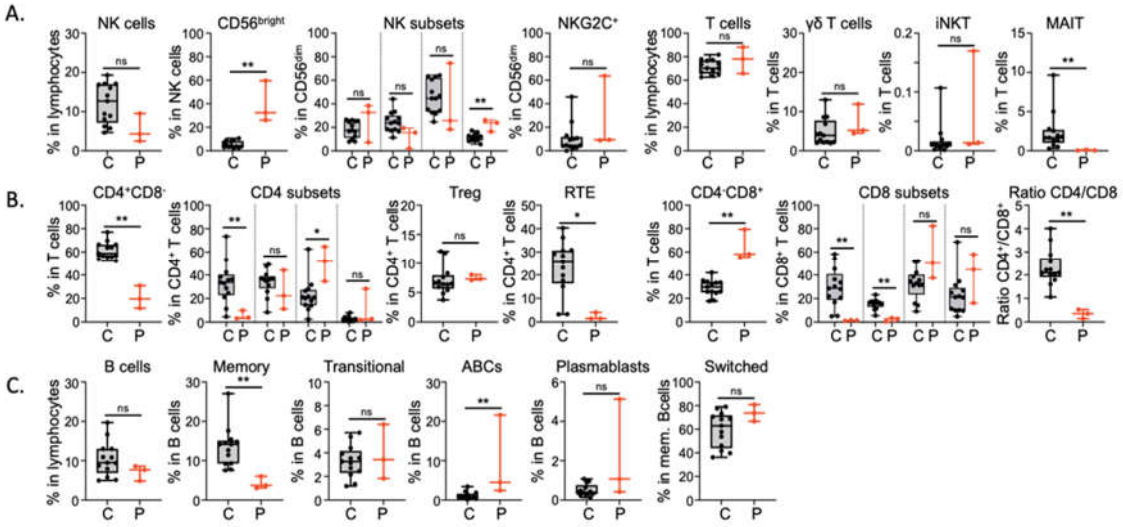

Figure 4. CyTOF analysis on peripheral blood. A. Proportion of total and subsets of NK cells, of total T cells, total T cells, γδ T cells, iNKT and MAIT cells. B. Proportion of total and naïve, central memory, effector memory and EMRA CD4+ T cells, T-regulatory, recent thymic emigrant T cells and of total and naïve, central memory, effector memory and EMRA CD8+ T cell subsets. C. Proportion of total and memory, transitional, Age-associated B cells (ABC), plasmablasts and switched B cell subsets. Age-matched healthy donors (black), patients (red).

3. Discussion

Human autosomal recessive (AR) STK4 deficiency was first reported in 2012 in 7 patients with progressive T cell deficiency, and a broad range of infectious susceptibilities [24,25]. Since then, 29 additional cases of STK4 deficiency have been reported. All variants identified are loss-of-function [10–12,25–38]. The clinical phenotype related to STK4 deficiency is characterized by recurrent pulmonary bacterial infections, recurrent skin infections, including HPV warts (9 out 36) [10,12,25,26,38] including 3 with syndromic EV [10–12] and mucocutaneous candidiasis, but also chronic EBV infections. Auto-immune manifestations were reported in 13 cases [11,12,24,30–

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32,37,38]. The immunological phenotype of patients with STK4 deficiency is characterized by a profound CD4 lymphopenia due to a decreased proliferation, increased susceptibility to apoptosis and dysregulation of the transcription factor Forkhead box protein O1 (FOXO1) and its downstream targets in T cells. Leukocytes also show defective adhesion and chemotaxis [10,22,25,38,39].

We report here three children from two independent families with rare variants in STK4 deficiency and a broad clinical phenotype, including syndromic EV for 2 of them. Respiratory infections were noted in P2 and P3, as reported in many cases (ref of Cagdas here). P1 had recurrent diarrhea with no pathogens identified. Gastroenteritis was already reported in patients with STK4 deficiency [38]. A negative deviation from the norm of growth curve was noted in the 3 patients reported here, as in previously reported before [34].

In term of immunologic phenotype, cytopenia is a common feature in STK4 deficiency, and we indeed observed it in the 3 patients reported here [38]. Furthermore, neutropenia is secondary to infections, autoimmunity, immunomodulatory agents, and chemotherapy [30,40]. In P3, neutropenia was developed during the infectious episodes. Allergic manifestations are also reported in STK4 deficiency (Asthma, atopic dermatitis) [38]. Despite P3 having high hyper IgE, none of the patients reported here developed any allergic symptoms for now.

Autoimmune diseases were also associated with STK4 deficiency. The presence of autoantibodies, such as antinuclear and anticardiolipin antibodies, has been described in STK4 deficiency [11,12,24,30,31,33,37,38]. The autoimmunity in STK4 deficiency may also be due to the defective regulation of development and function of regulatory T cells through modulation of FOXO1/FOXO3. In our patients, no autoimmune manifestation was reported so far.

Some patients with STK4 deficiency are particularly prone to EBV-driven infections and EBV-induced lymphoproliferation [38], this was absent in our patients.

To conclude, we describe here 3 new clinical phenotypes related to STK4 deficiency. We treated our patients with IVIG, antibacterial prophylactic agents associated with imiquimod application on the skin and skin protection from UV radiation for EV patients. Although HSCT is the curative treatment in most CIDs, the survival rate after HSCT is about 50% in STK4 deficiency [36] and further studies are needed to recommend HSCT as a safe therapy for patients with STK4 deficiency.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Ibn Rochd university hospital of Casablanca (protocol code 9/22 and date of approval: 22 April 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Upon request.

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Conflicts of Interest: The authors declare no conflicts of interest.

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