

Human Papillomavirus-induced Cutaneous and Mucosal Lesions in a Patient with Rothmund-Thomson Syndrome

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Rothmund-Thomson syndrome (RTS), first described by the German ophthalmologist August Rothmund, is a rare genodermatosis with autosomal recessive inheritance and potential multisystem abnormalities, affecting all ethnic groups. The clinical features of RTS include early-onset facial erythemas that later transition into poikiloderma, photosensitivity, rarefaction of piliferous structures (e.g. hair, eyebrows, and eyelashes), nail abnormalities, various ocular and bone defects, dental deformations, and gastrointestinal disorders (1). Importantly, patients with RTS have a significantly increased risk of malignant neoplasias, especially osteosarcoma and cutaneous squamous cell carcinoma (SCC). We report here a patient with RTS and a history of cutaneous SCC who presented with multiple human papillomavirus (HPV)-induced skin lesions, including high-grade vulvar dysplasia (Fig. S1¹) and palmoplantar verrucae vulgares.

CASE REPORT

A woman with a suspected diagnosis of RTS presented to our department for the first time at the age of 41 years because of several mucosal and cutaneous lesions that had developed within the last 6 months. The patient reported that first facial skin lesions occurred during early childhood, and expanded gradually (Fig. S2¹). During adolescence, she had experienced increasing loss of her scalp hair, eyebrows, and eyelashes. She reported an invasive cutaneous SCC that was diagnosed on the lateral edge of the left heel at the age of 22 years, and was removed surgically (Fig. S3¹). Further clinical manifestations included hyperkeratosis of the soles, skeletal abnormalities (osteopaenia and hypoplastic processus styloideus ulnae), quiescent inflammatory bowel disease (ileitis terminalis), and hypothyroidism. A recently performed check-up revealed no cardiological, ophthalmological, or auditory system pathologies. The patient was a non-smoker, and had no history of cervical or other HPV-related diseases and no previous or current immunosuppressive medication. The patient had no laboratory signs of immunodeficiency, HIV testing was negative and lymphocyte subpopulations including CD3⁺ T cells, CD4⁺ T cells, CD8⁺ T cells, CD19⁺ B cells, and natural killer cells were within normal ranges.

Clinical examination at first presentation in our department revealed poikiloderma with patchy cutaneous lesions including hypo- and hyperpigmentation, punctuate atrophy, and telangiectatic vessels, located predominantly on the cheeks and dorsal aspects of the upper extremities, characteristic for RTS (Fig. S4a¹). More-

over, an erythematous, erosive plaque, 1.5 cm in diameter, was located at the left thumb (Fig. S4b¹). Excision of the lesion with a 5-mm safety margin showed a well-differentiated SCC with a maximal depth of penetration of 2.6 mm (Fig. S4c¹). In addition, several plantar warts (Fig. S4e,f¹) and flat cutaneous warts (Fig. S4 h,i¹) were present.

Inspection of the genital region revealed a rapidly-grown verrucous, irregularly shaped leucoplakia located at the posterior fourchette (Fig. S1a¹). The patient had not received prior prophylactic HPV vaccination, but had attended regular cervical cancer screening programmes in the past. Histographically controlled excision of the lesion was performed and showed high-grade vulvar intraepithelial neoplasia (VIN, Fig. S1b¹).

In all of the lesions (warts, VIN, and SCC), HPV analyses were performed using alpha- and beta-HPV group-specific PCRs and bead-based multiplex hybridization (2–4). The VIN lesion was positive for the high-risk type HPV16, but no HPV-types were found in the SCC located on the thumb. All plantar and hand warts showed an infection with HPV57, a common cutaneous alpha-HPV-type frequently found in skin warts. Beta-HPV types were not detected. Immunohistochemical staining for p16^{ink4A}, an indirect marker of HPV E7 oncogene expression, showed strong positivity in the VIN lesion (Fig. S1c¹), but was negative in the cutaneous warts and the SCC (Fig. S4d, g, j¹).

To confirm the clinical diagnosis of RTS, mutation analysis of the *RECQL4* helicase gene on chromosome 8 was performed by PCR and Sanger sequencing, and revealed a heterozygous missense mutation c.3061C>T (p.R1021W) transmitted from the patient's mother. This pathogenic variant has been described previously as a causative mutation for RTS (5, 6). A second mutated allele was not detected with this method; however, exon or whole-gene deletions/duplications, as well as intronic variants are not detected, which might be the case in the current patient (7).

DISCUSSION

To date, fewer than 350 cases of RTS have been reported in the medical literature (8). Based on clinical and molecular findings, 2 types of RTS have been distinguished. Type 1 is characterized by poikiloderma, ectodermal dysplasia, and juvenile cataracts, and is caused by mutations in *ANAPC1*, encoding a scaffold subunit of the anaphase-promoting complex (9). Type 2 presents with poikiloderma, congenital bone defects, and an increased risk of osteosarcoma in childhood and cutaneous SCC later in life. The latter is caused by homozygous or compound heterozygous mutations in the *RECQL4* helicase gene (8, 10). Accordingly, the present case can be classified as type 2 RTS.

Initially, cutaneous lesions in RTS appear early after birth, with facial erythema and blistering and subsequent

¹<https://www.medicaljournals.se/acta/content/abstract/10.2340/00015555-3596>

involvement of the extensor surfaces of the extremities and buttocks as the clinical hallmark (11). These acute symptoms eventually reach a chronic poikilodermatous phase, persisting through life. Other dermatological findings in RTS, besides photosensitivity, comprise hair abnormalities (e.g. sparse hair on scalp, eyelashes, and eyebrows, absent pubic and axillary hair), nail abnormalities (e.g. dystrophic nails and pachyonychia), café au lait spots, and palmoplantar hyperkeratosis. Besides cutaneous findings, several other organ systems can be affected, including dental-, gastrointestinal-, auditory-, respiratory-, and haematological pathologies (8). Neurocognitive development is usually unaffected in RTS. Most importantly, differential diagnoses of RTS include other conditions associated with juvenile poikiloderma, such as Kindler syndrome, dyskeratosis congenita, and poikiloderma with neutropaenia or genodermatoses with prominent telangiectasias (e.g. Werner syndrome, ataxia-telangiectasia, or Bloom syndrome).

RECQL4 helicase gene mutations in patients with type 2 RTS cause genomic instability and cancer predisposition. The most frequent malignancies in RTS are osteosarcoma, particularly occurring in childhood, and cutaneous SCC (1, 12). The prevalence of epithelial tumours in RTS has been estimated to be 5%, with a mean age of onset of 34 years (11). In line with this, our patient developed 2 cutaneous SCCs at a young age (22 and 41 years), 1 of them located at a non-sun exposed site (left heel). Moreover, the patient developed high-grade VIN within a short period of time (6 months). To date, anogenital (pre)malignant lesions have not been reported in RTS, but 3 patients of RTS exist who developed SCC of the tongue (11). To our best knowledge, HPV analysis was not performed in these cases. The VIN lesion in the current patient contained HPV16, a frequent and oncogenic HPV-type preventable by both the bivalent and nonavalent prophylactic HPV-vaccine. The current patient had no typical risk-factors for persistent or multiple HPV infection, such as immunodeficiency, smoking, or high-risk sexual behaviour. The *RECQL4* helicase gene encodes ATP-dependent DNA helicase Q4, which plays an important role in maintaining genomic stability due to its interface in DNA repair, recombination and replication (1). Mutations of *RECQL4* lead to an impaired genomic stability and cancer development. It is possible that HPV serves as co-carcinogen in the skin carcinogenesis of RTS, inhibiting DNA damage repair and/or facilitating the accumulation of DNA breaks and mutations, as also shown in epidermodysplasia verruciformis, a genodermatosis with an increased risk for the development HPV-induced precancerous lesions and SCCs, especially in sun-exposed areas. We could not detect beta-HPVs in the lesions of the patient described here, however (13, 14).

In conclusion, we report here the occurrence of multiple alpha-HPV-induced (pre)malignant mucosal and benign cutaneous lesions in a patient with RTS. This case underlines the importance of whole-body examinations in patients with rare genodermatoses, such as RTS, including

inspection of the oral and anogenital region, as these patients might develop mucosal lesions and skin cancer on non-sun exposed areas. Moreover, this case strengthens the importance of widespread HPV vaccination, in particular in individuals with rare disorders with increased risk of malignancies.

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Permission is given by the patient to publish the clinical pictures.

The authors have no conflicts of interest to declare.

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