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**TITLE: SCHOPF-SCHULZ-PASSARGE SYNDROME: A RARE
ECTODERMAL DYSPLASIA WITH A DELAYED DIAGNOSIS**

Running heading: Schopf-Schulz-Passarge Syndrome

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MANUSCRIPT TEXT

Case Report

A 58-year-old female of German and English ancestry, born of a non-consanguineous marriage, presented with bilateral eyelid cysts, palmoplantar keratoderma, nail dystrophy and hypodontia (Fig. 1). She was diagnosed with an uncharacterised ectodermal dysplasia 25 years prior. No family members were affected.

Palmoplantar keratoderma first appeared at age 31. Multiple eyelid cysts appeared at the age of 39. She reported abnormal dentition from childhood, with conical primary teeth and agenesis of permanent teeth. She has worn complete dentures since the age of 13. She recalls dystrophic nail changes from childhood. Additional features noted on examination included palmoplantar hyperhidrosis, perifollicular hyperkeratosis on her shins and scaling on the tip of her nose. There was no associated hair disorder. At age 59 she had a nodular basal cell carcinoma excised from her neck.

A diagnosis of Schopf-Schulz-Passarge Syndrome (SSPS) was suspected and histopathology from a punch biopsy taken from her palm revealed acrosyringal adenomatosis consistent with that diagnosis. Molecular genetic analysis revealed two nonsense mutations in the *WNT10A* gene, p.Cys107* and p.Arg128*.

A number of treatments were trialled for the palmoplantar keratoderma with minimal symptomatic improvement. These treatments included oral acitretin, 20% urea cream, narrowband UVB phototherapy, calcipotriol/betamethasone dipropionate foam and propantheline for the hyperhidrosis.

Discussion

Ectodermal dysplasias are genetic disorders that affect the skin and skin appendages. They are classified according to which appendages demonstrate abnormalities. This patient had involvement of her skin, nails, and teeth. Her hair was normal and she was able to sweat. The main differential diagnoses considered were odonto-onycho-dermal dysplasia (OODD) and SSPS.

SSPS is rare, with less than 50 cases previously reported in the literature¹. The first description was in 1971 of two sisters born of a consanguineous marriage who presented with cysts on the upper and lower eyelids, hypodontia, hypotrichosis, palmoplantar keratoderma and onychodystrophy².

Eyelid cists (apocrine hidrocystomas) are the cardinal finding in SSPS and differentiate it from other ectodermal dysplasias. Early diagnosis is rare, because the eyelid cysts appear at a mean age of 50 years and are asymptomatic¹. This results in a late diagnosis at a mean age of 60 years, despite the other clinical features presenting early in life¹. Our patient had features of an ectodermal dysplasia from childhood, however her diagnosis was only confirmed at the age of 58.

Palmoplantar keratoderma is usually diffuse and non-transgrediens. Histopathology may reveal proliferation of acrosyringeal epithelium. The majority of patients have abnormalities in primary or permanent dentition. No effective treatment for SSPS has been described.

SSPS is thought to be inherited as an autosomal recessive trait, however multiple studies have reported phenotypic manifestations in heterozygous carriers^{1,3,4}. The *WNT10A* gene on chromosome 2 encodes proteins that are involved in the development and regulation of ectodermal tissue. Adaimy et al. first identified mutations in the *WNT10A* gene as the cause for OODD⁵. Bohring et al. subsequently identified that *WNT10A* mutations were involved in the pathogenesis of other ectodermal dysplasias, including SSPS⁴. To date, 10 different mutations in the *WNT10A* gene have been linked to SSPS^{1,3,4,6} (Table 1). Our patient had two heterozygous nonsense mutations - p.Cys107* which is the most common mutation reported in SSPS, and p.Arg128* which has not previously been reported in SSPS⁶.

Several benign and malignant tumours have been described in association with SSPS, including squamous cell carcinomas, basal cell carcinomas, eccrine porocarcinomas and eccrine syringofibroadenomas³.

In summary, we describe a patient with SSPS, a rare ectodermal dysplasia, which is generally diagnosed later in life due to the delayed appearance of the characteristic eyelid

hidrocystomas. She has a unique genotype in that the p.Arg128* mutation has not previously been reported in SSPS.

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FIGURE/VIDEO LEGENDS

Figure 1: eyelid cysts and plantar keratoderma in Schopf-Schulz-Passarge Syndrome

This video clip taken using Vectra 3D imaging highlights the eyelid cysts and plantar keratoderma characteristic of Schopf-Schulz-Passarge Syndrome.

Figure 2: characteristic eyelid cysts in Schopf-Schulz-Passarge Syndrome

Figure 3: plantar keratoderma

TABLES

Table 1: *WNT10A* gene mutations in SSPS

Previously identified mutations in SSPS ^{1,3,4,6}	Mutations present in this case
p.Cys107* p.Phe288Ile p.Ala131Thr p.Glu390* p.Ser270Arg p.Cys362Arg p.Gly266Cys p.Trp277Cys p.Arg379Cys p.Arg248*	p.Cys107* p.Arg128*

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