

CLINICAL REPORT

Schöpf-Schulz-Passarge Syndrome: Further Delineation of the Phenotype and Genetic Considerations

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Schöpf-Schulz-Passarge syndrome is a rare ectodermal dysplasia, characterized chiefly by multiple eyelid apocrine hidrocystomas, palmo-plantar keratoderma, hypodontia, hypotrichosis and nail dystrophy. The clinical spectrum and the most likely inheritance pattern(s) have not yet been completely defined. We report here on two, unrelated patients presenting with additional, previously unreported features, including hypoplastic nipples and optic atrophy. Both individuals were born to consanguineous parents, and one also has affected siblings. A literature review identified 23 additional cases. Multiple eyelid apocrine hidrocystomas, described in all of the cases, are the hallmark of this condition, although they usually appear in adulthood. The concomitant presence of eccrine syringofibroadenoma in most patients and of other adnexal skin tumours in 44% of affected subjects indicates that Schöpf-Schulz-Passarge is a genodermatosis with skin appendage neoplasms. However, the risk of skin and visceral malignancies is not increased. Pedigree study demonstrates that 9 of the 13 published familial cases may be explained by an autosomal recessive mutation, while the remaining pedigrees show apparent vertical transmission compatible with genetic heterogeneity. The benign disease course and advanced age at diagnosis could also suggest locus homogeneity for a recessive mutation with instances of pseudodominant inheritance. **Key words:** autosomal recessive; ectodermal dysplasia; genodermatosis; skin appendages; tricho-odonto-onycho-dermal dysplasia; tumour predisposition.

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Schöpf-Schulz-Passarge syndrome (SSPS) was first described in two sisters showing the unusual combination of multiple eyelid apocrine hidrocystomas (EACHs), palmo-plantar keratoderma (PPK), hypodontia, hypotrichosis, nail dystrophy, and facial telangiectases (1). Given the developmental abnormalities in teeth, hair and nails, SSPS was included in the heterogeneous group of ectodermal dysplasias with the appellation of

“tricho-odonto-onycho-dermal dysplasia” (2). Since its original description, the publication of several additional cases has outlined a constellation of ancillary features, rendering the SSPS clinical spectrum particularly wide and still not completely delineated. Moreover, although SSPS was originally described as an autosomal recessive condition, alternative patterns of inheritance have been proposed for single pedigrees (3, 4).

We report here on two SSPS patients presenting with previously undescribed ancillary features. Both individuals were born to consanguineous parents, and one also has affected siblings. A literature review was performed in an attempt to define the SSPS clinical spectrum and the most likely inheritance pattern(s).

CLINICAL REPORT

Patient 1

A 65-year-old woman was referred to our outpatient clinic for long-lasting, generalized nail fragility that became evident in childhood and had worsened progressively throughout life. The patient also complained of palmo-plantar redness and hypotrichosis since the same age. She developed a telangiectatic rosacea on the cheeks and nose at 20 years of age, and cystic lesions along the eyelid margins some years later. Deciduous teeth erupted and developed normally, but several persisted until the age of 16 years, due to the absence of most permanent teeth. At that time, all remaining deciduous teeth were extracted and the patient was treated with a fixed prosthesis. She has been myopic since early childhood and a diagnosis of bilateral optic atrophy was established by funduscopy at 45 years of age. She has never complained of photophobia.

On physical examination, the palms and soles appeared erythematous, mildly thickened and partially covered by fine scales that were more pronounced on the plantar regions. These lesions were well demarcated and displayed neither progression nor transgression (Fig. 1a). Her hair was sparse and brittle (Fig. 1b): there was little body hair, and the axillae and pubis showed very scanty terminal hair. Fingernails presented severe onychodystrophy consisting of longitudinal ridging, splitting, koilonychia, onycholysis and pterygium unguis (Fig. 1c). Toenail involvement was less pronounced. More than 12 opalescent



Fig. 1. Clinical features of patient 1, a 65-year-old woman. (a) Palmo-plantar keratoderma; note the erythema demarcation at the wrist joint. (b) Sparse, thin scalp hair. (c) Onychodystrophy consisting of longitudinal ridging, mild splitting, koilonychia, and pterygium unguis. (d) Opalescent and translucent cyst-like lesions of the eyelid margins. (e) Telangiectatic rosacea. (f) Disseminated milia over the nasal tip and columella. (g) Bilateral hypoplastic nipples. (h) Panoramic radiograph showing severe oligodontia with only seven erupted permanent teeth.

Approval has been given by the patient to publish these figures without masking.

and translucent cyst-like lesions, 1–3 mm in diameter, were distributed along the margins of the upper and lower eyelids (Fig. 1d). The skin of the cheeks and nose was intensely red with interspersed telangiectases that were more prominent on the nose tip, where some small milia were visible (Fig. 1e, f). Her face had a peculiar aspect reminiscent of the “bird-like appearance” described by Monk et al. (5). This facial gestalt was most probably related to an alveolar process hypoplasia secondary to oligodontia. Moreover, the nipples and areolae were disproportionately small (Fig. 1g). An orthopantomographic radiograph confirmed the presence of only seven permanent teeth (Fig. 1h).

The patient was born to consanguineous (first cousins once removed) unaffected parents. She has an older sister and brother, as well as three children who are all healthy.

Patient 2

The proband was a 73-year-old man who requested dermatological evaluation for thickening and scaling of the palms and soles. Plantar lesions were more pronounced and had been present for more than 30 years. He also complained of multiple small eyelid cyst-like lesions that had appeared progressively since the age of 50 years. Onychodystrophy of the hands and feet

and hypotrichosis of the scalp have been present since early childhood. At 30 years, the patient developed rosacea-like skin lesions involving the cheek and nose. In adulthood, he has suffered from marked palmo-plantar hyperhidrosis, which has gradually decreased. As for patient 1, his normal deciduous teeth persisted until the end of the second decade of life due to the complete absence of permanent dentition. Therefore, the remaining deciduous teeth were extracted and the patient received a removable prosthesis. He did not complain of photophobia.

On physical examination, the skin of the palmo-plantar surfaces was erythematous and covered with scales, which were more pronounced on the soles (Fig. 2a). The nails were abnormal, presenting longitudinal ridging, koilonychia, onycholysis and pterygium unguis. These anomalies were more prominent on the index fingers and on II–V toes (Fig. 2b). The scalp hair was fine and extremely scanty. The skin of the cheeks and nose appeared erythematous and telangiectatic without milia. Body hair, especially in the axillary folds and pubis, was sparse, and nipples and areolae appeared hypoplastic (Fig. 2c). Many small 1–2 mm cyst-like lesions were localized along the margins of the upper and lower eyelids (Fig. 2d). On oral cavity examination, no teeth were visible. An ophthalmological survey excluded any anomaly.

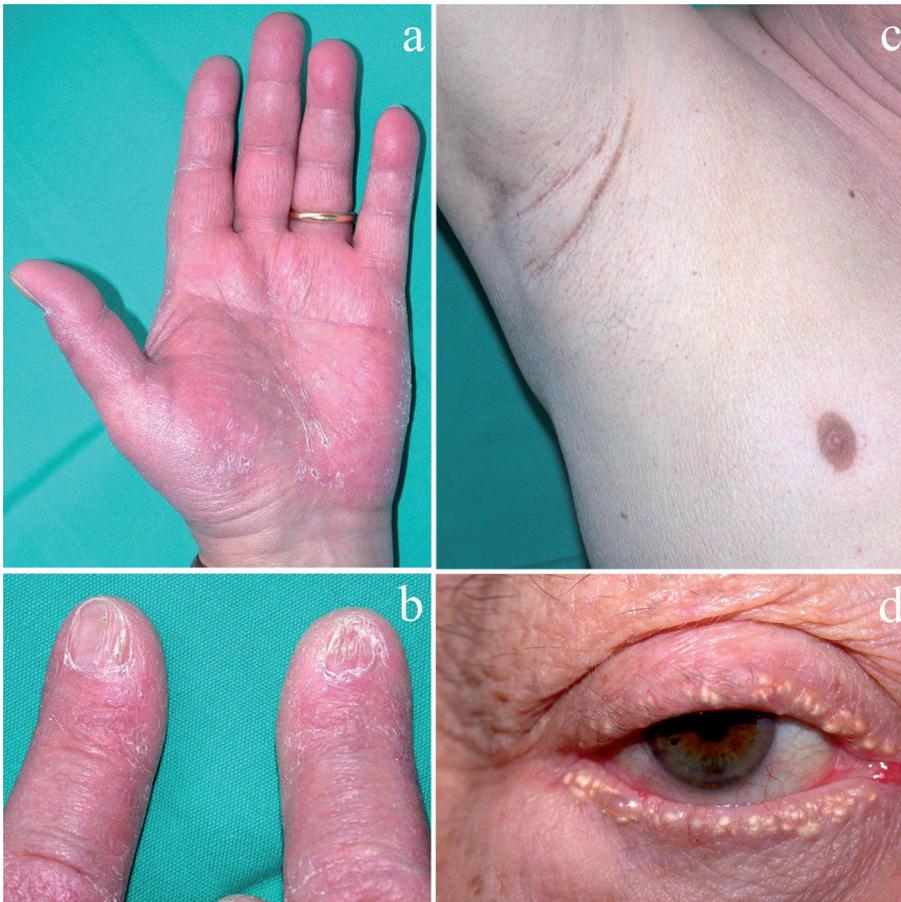


Fig. 2. Clinical features of patient 2, a 73-year-old man. (a) Eczematoid palmar keratoderma with sharp demarcation at the wrist joint. (b) Onychodystrophy of the index fingers with severe onycholysis, pterygium unguis and splitting. (c) Sparse axillary fold hair and slightly hypoplastic right nipple. (d) Multiple apocrine hidrocystomas of the eyelid margins.

Light microscopy of a cystic lesion of the eyelids revealed a wide cavity in the dermis, lined mostly by a double layer of epithelial cells. Inner layer cells were columnar and showed decapitation secretion. Histological examination of a skin biopsy from the left plantar surface displayed compact hyperkeratosis and a marked proliferation of acrosyringial epithelium forming irregularly anastomosing strands and thin septa with occasional ducts extending within the dermis. The areas between the strands were filled with a richly vascular fibrous stroma and showed mild infiltration of lymphocytes and plasma cells. No cytological atypia or mitotic figures were seen (Fig. 3). These findings are consistent with EACH and eccrine syringofibroadenoma (ESFA), respectively.

The proband was born to consanguineous (i.e. third cousins) healthy parents and has two brothers who display similar characteristics, including PPK, hypotrichosis, nail dystrophy, multiple eyelid cysts, telangiectatic rosacea and oligodontia. His sister is unaffected, and his and siblings' children are all healthy (Fig. 4).

LITERATURE REVIEW

The search for additional published SSPS cases revealed 23 patients (9 females and 14 males) from 19

families (1, 3–15). Among the 12 pedigrees with two or more affected individuals, 22 further subjects (13 females and 9 males) were reportedly affected, but no clinical data was available. In the seven sporadic cases, six were from unrelated parents and one from consanguineous parents (6–8, 11, 13, 14). Consanguinity was also registered in two familial cases (1, 5). Age at diagnosis ranged from 35 years (8) to 80 years (10), with a mean of 64 years. Fig. 4 shows the pedigree of the 13 published familial cases, including our own (i.e. patient 2). Sex, age at diagnosis, and the clinical characteristics of the reviewed and present patients are summarized in Table I.

DISCUSSION

The literature review demonstrates that the SSPS phenotypic spectrum is extremely variable, ranging from full-blown phenotypes to milder forms limited to isolated palpebral and tooth involvement (5). Multiple EAHCs seem to be the hallmark of this condition (see Table I). The specificity of this feature is emphasized by Alessi et al. (16) who outline that although this abnormality often comes in isolation, the only syndromes which may present this feature are SSPS and focal dermal hypoplasia. However, EAHCs may

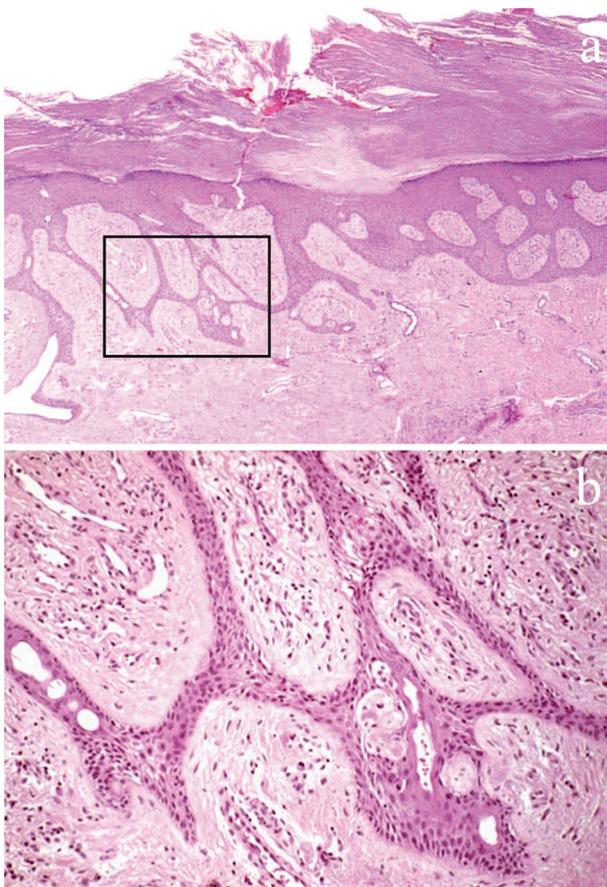


Fig. 3. Biopsy specimen from the left sole of patient 2. Compact hyperkeratosis and sponge-like masses of tumour epithelium with occasional ducts (on the left), fibrovascular stroma, and dilated capillaries are evident (a; original magnification $\times 40$). Magnification of inset in (a) showing marked proliferation of acrosyringeal epithelium forming irregular anastomosing strands within the dermis (b; original magnification $\times 250$).

not be easily detectable in all cases, as this feature always appears in adulthood (1, 4, 8–10, 14, 15). This probably explains the advanced mean age at diagnosis of SSPS. Starink (7) showed that the histological features of PPK reported in SSPS are always compatible with ESFA. This observation was subsequently confirmed by various reports (12, 13, 15) and, retrospectively, also by Nordin et al. (10). Therefore, skin biopsy of palmo-plantar lesions could help differential diagnosis in non clear-cut phenotypes. In fact, although palmo-plantar ESFA is also reported in single cases of Clouston syndrome, the clinical and histological presentation of ESFA in this condition is distinct from that observed in SSPS (17).

The hypothesis that SSPS may be considered a cancer-prone syndrome was originally introduced by Perret (6). Despite the subsequent description of several cases with skin neoplasms, this association has never been sufficiently underlined. The observation of EAHCs in all cases and of ESFA in 10 of 11 patients undergoing skin biopsy indicates that multiple skin appendage tumours are a major feature of SSPS. Interestingly, a wider spectrum of additional skin appendage neoplasms is observed in 44% of the patients (see Table I). Multiple adnexal tumours are also symptomatic of other genodermatoses, such as Cowden, Birt-Hogg-Dube, Gorlin, and Muir-Torre syndromes (18). However, in contrast to these conditions, from which SSPS can be easily differentiated, the latter implies a very low risk of skin and internal organ malignancies. In fact, the occasional observation of extracutaneous neoplasms seems fortuitous given to the rarity and non-specificity of these lesions. Therefore, SSPS is an ectodermal dysplasia with adnexal tumours, but not a true cancer-prone syndrome. Interestingly, two further conditions,

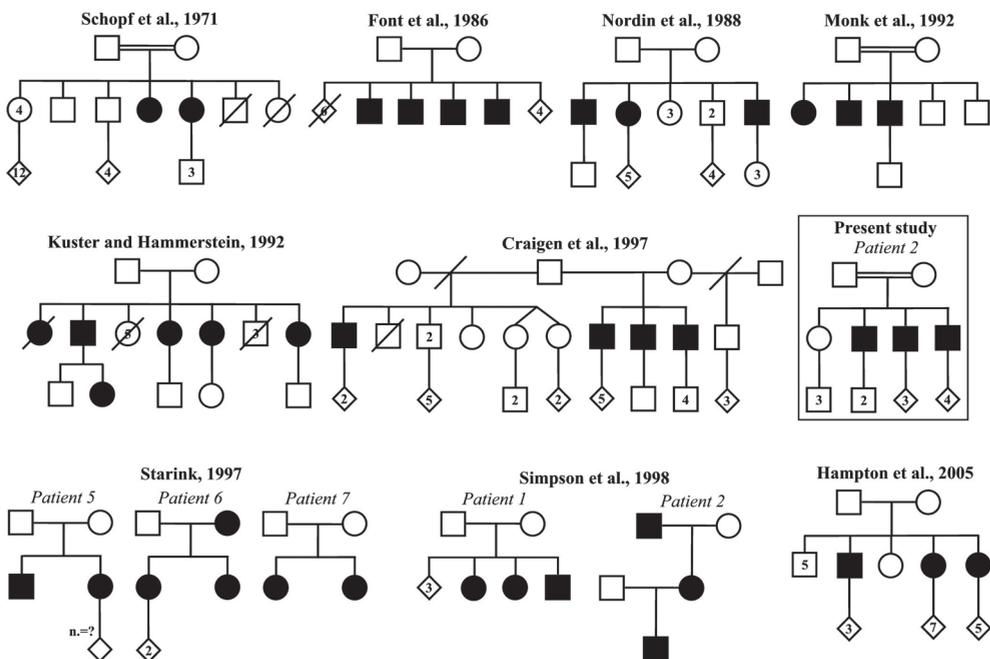


Fig. 4. Pedigree of the published familial cases of Schöpf-Schulz-Passarge syndrome. Pedigree of patient 2 is highlighted in a box.

Table I. Characteristics of published patients presenting Schöpf-Schulz-Passarge syndrome

Author/Patient no. (Ref.)	Sex	Age at diagnosis (years)	PPK	Nail dyst.	Hypo-trichosis	Abnormal dentition	EAHCs	Adnexal tumours ²	Rosacea-like lesions	Other skin features	Other findings
Schöpf et al., 1971 (1)	F	68	+	+	+	+	+	–	+	–	–
Burket et al., 1984 (8)	M	35	+	+	+	+	+	FITs (multiple)	+	–	–
Font et al., 1986 (9)	M	67	+	+	+	+	+	BCC	–	Mi	PP, VD
Nordin et al., 1988 (10)											
Patient 1	F	80	+ ¹	+	–	+	+	EP	+	–	–
Patient 2	M	75	+ ¹	+	+	+	+	EP	+	–	–
Patient 3	M	83	+	+	–	–	+	BCC	–	–	–
Perret, 1989 (6)	M	75	+	–	+	+	+	–	–	2 SCCs	–
Monk et al., 1992 (5)											
Patient 1	F	62	+	+	+	+	+	BCC	–	–	BLF, HN
Patient 2	M	58	–	–	–	+	+	–	–	–	BLF
Patient 3	M	51	+	+	+	+	+	–	–	–	BLF
Küster & Hammerstein, 1992 (3)	F	43	+	+	+	+	+	–	–	BA	–
Craigien et al., 1997 (4)	M	56	+	+	+	+	+	–	–	–	–
Starink, 1997 (7)											
Patient 4	F	78	+	+	+	+	+	mESFA	–	–	–
Patient 5	F	59	+	–	+	+	+	–	–	–	–
Patient 6	F	73	+	+	+	+	+	BCC	–	–	BC
Patient 7	F	71	+	+	+	+	+	–	–	–	–
Verplancke et al., 1998 (11)	M	53	+	+	+	+	+	2 FITs, EP	+	–	–
Simpson et al., 1998 (12)											
Patient 1	M	64	+ ¹	+	–	+	+	EHC	–	Mi	–
Patient 2	M	74	+	+	–	+	+	–	–	–	–
Dot et al., 2000 (13)	M	71	+ ¹	+	+	+	+	2 BCCs	–	–	MD
Gkolfinopoulos et al., 2001 (14)											
Patient 1	F	49	+	+	+	+	+	–	–	–	BLF
Patient 2	M	56	+ ¹	+	+	+	+	–	–	MDH	–
Hampton et al., 2005 (15)	M	69	+	+	+	+	+	–	–	–	–
Present study											
Patient 1	F	65	+	+	+	+	+	–	+	HyN, Mi	BLF, OA, UFs
Patient 2	M	73	+ ¹	+	+	+	+	–	+	HyN	–
Total n (%)			24/25 (96%)	22/25 (88%)	20/25 (80%)	24/25 (96%)	25/25 (100%)	11/25 (44%)	7/25 (28%)	7/25 (28%)	8/25 (32%)

¹PPK is complicated by palmo-plantar hyperhidrosis.

²Other than palmo-plantar benign eccrine syringofibroadenoma.

dyst: dystrophy; BA: benign acanthoma; BC: breast cancer; BCC: basal cell carcinoma; BLF: bird-like facies; EAHC: eyelid apocrine hidrocystoma; EHC: eccrine hidrocystoma; EP: eccrine poroma; F: female; FIT: follicular infundibulum tumour; HN: hypernephroma; HyN: hypoplastic nipples; M: male; MD: macular degeneration; MDH: mild diffuse hyperkeratosis; mESFA: malignant eccrine syringofibroadenoma; Mi: milia; OA: optic atrophy; PP: photophobia; PPK: palmo-plantar keratosis; UF: uterine fibroma; VD: vitreous degeneration.

i.e. Bazex-Dupré-Christol and Rombo syndromes, show features of ectodermal dysplasia together with proneness to adnexal tumours. However, the presence of atrophoderma vermiculatum, the predilection for basal cell carcinomas, and the absence of palmo-plantar ESFA and EAHCs in these two syndromes facilitate differential diagnosis (19, 20).

In addition to the classical SSPS features, our patients also show nipple and areola hypoplasia, which has never been reported in this condition. However, this finding is perfectly in line with the abnormal cutaneous development characteristic of ectodermal dysplasias, and its actual frequency in SSPS might be underestimated, possibly as a result of incomplete evaluation. Nipple hypoplasia may represent an interesting clue in elucidating the pathogenesis of SSPS. In fact, mammary gland, tooth and hair follicle embryonic developments share the activation of similar sets of signalling molecules before proceeding

in divergent pathways. In particular, emerging evidence demonstrates the primary role of the WNT/ β -catenin pathway in early mammary gland, tooth and hair development (21). This is also confirmed by the identification of pathogenic mutations in the *PORCN* and *WNT10A* genes in patients affected with focal dermal hypoplasia and odonto-onycho-dermal dysplasia, respectively (22, 23). It is noteworthy that the latter is an ectodermal dysplasia that shares unusual features, including facial telangiectases and PPK, with SSPS. Therefore, *WNT10A* and other co-expressed WNT genes may be good candidates for SSPS. These genes include the WNT effector protein LEF1, which is commonly mutated in adnexal tumours of the sebaceous type (24).

The relevance of optic disc atrophy seen in patient 1 remains to be established, as the occurrence of eye globe findings is low in SSPS and could be, in part, related to the advanced age at diagnosis (8, 13).

Schöpf-Schulz-Passarge syndrome was first described as an autosomal recessive condition (1). On the basis of the literature review (see Table I), nine pedigrees with two or more affected siblings and healthy parents, as well as two sporadic cases with consanguineous parents (including our patient 1) fit this hypothesis (1, 5, 7, 9, 10, 14, 15). Conversely, in three families the disease is clearly transmitted in a dominant fashion with occasional healthy or non-penetrant carriers (3, 7, 12). Craigen et al. (4) described a pedigree with three affected brothers and an affected half-sibling. In this pedigree, the authors cited either uniparental isodisomy for an autosomal recessive trait or an autosomal dominant mutation with lack of penetrance to explain disease transmission. Therefore, genetic heterogeneity with both autosomal recessive and dominant variants could be hypothesized for SSPS. However, no differential expression of the disease has been observed between families with apparently different inheritance patterns. Moreover, in the four pedigrees with vertical transmission of the disease, pseudodominant inheritance for an autosomal recessive mutation cannot be excluded. Accordingly, although SSPS is apparently rare, its benign natural history and advanced mean age at diagnosis suggest that the frequency of the disease and, consequently, of healthy carriers could be underestimated. Further molecular studies are required in order to clarify this point.

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