Clinicopathological diversity of syringomas

A study on current clinical and histopathologic concepts

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Introduction

Usually, syringomas display a wide spectrum of benign adnexal neoplasms derived from the intraepidermal part of eccrine sweat ducts.¹ Women are more frequently affected than men. Syringomas mainly occur in the periorbital area, but also affect the scalp, forehead, neck, abdomen and extremities. A variety of clinical presentations of syringomas have been published, as well as cases associated with Down syndrome¹ and familial syringoma. The eruptive occurrence of multiple syringomas in healthy persons has been reported rarely. We report a small case series of patients with syringomas, highlighting the different clinicopathologic manifestations and variations, and review the recent literature.

Discussion

Histopathology findings and variants. In general, syringomas present as symmetrical and well-delimited lesions located in the upper part of the dermis. Usually, there is no connection to the overlying epidermis. Syringomas are composed of single-to-double-layered epithelial cells with pale eosinophilic cytoplasm. Epithelial cells, forming nests, cords or tubules, with a typical comma-like tail characterize the neoplasm. Within the tubular lumen, PAS-positive eosinophilic material exists.¹ Four clinical variants have been distinguished, following the proposal of Friedman and Butler in 1987, as follows:² local, disseminated, syringoma associated with Down syndrome, and inherited forms. Thus, several additional entities of histomorphologic characteristic features have been described in the recent literature, as discussed in the following.

Eruptive syringomas are commonly very rare.³ In a review of the literature by Soler-Carrillo et al.³ Sixty-four cases (48 females and 16 males) were evaluated between 1872 and 1999; the ages ranged between 1 and 77 years. In general, women are more frequently affected with eruptive syringomas than men; in the patient cohort reviewed by Soler-Carrillo et al.,³ 90% were females. In most cases, syringomas are asymptomatic

small papules, preferentially located on the neck, trunk, axillae, shoulders, abdomen and pubic area. The initial clinical diagnosis differs in most cases, in contrast to the classical finding of eye lid syringomas, where histopathologic confirmation is not required for diagnosis. Hence, definitive diagnosis of an eruptive syringomas can only be verified by histologic examination (Figs. 2 and 7).

A unique syndrome that includes eruptive syringomas is the *Nicolau-Balus syndrome*, consisting of eruptive syringomas of the disseminated micropapular type, milium cysts and atrophoderma vermiculata.⁴ Seven reports on eruptive syringomas in patients with Down syndrome have been published.^{3,5-8} Further associations included urticaria pigmentosa, simulating milia and familial cases of eruptive syringomas.³

Although the definition of syringomas as benign neoplasms of the eccrine duct is widely accepted, the pathomechanisms and the genuine neoplastic character of eruptive syringomas are controversial. As reported in two cases by Requena et al.⁹ eruptive syringoma occur as a consequence of chronic inflammatory processes of the skin involving adnexal structures. The authors propose the term, "syringomatous dermatitis," to outline the assumed underlying inflammatory reaction because the patients revealed eczematous dermatitis with residual lesions that could be histopathologically-diagnosed as an eccrine syringoma.⁹

Supporting this theory of an inflammatory impulse leading to proliferation of parts of the eccrine duct epithelium, there are several reports of syringomas in scarring alopecia (Fig. 1),¹⁰⁻¹² prurigo nodularis,¹³ and following radiation therapy;¹⁴ the inflammatory trigger has not been elucidated. Syringomatous changes have even been reported in melanocytic lesions, mostly as an incidental finding.¹⁵⁻¹⁷ As presented in our case series, syringomatous proliferations are found in scarring alopecia of the scalp due to lichen planopilaris and in association with a lentiginous melanocytic proliferation (patients #1 and #4).

In the recent literature, the influence of hormones on the development of syringomas is discussed. This has been confirmed by the observation that syringomas have a much higher incidence in females and occur frequently before and around puberty.⁹ Further, pruritus is often associated with the menstrual cycle.¹⁸ The influence of hormones on the syringomatous reaction process is further supported by observations of an aggravation or manifestation of vulvar syringomas during pregnancy.^{19,20} Vulvar syringomas most often present as multiple flesh-colored or brown papules on the labia majora of women

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Figure 1. Reactive syringomatous proliferation in conjunction with scarring alopecia due to lichen planopilaris (patient #1), H&E, x200

Table 1. Clinical data

Number	Age	Gender	Location	Clinical findings	Accompanying (pathologic) findings	Symptoms	Familial history
1	67	f	Capillitium	Coincidental finding, no clinical relevance	Severe scarring alopecia due to lichen planopilaris	Asymptomatic	No
2	36	f	Vulva, labia majora	Multiple bilateral brownish papules	Morbus Crohn	Severe pruritus	No
3	18	f	Whole body	Eruptive disseminated brown papules	None	Slightly pruritic	No
4	75	f	Left preauricular region unilateral	Several yellow-brown papules	Coincidental finding in an excision specimen of a lentigo maligna	Asymptomatic	No
5	63	f	Lower eye lids bilateral	Several pale-yellow papules	None	Asymptomatic	No
6	50	f	Whole face	Disseminated yellow-brown papules	None	Asymptomatic	No
7	46	f	Periorbital region and forehead	Multiple bilateral brown papules	Psoriasis vulgaris	Severe pruritus	no
8	37	f	Periorbital	Multiple bilateral pale papules	None	Severe pruritus	No
9	63	f	Infraorbital on both sides	Multiple bilateral brown pale papules	Polymorphic light dermatosis	Slightly pruritic	No

in the third decade of life.²¹ Vulvar syringomas are thought to be a common cause of a mild-to-severe pruritus of the vulva, and therefore should be included in the differential diagnosis of vulvar pruritus.²¹ In case #2, syringomas were responsible for severe vulvar pruritus and also associated with chronic inflammatory bowel disease.

A very rare variant of syringomas is the so-called “miliun-like” syringomas, first described in 1987 by Friedmann and Butler.² Because of the syringomas unique clinical and histologic pattern, they must be distinguished from simple miliae. Histopathologically, miliun-like syringomas present as a keratinous cyst opening on the skin surface with numerous epithelial

strands in the surrounding dermal tissue. Typically for syringomas, ductal structures with eosinophilic amorphous material can be found.² Only 31 cases of these syringoma variants have been reported in the literature. In one of these cases, an association between trisomy 21 and focal calcification was found.²²

Very rare cases of syringomas with an atypical appearance have been described as unilateral lesions^{23,24} or simulating urticaria pigmentosa^{25,26} due to an increased content of mast cells. Furthermore, clear cell variants of syringomas have been described.²⁷ Clear cell syringomas represent rare histologic variants of syringomas with a bright and clear cytoplasm of the ductal epithelial cells due to increased content of intracellular glycogen. Clear-cell syringomas are clinically indistinguishable from ordinary syringomas and are thought to be a cutaneous marker for diabetes mellitus.²⁸⁻³⁰ None of the cases presented herein were milium-like or clear-cell-syringomas. In some cases, differential diagnosis between the so called plaque-type syringomas and microcystic adnexal carcinoma (MAC) of the skin can be very difficult, especially in superficial skin probes. MAC infiltrate much deeper into the dermis with regular involvement of subcutaneous structures and perineural and vascular-adventitial infiltration.³¹ In order to avoid unnecessary and even disfiguring surgery, histopathologic diagnosis of these plaque-type syringomas is mandatory.³²

Most syringomas are harmless and benign, but of an aesthetically-disfiguring nature. Regression of lesions in adulthood has been observed, but is exceptional. Therapeutic efficacy is often frustrating, due to the slow growth and multicentric occurrence and the risk of scarring due to therapeutic

Figure 2. Extensive syringoma located in the vulva, causing severe pruritus (patient #2), H&E, x100

Figure 3. Representative lesion of an eruptively disseminating syringomatosis (patient #3), H&E, x100.

Figure 4. Facial syringoma of patient #6 with fibrosing stroma reaction, H&E, x100.

Figure 5. PAS-positive staining of amorphous material within the cystic lumens, PAS stain, x200.

Figure 6. Epithelial cords lined by one or two layers of polygonal epithelial cells with comma-like tails, stained with cytokeratin marker AE1/AE3, $\times 100$.

Figure 7. Disseminated brownish papules at the chest and mammary of patient #3.

procedures. Treatment modalities, such as topical or systemic retinoids, electrodissection, laser ablation, cryosurgery, dermabrasion, electrocaustic therapy and chemical peelings have been attempted. However, all therapeutic options bear the risk of recurrence.³³⁻³⁵ Recently, there have been reports of successful treatments of syringoma with topical atropine.³⁶

Systematic approaches to all these therapeutic options are still lacking.

In summary, syringomas are benign neoplasms of the intra-epidermal portion of the eccrine sweat duct and typically affect females in the facial regions, predominantly in the periorbital region. There have been a number of published clinical and

histomorphologic variants (familial, milium-like, clear-cell, urticaria pigmentosa-like and vulvar), as well as many associated diseases and coincidental findings, such as Down syndrome or diabetes mellitus.

Materials and Methods

Nine patients with syringomas were referred to our department for evaluation between 2001 and 2008. All patients were females, with an age between 18 and 75 years (mean age, 50.5 years). The patient characteristics are summarized in Table 1.

In the cases presented, syringomas appeared as single or disseminated papules, yellow to brown in color, on the face in six of nine cases. Five of these patients had slight-to-severe pruritus. An eruptive occurrence was diagnosed in only one case. Of note, this 18-year-old female patient (#3) presented with a 3-year history of multiple skin lesions (Fig. 7). The disease started with few papules on the anterior neck and subsequent spread to the entire chest, abdomen, back and upper extremities. The submammary region was also affected. Syringomas were not present on the face, the palmoplantar region, or the lower extremities. The lesions were nearly asymptomatic, except for mild and occasional pruritus. Previous treatments with topical corticosteroids and phototherapy yielded no persistent improvement.

No laboratory abnormalities were detected in any cases. No family history of skin diseases or syringomas was reported. The physical examinations revealed multiple, disseminated, brown, isomorphic lesions, 1–5 mm in diameter, without follicular distribution. The Darier sign was negative. The remainder of the physical examination was without pathologic findings.

In one case, a syringomatous proliferation was observed coincidentally in a skin biopsy from the capillitium, associated with severe lichen planopilaris (#1; Fig. 1) in a further case (#4) as a dermal reaction pattern in an excision biopsy from a lentigo maligna. One patient had vulvar syringomas associated with severe vulvar pruritus (#2; Fig. 2) and a coincidental occurrence of Crohn's disease. In two cases, an association with psoriasis vulgaris (#7) and polymorphic light eruption (#9) could be

observed. None of the patients suffered from diabetes mellitus or trisomy 21.

Dermatopathologic findings. Skin biopsies of the patients presented were obtained either for diagnostic reasons or before laser ablation. All samples revealed a normal epidermis overlying a dermis filled with multiple cystic ducts and epithelial cords lined by one or two layers of polygonal epithelial cells with comma-like tails (Figs. 2 and 3). Mild fibroplasia of the surrounding stroma was observed (Fig. 4). The ductal lumens were filled with amorphous, periodic acid-Schiff (PAS)-positive material (Fig. 5). Routinely, haematoxylin-eosin staining was performed; special stains included the PAS reaction and elastica-van-Gieson stain, as well as immunohistochemical stains with cytokeratin markers (MN116 and AE1/AE3) epithelial cords lined by one or two layers of polygonal epithelial cells with comma-like tails (Fig. 6).

Conclusion

Syringomas occur frequently and predominantly affect women. These adnexal neoplasms are harmless and benign, but of an aesthetically-disfiguring nature since most often the face is affected. The histopathologic features are monomorphous with intriguing variations, e.g., clear-cell or milium-like variants. In the current literature, there is increasing evidence that the occurrence of eruptive syringomas or coincidental findings of these neoplasms in skin biopsies from scarring alopecia have to be discussed as an inflammatory dermal reaction pattern concerning the acrosyringium, the so-called syringomatous proliferation due to distinct inflammatory or hormonal stimuli.

As seen in the cases presented, most of the above-described variants of syringomas were found in the small patient cohort of our department. In agreement with recent reports, we also propose the term, reactive syringomatous proliferation, for most associations and coincidental findings of syringomas due to the absence of clinical features of a distinct clinicomorphologic entity.

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