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Cysts, Sebum, Papillae-*Syringocystadenoma papilliferum*

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Abstract

An exceptional, benign cutaneous adnexal tumour, *Syringocystadenoma papilliferum* is contemplated to arise from apocrine glands, apo-eccrine glands and infrequently from eccrine glands. *Syringocystadenoma papilliferum* concurs with conditions such as nevus sebaceous, verrucae, basal cell carcinoma, verrucous carcinoma, condylomata acuminata, apocrine nevi, eccrine or apocrine neoplasm such as tubular apocrine adenoma, apocrine hidrocystoma or papillary apocrine adenoma, trichoadenoma, apocrine cystadenoma, clear cell syringoma, metaplastic adenocarcinoma and ductal carcinoma. *Syringocystadenoma papilliferum* delineates sebaceous induction also cogitated in dermatofibroma and melanocytic nevi. Exophytic, papillary arrangement with stratified squamous epithelium is cogitated along with ducts lined by bi-layered epithelium. Immune reactivity to carcino-embryonic antigen (CEA), epithelial membrane antigen (EMA), variably gross cystic disease fluid protein -15(GCDFP-15), cytokeratins CK7 and CK19 is delineated. On dermoscopy, an exophytic papillary pattern of growth, centric depression, superficial erosions, crusts or ulcerated lesion and polymorphic blood vessels are demonstrated. Syringocystadenocarcinoma papilliferum and syringocystadenocarcinoma papilliferum in situ are distinct malignant analogues.

Keywords: Verrucous; Condylomata Acuminate; Eccrine; Dermatofibroma; Hamartoma; Pleuri-Potent Cells

Abbreviations: EGFR: Epidermal Growth Factor Receptor; CEA: Carcino Embryonic Antigen; EMA Epithelial Membrane Antigen.

Preface

Syringocystadenoma papilliferum is cogitated as an exceptional, benign cutaneous adnexal tumour. *Syringocystadenoma papilliferum* was initially propounded to be a hamartoma which is essentially an aberrant aggregation of normal tissue with congregation of follicular and infundibular structures, apocrine glands, epithelium lined ducts and sebaceous articulations. An estimated 50% instances of *Syringocystadenoma papilliferum* appear at birth and around 15% to 50% instances evolve during puberty or early childhood [1,2]. Origin of the tumour is contemplated to be chiefly from apocrine glands and infrequently from eccrine glands. Apo-eccrine glands are also implicated in the genesis of the tumefaction. Pleuri-potent cells are incriminated in tumour evolution. Allelic deletions are delineated in chromosome 9p21, p16 and 9q22 (the patched gene). Special histological stains, cogent immune histochemistry and electron microscopy indicate a divergent origin of the tumour which is thus variably cogitated as being of apocrine, eccrine, or apo-eccrine glandular morphogenesis. Cutaneous adnexal tumours are a

heterogeneous coterie of neoplasm which are challenging to ascertain on clinical exemplification and histology.

Disease Characteristics

Syringocystadenoma papilliferum is an exceptional, benign adnexal tumour commonly situated in the scalp or face of children or adolescents. An estimated one fourth instances delineate lesions situated in alternative sites. Approximately one third of lesions are affiliated with an organoid nevus. *Syringocystadenoma papilliferum* concurs with conditions such as nevus sebaceous in an estimated 8% to 19% of subjects, verrucae, basal cell carcinoma, verrucous carcinoma, condylomata acuminata, apocrine nevi, eccrine or apocrine neoplasm such as tubular apocrine adenoma, apocrine hidrocystoma or papillary apocrine adenoma, trichoadenoma, apocrine cystadenoma, clear cell syringoma, metaplastic adenocarcinoma and ductal carcinoma [2,3]. An intraductal carcinoma of the breast and invasive carcinoma of ectopic breast tissue situated on the vulva are rare lesions which can be associated with *Syringocystadenoma papilliferum*. *Syringocystadenoma papilliferum*, apocrine hidrocystoma and tubular papillary adenoma are contemplated as heterogeneous cutaneous neoplasm.

As morphological features pertaining to benign adnexal neoplasm can concur in a singular lesion, a nomenclature of "tubulocystic adenoma with apocrine differentiation" can be proffered for aforesaid lesions. An estimated 10% of *Syringocystadenoma papilliferum* can progress to a basal cell carcinoma. The concordance is attributed to identical allelic deletions cogitated in human homologue of Drosophilia patched gene (PTCH). *Syringocystadenoma papilliferum* is concurrent with apocrine hidrocystoma and emerges from multi-potent, undifferentiated cells which sequentially differentiate towards the dual cellular genealogy. *Syringocystadenoma papilliferum* is probably the sole neoplasm which triggers the differentiation of primeval cells into an apocrine hidrocystoma [3,4]. *Syringocystadenoma papilliferum* delineates sebaceous induction, a phenomenon which is usually cogitated in lesions such as dermatofibroma and melanocytic nevi.Sebaceous induction elucidated in *Syringocystadenoma papilliferum* is essentially defined as the occurrence of two or more rudimentary sebaceous glands enveloping extraneous zones of the cutaneous lesion in the absence of a normal hair follicle.

Although the aetiology is obscure, mechanics of sebaceous induction involves pleuri-potent cells composing immature sebaceous articulations at a specific anatomic site, growth factors secreted by contingent lesions such as a dermatofibroma, apocrine hidrocystoma or *Syringocystadenoma papilliferum*, a cogent alteration of micro-environment, ectopic hedgehog signalling and declining mobilization of β catenin [4,5]. Undifferentiated, peripherally arranged sebocytes are intensely immune reactive to epidermal growth factor receptor (EGFR) and the pertinent molecule (EGFR) with specific ligands are implicated in the differentiation of sebocytes and efficient lipogenesis. Immature sebocytes are responsive to epidermal growth factor receptor (EGFR) and EGFR signalling is delineated in configuring sebaceous induction. Rudimentary or primeval sebaceous glands are exceptionally cogitated in nevus sebaceous [5,6].

Malignant Analogues

Syringocystadenocarcinoma papilliferum is a malignant transformation which can be discerned in conjunction with the benign *Syringocystadenoma papilliferum*. Syringocystadenocarcinoma papilliferum can metastasize to regional lymph nodes. Syringocystadenocarcinoma papilliferum in situ is characterized by a haphazard proliferation of atypical epithelial cells accumulated within the papillary architecture of *Syringocystadenoma papilliferum*. The lesion is devoid of tumour infiltration of the encompassing dermis. Morphology of syringocystadenocarcinoma papilliferum is identical to syringocystadenocarcinoma papilliferum in situ, thereby indicating that the non-infiltrative, cystic constituents precede an infiltrative pattern of tumour evolution [6,7]. An axillary localization with predisposition for malignant transformation is exceptional for in situ carcinoma. In situ variant describes an intracystic proliferation of aberrant epithelium and is devoid of dermal infiltration. Lesions depict a morphological continuum from a benign neoplasm to diverging gradations of atypia and an invasive syringocystadenocarcinoma papilliferum. However, mechanics of grading the exceptional, infiltrative tumefaction remain obscure. In situ variant can be appropriately alleviated with a comprehensive surgical elimination. Syrinogocystadenocarcinoma papilliferum can concur with the benign equivalent. It can be challenging to determine estimated risk of malignant transformation of *Syringocystadenoma papilliferum* on account of rare incidence of neoplasm [7,8].

Clinical Elucidation

Syringocystadenoma papilliferum discerned on the scalp at puberty can accompany a congenital nevus sebaceous. Of disputed origin, *Syringocystadenoma*

papilliferum has a predilection for frontal, ventral and temporal region of the scalp and forehead. Additional sites incriminated are chest, upper arms, male and female breast, eyelids, scrotum, thigh or exceptionally female genitalia. Solitary or numerous linearly configured papules, plaques or a divergent clinical configuration of an elevated, warty plaque or an uneven, flattened, greyish or reddish region can be cogitated. A magnitude of 1 centimetre to 3 centimetres is elucidated in commonly solitary lesions. Clinical representation of a plaque, nodule, verrucae or a lobulated exterior is enunciated. Alopecia is a frequent accompaniment of lesions of the scalp. Lesions usually amplify at puberty with the appearance of crusts and papillomatous excrescences [8,9].

Histological Elucidation

Syringocystadenoma papilliferum comprises of inverted duct like architecture with a lining squamous epithelium which metamorphoses into dual layer of cuboidal or columnar epithelium. Circumscribing stroma demonstrates an abundance of plasma cells. Distended ducts tend to configure cystic spaces or villous projections. Sebaceous glands cogitating *Syringocystadenoma papilliferum* can exhibit distinctive features [2,3]. An absence of sebaceous hyperplasia is noted along with immature and reduced quantities of sebaceous glands which lack an evolutionary concordance with subject's age. Rudimentary sebaceous glands are delineated. Papillae and ductal configurations are devoid of cystic dilatation or cavities and lack continuity with superficial epidermis or infundibulum of hair follicles. An exophytic, papillary arrangement with a gradually transforming stratified squamous epithelium is cogitated abutting superficial epidermis accompanied by ducts lined by bi-layered epithelium. Numerous, variable configurations akin to ducts and cystic expanse validate the morphology of *Syringocystadenoma papilliferum* [9,10].

Immune Histochemical Correlation

Immune reactivity to carcino-embryonic antigen (CEA) and epithelial membrane antigen (EMA) is frequently represented in the epithelial cells. Gross cystic disease fluid protein -15(GCDFP-15) is variably elucidated in the tumour cells. Luminal columnar cells and basal cuboidal cells are immune reactive to cytokeratin (CK7) and beyond > 70% cells are immune reactive for CK19. Immune reactivity within basal cuboidal cells for cytokeratin (CK19) is divergent. Elucidation of immunoglobulin (IgA) and secretory component is discerned. Basal cuboidal cells tend to induce plasma cell ingress identical to the immune secretory glands [10,11]. Immune reactivity for CK AE1 and variable expression of S100 protein is cogitated. Malignant category exemplifies an immune staining pattern recapitulating the superficial non- infiltrative and deep-seated, infiltrative portion of the tumour. Dual components are immune reactive to CEA, S100 protein and cytokeratins especially CK8.The infiltrating segment is immune reactive to EMA. In situ variant is immune reactive to CK AE1 with a varying reactivity to CEA and non reactivity to S-100 protein [11,12]. Immune reactivity to Ki 67 antibody implies an enhanced proliferation of atypical epithelial cells. P63 is cogitated as a superior antibody for elucidating basal cells within the in situ tumour subcategory and can be employed for discovering tumour infiltration at varying depths in multiple paraffin embedded sections. Immune histochemical elucidation is inadequate in expressing malignant transformation as staining of normal columnar or atypical epithelium is essentially quantitative and divergent. Eccrine origin of the tumefaction is contemplated on account of elucidated eccrine specific immune marker IKH4 [3,4].

Dermoscopic Manifestations

Syringocystadenoma papilliferum on dermoscopy is characterized by an exophytic papillary pattern of growth. A centric depression, superficial erosions, crusts or ulcerated lesion and polymorphic blood vessels are cogitated in a majority of instances. Oily, amorphous, milky white zone is discovered on account of luminal disposition of tumour confined to the aerola or mammary region [11,12]. Predominantly nodular lesions consistently exhibit aberrant blood vessels, papillary lesions depict exophytic pattern of growth whereas plaque like lesions are demonstrated at the periphery. *Syringocystadenoma papilliferum* in combination with nevus sebaceous enunciate a confluence of yellowish red areas or amorphous yellow zones. A whitish, central region with a circumscription of linear vessels is cogitated. Additionally, pinkish white globular configurations with variably disposed linear or hairpin blood vessels and a yellowish crust is enunciated. Yellow tinted, globular articulations are delineated in an erythematous backdrop with lesions essentially comprised of exophytic, whitish red papillary arrangements. Linear and polymorphic blood vessels are exemplified within blue-tinged globular framework. When associated with multiple pigmented trichoblastoma, *Syringocystadenoma papilliferum* located on the scalp delineates a non-homogenous, greyish blue zone abutting a peripheral, linear vascular pattern [12-25] (Figures 1-15).

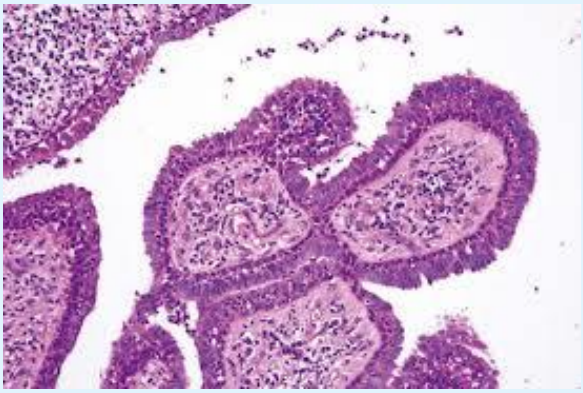

Figure 1: Papillary stalks lined with double layered cuboidal epithelium and stromal aggregates of plasma cells [14].

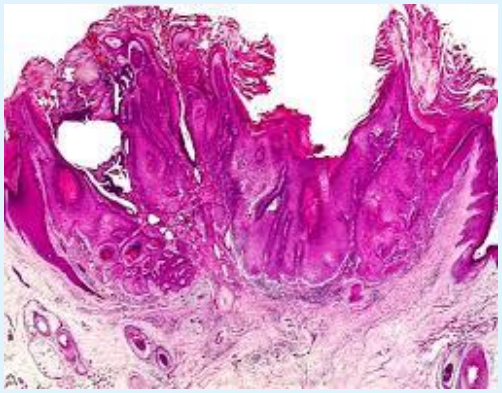

Figure 2: Papillary stalks and cystic dilatation of *Syringocystadenoma papilliferum* with accompanying foci of squamous cell carcinoma [15].

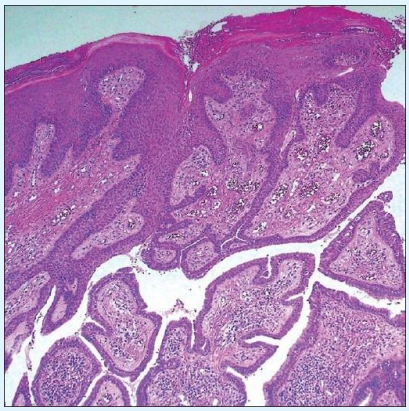

Figure 3: Papillae and stalks of *Syringocystadenoma papilliferum* with enveloping stratified epithelium [16].

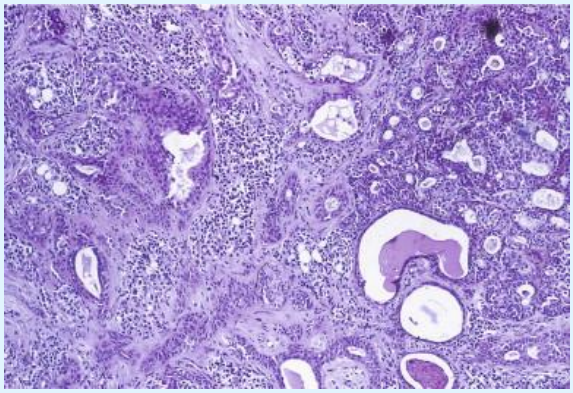

Figure 4: Cysts and tubules of *Syringocystadenoma papilliferum* with stromal fibrosis and plasma cell exudates [17].

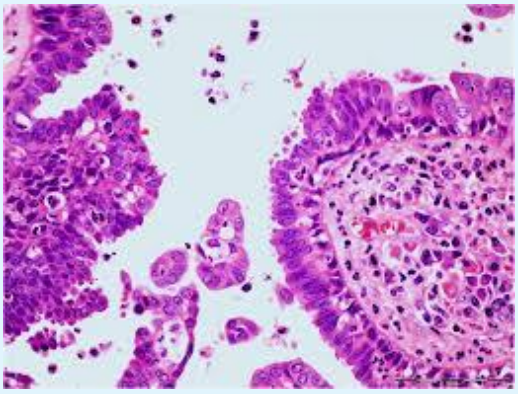

Figure 5: Dual layered cuboidal epithelium with stromal aggregates of plasma cells [18].

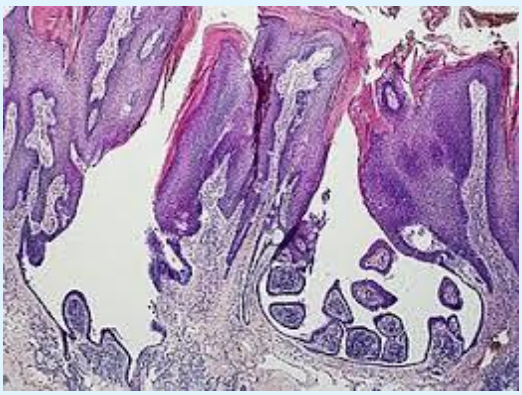

Figure 6: Cavities, stalks and papillae of *Syringocystadenoma papilliferum* [19].

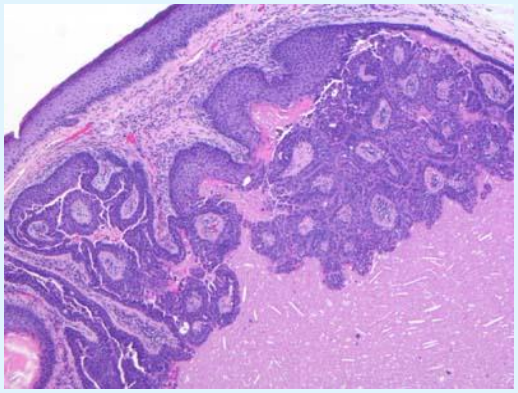

Figure 7: Superimposed epithelium overlying tubules, cysts and cavities with a peripheral chronic inflammatory infiltrate recapitulating *Syringocystadenoma papilliferum* [20].

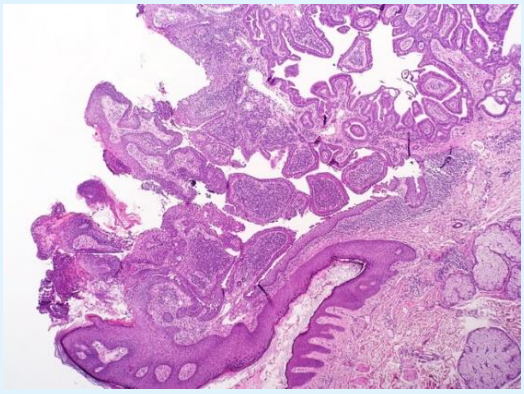

Figure 8: Epithelium lined papillary projections and cysts of *syringocystdenoma papilliferum* [21].

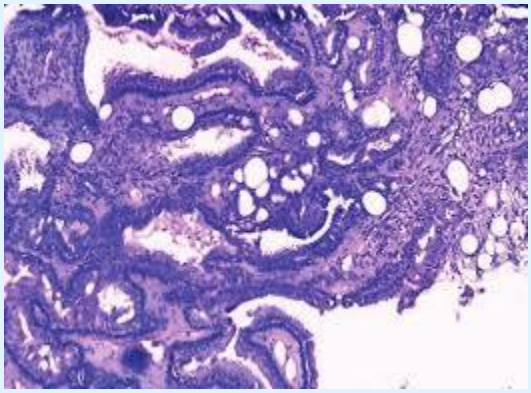

Figure 9: Papillae lined with cuboidal epithelium and fibro-vascular stalk with plasma cell ingress [22].

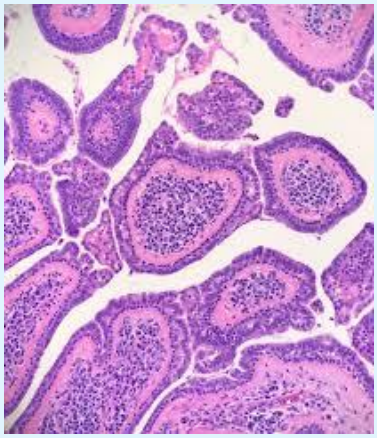

Figure 10: Plasma cell aggregates confined to the stalks, papillae and stroma of *syringocystdenoma papilliferum* [23].

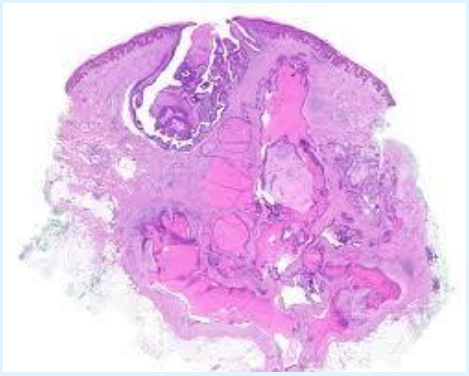

Figure 11: Whole mount view of *syringocystdaenoma papilliferum*, invaginating from superimposed epithelium [23].

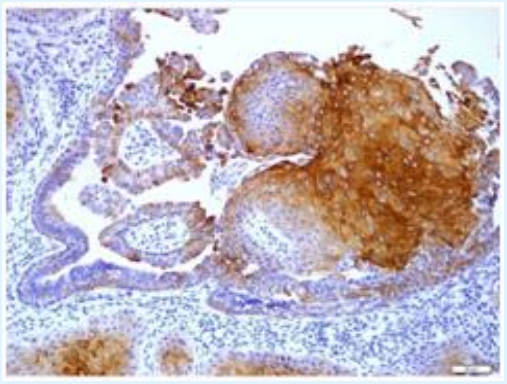

Figure 12: Immune reactivity to CK5/6 in *Syringocystadenoma papilliferum* [24].

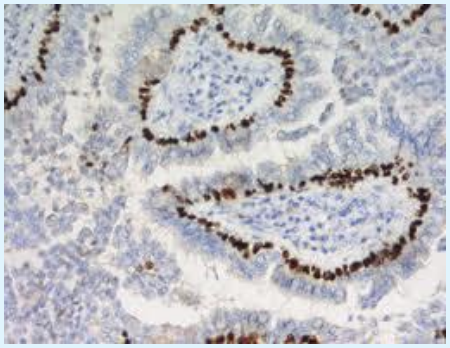

Figure 13: Immune reactive anti p63 in basal cell nuclei in *Syringocystadenoma papilliferum* [25].

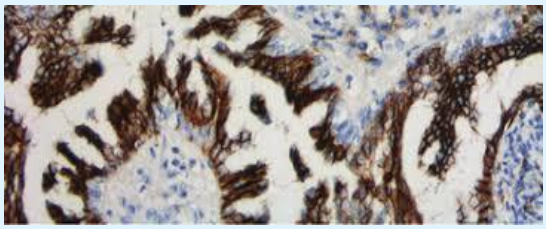

Figure 14: Immune reactive anti CD56 in proliferating cells of *Syringocystadenoma papilliferum* [25].

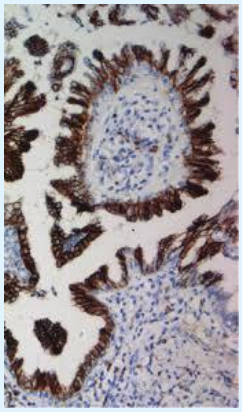

Figure 15: Immune reactive anti CD56 in proliferating cells of *Syringocystadenoma papilliferum* [25].

Differential Diagnosis

Syringocystadenoma papilliferum necessitates a demarcation from nevus sebaceous, a lesion contemplated as a complex hamartoma and constituted of sebaceous glands with adjunctive adnexal structures. Sebaceous glands comprising nevus sebaceous can display signs of excessive maturity. Additionally, absence or reduced quantification of sebaceous glands is cogitated in an estimated 10% to 20% individuals, especially infants. Sebaceous hyperplasia is commonly elucidated at puberty. Miniature lobules of sebaceous glands and glandular articulations are continuous with or directly extend to the superficial epidermis or a characteristic adherence to infundibular region of hair follicles is exemplified [2,4]. *Syringocystadenoma papilliferum* arising in the female genitalia mandates a distinction from hidradenoma papilliferum which represents a benign, asymptomatic tumefaction of apocrine sweat glands. A dome shaped tumour emerges from the inter-labial sulcus. On histology, hidradenoma papilliferum characteristically demonstrates complex, delicate, branched, frond like papillae with a fibro-vascular core. The tumefaction lacks continuity to extraneous epithelium. Papillae and fibro-vascular stalk displays a dual epithelial layering, external cuboidal to columnar epithelial cells and intrinsic myoepithelial cells. Absence of plasma cells in the papillary stalks is also cogitated [3,5] (Table 1).

Antibody	Basal Cells	Columnar Cells	Atypical Cells
AE1/AE3	+++	+++	+++
BCCK	+++	+++	+++
Ber-Ep4	-	+/++	+/++
CK5/6	+++	++	++
CK7	+	++	++
CK8	-	+++	+++
EMA	-	++	++
p63	+++	-	-
CEA	-	-	+
CD56	-	+	+++
S-100	-	-/+	+/++
SMA	++	-	-
VIM	++	+	+
Ki67	~10%	~3%	~50%

BCCK- basal cel cytokeratin, EMA- epithelial membrane antigen, CEA- carcinoembryonic antigen, S-100- S-100 protein, SMA- smooth muscle actin, VIM- vimentin

Table 1: Immune profile of *syringocystadenocarcinoma papilliferum in situ* [4].

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