

Clinicopathological Features of Syringocystadenoma Papilliferum and Its Malignant Counterpart: A Single-Center Experience

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Abstract

Purpose: Syringocystadenoma papilliferum (SCAP) is a rare benign adnexal tumor with a distinctive histomorphology. Occasionally, there is a diagnostic difficulty, especially in separating it from its malignant counterpart, syringocystadenocarcinoma papilliferum (SCACP). Our study was designed to assess the clinicopathological features of SCAP and to identify features that could help differentiate it from its malignant counterpart at the other end of the spectrum. **Materials and methods:** A retrospective analysis of 11 SCAP cases and one SCACP case diagnosed over a 15-year period at a single institution was performed. Clinical data and histopathological features were evaluated, and statistical analyses were conducted to assess associations between selected variables. **Results:** The cohort had a slight female predominance (54.5%) with a mean age of 46.5 years. The most common site was the scalp, with rare sites including the axilla and scrotum. All cases showed classic histological features of prominent papillary architecture and abundant plasma cell infiltrates. Endophytic growth was the predominant pattern (72.7%). Ulceration was observed in 4 cases, including the malignant case. Notably, benign cases exhibited up to 5 mitoses per 1 mm² and minimal atypia in 45.5% of cases, with no significant association between mitotic activity and atypia. A case of SCACP was diagnosed based on infiltrative growth and atypia. **Conclusion:** Our study indicates that mitotic activity and mild atypia, by themselves, do not should not be interpreted as sufficient evidence of malignancy; infiltrative growth and other features of aggressive behavior need to be considered. Larger studies need to be designed to refine these criteria.

Keywords: Adnexal neoplasms, syringocystadenoma papilliferum, syringocystadenocarcinoma papilliferum

1. Introduction

Syringocystadenoma papilliferum (SCAP) is a rare benign cutaneous adnexal tumor, first described by Stokes in 1917, and is thought to originate from apocrine and/or eccrine sweat glands¹. To date, approximately 730 cases have been reported, the majority of which are located in the head and neck region, particularly the scalp and face². More rarely, cases involving the eyelid, vulva, scrotum, breast, trunk, and extremities have been described³⁻⁹. Molecular studies have demonstrated that sporadic SCAP cases harbor BRAF V600E and

HRAS mutations, whereas lesions arising in association with nevus sebaceous (NS) share the underlying HRAS mutation characteristic of the nevus¹⁰. These findings suggest a central role for the RAS/MAPK pathway in tumor pathogenesis and indicate a possible shared biological background with other apocrine tumors, such as tubular apocrine adenoma and papillary eccrine adenoma¹¹. In addition to these associations, SCAP has been reported in conjunction with NS, basal cell carcinoma (BCC), and verrucous carcinoma^{3,12}. Although most cases are congenital, lesions may also develop later in life. While these tumors typically follow a benign clinical course, rare cases may undergo malignant transformation, giving rise to syringocystadenocarcinoma papilliferum (SCACP). This study aimed to evaluate the clinical and histopathological features of SCAP cases within the malignancy spectrum and rare SCAP cases obtained from our institution's archives, and to identify findings that can serve as reliable indicators of malignancy and provide practical benefits to clinicians or pathologists in differential diagnosis.

2. Material and Methods

2.1. Study Design, Data Collection

This study included a total of 11 cases of SCAP and one case of SCACP diagnosed over the past 15 years at Ondokuz Mayıs University, reflecting the rarity of these tumors. The study was retrospective, and given the uncommon nature of these lesions, may be considered a relatively comprehensive series from our institution. Histological slides were retrieved from the archives and re-evaluated independently by two pathologists (DB, LY). There were no discrepancies between the diagnoses made by the pathologists. Clinical and pathological data were systematically recorded. This study was approved by the Institutional Ethics Committee of Ondokuz Mayıs University Hospital (protocol number 2026/258, approval date: 29.04.2026)

2.2. Statistical Analysis

Statistical analyses were performed using Jamovi software (version 2.6.26). Descriptive statistics for numerical variables were presented as mean $\pm$ standard deviation and median (minimum-maximum); for categorical data, they were expressed as frequencies and percentages. The association between NS and congenital tumors, as well as the relationship between the presence of mitosis and atypia, was evaluated using Fisher's exact test due to small sample size. A p-value of <0.05 was considered statistically significant.

3. Results

Among patients with SCAP, 45.4% (5/11) were male, and 54.5% (6/11) were female. Median age of patients was 51 years (range 7-77, mean 46.5 ± 21.2). Regarding clinical onset, the lesions were congenital in 3 cases, whereas 4 patients reported acquired lesions with a symptom duration ranging from 3 to 60 months. No statistically significant association was observed between congenital tumors and NS ($p=0.152$); however, the study was underpowered to detect associations because of the small sample size.

3.1. Localization and Clinical Findings

The most common site of tumor involvement was the scalp, observed in 8 patients. Other head and neck locations also constituted the majority, including one case on the cheek and another on the neck. In addition, one case each was identified in the scrotum and axilla. The symptomatic distribution was analyzed based on individual occurrence rates. Swelling was the most prevalent symptom, reported by 63.6% ($n=7$) of the patients. This was followed by erythema and roughened surface, both appearing in 27.3% ($n=3$) of the patients. Discharge was recorded in 18.2% ($n=2$) of the patients. Clinical data were unavailable for one patient (9.1%) (Figure 1). Notably, several patients presented with

overlapping symptoms; the most frequent clinical combinations were swelling associated with discharge and roughened surface associated with erythema, each occurring in 18.2% of the total patient group (Table 1).

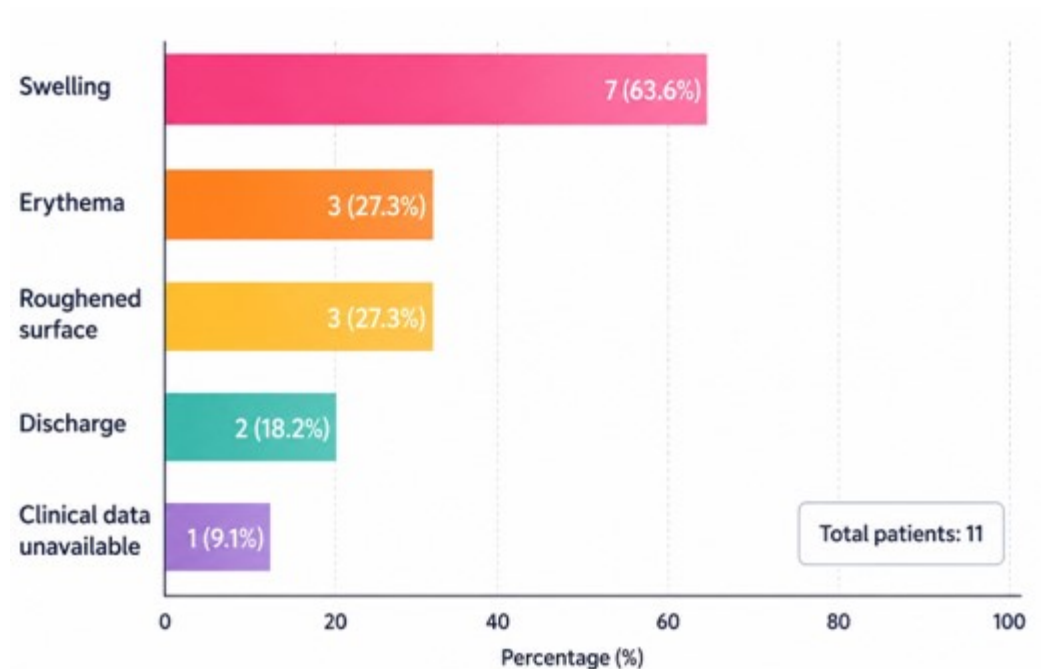


Figure 1. Individual symptom frequencies

Table 1: Distribution of symptoms and combinations thereof.

Symptoms	Counts	% of Total
Swelling	4	36.4%
Roughened surface, erythema	2	18.2%
Swelling, discharge	2	18.2%
Roughened surface	1	9.1%
Swelling, erythema	1	9.1%
N/A	1	9.1%

N/A: Data unavailable

3.2. Clinical Outcomes

Surgical treatment began with biopsy followed by total excision in 2 cases, while primary excision was performed in the remaining cases. Surgical margins were negative in 11 SCAP patients. Only one SCAP case had positive margins. 10 patients diagnosed with SCAP underwent a postoperative clinical assessment within 1 month after excision, after which routine follow-up was discontinued. Therefore, a formal follow-up duration was not available for these patients. A patient with SCACP and a SCAP with positive surgical margin was followed up for 12 months, at 3 and 6 months post-surgery, after which routine follow-up was terminated. The total follow-up period was 12 months. No recurrence was observed.

3.3. Macroscopic and Histopathological Findings

Upon macroscopic examination, most lesions were nodular (n=9, 81.8%), while the remaining cases presented as plaque-like (n=2, 18.2%). Median size of tumors was 6 mm (range 2-20 mm, mean 8.18 ± 5.36 mm).

Histopathologically, all tumors demonstrated direct connections to the epidermis. The infiltrate was characterized by typical plasma cells accompanied by intraepithelial neutrophil-rich inflammatory cell infiltration (Figure 2). Additionally, ulceration was observed in 27.3% (n=3) of the SCAP cases. All cases involving ulceration showed an endophytic growth pattern.

The growth patterns of the lesions were evaluated, with endophytic growth being the most dominant type, observed in 72.7% (n=8) of the cases. Exophytic growth was identified in 18.2% (n=2) of the patients, while a mixed pattern (both exophytic and endophytic) was recorded in 9.1% (n=1) of the study group. Overall, lesions with an endophytic component (either isolated or mixed) accounted for 81.8% of the total cases.

Regarding the general architectural patterns of the lesions, a papillary pattern was the most dominant feature, present in all cases (n=11, 100%). Specifically, 72.7% (n=8) of the lesions exhibited purely papillary morphology. The remaining cases showed more complex, mixed architectural patterns: 9.1% (n=1) presented with a combination of cribriform, tubular, solid, and papillary structures; 9.1% (n=1) demonstrated a papillary and tubular pattern; and 9.1% (n=1) showed a cystic, papillary, and tubular configuration. When the architectural patterns were analyzed individually, tubular component was 27.3% (n=3) (Table 2).

Table 2. Distribution of the overall microscopic patterns of the lesion.

Microscopic pattern of the lesion	Counts	% of Total
Papillary	8	72.7%
Papillary, cribriform, tubular, solid	1	9.1%
Papillary, tubular	1	9.1%
Papillary, tubular, cystic	1	9.1%

Mitotic activity was assessed in all cases to evaluate the proliferative characteristics of the lesions. The majority of the study group exhibited low mitotic counts, with no mitotic figures observed in 63.6% (n=7) of the cases. Among the remaining cases, 9.1% (n=1) showed 1 mitosis per 1mm², 18.2% (n=2) showed 3 mitoses, and 9.1% (n=1) exhibited a maximum count of 5 mitoses. The maximum count of mitoses was observed in a SCAP case. Minimal atypia was present in 45.5% (n=5) of cases. No significant association was observed between mitotic count and the presence of atypia (p=0.152), however, this finding should be interpreted cautiously given the small sample size. No necrosis was observed in the tumors. Accompanying nevus sebaceous morphology was present in 27.27% of cases (n=3). In addition, BCC was present in 18.18% of cases (n=2).

Within the study spectrum, one specific case was identified as SCACP in a 73-year-old male patient. The lesion, located on the scalp, presented as a nodular mass measuring 20 mm in diameter, with a clinical duration of 40 months. Both endophytic and exophytic growth were observed, accompanied by ulceration. In contrast to the predominantly papillary and benign architecture of the other 11 tumors, the general pattern of this tumor was predominantly solid, containing squamous eddies, clear cell changes, and eosinophilic basement membrane-like material situated between solid nests. Distinct infiltrative tumor islands were present at the periphery of the lesion. The tumor cells displayed cytological atypia (Figure 3). The mitotic rate was recorded as 3 mitoses per 1 mm². Apart from tumor-specific plasma cells, no inflammatory reaction was observed around the tumor.

No necrosis was observed (Table 3). Immunohistochemistry was not systematically available in our series. It was only performed on 2 cases, and in these cases, CEA and EMA were positive in ductal cells, and p63 was positive in basal cells. In these two cases, one with only 3 mitoses per 1 mm² and minimal atypia, and the other diagnosed with SCACP, the Ki67 proliferation index reached rates as high as 20% in the areas where it was most concentrated.

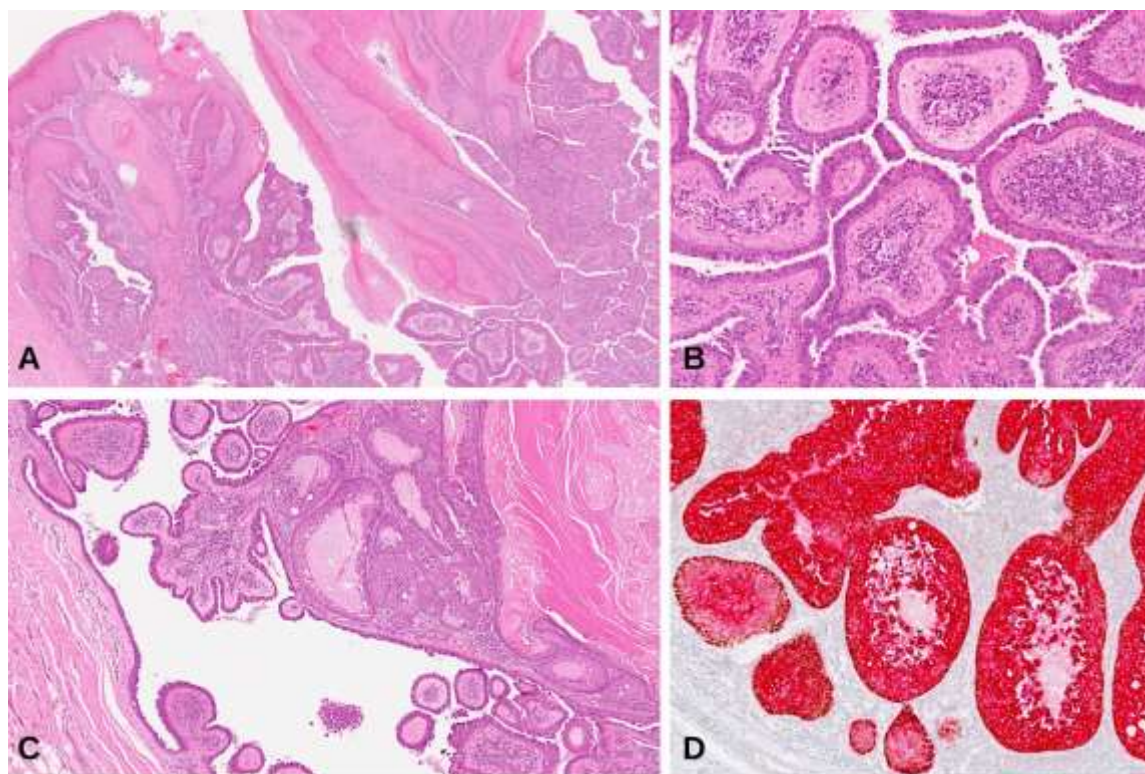


Figure 2. Histomorphological appearance of syringocystadenoma papilliferum. A: Papillary tumor showing endophytic development from the epidermis (H&E: 30X). B: Plasma cell infiltration in fibrotic stroma in the centers of the papillae (H&E:100X). C: Keratin material in the duct in the upper right, as well as areas of intracystic tumor development on the left (H&E:40X). D: p63-positive cuboidal cells in the outermost layer and keratin7-positive columnar cells in the innermost layer (DAB-P63, AEC-keratin7: 100X).

Table 3. Clinical and histopathological characteristics of tumors

Case No	Year at diagnosis	Gender	Age	Location	Size (mm)	Time since Onset (months)	Diagnosis	Associated lesion	Ulcer	Mitosis (/1mm ²)	Atypia
1	2014	Female	44	Scalp	4	Congenital	SCAP	NS	Absent	Absent	Absent
2	2013	Male	25	Scalp	4	Congenital	SCAP	Absent	Present	Absent	Absent
3	2015	Female	69	Scalp	8	60	SCAP	Absent	Absent	Absent	Absent
4	2016	Male	77	Cheek	9	N/A	SCAP	Absent	Absent	Absent	Absent
5	2019	Female	30	Neck	6	N/A	SCAP	Absent	Absent	Absent	Minimal
6	2023	Female	51	Scalp	6	3	SCAP	BCC	Present	Absent	Absent
7	2022	Female	7	Scalp	11	Congenital	SCAP	NS	Present	1	Absent
8	2021	Male	62	Scalp	2	N/A	SCAP	NS, BCC	Absent	Absent	Minimal
9	2025	Male	60	Scrotum	5	N/A	SCAP	Absent	Absent	5	Minimal
10	2020	Female	31	Scalp	20	3	SCAP	Absent	Absent	3	Minimal
11	2025	Male	56	Axilla	15	40	SCAP	Absent	Absent	3	Minimal
12	2023	Male	73	Scalp	20	40	SCACP	NS	Present	3	Present

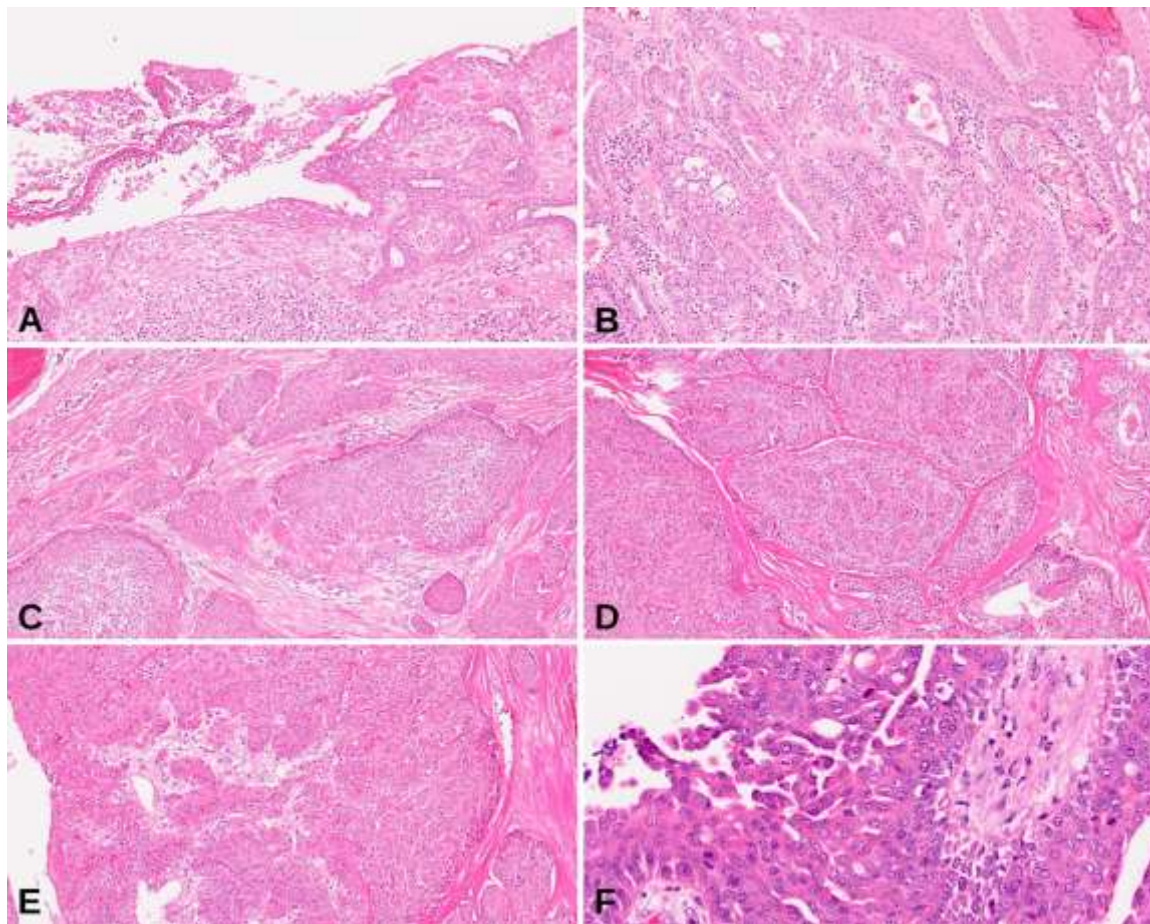


Figure 3. Histomorphological appearance of syringocystadenocarcinoma papilliferum. A: Ulceration on the tumor surface (H&E: 50X). B: Tumor areas in a tubular and cribriform pattern (H&E:100X). C: Infiltrative areas in a solid pattern at the tumor periphery (H&E:100X). D: Basement membrane-like material around infiltrative tumor areas and squamous eddies in the tumor (H&E:100X). E: Clear cell areas within the tumor (H&E:100X). F: Atypical and mitotic active areas of the tumor (H&E:400X).

4. Discussion

Approximately 30–40% of SCAPs arise in association with NS, and these lesions are typically congenital. In our series, 4 of 12 cases showed an association with NS, half of which were congenital^{3,8}. De novo SCAPs, on the other hand, tend to develop more frequently after puberty. Although the presence of congenital cases in our cohort supports this tendency, no statistically significant association was demonstrated. The rate of coexistence with BCC was higher in our series compared with that reported in Helwig's study³.

4.1. Demographic Profile and Clinical Features

The age range of reported cases in the literature is generally between 2 and 70 years, and this wide distribution is attributed to the congenital nature of the tumor⁷. In our study, however, one patient was older than typically reported (77 years), and the onset time of the lesion in this case was unknown. Although some studies have reported a male predominance, our series showed a slight female predominance^{3,8}.

One of the notable findings of our study was the presence of rare anatomical locations. Axillary and scrotal involvement, which has been rarely reported in the literature, was also observed in our series^{6,13}. Given that these regions are rich in apocrine glands, they represent biologically plausible sites for tumor development and should be considered in the differential diagnosis.

Although three clinical variants have been previously described (verrucous plaque, irregular red/gray lesion, and, more rarely, linear papules) the most common clinical presentation in our series was a mass-like swelling¹⁴. Clinical diagnosis or subtyping is

generally not feasible, and diagnosis is primarily based on characteristic histomorphological features.

4.2. Malignant Counterpart

In SCAP cases, surgical excision is generally sufficient for treatment. However, malignant transformation may rarely occur, leading to the development of SCACP. SCACP was first described in 1980 by Dissanayake and Salm¹⁵. To date, fewer than 90 SCACP cases have been reported in the literature^{16–18}. Most of these cases are thought to arise through malignant transformation of a pre-existing SCAP, while some are believed to develop de novo. Similar to SCAP, an significant association between SCACP and NS has also been reported^{16,19,20}.

The mean age of patients with SCACP was 66.3 years (range: 15–96 years), with a male predominance (59%). The average lesion size ranges from 3 mm to 160 mm¹⁶. Although lesions are most commonly located on the scalp and in the head and neck region, extremely rare localizations such as the ear, axilla, arm, trunk, breast, perianal region, genital area, and thigh have also been reported^{16,21–24}. The case in our study was consistent with the clinical and demographic features reported in the literature.

The local recurrence rate has been reported as 30–40%, while regional lymph node metastasis occurs in approximately 20% of cases and distant metastasis in about 6%^{16,23}. Considering the high risk of local recurrence, wide local excision with clear margins is recommended for treatment. Locally advanced tumors or cases with locoregional metastasis have been successfully treated with radiotherapy or chemotherapy⁷.

4.3. Histomorphology

SCAPs are arranged as enlarged papillary and cystic structures that open into the epidermis or follicle and grow towards the dermis. Apocrine differentiated deep glandular epithelium contains ducts with papillary projections, usually lined with two cell layers: an outer cuboidal myoepithelial layer and an inner columnar epithelial layer. Papillary structures often contain connective tissue rich in plasma cells^{14,25}. The endophytic growth pattern, the presence of plasma cells, and the predominance of papillary architecture are important diagnostic findings because they are present in all cases.

The histological and immunohistochemical characteristics of SCACP may not be clearly distinguishable from those of SCAP. The presence of ulceration and bleeding are associated with malignant progression²⁶. In our study, ulceration was identified in a total of four cases, including the malignant case. In the three ulcerated cases that were evaluated as benign, no atypia or increased mitotic activity was observed. Immunohistochemical positivity for EMA, CEA, and keratin7, indicating ductal differentiation, is among the most commonly encountered findings. It has been emphasized that the positivity of these markers may be partially reduced, particularly in areas showing desmoplastic growth²⁷. Although these tumors are diagnosed histomorphologically, immunohistochemistry is usually not required. However, when findings suggestive of malignancy are observed, as in the two cases in our study, markers indicating ductal differentiation and proliferation markers such as Ki67 can be used to support the diagnosis.

The main criteria evaluated for malignant transformation include infiltrative borders, increased mitotic activity, asymmetry, intraepidermal pagetoid spread, infiltration into subcutaneous adipose tissue, necrosis, and cytological atypia¹⁸. In our study, the presence of up to 5 mitoses per 1 mm² and minimal atypia in 45.5% of benign cases, along with the lack of association between mitosis and atypia, support that these findings alone cannot be considered definitive criteria for malignancy. In other words, not every increase in mitotic activity or presence of atypia is indicative of malignancy. This finding, which does not fully align with the current histopathological criteria used in the evaluation of

malignant tumors, is noteworthy in our study but requires confirmation in larger case series due to the limited number of cases.

The main limitations of this study include its single-center and retrospective design, as well as the limited sample size; however, the inclusion of rare tumors and atypical localizations enhances the value of the study.

This rare tumor exhibits highly characteristic histomorphological features in most cases. However, our findings suggest that differentiating SCAP from its malignant counterpart, SCACP, despite its typical morphological features, may be difficult in some cases. Our findings highlight that careful assessment of infiltrative growth patterns and other features of aggressive behavior is critical for accurate diagnosis, particularly given the risk of recurrence. Despite the limitations of this single-center retrospective study, our results provide practical morphological clues for differential diagnosis and underscore the need for larger, multicenter prospective studies to refine diagnostic and prognostic criteria.

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Ethics Approval and Consent to Participate: This study was approved by the Institutional Ethics Committee of Ondokuz Mayıs University Hospital (protocol number 2026/258, approval date: 29.04.2026) and was performed in accordance with the tenets of the Declaration of Helsinki. This study did not involve any human participants or animals performed by the authors. Owing to the retrospective nature of the study and the use of archival material, the requirement for written informed consent was waived.

Availability of Data and Materials: Dataset available on request from the corresponding author.

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Abbreviations: SCAP: Syringocystadenoma papilliferum NS: Nevus sebaceus BCC: Basal cell carcinoma SCACP: Syringocystadenocarcinoma papilliferum

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