Diagnostic Pitfalls in Syringocystadenocarcinoma Papilliferum

Case Report and Review of the Literature

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We report the first case, to our knowledge, of syringocystadenocarcinoma papilliferum with p63-verified squamous differentiation and extensive dermal invasion accompanying in situ components. An 86-year-old woman presented with a neoplasm on the neck, and the intralobular heterogeneity typical of these neoplasms led to an initial diagnosis on needle biopsy favoring squamous cell carcinoma. Excision illustrated diverse morphology, raising a broad differential diagnosis, including more common extracutaneous malignancies, such as breast, gastrointestinal, and ovarian primary tumors. Fortuitous sectioning revealed a focal connection to the skin surface with evidence of apocrine differentiation allowing final diagnosis as syringocystadenocarcinoma papilliferum. Our literature review shows the histologic and immunohistochemical features of syringocystadenocarcinoma papilliferum are not well defined outside of their clear morphologic overlap with syringocystadenoma papilliferum. We describe our findings and diagnostic pitfalls to help pathologists encountering this unusual apocrine neoplasm.

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Syringocystadenocarcinoma papilliferum is the rare malignant counterpart of a more common, benign adnexal neoplasm known as syringocystadenoma papilliferum. Since its first description in 1980, there have been only 12 reported cases, to our knowledge, of syringocystadenocarcinoma papilliferum (Table 1), although earlier reports suggested malignancy in syringocystadenoma papilliferum-like lesions or benign syringocystadenoma papilliferum with lymph node metastases.2,3 The diagnosis remains controversial because some authors maintain that there have been no well-documented cases of malignant transformation in syringocystadenoma papilliferum.4 We report a case of syringocystadenocarcinoma papilliferum showing focal morphologic similarity to syringocystadenoma papilliferum, but with cytologic malignancy and clear evidence of invasion.

Despite a few distinctive morphologic findings, many histologic and immunophenotypic features of this malignancy show significant overlap with more common metastatic adenocarcinomas, familiar to a surgical pathologist. Our report and review of the literature explores the potential diagnostic pitfalls that may result from the heterogeneity of these neoplasms. In addition, we provide the first description, to our knowledge, of squamous differentiation in the invasive component, which resulted in an initial diagnosis of invasive, poorly differentiated malignancy consistent with squamous cell carcinoma. We illustrate key histologic findings that allow for characterization as a primary cutaneous neoplasm and further classification as an apocrine malignancy.

REPOR CASE

An 86-year-old woman with no prior history of malignancy presented with a left neck mass. The mass had been present for 4 months and was initially treated as an infected sebaceous cyst with incision and drainage. Despite drainage and oral antibiotics, a large, asymmetric, exophytic and discolored lesion recurred at the incision site. The clinical impression was concerning for malignancy, and a needle core biopsy was performed.

Histologic sections showed infiltrating spindle cells within desmoplastic stroma. The invasive tumor cells stained strongly with cytokeratin AE1/3 and, weakly, with cytokeratin (CK) 5/6, with patchy nuclear p63 staining. The spindled morphology and p63 immunostaining supported an interpretation of the needle core biopsy as invasive, poorly differentiated carcinoma consistent with poorly differentiated squamous cell carcinoma. The patient had no clinical or radiographic evidence of a head and neck or lung primary, and her cancer was staged as T4N0M0 (stage IV) primary cutaneous squamous cell carcinoma of the neck. Surgical resection with cervical lymph node dissection was performed after a preoperative metastatic workup was confirmed to be negative.

Gross pathologic review demonstrated a skin ellipse with a central large, erythematous to violaceous, asymmetric papule with lobulated contours (Figure 1). There was a 4.5 x 4.0 x 4.0-cm, poorly circumscribed, firm, tan-white dermal-based mass, infiltrating into surrounding adipose tissue and muscle. Histologic sections confirmed an adenocarcinoma extensively involving the dermis and forming irregular, solid, and cystic glandular structures. Many cystic spaces contained complex micropapillary epithelial projections lined by variably single to multilayered, atypical, large, overlapping cells with high nuclear to cytoplasmic ratios. Immunohistochemical stains were positive for p63, CK AE1/3, and CK 5/6, with focal positivity for CD10, and with loss of expression for S100, MelanA, and desmin.

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mic ratios and coarse chromatin. Some areas showed a second population of cells with features of squamous differentiation, including abundant eosinophilic cytoplasm and intracellular bridges. A vigorous desmoplastic stromal response accompanied the widespread invasion and contained numerous plasma cells and lymphocytes. In some areas, the squamous element was seen spilling out of the glandular spaces as a poorly differentiated spindle cell carcinoma and blending deceptively with the adjacent desmoplastic stroma (Figure 2). A needle biopsy through these areas could be interpreted as an invasive squamous cell carcinoma because it would lack adequate representation of the glandular elements.

The glandular component demonstrated striking heterogeneity, raising a broad morphologic differential diagnosis, including various metastatic adenocarcinomas. The complex micropapillary architecture suggested metastatic ovarian carcinoma. In some areas, the glands were dilated with lining cells showing intracellular mucin production, and many glands contained central necrosis with neutrophils and cellular debris, reminiscent of the dirty necrosis seen in primary colonic adenocarcinomas. In other areas, the glands contained large oncocytes cells marked by abundant, dense eosinophilic cytoplasm and round nuclei with prominent nucleoli, compelling a consideration of metastatic breast carcinoma with apocrine features or even a Hu

This epithelial transition is a valuable indication of the neoplasm’s ability to recapitulate the normal physiologic relationship of the apocrine gland to the infundibulum of the hair follicle (Figure 4). It characterizes the benign primary cutaneous apocrine neoplasm syringocystadenocarcinoma papilliferum, which also shows a papillary architecture and elicits a lymphoplasmacytic inflammatory response. Other histologic hints include the decapitation secretion that provides evidence of apocrine differentiation. The clearly malignant features of this neoplasm required diagnosis as syringocystadenocarcinoma papilliferum, a rare, malignant, primary cutaneous adnexal carcinoma. The neoplasm extended to multiple resection margins with evidence of perineural invasion. Although the accompanying lymph nodes were negative for involvement, the patient received adjuvant radiation therapy. A posttreatment positron emission tomography scan was negative.

Immunohistochemical analysis was useful in confirming the diagnosis, although there is no definitive immunoprofile that can discriminate between a primary cutaneous and a metastatic adenocarcinoma. Immunohistochemistry provided further support to the apocrine nature of the neoplasm and helped to exclude a metastatic adenocarcinoma. The invasive neoplasm was positive for pancytokeratin, carinoembryonic antigen, CK7, and estrogen receptor, with focal cancer antigen-125 positivity. It was negative with CK20, gross cystic disease fluid protein-15, Wilms tumor 1, CDX-2, S100, and thyroid transcription factor 1. As on the needle biopsy, p63 immunostain was positive in the invasive neoplastic component (Figure 3). The overall histologic findings were diagnostic of syringocystadenocarcinoma papilliferum. Sampling revealed focal characteristic connections to the epidermal surface that allowed classification as a primary cutaneous adnexal malignancy (Figure 3). In just 2 foci, the malignant neoplasm connected to the epidermal surface via a funnel-shaped opening, and the epithelium in those regions displayed a gradual transition of stratified squamous epithelium at the surface to glandular epithelium within the cystic space.

Table 1. Reported Cases of Syringocystadenocarcinoma Papilliferum

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Age, y/Sex</th>
<th>Location</th>
<th>Size, cm</th>
<th>Duration and Clinical Description</th>
<th>Comments and Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissanayake and Salm, 1980</td>
<td>74/F</td>
<td>Scalp</td>
<td>6.5 x 5.5 x 3.5</td>
<td>Present for 30 y with secretion and recent enlargement</td>
<td>In situ carcinoma, no recurrence after 6.75 y</td>
</tr>
<tr>
<td>Seco Navedo et al, 1982</td>
<td>50/F</td>
<td>Scalp</td>
<td>6.5 x 6.5 x 2</td>
<td>Present since birth with recent increase in size</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>Numata et al, 1985</td>
<td>52/F</td>
<td>Chest</td>
<td>13 x 8 x 5</td>
<td>Present for 20 y, painful and enlarging</td>
<td>Axillary lymph node metastasis</td>
</tr>
<tr>
<td>Bondi and Urso, 1996</td>
<td>47/M</td>
<td>Scalp</td>
<td>2.5</td>
<td>Unknown duration</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Ishida-Yamamoto et al, 2001</td>
<td>61/M</td>
<td>Perianal</td>
<td>6</td>
<td>Present for &gt;10 y, painful with recent enlargement, exophytic</td>
<td>In situ carcinoma with pagetoid spread; no recurrence or metastasis after 11 mo</td>
</tr>
<tr>
<td>Arai et al, 2003</td>
<td>64/M</td>
<td>Scalp</td>
<td>3.5 x 2.5 x 1.2</td>
<td>Present for 2 y, gradually increasing in size, bleeding</td>
<td>In situ carcinoma</td>
</tr>
<tr>
<td>Chi et al, 2004</td>
<td>60/M</td>
<td>Auricle</td>
<td>4 x 4 and 1 x 1</td>
<td>Present for decades, 2 lesions, became painful, ulcerated, and pruritic</td>
<td>Treated with Mohs micrographic surgery; no recurrence or metastasis after 6 y</td>
</tr>
<tr>
<td>Woestenborghs et al, 2006</td>
<td>81/F</td>
<td>Scalp</td>
<td>1.5 x 0.5</td>
<td>Unknown duration, raised with bleeding</td>
<td>In situ carcinoma with pagetoid spread</td>
</tr>
<tr>
<td>Kazakov et al, 2007</td>
<td>60/F</td>
<td>Scalp</td>
<td>3 x 2 x 1</td>
<td>At least 30 y, with ulceration and recent enlargement</td>
<td>In situ arising in association with SCAP and sebaceous carcinoma; lost to follow-up</td>
</tr>
<tr>
<td>Park et al, 2007</td>
<td>65/M</td>
<td>Suprapubic</td>
<td>3.5 x 3.4</td>
<td>Present for 2 y, increasing in size with pain and hemorrhage</td>
<td>No recurrence or metastasis after 2 y</td>
</tr>
<tr>
<td>Langer and Ott, 2009</td>
<td>83/M</td>
<td>Perianal</td>
<td>1.5</td>
<td>Slow growing, nodular</td>
<td>In situ carcinoma</td>
</tr>
<tr>
<td>Present case, 2009</td>
<td>86/F</td>
<td>Neck</td>
<td>4.5 x 4 x 4</td>
<td>Present for 4 mo</td>
<td>In situ component adjacent to clearly invasive tumor; squamous differentiation</td>
</tr>
</tbody>
</table>

Abbreviation: SCAP, syringocystadenoma papilliferum.
Figure 1. A 4.5 × 4.0 × 4.0-cm, erythematous to violaceous, lobulated papule on the left neck.

Figure 2. Large, solid cystic structures lined by complex micropapillary projections comprise most of the tumor. Many glandular spaces show squamous differentiation, and the invasive squamous component merges deceptively with the background desmoplastic stroma (hematoxylin-eosin, original magnification ×200).

Figure 3. Focal connection to the epidermal surface supports characterization as a primary cutaneous neoplasm. The gradual transition from stratified squamous to glandular epithelium is evidence of apocrine differentiation (hematoxylin-eosin, original magnification ×50).

Figure 4. The healthy, physiologic relationship of the apocrine gland to the hair follicle. The apocrine gland has its origin at the follicular infundibulum, characterized histologically by a gradual transition from stratified squamous epithelium at the epidermal surface to a bilayered duct within the dermis (inset). This characteristic epidermal transition is evidence of apocrine differentiation and is recapitulated in both syringocystadenoma papilliferum and syringocystadenocarcinoma papilliferum.

Figure 5. A p63 immunostain highlights a discontinuous, residual basal/myoepithelial cell layer around many gland structures and is positive in areas of squamous differentiation (original magnification ×200).
These neoplasms are often raised and in the healthy apocrine gland are 2 "A few cells in the outer cell layers in the tubular and cystic structures were reported a 13 positive with focal cancer antigen-125 expression.

A comparison of our skin surface may be papillary or exophytic. There was no evidence of invasion, and "the underlying myoepithelial layer was highlighted by CK14 and actin staining." Ki67 expression was increased in “morphologically atypical” regions.

d Cytokeratin 5/6 was positive in basal cells. Ki-67 was expressed in greater than 50% of cells.

d p63 positive in invasive carcinoma with squamous differentiation and discontinuous basal layer in situ areas. The Ki-67 staining was increased and ranged from 20% to 70% of cells. Additionally, estrogen receptor was positive with focal cancer antigen-125 expression.

been reported in normal apocrine glands. A comparison of our immunohistochemical stains with previously reported results is detailed in Table 2.

**COMMENT**

We report a case of syringocystadenocarcinoma with some unique histologic features that proved diagnostically challenging on initial biopsy. Syringocystadenocarcinoma papilliferum is a rare neoplasm of apocrine glands and is the malignant counterpart of the more common benign syringocystadenoma papilliferum. Syringocystadenocarcinoma papilliferum is typically described as a long-standing lesion, most common on the head and neck of middle-aged or elderly individuals but is also reported in the skin of the scalp, back, chest, suprapubic area, and perianal region. These neoplasms are often raised and nodular and may be associated with ulceration, secretion, or pain. The skin surface may be papillary or exophytic as the name papilliferum implies.

Histologically, syringocystadenocarcinoma papilliferum resembles syringocystadenoma papilliferum and is marked by funnel-shaped epidermal invaginations demonstrating a gradual transition from keratinizing squamous epithelium at the surface to variable layers of glandular epithelium within subjacent cystic spaces. This epithelial transition mirrors the physiologic epithelial transition of the apocrine gland to the follicular infundibulum (Figure 4). In the healthy apocrine gland are 2 layers of bland epithelial cells, an inner luminal layer and an outer basal layer, which are also present lining the papillary projections of the benign syringocystadenoma papilliferum. In the malignant counterpart, the epithelial cells vary in thickness and show malignant cytologic features, including nuclear irregularity, and coarse chromatin.

Our case is unique in several aspects. It is the first report, to our knowledge, to document the presence of a high-grade, spindle cell component originally considered to be a high-grade squamous cell carcinoma. The invasive carcinoma, together with an in situ element, also supports the idea that syringocystadenocarcinoma papilliferum arises out of a syringocystadenoma papilliferum.

Secondly, unlike previous reports that describe a long-standing lesion with new onset of bleeding or ulceration accompanying the malignant progression, our patient presented with a rapidly progressing malignancy and noticed the mass just 4 months before initial biopsy. This case illustrates how syringocystadenocarcinoma papilliferum may mimic a metastatic malignancy to the skin. A metastatic lesion is far more likely, and previous authors have included breast, gastrointestinal tract, and thyroid primary tumors in the differential diagnosis. Distinguishing syringocystadenocarcinoma papilliferum from mammary carcinomas may be a particular challenge because of the apocrine histologic features and sometimes shared estrogen receptor expression. Earlier reports of syringocystadenocarcinoma papilliferum describe adenoid cystic and cribriform patterns, as well as pagetoid spread within the overlying epidermis. Additionally, Numata et al. reported a 13 × 8 × 5-cm syringocystadenocarcinoma papilliferum involving the chest wall in a 52-year-old woman with axillary lymph node metastasis, demonstrating that not only the histology but also the clinical staging may cause diagnostic confusion.

Our case showed that metastatic ovarian carcinoma may enter the differential diagnosis, especially given the high-grade morphology, compact micropapillary architecture, central necrosis, and cancer antigen-125 immunostaining typical of ovarian serous carcinoma. Other areas showed a pattern with endometrioid features, not previously documented. The histologic variability of syringocystadenocarcinoma papilliferum compels consideration of a broad range of differential diagnoses.

Immunohistochemistry helps to confirm the diagnosis, but as our case shows, it may mislead. A review of the literature, along with our own experience, is displayed in Table 2. The benign syringocystadenoma papilliferum has been reported to show carcinoma and epithelial membrane antigen expression at the apical portion of the luminal cells as well as CK7 positivity in the...
luminal cells, whereas the basal cells express other keratins, such as CK5/6 and CK14, with patchy smooth muscle actin staining. It is not surprising to see a similar staining pattern in the malignant counterpart in our case (Table 2). Still, immunohistochemistry cannot distinguish between syringocystadenocarcinoma and metastatic carcinoma. For example, many adenocarcinomas express carcinoembryonic antigen, including breast, lung, and colon primary tumors. Cytokeratin 7 is another marker that may be positive in both primary cutaneous and extracutaneous malignancies. Some authors have suggested that the pattern of CK7 staining may be helpful in discriminating primary adnexal neoplasms from metastatic adenocarcinomas because primary lesions tend to have focal, rather than diffuse, CK7 immunostaining. This is not entirely specific, however, and our example of a primary cutaneous adnexal malignancy demonstrated strong, diffuse CK7 positivity. Similarly, adnexal neoplasms may express estrogen receptor, as in our case; however, breast carcinomas and ovarian neoplasms are also frequently positive.

Perhaps the most instructive aspect of our case is the interpretation of the needle core biopsy, where areas of squamous differentiation led to an initial diagnosis of malignancy consistent with squamous cell carcinoma. This was a reasonable interpretation, particularly in the head and neck. The spindle areas showed strong cytokeratin AE1/3 staining and convincing p63 staining, emphasizing that not every p63-positive spindle cell malignancy of the head and neck is a primary squamous cell carcinoma. Cutaneous adnexal neoplasms have also been reported to express p63, and some authors argue p63 expression favors a diagnosis of primary adnexal neoplasm over metastatic adenocarcinoma with a sensitivity and specificity of 91% and 100%, respectively. Ivan et al have also demonstrated that adenocarcinomas in the skin, showing expression of p63 in more than 25% of the cells or in a peripheral pattern labeling preexisting myoepithelial cells, support a primary cutaneous origin. Furthermore, the prognostic significance of p63 staining in this case remains unclear, as some investigators have correlated p63 staining with poor prognosis in other settings.

The surgical pathologist should recognize this rare neoplasm because a correct diagnosis may affect patient treatment and prognosis. The reported patients with syringocystadenocarcinoma papilliferum have done well with surgical excision alone, with only 2 reported cases of regional lymph node metastases and no distant metastases. Eighteen months after treatment, our now 88-year-old patient has experienced a local recurrence but has refused treatment. In summary, we report a novel case of syringocystadenocarcinoma papilliferum demonstrating the coexistence of invasive and in situ carcinoma, serving as histologic evidence of malignant progression. This case illustrates the shortcomings of a needle core biopsy in this setting and the importance of maintaining a broad differential diagnosis to reach the correct diagnosis and provide the best possible patient care.

We wish to thank Charles Fredman for his artistic recreation of the pilosebaceous unit.

References