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Syringoid eccrine carcinoma: a clinicopathological and immunohistochemical study of four cases

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ABSTRACT

Background Syringoid eccrine carcinoma (SEC) is a rare malignant adnexal tumour with variable presentations.

Aim To examine the clinicopathological and immunohistochemical features of SEC.

Methods Four cases were reviewed by three dermatopathologists and the immunohistochemical profile was examined using antibodies against CK5/6, CK7, CK14, CK20, LMWK, HMWK, EMA, mCEA, p63, ER, PR, AR, S-100 and Ber-EP4.

Results The cases occurred in two men and two women, ranging in age from 61 to 87 years (mean 68.5). Two of the lesions were from the face and two from the trunk. All four lesions were composed of an atypical infiltrative mass with syringoma-like tadpole morphology with ductular differentiation and prominent desmoplasia. Three cases demonstrated perineural invasion and two had positive lymph node metastases. Immunostaining was variable. Immunohistochemistry positivity was as follows: three out of four cases were positive for CK5/6, CK7 (2/4), CK14 (1/3), CK20 (0/2), HMWK (0/2), LMWK (1/2), EMA (3/4), mCEA (4/4), p63 (2/3), ER (2/3), PR (1/2), AR (0/3), S-100 (0/3) and Ber-EP4 (2/2).

Conclusion SEC can present on the trunk and are not limited to the head and neck region. In addition to syringoma-like tadpole structures and glandular differentiation, these tumours can also exhibit squamoid and cribriform growth patterns. Immunostaining in SEC is variable and this variability is believed to stem from this tumour's ability to differentiate along multiple routes, including sweat secretory and/or ductal differentiation.

Primary eccrine carcinomas are rare tumours and make up less than 0.01% of all skin cancers.[1 2] The classification of these lesions is very complex and many different terms are used to describe the same tumour, as a wide histological spectrum is often seen and the exact origin of many of these lesions is not known.[3–6]

Syringoid eccrine carcinoma (SEC) is an extremely rare malignant adnexal tumour of eccrine origin. First described as eccrine epithelioma by Freeman and Winkelmann in 1969,[7] SEC have also been reported under many different labels, including eccrine carcinoma, squamoid eccrine ductal carcinoma, sclerosing sweat duct carcinoma, syringomatous carcinoma, malignant syringoma, sweat gland carcinoma with syringomatous features and the previously mentioned eccrine epithelioma (basal cell tumour with eccrine differentiation).[1–12] Histologically, SEC exhibit syringoma-like tadpole morphology composed of basaloid cells with ductal differentiation within a fibrocollagenous matrix. There is variable cytonuclear atypia and mitotic activity and commonly lymphovascular and perineural invasion. SEC show an infiltrative growth pattern, with deep invasion and often extension into the subcutaneous tissue, which distinguishes this malignancy from its benign counterpart, syringoma. These tumours commonly recur locally and have a potential for distant metastasis.[1 2 5–9] Immunohistochemically, SEC have been reported to express cytokeratins, epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA).[8 11–18]

We report four further cases of this rare skin tumour, with the purpose of highlighting the clinicopathological characteristics of this tumour and the role of immunohistochemistry. We also discuss the differential diagnosis and possible histogenesis of the tumour.

MATERIALS AND METHODS

Four cases were selected of SEC accessioned during the period of 2001–10 in the Department of Anatomic Pathology, University Health Network, Canada. Pertinent demographic and clinical data were retrieved from the electronic medical records. The cases occurred in two men and two women, ranging in age from 61 to 87 years (mean 68.5). Two of the lesions were from the head and two from the trunk.

Accepted criteria on haematoxylin and eosin sections in conjunction with immunohistochemistry were used to make the diagnosis and only clear-cut cases were selected. Three dermatopathologists reviewed the cases and immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue sections in a Ventana XT instrument (Ventana Systems, Tucson, Arizona, USA). Immunostaining was performed according to our laboratory's usual methods and the primary antibodies that were used are listed in table 1.

RESULTS

Table 2 summarises the clinicopathological results.

Case 1

A man in his early 60s (60–64 years) presented with a nodular lesion of the chin. Initial biopsy, performed at an outside hospital, suggested a diagnosis of sclerosing basal cell carcinoma (BCC) and the patient underwent surgical excision of the lesion. The tumour was subsequently found to have positive margins, with extension to the deep margin. The patient was subsequently lost to follow-up and no further surgical or adjuvant treatments were done. Over time, the patient noticed increasing paraesthesia of his chin and lip, as well as discomfort around the area of the lesion. The patient presented 7 years later and imaging

Table 1 Antibodies with source, dilution and antigen retrieval methods used in the study

Antibody	Clone	Source	Dilution	Antigen retrieval
CK5/6	D5/16 B4	DakoCytomation	1:50	HIER (high pH buffer)
CK7	OV-TL 12/30	Dako	1:200	Protease 4 min
CK14	LL002	Vector	1:50	HIER ccl mild
CK20	Ks20.8	DakoCytomation	1:100	Protease 4 min
LMWK	Cam5.2	Becton-Dickinson	1:50	Protease 16 min
HMWK	34betaE12	Cell Marque	Pre-diluted	Protease 4 min
EMA	E29	Cell Marque	Pre-diluted	No pretreatment
mCEA	B80.1	Biomeda	1:5000	Protease 4 min
p63	7JUL	Vector Laboratories	1:50	HIER ccl mild
ER	SP1	Ventana	Pre-diluted	HIER ccl mild
PR	16	Vector Laboratories	1:100	HIER ccl standard
AR	F39.4.1	BioGenex	1:100	HIER pH 6.0 citrate
S-100	Polyclonal	Ventana	Pre-diluted	No pretreatment
Ber-EP4	Ber-EP4	Dako	1:200	Protease 4 min

AR, androgen receptor; CK, cytokeratin; EMA, epithelial membrane antigen; ER, oestrogen receptor; HMWK, high molecular weight keratin; LMWK, low molecular weight keratin; mCEA, monoclonal carcinoembryonic antigen; PR, progesterone receptor.

confirmed an abnormal mass involving the outer periosteum of the anterior mandible, with extension along the right anterior mandible, with near total lower lip involvement. An initial punch biopsy of the lesion demonstrated a poorly differentiated carcinoma likely to be of eccrine origin. The patient underwent bilateral neck dissection, with total lip resection with marginal mandibulectomy and reconstruction. The lesion measured 2.2×1.3×1.2 cm and was seen to invade through cortical bone. Microscopic examination of this mass revealed an infiltrative tumour showing variable patterns, including areas of infiltrating cords of basaloid cells, cribriform structures and tubular structures with tadpole-like forms. Towards the surface, the lesion appeared to originate from the surface epithelium coursing downwards in slender trabeculae suggestive of eccrine ducts. There was prominent perineural invasion and a single ipsilateral lymph node was positive for metastasis (see figure 1).

Table 2 Summary of patient demographics, location and morphological findings

Case	1	2	3	4
Age, years	60–64	60–64	60–64	85–89
Sex	M	M	F	F
Location	Face	Face	Chest	Chest
Growth patterns				
'Tadpole' shaped ducts	+	+	+	+
Strands	+	+	+	+
Cribriform	+	+	+	–
Squamoid	–	–	+	–
Glandular differentiation	+	+	+	+
Eosinophilic secretions	–	+	+	–
Pagetoid cells	–	+	–	–
Desmoplasia	+	+	+	+
Cellular features				
Atypia	Mod	Min	Sign	Mod
Nucleoli	Prom	Inc	Prom	Prom
Mitotic figures	Rare	Rare	Abun	Rare
Atypical figures	–	–	+	–
Invasion				
Margins positive	–	–	–	–
Perineural	+	+	–	+
Lymphovascular	+	–	–	–
Lymph nodes positive	+	+	–	–

Abun, abundant; Inc, inconspicuous; Min, minimal; Mod, moderate; Prom, prominent; Sign, significant.

Case 2

A man in his early 60s (60–64 years) presented with a large left-sided facial mass, involving the cheek, nose and two-thirds of the left lower eyelid. The mass had been growing slowly for over 15 years, with a significant growth recently. The mass was a hard nodule measuring 3.5 cm, fixed to the underlying bone with suspected invasion of orbital bone. Initially a punch biopsy demonstrated a diagnosis of a poorly differentiated adenocarcinoma. The patient underwent a left maxillectomy and ethmoidectomy with left neck dissection. Microscopic examination of this mass revealed a tumour demonstrating variable patterns of growth, including sheet-like, tubular and cribriform growth patterns. The tumour was seen to have a possible epidermal connection, and arising from the acrosyringeal portion of sweat glands. Pagetoid cells were also identified. There was prominent perineural invasion but no lymphovascular invasion within the sections examined. Four out of 34 lymph nodes examined were positive for tumour.

Case 3

A woman in her early 60s (60–64 years) presented to an outside hospital with a chest lesion and underwent an excisional biopsy. Microscopic examination of this mass revealed a tumour present in the superficial dermis with no evidence of an epidermal attachment or origin. The tumour showed variable patterns, including tubular, cribriform and squamoid growth (see figure 1). The tumour was seen to be confined to the dermis. Mitotic figures were prominent with rare atypical forms. The dermis had extensive solar elastosis and an extensive lymphocytic inflammatory reaction.

Case 4

A woman in her late 80s (85–89 years) presented with a chest lesion and underwent a skin biopsy. Microscopic examination of this mass revealed a tumour demonstrating variable patterns of growth, including strands, small tubular structures, and tadpole-like glandular structures within a desmoplastic stroma. Perineural invasion was identified. Numerous calcifications were also present throughout the lesion.

Immunohistochemistry

Table 3 summarises the immunohistochemical results.

Immunostaining was variable among all four SEC cases. Cytokeratin (CK)5/6 was expressed in three of four cases while

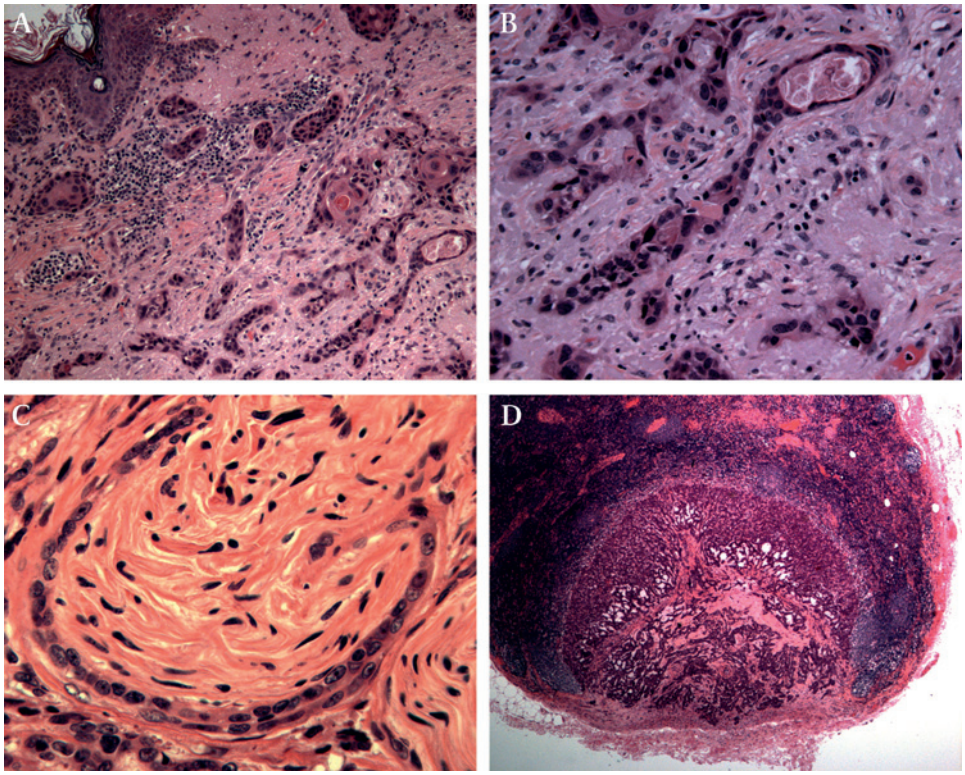

Figure 1 Representative haematoxylin and eosin (H&E) slides of: (A, B) case 3, demonstrating syringoma-like tadpole morphology, strands and a squamoid growth pattern; (C) case 1, perineural invasion; (D) case 1, a lymph node displaying a metastasis. H&E at (A) 10×, (B) 20×, (C) 40×, (D) 2.5×.

CK7 was expressed in two of four cases and CK14 in two of three cases. CK20 expression was not present in two cases examined. EMA was expressed in three of four cases, and monoclonal CEA in all four cases. The immunohistochemistry marker p63 stained positively in two of the three cases. Oestrogen receptor (ER) was diffusely positive in case 2 and focally positive in case 3, but negative in case 1. Progesterone receptor (PR) was positive in case 2 only (1/2). Androgen receptor and S-100 was negative in all three cases assessed. Ber-EP4 was expressed in two of two cases examined.

DISCUSSION

Primary eccrine tumours are a large and diverse group of benign and malignant neoplasms with a complex classification as these lesions demonstrate a wide histological spectrum and no universally accepted terminology.[1–13]

Table 3 Immunohistochemistry findings in four cases of SEC

Antibody	Case 1	Case 2	Case 3	Case 4
CK5/6	+	–	+	+
CK7	–	+	+focal	–
CK14	+	–		+
CK20	–	–		
LMWK		+		–
HMWK		–		–
EMA	–	+	+	+
mCEA	+focal	+	+	+
p63	+	–	+	
ER	–	++	+focal	
PR	–	+		
AR	–	–	–	
S-100	–	–	–	
Ber-EP4	+focal	+		

–, ±, +, ++: Staining intensity; negative, weak, moderate and strong, respectively.
Focal: a few positive staining cells (approximately <30% of tumour cells).
AR, androgen receptor; CK, cytokeratin; EMA, epithelial membrane antigen; ER, oestrogen receptor; HMWK, high molecular weight keratin; LMWK, low molecular weight keratin; mCEA, monoclonal carcinoembryonic antigen; PR, progesterone receptor; SEC, syringoid eccrine carcinoma.

SEC is a primary eccrine carcinoma, described under many different labels. To our knowledge, well over 40 cases have been reported under the name of SEC and its synonyms.[1 2 5–9 11–13 17–26] Clinically, SEC have no predilection for either sex and they most often present in the fifth and sixth decades of life. The clinical appearance of SEC is not specific; however, most lesions present as nodules or plaques that measure over 1 cm on the head and neck, and less commonly the trunk. Ulceration is rare. These lesions have been reported to be present for several years with a characteristic slow evolution. SEC are locally aggressive lesions with deep invasion and perineural invasion, and commonly recur after excision. Treatment is mainly surgical excision with clear margins being the method of choice in localised lesions.[2 18 26] Chemotherapy and radiation therapy have been used for metastatic lesions.

As previously mentioned, morphologically, SEC is characterised by a tubulocystic proliferation with typical syringoma-like tadpole ductal structures set within a dense fibrocollagenous matrix. Cells show mild to marked nuclear atypia, usually of moderate atypia and a variable number of mitoses. Deep invasion with extension into the subcutis and muscle is commonly seen, as is perineural invasion. The immunophenotype of SEC is not specific and is often not consistent. Expression of cytokeratins and CEA is consistently positive in tumour cells. Other antigens, such as EMA, Ber-EP4, ER and PR have also been reported to be positive in SEC.[5 13–17]

A study by Ohnishi *et al*[13] analysed the expression profile of cytokeratins in normal eccrine sweat glands and in a single case of SEC. The SEC tumour cells demonstrated the expression of CK7, 8, 18 and 19, especially in large luminal cells, cytokeratins that are normally expressed in the glandular secretory portion of eccrine sweat glands, and in a smaller number of tumour cells there was expression of stratified epithelial CK5 and 14, cytokeratins normally expressed in the ductal portion of eccrine

Table 4 Differential diagnosis of cutaneous benign and malignant lesions with morphology overlapping with SEC[13–17 29–37]

	Microscopic features	Immunohisto-chemistry
Benign		
Syringoma	Small and round tumour 'Tadpole' shaped ductal structures Keratinous cysts Ample pink cytoplasm Sclerotic, dense and red stroma	CEA + EMA + CK10 + CK6 + CK19 + ER,PR ±
Desmoplastic trichoepithelioma	Central dell 'Tadpole' shaped ductal structures Sclerotic stroma Clefts between collagen fibres Calcifications Keratinous cysts	CEA− CD34 + Bcl-2 + BerEP4 ± CK15 + CK903 +
Malignant		
SEC	Poorly circumscribed Tubulocystic proliferation 'Tadpole' shaped ductal structures Desmoplastic stroma Cellular atypia and mitoses are common Perineural invasion	CEA + EMA ± p63 ± BerEP4 + CK5/6 ± CK7 ± CK14 ± ER,PR ±
Sclerosing BCC	Epidermal connection Infiltrative basaloid cells, in palisading arrangement Can have 'tadpole' shaped ductal structures, but uncommon Prominent sclerotic stroma Cellular atypia is common	CEA − BerEP4 + CD10 + CK7 ±
Microcystic adnexal carcinoma	Poorly circumscribed Superficial keratinous microcysts Glandular differentiation in deeper areas with small lumina formed by basaloid cells 'Tadpole' shaped ductal structures Compressed thin cords of basaloid cells Sclerotic stroma Cytologic atypia and mitoses are uncommon Lymphoid aggregates Perineural invasion	CEA ± EMA + BerEP4 ± CK15 + CK903 + CK7 ±
Adenoid cystic carcinoma	Nests of basaloid cells Cribriform architecture with mucinous and/or hyaline material Perineural invasion	CEA− CK7 + EMA +
Infundibular carcinoma	Hair follicular infundibulum attachment Sheets of basaloid cells Small nests superficially Pseudoglandular pattern deep Squamous differentiation Desmoplastic stroma	p63 + BerEP4− HMWK + CK7 + CK14 +

BCC, basal cell carcinoma; Bcl-2, B-cell lymphoma 2; CD, cluster of differentiation; CEA, carcinoembryonic antigen; CK, cytokeratin; EMA, epithelial membrane antigen; ER, oestrogen receptor; HMWK, high molecular weight keratin; PR, progesterone receptor; SEC, syringoid eccrine carcinoma.

sweat glands. The authors concluded that the studied case of SEC differentiated mainly towards the eccrine sweat secretory cells, as the majority of the tumour cells expressed glandular cytokeratins and had the appearance of large luminal cells. A study by Langbein *et al*[27] characterised a novel human type II epithelial keratin, K1b, which was demonstrated to be specifically expressed in luminal duct cells of the eccrine sweat gland. Moreover, the study revealed that there are complex differences in cytokeratin expression in the different compartments of the eccrine sweat gland and that these different layers exhibit a sequential keratin expression.

SEC may be difficult to differentiate from sclerosing BCC, trichilemmal carcinoma, infundibular carcinoma, primary cutaneous adenoid cystic carcinoma (PCACC), microcystic adnexal carcinoma and visceral adenocarcinoma with skin metastases (table 4).[13–17 28–37] Concerning BCC, these lesions lack ductal differentiation, whereas SEC do not demonstrate the characteristic palisading arrangement seen in BCC and other hair follicular-derived carcinomas. Furthermore, CEA is not present in BCC but is expressed in SEC, similar to other eccrine neoplasms.[13–17] PCACC demonstrate nests of basaloid cells, characteristic sieve-like cribriform growth and mucin production, features that are not present in SEC; however, immunohistochemically, SEC and PCACC are similar. Microcystic adnexal carcinomas display both eccrine and follicular differentiation, with basaloid cells forming keratin-filled cysts, which are not present in SEC.[29]

Visceral adenocarcinomas with skin metastases, such as carcinoma of the breast, lung or kidney, can be differentiated from SEC usually through morphology and immunohistochemistry. Combinations of immunohistochemical markers, such as mammoglobulin and gross cystic disease fluid protein for breast carcinoma, thyroid transcription factor 1 for lung carcinoma and CD10 and renal cell carcinoma marker for renal cell carcinoma can assist in the differential diagnosis; however, clinicopathological correlation, morphology and the relationship of the tumour with the epidermis and other adnexal structures are crucial.[30–37]

In our case series, the clinicopathological and immunohistochemical findings were similar to SEC cases previously reported. Three of the four cases were in patients in their sixties and two were present on the head and neck. The remaining two cases were from the trunk. All tumours demonstrated typical SEC morphology with syringoma-like tadpole-like ductal structures and prominent desmoplasia (see figure 1). Perineural invasion was common and prominent, present in three of the four cases. However, there was variability in the growth pattern between cases, with some cases demonstrating cribriform (cases 1–3) and/or squamoid (case 3) growth patterns in addition to the typical tadpole-like ductal morphology and desmoplasia. Metastases to regional lymph nodes were also common in our cases, being present in more than one case (cases 1 and 2).

By immunohistochemistry, all of our cases expressed cytokeratins; however, there were variations in the expression of all markers, with the exception of monoclonal CEA. The most common cytokeratins expressed were CK5/6, CK7 and CK14. Interestingly, all cases expressed at least one cytokeratin that is normally present in both the glandular secretory portion (CK7) and the ductal portion of eccrine sweat glands (CK5/6, CK14), with the exception of case 2, which only expressed CK7. Case 2 also demonstrated strong expression of ER, in addition to PR and EMA. EMA was positive in three of the four cases. Previous studies have demonstrated that the majority of primary adnexal tumours strongly express p63 and retain p63 expression within their metastases.[35 36] In our study, expression of p63 was present in only two of three cases examined. Both cases 1 and 2 had lymph node metastases, but only case 1 had positive immunohistochemistry for p63.

The discordance in naming and variation in both the clinicopathological and immunohistochemical staining profile of SEC may be due to a lack of understanding and an unclear origin of these complex lesions.[9] SEC are currently believed to be of sweat gland differentiation, with tumour cells exhibiting morphological, ultrastructural and immunohistochemical features of both the dermal duct and secretory portion of normal sweat glands.[1 2 5–9 11–17 27 37] Similar to past reports, we believe that these lesions are composed of tumour cells that can differentiate between both sweat secretory cells and dermal ductal cells, recapitulating the normal sweat gland. Significant differences in the degree of differentiation between these individual compartments, ductal and secretory, could explain the

Take-home messages

- SEC can present on the trunk and are not limited to the head and neck region as previously thought.
- SEC demonstrate syringoma-like tadpole structures, glandular differentiation and desmoplasia, but other growth patterns such as squamoid and cribriform may be present.
- Immunostaining in SEC is variable with carcinoembryonic antigen being the most consistently expressed immunohistochemical marker.
- The differential diagnosis of SEC includes syringoma, desmoplastic trichoepithelioma, BCC, microcystic adnexal carcinoma, adenoid cystic carcinoma and infundibular carcinoma.

variance in both the morphology and immunohistochemistry seen in SEC, as well as possibly in the behaviour of these lesions. Similar to other adnexal tumours, the keratin profile of SEC is variable and the role of myoepithelial cells within SEC is still controversial. These features may further contribute to the complexity and variability seen in these lesions.[5 10 13 17 18 30 35]

A few authors have suggested an apocrine nature to SEC; however, most reported cases of SEC, in addition to our series, did not express androgen receptor.[31] Others have demonstrated negative staining with the apocrine markers gross cystic disease fluid protein-15 and human milk fat globulin 1, as well as CK1 and 10, making apocrine differentiation in SEC unlikely.[13 19]

In conclusion, SEC can be found on the trunk in addition to the head and neck region, and demonstrate significant variability in immunohistochemistry, with the exception of monoclonal CEA. We believe that this variability seen in SEC is from this tumour's ability to differentiate variably along multiple routes, including sweat secretory and/or ductal differentiation. Future studies with new markers, discriminatory keratins and a larger sample size may help elucidate SEC origin and differentiation.

Competing interests None declared.

Ethics approval This study received ethics approval from the Research Ethics Board University Health Network.

Contributors Dermatopathologists SS, AAH and DG diagnosed all four cases. Anatomical pathology resident MS and SS, AAH and DG analysed and studied the cases, and drafted, submitted and revised the paper.

Provenance and peer review Not commissioned; externally peer reviewed.

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