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CASE STUDY

A case of cribriform carcinoma of the skin: a newly described rare condition

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Primary cribriform carcinoma of the skin is an indolent, rare, adnexal tumor. Although its malignant potential remains uncertain, no recurrence or metastasis has been reported. A 33-year-old man presented with a solitary, erythematous, subcutaneous nodule on the right knee. The clinical impression was epidermal cyst, and the resected tumor demonstrated a well-circumscribed mass in the dermis and subcutis. The tumor was composed of two regions: a solid component and a cribriform component. The solid component (90%) showed multiple solid nests of epithelial cells. Individual cells had large, oval-to-round, hyperchromatic, pleomorphic nuclei with a nuclear groove. The cribriform component (10%) showed similar neoplastic cells with many prominent lumina. Some lumina had an eosinophilic substance that exhibited a positive periodic acid-Schiff reaction. No recurrence or metastasis was observed within a follow-up period of eight months after excision. In conclusion, we report the first case of primary cribriform carcinoma of the skin in Korea.

Key Words: Cribriform carcinoma; Apocrine tumor; Skin tumor

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Cribriform carcinoma of the skin (primary cutaneous cribriform carcinoma [PCCC]) is an indolent, rare, adnexal tumor with a presumed apocrine lineage. The first global case was described in 1998 [1], and the most recent (4th) World Health Organization (WHO) classification for skin now includes this condition. Currently, only 42 cases have been reported in the English literature (Table 1) [1-7]. The female-to-male ratio is 2:1, with a median age of 47 years (range, 20 to 77 years). Most cases involve the extremities (85%). Although its malignant potential remains uncertain, no recurrence or metastasis has been reported.

Herein, we report the first Korean case of primary cribriform carcinoma of the skin.

CASE REPORT

A 33-year-old man presented with a solitary, erythematous, subcutaneous nodule on the right knee (Fig. 1A), which had developed a few months prior. The clinical impression was epidermal cyst. His past medical history comprised intracranial hemorrhage due to arteriovenous malformation 10 years previous.

After the patient underwent systemic evaluation, including positron emission tomography–computed tomography (PET-CT) and gastric endoscopy, the mass was confirmed as a primary skin tumor, and resection was performed. The resected tumor was a well-circumscribed, yellowish-white, fibrotic, firm, 2.0 × 1.2 × 0.7-cm mass (Fig. 1B).

Histologically, the tumor was a well-circumscribed mass of the dermis and subcutis. The tumor was composed of (Fig. 2A) a predominantly solid component (90%) and a predominantly cribriform component (10%). The solid component showed multiple solid nests of epithelial cells. Individual cells had large, oval-to-round, hyperchromatic, pleomorphic nuclei with a nuclear groove (Fig. 2B). The cytoplasm was eosinophilic and scant. The cribriform component showed similar neoplastic cells with many prominent lumina, giving rise to a cribriform pattern with a thin, thread-like, intraluminal bridge (Fig. 2C). Some lumina had an eosinophilic substance that exhibited a positive periodic acid–Schiff reaction (Fig. 2D). At the periphery of the tumor, multifocal lymphoid aggregates (Fig. 2E), desmoplastic reaction, and some infiltrative tumor cell clusters were present (Fig. 2F).

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Table 1. Summary of reported cases

Case No.	Study	Year	Age (yr)	Sex	Site	Clinical diagnosis	Size (cm)	Treatment	F/U period	Prognosis	Positive IHC	Negative IHC	Comments
1	Current case	2020	33	M	Lower extremity (Rt. knee)	Epidermal cyst	2.0	Excision	8 mo	NROMD	S100 (diffuse, luminal component; patchy, solid component), EMA (patchy, luminal component; diffuse, solid component), CK7, CK5/6 (patchy), CD117 (patchy), EpCAM (patchy), CEA (intraluminal), p63 (rare)	CK20, GCDFP-15, ER, calponin, SMA	History of intracranial hemorrhage due to arteriovenous malformation No evidence of other malignancies
2	Requena et al. [1]	1998	NA	NA	Lower extremity	NA	NA	Excision	NA	NA	NA	NA	First description Reported as mainly women with a mean age of 44 years (range, 20 to 55) Two cases of recurrent tumor after incomplete excision
3			NA	NA	Lower extremity	NA	NA	Excision	NA	NA	NA	NA	
4			NA	NA	Lower extremity	NA	NA	Excision	NA	NA	NA	NA	
5			NA	NA	Upper extremity	NA	NA	Excision	NA	NA	NA	NA	
6			NA	NA	Pubis	NA	NA	Excision	NA	NA	NA	NA	
7	Adamski et al. [5]	2005	37	M	Lower extremity (Lt. popliteal fossa)	NA	2.0	Excision	2 yr	NROMD	CK7	CK20, GCDFP-15, S100	-
8	Fernandez-Flores et al. [4]	2007	62	F	Lower extremity (Lt. popliteal fossa)	NA	0.8	Excision	NA	NROMD	CK AE1/AE3, CAM 5.2, CK7, EMA, ER (2+, 1%–5% cells), c-erbB-2 (2+, 50%–75% cells), p53 (1+, 1%–5% cells), S100 (2+, 50%–75% cells)	CK20, CEA, PR, GCDFP-15, CD15, SMA	-
9	Rutten et al. [2]	2009	48	M	Lower extremity (Rt. thigh)	Dermatofibroma (histiocytoma)	-	Excision	18 yr	NROMD	CK MNF116, CK AE1/AE3, CAM 5.2, CK7, CEA (more prominent in the ductal structures), EMA (more prominent in the ductal structures)	CK20, GCDFP-15, S100, α-SMA, MSA, calponin, CD68, vimentin	-
10			51	F	Upper extremity (Rt. forearm)	Cyst	-	Excision	NA	NA			-
11			44	F	Back	Dermatofibroma (histiocytoma)	-	Excision	13 yr	NROMD			-
12			77	F	Neck	NA	-	Excision	NA	NA			Recurrent tumor after incomplete excision
13			32	F	Lower extremity (Rt. thigh)	Dermatofibroma (histiocytoma)	-	Excision	9 yr	NROMD			-
14			42	F	Lower extremity (Rt. thigh)	Dermatofibroma (histiocytoma)	-	Excision	NA	NA			-
15			34	F	Upper extremity (Rt. arm)	Dermatofibroma (histiocytoma)	-	Excision	11 yr	NROMD			-
16			40	M	Upper extremity (Lt. forearm)	Dermatofibroma (histiocytoma)	-	Excision	NA	NA			-
17			23	M	Lower extremity (Lt. calf)	NA	-	Excision	NA	NA			-
18			20	F	Rt. buttock	Cyst	-	Excision	NA	NA			No evidence of other malignancies
19			67	F	Lt. preauricular area	BCC vs. adnexal tumor	-	Excision	8 yr	NROMD			-
20			60	M	Lower extremity (Rt. foot dorsum)	Dermatofibroma (histiocytoma)	-	Excision	4 yr	NROMD			-
21			54	F	Upper extremity (acral)	NA	-	Excision	NA	NA			-

(Continued to the next page)

Table 1. Continued

Case No.	Study	Year	Age (yr)	Sex	Site	Clinical diagnosis	Size (cm)	Treatment	F/U period	Prognosis	Positive IHC	Negative IHC	Comments
22			49	F	Lower extremity (Lt. thigh)	Dermatofibroma (histiocytoma)	-	Excision	4 yr	NROMD			-
23			59	F	Lt. shoulder	Dermatofibroma (histiocytoma)	-	Excision	NA	NA			-
24			28	M	Lower extremity (Rt. lower leg)	NA	-	Excision	NA	NA			-
25			54	M	Upper extremity (Rt. hand)	NA	-	Excision	NA	NA			-
26			50	F	Upper extremity (Rt. hand)	NA	-	Excision	NA	NA			-
27			70	M	Rt. trunk	Long-standing lesion	-	Excision	6 yr	NROMD			-
28			64	F	NA	Dermatofibroma (histiocytoma)	-	Excision	5 yr	NROMD			-
29			40	F	Lower extremity (Lower arm)	NA	-	Excision	5 yr	NROMD			-
30			64	M	Upper back	Dermatofibroma (histiocytoma) or cyst	-	Excision	3 yr	NROMD			-
31			54	M	Lower extremity (Lower arm)	NA	-	Excision	3 yr	NROMD			-
32			44	F	Upper extremity (Lt. thumb)	NA	-	Excision	2 yr	NROMD			-
33			36	F	Lower extremity (Lt. anterior thigh)	Dermatofibroma (histiocytoma)	-	Excision	NA	NA			-
34			26	F	Lower extremity (Lt. posterior leg)	Fibroma	-	Excision	NA	NA			-
35	Arps et al. [3]	2015	41	F	Lower extremity (leg)	Epidermal inclusion cyst	0.6	Excision	NA	NROMD	S100 (diffuse in three cases, patchy in one case), CD117 (diffuse in two cases, patchy in one case), CK5/6, CK7, EpCAM, CEA (luminal), EMA (luminal), p63 (rare)	CK20, GCDFP-15, ER, PR, calponin, SMA	-
36			32	F	Upper extremity (elbow)	NA	0.5	Excision	NA	NA			-
37			35	M	Lower extremity (leg)	NA	0.5	Excision	NA	NROMD			-
38			59	F	Upper extremity (arm)	NA	0.4	Excision	NA	NA			-
39			61	M	Upper extremity (arm)	Mobile nodule	0.7	Excision	NA	NA			-
40			31	M	Lower extremity (leg)	Dermatofibroma	1.2	Excision	NA	NA			-
41	Yokota et al. [7]	2017	39	F	Upper extremity (Rt. forearm)	NA	0.5 (clinical)	Excision	15 mo	NROMD	CK5/6, CK7, CA15-3, CA125, CD117, S100 (partially), p53 (partially), p63 (partially)	CK20, calponin, GCDFP-15, mammaglobulin, MUC1, ER, AR, D2-40	Stable in size for more than 10 years, no evidence of other malignancies
42	Bogner et al. [6]	2018	65	M	Lt. lateral neck	NA	0.6 (clinical)	Excision	3 mo	NROMD	CK7 (strong), EMA (strong), CAM 5.2 (strong), EpCAM (lesser degree), CEA (in some of the lumina), p63, p40	CK20, D2-40, TTF-1, CDX-2, hepatocyte antigen, PSA, PSAP, calponin, S100	No evidence of other malignancies

F/U, follow up; IHC, immunohistochemical staining; Rt., right; Lt., left; NROMD, no recurrence or metastatic disease; EMA, epithelial membrane antigen; CK, cytokeratin; EpCAM, epithelial cell adhesion molecule; CEA, carcinoembryonic antigen; GCDFP-15, gross cystic disease fluid protein-15; ER, estrogen receptor; SMA, smooth muscle actin; MSA, muscle specific antigen; NA, data not available; S100, S-100 protein; PR, progesterone receptor; BCC, basal cell carcinoma; MUC1, mucin1; AR, androgen receptor; TTF-1, thyroid transcription factor 1; PSA, prostate-specific antigen; PSAP, prostatic acid phosphatase; +, >50% of tumor cells are positive; patchy, 25%–50% of tumor cells are positive; rare, < 1% of tumor cells are positive.

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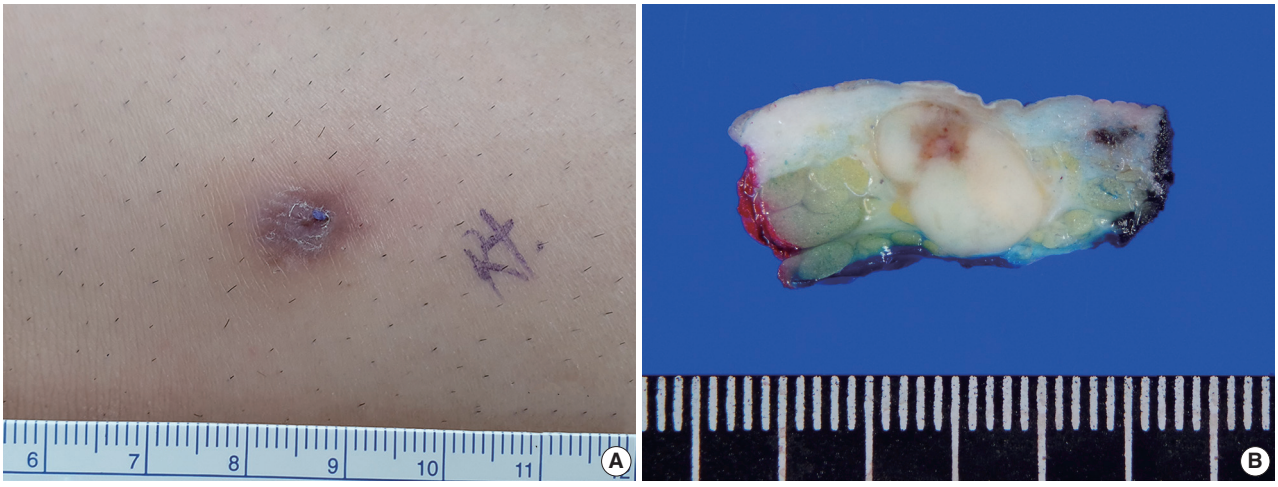

Fig. 1. Gross appearance of the mass. (A) A solitary, erythematous, subcutaneous nodule on the right knee. (B) The cut surface of the mass is well-circumscribed, yellowish-white, fibrotic, and firm.

The epidermis was neither involved with nor connected to the tumor.

The two components of the tumor displayed distinctive immunohistochemical staining patterns for epithelial membrane antigen (EMA) (Fig. 3A) and S-100 protein (Fig. 3B). The predominantly solid component exhibited diffuse immunopositivity for EMA and focal immunopositivity for S100 protein, while the predominantly luminal component exhibited focal immunopositivity for EMA and diffuse immunopositivity for S-100 protein.

Given its histopathologic features, the mass was diagnosed as PCCC. No recurrence or metastasis was observed within a follow-up period of 8 months after excision.

DISCUSSION

PCCC is a rare, newly described, unique, adnexal neoplasm with an indolent clinical course. Currently, no recurrence or metastasis has been reported. In few cases, remnants have been reported after incomplete excision [1,3]. Accurate diagnosis and exclusion of metastasis are important for avoiding over-treatment.

In cases of primary skin neoplasms, the differential diagnosis should include tumors that can show a cribriform pattern: adenoid cystic carcinoma, secretory carcinoma, and tubular adenoma (eccrine papillary adenoma). The histopathologic features for differential diagnoses are listed in Table 2. Adenoid cystic carcinoma can be distinguished by the presence of basaloid epithelial cells with more uniform nuclei surrounding the pseudolumina. The presence of frequent perineural invasion and small true ducts with myoepithelial cell differentiation are points of differential diagnosis. Secretory carcinoma exhibits tubules and microcysts with conspicuous intraluminal secretions, but back-to-back proliferation and cuboidal neoplastic cells are characteristic compared with PCCC. Tubular adenoma can show dilated cystic spaces with attenuated epithelium, micro-papillae, and focal intraluminal bridging, mimicking PCCC. However, this condition lacks cytologic atypia and mitotic activity and involves accumulation of basal/myoepithelial cells.

Histopathologically, metastatic tumors that show a cribriform pattern shold be excluded. A cribriform pattern can be seen in cancers of various organs, including the breast (adenoid cystic carcinoma and cribriform adenocarcinoma), prostate (ductal carcinoma and acinar carcinoma), stomach, colon, lung, thyroid (cribriform-morular variant of papillary thyroid carcinoma), uterine endometrium, and salivary gland [8-10]. To exclude metastasis, imaging studies, such as PET-CT and CT, and immunohistochemical staining are required.

Immunohistochemical staining results are listed in Table 1. Although decapitation secretion in the luminal border supports apocrine differentiation, gross cystic disease fluid protein-15, a marker for the apocrine gland, was negative in previous reports [1-7] and in our case. The S-100 protein, a marker for the eccrine gland, demonstrated variable results (diffuse positive, focal positive, and negative) in previous reports [1-7]. Our case showed more prominent S-100 protein in the luminal component. EMA was positive in previous reports [1-7]. Rutten et al. [2] reported more prominent EMA in the luminal structures, while our case showed more prominent EMA in the solid component.

The relatively mutually exclusive immunohistochemical staining patterns of EMA and S-100 protein may be associated with

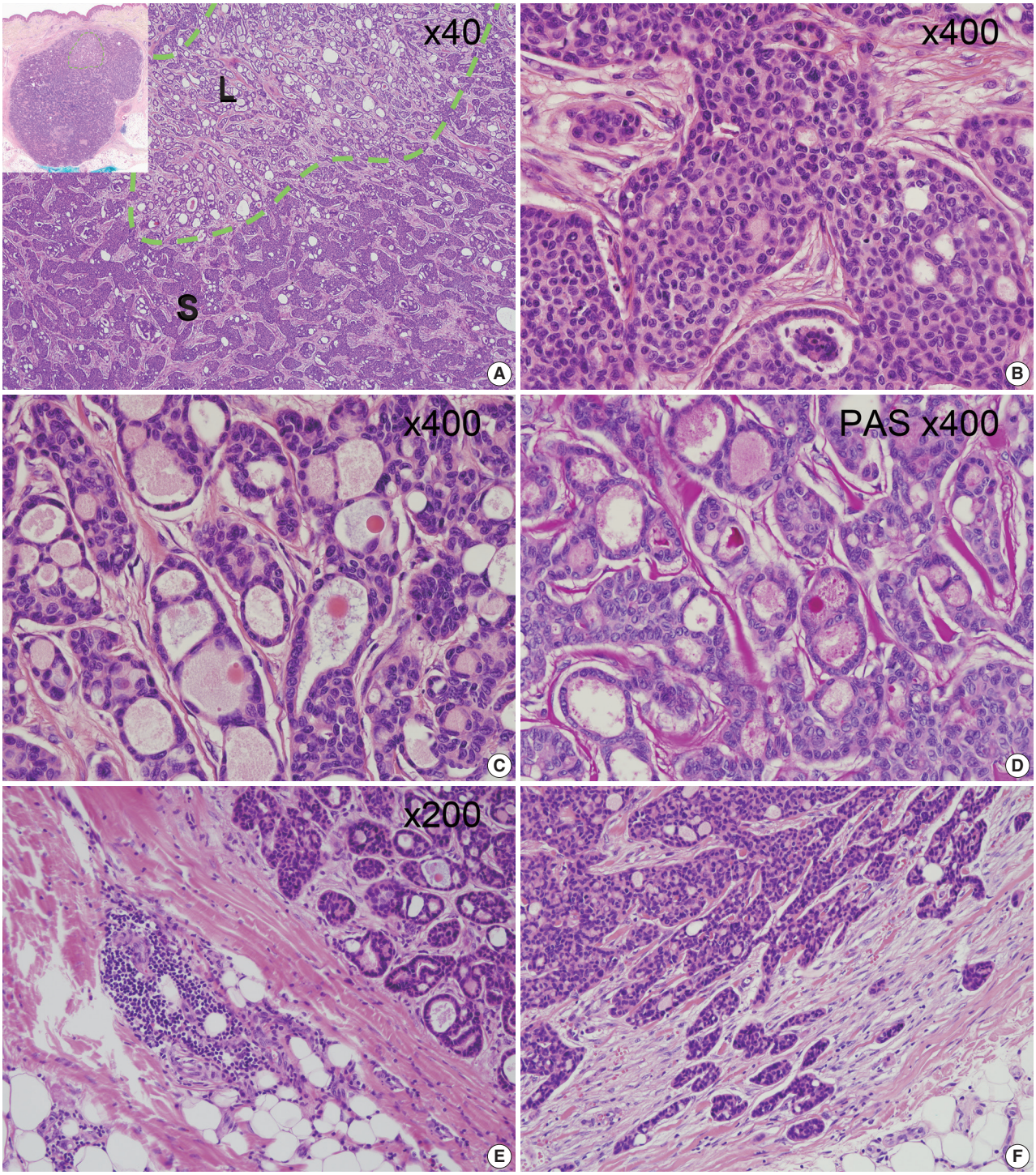

Fig. 2. Histopathologic features of the mass. (A) The mass exhibited a predominantly solid component (90%) and a predominantly cribriform component (10%, inside the green line). (B) The predominantly solid component revealed pleomorphic nuclei. (C) The predominantly cribriform component had similar cytologic features to those of the solid component and demonstrated many prominent small lumina with a thin thread-like intraluminal bridge (cribriform pattern) along with an occasional eosinophilic substance. (D) The intraluminal eosinophilic substance with periodic acid–Schiff reaction. (E) Multifocal lymphoid aggregates at the periphery. (F) Infiltrative tumor clusters at the periphery. S, predominantly solid component; L, predominantly luminal component.

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architectural differentiation, and further research is needed.

In conclusion, we report the first case of cribriform carcinoma of the skin in Korea. Pathologists should be aware of cribriform carcinoma of the skin to avoid over-treatment.

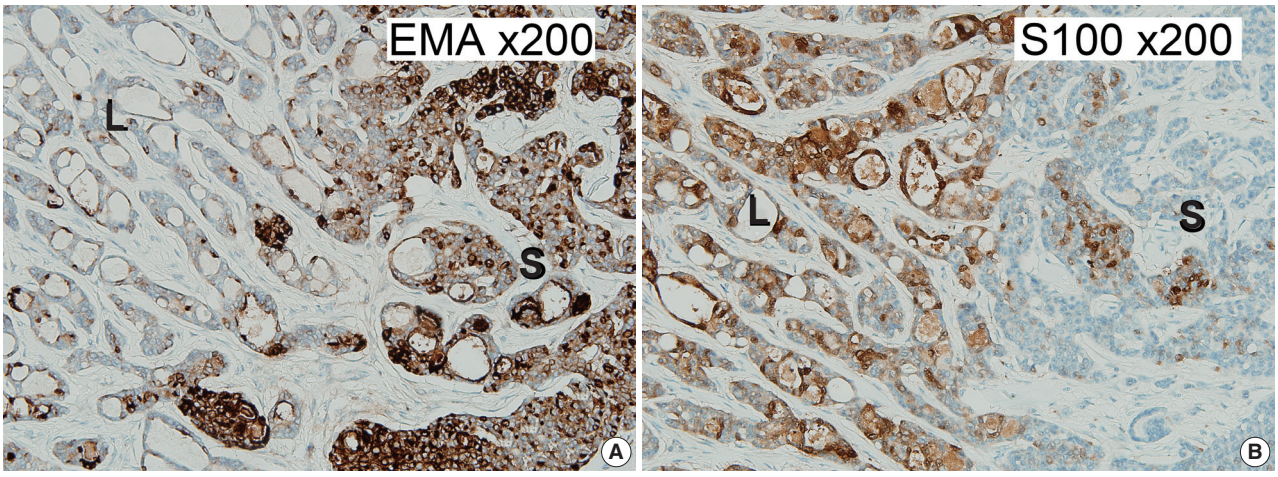

Fig. 3. Results of immunohistochemical (IHC) staining. (A) IHC for epithelial membrane antigen: diffuse immunopositivity for the predominantly solid component (on the right) and focal immunopositivity for the predominantly luminal component (on the left). (B) IHC for S-100 protein: diffuse immunopositivity for the predominantly luminal component (on the left) and focal immunopositivity for the predominantly solid component (on the right). S, predominantly solid component; L, predominantly luminal component.

Table 2. Histopathologic characteristics of cribriform carcinoma and similar tumors

	Cribriform carcinoma	Adenoid cystic carcinoma	Secretory carcinoma	Tubular adenoma
Architecture	Usually well-circumscribed	Poorly circumscribed	Intradermal, circumscribed	Well circumscribed
	Mixed variable portion of solid and cribriform	Composed of lobules, islands, and cords of basaloid cells with numerous cystic and ductular spaces	Back-to-back proliferation of tubules and microcysts	Variable sized tubules with attenuated epithelium
	No back-to-back appearance		Cuboidal cells	Micro-papillae, and focal intraluminal bridging
	No cuboidal cells		Sclerotic stroma	Paucicellular fibrous stroma
	Desmoplastic stroma			Recognition of myoepithelial layer
Intra-(pseudo) luminal substance	Eosinophilic substance with PAS reaction	Mucin or basement membrane material that stains with mucicarmine, Alcian blue, and colloidal iron	Conspicuous intraluminal secretions	Eosinophilic proteinaceous material
Nuclei	Pleomorphic	Uniform	Mildly pleomorphic	Uniform
Mitosis	Rare	Rare	Rare to few	Absent
Perineural invasion	Absent	Present, frequent	Absent	Absent
Immunohistochemical staining	Variable CK (MNF116, AE1/AE3, CAM5.2, and CK7)	EMA and monoclonal CEA	S100 protein, mammaglobin and STAT5A	HMFG-1 and GCDFP-15
	EpCAM	S100, p63, GFAP, SMA, MSA and calponin: often stain peripheral cells (myoepithelial differentiation)	NTRK3: variable	EMA and CEA: luminal cells
	CD117, S100, and p63: variable			S100 and SMA: myoepithelial cells
	CEA, EMA: highlight ductal component			
Reference	[11,12]	[12,13]	[12,14]	[3,12,13]

PAS, periodic acid-Schiff; CK, cytokeratin; EMA, epithelial membrane antigen; CEA, carcinoembryonic antigen; S100, S-100 protein; GCDFP-15, gross cystic disease fluid protein-15; EpCAM, epithelial cell adhesion molecule; GFAP, glial fibrillary acidic protein; SMA, smooth muscle actin; MSA, muscle specific antigen.

Ethics Statement

This study was approved by the Institutional Review Board of Asan Medical Center (IRB 2020-0364). Formal written informed consent was not required, with a waiver from the appropriate Institutional Review Board.

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Conflicts of Interest

CSP, a contributing editor of the *Journal of Pathology and Translational Medicine*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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