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Palisading Adenocarcinoma of the Sublingual Gland: Report of Two Rare Cases

Ayse Nur YUKSEL[1], Asli AYDOGDU YESILOGLU[2], Gulsah ACAR YUCEANT[3], Betul Ulya DURMUS[1], Aysun Hatice UGUZ[2], Kayhan BASAK[1]

Department of Pathology, [1]University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye and [2]Cukurova University, Faculty of Medicine, Adana, Türkiye, [3]Department of Otorhinolaryngology, Head and Neck Surgery, University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye

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ABSTRACT

Palisading adenocarcinoma is a recently recognized, biphasic salivary gland tumor with a distinctive histomorphological pattern. Its low rate of local recurrence and absence of documented metastatic potential make accurate recognition clinically relevant. We report two cases of palisading adenocarcinoma arising in the sublingual gland of female patients aged 39 and 54 years. Both tumors were well-circumscribed and encapsulated, and showed solid growth composed of trabecular and islet-like structures with prominent peripheral palisading, admixed with ductal elements, with focal necrosis observed in one case. Immunohistochemically, the solid component demonstrated diffuse CD56 positivity, while chromogranin, synaptophysin, and INSM1 were negative. The ductal component showed strong CK7 expression with basal staining for p63, p40, and calponin. Although palisading adenocarcinoma lacks a characteristic diagnostic genetic alteration, its distinctive biphasic architecture, characteristic immunophenotype, and favorable clinical behavior warrant recognition as a distinct entity.

Keywords: Palisading adenocarcinoma, Salivary gland, CD56

INTRODUCTION

Palisading adenocarcinoma, first described by Bishop et al. in 2023, is a recently recognized salivary gland carcinoma characterized by a distinctive biphasic histological pattern (1). Although the first case was reported in the sublingual gland, subsequent cases have been described in the submandibular gland, parotid gland, and other anatomic sites (2–6). Palisading adenocarcinoma shows a relatively uniform constellation of histomorphological features, with only minor variability among reported cases. The absence of any specific identified genetic alteration in published cases appears to be the main reason why this rare tumor has been overlooked until now. Herein, we report two additional cases from two centers in Türkiye, aiming to further delineate the clinicopathological spectrum of palisading adenocarcinoma and to highlight both shared and variable histological features.

CASE 1

A 39-year-old woman presented with a left sublingual mass located in the floor of the mouth. The patient had noticed a painless nodule behind the lower teeth for the last 2 months. Magnetic resonance imaging revealed a mass not clearly demarcated from the sublingual gland (Figure 1). A core biopsy was performed and reported as a benign salivary gland tumor with a biphasic cellular component, and excision was recommended for definitive diagnosis. There was no prior fine needle cytological examination performed. The following surgical excision showed a morcellated mass with 3x2x2 cm dimensions. Microscopically, a capsule was identified, although its integrity could not be fully assessed (Figure 2A,C). Histopathological examination demonstrated that the tumor was composed of two distinct cellular components. The dominant component formed well-demarcated trabecular and nested patterns, with peripheral palisading and occasional pseudorosette formation. The tumor cells had pale eosinophilic cytoplasm, vesicular nuclei, and prominent nucleoli, with mild to moderate nuclear atypia in focal areas. A secondary component consisted of duct-forming cells and scattered infiltrating small cell groups with narrow lumina. No necrosis, lymphovascular invasion, or perineural invasion was identified.

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Correspondence: Kayhan BAŞAK
Department of Pathology, University of Health Sciences,
Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Türkiye
E-mail: kayhan.basak@sbu.edu.tr Phone: +90 216 458 30 00 / 31208

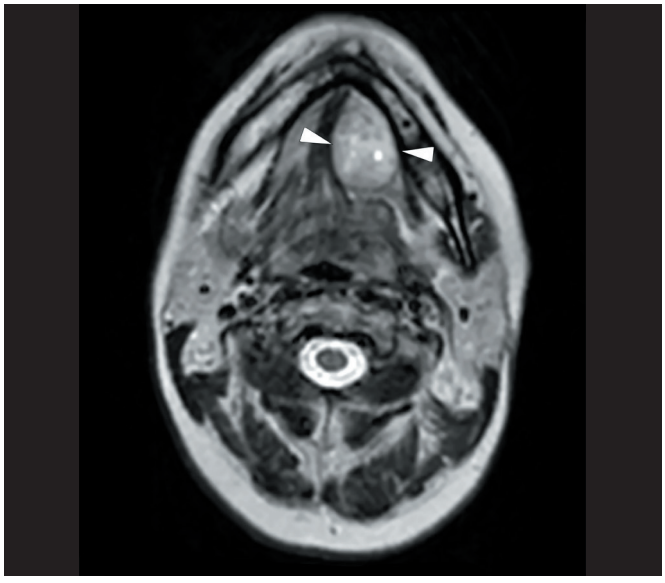


Figure 1: Axial MRI of Case 1 demonstrating a solid mass measuring 3 cm in greatest diameter arising in the left sublingual gland (between white arrowheads).

Immunohistochemically, the dominant pale cell population was negative for chromogranin (Ventana, LK2H10), synaptophysin (Zetacorp, ZM208) and INSM-1 (Santa Cruz, A8), but showed diffuse and strong CD56 positivity (Zetacorp, 123C2.D5). S100 (Ventana, 4C4.9) and SOX10 (Figure 3A) (Zetacorp, ZM10) were negative in the dominant component, whereas SOX10 (Figure 3D) highlighted the ductal cells. The ductal component showed strong positivity for pancytokeratin (Ventana, AE1/AE3), CK7 (Figure 3B) (Ventana, SP52) and CK5/6 (Ventana, D5/16 B4). In contrast, the predominant solid component showed only weak and diffuse pancytokeratin staining CK (AE1/AE3). β-catenin (Cell Marque, 14) demonstrated diffuse membranous positivity. p63(Zeta Corp, 4A4) (Figure 3C), p40, and calponin (Ventana, EP798Y) were negative in the dominant component but showed basal-type staining in the ductal structures. PLAG1 (Abcam, 8D8C5) was negative. Additional markers, including mammaglobin, DOG1, androgen receptor, estrogen receptor, GFAP, GATA3, NOR1,

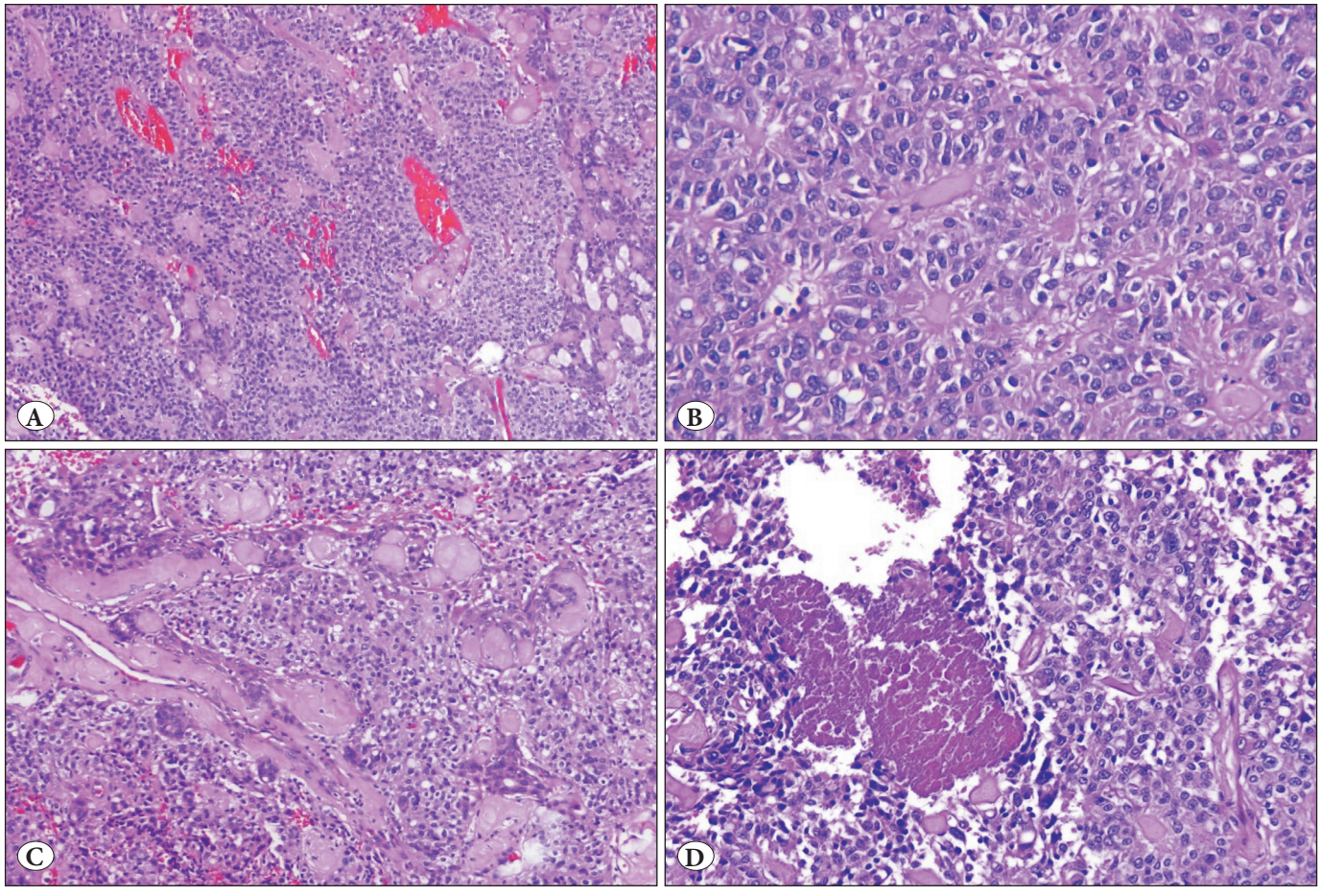


Figure 2: The tumor exhibits prominent palisade structures **(A)** (Case 1) (x100, H&E), and rosette-like structures forming a neuroendocrine-like growth pattern **(B)** (Case 2) (x400, H&E). Areas of stromal hyalinization **(C)** (Case 1) (x200, H&E) and focal necrosis are observed in the tumor tissue **(D)** (Case 2) (x400, H&E).

and SMA, were negative in both components. The Ki-67 proliferation index was approximately 6–7%, and mitotic activity ranged from 2 to 4 per 10 high-power fields. Targeted RNA sequencing using a TruSight RNA Pan-Cancer panel did not reveal any specific gene fusions or pathogenic variants for 1385 target genes and 21043 target exonic regions (TruSight RNA Pan_Cancer TSO 500-HT, NextSeq/Novaseq). No local recurrences or distant metastases were observed during the 23-month clinical follow-up period.

CASE 2

A 54-year-old woman presented with a sublingual mass in the floor of the mouth that had been present for approximately four years. Magnetic resonance imaging demonstrated a well-delineated lesion. There was no prior fine needle cytological examination performed. Gross examination revealed a well-circumscribed, solid, encapsulated mass measuring 2x2x1.8 cm. Histologically, the tumor closely resembled that of Case 1, although peripheral palisading was more prominent (Figure 2B), but it contained a small focus of tumor necrosis (Figure 2D). Tumor showed diffuse positivity with CD56 and negativity for chromogranin and synaptophysin. Patchy SOX10 staining was observed. The ductal component showed strong positivity for pancytokeratin, CK7, and CK5/6, whereas the predominant solid component was negative for pancytokeratin. Molecular analysis could not be performed due to unavailability of suitable tissue. No local recurrence or distant metastasis was identified during a 20-month clinical follow-up period.

DISCUSSION

Interestingly, palisading adenocarcinoma is a rare salivary gland tumor that lacks a distinctive signature genetic profile, exhibits a unique biphasic pattern, and was potentially overlooked in previous years. Reports show a marked female predominance, with patient ages ranging from 33 to 74 years (1–6) and tumor sizes ranging from 1.4 to 10 cm (1,3–5). The tumor is among those reported to be present

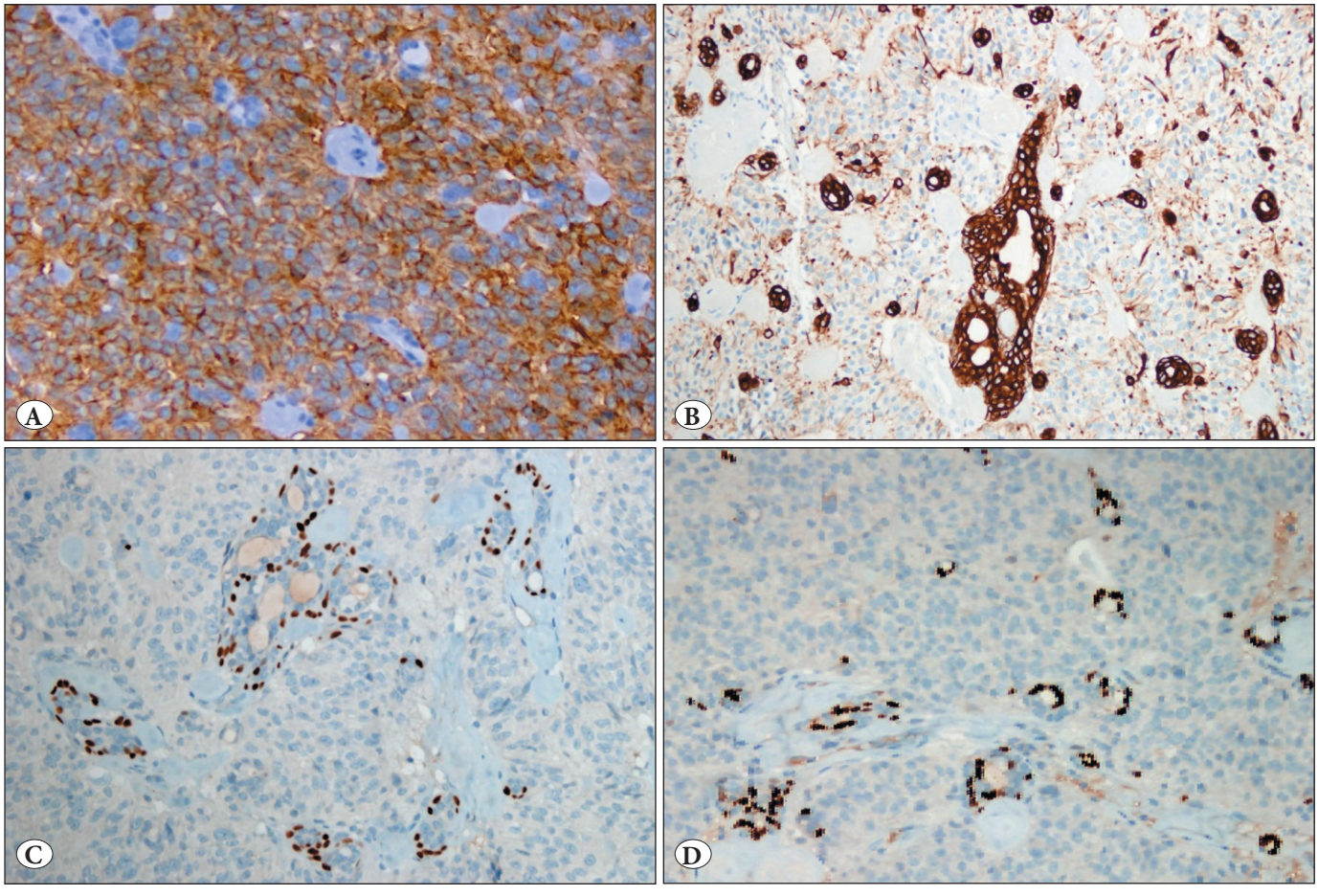


Figure 3: Diffuse strong CD56 expression **(A)** (Case 2) (x400), strong expression in the ductal component with weaker expression in the intervening epithelial cells CK7 **(B)** (Case 1) (x200). Basal expression in the ductal component with p63 **(C)** (Case 1) (x200) and expression of SOX10 in the ductal component **(D)** (Case 1) (x200).

Table I: Demographic and tumor characteristics of reported and current cases.

Author	Case no	Age	Sex	Tumor location	Side	Region	Tumor size (cm)	Treatment	Outcome	Month	Metastases	Recurrences	Borders	Lymphovascular invasion	Perineural invasion	Mitosis/10HPF	Necrosis	TALP
Present study	1	39	F	Sublingual gland	Left	Türkiye	3	S	NED	18	No	No	Well-defined	No	No	2-4	No	No
	2	54	F	Floor of mouth	Medial	Türkiye	2	S	NED	15	No	No	Well-defined	No	No	Low	Focal	No
Bishop et al. (1)	1	50	F	Sublingual gland	NS	NS	2,5	S	NED	56	No	No	4 well-circumscribed, 5 infiltrative growth	1 of 9	2 of 9	Low, mean 2.2	No	NS
	2	49	F	Submandibular gland			1,4	S	NED	7								
	3	47	F	Submandibular gland			3,2	S	NED	132								
	4	60	F	Sublingual gland			3,1	S+RT	NED	4								
	5	74	M	Sublingual gland			5,2	S	NED	6								
	6	52	F	Sublingual gland			2,5	S	NED	36								
	7	45	F	Sublingual gland			2	S	NED	24								
	8	72	F	Sublingual gland			3	S	NED	None								
	9	61	F	Sublingual gland			3,2	S	NED	160								
Manini et al. (2)		65	F	Submandibular gland	Left	NS	4	S	NED	7	No	no	Well-delimited, but not encapsulated	No	No	Very scarce	No	NS
Rivera et al. (3)		61	F	Sublingual gland	Left	NS	3	S	NS	NS	NS	NS	unencapsulated but fairly well-defined	NS	NS	Low	No	Yes
Dababneh et al. (4)		58	F	Submental area	Left	Türkiye	2,5	S	NED	180	No	No	Well-demarcated, thickly encapsulated	No	No	NS, low	No	NS
Zhang et al. (5)	1	33	F	Submandibular gland	Left	NS	NS	S	NED	120	No	No	Pushing invasion	NS	NS	NS	NS	Yes
	2	41	F	Floor of mouth	NS	NS	3	S	None	Lost to follow	Yes	Yes	Well-circumscribed	NS	NS	NS	NS	NS
	3	39	F	Submandibular gland	Left	NS	3	S	None	NS	NS	NS	Well-circumscribed	NS	NS	NS	NS	NS
	4	61	F	Parotid gland	Right	NS	10	S	NED	36	No	No	Pushing invasion	Yes	NS	Low	NS	NS
	5	68	F	Parotid gland	Right and Left	NS	10	S	None	96	No	Yes	NS	NS	NS	NS	NS	NS
	6	72	F	Neck	Right and Left	NS	NS	None	AWD	NS	NS	NS	NS	NS	NS	Low	NS	NS
Huang et al. (6)		38	F	Parotid gland	Right	NS	NS	S	No	NS	Yes*	8th year	NS	Yes	Yes	1-3	No	Focal

* Multiple lymph node metastasis, **NED:** no evidence of disease, **NS:** Not specified, **AWD:** Alive with disease, **TALP:** Tumor associated lymphoid proliferation, **F:** Female, **M:** Male

Table II: Reported immunohistochemical and molecular characteristics of the cases.

		Present study		Bishop et al. (1)	Manini et al. (2)	Rivera et al. (3)	Dababneh et al. (4)	Zhang et al. (5)	Huang et al. (6)
				9 Cases				6 Cases	
Predominant cell type	AE1/AE3	WP	N	7 of 9	P	V		WP	
	CAM5.2						WP		
	EMA							NATC	
	CK5/6			7 of 7		SP	N		
	CK7						N		
	CK8/18							SP	WP
	CK19								
	MUC4							NATC	
	CD56	SP	DP	9 of 9	P	P	DP	SP	DP
	Chromogranin	N		0 of 9	N	N	N	NATC	
	Synaptophysin	N		0 of 9	N	N	N	NATC	N
	INSM-1	N				N	N	NATC	N
	SOX10	N	P			N	N	NATC	
	PLAG1	N							
	TTF-1								N
	Ki67	6–7%			<2%				Low
	p63	N			N		N	Low	
	p40	N			N	N			
	S100	N		4 of 9	N	V		S	P
	DOG1	N			N			NATC	N
	NOR1	N							
	CD117				N			NATC	
	Calponin	N			N	N			
	SMA	N				N		N	
	GFAP	N				N			
	p53								
	Androgen receptor	N			P			NATC	
	Estrogen receptor	N						NATC	
	Progesterone receptor							NATC	
	Vimentin				P			SP	
	CD10					N		NATC	
	GATA3	N				N			
	ALK					N			
	Mammaglobulin	N						NATC	
	GCDFP15							NATC	
	CEA							NATC	
	β-catenin	UM						UM	
	Molecular findings	Any gene mutations with NGS	NP	Any fusions or obvious driver mutations with NGS	NP	WES and RNA sequencing did not reveal significant findings	NP	NP	Any gene mutations or MSI with NGS

Table II continue

		Present study		Bishop et al. (1)	Manini et al. (2)	Rivera et al. (3)	Dababneh et al. (4)	Zhang et al. (5)	Huang et al. (6)
				9 Cases				6 Cases	
Ductal cells	AE1/AE3	SP		9 of 9	SP	P		SP	
	CAM5.2					SP			
	EMA							NATC	
	CK5/6	SP	SP	7 of 7		P	P		SP
	CK7	SP	SP				P		SP
	CK8/18							SP	SP
	CK19							EP	
	MUC4							NATC	
	CD56					N	N		
	Chromogranin					N		NATC	N
	Synaptophysin					N		NATC	N
	INSM-1					N		NATC	
	SOX10	P				P		NATC	Focal
	PLAG1	N							
	TTF-1								N
	Ki67							Low	
	p63	BP					AP	PP	BP
	p40	BP				N		PP	BP
	S100					P	N	S	BP
	DOG1	N						NATC	N
	NOR1	N							
	CD117							NATC	
	Calponin	BP				N		PP	
	SMA	N				N	N	N	
	GFAP	N				N	N		
	p53						Wild		
	Androgen receptor	N						NATC	
	Estrogen receptor	N						NATC	
	Progesterone receptor							NATC	
	Vimentin							SP	
	CD10								
	GATA3	N							
	ALK								
	Mammaglobulin	N						NATC	F
	GCDFP15							NATC	
	CEA							NATC	
	β-catenin	UM						UM	

P: Positive, **N:** Negative, **WP:** Weak positive, **DP:** Diffuse positive, **SP:** Strongly positive, **V:** Variable, **UM:** Uniformly membranous, **EP:** Exclusively positive, **AP:** Abluminal positive, **PP:** Periductal positive, **S:** Scattered, **F:** Focal, **NP:** Not performed, **NATC:** Negative in all tested cases, **MSI:** Microsatellite instability.

for a period of 1 to 12 months (4,5). Although the first case was reported in the sublingual gland, they have also been reported in the submandibular gland, parotid gland, orbit, and maxilla. Among the cases reported to date, three involved Turkish patients, while the majority were reported in the Eastern Hemisphere (1-6).

Although there are only a few reports available, the demographics, tumor location, size, growth pattern, invasive features, immunohistochemical profile, molecular findings, treatment, and follow-up data for these cases are quite heterogeneous and are summarized in Table I and Table II. Histologically, all reported cases are composed of cells with pale eosinophilic cytoplasm, round to oval nuclei, and prominent nucleoli, arranged in trabeculae and islets with characteristic peripheral palisading (1,4). Hyalinized stroma, thick-walled vessels, and diastase-resistant PAS-positive basement membrane–like material have been described (6). Ductal structures with a discontinuous basal layer highlighted by p63, p40, or calponin represent a key diagnostic feature. Most tumors are well-circumscribed and encapsulated (4), with infrequent infiltrative growth, perineural invasion, or lymphovascular invasion (1). Mitotic activity (1,2,6) and Ki67 proliferation indices are generally observed to be low (5,6). Additional reported features include giant cells with hyperchromatic bizarrely atypical nuclei, sparse microcalcifications (1,2,5), tumor-associated lymphoid proliferation (3,5), prominent sclerosis or hyalinization (1,3), and highly collagenized strands of fibrous tissue or septae (2,6). Although not yet reported in the literature, focal necrosis was observed in one of our cases. Histologically, it is not possible to speculate on the relationship between the presence of necrosis and recurrence, metastasis, and prognosis. The increasing number of cases in the literature and the follow-up of our case with necrosis may provide further insights in the future.

Palisaded adenocarcinoma appears to have a distinct immunohistochemical phenotype showing minor changes consistent with a different histological pattern. The solid component typically expresses CD56(1–6) and variably expresses pancytokeratin (AE1/AE3)(1,2,4,6), androgen receptor (2,6), vimentin (2,5) and CK8/18 (5). S100 (1,3,5) and CK8/18 (6) have been reported as variable for the solid component. p63, p40, calponin, chromogranin, synaptophysin, DOG-1, CD117, GFAP, ALK, SOX10, S-100, synaptophysin, chromogranin, INSM1, estrogen receptor, progesterone receptor, EMA, mammaglobin, GCDFP15, MUC4 and CD10 were reported as negative (1–3,5). It was positive for ductal component cytokeratin (AE1-AE3) (2,5), CK5/6(1,6), SOX10, CD117 and DOG1(1,3), CK7 (5,6), CK19 (5) and CK8/18 (6), negative for CD56 (1) and focally positive for mammaglobin (6). Calponin, p63, p40 (1,5,6), and S100 (6) were periductal positive and SMA was always negative (1,3,5). β-catenin was reported to be uniformly membranous, similar to our case (5). EBV and human papillomavirus were reported negative (1). Molecular studies to date, including next-generation sequencing and whole-exome sequencing (5) have not identified recurrent gene fusions or driver mutations or microsatellite instability (1,6) and RNA sequencing did not reveal significant findings for potential recurrent gene alterations (3). All cases except one that received postoperative radiation therapy (1) were treated surgically (1,5,6). Apart from local recurrence in two cases (one of which was nine years later) (5), no recurrence or distant metastasis was reported in the other cases during follow-up periods of up to 160 months.

The authors agree that this tumor appears to be on the histological similarity to neuroendocrine neoplasms. However, histologically, it resembles neuroendocrine carcinomas but is negative for markers other than CD56 (1–6). Recognition of the characteristic biphasic pattern, together with diffuse CD56 positivity in the solid component, is therefore essential for accurate diagnosis. Although some genetic alterations have been identified (5), a diagnostic signature mutation for palisading adenocarcinoma has not yet been established.

Conflict of Interest
Authors have no such conflict of interest.

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