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Original Research

Hyalinizing clear cell carcinoma of the anterior lingual salivary gland: A case report and review of the literature☆

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ABSTRACT

Hyalinizing clear cell carcinoma (HCCC) is a low-grade epithelial tumor classified as a subtype of salivary gland carcinoma. HCCC occurs most frequently on the palate and base of the tongue. Noteworthy, HCCC arising in the anterior of the tongue is quite rare and it has yet to be fully characterized in the clinical literature. Herein, we present a case of a 59-year-old man with HCCC on the anterior of the tongue. A present case was confirmed by a detection of *EWSR1-ATF1* fusion gene with a same breakpoint that previously reported in HCCC cases. To our knowledge, this report represents the rare case of HCCC arising in the anterior of the tongue in the literature.

1. Introduction

Hyalinizing clear cell carcinoma (HCCC) is an extremely rare neoplasm of salivary gland origin with a low-grade indolent nature [1]. The incidence of HCCC is less than 1% in all malignant salivary gland tumors [2]. This tumor usually arises in minor salivary glands of adult women involving mainly in the palate, tongue, and floor of the mouth [3]. Daniele et al. were reviewed 122 cases of HCCC emerged in the oral cavity up to 2014 [4]. The most involvement were the tongue (n = 39: 32.0 %) and most frequent sites of occurrence in tongue seem to be the base of tongue [1,5]. HCCC presents as a small and painless mass that seldom ulcerates. Histologically, HCCC demonstrates cords, trabeculae, and nests of monomorphic clear epithelial cells, as well as cells with eosinophilic granular cytoplasm [1]. Herein, we report a rare case of HCCC that originated from the anterior lingual salivary gland. Moreover, we reviewed relevant literature of HCCC in the tongue.

2. Methods

2.1. RT-PCR

Total RNA was obtained from Formalin-fixed paraffin-embedded (FFPE) samples using NucleoSpin total RNA FFPE (Macherey-Nagel). The cDNA was synthesized from 1 μg total RNA using a PrimeScript RT reagent kit (Takara Bio). The primers used for detecting *EWSR1-ATF1* fusion gene by RT-PCR analysis are the following; the forward primer, 5'-caaggattaaatgacagtgtgactc-3', and the reverse primer, 5'-ctttctgtgaggagcctatg-3'. The aliquots of the total cDNA were amplified with Tks GflexTM DNA Polymerase (Takara Bio), and amplification was performed in a T100TM thermal cycler (Biorad) for 40 cycles following an initial denaturation at 98 °C for 10 s and 62 °C for 30 s. Then, the sequence was confirmed by direct sequencing methods with an ABI Prism 310 sequence analyzer (Applied Biosystems, Foster City, CA, USA).

Abbreviations: HCCC, hyalinizing clear cell carcinoma; PET-CT, positron emission tomography-computed tomography; FDG, fluorodeoxyglucose; RT-PCR, reverse transcription polymerase chain reaction; PAS, periodic acid–Schiff; SUVmax, maximum standardized uptake value

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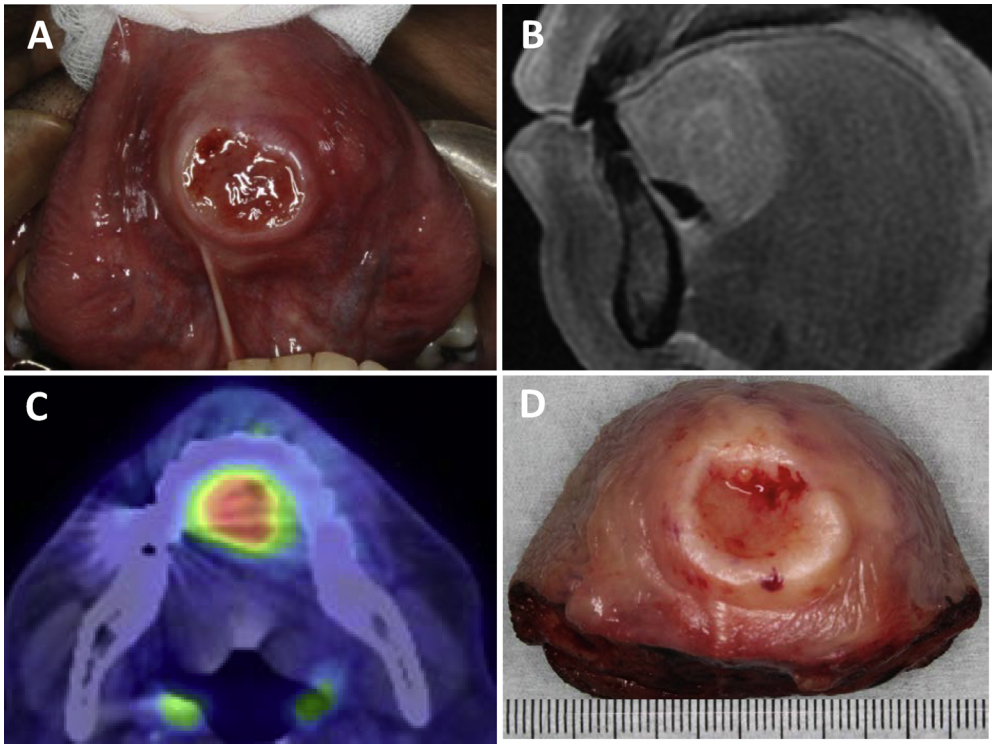

Fig. 1. Clinical and image photographs.
(A) Clinical photograph of the tumor at the first visit. (B) MRI image. (C) PET-CT image. (D) Surgical resected specimen.

2.2. Literature review

A natural language search was performed to identify HCCCs using the PubMed, the J-stage system to the present from 1983. Search terms included “hyalinizing clear cell carcinoma” and “clear cell carcinoma” in the final diagnosis. All cases selected the cases arose from the tongue.

3. Case report

A 59-year-old Japanese man with no significant past medical history was referred to our department because of a growing painless mass on the inferior surface of the tongue. An intra-oral examination revealed an extroverted and ulcerated mass measuring 2.8 × 2.1 × 1.5 cm in size, on the inferior surface of the tongue (Fig. 1A). On palpation, the mass was elastic hard without tenderness. There was no clinical evidence of cervical lymphadenopathy. Magnetic resonance imaging showed a relatively clear boundary mass, a low signal in a T1 weighted image, and an intermediate signal in a T2 weighted image (Fig. 1B). After contrast administration, a homogeneous enhancement inside the rounded image was evident. Positron emission tomography-computed tomography (PET-CT) demonstrated abnormal accumulation of FDG (with an SUVmax = 6.9) confined to the tongue tip (Fig. 1C). No significant abnormalities were noted in the laboratory examinations including tumor markers such as SCC, CEA and CYFRA.

Complete tumor resection, partial glossectomy with an approximately 1 cm safe margin was performed (Fig. 1D). Reconstruction with a free forearm flap was performed on the defect at the tip of the tongue. Histologically, non-encapsulated but well-circumscribed tumor mass occupied in the muscle layer of the anterior tongue but not have continuous contact with epithelial layer (Fig. 2A). Follicular lymphoid infiltration predominantly observed around the mass and atrophic minor salivary glands were found in the surrounding area (Fig. 2B). Tumor cells with clear cytoplasm were arranged in trabeculae, cords, or irregular solid nests surrounded by hyalinizing stroma, without keratinization and duct formation (Fig. 2C and D). Tumor cells demonstrated small nuclei, mild to moderate atypia, and little mitosis. Tumor cells were classified fearlessly element compose of cells with clear cytoplasm and element composed of cells with pale eosinophilic cytoplasm (Fig. 2D). The clear cells were positive for periodic acid–Schiff (PAS), but negative for diastase digested PAS (dPAS) (Fig. 2E and F). Moreover, mucus-producing cells were not observed. Therefore, we excluded mucoepidermoid carcinoma in the differential diagnosis. Indeed, the CRT1/3-MAML2 fusion gene, which is specific for mucoepidermoid carcinoma, was not detected by RT-PCR (data not shown).

Immunohistochemically, the tumor cells were diffusely positive for p63, but negative for S-100, alpha-smooth muscle actin (αSMA), glial fibrillary acidic protein (GFAP), and vimentin (Fig. 3A–D). Ki-67 index was less than 10 % (Fig. 3E). As no differentiation into myoepithelium was observed, epithelium-myoepithelial carcinoma was also ruled out. Moreover, PET-CT revealed no obvious abnormal accumulation except for at the tongue apex. This result ruled out metastasis from other primary tumors with clear cells, such as renal cell carcinoma. Indeed, CD10, a marker for renal cell carcinoma, was negative for this tumor. From these histological examinations, we diagnosed the present case as a HCCC.

To confirm the diagnosis of HCCC, we examined the detection of

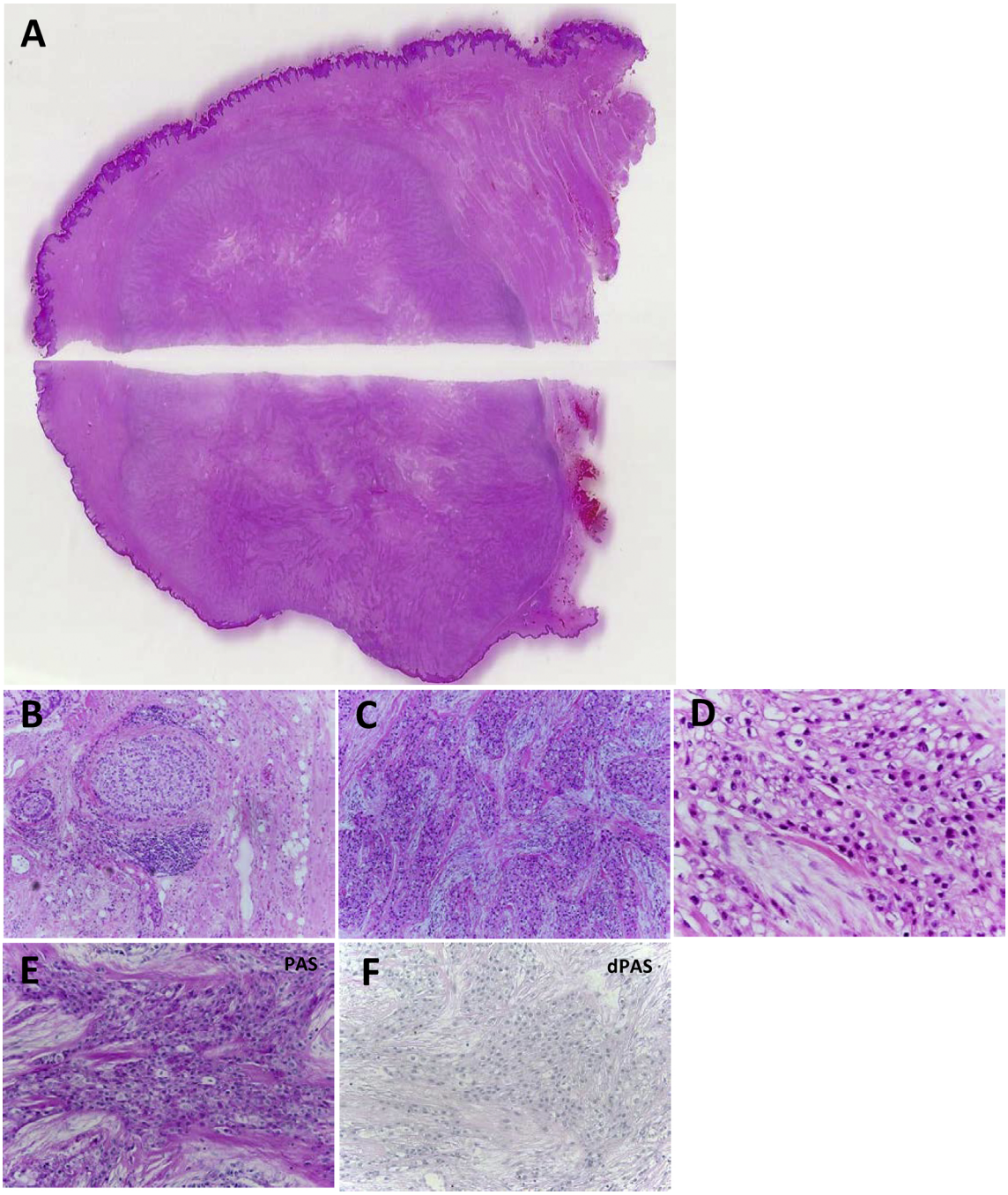

Fig. 2. Histopathological findings of the present case.
(A) H-E stain, macroscopic image. (B and C) H-E stain, ×40. (D) H-E stain, ×200. Tumor cells with clear cytoplasm were arranged in trabeculae, cords, or irregular solid nests surrounded by hyalinizing stroma. (E) PAS stain, x100. (F) dPAS stain, x100. The tumor cells showed granular PAS positivity and diastase sensitivity.

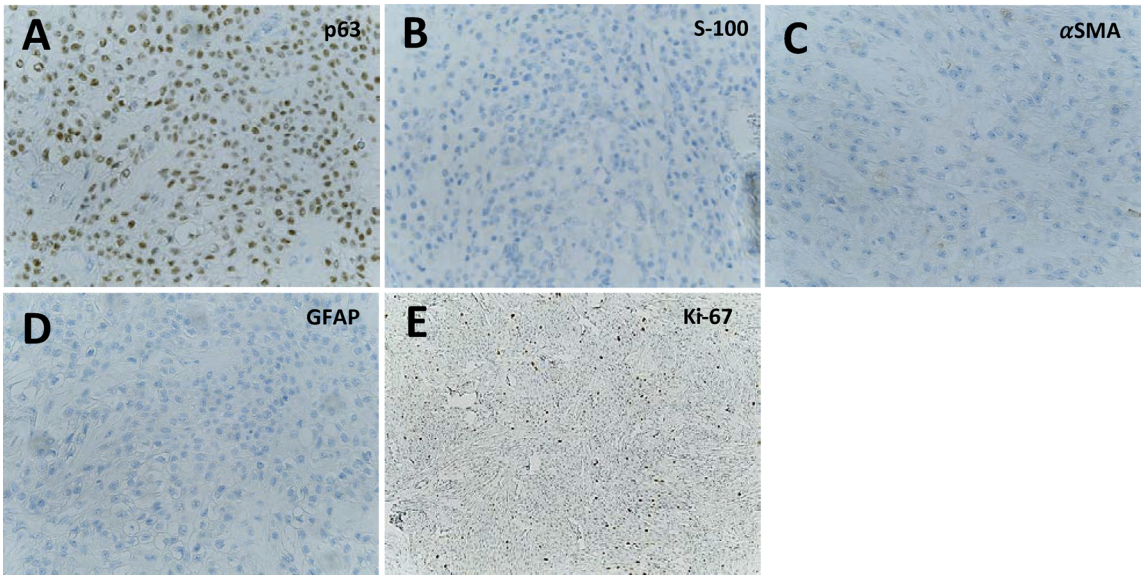

Fig. 3. Immunohistochemical findings of the present case.
(A) p63, x200. (B) S-100, x200. (C) αSMA, x200. (D) GFAP, x200. Tumor cells were positive for p63, but not S-100, αSMA, and GFAP. Moreover, vimentin, CD10 and Adipophilin are also negative (data not shown). (E) Ki-67, x40.

EWSR1-ATF1 fusion transcripts by RT-PCR using an FFPE sample of this tumor. We could observe the *EWSR1-ATF1* fusion gene (Fig. 4A). The direct sequence of the EWSR1-ATF1 fusion transcript revealed that exon 11 of EWSR1 was fused to exon 3 of ATF1 (Fig. 4B), indicating that the breakpoint is the same as that found in HCCC [6].

The patient's postoperative course has been uneventful, with no significant complications. He has not undergone postoperative adjuvant therapy. So far, during the postoperative follow-up period of 5 years, there is no evidence of local recurrence, and cervical lymph node and distant metastases.

4. Discussion

Concerning the origin of tongue tumors, reports of HCCC derived from the anterior lingual salivary gland are limited [2]. In the present paper, we focused on previous reports of HCCC derived from tongue. Fig. 5 shows the distribution of tongue HCCC by the male-female ratio. It is extremely rare in children, and women are more commonly affected than men. Present literature review showed the 8.2 % in the anterior and sublingual tongue against 77.6 % in the base of tongue in 49 cases of tongue HCCC (Table 1). In our case, minor salivary gland tissue was found at a site extremely close to the tumor and it was considered to be a part of the anterior lingual salivary gland, and the sublingual gland was intact. Goldblatt et al. reported on 55 patients with primary minor salivary gland tumors of the tongue from the files of the Armed Forces Institute of Pathology. They found that most of the benign tumors occurred from the front and middle of the tongue, whereas most of the malignant tumors occurred in the tongue base [7].

As HCCC is less likely to cause lymph node and distant metastases, the nature of HCCC is comparatively better prognosis [4]. Yang et al. reported that only 17.3 % of HCCC cases (14/81 cases) showed lymph node metastasis, and that 2.9 % (2/70 cases) presented with distant metastases [8]. Solar et al. also reported that 25 % of HCCC cases (13/52 cases) had metastasis at initial presentation [9]. Similarly, 26.5 % (13/49) of the tongue HCCC cases had metastasis at the initial diagnosis, and 14.3 % (7/49) had a recurrence in the present literature review (Tables 1 and 2). As previously shown that most of the malignant tumors occurred in the tongue base [7], the base of tongue is the most predominate involvement in the cases with metastasis (73.3 %, 11/15 cases) and with a recurrence (55.6 %, 5/9 cases). Therefore, the prognosis of those in anterior tongue may expect the benign course. However, the prolonged follow up is required because cervical lymph node metastasis can be emerged after a decade (Case 14, Case 19) [10,11]. The best treatment for patients with HCCC is wide local excision combined with regional lymph node dissection, if lymph node metastasis is suspected [8].

Albergotti et al. showed that "necrosis" was significantly associated with risk of recurrence, and "positive margins" and "lymph node status" were associated with the risk of recurrence in 130 cases of HCCC [12]. In the tongue HCCC, "necrosis" was not associated with the metastasis, but the "lymph node status" was associated with the poor prognosis (Tables 1 and 3). Lymph node metastasis was not observed in HCCC derived from the anterior lingual salivary gland including the present case. Although the good prognosis may expect in tongue HCCC, we suggest that the prolonged follow-up should be required.

Clear cells are also found in other salivary gland tumors including epithelial-myoepithelial carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, sebaceous carcinoma, clear cellular oncocytoma, and metastatic renal cell carcinoma [13]. Therefore, it is difficult to differentiate HCCC from other tumors based only on the presence of clear cells. One important distinction is that mucoepidermoid carcinoma has mucus-producing cells. In our case, Alcian blue staining showed negative and the CRT1/3-MAML2 fusion gene was not detected. Therefore, mucoepidermoid carcinoma can be excluded. Acinic cell carcinoma has a low percentage of clear cells and does not contain glycogen, and epithelial-myoepithelial carcinoma has a bilayer of proliferating tumor cells and expresses the myoepithelial marker [2]. Clear cell oncocytoma is a mixture of eosinophilic cells, and it exhibits a clear film formation

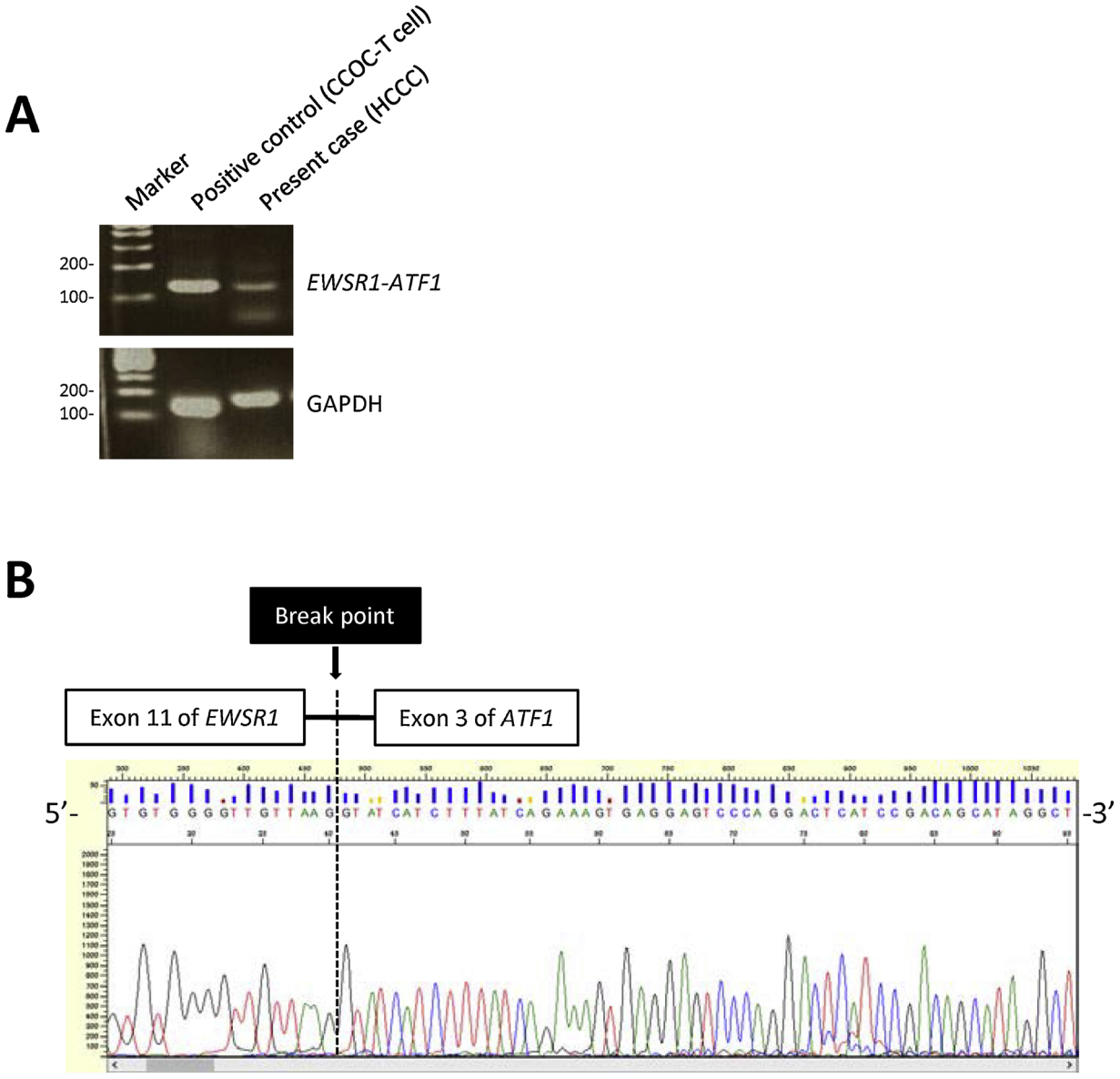

Fig. 4. *EWSR1-ATF1* fusion gene in HCCC case. (A) The *EWSR1-ATF1* fusion gene was detected by RT-PCR using FFPE sample. CCOC-T cells are used for positive control [38]. (D) Sequences of *EWSR1-ATF1* fusion gene in HCCC case. This image of the RT-PCR product sequencing reveals fusion between *EWSR1* exon 11 and *ATF1* exon 3.

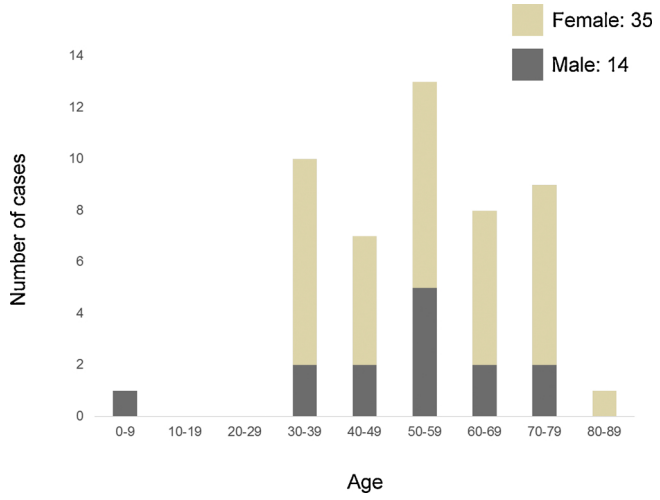

Fig. 5. The distribution of tongue HCCC by the male-female ratio.

with no invasion to the surrounding tissues. In addition, sebaceous adenocarcinoma was ruled out, because of the presence of dPAS positive glycogen granules and the absence of adipophilin expression.

The previous immunohistochemical studies have revealed that tumor cells shows positive for p63 and negative for S-100, αSMA, and vimentin in tongue HCCC cases (Table 3). In addition, the identification of the *EWSR1-ATF1* fusion gene is very useful in accurately diagnosing HCCC [5,6]. Indeed, *EWSR1* rearrangements are not observed in other salivary gland tumors with clear cell change [6]. The *EWSR1-ATF1* fusion gene was also detected in a present case (Fig. 4). Interestingly, breakpoint of the *EWSR1-ATF1* fusion gene in a present case was the same as that previously reported [6].

In conclusion, HCCC might be regarded as a tumor with benign behavior, but regional lymph node dissection with surgical resection with sufficient safe margin is the recommended treatment. Here, we report a case of tongue HCCC that occurred at an extremely rare site with good treatment results obtained by surgery.

Table 1
Clinical data of previously reported 49 tongue HCCC cases.

Case No.	Country	Age	Sex	Site in tongue	Size* (cm)	Metastasis	Treatment	Diagnosis	Prognosis (follow-up periods)	Authors	Reference
1	JPN	59	M	Anterior	2.5	None	Ex	EWSR1-ATF1 fusion	NED (5 years)	Present case	–
2	USA	71	F	Base	1.8	Cervical LNs	CR	NA	NA	Hwang et al.	[14]
3	CAN	68	F	Base	3	Cervical LNs	Ex/SND	EWSR1-CREM fusion	NED (1.5 years)	Chapman et al.	[15]
4	CHN	47	F	Base	2	None	Ex	EWSR1 rearrangement	NED (85 months)	Yang et al.	[8]
5		67	M	Base	2.9	None	Ex	EWSR1 rearrangement	NED (80 months)		
6		72	F	Base	4.8	None	Ex	EWSR1 rearrangement	NED (46 months)		
7	CHN	56	F	Base	1.5	None	Ex	EWSR1 rearrangement	NED (78 months)	Zhao et al.	[16]
8		38	F	Base	0.8	None	Ex	EWSR1 rearrangement	NED (46 months)		
9	TWN	64	F	Base	3.4	None	NA	EWSR1-ATF1 fusion	NED (NA)	Hsieh et al.	[5]
10		33	F	Base	1.4	None	NA	EWSR1-ATF1 fusion	NED (NA)		
11		39	F	Base	2	Cervical LNs	NA	EWSR1-ATF1 fusion	Rec (3 years)		
12	USA	75	F	Base	1.1	NA	Ex	EWSR1 rearrangement	NA	Hermandez-Prera et al.	[11]
13		74	F	Base	2	NA	Ex	EWSR1 rearrangement	NED (4.4 years)		
14		37	F	Base	2.4	NA	Ex	EWSR1 rearrangement	Rec (9.8 years)		
15	USA	47	F	Base	1.1	Cervical LNs	Ex/RND/RT	EWSR1 rearrangement	NED (48 months)	Albergotti et al.	[12]
16	AUS	52	M	Sublingual	2.5	None	Ex	EWSR1 rearrangement	NED (1 year)	Daniele et al.	[4]
17	USA	65	F	Base	5.4	Vertebral body	RT	EWSR1 rearrangement	NED (6 weeks)	Newman et al.	[17]
18	JPN	52	M	Base	1.8	None	Ex/RT	ESWR1-ATF1 fusion	NED (3 months)	Nakano et al.	[18]
19	USA	37	F	Base	2.4	None	Ex	IHC	Rec (10 years)	Su et al.	[10]
20	JPN	56	F	Base	3.6	None	Ex	IHC	NED (1.25 years)	Watanabe et al.	[19]
21	ESP	47	F	Base	4.5	None	Ex	His	NED (3 years)	Moreno Zafra	[20]
22	USA	60	F	Lateral side	2.4	None	Ex	IHC	NA	Roby et al.	[21]
23	CAN	61	M	Lateral side	3	Cervical LNs	RT	EWSR1 rearrangement	Rec (10 months)	Jin et al.	[22]
24	USA	76	F	Base	3.1	None	Ex	EWSR1-ATF1 fusion	Rec (9 years)	Antonescu et al.	[6]
25		53	F	Base	4.5	None	Ex	EWSR1-ATF1 fusion	NED (12 years)		
26		54	F	Base	1.8	None	Ex	EWSR1-ATF1 fusion	NED (3 years)		
27	ITA	75	F	Base	2.2	None	Ex/RND	IHC	NED (1.5 years)	Casani et al.	[23]
28	IND	73	M	Base	3	None	Ex	IHC	NED (1 year)	Masiliamani et al.	[24]
29	USA	59	F	Base	3	None	NA	IHC	NED (NA)	O'Sullivan-Mejia et al.	[2]
30		72	F	Anterior	1.8	None	NA	IHC	Rec (1 year)		
31	ITA	52	F	Base	2	None	Ex	IHC	NED (1 year)	Lai et al.	[25]
32	IND	57	M	Base	3	None	Ex/RT	IHC	NED (18 months)	Pujary et al.	[26]
33	CHN	58	M	Base	1	None	Ex	IHC	NED (10 years)	Yang et al.	[27]
34		65	F	Base	6	Cervical LNs	Ex	IHC	DOD (26 months)		
35	JPN	66	F	Base	4	Cervical LNs	Ex/RND	His	NED (21 months)	Suzuki et al.	[28]
36	JPN	80	F	Lateral side	2.4	None	CM	IHC	DOC (8 months)	Fujita et al.	[29]
37	IRL	57	F	Base	3.5	Cervical LNs	Ex/RND	IHC	DOD (10 months)	O'Regan et al.	[30]
38	IND	35	M	Base	3	None	Ex/RT	IHC	NED (18 months)	Balakrishnan et al.	[31]
39	PRT	NA	F	NA	NA	None	Ex	IHC, EMS	NED (26～49 months)	Felix et al.	[32]
40	USA	32	M	Base	2.5	Cervical LNs	Alternative therapy	NA	REC (2 years)	Milchgrub et al.	[33]
41	GBR	39	F	Base	NA	Cervical LNs	Ex/RND	IHC	NED (6 years)	Rinaldo et al.	[34]
42	MYS	31	F	Lateral side	1	Cervical LNs	Ex/RT	His	NED (2.5 years)	Rajab et al.	[35]
43	USA	51	F	Base	3	NA	Ex	IHC, EMS	DOD (0 year)	Milchgrub et al.	[1]
44		34	F	NA	2.5	Cervical LNs	Ex/RT	IHC, EMS	NED (11 years)		
45		48	M	Base	2	None	Ex	IHC, EMS	NED (18 months)		
46		42	F	Base	1.5	None	Ex	IHC, EMS	NED (24 months)		
47		77	M	Base	2.5	None	Ex	IHC, EMS	DOD (24 months)		
48	USA	1	M	Dorsum	1.5	None	Ex	IHC, EMS	NED (2.5 years)	Uri et al.	[36]
49	USA	48	M	Sublingual	2	None	Ex	His, EMS	NED (6 years)	Chaudhry et al.	[37]

NA: data not available, F: female, M: male, LN: lymph node, Ex: Excision, CR: Chemo-radiation, SND: selective neck dissection, RND: Radical neck dissection, RT: radiotherapy, CM: conservative management, His: Histology, IHC: immunohistochemistry, EMS: electron microscopic studies, Rec: Recurrence, NED: no evidence of disease, DOD: dead of the disease, DOC: dead of other cause. *The size is showing with largest diameter.

Table 2
Clinical characteristics of the 49 reported tongue HCCC.

Location in tongue		Anterior/Sublingual	Base	Dorsum	Lateral	NA	Total
No. of cases (%)		4 (8.2 %)	38 (77.6 %)	1 (2.0 %)	4 (8.2 %)	2 (4.0 %)	49
Median Age (range)		55.5 (48 – 72)	57.0 (32 – 77)	1 (1 – 1)	60.5 (31 – 80)	34 (34-NA)	57.5 (1 – 80)
Sex	M	3	9	1	1	0	14
	F	1	29	0	3	2	35
	M:F ratio	03:01	09:29	01:00	01:03	00:02	02:05
Median Size (cm)		2.2	2.3	3.3	2.4	2.5	2.5
Metastasis at the initial diagnosis		0 (0%)	10 (26.3 %)	0 (0 %)	2 (50 %)	1 (50 %)	13 (26.5 %)
Recurrence (%)		1 (25 %)	5 (13.2 %)	0 (0 %)	1 (25 %)	0 (0 %)	7 (14.3 %)
Dead of the disease (%)		0 (0%)	4 (10.5 %)	0 (0 %)	0 (0 %)	0 (0 %)	4 (8.2 %)

NA: data not available.

Table 3
Histological data of previously reported 49 tongue HCCC cases.

Case No.	Margin	Necrosis	Mucin	PAS	p63	S-100	SMA	Vimentin	Authors	Reference
1	–	–	+	+	+	–	–	NA	Present case	–
2	NA	NA	NA	NA	+	–	–	NA	Hwang et al.	[14]
3	+	–	+	+	+	–	–	NA	Chapman et al.	[15]
4	NA	NA	NA	NA	NA	–	–	–	Yang et al.	[8]
5	NA	NA	NA	NA	NA	–	–	–		
6	NA	NA	NA	NA	NA	–	–	–		
7	–	–	NA	NA	+	–	NA	NA	Zhao et al.	[16]
8	–	–	+	NA	+	–	NA	NA		
9	NA	+	+	NA	+	–	–	NA	Hsieh et al.	[5]
10	NA	+	–	NA	+	–	–	NA		
11	NA	–	+	NA	+	–	–	NA		
12	NA	–	–	NA	+	–	–	NA	Hermandez-Prera et al.	[11]
13	NA	–	–	NA	+	–	–	NA		
14	NA	–	–	NA	+	–	–	NA		
15	+	–	NA	NA	NA	NA	NA	NA	Albergotti et al.	[12]
16	NA	NA	+	NA	+	NA	NA	NA	Daniele et al.	[4]
17	NA	+	–	+	+	–	–	NA	Newman et al.	[17]
18	NA	–	+	+	+	–	–	NA	Nakano et al.	[18]
19	–	NA	–	NA	+	–	–	–	Su et al.	[10]
20	NA	NA	NA	+	NA	–	–	–	Watanabe et al.	[19]
21	–	+	NA	+	NA	NA	NA	NA	Moreno Zafra	[20]
22	–	–	–	+	+	–	–	NA	Roby et al.	[21]
23	NA	+	NA	NA	+	NA	–	–	Jin et al.	[22]
24	NA	–	NA	NA	NA	–	–	NA	Antonescu et al.	[6]
25	NA	–	NA	NA	NA	–	–	NA		
26	NA	–	NA	NA	NA	–	–	NA		
27	NA	NA	–	+	NA	–	NA	+	Casani et al.	[23]
28	NA	–	NA	+	NA	–	–	–	Masiliamani et al.	[24]
29	NA	NA	–	+	+	–	NA	NA	O'Sullivan-Mejia et al.	[2]
30	NA	NA	NA	NA	+	–	NA	NA		
31	NA	NA	NA	+	NA	–	–	–	Lai et al.	[25]
32	NA	NA	–	+	NA	–	NA	–	Pujary et al.	[26]
33	NA	NA	–	+	NA	–	–	–	Yang et al.	[27]
34	NA	NA	–	+	NA	–	–	–		
35	–	NA	NA	NA	NA	NA	NA	NA	Suzuki et al.	[28]
36	NA	NA	+	+	NA	–	–	NA	Fujita et al.	[29]
37	NA	NA	+	+	NA	–	–	–	O'Regan et al.	[30]
38	NA	NA	NA	+	NA	NA	NA	NA	Balakrishnan et al.	[31]
39	–	NA	NA	+	NA	–	NA	NA	Felix et al.	[32]
40	NA	NA	NA	NA	NA	NA	NA	NA	Milchgrub et al.	[33]
41	NA	NA	NA	NA	NA	–	–	–	Rinaldo et al.	[34]
42	NA	NA	NA	+	NA	NA	NA	NA	Rajab et al.	[35]
43	NA	NA	–	+	NA	–	–	NA	Milchgrub et al.	[1]
44	NA	NA	–	+	NA	–	–	NA		
45	NA	NA	–	+	NA	–	–	NA		
46	NA	NA	–	+	NA	–	–	NA		
47	NA	NA	–	+	NA	–	–	NA		
48	NA	+	–	+	NA	NA	NA	NA	Uri et al.	[36]
49	NA	NA	+	+	NA	NA	NA	NA	Chaudhry et al.	[37]

NA: data not available.

Ethical approval

Not required.

Patient consent

Not required.

Declaration of Competing Interest

None.

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