Desmoplastic Small Round Cell Tumor of the Submandibular Gland: A Case Report and Literature Review

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Case report

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Abstract

Background

Desmoplastic small round cell tumor (DSRCT) was a rare and aggressive malignant tumor mostly occurring in the abdominal and pelvic cavity of young patients. However, few cases had been reported concerning DSRCT located in the head and neck region.

Case presentation

A 25-year-old man was referred to our hospital due to the enlargement of the right submandibular mass. Magnetic resonance imaging revealed a 3 cm×2 cm solid nodule located in the right submandibular, and physical examination showed no other occupying lesion elsewhere. Histologically, the tumor was composed of various-sized small round cell nests, embedded in an abundant desmoplastic stroma. Immunohistochemically, the tumor cells were typically positive for epithelial (CK and EMA), mesenchymal (Vimentin and Desmin), and neuroendocrine marker (CD56, NSE, Syn and CgA), but negative for WT-1. Fluorescence in situ hybridization (FISH) revealed the presence of a break-apart involving *Ewing sarcoma region 1 (EWSR1)* gene. This tumor was finally diagnosed as DSRCT in the right submandibular gland. The patient received chemotherapy and radiotherapy, and showed recurrence after 17 months of follow-up.

Conclusions

DSRCT of the submandibular gland is rare, the diagnosis of this tumor in uncommon location relies on the histomorphology, immunophenotype and *EWSR1* gene detection. Differential diagnosis including primary salivary gland tumors and the other small round cell tumors needs to be excluded.

Background

Desmoplastic small round cell tumor (DSRCT) was a rare and highly malignant tumor which involved the abdominal or pelvis organs in young men with a mean age of 22 years[1]. Extra-abdominal DSRCT was reported occurring in the lung[2], brain[3], nasal cavity and paranasal sinuses[4], soft tissues and bone[5]. However, few cases of DSRCT had been reported in submandibular gland[6-9]. Herein, we present a case of a primary submandibular gland DSRCT in a 25-year-old man who has survived for 17 months with local recurrence, and summarize the clinical and pathological features of DSRCT in this uncommon location.

Case Presentation

A 25-year-old man noticed a mass in the right submandibular region with no specific medical history in the past. Eight months after discovery, the mass grew rapidly, characterized by a hard texture, poor mobility, adhesion to surrounding tissues, and no obvious tenderness. Magnetic resonance imaging (MRI)

revealed a 3.0 cm×2.0 cm nodule in the right submandibular gland (**Figure 1**). Physical examination and preoperative computed tomography scan showed no tumors elsewhere, followed by complete resection of the nodule.

Grossly, the mass showed a 3.0 cm×2.0 cm×1.8 cm in size with a gray appearance, and there was no evident macroscopic hemorrhage or necrosis of tumor on the cut surface. Histologically, the tumor was composed of small round tumor cell nests with different sizes and shapes, surrounded by abundant hyperplastic fibrous tissue (**Fig 2A-C**). The tumor was infiltrative, invading right submandibular gland, and residual normal tissue could be identified. Necrosis could be seen in the center of large tumor cell nests which arranged in a palisade pattern (**Fig 2D**). The tumor cells were small to medium-sized, with sparse cytoplasm, unclear borders, round or oval hyperchromatic nuclei, inconspicuous nucleoli, and nerve invasion were readily seen (**Fig 2E-F**). Immunohistochemistry results indicated that the tumor cells had epithelial, neuroendocrine and myogenic multiple differentiation and expression patterns. The antibodies were summarized in **Table 1**. The tumor cells were immunoreactive for epithelial markers CK (**Fig 3A**) and EMA (**Fig 3B**) with a diffuse cytoplasmic pattern, Vimentin (**Fig 3C**) and Desmin with dot-like paranuclear cytoplasmic positivity (**Fig 3D**), and strong membrane and cytoplasm immunoreactivity for CD56 (**Fig 3E**), CgA (**Fig 3F**), Syn and NSE (**Fig 3G**). In addition, the tumor cells were also immunoreactive for E-cadherin, Fli-1, CD99 (**Fig 3H**), but negative for WT1, myogenin, S-100, CK5/6, p63, Melan-A, actin, TTF-1. The Ki-67 labeling index was almost 50%. Fluorescence in situ hybridization findings (FISH) revealed EWSR1 split signals were detected in 86% tumor cells (>15% were diagnostic). The final diagnosis of DSRCT depended on the postoperative pathological examination with immunohistochemistry and FISH results.

The patient received adjuvant chemotherapy (ifosfamide and etoposide) and radiotherapy (PGTV_{tb}: 66Gy/30f, PTV1: 60Gy/30f) after surgery, and exhibited recurrence at 17 months of follow up.

Discussion

DSRCT was a highly aggressive and rare mesenchymal tumor first described as a separate identity by Gerald and Rosai in 1989[10]. DSRCT characteristically arose in abdominal or pelvis cavity in young men, only 6% of DSRCTs occurred in sites outside the abdomen[11]. DSRCT of submandibular gland as in the case presented here had similar morphologic and immunophenotypic features to the previously reported cases. Histologically, DSRCT was characterized by well-defined and variable-sized nests comprised of small to medium tumor cells with apparent collagen background. Immunohistochemically, DSRCT had a polyphenotypic immunoprofile with neoplastic cells expressing epithelial, mesenchymal, and neuroendocrine markers. WT-1 was considered as a useful antibody for the diagnosis of DSRCT and differentiating it from other tumors with small blue cell morphology. Frequent strong nuclear expression of WT1 had been reported in DSRCT was attributed to *EWSR1-WT1* gene fusion[12]. However, WT1, Clone EP122, was negative expression in our study. Kanako C et al. demonstrated that Clone of N-WT1 and 6F-H2 antibodies resulted in negative or abnormal expression of cytoplasm. And their research recommended using C-WT1 antibody[13]. In addition, Paul et al. report showed that a small number of

cases were indeed C-WT1 (Clone: C19) negative[12]. Therefore, it was recommended to perform molecular detection so as to avoid diagnostic pitfall. We then performed FISH assay in order to determine whether *EWSR1* gene fracture was presented. Not surprisingly, *EWSR1* split signals were detected in 86% of the tumor cells, which conclusively confirmed the diagnosis of DSRCT.

DSRCT needed to be differentiated from primary salivary gland tumors. Poorly differentiated myoepithelial carcinoma, the solid variant of basal cell adenocarcinoma (BCA) and adenoid cystic carcinoma (ACC) also had similar morphological areas which were composed of large solid tumor island. Lack of myoepithelial differentiation (actin and S-100 negative) and expression of neuroendocrine markers (CD56, NSE, Syn and CgA) would be helpful in excluding BCA and ACC. Moreover, the tumor islands of DSRCT were lack of peripheral palisade structures in BCA or the focal presence of cribriform structures and hyaline globules in ACC. CD117, frequently used for the diagnosis of ACC, had been demonstrated to be negative or focal positive expression in DSRCT[12].

Although it's also rare, the other small round cell tumors, such as Ewing sarcoma, small cell carcinoma, rhabdomyosarcoma and malignant melanoma, were still need to be excluded. It was reported that CD99, a marker frequently used for the diagnosis of Ewing's sarcomas/PNET, had been shown to be positive in 57% of DSRCT[12]. Fli-1 was also found to be positive expression in the current study. Given this finding, CD99 and Fli-1 had a limited role in distinguishing DSRCT from Ewing's sarcomas and primitive neuroectodermal tumors. Primary small cell carcinoma in the salivary glands was rare, and most occur in patients older than 50 years of age[14]. Positive for CD56 and neuroendocrine marker may increase the risk of misdiagnosis as small cell carcinoma. Abundant desmoplastic stroma and collagenous background may be an important clue for DSRCT. Rhabdomyosarcoma in young patients was a differential diagnosis should also be included. Unlike rhabdomyosarcoma, DSRCT was negative for myogenin and myoD1.

So far, the origin of DSRCT remains unclear. Although the common site of DSRCT, peritoneum-lined surfaces, suggested that it may be derived from the mesothelium, immunohistochemical expression (CK5/6 and calretinin negative) and ultrastructural level did not support tumor cells with mesothelium differentiation[7]. Furthermore, there was no mesodermal distribution in the submandibular area. It seemed reasonable to explain that the tumor cells may originate from multipotential differentiated primitive mesenchymal cells or neuroectodermal tissue.

Table 2 summarizes the clinical and pathological features of submandibular gland DSRCT reported previously in the English-language literature. All 5 cases, including the present one, occurred in males, and the age ranged from 24 to 41 years (mean age, 30 years). All 5 tumors reported were less than 5cm in size. According to the previously reports, the prognosis of intra-abdominal DSRCT was particularly poor, median survival ranged from 17 to 25 months, and 5-year survival rates was around 15%[15]. Lymph node metastases had occurred in most cases at the time of diagnosis. Moreover, tumor occurring in the abdominal cavity was relatively hidden, and the tumor appeared to be progressive when it was discovered. However, the prognosis of DSRCT in this uncommon location remained unknown. Of the 5

patients presented in the Table 2, 3 were alive at the time of publication, one died with systemic metastasis at 25 months, and another one who had a history of diabetes mellitus and end-stage renal failure died of disease at 5 weeks. It was worthy of note that both of them had nodal metastasis. It was reasonable to speculate that lymph node metastasis was a risk factor for poor prognosis. On the other hand, the early occurrence of local mass in submandibular gland provided a higher chance of complete surgical resection. In our case, the patient showed recurrence after 17 months follow up.

Conclusions

In summary, we report a rare primary DSRCT arising from the submandibular gland of a young man. DSRCT is diagnosed mainly based on the radiological findings, histological features, immunohistochemical and molecular examination. Prognostic factors related to DSRCT in this uncommon location remain to be further studied.

Abbreviations

DSRCT: desmoplastic small round cell tumor; MRI: Magnetic resonance imaging; CK: cytokeratin; EMA: epithelial membrane antigen; NSE: neuron-specific enolase; CgA: chromogranin A; Syn: synaptophysin; WT1: Wilms tumor 1; EWS: Ewing sarcoma; EWSR1: Ewing sarcoma region 1; FISH: fluorescence in situ hybridization; RT-PCR: reverse transcription polymerase chain reaction; N-WT1: WT1 antibody detecting the N-terminal region; C-WT1: WT1 antibody detecting the C-terminal region; PGTV: planned gross tumor volume of tumor bed; PTV: planned treatment volume.

Declarations

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Availability of data and materials

Not applicable

Consent for publication

The patient provided informed consent to publish the detailed data in this case report.

Statement of Ethics

The present study was approved by the Ethics Committee of the author's organizations (No.202010139).

Competing interests

The authors have no conflicts of interest to declare.

Authors' contributions: LQJ and YXL performed pathologic diagnosis and writing of manuscript and collected clinical data and follow-up of the patient. All authors read and approved the final manuscript prior to submission.

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Tables

Table 1. List of antibodies

Antibody	Dilution	Clone	Company	Retrieval
NSE	1:1500	5E2	Neomaker	EDTA
CgA	1:200	LK2H10	Neomarker	EDTA
Syn	1:200	UMAB112	Neomarker	EDTA
CD56	1:50	UMAB83	Serotec	EDTA
CK-pan	1:500	AE1/AE3	DAKO	EDTA
EMA	1:1000	UMAB57	DAKO	EDTA
Desmin	1:100	EP15	DAKO	EDTA
Vimentin	1:100	UMAB159	DAKO	EDTA
Ki-67	1:200	UMAB107	Neomaker	EDTA
CD99	1:100	HO36-1.1	DAKO	EDTA
Fli-1	1:400	G146-22	DAKO	EDTA
E-cadherin	1:200	UMAB184	DAKO	EDTA
WT-1	1:200	EP122	Neomaker	EDTA
S-100	1:4000	15E2E2+4C4.9	DAKO	EDTA
P63	1:400	4EA+UMAB4	DAKO	EDTA
CK5/6	1:400	OT11C7	DAKO	EDTA
Myogenin	1:800	EP162	DAKO	EDTA
Melan-A	1:400	A103	Neomarker	EDTA
Actin	1:100	HHF-35	Neomarker	EDTA
TTF-1	1:200	2G9A10F5	Neomarker	EDTA

NSE: neuro-specific enolase; **CgA:** chromogranin A; **Syn:** synaptophysin; **EMA:** epithelial membrane antigen; **WT1:** wilms tumor 1; **CK:** cytokeratin; **Fli-1** friend leukemia virus integration-1; **TTF-1** thyroid transcription factor-1

Table 2 DSRCT of submandibular gland as reported in literatures

	Cho et al	Santos	Yin et al	Pang et al	Current case
Sex/age (y)	M/26	M/36	M/24	M/41	M/25
Location and tumor size (cm)	Left 4×3.7×3	Right 5×4	Right 4×4	Left 5×5	Right 3×2×1.8
Clinical features	10 mo history of mass	8 mo history of mass	1 mo history of mass growing rapidly	with a history of diabetes mellitus and end-stage renal failure	8 mo history of mass
Lymph node Metastasis	Positive	NS	NS	NS	NS
Resection margin	NS	Negative	Negative	Negative	Negative
Additional therapy after operation	ChT, RT	RT	ChT, RT	ND	ChT, RT
Outcome (mo)	6(metastasis) 25 (DOD)	10 (ANR)	7 (ANR)	5 weeks (DOD)	17 (recurrence)

M: male; mo: month; NS: not specified; ND: not done; ChT: chemotherapy; RT: radiotherapy; ANR: alive and no recurrence; DOD: died of the disease

Figures

Figure 1

Magnetic resonance imaging (MRI) showed a well-demarcated homogeneous mass in the right submandibular gland.

Figure 2

Microscopic features of hematoxylin-eosin stained paraffin sections of DSRCT. (A) The tumor cells formed solid cellular nest with invasive boundary into salivary gland. (B) The tumor was comprised of well-defined and variable-sized nests in a desmoplastic stroma. (C) The tumor cells were small to medium size with inconspicuous nucleoli. (D) Central necrosis of tumor nest was occasionally seen. (E) Tumor nest invaded into salivary gland tissue, and nerve invasion were readily seen (F).

Figure 3

Positive immunostaining of DSRCT for epithelial markers (A: CK, B: EMA), mesenchymal (C: Vimentin, D: Desmin), neuroendocrine markers including CD56 (E), CgA (F), NSE (G) and CD99 (H). EWSR1 split signals (I) in tumor cells were detected by FISH analysis.

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