Desmoplastic Small Round Cell Tumor of the Head and Neck: A Clinicopathological, Immunohistochemical and Molecular Analysis of Three Cases with Literature Review

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Abstract
Desmoplastic small round cell tumor (DSRCT) is a rare aggressive malignancy typically originating from the abdominal or pelvic cavity. DSRCT presenting as a primary head and neck tumor has rarely been described in the literature. We present three cases of DSRCT arising in the head and neck to further characterize its clinicopathological features. All three patients were male and aged 36, 30 and 17 years. The involved sites included the orbit (1 case) and submandibular gland (2 cases). The tumors ranged in size from 2.4 to 3.5 cm (mean, 2.1 cm). Histologically, all tumors showed irregular-shaped, variable-sized nests of small round cells deposited in an abundant desmoplastic stroma. Tumor cells contained scant amounts of eosinophilic cytoplasm and small hyperchromatic nuclei with inconspicuous nucleoli. Immunohistochemically, the tumors were positive for keratin (AE1/AE3) (3/3), desmin (3/3), vimentin (2/2), NSE (1/1) and EMA (1/1). Fluorescence in situ hybridization (FISH) analysis demonstrated the presence of EWSR1 and WT1 rearrangements in all three cases. All patients received surgery and adjuvant chemotherapy and/or radiotherapy. There was no evidence of recurrence and metastasis in two patients, and the third suffered lung metastasis. DSRCT arising in the head and neck represents an extremely rare condition. It is easily mistaken as poorly differentiated carcinoma due to similar morphology and expression of epithelial markers. Immunohistochemistry assay in conjunction with molecular detection of EWSR1::WT1 fusion will be helpful for arriving at an accurate diagnosis to avoid misdiagnosis and inappropriate treatment.

Keywords
desmoplastic small round cell tumor, head and neck, EWSR1, fluorescence in situ hybridization, differential diagnosis

Introduction
Desmoplastic small round cell tumor (DSRCT) is an extremely rare malignant tumor that commonly manifests as an intra-abdominal or pelvic mass with a predilection for young males. It typically shows co-expression of epithelial, mesenchymal and neural markers and harbors a characteristic t (11; 22) (p13; q12) translocation resulting a specific EWSR1::WT1 fusion gene transcript.1,2 Extra-abdominal involvements, such as central nervous system, mediastinum, pleura, lung, paratesticular region, bone and soft tissue, are very uncommon, comprising less than 5% of DSRCT.1-6 Manifestations in the head and neck are even more rare. To date, only 22 patients diagnosed with DSRCT have been reported in the English literature.3-25 Due to its rarity and unexpected occurrence in the head and neck, DSRCT is likely to be misdiagnosed as other malignancies by clinicians and pathologists. Herein, we present three additional cases of DSRCT arising in the head and neck to enhance the recognition of its clinicopathological features and avoid diagnostic and therapeutic pitfalls.

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Case Presentation

Clinical Findings

Case 1. A 36-year-old male presented with decreased visual acuity in his right eye with difficulty in eye opening for more than one month. B-ultrasound showed a well-defined solid mass with uneven internal echoes on the posterior pole of right orbit, measuring approximately 22.2 × 20.7 mm. A computed tomography (CT) scan revealed an ovoid, well-circumscribed soft tissue mass with slight enhancement in the right orbital roof, measuring approximately 2.4 × 2.1 × 1.6 cm in size (Figure 1A). Magnetic resonance imaging (MRI) displayed a solid heterogeneous mass in the right orbital roof (Figure 1B). Then, the patient was treated with a local excision of the tumor. The referring diagnosis was poorly differentiated carcinoma. To confirm the diagnosis, the pathological materials were sent to our department for further consideration. After re-evaluation of the H&E slides with application of immunohistochemistry and FISH analysis, the diagnosis of DSRCT was finally rendered. The patient received postoperative chemotherapy and radiotherapy. There was no evidence of local recurrence or metastasis 14 months after surgery.

Case 2. A 30-year-old man went to the clinic of a local hospital because of the left submandibular gland mass for several months. After admission, the patient underwent a complete excision of the mass. Intraoperatively, two masses were identified, measuring approximately 3.5 × 3.8 × 2.5 cm and 1 × 0.8 × 0.6 cm, respectively. The lesion was considered as poorly differentiated carcinoma with neuroendocrine differentiation by the referring pathologist. The patient was treated with an adjuvant chemotherapy after surgery. Unfortunately, CT scan revealed multiple metastatic nodules in bilateral lungs 5 months later. Then, the patient came to our department for further diagnosis. With the adjunctive study of immunohistochemistry and FISH, the lesion was re-diagnosed as DSRCT.

Case 3. A 17-year-old man complained of a slowly enlarging and painless mass of the left submaxilla for more than one year. Physical examination revealed a well-defined solid mass in the left submandibular gland, measuring approximately 2.5 × 2.0 cm. MRI showed a solid homogeneous mass of the left submandibular gland, suspicious of lymphoma or mixed tumor. Subsequently, the patient underwent a complete excision of the tumor. The referring pathologist suggested a diagnosis of poorly differentiated squamous cell carcinoma. Tissue sections were sent to our department and finally diagnosed as DSRCT. Then, the patient received an adjuvant chemotherapy. There was no evidence of local recurrence or metastasis 8 months after surgery.

Pathological Features

Grossly, all specimens presented multinodular masses ranging from 2.4 to 3.5 cm in maximum diameter (mean, 2.1 cm). On the cut surface, all three tumors were solid and firm in consistency and grayish-white in color. Histologically, all three lesions showed similar morphological features, which consisted of uniform and small round, oval cells embedded in an abundant desmoplastic stroma (Figure 2A). Tumor cells were arranged in small clumps, large nests, trabecular or cord-like pattern (Figure 2B, 2C), possessing hyperchromatic nuclei with inconspicuous nucleoli and pale eosinophilic cytoplasm with indistinct borders (Figure 2D). The mitotic figures were easily identified. The desmoplastic stroma was composed of spindle cells mimicking fibroblasts/myofibroblasts with hyaline...
degeneration and vascular proliferation in some areas. Case 2 extensively infiltrated the peripheral nerves. The tumor showed lymph node metastasis in case 3.

**Immunohistochemical and Molecular Findings**

Immunohistochemically, the tumors showed positivity for keratin (AE1/AE3) (3/3) (Figure 3A), desmin (3/3), vimentin (2/2), CD99 (2/2), synaptophysin (1/3), NSE (1/1), EMA (1/1) (Figure 3B) and SMARCB1 (INI-1) (1/1). Besides, desmin and vimentin displayed a paranuclear cytoplasmic dot-like positivity pattern (Figure 3C, 3D). Other markers, including WT1, ERG, FLI1, MyoD1, myogenin, chromogranin A, CD56 and TTF1, were all negative. The Ki-67 index was 40%∼50%.

FISH assay was carried out in all three cases using the EWSR1 (22q12) Dual Color, Break Apart Rearrangement Probe and WT1 (22q12) Dual Color, Break Apart Rearrangement Probe. All three cases had the EWSR1 (Figure 4A) and WT1 (Figure 4B) rearrangements.

**Discussion**

Desmoplastic small round cell tumor is a unique mesenchymal neoplasm with distinct histological features and multiphenotypic differentiation, which was first described by Gerald and Rosai in 1989.26 It is a highly aggressive tumor with a predilection for adolescent males and occurs predominantly in the abdominal and pelvic cavity. Isolated cases of extra-abdominal involvement have been reported in the central nervous system, mediastinum, pleura, lung, paratesticular region, bone and soft tissue.1–5 The presentation of DSRCT as a primary head and neck lesion is even extremely rare. To our knowledge, only 22 cases have been documented in previous literatures.5–25 In this study, we present a small series of three additional cases of DSRCT in the head and neck to increase the reported number to 25. The clinicopathological features of 25 cases are summarized in Table 1. Like classic intra-abdominal DSRCT, DSRCT of the head and neck also occurred in the second to third decade of lifetime, with a mean and median age of 26 and 25 years (range, 4 to 61 years), respectively. Compared with intra-abdominal DSRCT (male : female, 5:1),7,11 there was a more prominent male predilection with a male to female ratio of 24:1. Tumors arose in the salivary glands (8 cases), brain (4 cases), orbital region (4 cases), sinonasal region (4 cases), cranium (3 cases), middle ear (1 case) and neck (1 case). Tumor size (available in 17 cases) ranged from 1.5 to 8 cm in maximum diameter (mean, 4.1 cm). Clinically, most tumors presented as slowly growing painless masses, and the majority of patients (22 cases) presented with neurologic symptoms. The most frequent symptoms were headache (22 cases), visual disturbance (6 cases), hemiparesis (4 cases), seizure (3 cases), cranial nerve palsy (3 cases), anosmia (2 cases), and facial nerve paralysis (1 case). The most frequent symptom was headache (70% of patients). Surgical resection is the primary treatment, with more than 80% of patients undergoing a gross total or near-total resection. Despite surgery, the 5-year survival rate was only 51% (13 of 25 cases), with only 6 of 25 patients alive at last follow-up. The most frequent cause of death was tumor recurrence (10 of 13 cases), which ranged from 1 to 24 months (mean, 9.8 months). One patient died of cranial nerve injury due to recurrence and one patient died of pneumonia. These findings underscore the importance of close follow-up and prompt treatment of recurrent disease.
enlarging masses or swelling of soft tissue, occasionally with pain. The specific symptoms and signs of DSRCT depend on the tumor location and involved organs or tissues.\textsuperscript{5,11,13,14,17,18,22}

Histologically, most DSRCTs are typically characterized by sharply-demarcated, variable-sized nests or sheets of small round or oval cells embedded in a hypervascular desmoplastic stroma. In some cases, tumor cells may be arranged in large nests with central necrosis, tubular-like structures, and trabecular or cord-like patterns. Other unusual features, including Homer Wright-like rosettes, papillary structures, zones resembling transitional cell carcinoma and myxoid stroma, can also be identified occasionally.\textsuperscript{2,7,27} In addition, tumor cells may also show rhabdoid, spindled, pleomorphic, vacuolated, signet-ring or larger cell morphology.\textsuperscript{25,27} Rare cases simply consist

Figure 3. Immunohistochemical features of DSRCT. The tumor cells showed diffuse and strong positivity for AE1/AE3 (A) and EMA (B). Desmin (C) and vimentin (D) showed a paranuclear cytoplasmic dot-like immunostaining.

Figure 4. Molecular features of DSRCT. FISH assay displayed the presence of EWSRTI (A) and WTI rearrangements (B).
| Case No. | Source | Age (years) | Sex | Location | Symptom                                                                 | Size (cm) | EWSR1::WT1 | WT1 (IHC) | Treatment | Metastasis | Recurrence (months) | Follow-up (months) |
|---------|--------|-------------|-----|----------|-------------------------------------------------------------------------|-----------|-------------|-----------|------------|-------------|---------------------|-------------------|
| 1       | He JR et al (2018) | 16 | M | Left orbit | Pain swelling and a palpable nodule                                      | 1.5       | /           | (+)       | Surgery    | N           | N                   | NED, 12           |
| 2       | Xu J et al (2018) | 59 | M | Right middle ear | Hearing loss, tinnitus and recurrent headache                           | NA        | /           | /         | Surgery, CT and RT | N           | N                   | NED, 48           |
| 3       | Bengu CH et al (2017) | 4  | M | Right orbit | Swelling and ptosis                                                      | 3.2       | /           | (+)       | Surgery, CT and RT | N           | N                   | NED, 12           |
| 4       | Hu CY et al (2017) | 47 | M | Maxillary sinus | Epistaxis                                                              | 4.1       | /           | (+)       | Surgery, CT and RT | N           | Y,4                 | DOD, 12           |
| 5       | Khachaturov V et al (2015) | 6  | M | Calvarium | Right anterior ear pain and swelling                                     | NA        | (+)         | (-)       | Surgery, CT and RT | N           | N                   | AWD, 5            |
| 6       | Thondam SK et al (2015) | 27 | M | Suprasellar | Frontal headaches, drowsiness, and bitemporal hemianopia                | NA        | (+)         | (+)       | Surgery, CT and RT | Y           | Y,4                 | DOD, 20           |
| 7       | Faras F et al (2015) | 11 | M | Left upper Cervical region | A left neck mass                                                        | 4.0       | (+)         | (+)       | Surgery, CT and RT | N           | N                   | NED, 39           |
| 8       | López F et al (2013) | 61 | M | Right ethmoid sinus | Respiratory insufficiency and nosebleeds                              | 8         | (+)         | (+)       | Surgery and RT | N           | N                   | NED, 29           |
| 9       | Pang B et al (2011) | 41 | M | Left submandibular gland | /                                                                      | 5         | (+)         | (+)       | Surgery       | Y           | N                   | DOD, 4 (other causes) |
| 10      | Rekhi B et al (2010) | 25 | M | Left maxillary sinus | Left sided nasal blockage and intermittent bloody nasal discharge      | 4.5       | /           | /         | Surgery, CT and RT | N           | Y,3                 | NA                |
| 11      | Küpeli S et al (2010) | 16 | M | Left Mandible | Tough swelling on the left side of his face                             | NA        | /           | /         | CT and RT    | Y           | N                   | DOD, 22           |
| 12      | Neder L et al (2009) | 37 | M | Cerebellopontine angle | Left-sided hearing loss and tinnitus                                  | NA        | (+)         | (+)       | Surgery, CT and RT | Y           | DOD, 24             |
| 13      | Neder L et al (2009) | 39 | M | Cerebellopontine angle | Gait imbalance and bilateral, lower limb weakness                     | NA        | (+)         | /         | CT and RT    | N           | N                   | AWD, 27           |
| 14      | Yin WH et al (2010) | 24 | M | Right submandibular mass |                                                   | 4         | (+)         | (+)       | Surgery, CT and RT | N           | N                   | NED, 7            |

(continued)
Table 1. (continued)

| Case No. | Source | Age (years) | Sex | Location | Symptom | Size (cm) | EWSR1::WT1 | Treatment | Metastasis | Recurrence (months) | Follow-up (months) |
|----------|--------|-------------|-----|----------|---------|-----------|------------|-----------|------------|---------------------|-------------------|
| 15       | Santos GP et al (2009) | 36 | M | Right submandibular gland | An increase mass in size with pain | 4 | (+) | (+) | Surgery and RT | N | N | NED, 10 |
| 16       | Cho K et al (2008) | 26 | M | Left submandibular gland | A left submandibular mass | 4 | (+) | / | Surgery, CT and RT | Y | Y, 6 | DOD, 25 |
| 17       | Yoon M et al (2005) | 32 | M | Left orbit | Visual disturbances, proptosis and loss of vision | 2.5 | / | (+) | Surgery and RT | N | N | NED, 11 |
| 18       | Lae ME et al (2002) | 21 | F | Bilateral ethmoidal sinuses | Chronic sinusitis | 8 | (+) | (+) | Surgery, CT and RT | N | N | NED, 26 |
| 19       |       | 27 | M | Scalp soft tissues, bone marrow involvement | Weight loss and headache | NA | / | / | Surgery and CT | N | N | NED, 13 |
| 20       | Hill DA et al (2000) | 5 | M | Parotid | / | NA | (+) | (+) | NA | NA | NA | NA |
| 21       | Wolf AN et al (1999) | 23 | M | Left parotid | A slowly growing mass | 5 | (+) | / | Surgery, CT and RT | N | N | NED, 10 |
| 22       | Tison V et al (1996) | 24 | M | Left posterior cranial fossa | Headache, vomiting, vertigo and impaired hearing | 4 | (+) | / | Surgery, CT and RT | N | N | NED, more than 24 |
| 23       | Current cases, case 1 | 36 | M | Right orbit | Vision decline and difficulty in opening the right eye | 2.4 | / | (−) | Surgery, CT and RT | N | N | NED, 14 |
| 24       | Current cases, case 2 | 30 | M | Left submandibular gland | A left submandibular gland mass | 3.8, 1 | / | (−) | Surgery and CT | Y | N | NA |
| 25       | Current cases, case 3 | 17 | M | Left submandibular gland | A slowly enlarging and painless mass | 2.5 | / | (−) | Surgery and CT | N | N | NED, 8 |

AWD alive with disease, CT chemotherapy, DOD dead of disease, IHC, immunohistochemistry, N no, NA not available, NED no evidence of disease, RT radiation therapy, Y yes.
of solid sheets of round cells without desmoplastic stroma, making identification of this rare tumor even more difficult.

DSRCT has a distinctive immunohistochemical feature. The tumor demonstrates multiphenotypic differentiation with co-expression of epithelial (keratin, EMA), mesenchymal (desmin, vimentin) and neural markers (NSE). Of note, typical examples of DSRCT usually display a unique paranuclear cytoplasmic dot-like staining of desmin and vimentin. The reported cases of DSRCT in the head and neck showed variable expression of AE1/AE3 (95.7%, 22/23), EMA (70.6%, 12/17), desmin (91.7%, 22/24), vimentin (100%, 17/17) and NSE (76.2%, 16/21), which are almost in line with intraabdominal tumors. More than 95% of DSRCT harbors a unique cytogenetic abnormality, t (11; 22) (p13; q12), which fuses the amino terminus of EWSR1 gene on 11p13.30,31 All tested cases (20/20, 100%) of DSRCT in the head and neck possessed EWSR1::WT1 gene translocation. Besides, immunohistochemistry for WT1 amino terminus and carboxy terminus antibodies may be useful to identify EWSR1::WT1 transcript despite the presence of some controversies regarding the epitope specificity of WT1 antibody.32 Most of previous studies revealed that DSRCT showed nuclear expression of WT1 antibody (Clone: C-19) to the carboxy terminus with positive rates of 70%~100%, but no expression of WT1 antibody (Clone:6F-H2) to the amino terminus.21,28,32 In this series, three cases were all negative for WT1 amino terminus antibody. However, the other two studies reported that DSRCT displayed discrete nuclear or paranuclear cytoplasmic staining of WT1 antibody to the amino terminus, with positive rates of 91% (29/32) and 81.4% (22/27), respectively.27-29 Murphy et al found that some cases had novel fusion transcripts or expressed full-length WT1, resulting in nuclear staining for WT1 N-terminal antibody; they proposed that fusion transcripts in DSRCT resulted in the altered immunostaining pattern for WT1.32 Hence, interpretation of WT1 immunostaining requires knowledge of antibody target epitopes and correlation with results of molecular testing for the EWSR1::WT1 fusion transcript. Among DSRCT in the head and neck, 50% (6/12) of cases were immunoreactive for WT1. However, the antibody type and immunostaining pattern were uncertain in most cases, because these cases were mainly from isolated case reports or small series.

The histogenesis of DSRCT is still uncertain owing to few studies focused on it in the literature. Originally, DSRCT was speculated to derive from mesothelial or submesothelial cells, given that it mainly occurs in the mesothelial-lined cavities and expresses both epithelial and mesenchymal markers.7 However, some tumors arising in locations not lined by mesothelial cells challenged this hypothesis. Furthermore, there are no ultrastructural features of mesothelial differentiation in DSRCT,29,33 which also does not support the above viewpoint. Therefore, the issue of origin of DSRCT remains to be studied.

The main differential diagnosis of DSRCT embraces a variety of malignancies with small round cell morphology, especially poorly differentiated carcinoma (including neuroendocrine carcinoma), Ewing sarcoma (ES) and alveolar rhabdomyosarcoma (ARMS). Due to the uncommon tumor site as well as similar histologic features and expression of epithelial markers, all three cases in this series were initially misdiagnosed as poorly differentiated carcinoma by the referring pathologists. But different from DSRCT, poorly differentiated carcinoma usually lacks prominent desmoplastic stroma and expression of desmin. Moreover, it is also absent of EWSR1::WT1 fusion. In addition, ES, especially adamantinoma-like Ewing sarcoma (ALES), also needs to be differentiated from DSRCT, because both tumors have overlapping immunophenotype and cytogenetic features. ALES is prone to occur in the head and neck and also express AE1/AE3.34 However, ALES is generally positive for CD99 (membrane staining), NKKX2.2 and p40,35 but usually negative for desmin.36 More importantly, ES, including ALES, possess EWSR1::FLII fusion instead of EWSR1::WT1 fusion in DSRCT.31 Finally, ARMS can be confused with DSRCT. The application of myogenic markers of myogenin and MyoD1 is helpful in the distinction between ARMS and DSRCT; again, the detection of FOXO1 translocation by FISH can also distinguish the two entities. Other small round cell tumors occurring in the head and neck may also enter into the differential diagnosis of DSRCT, such as malignant melanoma and neuroblastoma. The positive staining of melanotyic markers in melanoma, including S100 protein, SOX10, HMB-45 and Melan-A, helps to distinguish it from DSRCT. Although neuroblastoma and DSRCT are both positive for NSE, neuroblastoma is usually negative for AE1/AE3 and desmin. It is worth noting that abdominal DSRCT can develop metastasis to the head and neck region occasionally.37 In such settings, detailed medical history data and careful clinical examinations are warranted in the distinction. All three patients reported in this study had no special clinical history.

So far, the treatment of DSRCT remains challenging. Despite a comprehensive therapeutic strategy of surgery, radiotherapy and chemotherapy applied, the overall prognosis remains very poor, with approximately 29% for a 3-year survival and just 18% for a 5-year survival,8 respectively. Recently, some reports revealed that patients treated with aggressive surgery and intense alkylator therapy (P6 protocol: vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide) had a better prognosis.6 Besides, patients with superficial DSRCT also have a better outcome, because earlier clinical manifestations and symptoms offer a greater opportunity of complete
surgical excision. Among DSRCT of the head and neck, 6 of 22 (27.3%) patients with follow-up information died, with five cases dead of the disease and one dead of other causes. Two patients were alive with disease, and the other 14 remained well with no evidence of disease. Due to the limited follow-up duration, the prognosis of DSRCT in the head and neck is difficult to compare with that of intra-abdominal DSRCT. Therefore, whether there is a difference in the prognosis between the two subsets still need to be elucidated in the future.

In summary, we describe three cases of extra-abdominal DSRCT arising primarily in the head and neck. Due to the unexpected occurrence of DSRCT in this unusual site and similar histological and/or immunohistochemical features, it may be easily misinterpreted as other small round cell tumors, especially poorly differentiated carcinoma (including neuroendocrine carcinoma). This study further demonstrates the importance of including DSRCT into the differential diagnosis of small round cell tumors of the head and neck, particularly those affecting the young patients and expressing of epithelial markers. In challenging cases, molecular assays of EWSR1::WT1 fusion by RT-PCR, FISH or next-generation sequencing will be helpful for establishing a correct diagnosis.

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Author’s contribution
SM drafted the manuscript; SMY and JXB collected clinical and follow-up data of three cases; BQM interpreted FISH results; WQF, ZL and LIW participated in histological diagnosis and immunohistochemical evaluation; WJ and YL participated in histological diagnosis and proofread the paper. All authors read and approved the final manuscript.

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Informed Consent
Not applicable, because this article does not contain any studies with human or animal subjects.

Trial Registration
Not applicable, because this article does not contain any clinical trials.

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