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Letter to the editor

Clinical and molecular heterogeneity of head and neck spindle cell and sclerosing rhabdomyosarcoma

Introduction

Spindle cell and sclerosing rhabdomyosarcoma (sRMS/scRMS) accounting for 5–10% of all RMS, were recently reclassified as a stand-alone pathologic entity in the latest WHO classification of soft tissue tumors [1]. Spindle cell RMS was first described by the German–Italian Cooperative Sarcoma Study on the basis of its distinct clinicopathologic features and favorable outcome, resulting in separation from the more common embryonal RMS (ERMS) [2]. Sclerosing RMS was first defined by Mentzel and Katenkamp as a 'sclerosing pseudovascular RMS in adults' [3]. As both spindle cell and sclerosing RMSs have similar clinical presentations in the paratesticular or head and neck region, affecting both pediatric and adult age groups with a male predilection [4,5] and overlapping histologic features, it was suggested that they may represent a single pathologic entity sharing clinical, morphologic and genetic features [3,6–8].

Our group has recently demonstrated that *MYOD1* mutations are a recurrent finding in both pediatric and adult sRMS/scRMS patients [8], and that in pediatric patients *MYOD1*-mutant tumors are associated with a poor prognosis [9]. Furthermore, we have previously shown that congenital/infantile sRMS have distinct genetic abnormalities and are characterized in most cases by the presence of *NCOA2* and *VGLL2* related fusions, being overwhelmingly associated with a favorable outcome, long-term survival and lack of distant metastases [9,10]. In this study, we further investigate the clinicopathologic and molecular features of sRMS/scRMS presenting in the head and neck region at our institution.

Materials and methods

The study was approved by the institutional review board of Memorial Sloan Kettering Cancer Center (MSKCC), New York. We have searched the MSKCC Department of Pathology patient charts for diagnosis of RMS involving the head and neck regions from 1996 to 2015. All cases with material available were re-reviewed and reclassified based on the 2013 WHO classification, applying strict morphologic criteria to identify cases of spindle cell/sclerosing RMS. The clinical features include the following: age, gender, anatomic site, size, pre-therapy stage, treatment, recurrence and follow-up information were obtained from the medical records in all cases. For each case, the hematoxylin-eosin stained sections and immunohistochemical profiles (myogenin, desmin) were reviewed. Unstained slides available in 12/13 cases were used for further molecular characterization, including FISH or RT-PCR for *PAX3/7-FOXO1* fusions, PCR and targeted sequencing for hot-spot *MYOD1* and *PIK3CA* mutations and FISH using custom BAC probes for *NCOA2* and *VGLL2* gene rearrangements, as previously described [8].

Results

Clinical features

The clinical features are summarized in Table 1. Thirteen cases of spindle cell/sclerosing RMS were identified from our institutional and consultation archival files. Three cases were previously included in the study by Mosquera et al. [10], two of which were also studied in the study by Agaram et al. [8] and the third case was also studied by Alaggio et al. [9]. There were 8 males and 5 females with a wide age range at diagnosis 0.7–72 years (mean: 29), including 5 children (0.7–17 years, 1 infant) and 8 adults (27–72 years). The anatomic sites comprised various locations: buccal/masticator space (3), soft tissue of the mandible (2), tongue (2), neck (2), infratemporal fossa (1), soft tissue of skull (1), hypopharynx (1) and nasolabial/cheek (1). Three of the cases were considered as parameningeal sites, while the remaining were non-parameningeal, non-orbital sites. The tumor sizes ranged 0.8–10.5 cm with 7 cases being larger than 5 cm in greatest dimension. The images (MRI) showed large masses causing a mass-effect, erosion and destruction of nearby bony structures (Fig. 1). Tumor staging was applied according to the Intergroup Rhabdomyosarcoma Study Group pretreatment classification: stage 1 (9), stage 3 (1) and stage 4 (3). The metastatic sites included lung (1), and spine and pelvis (2). None of the patients presented with bone marrow involvement on pre-therapy evaluation. All patients except one were treated with multimodality therapy with a combination of surgery and chemotherapy and/or radiotherapy.

Morphologic and Immunophenotypic features

Eight cases were classified as spindle cell and five cases as sclerosing RMS. The morphologic appearance of spindle cell RMS was that of compact spindle cells arranged in intersecting fascicles with a herring-bone, fascicular or fibromatosis-like growth pattern. The sclerosing RMS was defined as a proliferation of spindle to round cells embedded in an extensively hyalinized stroma showing a distinctive pseudoalveolar or pseudovascular pattern. Both histologic variants showed limited if any evidence of strap cells, rhabdomyoblastic differentiation, or nuclear pleomorphism. These features typically are associated with ERMS. Additionally, the typical myxoid stromal component seen in most ERMS was not present in either spindle or sclerosing RMS.

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Table 1
Clinical features and follow-up data of spindle and sclerosing RMS arising in the head and neck.

Case #	Age/sex	Site	Size (cm)	Diagnosis	Stage	Therapy	Recurrence	Follow-up duration	Vital status
1[a,b]	34y/F	Buccal/masticator space	2.4	Sclerosing RMS	1	Surgery, CT and RT	DR	43 mos	DOD
2[a,b,c]	14y/F	Infratemporal fossa	7.3	Sclerosing RMS	3	CT and RT	LR	26 mos	DOD
3	17y/F	Buccal/masticator space	3.5	Sclerosing RMS	1	Surgery, CT and RT	–	31 mos	Alive (NED)
4	28y/M	Buccal/masticator space	10.5	Sclerosing RMS	4	CT and RT	–	12 mos	DOD
5	33y/M	Soft tissue mandible	5.8	Sclerosing RMS	1	Surgery, CT and RT	LR (2), DR	65 mos	DOD
6	27y/F	Soft tissue skull	5.1	Spindle cell RMS	4	Surgery, CT and RT			
7	14y/M	Tongue	1.1	Spindle cell RMS	1	Surgery			
8[a,c]	0.7y/M	Neck	6.5	Spindle cell RMS	1	Surgery, CT and RT	LR	60 mos	Alive (NED)
9	72y/M	Neck	9.1	Spindle cell RMS	1	Surgery, CT and RT	–	29 mos	Alive (NED)
10	41y/M	Soft tissue mandible	4.5	Spindle cell RMS	1	Surgery and RT	–	4 mos	Alive (NED)
11	60y/M	Hypopharynx	8.3	Spindle cell RMS	4	Surgery, CT and RT	–	14 mos	DOD
12	33y/M	Tongue	0.8	Spindle cell RMS	1	Surgery and CT	–	94 mos	Alive (NED)
13	1.75y/F	Nasolabial/cheek	1.0	Spindle cell RMS	1	Surgery and CT	–	7 mos	Alive (NED)

Stage, according to the Intergroup Rhabdomyosarcoma Study Group pretreatment staging classification.
CT – chemotherapy, (–) – negative, RT – radiotherapy, LR – local recurrence, DR – distant recurrence, DOD – died of disease, NED – no evidence of disease.
[a] Cases included in the study by Mosquera et al.
[b] Cases included in the study by Agaram et al.
[c] Cases included in the study by Alaggio et al.

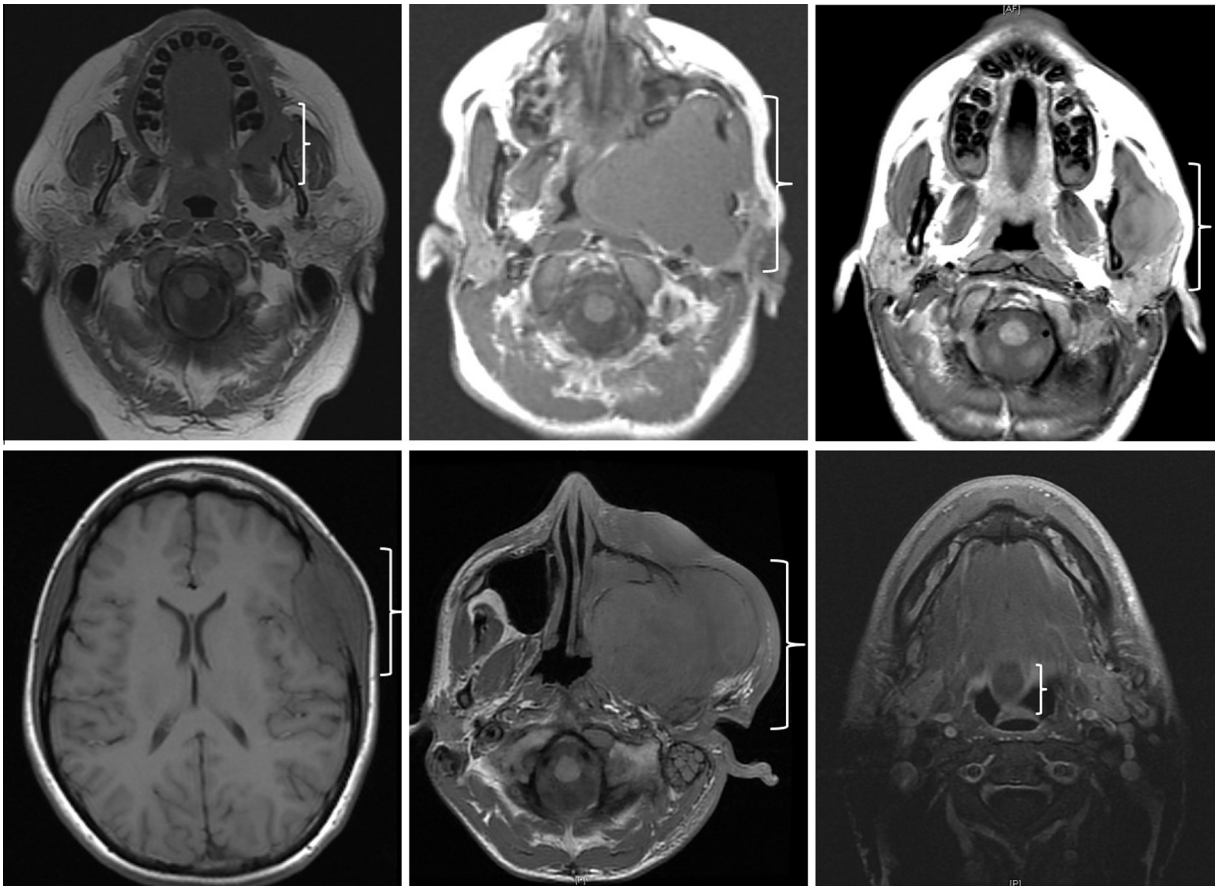

Fig. 1. Radiographic findings of head and neck spindle cell/sclerosing rhabdomyosarcoma. MRI axial views of 6 patients showing large tumor masses causing a mass-effect, erosion and destruction of nearby bony structures.

Immunohistochemical analysis showed reactivity for desmin and myogenin in all cases. The desmin expression was mostly diffuse and strong, while myogenin reactivity was focal to rare positive cells in 11/13 cases. Results are summarized in Table 2. Additionally, 7/7 cases tested were positive for myoD1 in a diffuse pattern (Figs. 2 and 3). Other stains performed in a subset of cases showed that 5/9 were positive for SMA (with 4/5 cases exhibiting only focal staining), 1/10 was positive for cytokeratin (AE1:AE3) and 1/3 was positive for CD99.

Molecular results

Results of molecular features are summarized in Table 2. Seven cases, including all 5 sclerosing RMS, were investigated for