

Original Article

Spindle cell/sclerosing rhabdomyosarcoma: case series from a single institution emphasizing morphology, immunohistochemistry and follow-up

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Abstract: Spindle cell/sclerosing rhabdomyosarcoma is a rare skeletal-muscle tumor with distinctive clinicopathologic characteristics. 10 cases (6 cases of spindle cell rhabdomyosarcoma and 4 cases of sclerosing rhabdomyosarcoma) were composed of 6 males and 4 females aging from 5 months to 57 years, with median age 33 years, most of who represented a painless solid mass. Histologically, the tumors were composed of fascicles of spindle cells or primitive round cells embed in sclerotic matrix with presence of rhabdomyoblasts in varying proportion. Immunohistochemically, the tumor cells expressed MyoD1 (10/10), Desmin (10/10), myogenin (6/10), AE1/AE3 (2/10), EMA (2/10), but were negative for SMA, caldesmon, S-100. All of the patients underwent a complete surgical resection without or with chemotherapy (2/10) or radiotherapy (1/10). During the follow-up period (1 to 24 months), 1 patient was succumbed, and 2 cases showed in situ recurrence with 1 of them adopting metastasis. Our cases further demonstrate there do present some clinicopathologic relations between spindle cells rhabdomyosarcoma and sclerosing rhabdomyosarcoma, but the latter seems to have a better prognosis. Exact grading and staging contribute to predict the outcome.

Keywords: Spindle rhabdomyosarcoma, sclerosing rhabdomyosarcoma, pathology, immunohistochemistry, differential diagnosis, prognosis

Introduction

Rhabdomyosarcoma (RMS) is most frequently malignant soft tissue tumor developing in the childhood and adolescence with skeletal muscle differentiation. Traditionally, it falls into three main groups: embryonal, alveolar and pleomorphic. However, both spindle and sclerosing subset were reported subsequently [1-3]. Spindle RMS was originally defined as a variant of embryonal RMS predominantly affecting children with a favorable prognosis compared to other categories of RMS, but adult patients were also appreciated subsequently, however, with evidences from sporadic cases showing no prognostic advantage [1, 2, 4]. Sclerosing RMS was recently recognized and also can develop in either pediatric or adult population [3, 5]. In light of existence of morphologic overlap and clinical similarities, both of the two entities shared a common designa-

tion as “spindle cell/sclerosing rhabdomyosarcoma” in newly WHO classification [6]. As an uncommon subtype of RMS, spindle cell/sclerosing RMS was only described by limited literature, most of which were reported by case studies. To further understand the clinicopathologic features, we herein retrospectively reviewed 10 cases from our institution emphasizing the distinctive morphology, immunohistochemistry and follow-up.

Materials and methods

Cases diagnosed as Spindle cell or sclerosing RMS from 2010 to 2014 in the first affiliated hospital of Zhengzhou university were selected and reviewed. Complete clinicopathologic and follow-up data were obtained through the records or inquiring by phone. Grading and staging were performed by FNCLCC and AJCC assessment system [7, 8]. All of the surgical specimens were fixed in 4% formalin, embed-

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Table 1. Clinical Features and Follow-up Data

Case no.	Diagnosis (RMS)	Age/sex	site	Size (cm × cm × cm)	Presentation	Treatment	Grade ^a	Stage ^b	Follow-up (mo)
1	Spindle cell	42 y/M	Left upper arm	5.2×3.2×2.5	Painless solid mass with poor mobility and related demarcation	Surgery and chemotherapy	3	III	DOD (24)
2	Spindle cell	30 y/M	Left lower quadrant of abdomen wall	14.0×9.8×9.0	Painless and cystic-solid mass with demarcation and peritoneum involved focally	Surgery	3	III	In situ Rec (10)
3	Spindle cell	49 y/M	Next to left glottis in larynx	2.4×1.8×1.5	Hoarseness; solid mass with focal calcification and cervical lymphadenopathy	Surgery and radiotherapy	1	I B	AWOD (5)
4	Spindle cell	5 mo/F	Left orbit	2.8×2.7×0.6	Left eye swelling, expanded palpebral fissure and proptosis	Surgery	2	II A	AWD (5)
5	Spindle cell	28 y/M	nasopharynx	5.0×5.0×1.0	Nasal obstruction, rhinorrhoe and occasional headache; solid mass involved sphenoid sinus	Surgery	3	III	AWD (1)
6	Spindle cell	52/M	Left thigh	21×9.0×8.5	Solid mass with heavy tenderness; mobility limitation	Surgery	2	IV	In situ Rec and metastasis to stomach (12)
7	sclerosing	24/F	Back of right hand	3.4×2.5×1.5	Solid and demarcated mass gradually increase during 10 years and repeatedly recurred	Surgery	1	I A	NED (1)
8	sclerosing	18/M	Right groin	16.5×9.0×9.0	Painless solid mass with compressed peripheral vessels	Surgery and chemotherapy	1	I B	AWOD (6)
9	sclerosing	36/F	Left pars buccalis	4.8×3.5×2	Solid increasing mass with ulcer formation and pain feelings	Surgery	1	I A	AWOD (8)
10	sclerosing	57/F	Right parotid gland	2.3×1.8×1.5	Solid painless mass with mouth-opening limitation	Surgery	1	I A	AWOD (13)

a, using FNCLCC grading system; b, sing AJCC anatomic staging system; AWD, alive with diseases; AWOD, alive without evidence of disease; DOD, die of disease; mo, months; NA, not available; NED, no evidence of disease; Rec, recurrence.

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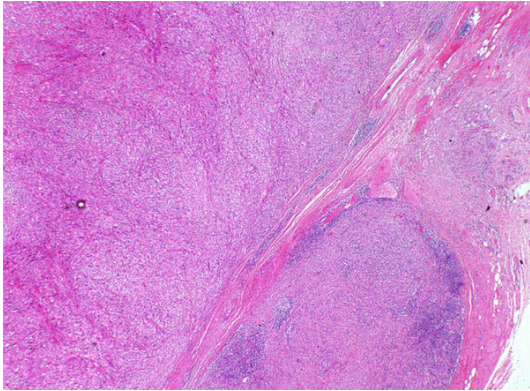


Figure 1. Multiple nodules of spindle cells infiltrating normal tissues in pushing type.

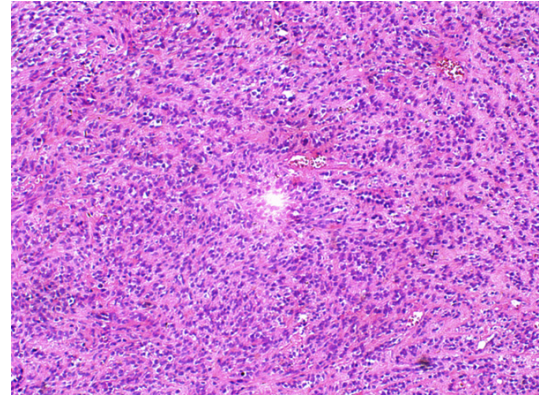


Figure 4. Primitive-like small round cells arranging in cords or strands with intensely hyalinized matrix.

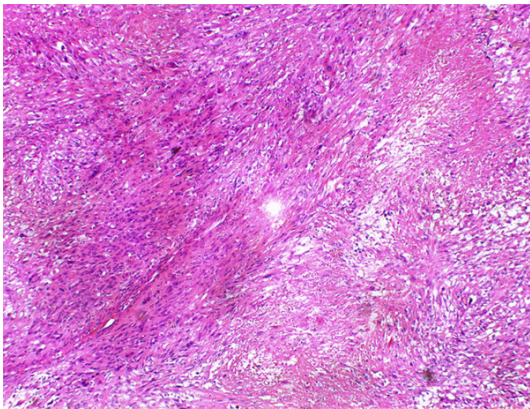


Figure 2. Intersecting fascicles of spindle tumor cells with significant necrosis.

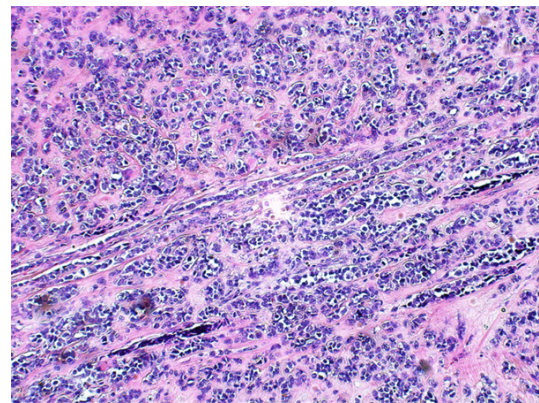


Figure 5. Small alveolar or packet growth pattern embedded in sclerotic stroma.

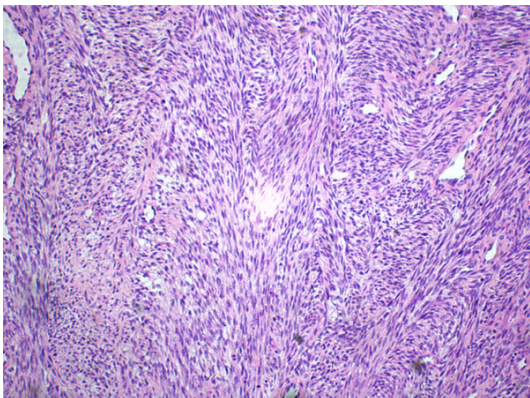


Figure 3. Herringbone growth pattern mimicking adult fibrosarcoma.

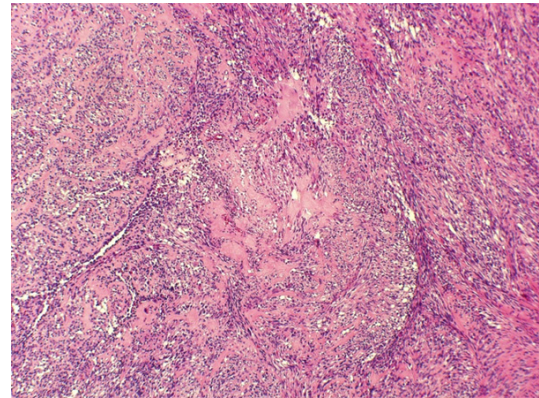


Figure 6. Transition zone between spindle cell and sclerosing area.

ded routinely in paraffin and stained with hematoxylin and eosin. Immunohistochemical studies were performed using commercial antibodies in the Ventana BenchMark XT instrument

(Ventana System, Tucson AZ). The antibodies included desmin, myogenin, MyoD1, SMA, caldesmon, AE1/AE3, EMA, S-100 and Ki-67 (all above from Ventana, prediluted).

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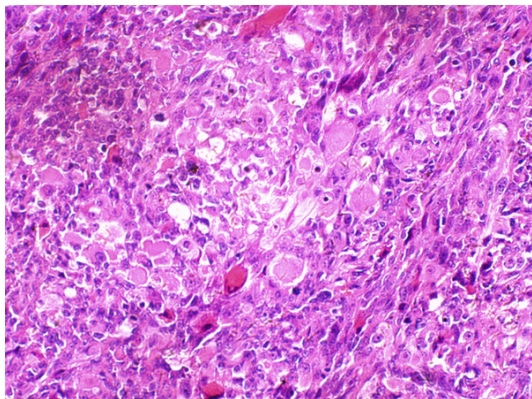


Figure 7. Focal presence of rhabdomyoblasts.

Results

Clinical findings and follow-up

The main clinical and follow-up data were summarized in **Table 1**. Cases were composed of 6 cases of spindle cell RMS and 4 cases of sclerosing RMS containing 6 males and 4 females aging from 5 months to 57 years (median, 33 years; mean, 34 years). The tumor involving the anatomic locations including upper arm, abdominal wall, glottis, orbit, nasopharynx, thigh, hand and groin, most of which affecting trunks or extremities presented with a solid painless mass with a relative demarcation in physical examination. But the bulky lesions or local nerve compression can result in hoarseness (case 3), protopsis (case 4), nasal obstruction (case 5), mobility limitation (case 6, 10), peripheral vessels compression (case 8), and painful feelings (case 6, 9). All of patients denied familial heredity diseases and underwent a complete tumor resection with or without additional adjuvant chemo- (case 1, 7) or radio- (case 3) therapy. Generally, the spindle variant in our series was more likely to have a high grading and staging compared to sclerosing variant and accordingly, 1 patient was succumbed and 2 patients suffered from in situ recurrence, one of who was clinically manifested evidences of metastasis during the follow-up period. Another 5 cases of sclerosing RMS in our group had relatively low grading and staging and therefore behaved a good prognosis in our group.

Pathological findings

Grossly, the pinkish-grey or grayish solid tumors ranging from 2.3 cm to 21 cm in maximum

diameter, tended to be well circumscribed with a firm, gray-white to tan cut surface, some of which possessed a gritty texture, necrosis or cystic degeneration. Histologically, in 6 cases (case 1 to case 6), the tumor predominantly consisted of sheets or multiple nodules of spindle cells arranging in whorls or fascicles infiltrating normal muscles or adipose tissues, usually, in pushing type that stimulated leiomyosarcoma (**Figure 1**). Perivascular accentuation, significant necrosis (**Figure 2**), inflammatory infiltration and hemorrhage also can be appreciated. Areas of case 1 imparted an evident herringbone growth pattern mimicking adult fibrosarcoma (**Figure 3**). The spindle tumor cells had elongated and fusiform nuclei, small nucleoli and abundant eosinophilic cytoplasm with varying nuclear atypia, mitotic activity and pleomorphism. In the remaining cases (case 7 to case 10), undifferentiated small round cells were mainly interpreted as cords, strands (**Figure 4**), alveolar or packet pattern (**Figure 5**) embed in intensely hyalinized matrix with a little eosinophilic or pale cytoplasm, inconspicuous nuclei and nucleoli with or without mitotic figures. Necrosis was relatively uncommon compared with the former 6 cases. More or less, transition zones between spindle cell and sclerosing areas (**Figure 6**) and presence of rhabdomyoblasts (**Figure 7**) can be found when performing an attentively observation. The immunohistochemical profile was summarized in **Table 2**. Most of tumor cells were typically positive for MyoD1 (10/10) (**Figure 8**), Desmin (10/10) (**Figure 9**) and focally positive for myogenin (6/10) (**Figure 10**), but totally negative for SMA, caldesmon, S-100. Only two cases focally expressed AE1/AE3 and EMA. Proliferative index Ki67 varied from 15% to 80%.

Discussion

Spindle cell RMS first reported by Cavazzana et al, mainly arise in paratesticular region and followed by the head and neck in pediatric population and has a better prognosis with lower lymph node metastasis and favorable 5-year survival compared to other subtypes of RMS [1, 9]. Cases of adults affected were subsequently founded, but head and neck region and extremities are the most frequent anatomic locations [4, 10, 11]. The prognosis seems to be aggressive, however, still better than other adult RMS, such as polymorphic variant [12]. A mass with or without pain is the most common complaint,

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Table 2. Immunohistochemical profiles of spindle cell/sclerosing RMS

Case no.	Desmin	Myogenin	MyoD1	SMA	Caldesmon	AE1/ AE3	EMA	S-100	Ki-67
1	++	-	+++	-	-	+	++	-	80%
2	++	+	++	-	-	-	-	-	70%
3	+++	+	++	-	-	-	-	-	15%
4	+	-	++	-	-	-	-	-	30%
5	+++	+	+++	-	-	++	+	-	60%
6	+++	-	+++	-	-	-	-	-	60%
7	+++	++	+++	-	-	-	-	-	50%
8	+	++	+++	-	-	-	-	-	50%
9	+++	++	+++	-	-	-	-	-	70%
10	+++	-	++	-	-	-	-	-	30%

-, negative; +, tumor cell expressed less than 10%; ++, tumor cells expressed 10%-50%; +++, tumor cells expressed above 50%.

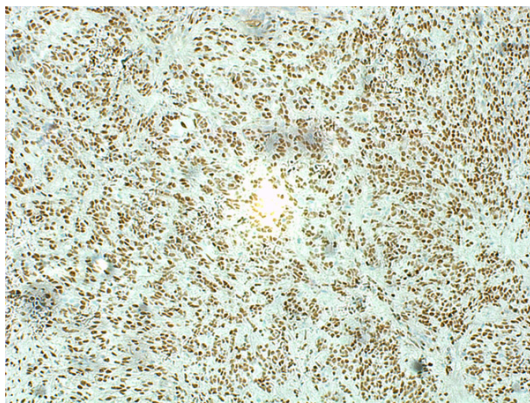


Figure 8. MyoD1 was diffusely expressed.

which usually demonstrates a firm and fine demarcation from surrounding tissues in gross examination [1]. Histologically, spindle cell RMS is typically composed of long fascicles of relatively uniform spindle cells arranged in intersecting or herring bone pattern mimicking leiomyosarcoma or fibrosarcoma. The majority of tumor cells have pale and eosinophilic indistinct cytoplasm with small and long nuclei with vesicular chromatin and small nucleoli. Significant mitotic activity usually can be seen. Sclerosing RMS, originally reported by Mentzel et al, also can rise in pediatrics or adults, but paratesticular region is rarely implicated [2, 3]. Microscopically, the prominent hyaline matrix separate the undifferentiated round or oval tumor cells into cords, nests, or small alveolar patterns, frequently reminiscent of sclerosing epithelioid fibrosarcoma, chondrosarcoma or even angiosarcoma [2, 13].

However, cases with synchronous presentation of areas of spindle cells or small primitive-like cells embed in abundant collagen stroma can be founded, suggesting their morphologic overlaps and therefore these two entities have shared the same designation, namely, "spindle cell/sclerosing RMS" [6]. Although scattered rhabdomyoblasts with eccentric nuclei

and significant ample eosinophilic cytoplasm might suggest there existed relevance between spindle cell/sclerosing RMS and embryonal RMS, clear genetic data link have been not yet founded [13-15]. By immunohistochemistry, tumor cells usually show strong and diffuse positivity for desmin and MyoD1, and a variable extent of nuclear reactivity for myogenin from focal to diffuse pattern, with or without focal expression of cytokeratin [5, 16].

Other RMS subtypes have different pathologic features from spindle cell/sclerosing RMS. Although sclerosing RMS may have a pseudo-vascular or acinar growth pattern, the prominently hyaline stroma, smaller alveolar spaces and focal presence of fascicles of spindle cells are different from alveolar RMS. In addition, the latter tends to consistently express both MyoD1 and myogenin and was therefore distinct from the priority of MyoD1 expression in spindle cell/sclerosing RMS [17]. As we discussed above, the real relationship between embryonal RMS and spindle cell/sclerosing RMS is still controversial, but ubiquitous strap- or radpole-like rhabdomyoblasts with abundant eosinophilic cytoplasm in a myxoid matrix and scattered nuclear expression of MyoD1 and myogenin are far more likely to support embryonal RMS [18]. Accurate diagnosis also needs to rule out several entities with spindle and sclerotic morphology, including sarcomatoid carcinoma, spindle cell melanoma, malignant peripheral nerve sheath tumor with or without rhabdomyosarcoma differentiation, leiomyosarcoma, fibrosarcoma, sclerosing epithelioid fibrosarcoma,

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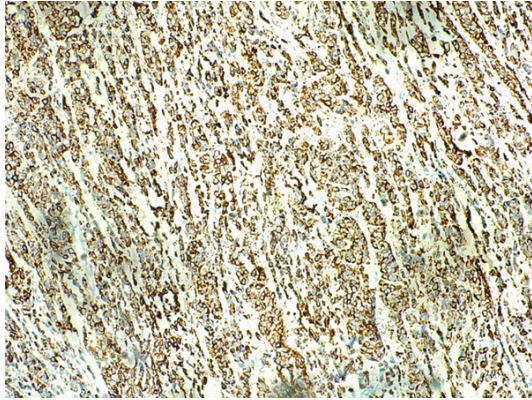


Figure 9. Diffuse immunoreactivity for Desmin.

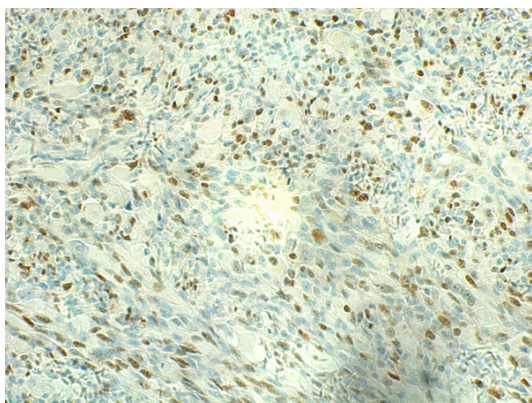


Figure 10. Myogenin was focally positive.

osteosarcoma and so on [2, 16, 19]. However, deficiency of relationship with nerve fibers, “marble-like” growth pattern with myxoid matrix, better differentiated epithelial areas, lace- or filigree-like neoplastic bone, and broad-spectrum cytokeratins (focal positivity permissible), CK5/6, P63, S-100, HMB45, CEA, SMA, caldesmon expression, and presence of typical immunophenotype feature of MyoD1 and myogenin can easily tell them apart.

Although the consensus of optimal treatment for spindle cell/sclerosing RMS has been not reached, the mainstay therapeutic method should also, similar to most soft tissue tumors, be surgery and adjuvant chemotherapy or radiotherapy can be added [19]. 2 cases and 1 case in our group received a chemotherapy and radiotherapy after tumor resection, but whether the adjuvant treatments worked was unclear. Lesions developing in some anatomic locations are hard to be eliminated may have a recurrent risk, such as case 4 and 5 in our

series which need a close supervision. Generally, spindle cell/sclerosing RMS has a relatively favorable outcome in pediatric group, but worse prognosis in adults with a higher propensity of recurrence and metastasis [6, 9, 19]. In our limited cases, influence of prognosis derived from age seems insignificant but more relate to the grading and staging. In addition, our group of spindle subtype presented with more common necrosis, mitotic images and rhabdomyoblasts with a comparatively higher grading and staging in clinic and therefore more frequent recurrence, metastasis and even mortality. However, that situation still needs ongoing follow-up in our cases and more prognostic data from other replications.

In conclusion, spindle cell/sclerosing RMS is a rare skeletal-muscle tumor with distinct morphology, immunohistochemistry and relatively favorable prognosis. An accurate diagnosis based on the well-known recognition and an exact clinical grading and staging contribute to predict the outcome of this entity.

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Disclosure of conflict of interest

None.

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