

RESEARCH ARTICLE

Rhabdomyosarcoma - an Epidemiological and Histopathologic Study of 277 Cases from a Major Tertiary Care Center in Karachi, Pakistan

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Abstract

Aim: To present the epidemiologic data (age, gender, size etc) and histopathologic and immunohistochemical features of cases of rhabdomyosarcoma (RMS) reported in our department. **Settings:** Section of Histopathology, Department of Pathology and Microbiology, Aga Khan University Hospital, Karachi, Pakistan. **Duration:** All cases of RMS diagnosed between January 1, 2003 and December 31, 2012 were included in the study. **Results:** A total of 277 cases were included. Embryonal rhabdomyosarcoma (ERMS) was by far the dominant histologic type (87.4%) followed by alveolar type (ARMS)(9.4%). ERMS was much more common in males (64.0%) and over 65% of cases occurred in the first decade of life (over 90% in the first two decades). Head and neck region was commonest site for ERMS (46.7%), followed by the genitourinary system (16.1%). Over 65% cases of ARMS occurred in the extremities. Over 80% cases of ARMS occurred in the first 3 decades of life. Immunohistochemical staining for Desmin and MyoD1 was positive in 96.7% and 85.4% respectively. **Conclusions:** The epidemiologic data and microscopic findings in our patients are similar to international published data on rhabdomyosarcoma.

Keywords: Rhabdomyosarcoma - embryonal type - alveolar type - pleomorphic type - epidemiology

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Introduction

Rhabdomyosarcoma is the commonest soft tissue sarcoma in children and adolescents (Ognjanovic et al., 2009). Most cases occur in children under 10 years age and less than 20% occur in adolescents (Gurney et al., 1996; Ognjanovic et al., 2009). Embryonal rhabdomyosarcoma (ERMS) is the most common histologic subtype comprising about 60% of all rhabdomyosarcomas (Sultan et al., 2009). ERMS is defined as a primitive, malignant soft tissue tumor with phenotypical and biological features of embryonic skeletal muscle cells (WHO, 2013). Embryonal RMS, botryoid type is a variant of ERMS with a characteristic gross (polypoid or grape-like) and histologic (aggregates of tumor cells tightly abutting an epithelial surface/cambium layer) appearance and comprises about 6% of all RMS (Newton et al., 1995; WHO, 2013). Alveolar RMS (ARMS) is the second most common subtype comprising of about 30% of all RMS, is more common in adolescents and young adults, unlike ERMS is uncommon in young children (under 10) and has a peak incidence between 10 and 25 years of age (Newton et al., 1995). By definition, it has a monomorphic population of primitive cells with round nuclei and features of arrested myogenesis (WHO, 2013). Other

RMS subtypes include pleomorphic rhabdomyosarcoma (PRMS, which mainly occurs in the sixth to seven decades of life (Stock et al., 2009); and spindle cell/sclerosing RMS which is an uncommon subtype comprising 5-10% of all rhabdomyosarcomas (Chiles et al., 2004). Except for ARMS which shows no gender predilection, all other subtypes are more common in males (Parkin et al., 1988; Chiles et al., 2009; Ognjanovic et al., 2009; Stock et al., 2009). ERMS is much more common in whites, while ARMS does not show any racial or geographic predilection (Chiles et al., 2009; Ognjanovic et al., 2009). About half of ERMS occur in the head and neck and about half in the genitourinary tract, while ARMS most commonly occurs in the extremities (Harms, 1995; Raney et al., 2011).

The Intergroup Rhabdomyosarcoma Studies (IRS) group proposed a classification of rhabdomyosarcoma based on prognosis and divided RMS into three groups: superior prognosis (botryoid RMS and spindle cell RMS), intermediate prognosis (ERMS) and poor prognosis (ARMS and PRMS) (Newton et al., 1995). Age is an independent prognostic factor; children aged 1-9 years have a better prognosis. Stage and site of origin are also important prognostic factors (Meyer and Spunt., 2004; Oshi et al., 2004; Arndt et al., 2009).

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The aim of this study is to present epidemiologic data (age, gender, site) as well as pathologic findings (microscopic, immunohistochemistry) in a large series of patients diagnosed over a period of 10 years in the largest center for histopathology in Pakistan. To our knowledge, this is the largest series on Rhabdomyosarcoma from Pakistan, a populous country in South Asia with a population of nearly 190 million. Earlier, Bhurgri et al published data of rhabdomyosarcoma in Karachi, 1998-2002 (Bhurgri et al., 2004). We receive cases from the whole country through our collection points located all over Pakistan.

Results

A total of 277 cases of rhabdomyosarcoma were diagnosed during the period 2003 to 2012. Rhabdomyosarcoma comprised 13.8% of all soft tissue sarcomas diagnosed in our section during the study period. Embryonal rhabdomyosarcoma was the overwhelming predominant histologic type occupying for 87.4% of all cases. This was statistically significant (p-value:0.01). The breakup is shown in Table 1.

Table 1. Break-down of Cases According to Histologic Type (n=277)

Serial no	Histologic Type	Number	Percentage (%)
1	Embryonal (including Botryoid variant)	242	87.4
2	Alveolar	26	9.4
3	Plemorphic	5	1.8
4	Rhabdomyosarcoma NOS	4	1.4

Table 2. Age-wise Distribution of ERMS (n=242)

Serial no	Decade (years)	Number	Percentage (%)
1	0-10	159	65.7
2	11-20 yrs	62	25.6
3	21-30	14	5.8
4	>31	7	2.5

Table 3. Age-wise Distribution of ARMS (n=26)

Serial no	Decade (years)	Number	Percentage (%)
1	0-10	9	34.6
2	11-20 yrs	72	6.9
3	21-30	5	19.2
4	31-40	2	7.7
5	>40	3	11.5

Table 4. Break-down of ERMS Cases According to Location (n=242)

Serial no	Site	Number	Percentage (%)
1	Head and neck	113	46.7
2	Genitourinary system	39	16.1
3	Abdomen	17	7
4	Pelvis	8	3.3
5	Retroperitoneum	2	0.8
6	Perineum/anal region	9	3.7
7	Trunk	9	3.7
8	Extremities	24	9.9
9	Other sites*	10	4.1
10	Site not known	11	4.6

*The other sites included: vertebrae/spine (5 cases), kidney (2 cases) and mediastinum (3 cases).

There were 26 cases of Botryoid variant comprising 10.7% of embryonal rhabdomyosarcomas and 9.4% of all rhabdomyosarcomas. Of the 242 cases of ERMS, 155(64.04%) were males and 87(35.96%) were females. Male to female ratio was 1.78:1. The predominance of ERMS in males was statistically significant (p-value:0.006). Age range for ERMS was 4 months to 65 years with mean and median age of 9 and 8 years respectively. The decade wise breakup of ERMS cases is shown in Table 2.

As shown in Table 2, 65.7% cases of ERMS occurred in the first decade of life. This finding was statistically significant (p-value:0.094). Out of the 242 cases of ERMS, 109(45.04%) occurred in patients 5 years of younger. This finding was statistically significant (p-value:0.001). The 26 cases of ARMS were evenly distributed between males and females i.e. 13 cases each. Age range was 2 to 74 years with mean and median age of 21 and 24 years respectively. The decade wise breakup of ARMS cases is shown in Table 3.

Head and neck was the commonest site of ERMS with 47.7%. The breakup of ERMS according to location is given in Table 4.

The further break up of head and neck and genitourinary cases of ERMS is given in Table 5.

The majority of 26 cases of ARMS (65.4%) were located in the extremities. The breakdown of 26 cases of

Table 5. Break-down of ERMS Head and Neck and Genitourinary Cases (n=152)

Serial no	Location	Number	Percentage(%)
	(A) Head and Neck	113	
1	Nose & Paranasal sinuses	21	18.6
2	Nasopharynx	9	8
3	Orbit/periorbital soft tissue	23	20.3
4	Oral/oropharynx/cheek/palate	20	17.7
5	Ear	6	5.3
6	Tongue	1	0.9
7	Conjunctiva	1	0.9
8	Parotid	1	0.9
9	Jaw	14	12.4
10	Face	2	1.8
11	Skull	5	4.4
12	Neck	5	4.4
13	Sphenoid	4	3.5
14	Parameningeal	1	0.9
	(B) Genitourinary System	39	
1	Urinary bladder	22	56.4
2	Testicular/paratesticular soft tissue	9	23.1
3	Prostate	2	5.1
4	Vagina	5	12.8
5	Cervix	1	2.6

Table 6. Breakup of Cases of ARMS According to Location (n=26)

Serial no	Site	Number	Percentage (%)
1	Extremities	17	65.4
2	Head and Neck	5	19.2
	Neck	2	
	Nose	1	
	Nasopharynx	1	
	Retrolubar	1	
3	Trunk	3	11.5
4	Abdomen	1	3.8

ARMS is given in Table 6.

Desmin was the main immunohistochemical(IHC) stain used to confirm the diagnosis. It was performed on 272 out of 277 cases. It was positive in overwhelming majority of cases i.e in 268 out of 272 cases (96.7%) in which it was performed. We acquired the IHC stain MyoD1 in 2006 and started performing it together with Desmin in suspected cases of RMS. It was performed in 103 cases (out of 277 in this study), was positive in 88 out of 103 cases (85.4%) and was negative in 15 cases (14.6%). CD99 (MIC 2) was another marker which was commonly performed in these cases. It was positive in 29 cases (19.3%) and negative in 121 cases (80.7%). Smooth muscle actin (ASMA) was performed in 63 cases. It was positive in 27 cases (42.8%) and negative in 36 cases (57.2%). Other IHC markers performed in these cases (as routine workup of small round blue cell tumors) included LCA in 136 cases, negative in all, which was acquired in 2008 and performed in 12 cases, negative in all. Broad spectrum cytokeratins were performed in 118 cases and were negative in 112 (94.9%) and positive in 6 cases (5.1%).

Out of the total 277 cases included in the study, 8 were blocks received for second opinion. Of the remaining 269 cases, 117(43.5%) were incisional biopsies, while 152 (56.5%) were excisional biopsies/resection specimens.

Discussion

Rhabdomyosarcoma is the most common soft tissue sarcoma worldwide in children under 15 years of age and one of the commonest in adolescents and young adults. Studies from Asia and Africa (Missaoui et al., 2010; Liu et al., 2014) also endorse this. It comprises about 8% of all malignant tumors in children and 2 to 5% of all adults sarcomas (Gurney et al., 1997; Hawkins et al., 2001). Rhabdomyosarcoma comprised 13.8% of all soft tissue sarcomas diagnosed in our section during the study period. ERMS constituted the overwhelming majority (87.4%) of cases in our study. This percentage is much higher than that reported in literature which is around 60% (Ognjanovic et al., 2009). Similarly, the Botryoid variant of ERMS was more common in our study (9.4% of all cases) compared to previously published data i.e. around 6% (Newton et al., 1995). Owing to the overwhelming majority of ERMS in our study, the percentage of ARMS was correspondingly (19.4%) which is much lower than that reported in literature which is about 31% (Newton et al., 1995).

In our study, there were no cases of sclerosing or epithelioid RMS which are rare or recently described entities (Chiles et al., 2004; Jo et al., 2011). It may be possible that few of the cases diagnosed as ERMS in our study in the earlier years may actually represent sclerosing variant of RMS since this variant occurs in both children and adults and mainly involves head and neck and paratesticular region (Cavazzana et al., 1992; Chiles et al., 2004). We may in future review all cases of RMS to detect any cases of sclerosing RMS in our series. We are yet to see a definite case of epithelioid RMS, a new entity which is not yet included in the WHO Classification

(Jo et al., 2011).

Botryoid RMS comprised 9.4% of all cases in our series, a figure slightly higher than the approximately 6% recorded in published series (Newton et al., 1995). This variant usually occurs in mucosa lined hollow organs like nasopharynx, nasal cavity, vagina, urinary bladder etc and enjoys an unrestricted growth in such hollow organs resulting in its characteristic grape like appearance (Newton et al., 1995). ERMS cases in our series were much more common in males (M:F ratio 1.7:1) Published data from US and Canada show similar figures (Parkin et al., 1988; Ognjanovic et al., 2009). As shown in Table 1, almost 66% cases occurred in the first decade of life, while just over 45% occur in patients 5 years or younger. Western studies also show that most children are aged less than 10 years and about 36% occur under 5 years of life(Gurney et al., 1996; Ognjanovic et al., 2009).

ARMS cases were evenly distributed among males and females. Western literature also shows no gender predilection(WHO, 2013). As shown in Table 3, over 45% of ARMS occurred between the ages 11 to 30 years, while over 34% occurred in the first decade of life. International data shows that peak incidence is between 10 to 25 years of age with median age between 6.8 and 9.0 years (Caillaud et al., 1989).

As shown in Table 4, the most common location for ERMS in our series was head and neck (46.7%) followed by genitourinary system (16.1%). Western data shows that almost one half cases of ERMS occur in the head and neck region and one half occur in the genitourinary system, less than 9% occur in the extremities (Raney et al., 2011). In our study, almost 10% cases of ERMS occurred in the extremities. Within the head and neck, the commonest sites, as shown in Table 5 were paranasal sinuses and nasopharynx, orbit and periorbital soft tissues and oral cavity. Within the genitourinary system, the commonest sites for ERMS, as shown in Table 5, were urinary bladder followed by testis and paratesticular soft tissue. Head and neck and genitourinary system were also the commonest sites for cases of botryoid RMS in our series. International data also show these are the commonest locations for ERMS (Newton et al., 1995). As shown in Table 4, a number of cases in our study occurred in the abdomen, pelvis, retroperitoneum, perineum etc and 2 cases were seen in kidney. Western data also shows these sites to be common locations for ERMS. ERMS also occur in viscera like kidney and heart (WHO, 2011; Arndt et al., 2009). Similarly, a number of our cases occurred in the soft tissues of the trunk. Western data also shows similar features (WHO, 2011).

In our study, over 65% cases of ERMS were located in the extremities, while head and neck was also a relatively common site (Table). Western data also shows that ARMS occurs most commonly in the extremities while head and neck is another common location (Harms, 1995; Yasuda, 2009).

Desmin was the main IHC stain used to confirm the diagnosis and showed a high degree of sensitivity (positive in 96.7% cases). It is however, not as specific as myoglobin or myogenin, being positive in both striated and smooth muscle (Molenaar, 1985). We started using Myo D1 in

2006 and since then it is regularly performed in suspected RMS cases. As shown in our results, it also showed a high degree of sensitivity (over 85%). However, we have only recently acquired myogenin and this antibody plays an important role in the diagnosis of RMS cases. Studies have shown that these IHC stains (Myo D1 and myogenin) are highly specific and sensitive (only nuclear staining is specific) and are currently favoured for the confirmation of a diagnosis of RMS (Cessna, 2001; Morotti, 2006).

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