Childhood Rhabdomyosarcoma: A Review of 35 Cases and Literature.

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ABSTRACT:

BACKGROUND: Rhabdomyosarcoma is one of the most frequent soft tissue sarcomas in children. It constitutes a unique group of soft tissue sarcomas found in children, primarily infants, toddlers and preschool pupils.

OBJECTIVE: The purpose of this review is to examine all the cases of histologically confirmed childhood rhabdomyosarcomas; to re-examine the review pattern, and review recent advances in the biology of this neoplasm.

MATERIALS AND METHODS: the sample consisted of 35 histologically confirmed rhabdomyosarcomas between January, 1996 and 2005. The specimens consisted of excision, incision and tru-cut biopsies. Fresh sections were cut from paraffin embedded tissue blocks and stained with haematoxylin and eosin. The slides were reviewed by three pathologists. The sites of biopsies were noted from the referral forms.

RESULTS: Thirty five cases of paediatric rhabdomyosarcomas were recorded out of a total of 55 cases during the period of study. This represents 63.6% of all cases of rhabdomyosarcomas. The commonest anatomical sites were head and neck regions which accounted for 21 cases of the 35, while retroperitoneal, vagina and testis accounted for 8, 3 and 3 respectively. The highest proportion of cases occurred in ages 6-15 years. The embryonal subtype accounted for highest proportion, followed by alveolar, pleomorphic and spindle types respectively.

CONCLUSION: This study shows that childhood rhabdomyosarcomas are prevalent in this region, and that the most prevalent of the variants is embryonal rhabdomyosarcoma. The commonest anatomical sites were head and neck regions and the highest proportion of cases occurred in ages 6-15 years.

INTRODUCTION

Rhabdomyosarcoma is one of the most frequent soft tissue sarcomas in children. It constitutes a unique group of soft tissue sarcomas found in children, primarily infants, toddlers and preschool pupils. [1-3] This neoplasm shares a propensity to undergo myogenesis, a well defined process that occurs during embryonic and fetal development. As a result these neoplasms tend to resemble stages of muscle formation that resemble prenatal and postnatal life. [2] As a group these neoplasms constitute most the common tissue sarcomas[1]. The unusual feature of this neoplasm is its rarity in adults.

A common misconception is that rhabdomyosarcomas arise in skeletal muscle, but in fact many paediatric examples arise in sites such as urinary bladder, prostate, vagina and gallbladder that are devoid of striated muscle fibres. However, certain subtypes typically in the extremities likely originate from myoblast, particularly those types associated with genetic fusions.[3] The exact origin of extramyogenous rhabdomyosarcoma is not known but they can be induced by genetic manipulation and might be reproduced through tumorigenic influence.[4]

Another misconception is that rhabdomyosarcoma represents a single tumour type whereas there are distinct clinical, pathological and molecular subtypes. These differences show that the various types of clinical rhabdomyosarcoma have different pathophysiological phenomena that show cellular and biological behaviour of a developing muscle.[5] It is important because clinical outcome of each variant is significantly different.

The purpose of this review is to examine all the cases of histologically confirmed childhood rhabdomyosarcomas seen at Jos University Teaching Hospital; to re-examine the morphological pattern, and extensively review recent advances in the biology of this neoplasm.

METHODS AND MATERIALS

The sample consisted of 35 histologically confirmed rhabdomyosarcomas seen at Jos University Teaching Hospital between January 1996 and 2005. The specimen consisted of excision, incision and tru-cut- biopsies from various anatomical locations. Fresh tissue blocks were cut from paraffin embedded tissue blocks. Each was reviewed by three pathologists. The diagnosis was based on morphological features. The sites of biopsies were noted from the referral forms.

Criteria for the diagnoses were based on histological variants. The key cell to be recognized by routine microscope is the rhabdomyoblast, a cell with an eccentric round nucleus and variable amount of eosinophilic cytoplasm. The rhabdomyoblast may assume a variety of shapes which have been described as strap, tadpole, tennis racquet and spider cell. Sometimes cross striation may be demonstrated by staining with phosphotungstic acid haematoxylin .

Histological subtypes include:

A. Embryonal rhabdomyosarcoma which shows

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loose, myxoid stroma that has resemblance to young granulation tissue.

B. Alveolar rhabdomyosarcoma, which form cellular nests of proliferating rhabdomyoblasts separated by fibrovascular core and may contain discohesive round to oval cells. The cells may also grow in cords or clusters.

C. Pleomorphic variant is a mixture of large syncytial-like cells with giant cells and numerous rhabdmyoblasts.

D. Spindle cell variant: the cells are spindle shaped with brightly eosinophilic cytoplasm (spider-like cells).

Rhabdomyosarcomas were classified according to these morphological appearances. Extensive literature review of the pathyophysiology of these neoplasms was undertaken. Tables and figures were used to illustrate and demonstrate some of the various types of rhabdomyosarcomas.

RESULTS

A total of 35 cases of paediatric rhabdomyosarcomas were recorded out of a total of 55 cases during the period of study. This represents 63% of all cases of rhabdomyosarcomas. The commonest anatomical sites were head and neck regions which accounted for 21 cases of the 35, while retroperitoneal, vagina and testis accounted for 8, 3 and 3 respectively. The highest proportion of cases occurred in ages 6-15 years. (Table 1)

Table 2- Shows the distribution of the various types of rhabdomyosarcomas. The embryonal subtype accounted for highest proportion, followed by alveolar, pleomorphic and spindle types respectively.

Figure 1- Shows embryonal rhadomyosarcoma with loose myxoid stroma, strap like cells with eccentric nuclei and abundant eosinophilic cytoplasm. This was a specimen from vagina of a 3-year-old female child.

Figure 2- Shows nests of solid spherical to spindle cells arising from fibrous septae, giving the characteristic alveolar growth pattern.

Figure 3- Shows Pleomorphic rhabdomyosarcoma with mixture of giant cells, numerous rhabdomyoblasts, spindle and spherical cells.

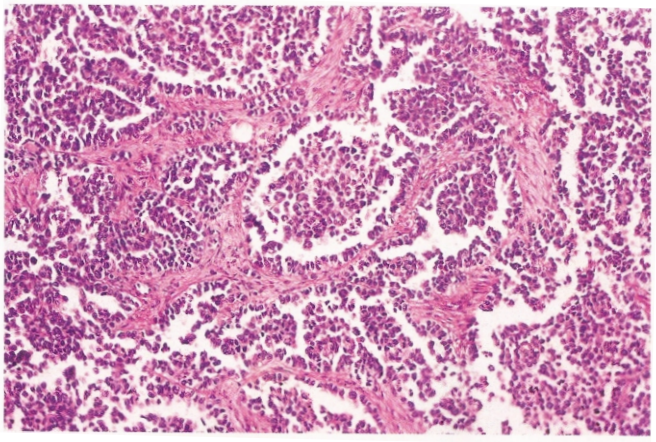

Figure 2- Shows nests of soild spherical to spindle cells arising from fibro-septae , giving the characteristic alveolar growth pattern

TABLE 1: Age and anatomical distributions of childhood rhabdomyosarcoma.

Age group	Head/Neck	Retroperitoneal	Vagina	Testis	Total
0-5	3	1	2	-	6
6-10	10	3	-	2	15
11-15	5	3	1	-	9
16-18	3	1	-	1	5
Total	**21**	**8**	**3**	**3**	**35**

Table 2: Histological subtypes of childhood rhabdomyosarcomas

Types	Frequency	Percentage
Embryonal rhabdomyosarcoma	19	54.3
Alveolar rhabdomyosarcoma	8	22.8
Pleomorphic rhabdomyosarcoma	5	14.3
Spindle rhabdomyosarcoma	3	8.6
Total	**35**	**100**

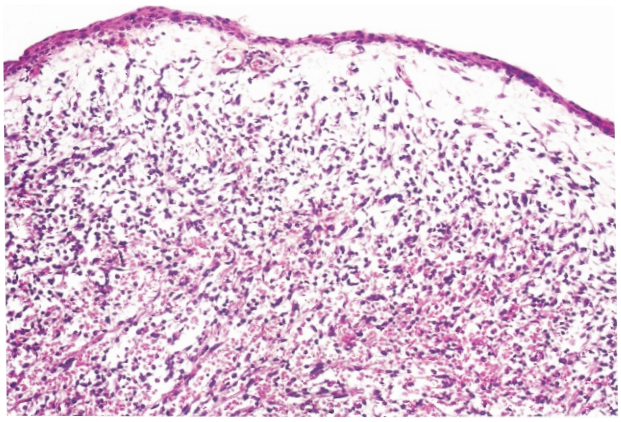

Figure 1- Shows embryonal rhadomyosarcoma with loose myxoid stroma strap like cells with ecentric nuclei and abundant eosinophilic cytoplasm. Specimen from vagina of a 3-year-old female child

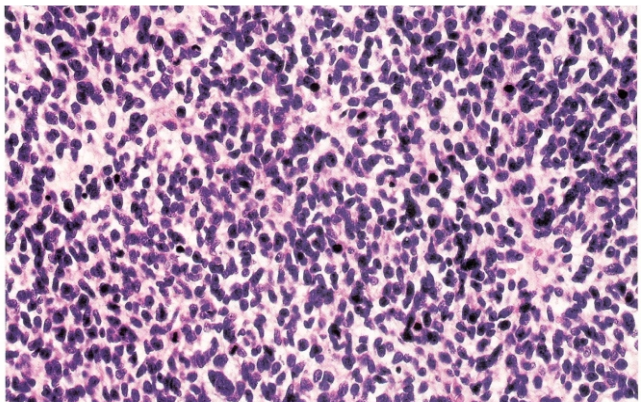

Figure 3-Pleomorphic rhabdomyosarcoma with mixture of giant cells, numerous rhabdomyoblasts, spindle and spherical cells

DISCUSSION

We present 35 cases of childhood rhabdomyosarcomas from our centre. This figure accounted for 63.5% of all cases of rhabdomyosarcomas in Jos. In this review embryonal rhabdomyosarcoma was the commonest histological variant. In the past Horn and Enterline classified rhabdomyosarcomas as botryoid, embryonal, alveolar and pleomorphic. However this system of classification depended on the morphological appearance of the cells.

With the advent of immunohistochemistry in the diagnosis, the sheme has changed, what was called botryoid is embryonal rhabdomyosarcoma, which is characteristically located in the vagina, urinary bladder or extra hepatic bile ducts.[1,2,3]. Botryoid lesions are considered as variant of embryonal rhabdomyosarcoma with superior prognosis. [1,2]. Embryonal rhabdomyosarcoma is the variant that has greater tendency of developing muscle. [6] As such they are characterized by variable zone of condensation that produces alternating foci of hypocelluarity and hypercelluarity. Like embryonic muscle, the dense zone typically contains areas of more overt myogenesis. Whereas loose areas closely resemble primitive mesenchyme and lie in loose gelatinous matrix. A cellular proto-oncogene called PAX3 or PAX7 a transcription gene is believed to initiate myogenesis through myoD expression. [1, 3] In embryonal rhabdomyosarcoma, precursor cells appear to have awaken the quiescent impulses to develop muscle, resulting in neoplastic stem called rhabdopoeitic sarcoma as described by Masson. [5,6]

Embryonal rhabdomyosarcoma responds poorly to both surgery and chemotherapy even if the diagnosis is done early.[1,6] Arya in Iran reported a case of testicular embryonal rhabdomyosarcoma which in spite of chemo and radiotherapy came down with multipledistant metastasis that resulted in death 17 months after diagnosis. [7] Also, Terrier Lacombe et al in France reported a case of rhabdomyosarcoma in a testicular teratoma in which during follow-up metastases arose rapidly from the purely embryonal, rhabdomyosarcomatous component. [8] Except in children where prognosis is poor long term survival has been repoted.[9] Little evidence is found in the literature to suggest that any other than surgical removal, is of value in the treatment of rhabdomyosarcoma, radiation and chemotherapy appear to have little effect. [10] The 5 year survival in the past in these patients was 10-35%. In a review of 21 cases by Hayes and colleague, and a similar study by Hilgers showed that one third had relapse as a result of residual disease following incomplete surgery.[2,11]

Alveolar rhabdomyosarcoma was the next most common in this series and accounted for 22.8%. it is more commonly seen in older children as it was in the present review . Alveolar rhabdomyosarcoma comprises a distinct and relatively well characterized subgroup that tends to arise from extremities and axial musculatures. In contrast to embyonal rabdomyosarcoma the alveolar rhabdomyosarcomas may arise from nose, paranasal sinuses, ear similar to head and neck region. The tumour typically produce fibrovascular septae that outlines clusters and nests of primitive cells which appear as aggregates that appear to float in the middle of alveolar spaces, hence the name. cells with nearly myoblastic differentiation tend to hang from the fibrous septae. Some alveolar rhabdomyosarcoma contain myogenic giant cells. The biological behavior of alveolar rhabdomyosarcoma is the result of unique reciprocal translocation between (2,13,)(35,q14). [1,3]. This reciprocal translation results in a fusion between the PAX3 gene on chromosome 2q35 and the FKHR gene also called FOXO1, on chromosome 13q14. PAX3 encodes a DNA transcription factor that plays a major role in the ignition of embryonic myogenessis within the myotome. [1,11,12] FKHR encodes a molecules that regulates the aging process and myoblasts conjunction.[1] The fusion of PAX3-FKHR results in the activation of downstream event leading to synthesis of cell cycle andapoptosis proteins as well as myogenesis.[1,2] In contrast fusion negative tumours regardless of historical classification shows relative lack of homogeneity. To date the occurrence of the PAX3-FKHR has been essentially limited to alveolar rhabdomyosarcoma in which alternate fusion appear 20% of cases. This alternate fusion is PAX&-FKHR which results from (1, 13)(p36, q14) reciprocal translocation [1,2,13,14] It has been demonstrated that patients with this translocation tend to have better prognosis even with metastasis [1,15]

Pleomorphic rhabdomyosarcomas accounted for 14.2% of the tumours examined. This occurred in the older children and were mostly located in the retroperitoneal region and from the extremities. Pleomorphic rhabdomyosarcoma is reported to have been described first by Stout [1,16,17] as pleomorphic sarcoma from musculature of adults. It is a high grade sarcoma composed of larger interlacing spindle cells containing irregular hyperchromatic nuclei and numerous abnormal mitoses. This tumour carries poorer prognosis.

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