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Orbital Embryonal Rhabdomyosarcoma in Karachi (1998-2002)

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Abstract

Objective: To study the epidemiology of ocular Rhabdomyosarcoma (ORMS) in Karachi.

Methods: Incident ORMS cases resident of Karachi, registered at Karachi Cancer Registry (KCR) during 1st January 1998 to 31st December 2002 were included in the study. The data were classified using ICD-O2; computerized with Canreg-3, and analyzed using SPSS 10.0.

Results: Ten cases of ORMS were reported to KCR during 1998-2002. RMS originated in the orbit in eight cases, conjunctiva in one and eyelid in one. Nine cases presented with proptosis, associated with conjunctivitis in four cases. One case presented with eyelid swelling. The crude annual incidence rate was 0.13/100,000, the age standardized rate was 0.3/100,000. The mean age of childhood cases was 10.4 years (95% CI 4.0; 16.7); and adult cases was 24.8 years (95% CI 12.8; 36.7). At presentation, eight patients were older than 10 years and three were older than 20 years. Five cases were categorized as childhood malignancies. Tumors were a TNM stage III disease at presentation in eight cases; survival at the end of one year was 70%, and at the end of two years 20%. There were no survivors at the end of three years.

Conclusion: ORMS in Karachi is a disease with a dismal survival. It may reflect a late presentation, or shorter adult ORMS survival or a manifestation of a different genetic pattern, associated with rapid evolution and poor prognosis. Health education for the population, especially parents and health providers is essential for early ORMS diagnosis. Pediatricians, ophthalmologists and health professionals, can play a vital role. Healthcare planning should focus on capacity building for ophthalmologic screening. Cytogenetic studies are advised to determine the genetic pattern (JPMA 54:561;2004).

Introduction

Rhabdomyosarcoma (RMS) is composed of cells with histopathological features of striated muscle in various stages of embryogenesis. Ocular RMS (ORMS) is the occurrence of this tumor in the area of the eye, mostly ocular soft tissues but rarely the orbit or ocular adnexal structures and even within the eye. RMS is the most common primary malignancy of the orbit in children; the most common intraocular malignant lesion being retinoblastoma. Primarily a childhood tumor, the average age at presentation is 4-7 years.[1-3] RMS has also been observed in adults.[4-9]

Derived from primitive undifferentiated mesenchymal cells, RMS can be divided into 4 major histologic categories: embryonal, alveolar, botryoid embryonal, and pleomorphic. Embryonal RMS (ERMS) is the most common subtype observed in children, accounting for 40-60% of all RMS cases in this age group.[10,11] These tumors are most commonly observed either in the genitourinary region or the head and neck region.

Histologically, they have high cytologic variability, representing several stages of skeletal muscle morphogenesis. Desmin and muscle specific actin are immunochemical stains used for identifying RMS, though these stain smooth muscle as well. Myogenin and MyoD1 are more specific for skeletal muscle.[11] Ultrastructural studies are largely of academic interests and for confirmation of RMS if facilities are available. At present three methods of RMS staging or its modifications are in use, group staging, TNM and Risk classification. (Tables 1-2).[12-14] Embryonal RMS (ERMS) cells show a loss of specific genome material from the short arm of chromosome 11 (11p15), suggesting the presence of a tumor suppressor gene. Another molecular

feature characteristic of embryonal RMS is its lack of gene amplification. The cellular DNA content of embryonal RMS is hyperdiploid.[15-18]

RMS clinically presents with ptosis (droopy eyelid), and/or unilateral proptosis (eye prominence), as a sub-conjunctival tumor, dislocation of the lens, or impairment of ocular mobility. It is usually found in the superonasal orbit (that is under the upper lid near the nose). Due to its variable manifestations it may imitate orbitocellulitis, chalazae, epibulbar papilloma or as naso lacrimal duct obstruction.[11,19,20] Rapid evolution, tumour burden (tumour size >5.cms.) and regional lymph node involvement are indicators of poor prognosis. Computed axial tomography (CT-scan) and magnetic resonance imaging (MRI) typically show a mass adjacent to or attached to one of the ocular or orbital muscles. CT is particularly helpful because it shows orbital bone tumor invasion and characteristic focal calcification. Magnetic resonance (MR) imaging allows this tumor to be differentiated from pseudogliomas, such as Coats disease and retrolental fibroplasia. CT and MR imaging help in the differentiation from dermoid, cavernous hemangioma, and lymphangioma.[21]

Early diagnosis, complete surgical resection followed by a combination of chemotherapy and irradiation offer approximately 70 to 90% 3-year survival. RMS is considered controlled if there is no recurrence after 3 years.[22-24] The objective was to study the epidemiology of ORMS and identify it as a malignancy with a good prognosis if diagnosed and treated early.

Methods

Incident RMS cases recorded at the Karachi Cancer Registry during 1st January 1998 to 31st December 2002 were reviewed. The data were classified using ICD-O2 (International Classification of Diseases-Oncology, 2nd edition) and computerized using a customized version of Canreg-3, with internal checks on the validity of the entered data.[19] Manual and computerized validity checks for the

Table 1. ORMS staging system.

Group staging system				
Group I	13%	localized disease	complete surgical resection	no regional nodal involvement.
Group IIA	21%	Grossly resected	microscopic residual disease	no regional involvement.
Group IIB		complete resection	no residual disease	regional nodal involvement.
Group IIC			microscopic residual disease	regional nodal involvement.
Group III	48%	incomplete resection	gross residual disease.	
Group IV	18%	Distant metastasis		
TNM staging system				
Stage I	Disease is localized and involves the orbit, the head and neck region			
Stage II	Localized disease of any unfavorable primary site not included in the stage I category.			The primary tumor must be < or = 5 cm in diameter.
Stage III	Localized disease of any unfavorable primary site not included in the stage I category.			Primary tumor is > 5 cm in diameter and/or it involves regional lymph nodes.
Stage IV	Metastatic disease at the time of diagnosis.			
Risk classification				
Low risk	(1) occurring at a favorable site (stage I)			
(Embryonal RMS)	(2) occurring at an unfavorable site with complete resection (group I),			
	(3) occurring at an unfavorable site with microscopic residual			
	disease (group II)			
Intermediate risk	(1) embryonal RMS occurring at an unfavorable site with gross residual			
	disease (group III)			
	(2) metastatic embryonal RMS and are younger than 10 years			
	(3) any nonmetastatic alveolar RMS at any site			
High risk	Metastatic disease unless younger than 10 years and have embryonal metastasis			

cancer data were performed as per recommendations of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR).[25-27] This involved factors influencing comparability i.e., classification and coding. For precision only cases diagnosed microscopically were included in the study. The residency status of cases was re-ascertained and rechecked. People residing in the specified geographical regions for more than six months were considered residents. Demographical variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging. Tumors were categorized according to the UICC, TNM staging system, to standardize with the staging systems in other parts of the world.[12]

Incidence rates were calculated based on the 1998 census (copy obtained from the Sindh Bureau of Statistics), assuming an annual growth rate of 3.5%.[28] The growth rate was based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given 'standard' age distribution.[29] The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population, averaged over the number of years for which data are presented. The data were analyzed using SPSS 10.0.

Results

Eighteen cases of RMS were reported to the Karachi Cancer Registry during a five-year period, 1998-2002. Ten cases were residents of Karachi Division (population of 9,802,134; males 5,261,712, females 4,540,422). RMS originated in the orbit in eight (80%) cases, conjunctiva in one (10%) case and eyelid in one (10%) case. Nine cases presented with proptosis, associated with conjunctivitis in four cases. One case presented with eyelid swelling. Six cases were observed in the right eye, whereas four were observed in the left eye. The crude annual incidence rate was 0.13/100,000, the age standardized rate was 0.3/100,000.

The mean age of childhood cases was 10.4 years

Table 2. ORMS comparative studies.

	Feng et al[3] (n=10)	Takahashi et al[2] (n=35)	Haik et al[30] (n=18)	Shields et al[22] (n=33)	Karachi (n=10)
Orbit	9	-	4	25	8
Conjunctiva	1	-	14	4	1
Eyelid	2	-		1	1
Uveal tract	-	-		3	
Proptosis	-	-	-	10	5
Eyelid	-	-	-	7	1
Blepharoptosis	-	-	-	6	4
Initial diagnoses					
Rhabdomyosarcoma	-	-	-	8	10
Conjunctivitis	-	-	-	5	-
Cellulitis	-	-	-	5	-
Pseudotumor	-	-	-	4	-
Mean age	4.2	5.2	6.0; 21.0	10.0	10.4; 24.8
Recurrence (total)	-	43	15	10	2
Local	-	-	-	6	2
Lymph node spread	-	20	8	2	-
Distant metastasis	-	23	7	2	-
Tumor-related death	-	-	7	1	10

(95% CI 4.0; 16.7); minimum 3 years, maximum 14 years, range, 11 years. The mean age of adult cases was 24.8 years (95% CI 12.8; 36.7); minimum 16 years, maximum 35 years, range, 19 years. At presentation, eight patients (80%) were older than age 10 years and three patients (30%) were older than 20 years. Only five cases (50%) could be categorized as childhood malignancies (0-14 years). Two cases presented at the age of 35 years, a male and a female. The gender-ratio (M:F) was 2.3.

All ten cases were clinically diagnosed as RMS, and histologically verified. Immunochemistry studies were positive for desmin, vimentin, and HHf35 actin and negative for epithelial markers, (Cytokeratin CAM 5.2 and MNF) and S100. Leucocyte Common Antigen (LCA), PAN B and T, and retinoblastoma markers were also negative. Ultra structural and cytogenetic studies were not conducted on any histopathological specimen. Treatment included multimodality effort, which included surgical debulking and/or enucleation, chemotherapy, and radiotherapy for all patients. Tumors classified according TNM staging were a stage III disease at presentation in eight (80%) cases and stage I in two (20%) cases. The two Stage I, RMS were adult cases, both presented with a recurrence within a year of treatment. Survival at the end of one year was 70% and at the end of two years 20%. There were no survivors at the end of 3 years.

Discussion

ORMS is an uncommon disease, the incidence rates are not calculated, and therefore not a parameter of comparison. There are few published articles, mostly single centre studies, and a few registry reports consisting of 10-35 cases or single case reports of adult ERMS.[1-11] Predominantly a childhood malignancy, it is rarely observed in adults. Contrary to this in our series of ten cases, we observed an equal distribution of adult and childhood orbital ERMS.

Most studies report an early presentation and diagnosis, a mass or area of localized swelling usually marks initial presentation. The mean age reported in different series is 5.2 years by Takahashi et al[2], 4.2 years by Feng et al[3], 6 years by Haik et al[30], 7-8 years by Parham[11] and 10 years by Sheild et al.[22] Amongst children, a late presentation of ORMS was observed in Karachi, despite obvious lesions associated with pain, in half the patients. The mean age at diagnosis was 10.4 years, with two cases presenting at 14 years of age. The mean age being reported, here is therefore the highest documented and the plausible reason could be a late diagnosis. Three out of the five childhood cases presented with an erosion into the paranasal sinuses and facial bones.

Primary ERMS is extremely rare in adults. The oldest documented age is 38 years; the highest age in our series is 35 years. In the adult cases, presentation was earlier, with a time lapse of 3-4 weeks before diagnosis. The presenting complaints were conjunctivitis in four cases, and eyelid swelling in one case.

The cases were categorized by TNM (tumor, node, metastasis) system which takes the size and location into consideration. The other available options were 'Initial staging system', adopted by the first 3 intergroup RMS studies, which group patients based on extent of disease and completeness of initial surgical resection. As we did not have reliable information of the surgical process and residual disease this system could not be utilized. The TNM staging does not take the extent of surgery into account, thus it was more feasible for our system. The risk classifications, is more appropriate for planning treatment options.

The survival in Karachi is the lowest reported in literature. Shield et al[22] reported a 70% 5-year survival with gross disease following surgery (Risk group III); 90% 5-year survival in patients without residual disease (Risk group I) and an 80% 5-year survival with microscopic residual disease (Risk group II), when ORMS is seen in children younger than 10 years of age. Takahashi[2] et al reported a 52% 3-year survival in 1970's, and 86% in the 1980's in childhood ORMS. Haik[30] et al reported a 61% six-year survival.

Cytogenetic studies were not conducted therefore one remains in doubt if the late mean age of childhood ORMS and the adult presentation are not a manifestation of a different genetic pattern, more compatible with a rapid evolution and poor prognosis.

Conclusion

ORMS in Karachi is a disease with a poor prognosis and a dismal survival. Cytogenetic studies are advised to determine the genetic pattern. Health education for the population, especially parents and health providers is essential for early ORMS diagnosis. Pediatricians, ophthalmologists and health professionals, can, play a vital role. Healthcare planning should focus on capacity building for ophthalmologic screening.

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