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Immunohistochemical Markers in Head and Neck Rhabdomyosarcoma of Pediatric Population – A Systematic Review

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Abstract

Background: Mesenchymal cell origin tumor with malignant nature, rhabdomyosarcoma, a sarcoma of solid tumor type in pediatric population, presents different varied muscle cells architecture in the oral and maxillofacial region. Immunohistochemistry plays a pivotal role in the differentiation of rhabdomyosarcoma from other soft tissue tumors of pediatric population.

Material and Methods: Major databases such as Medline were explored detailed literature search in resulting in a systematic review pertaining to immunohistochemistry of rhabdomyosarcoma especially in the oral and maxillofacial region of pediatric population, leading to determination of anatomy, classification, histopathology, age, gender and immunohistochemical markers.

Results: Seven original research scientific articles pertaining to the head and neck pediatric rhabdomyosarcoma were highlighted depicting heterogenous cellular features, which is to be confirmed by immunohistochemistry.

Conclusion: Histopathology plays an important role in the diagnosis of pediatric head and neck rhabdomyosarcoma whereas immunohistochemistry is the main differentiation factor in case of subtypes, nature, management and prognosis.

Keywords: Pediatric; Rhabdomyosarcoma; Head; Neck; Oral; Maxillofacial; Pathology; Immunohistochemistry

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Introduction

A soft tissue malignant tumor of cellular diversity and variable cellular differentiation of muscle cells with mesenchymal cell origin denotes Rhabdomyosarcoma (RMS), which accounts for approximately 5% of pediatric neoplasms of malignant nature. During first decade of life, identification of rhabdomyosarcomas accounts for more than 50%. The four main RMS subtypes are embryonal, alveolar, pleomorphic, and spindle/sclerosing RMS, as per World Health Organization (WHO). Sites of occurrence are head, neck, extremities and genitourinary tract. Sites of involvement are orbit, middle ear, nasal cavity, paranasal sinuses, nasopharynx and infratemporal fossa, parameningeal, non-parameningeal in which parameningeal sites are those adjacent to meninges as nasal cavity, paranasal sinuses, nasopharynx, middle ear/mastoid, parapharyngeal space, infratemporal fossa and pterygopalatine fossa, oral cavity, oropharynx, face, cheek, parotid region and soft tissue of the neck [1-5]. The immunohistochemical reactions included vimentin, desmin, myogenin, MyoD1, AE1/AE3, p53, PCNA, Ki67, C-erbB2, FAS and CDK4. Embryonal, alveolar and pleomorphic are the types of RMS. Classic, spindle cell and botryoid are the types of ERMS. Mesenchymal cells tend to differentiate into cross-striated muscle cells in ERMS, being a moderately cellular tumor with loose myxoid stroma with smaller sized cell nuclei. Two additional subtypes of embryonal rhabdomyosarcoma such as sarcoma botryoide and spindle cell rhabdomyosarcoma have been documented. Multimodal treatment with multi-agent chemotherapy, radiation and

surgery confers the greatest chance for survival in the treatment of head and neck RMS. Li-Fraumeni syndrome (tumor protein p53 mutations), Beckwith-Wiedemann syndrome (11p15 defects), von Recklinghausen disease (neurofibromatosis type 1 mutations), cardiofaciocutaneous syndrome (B-Raf mutations) and Noonan syndrome [Rat Sarcoma (RAS)/mitogen-activated protein kinase signaling pathway mutations) are associated with RMS. Oncogenic mutations involving the anaplastic lymphoma kinase, RAS, fibroblast growth factor receptor 4, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha or catenin-cadherin-associated protein beta 1 genes gives rise to ERMS. Translocation between the fork head box protein O1 transcription factor gene (which is located on chromosome 13) and either the paired box (PAX)3 transcription factor gene on chromosome 2 or the PAX7 gene on chromosome 1, and mutations in the v-Myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog and the c-Met genes gives rise to ARMS. Pleomorphic RMS occurs in both children and adults, with higher rates of recurrence and metastasis [6-8]. The aim of this study was to review original research pertaining to rhabdomyosarcoma of head and neck region in pediatric population, which entails anatomy, classification, age, gender, clinical presentation, histopathology and immunohistochemistry.

Material and Methods

"Pediatric" AND "rhabdomyosarcoma" AND "head and neck were the words used in MEDLINE database using advance search strategy targeting different article categories between 2023 to 2010. The result was 52 articles, out of which we selected 7 articles based in the inclusion criteria. Inclusion criteria was of clinical case reports, case series, case studies, clinical trials, histopathologically confirmed cases, immunohistochemistry analysis, molecular analysis, primary tumor localization, age and scientific literature between 2010-2023. Exclusion criteria was of scientific literature devoid of original research, adults' cases, RMS of different sites in pediatric population and cases without histopathological or immunohistochemical confirmation. This systematic review was conducted to determine RMS in pediatric patients in relation to head and neck region following the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). PubMed, Lilacs, Embase, Scopus, and Web of Science were the source of electronic databases. The search strategy used Boolean operators (AND and OR): [ALL ("Rhabdomyosarcoma") AND (pediatric OR child OR children OR young OR adolescent OR geriatric) AND (head and neck)]. The following data were collected: First author, year, country of study, type of study, patient sex, patient age, tumor location, tumor classification, tumor stage, histopathological analysis, immunohistochemical analysis, treatment, follow-up, mean survival, and outcome. The quality of studies was assessed using the STROBE (Strengthening the Reporting of Observational Studies) checklist.

Results

Seven articles were included in this systematic review based on the selection criteria and PRISMA flow chart (Figure 1). We analyzed a total of 156 RMS cases mentioned in the seven articles reviewed. This included only original research articles and excluded articles pertaining to case reports of rhabdomyosarcoma in the head and neck region in patients of pediatric age. Anatomical sites included neck of paraspinal region, temporal bone, sphenoid sinus, ethmoid sinus, cavernous sinus, orbital region, sinonasal region, extradural space, nasopharynx, oropharynx, maxilla, mandible, buccal mucosa, conjunctiva and tongue. Subtypes included alveolar, spindle cell and embryonal. Age and gender distribution were observed. Histopathological features such as hyperchromatic nuclei, eosinophilic cytoplasm with small round blue cells were seen in embryonal type. Fibrovascular septa was seen in alveolar type. Hyper chromatic nuclei, scanty cytoplasm, spindle cells, myxoid stroma were seen in spindle cell type. Mesenchymal cells, myogenesis stages, rhabdomyoblasts with low cellular differentiation is observed in embryonal RMS. Fusion genes, SRF-FOXO1 and SRF-NCOA1 were discovered. SRF-fused RMS might be a new subtype based on histology and genomics. Vimentin, desmin, myoglobin, and muscle specific actin were strongly positive in alveolar type. Cytoplasmic positivity for desmin and nuclei positivity for myogenin were observed in embryonal RMS, along with positivity for MyoD1. Desmin, myogenin and MyoD1 positivity was observed in spindle cell type. Well-differentiated RMS, with specific translocations of the SRF gene, expressed desmin and heterogeneous staining for myogenin and myoD1 in a diffuse manner leading to a finding that no immunomarker is specific in any subtype of RMS (Table 1).

Discussion

Annual incidence of 4 to 7 million children 15 years of age or younger and a male predominance are characteristics of RMS. Myogenic transcriptional regulators include Myogenin and MyoD1 which are expressed earlier in skeletal muscle differentiation followed by desmin and myogenin. Ablative surgery, moulage technique with after loading brachytherapy and reconstructive surgery directed to the residual tumor after multiagent chemotherapy constitutes AMORE protocol. Patients' survival depends upon early diagnosis and management. Nasal obstruction, rhinorrhea, or recurrent otitis media forms the clinical scenario. Detection of sinonasal masses and delineation of the extent of the disease can be done by computed tomography and magnetic resonance imaging. Diagnosis can be confirmed by fiberoptic endoscopy and biopsy. Positive immunostains for desmin and myogenin and with negative staining for cytokeratin, epithelial membrane antigen, CD45, CD99, and S-100 are seen in RMS. Myogenin also stains ARMS. ARMS exhibits t(2;13) (q35;q14) translocation. Most common type of head and neck RMS is ERMS. Postoperative disfiguration, the high likelihood of leaving behind residual tumor, and the difficulty in excising any intracranial extension of the tumor are the postoperative complications. Origin from immature striated muscle dates to RMS which is one of the small round blue cell tumors of childhood mimicking neuroblastoma, Ewing's sarcoma, and lymphoma. Primitive spindle cells, often with a myxoid background are seen in ERMS associated with loss of heterozygosity at the 11p15 locus. Transcription factors that are physiologically expressed in the nuclei of striated muscular cells during embryonal and fetal development are MyoD1 and myogenin which are products of MYF3 and MYF4. Gross total tumor excision without distant disease, smaller tumor size (4-5 cm), younger age (4-10 years) and embryonal histology are favorable factors [9-13]. Facial asymmetry, enamel defects, bony hypoplasia, trismus, velopharyngeal insufficiency, tooth and root agenesis, malformed or missing teeth, microdontia, maxillary and mandibular hypoplasia, disturbance in root development, poor tooth development, root stunting and xerostomia were the oral manifestations observed. Anatomical site, classification, histopathology, immunohistochemistry, clinicopathological correlation and molecular insight are described in this systematic review. The most common soft tissue sarcoma in pediatric population is rhabdomyosarcoma. Meningeal or parameningeal are two types in

Table 1: Summary.

Author	Type	Location	Age	Gender	Year	Immunohistochemistry
Mariana P Rodríguez-Vargas, Francisco G Villanueva-Sánchez	ERMS	mandible, maxilla, mastoid conjunctiva	1-13 years	Males	2022	vimentin, desmin, myoglobin, and muscle specific actin, myogenin, MYO D1
Joanna Radzikowska, Wojciech Kukwa, Andrzej Kukwa, Anna M. Czarnecka, Maciej Kawecki, Fei Lian, Cezary Szczylik and Antoni Krzesk	ARMS	parameningeal	2-13 years	Males	2016	-
Cléverton Roberto de ANDRADE Ademar Takahama JUNIOR Inês Nobuko NISHIMOTO Luiz Paulo KOWALSKI Márcio Ajudarte LOPES	ERMS	Parameningeal orbit	14.3 years	-	2010	vimentin, desmin, myogenin, MyoD1, AE1/AE3, p53, PCNA, Ki67, C-erbB2, FAS and CDK4.
Atif Ali Ahmed, MD, and Maria Tsokos	SINONASAL	Ethmoid, frontal, maxillary	9-11 years	Females	2007	desmin and myogenin
Charhi H, Mansouri N, Harmouch A, Kili A, El Khorassani M, El Khattab M, Maher M, Sefiani S	ERMS	Orbit, cheek, maxilla, asopharynx	5.39 years	Males	2011	desmin, smooth muscle actin and myogenin
Eleanor Chen, Robert Ricciotti, Neal Futran, Dolphine Oda	ARMS	Maxillary sinus, cheek, alveolar ridge, palate	-	-	-	-
Ludimila Lemes Mour, Beatriz Della Terra Mouco Garrido, Nelson Leonel Del Hierro Polanco, Mattheus Augusto Siscotto Tobia, Viviane da Silva Siqueira, Cassia Maria Fischer Rubira, Paulo Sérgio da Silva Santos	SPINDLE CELL/SCLEROSING	Head and neck	-	-	-	-

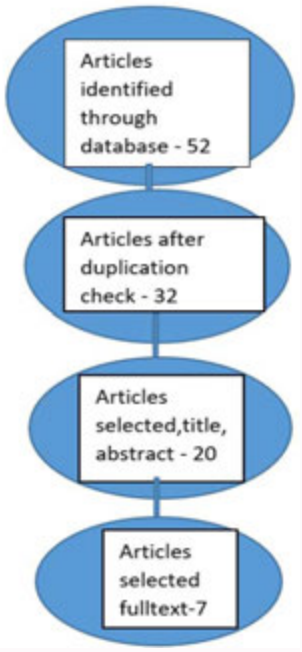

Figure 1: PRISMA flowchart.

head and neck RMS. The anatomical location in the head and neck region can be either parameningeal (nasopharynx, nasal cavities, paranasal sinuses, infratemporal and pterygopalatine fossae, and middle ear) or non-parameningeal. Prognosis and choice and course of treatment are decided by the anatomical location. In general, parameningeal RMS commonly presents with advanced disease and poor prognosis are observed in parameningeal type. Embryonal and alveolar are two main types of RMS. In younger children embryonal RMS is seen. In older children and adolescents, alveolar type is seen. Embryonal RMS affects the head and neck. Variable differentiated rhabdomyoblasts within loose, myxoid mesenchyme, with alternating areas of dense and loose cellularity are seen in embryonal RMS. ARMS is highly cellular and composed of primitive round cells with scant cytoplasm, hyperchromatic nuclei, fibrovascular septa, central loss of cellular cohesion and irregular alveolar spaces. Pale eosinophilic cytoplasm and blunted, ovoid fusiform, centrally located nuclei with small inconspicuous nucleoli are observed in spindle neoplastic cells. Histological classification includes embryonal rhabdomyosarcoma, with botryoid and anaplastic subtypes and alveolar rhabdomyosarcoma with solid variant. Myogenin stains >50% of tumor cell nuclei in alveolar RMS. 10% to 90% of tumor cells nuclei display variable myogenin stain in embryonal RMS. Strong nuclear MYOD1 staining is seen in spindle cell/sclerosing rhabdomyosarcoma [14-20]. Alveolar RMS exhibit vimentin, desmin, myoglobin and muscle specific actin. Embryonal rhabdomyosarcoma display nuclei positivity for myogenin and cytoplasmic positivity for desmin. Mutations in MYOD1, VGLL2, NCOA2, DCTN1::ALK fusion, joining exon 26 of the DCTN1 gene and exon 20 of the ALK gene, VGLL2 gene rearrangement, VGLL-2-related fusions, TFCP2 rearrangement or MEIS-NCOA2 fusion or CITED2 are found in pediatric population. mostly seen in adolescents and young adult patients myogenin, desmin, and MyoD1 are vital immunohistochemical markers for RMS. Positivity for myogenin >50% is seen in ARMS nuclei. Detection of the PAX3/PAX7-FOXO1 fusion gene is done by Fluorescence *in situ* Hybridization in case of ARMS. Nuclear HMGA2 positivity and relatively weak staining for AP2-beta is seen in ERMS. HMGA2 and EGFR positivity also seen. Positivity for EGFR is also evident. and negative staining for P-Cadherin [21-23]. COG for ARMS confirmation diagnosis uses and recognizes strong diffuse nuclear AP2-beta staining, with weak to absent HMGA2 staining is observed in confirmation of ARMS. Tumor behavior, prognosis, or plan of treatment is decided by the histology and immunohistochemical marker [24-27]. It should also be noted that it has been possible to identify an increasing variety of molecular anomalies in this type of sarcomas with the use of molecular techniques has enable us to identify various anomalies among the sarcomas. In our study, out of seven articles, only five articles had full details regarding rhabdomyosarcoma in relation to

head and neck region of pediatric population. Out of 52 articles, 32 were sent for duplication, resulting in prefinal 20 articles which had final output of seven articles.

Conclusion

Most common soft tissue sarcoma in children is Rhabdomyosarcoma. Epidemiological, histological and immunohistochemical aspects of head and neck RMS in children has been described. Survival for children with this malignancy has improved as a result of multiple factors, including better imaging and pathologic classification, use of multi-agent chemotherapy and use of appropriate radiotherapy especially in parameningeal primaries are the factors involved in quality of life and survival of pediatric population with RMS.

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