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Review Article

Pediatric soft tissue tumors of head and neck – An update and review

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ABSTRACT

Pediatric malignancies especially sarcomas are the most common and predominant cause of mortality in children. Such ongoing efforts are crucial to better understand the etiology of childhood cancers, get better the survival rate for malignancies with a poor prognosis, and maximize the quality of life for survivors. In this review article we authors aim to discuss relatively common benign and malignant connective tissue tumors (soft tissue tumor), focusing on current management strategies and new developments, as they relate to the role of the otolaryngologist– head and neck surgeon. Other rarer paediatric head and neck tumors beyond the scope of this review

1. Introduction

Pediatric cancers differ from the adult malignancies in both prognosis and distribution by histology and tumor site. The incidence pattern in adults the cancer rates tend to increase rapidly with increasing age unlike in children. In children relatively wide age range exists, with two peaks – the first in early childhood and the second in adolescence.[1]

Most of the pediatric tumors of maxillofacial region are benign, hemangioma being the most common benign tumor of infancy and childhood.[2] Although childhood cancer is relatively uncommon, it remains a significant cause of mortality in this population and is second only to accidents as a cause of death in children over 5 years of age. Data from the United States National Cancer Institute database suggest that the head and neck are involved in 12% of all childhood malignancies.[3] In literature, neoplasms of the head and neck region account for approximately 5% of all childhood malignancies.[4]

Ionising radiations, genetic factors, rays, chemotherapeutic agents, family history, infections, immuno deficiencies and congenital anomalies are the most commonly involved risk factors for these paediatric cancers. Even though many genetic conditions are associated with increased risks for childhood cancer, but they are thought to occur in only less than 5% of the conditions. Extremely small fraction of paediatric cancer is to arise due to environmental exposures compared to adult epithelial tumor.[1]

Curative therapy with chemotherapy, radiation and surgery may unfavourably affect a child's development & result in serious long term medical & psycho social effects in both childhood & adulthood. Probable undesirable delayed side effects include subsequent malignancy, early mortality infertility, reduced stature, cardiomyopathy, osteoporosis, pulmonary fibrosis, neurocognitive impairment affective mood disorders & altered social functioning. The core objective in this matter is to enhance the survival rate of a lot of children with cancer by coordinated participation and research trials.[1]

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Most common Paediatric tumors of head and neck are as follows (Table 1)

Vascular anomalies are congenital errors in vascular development. They frequently involve the head, neck, and oral cavity. They are subdivided into vascular tumors (hemangioma) and vascular malformations.[5–7]

However, the factors that have not changed are the complexity of vascular anomalies and the importance of a multidisciplinary approach, or therapeutic center, for the treatment and long-term follow-up of these patients. Under the global heading of vascular anomalies, these lesions predominately occur within the head and neck and affect approximately one in 22 children.[5,7]

Hemangiomas are the most common soft tissue tumors of infancy occurring approximately 5 to 10 % of 1yr old infant. The risk of haemangioma is 3 to 5 times more in girls than boys. Hemangiomas can be present at birth but usually arise shortly after birth and grow rapidly during the first year of life, but in next five yrs. there is slowing of growth & involution by 10 to 15yr of age.[1]

In 1982, Mulliken & Glowacki defined haemangiomas as vascular tumors with a growth phase marked by endothelial proliferation & hypercellularity and involution phase.[8]

Haemangiomas originate from the reticular dermis or subcutaneous tissues and appear as bluish or relatively colourless masses (previously called cavernous haemangioma). Compound haemangiomas have superficial and deep components and were previously called capillary cavernous haemangiomas. Compound haemangiomas have superficial and deep components and were previously called capillary cavernous haemangiomas.[9]

Active intervention should be considered in all disfiguring haemangiomas, to prevent potential psychosocial trauma and cosmetic deformity. The first line drug of choice for the treatment of life or sight-threatening haemangiomas is prednisolone. The response rate varies from 30 to 90% and depends on the dose, duration and age at start of treatment. Steroids are useful only in the proliferative phase. Interferon are also been used, but because of their potentially serious side effects, it is suggested that they are used only in steroid-resistant life and sight-threatening lesions.[8]

lymphangioma is a congenital malformation of the lymphatic system, frequently found at birth, with 90% diagnosed before the age of 2 years. A sub-type of lymphangioma is called cystic hygroma. It is composed of large lymph-containing cysts.[10] More than 90% of lymphangiomas occurs in the cervical region. In the oral cavity most commonly it can arise in larynx, orbit, tongue, floor of the mouth, and the cheek region.[11] Lymphatic malformations have a tendency to grow with the age of the child and rarely regress. The symptoms and complications depend on the location of the lesion. The most life-threatening complication of lymphangioma is acute airway obstruction. Lymphangioma can be diagnosed clinically, but imagistic studies are important for the confirmation of the diagnosis.[12]

Prenatal ultrasound, MRI especially a fetal MRI are used to detect cystic hygroma and vascular malformations. Surgical excision is the usual treatment of lymphangioma.[13] Awareness of potential airway involvement and possible complications is necessary to provide a safe anaesthetic to a patient with lymphangioma. Anesthetic concerns include bleeding, difficulty visualizing the airway, extrinsic and intrinsic pressure on the airway causing distortion, and enlarged upper respiratory structures, including the lips, tongue, and epiglottis.[14] This aspect is very important when a child is undergoing serial extraction or any other surgeries under general anaesthesia.

Tumors of neurogenic origin are a small but significant portion of head and neck masses in children. Neurofibromas and schwannomas are the most common nerve sheath tumours of the peripheral nerves in the head and neck region.[15]

Plexiform neurofibromas are pathognomonic of NF1. These lesions usually occur in early childhood and precede cutaneous neurofibromas.[16] sudden and rapid enlargement of an existing neurofibroma should be considered a sign of malignant transformation, until proved otherwise. There is a 4% chance of transformation into a malignant peripheral nerve sheath tumour in NF-1.[17]

Neurofibromatosis type 1 (NF-1), also known as Von Recklinghausen's disease, is a multisystem genetic disorder, characterized by increased cell proliferation and tumor development. It affects 1 out of 3000 to 4000 live births. Characteristically the pigmented skin lesions (due to the focal melanosis in the epidermis), cafe au lait spots and freckling, are the hallmark features of NF1. These lesions may be present at birth or become obvious during the early years of life.[18]

Rhabdomyosarcoma (RMS) is an aggressive malignant skeletal muscle neoplasm arising from embryonal mesenchyme. In records it accounts for over 50% of all pediatric soft tissue sarcomas. The head and neck region is the most common site for this tumor in children.[19] The period between 1975 and 2002, it was found that the 5-year survival rate for rhabdomyosarcoma has increased from 53% to 65% for children younger than 15 years and from 30% to 47% for adolescents aged 15 to 19 years.[20] Horn and Enterline, subdivided rhabdomyosarcomas into botryoid, embryonal, alveolar, and pleomorphic subtypes depending on morphologic features, without the benefit of immunohistochemical or genetic confirmation.[21]

The advent of collective combined contemporary, multi-agent chemotherapy, radiotherapy, and surgery has made the five-year survival rate is approximately 85% for this RMS subtype.[22] For patients with embryonal tumors, high

birth weight and large size for gestational age are associated with an increased incidence of rhabdomyosarcoma.[23] Genetic conditions associated with rhabdomyosarcoma include Li-Fraumeni cancer susceptibility syndrome, neurofibromatosis type I, Beckwith-Wiedemann syndrome and Basal cell nevoid syndrome.[24]

The prognosis for a child or adolescent with rhabdomyosarcoma is associated to the age of the patient, site of origin, widest diameter of the tumor, resectability, presence of metastases, number of metastatic sites or tissues involved, presence or absence of regional lymph node involvement, histopathologic subtype (alveolar vs. embryonal), and delivery of radiation therapy in selected cases.[25–28] Children aged 1 to 9 years have the best prognosis, the prognosis worsens in younger and older patients. In recent Intergroup Rhabdomyosarcoma Study Group (IRSG) trials, 5-year failure-free survival (FFS) was 57% for patients younger than 1 year, 81% for patients aged 1 to 9 years, and 68% for patients older than 10 years. Five-year survival for these groups was 76%, 87%, and 76%, respectively.[29]In addition; infants younger than 1 year may be less likely to receive radiation therapy for local control, because of concern about the high incidence of complications in this age group.[30,31]

The embryonal subtype is the most frequently observed subtype in children, accounting for approximately 60% to 70% of rhabdomyosarcomas of childhood.[24] An increased frequency of this subtype is noted in adolescents and in patients with primary sites. Pleomorphic rhabdomyosarcoma affect all ages and are more common in adolescents and young adults. In adults, pleomorphic rhabdomyosarcoma is associated with a worse prognosis.[24]

The embryonal and alveolar histologies have distinctive molecular characteristics that have been used for diagnostic confirmation, and may be useful for assigning therapy and monitoring residual disease during treatment. Unique translocations between the FKHR gene on chromosome 13 and either the PAX3 gene on chromosome 2 or the PAX7 gene on chromosome 1 are found in 70% to 80% of patients with alveolar histology tumors. Translocations involving the PAX3 gene occur in approximately 59% of alveolar rhabdomyosarcoma cases, while the PAX7 gene appears to be involved in about 19% of cases.[32] Patients with metastatic rhabdomyosarcoma having the PAX7-FKHR fusion gene appear to have a substantially better prognosis than those with the PAX3-FKHR.[33] Embryonal tumors they tend to exhibit loss of allelic heterozygosity and abnormalities in parental imprinting. Loss of allelic heterozygosity particularly affects loci at chromosome 11p15, and consistent loss of genomic material from the chromosome 11p15 region in embryonal tumors has been observed.[24]

Even though RMS has shown marked improvement in survival over the past decades, in addition to a poor prognosis for patients over ten-years old, diagnostic delay can have a profoundly unfavorable impact on prognosis.

Table 1: Most commonPediatric tumors of head and neck

Soft tissue tumors in head and neck region in children
1. Fibrous tissue tumors
• Juvenile fibromatosis,desmoids tumors
2. Lipomatous tumor
• Lipoma
• Lipoblastoma(fetal lipoma)
3. Skeletal muscle tumors
• Rhabdomyosarcoma
4. Endothelial tumors of blood & lymph vessels
• Haemangiomas
• Vascular malformations
• Lymphangioma-cystic hygroma
5. Neural tumors
• Neurofibroma/Neurofibromatosis
• Neuroblastoma(malignant)
6.Cartilage & bone tumors
• Osteochondroma (exostosis)
• Multiple hereditary exostosis
• Enchondroma
• Chondroblastoma
• Chondromyloid fibroma
• Osteoid osteoma
• Osteoblastoma
• Fibromas (non ossifying fibroma, fibrous cortical defect)
• Unicameral bone cysts
• Aneurysmal bone cyst
• Fibrous dysplasia
• Eosinophilic granuloma
• Osteosarcoma
• Ewings sarcoma
7 .Miscellaneous
• Granular cell tumor of infancy
• PNET of infancy
• Histiocytosis

Fibrous dysplasia was first described by Lichtenstein in 1938 as a disorder characterized by progressive replacement of normal bone elements by fibrous tissue.

Fibrous dysplasia (FD) is a sporadic benign skeletal disorder that can affect one bone (monostotic form), or multiple bones (polyostotic form), and the latter may form part of the McCune-Albright syndrome (MAS) or of the Jaffe-Lichtenstein syndrome (JLS).[34]

Malignant transformation is rare, and is usually precipitated by radiation therapy.[35]Malignant degeneration occurs in less than 1% of cases of fibrous dysplasia. Malignancies are almost exclusively osteosarcoma Sudden increase in the level of alkaline phosphatise is one of the symptoms for malignant transformation and for that reason its amount should be periodically observed.[36]

Usually the prognosis is good although the bad outcomes occur more frequently among young patients or those with polyostotic forms of the disorder.[37]

The radiotherapy increased malignant transformations more than 400 times.[36]

Severity and extent of Gsα mutation-associated diseases are not related to the stage of embryogenesis when the mutation occurred, but rather are functions of survival of mutated cells within the clone during migration, growth and differentiation, and of the ratio of mutated to normal cells at the affected anatomical site.[38]

Gender prevalence of FD is equal. The monostotic form is more common and affects the 20 to 30 years age group: polyostotic FD has its onset mainly in children younger than 10 years of age.[39]

In fibrous dysplastic bone, the increased expression of cAMP by the mutated lesional cells is associated with abnormal osteoblast differentiation and formation of defective bone.[40]

However, after surgical reduction of fibrous dysplastic lesions, particularly in younger subjects and when the lesions are more immature, is high (50%) so a conservative surgical approach will often require more than one intervention to control the clinical signs and symptoms.[41]

Osteosarcoma is the most common primary malignant neoplasm of bone.[42,43] Osteosarcomas of the head and neck represent a small percentage of osteosarcomas with studies reporting occurrences of less than 10%.[44–46]Though compared to incidence of osteosarcomas of long bones, the number of craniofacial osteosarcomas is very low, the prevalence of jaw osteosarcoma is in fact 10 times greater than that of osteosarcoma in the total body skeleton, considering that jaws represent only 0.86% of total body volume.[47] The incidence of head and neck osteosarcomas is observed to be even more uncommon if only the pediatric patient population is examined (age<18 yrs), accounting for less than 1% of all head and neck malignant tumor.[34] Radiation therapy, hereditary retinoblastoma, Paget's disease of bone, a history of fibrous dysplasia, or trauma are some of the factors known to predispose to the development of osteosarcoma.[48–51]

Osteosarcoma of the head and neck, including osteosarcoma of the jaw, typically occurs after the second decade, in contrast to osteosarcoma of the long bones, which usually occurs in the first and second decades of life.[52,53] Although osteosarcoma can occur in different anatomic sites, in pediatric patients mandible is most commonly involved site followed by the maxilla/maxillary sinus, and other sinuses (sphenoid, ethmoid sinuses).[34] It has been hypothesized that because the mandible retains growth centers for more than 30 years, osteosarcomas of the head and neck could occur more commonly in this location.[54,55]

The classic radiologic appearance of long-bone osteosarcomas called as 'sunburst' appearance is not pathognomonic for jaw osteosarcomas. The radiologic appearance of jaw osteosarcomas depends on the interplay of three processes: bone formation and mineralization, bone destruction, and periosteal bone formation. Radiologically, the lesions may range from predominantly radiolucent to radio-opaque lesions depending on the degree of ossification.[56]

Histologically, osteosarcoma can be of different subtypes including conventional osteoblastic osteosarcoma, chondroblastic, fibroblastic, anaplastic, telangiectatic, giant-cell rich, and small cell osteosarcomas. The fibroblastic subtypes have the best response to chemotherapy and the chondroblastic subtypes have the worst response.[57] Osteogenic sarcomas, predominantly osteoblastic subtype, with one chondroblastic subtype has been reported in one of the study of 22 cases of head and neck osteosarcomas in pediatric population.[34]

Wide surgical excision and adjuvant treatment with radiotherapy and/or chemotherapy are the recommended treatment for osteosarcomas.[58] Diagnosis of tumor in its early stages and complete resection are the most important factors in increasing prognosis of jaw osteosarcoma.[59,60] Anatomical limitations in face cause some difficulties in achivement of uninvolved margins[61] and for this reason local recurrence of the lesion is high (33%-69% percent).[59,62] Mandibular osteosarcomas have a better prognosis than maxillary tumors because of easier resectability, and the ability to obtain negative surgical margins.[63] A poorer outcome for maxillary tumors is expected, related to the difficulty in obtaining adequate resection margins, leading to increased incidence of local recurrence, residual disease, and death.[64] Distant metastases have been reported in 10–20% of patients with HNOS, compared with 53–75% of patients with disease arising outside the head and neck.[65]

Ewing's family of tumours (Ewing tumour) includes Ewing's sarcoma of bone and soft tissues, primitive neuroectodermal tumours (PNET), Askin tumour and other less frequent neoplasms.[65] PNET and Ewing's sarcoma were initially regarded as distinct clinicopathological entities, but it has more recently been argued that they actually represent the same tumour type, diverging only by a higher degree of neural differentiation in PNETs. Considering both clinical and morphological evidence along with recent data provided by molecular genetics, Ewing's sarcoma and PNET most likely represent, respectively, the poorly and well-differentiated ends of a spectrum of round-cell sarcomas exhibiting a partial neuroectodermal phenotype, which can be collectively termed as Ewing's family of tumours.[66] Ewing's sarcoma/PNET is the second most frequent bone tumour in the paediatric age group after osteosarcoma. It accounts for 4-6% of primary malignant bone tumors, peaks in the second decade of life, slightly more common in males.[67,68] Ewing tumours of bone usually appear in the diaphysis of long tubular bones, the femur and tibia being the most frequent sites. About one-third of cases

appear in the axial skeleton, mainly in the pelvis and the ribs.[69]

Involvement of the head and neck in Ewing's Sarcoma is rare, accounting for approximately 1 to 4% of cases.[68,70] In the head and neck region, the mandible and skull base are the two most common primary sites,[68,71] followed by the orbit, and nasal cavity with or without the paranasal sinuses.[72] The maxilla is also reported as the most common site of presentation.[73] It is most commonly seen in second decade of life with the age of presentation ranging from 7.5 to 14 year[74] and also 5 months to 22 years.[75] The most common clinical presentation of this tumor is painful swelling.[73–75]

Histopathologiclly, the neoplastic lobules are composed of small round cells exhibiting round or ovoid vesicular nuclei, a distinct nuclear membrane, small nucleoli, finely granular chromatin and poorly defined, scanty cytoplasm. The mitotic activity tends to be quite variable. Necrosis is almost always present and can be extensive, sometimes leaving collars of viable tumour cells around the richly ramified capillary network.[76] There are usually extensive deposits of cytoplasmic glycogen; the PAS stain is positive in more than half of the tumours.[66] Histopathological assessment of tumour necrosis after therapy using various grading systems correlates with overall survival.[77]

Strong expression for CD99, a cell-surface glycoprotein (the product of the MIC2 antigen) has been observed for Ewings sarcoma which plays a key role in the differential diagnosis of round-cell sarcomas. CD99 is considered as a sensitive but non-specific marker for Ewing sarcoma.[53,63] Genetic analysis is important in the diagnosis of Ewing's sarcoma. The central karyotypic anomaly is a t(11;22) translocation, with other variants found in about 15% of cases: a t(21;22), a t(7;22) and a t(17;22) and t(2;22).[77–82] Because of t(11;22), fusion of the Ewing's sarcoma (EWS) gene that contains an RNA-binding domain with the transcription factor FLI1 (friend leukaemia virus integration site 1) on chromosome 11q24 belonging to the ETS (avian erythroblastosis virus transforming sequence) family occurs in the molecular level which leads to the oncogenic conversion of the EWS gene.[83] Antibodies to the Fli-1 gene product as a sensitive marker of Ewing's family of tumors has been studied.[84,85] ESW gene 'split apart' probes coupled with morphological findings can impove the diagnostic accuracy of ES/PNET.[66]

The multidisciplinary treatment including surgery, radiotherapy and chemotherapy is the ideal approach for the treatment of Ewing's sarcoma. Complete resection of Ewing's sarcoma of head and neck region is difficult to achieve because of the anatomic location and also the extension of tumor to adjacent structures.[86] Multimodality therapy consisting of an initial biopsy, aggressive combination chemotherapy and localized radiotherapy can be the treatment of choice for Ewing's sarcoma of the head and neck region and may result in long-term survival.[73] In lesions that are initially unresectable and/or show a poor response to chemotherapy, radiation is used for local control. A good prognosis can be expected if the disease has not metastasized.[74] Large tumors were found to be associated with poorer outcome than those with smaller tumors.[87] Tumor volume has been shown to be an important prognostic factor in Ewing's sarcoma. In Ewing's sarcoma of head and neck which are locally advanced and/or surgically irresectable, it is difficult to consider tumor size and volume.[75] The multimodality treatment surgery, radiotherapy and chemotherapy has significantly improved the 5-year survival ratio, now reaching 40% to 75%.[88] The most common location for metastases in ES is the lungs, followed by bones and the bone marrow. The presence of metastasis is the main adverse prognostic factor and is associated with significantly worse relapse-free survival and only about 20% long term survivors.[75] Radical radiotherapy in the pediatric age group can lead to other complications in the pediatric patients. The use of high doses of radiation for tumors in the head and neck region may produce functional squeal and local complications, including fibrosis, contractures, anklyosis of the temporomandibular joint and also secondary malignancy. Combining surgery and postoperative radiotherapy can expose the patients to the sequel of both treatments.[75]

2. Conclusion

Very limited information is available about the clinical behavior and management of soft tissue tumors of the head and neck in children as most series describe pediatric and adult patients together. To better understand the natural history, clinical course of these tumors and to establish management recommendations for children, more case reports and case series are required in this field.

3. Authors contribution and declaration

We hereby declare that all the authors have contributed sufficiently in the intellectual content, conception, planning and designing the work and interpretation of the data (when applicable) and construction of the manuscript.

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None.

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