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CLINICAL PROFILE AND MANAGEMENT OF RHABDOMYOSARCOMA: AN UPDATE

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ABSTRACT Rhabdomyosarcoma is a malignant tumor of striated muscle origin and is the most common soft tissue sarcoma in children. It may occur in several sites like head and neck region, genitor-urinary tract and extremities. A multimodality approach with surgical excision, chemotherapy and radiotherapy is the frontline therapy for rhabdomyosarcoma. This review summarizes the clinical features and management of rhabdomyosarcoma in detail.

KEYWORDS : rhabdomyosarcoma presentation, surgical excision, radiotherapy

INTRODUCTION

Rhabdomyosarcoma is a malignant primitive mesenchymal tumor which consists of cells having histologic features of striated muscles in various stages of embryogenesis (1). It is the commonest soft tissue sarcoma and third most common extracranial solid tumor of children after Wilm's tumor and neuroblastoma (2). It can appear in a variety of forms in several sites in the body from head and neck to extremities making it a diagnostic challenge. It has been associated with large number of morbidity and mortality in the past, but recent advances in the diagnostic and therapeutic techniques have now resulted in better prognosis with more than 70% overall five-year survival (3). Multi-modality treatment approach including surgery, chemotherapy and radiotherapy is now the treatment of choice for rhabdomyosarcoma (4). This review aims to summarize the varied clinical presentations and the diagnostic and management strategies for rhabdomyosarcoma.

Epidemiology

Rhabdomyosarcoma consists of 4.5% of all cancers prevalent in the pediatric age group and 20% of malignant soft tissue carcinomas (5). On the other hand, only 1% of the adult malignancies are constituted by soft tissue sarcomas and rhabdomyosarcomas accounts for 3% of these sarcomas (6). The age distribution shows bimodal peak i.e. between 2-6 years and then between 10 to 18 years of age and has slight male predilection with male to female ratio of 1.3:1 (7). Most of the RMS cases occur sporadically, but may be associated with familial syndromes like neurofibromatosis I and Li-Fraumeni syndrome (8).

Pathology

Rhabdomyosarcomas are a part of small, round, blue-cell tumors of childhood (9). There are two types of rhabdomyosacrcoma on the basis of histopathology, namely embyonal (most common) and alveolar. The embryonal form is the most common form occuring in younger population specifically in the head and neck and genitor-urinary regions. It is characterized by spindle shaped cells, rich in stroma. The embryonal variant is further sub divide into botyroid and leiomyomatous forms. The alveolar form occurs in the older populations typically in the trunk and extremities. It is characterized by small, round cells aggregating along reminiscent spaces of pulmonary alveoli (10). The pathogenesis is unclear but disruption of skeletal muscle progenitor cell growth and differentiation is thought to play a role. MET-proto oncogene and macrophage migration inhibitory factor (MIF) and P53 are associated with tumor progression (11). Loss of heterozygosity at 11p15 locus is found in embryonal type of rhabdomyosarcomas. A characteristic translocation is found between long arm of chromosome 2 and 13, t(2;13)(q35;q14) in alveolar RMS. Increased expression of insulin growth factor II has been associated with both embryonal and alveolar types (12).

Clinical features

The presentation of this tumor is variable and depends on the site of origin, age and presence of metastasis. A patient with rhabdomyosarcoma usually presents in the outpatient department as an asymptomatic submucosal mass with or without the signs and symptoms resulting from the mass effect due to the growth of the tumor (2).

Rhabdomyosarcma may occur anywhere in the head and neck region (36%), genitor-urinary organs (24%) or the extremities (19%). Most of head and neck rhabdomyosarcomas occur in the parameningeal sites (16%) followed by orbit (10%) and 25% occur in other locations like scalp, face oropharynx larynx and neck (13). In children, head and neck are the most common sites while the incidence is lower in adults.

Orbital rhabdomyosarcomas may occur in the orbit, conjunctiva, eyelid and uveal tract. They commonly present with proptosis with or without ophthalmoplegia (14). Parameningeal ones may occur in the nasopharynx, nasal cavities, infratemporal fossa, pterygopalatine fossa, and middle ear. They often present with nasal, aural or sinus obstruction and mucopurulent discharge may be present (15). In the genitor-urinary tract, prostate and bladder are the commonest sites of origin. Tumors of the bladder often present as hematuria and urinary obstruction while, prostate tumors present as large pelvic masses resulting in urinary frequency and constipation due to mass effect on the bladder and intestines. Vaginal tumors seen in young children may present as blood stained discharge. Cervical and uterine tumors, on the other hand, are reported in older girls. In males, paratesticular tumors may have a presentation of inguinal or scrotal swelling in pre pr post pubertal age (16).

The third commonest site, the extremities are usually present with painful swelling with erythema of the overlying skin, usually in patients of the adolescent age group (17). Rhabdomyosarcoma in the trunk, perineal or perianal region, biliary tract is less commonly reported. Metastasis is most commonly found in the lungs followed by bone, bone marrow and lymph nodes (18).

Facial pain, sinonasal congestion and ear pain are some of the early signs which may lead to a false diagnosis of benign pathological conditions and may be overlooked (19). A study conducted in United States showed that a majority of the rhabdomyosarcoma patients presented with cranial nerve deficits at presentation depicting an advanced stage of the disease at the time of diagnosis (20).

Investigations

Apart from the standard hematological tests i.e. complete blood picture, liver and kidney function tests, electrolytes and urinanalysis, imaging studies like CT-scan and MRI are indicated. For metastatic disease, bone marrow aspiration, lumbar puncture for cerebrospinal fluid analysis, bone scan, and CT scan of brain lungs and liver, are required. CT scan finds its role in evaluation of bone erosion and abdominal adenopathy while MRI gives better definition of the primary tumor and the soft tissues surrounding it (2). Various studies suggest evaluating regional adenopathy, occult metastasis and persistent viable disease or recurrence may be improved with PET/CT compared to conventional imaging techniques (21). Clinical and radiological evaluation of regional and distant lymph nodes should also be done.

Treatment

Pre treatment clinical staging is of prime importance as the choice of therapy and prognosis of the disease depend on the degree to which tumor spread has occurred beyond the primary site. It is based on site and size of the primary tumor, the degree of invasion, nodal status and

presence or absence of metastases as shown in table 1 (22). A multimodal approach involving local control of the disease with surgery chemotherapy and radiotherapy is required.

Table 1: TNM staging

Stage 1
Tumor presents in a region with favorable prognosis
Tumor can be of any size, can show local invasion to nearby areas and/or spread to regional lymph nodes
Tumor should have distant spread
Stage 2
Tumor presents in a region with unfavorable prognosis
Tumor should be 5cm or smaller with no evidence of local invasion to nearby areas and/or spread to regional lymph nodes distant parts of body
Stage 3
Tumor presents in a region with unfavorable prognosis
Add one of the following: tumor is 5cm or smaller but has spread to nearby lymph nodes, tumor is larger than 5cm with/without spread to regional lymph nodes; in either case, cancer has not shown metastatic spread
Stage 4
Tumor may have started anywhere in the body and is of any size
Tumor shows metastatic spread

Surgery

Surgical resection is the key aspect and the main prognostic factor in the treatment. In a patient with suspected rhabdomyosarcoma, the primary resection is an important determinant of the outcome and therefore complete removal of the tumor mass with surrounding normal tissue should be done initially. Atleast 0.5 cm margins should be taken circumferentially. In situations where complete resection is not possible initial biopsy followed by neoadjuvant chemotherapy should be performed (10).

Chemotherapy

Rhabdomyosarcoma patients must be started on chemotherapy based on risk grouping. Vincristine, actinomycin-D and cyclophosphamide are the common drugs used in standard chemotherapy (23). Newer therapies include ifosfamide, vincristine and actinomycin-D (24).

Radiotherapy

Radiotherapy is used in rhabdomyosarcoma to improve the outcome and local control. In cases of head and neck or pelvic rhabdomyos arcoma complete surgical removal is quiet often not possible and this is when radiation plays an important role in the treatment. It is primarily given in group II patients (those having microscopic disease) and group III patients i.e. those with gross residual disease (25, 26).

Newer methods like intensity modulated radiotherapy (IMRT) and proton beam therapy may reduce risk of longterm sequelae compared to conventional three-dimensional conformal radiotherapy (27).

Prognosis

The prognosis of rhabdomyosarcoma depends on several factors like age of the patient, location and pathological characteristics of tumor. It has been observed that adult patients have poorer prognosis compared to children. Children with metastatic disease have poor survival rates, usually less than 25% (22).

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