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Scrotal Swelling: Case of Paediatric Rhabdomyosarcoma

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ABSTRACT
Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and represents a high-grade neoplasm of skeletal myoblast-like cells. A lot of research over years has improved our understanding of the disease. There are two major subtypes of RMS, based on the pathology image and are characterised by their own features and prognosis. Early diagnosis of the disease, its staging and treatment helps in preventing morbidity and mortality. ionizing radiation, or both. This article presents a case of RMS in a young boy and helps us to understand the disease. Whenever we come across any paediatric patient with unusual scrotal swelling, appropriate investigations should be done keeping in mind the probability of RMS. We also outline potential opportunities to further translate new biological insights into improved clinical outcomes.

INTRODUCTION

Soft tissue sarcoma accounts for ~7% of cancers in children and 1% of cancers in adults[1]. Rhabdomyosarcoma is most common soft tissue sarcoma of childhood. It is associated with high morbidity and mortality. Approximately half of the population of pediatric patients with soft tissue sarcoma have rhabdomyosarcoma (RMS), which is a high-grade, malignant neoplasm in which cancer cells have a propensity for myogenic differentiation. RMS can occur in different parts of body but most commonly affected areas are the head and neck region and the genitourinary tract. It is associated with high morbidity and mortality. In the last many years a lot of research and clinical trials have been carried out for the study of RMS and this has resulted in dramatic improvement in survival of many children[2-7]. The World Health Organization (WHO) also recognizes two rarer RMS subtypes. Pleomorphic RMS is a morphological variant of RMS that typically occurs in adults[8]. Like ERMS, unifying molecular genetic aberrations in pleomorphic RMS are not yet clear. In children, a spindle cell/sclerosing RMS variant is seen; those tumors arising in the head/neck region seem to be more likely to carry specific somatic mutations and have a poorer prognosis[8]. Despite many advances, the chance of cure for children with widely-metastatic and recurrent disease remains very low. Moreover, patients experience months of intensive, multifaceted therapies that can bring life-threatening acute toxicities and, in some cases, life-changing late effects.

CASE REPORT

A 14 year old boy presented in surgical OPD with complaints of Right Scrotal swelling since last 4 years. The swelling had gradually increased in size over by 6 cms size right scrotal swelling which was firm in consistency, nontenderand cough impulse was negative. The swelling was not separately palpable from the testis. The other side scrotum and both inguinal regions were normal. The patient was investigated with all routine blood parameters and an Ultrasound of scrotum with last 3-4 years. Patient had history of mild discomfort in view of the swelling. There was no history of any trauma or fever. There was no other significant history. On examination there was an 8 by 6 cms size swelling in inguinal region. The blood reports were normal, the USG showed minimal hydrocele on the right side with a testicular swelling. Depending on the investigations and the symptoms patient was posted for scrotal exploration. Intraoperative the swelling was arising from the right testis and involving the testicular tissue. The hydrocele fluid was drained and Excision of the right testis along with the growth was done. Wash was given with betadine and saline and incision was closed. Scrotal support bandage was given. The postoperative curse was uneventful and patient was discharged on the 3rd postoperative day. The suture removal was done on the 8th postoperative day. The histopathology of the specimen turned out to be Embroyanal Rhabadomyosarcoma. The patient was counselled regarding the same and Ctscan of Abdomen was done which was normal showing only thickened spermatic cord. The blocks were sent for Immunohistochemistry and patient was referred to Tata hospital for further management.

Patient was reviewed at Tata hospital and was advised Chemotherapy for further treatment.

CASE DISCUSSION

Sarcomas are rare type of tumours that develop in the supporting tissues of body such as bone, muscle or cartilage. Rhabdomyosarcoma is the most common soft tissue tumour occurring in children. RMS can occur in different parts of body but most commonly affected areas are the head and neck region and the genitourinary tract. The aetiology for the disease as per the studies carried out point out to Genetic and Environmental factors.

Genetic factors: The disease is associated with various syndromes due to autosomal dominant or recessive traits.

Li-fraumeni syndrome: LFS is a cancer predisposition syndrome with an autosomal dominant inheritance pattern that is associated with deleterious germline mutations (pathogenic variants) in the TP53 gene. These variants are reported to either inactivate the tumor suppression activity of TP53 or have a dominant negative impact[9].

Costello syndrome: (CS) CS is a rare, developmental disorder and cancer predisposition syndrome that is caused by heterozygous activating mutations in HRAS. CS is one of many conditions, including Noonan syndrome and neurofibromatosis type 1, that result in the overactivation of the Ras pathway and are often referred to as RASopathies[10].

Neurofibromatosis type 1 (NF!): NF1 is an autosomal dominant syndrome associated with inactivating mutations in NF1, a gene whose product is involved in the Ras pathway. NF1 includes multiple different features, including café au lait spots, benign tumors in nervous tissues (neurofibromas), optic gliomas and learning disabilities (Table 1)[11].

Noonan syndrome (NS): NS is another autosomal dominant syndrome that is caused by defects in several genes in the Ras pathway, including KRAS,

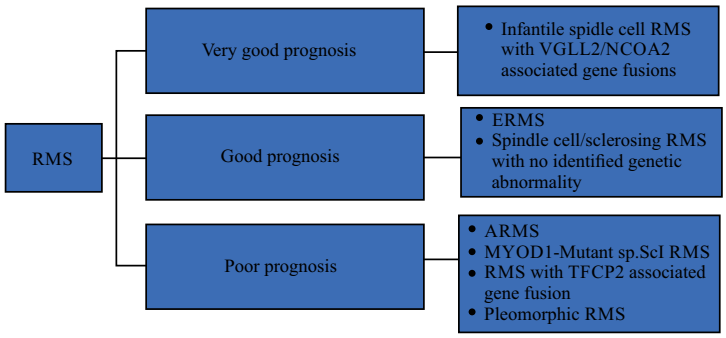

Fig. 1: Classification of RMS on basis of prognosis

Table 1: Heritable syndromes associated with an increased risk of RMS

Syndrome	Phenotypes	Associated genes
Li-fraumeni	Cancer susceptibility syndrome	TP53
Neurofibromatosis type 1	Systemic effects	NF1
DICER1	Cancer susceptibility syndrome	DICER1
Costello	Systemic effects	HRAS

NRAS, RAF1, BRAF, PTPN11, SOS1, SHOC2, or MEK1, which result in Ras pathway activation. Individuals with NS can display developmental delay, intellectual disabilities, distinctive facial features and congenital heart defects[12].

Environmental factors: Some reports have evaluated the role of parental exposures on the risk of RMS in the offspring. These exposures include recreational drug use, prenatal diagnostic radiation and various occupational exposures[13-17].

Classification: ERMS is a rare and highly malignant tumor. It is a soft tissue tumor that recapitulates the phenotypic and biological features of embryonic skeletal muscle. RMS is classified into 3 types Embryonal, Alveolar and Undifferentiated (Fig. 1).

- **Embryonal rhabdomyosarcoma:** (ERMS) is the most common subtype. The annual incidence of cases is 4.5 cases per 1 million children It is the most common subtype with children less than 5 years of age being most commonly affected. They are more common in males than females with a ratio of 1.4:1[18]. The tumours occur in equal proportion in the head and neck and the genitourinary system. Common locations in the genitourinary tract include the urinary bladder, prostate, vulva / vagina, cervix and paratesticular soft tissues[18,19]. Besides these two general regions, ERMS occur in the biliary tract, retroperitoneum, pelvis, perineum and abdomen and have been reported in various visceral organs, such as the liver, kidney, heart and lungs. The botryoid variant of ERMS arises beneath a mucosal epithelial surface, limiting it to organs such as the urinary bladder, biliary tract, vulva/vagina, cervix, pharynx, conjunctiva, or auditory canal. Botryoid tumors have a characteristic polypoid appearance with clusters of small, sessile or pedunculated nodules that abut an epithelial surface
- **Alveolar rhabdomyosarcoma (ARMS):** It is a cellular malignant neoplasm composed of a monomorphous population of primitive cells with round nuclei and features of arrested myogenesis. ARMS occur at all ages, more often in adolescents and young adults than in younger children. The median ages of occurrence is between 6.8 and 9.0 years. They occur less frequently than ERMS and comprise about 20% of all pediatric RMS. The male: Female ratio is approximately even and no geographic or racial predilection is reported. Alveolar rhabdomyosarcomas commonly arise in the extremities. Additional sites of involvement include the paraspinal and the perineal regions and the paranasal sinuses. Clinically, ARMS typically present as rapidly growing extremity masses. Tumors at other sites such as paranasal, perirectal and paraspinal mainly cause symptoms of compression of the surrounding structures. ARMS tend to be high stage lesions at presentation and form expansile, rapidly growing soft tissue tumors
- **Pleomorphic:** It is high grade sarcoma occurring in adults with round and spindle cells which display evidence of skeletal muscle differentiation with no evidence of embryonal or alveolar component. These lesions are more common in men and present at a median age in the 6th to 7th decade. These tumors usually occur in the deep soft tissues of the lower extremities but have been reported in a wide variety of other locations[20]. Clinically, most patients present with a rapidly-growing painful swelling. Tumors are usually large (5-15 cm), well circumscribed and often surrounded by a pseudocapsule. The cut surface is

tan and fleshy with variable hemorrhage and necrosis. Morphologically, these are pleomorphic sarcomas composed of undifferentiated round to spindle cells and an admixture of polygonal cells with densely eosinophilic cytoplasm in spindle, tadpole and racquet-like contours[21]. Genetically, PRMS show a complex karyotype with copy number alterations and unbalanced structural alterationsThe prognosis for these tumors is poor. The overall prognosis in the literature for PRMS is poor, with survival rates of 12.5 to 50% of 1-year to 20-month disease-free survival[22,23]

- **Spindle cell/sclerosing rhabdomyosarcoma (SpRMS):** SpRMS can occur as painless masses or can have symptoms due to compression. Grossly they are usually well circumscribed with sections showing a grey white whorled cut surface. Microscopically, Sp RMS can show a varying morphology. Some tumors show a bland spindle cell proliferation, with eosinophilic, fibrillary cytoplasm, resembling true smooth muscle differentiation. The cells are typically arranged in intersecting long fascicles, reminiscent of the "herring bone" pattern of adult-type fibrosarcoma. Some sclerotic areas may mimic osteosarcoma. Immunohistochemically, SpRMS show diffuse positivity for desmin. Myogenin usually shows rare focal positivity with some cases being negative. MyoD1 stain is positive in the tumor cells. Recently, some authors have suggested a higher incidence in adults than initially recognized, although the overall number of cases described is low[21]. Rhabdomyosarcomas have a propensity to metastasize and the common sites of metastasis are Lungs, Bone marrow and Lymph nodes[24-26]

Presentation: The presentation of patient depends upon the location and the size of the tumour. Initially patient may present with single lump which may be asympomatic. In case of RMS of the urogenital tract patient may have bleeding per urethra or frequency of micturation and sometimes a scrotal swelling. RMS of bladder or prostate can make it hard to urinate and show blood. RMS in genital area can present with painless scrotal swelling, in case of females can present with painless lump with a bloody smelling discharge A tumour near the eye may present with bulging eye or trouble with vision. If the tumour is near the ear then patient may have ear pain, headache or sinus congestion. Incase of abdominal system patient will have nausea/vomiting with abdominal pain. Besides these generalised symptoms of anorexia, weakness and weight loss will be present.

Diagnosis: Diagnosis preoperatively is difficult incases of genital RMS as patient generally present with Scrotal or vaginal swelling which is mistakenly considered to be benign as any other symptoms are absent. Imaging modalities like CT Scan, MRI of the affected system is done to look for the lesions. Surgical Excision biopsy of the swelling helps us to confirm the diagnosis. Depending upon the histopathology report additional Immunohistochemistry tests can be done to classify the tumour and help us to grade the tumour. Similarly MRI, PET scan help us to grade the tumour with respect to the locoregional spread and planning the treatment.

Treatment: Once the diagnosis is made a proper workup is required to grade the tumour and to know the stage. Besides the routine biochemical parameters, imaging studies like CT Scan, MRI help us in knowing the stage of disease. Various other investigations like Bone scan, PET Scan, Bone marrow aspiration will help us in ruling out the metastasis. As per the staging treatment options include Chemotherapy and Radiotherapy besides Surgery.

The two staging systems utilized in the management of rhabdomyosarcoma are the TNM (tumour, nodes and metastasis) staging system and the clinical grouping (CG) system. The TNM and CG staging systems complement each other and are used to assess prognosis and select treatment for patients with rhabdomyosarcoma. The rhabdomyosarcoma prognostic stratification classifies patients based on the above staging systems as low, intermediate, or high risk. The risk stratification is based on the clinical group, site, size, age, histology, metastases and lymph node status[27-29].

The Clinical Grouping of rhabdomyosarcoma is as follows:

Confined to the site of origin:

- Localized tumour, anatomically confined to the site of origin, the tumour can be completely resected
- Localized tumour, infiltrating locally into the adjacent structure, the tumour can be completely surgically resected

Local infiltration:

- Localized tumour, gross total resection is possible; however, microscopic residual disease is possible.
- Locally extensive tumour (may have spread to regional lymph nodes); however, complete surgical resection is possible
- Locally extensive tumour (may have spread to regional lymph nodes), the tumor can be completely surgically resected; however, microscopic residual disease is possible

Localized extensive tumour:

- Localized extensive tumour, gross residual disease after biopsy only
- Localized extensive tumour, gross residual disease is possible after major resection (greater than or equal to 50% tumor debulking)

Metastatic rhabdomyosarcoma:

- Any size primary tumor, with or without regional lymph node involvement, with distant metastases.
- The TNM Staging: This system classifies the tumour into 4 stages depending upon the tumor size, local spread and metastasis:

- **Stage 1:**
  - The tumor presents in a region with favorable prognosis
  - The tumor can be any size and can show local invasion to nearby areas and/or spread to regional lymph nodes
  - The tumor should have distant spread.

- **Stage 2:**
  - The tumour presents in a region with unfavorable prognosis
  - The tumor should be 5 cm or smaller with no evidence local invasion to nearby areas and/or spread to regional lymph nodes or distant parts of the body.
- **Stage 3:**
  - The tumor presents in a region with unfavorable prognosis
  - And one of the following: The tumor is 5 cm or smaller but has spread to nearby lymph nodes. The tumor is larger than 5 cm and with/without spread to regional lymph nodes, in either case, the cancer has not shown metastatic spread
- **Stage 4:**
  - The tumor may have started anywhere in the body and is of any size
  - The tumor shows metastatic spread
  - Once the staging of tumour is done we can plan for the treatment modality. The options available are the Surgical treatment, Chemotherapy and Radiotherapy. Newer techniques like the Molecular therapy and the Gene therapy are also tried

Surgery: Most of the times Surgical excision is done to reach to the diagnosis. Surgical excision is a Wide Local Excision to remove with a margin of normal tissue. As per the staging a Completion surgery may be required to do Radical Resection to remove the surrounding tissue.

In case of Genital RMS surgical excision is followed by Retroperitoneal Lymph node dissection (RPLND) to completely remove the affected tissue. A local therapy is rarely curative and early studies adding a systemic therapy improved survival from 10-30% to greater than 70%[30].

Chemotherapy: Multi-drug chemotherapy regimens significantly improved the outcome in patients with localized RMS, although no marked improvement has been observed in patients with metastatic RMS. The primary limitation has been an inability to improve significantly upon standard chemotherapy of VAC. Standard chemotherapy regimens for RMS The drugs to be used in Chemotherapy and the number of cycles depend upon the type of tumour and the general condition of the patient. For children in the low-risk group, the main combinations of drugs used are vincristine and dactinomycin (VA) or vincristine, dactinomycin and cyclophosphamide (VAC). For the intermediate-risk group, the most common regimens are vincristine, dactinomycin and cyclophosphamide (VAC) or vincristine, dactinomycin and cyclophosphamide, alternating with Vincristine and Irinotecan. The drugs for the High risk group are similar to the Intermediate group but the number of cycles is more. The Chemotherapy schedule practiced in North America include Vincristine, Actinomycin D and Cyclophosphamide (VAC), whereas those in Europe include Ifosfamide, Vincristine and Actinomycin D (IVA)[31-33].

Radiotherapy (RT): Most of the times in addition to surgery radiotherapy is required to eradicate the loco regional tissue involvement which may be inform of External Radiation therapy or Internal radiation therapy. In ERT the radiation is given to the affected cancerous tissue by external beam. Internal radiation uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer. It is used to treat cancer in areas like vagina, vulva, uterus, bladder, prostate, head or neck. The type and the amount of radiation to be given depends upon the age of the child, the type of tumour, affected lymph nodes and the remnant tumour mass after surgery. RT is used in almost all RMS patients (except Clinical Group I ERMS) to improve local control and outcome. The dose and volume of Radiation depends upon the staging and grouping, the most common doses being delivered in 1.8 Gy fractions. Currently it is recommended to give radiation after 4 cycles of chemotherapy. Delayed RT, beyond 24 weeks or omission of RT is associated with local recurrence.

Molecular therapy: While conventional anticancer drugs destroy not only cancer cells but also normal cells, molecular targeted drugs are thought to specifically attack cells with target molecules involved in growth and proliferation of cancer cells. These molecules, including insulin-like growth factor 1 receptor (IGF-1R), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor (VEGF), anaplastic lymphoma kinase (ALK), mesenchymal-epithelial transition factor (MET) and mammalian target of rapamycin (mTOR), are considered the candidates for molecular targets in patients with RMS[34]. To reduce the incidence of treatment-related AEs and to improve outcomes in patients with soft tissue sarcomas, including RMS, clinical trials for various molecular targeted drugs are being conducted.

Metastatic RMS: Metastatic disease has a poor prognosis but in a retrospective analysis carried out in Europe in patients with metastatic disease outcome was better with aggressive primary local control of tumour with combination of surgical treatment and radiotherapy[35]. Hence it is advisable that aggressive local treatment should be considered in patients with Metastatic RMS.

Recurrent RMS: Nearly one-third of patients diagnosed with localized RMS and over two-thirds of patients with metastatic RMS will experience disease recurrence following primary treatment, generally within three years. Relapses are more common in patients who have gross residual disease in unfavorable sites after initial surgery, in ARMS, in cases with lymph node involvement (N1), in tumors of more than 5 cm, in children older than 10 years and in those who have metastatic disease at diagnosis. Aspects of initial treatment, including extent of surgical resection, use of radiotherapy and chemotherapy regimen, are also associated with post-relapse outcomes, as are features of the relapse itself, including time to relapse and extent of disease involvement. The patients with stage 4 disease at diagnosis were most likely to develop recurrent disease and for patients with non-metastatic ERMS at diagnosis, higher stage was associated with worse post-relapse survival[36,37]. After the completion of initial therapy for RMS, routine follow-up surveillance imaging is recommended by both the European and North American cooperative groups to monitor for recurrence[38,39]. Given the data on the prognostic value of time to relapse, the expectation is that earlier detection could improve post-relapse outcomes. Several studies have investigated the role of such imaging in the early detection of relapse. While systematic surveillance imaging has been shown to detect relapses earlier than presentation of clinical manifestations (both patient-reported and clinician-detected the majority of relapses are diagnosed based on clinical symptoms, namely pain or recognition of a new mass[38-40].

CONCLUSION

Embryonal RMS is a rare and highly malignant tumour characterized by local invasion and early metastasis. The diagnosis of malignancy is mainly based on its Histopathological and Immunohistochemical manifestations. Early surgical excision in combination with Radiotherapy and Chemotherapy is recommended for its treatment which would reduce the recurrence of the tumour and improve the survival of the patients. As compared to other paediatric cancers RMS is still highly understudied due to its rare occurrence. To understand the aetiology of the disease we need to understand the Gene-Environmental interaction. There is a need to increase Environmental and Genetic studies to understand the disease and accordingly plan for treatment. The genetic studies will also help us to plan targeted novel therapies to cure the disease.

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