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Original Research Paper

Pathology

DIAGNOSTIC CHALLENGES IN CERVICAL EMBRYONAL RHABDOMYOSARCOMA IN YOUNG FEMALE: REVIEW OF LITERATURE.

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ABSTRACT Rhabdomyosarcoma is extremely rare; comprising 0.4 to <1% of cervical cancers in female. One of the least common sites for its occurrence in genitourinary tract is cervix and it requires to be differentiated from other sarcomas; particularly adenosarcoma as it has relatively better prognosis but there is not sufficient literature relating to the diagnosis and management of primary sarcoma cervix. We hereby report a case of 22-year-old female who presented with complaints of vaginal intermenstrual bleeding for 1.5 months. On physical and radiological examination was found to have a cervical mass measuring 3.3x4.4x4.5 cm. On microscopy the case was diagnosed as Embryonal Rhabdomyosarcoma cervix. Patient was managed conservatively by chemotherapy and is currently disease free. The aim and objective of our study is to discuss the approach while reporting the histopathology of sarcoma cervix with review of literature and how to differentiate between its close mimickers as therapeutics and outcome for each condition varies .

KEYWORDS : Case report, Embryonal Rhabdomyosarcoma, cervix, DICER1, adenosarcoma, botryoid,

INTRODUCTION

Rhabdomyosarcoma (RMS), a malignant mesenchymal tumor and the most common soft tissue neoplasm in children with common sites being head and neck region (35%) and genitourinary tract (25%).[1] In adults, it accounts for <5% of soft tissue sarcomas and <0.5% in the cervix. [2] According to latest WHO classification, it is divided into 4 histological subtypes – embryonal (ERMS); most common (58%), alveolar, undifferentiated and spindle cell. ERMS may present with a soft polypoidal mass; often grape like appearance and vaginal bleeding. Histologically it exhibits an alternative pattern of hyper and hypocellular areas with a loose myxoid stroma. Tumor cells are arranged in sheets and nests; stellate, spindled or round shape with scant or deeply eosinophilic cytoplasm, eccentric small vesicular nuclei and inconspicuous nucleoli. Botryoid RMS shows a subepithelial zone of stromal hypercellularity (cambium layer) beneath the cervical epithelium showing spindle shaped rhabdomyoblasts. Essential diagnostic criteria for ERMS are positivity for desmin, myogenin and MYOD1.[3] It has been associated with autosomal dominant DICER1 syndrome (pleuropulmonary blastoma familial tumor predisposition syndrome) and Sertoli Leydig cell tumor of ovary [4] Survival of these patients has improved due to intensive chemotherapy particularly Botryoid variant has a good prognosis [5]. The aim of our study is to discuss the approach while reporting the sarcoma cervix and to differentiate it from its other close mimickers like adenosarcoma. The importance lies in treatment decisions and the outcome.

Case History

A 22-year-old female presented with intermenstrual vaginal bleeding for 1.5 months. On examination, a polypoidal exophytic mass was seen arising circumferentially from cervix: friable and bled on touch Ultrasonography reported normal uterus with cervix bulky showing a well-defined echogenic mass- 3.3x4.4x4.5 cm along the posterior wall, protruding in the lumen. Bilateral ovaries and adnexa unremarkable. Impression given as suggestive of cervical polyp. Serum beta HCG was normal. MRI showed a well-defined lesion- 4.4x 2.3x2.7 cm arising from bilateral lips of cervix, hypointense on T1W1, hyperintense on T2W1. Mass extended into lower uterine segment with inferior extension into upper 2/3 rd of vagina (Figure.1). Bilateral parametrium, lateral pelvic wall and adnexa were free. No significant increased pelvic or inguinal nodes noted.

Multiple tissue biopsies of the mass were received in histopathology section aggregating to 2x1.5 cm, polypoidal and soft in appearance. Hematoxylin and Eosin (H&E) stained slides revealed fragmented tumor with alternate hyper and hypocellular areas (Figure.2). Hypercellular areas comprised of high-grade spindle cells arranged in sheets and nests. Individual cells were pleomorphic, round to oval, few stellate shaped with scanty eosinophilic cytoplasm, pleomorphic nuclei with vesicular chromatin. Multinucleated giant cells and bizarre cells also noted. Mitotic activity was 3-4 mitosis per high power field (Figure.3A & 3B). Areas of hemorrhage and necrosis also noted. Occasional focus showed entrapped benign epithelial gland below overlying surface epithelium (Figure.4). Hypocellular areas showed loose and myxoid stroma. On IHC, the spindle cells were positive for MyoD1, myogenin and desmin (Figure.5) while being negative for AE1/AE3, HMB45 and CD31. Based on above findings, a diagnosis of Botryoid ERMS was offered. Patient underwent excision of the mass was followed by six cycles of vincristine, dactinomycin, cyclophosphamide and actinomycin D. Till last update patient was alive and disease free.

DISCUSSION

One of the common differentials of cervical sarcomas is adenosarcoma. Histologically it has a fibrous stroma with leaf like growth resembling phyllodes and. malignant stroma mixed with benign epithelial elements. Other differentials include Malignant Mixed Mullerian Tumor (MMMT) or carcinosarcoma which shows biphasic pattern of high grade carcinomatous and sarcomatous elements. On IHC carcinomatous elements are positive for PAX8, EMA and cytokeratin (CK) in addition to sarcoma markers like desmin and myogenin. Leiomyosarcoma can also be considered because of the spindle shape of cells but it shows characteristic fascicular growth pattern with cigar shaped blunted palisading nuclei and hemangiopericytoma like vasculature. It is positive for HHF35, alpha smooth muscle actin, vimentin, desmin and H-caldesmon. Another differential is ESS of uterine origin which is usually seen in older females especially postmenopausal while RMS is seen in relatively younger age. Patients with high grade ESS

present with extrauterine spread and involve cervix which can be confused with other cervical sarcomas. ESS comprises of high-grade round cells with high mitotic activity and necrosis. On IHC,it is positive for cyclin D1 and c-kit while negative for H-caldesmon, desmin and Pan CK.

Comparing the literature (Table.1.), Rose Fanghong Li et al [6] reported maximum 20 cases of ERMS cervix with median age of 44.4 yrs all being botryoid type. Louis P Dehner et al [2] reported 14 cases of botryoid type with median age being 13 years. Average size of the tumor was 1.5-5 cm. Daya and Scully [7] reported 13 cases with predominant histology as botryoid. 62% were below 19 years. 82% presented as IRS stage –Group I with none having nodal or distant metastasis. Maya L Kriseman et al [8] reported 11 cases with median age being 18.4 years. The median size of tumor was 4 cm. 73% presented in stage IB (FIGO). On histology, 73% were botryoid subtype. 82% of the cases were treated with surgery along with radio and chemotherapy. Sarah E Ferguson et al [5] reported 8 cases with a median age of 48 years 79% presented with locoregional disease. On histology, 70% were botryoid type. Brand E et al [9] reported 4 cases of ERMS cervix botryoid type. Maximum cases were Stage IA. One of the patients aged 17 months had lung, bone and brain metastasis, received chemotherapy and was alive and disease free even after 8 years of diagnosis Schultz et al [10] reported 3 cases of Pleuropulmonary Blastoma and Sertoli Leydig Cell tumor of ovary in children. He described association of DICER1 mutation with above mentioned tumors and cervical ERMS. Comparing our case and above studies age shows a wide range with maximum cases occurring below 40 years age. The common presentation is vaginal bleeding and polypoidal mass along with limited disease spread, no nodal or distant metastasis reported Commonest histopathological subtype is botryoid. Majority received surgery along with radio and chemotherapy. On follow up, maximum did not report recurrence and mortality rate is also very low.

CONCLUSION

In this study we would like to emphasize the importance of keeping in mind the differential of ERMS botryoid type in patients presenting with vaginal bleeding and polypoidal mass especially in younger ages and adolescence. Also follow up for any other malignancies in particular Pleuropulmonary Blastomas and Sertoli Leydig Cell tumor of ovary along with DICER1 mutation. Botryoid variant of ERMS has a very good prognosis and survival rate if diagnosed and treated early.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for her images and other clinical information to be reported in the Journal. The patient understands that her name and initials will not be published, and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

Table.1. Comparison of different studies reporting ERMS cervix.

Author,Year of study	Number of cases(n)	Age Range(years)	Clinical Features	Associated Syndromes	Treatment Outcome & Survival
Rose Fanghong Li et al, 2013,	n=20	20 to 89	Vaginal bleeding	Not known	n=5(25%), no recurrence n=1(5%), recurrence of tumor n= (5%), death of pulmonary nodule (not investigated further0
Louis P Dehner et al,2012	n=14	9 months to 32 years	Polypoidal mass in n=12 and infiltrative lesion in n=2 cases	Pleuropulmonary blastoma in n=2, DICER1 mutation in n=1, Sertoli Leydig cell tumor of ovary & Nodular hyperplasia of thyroid in n=1	n=12(86%) disease free and alive
Daya & Scully,1988	n=13	12 to 26	Vaginal bleeding in n=9 Vaginal mass in n=4	Setoli Leydig cell tumor of ovary in n=2	Death due to primary tumor in n=1
Maya L Krisemann et al,1980-2010	n=11	3 to 49	All with vaginal bleeding and mass in n=4	Sertoli Leydig cell tumor of ovary,pineoblastoma, thyroid carcinoma along with parathyroid adenocarcinoma in n=3	Local recurrence in n=3 Death in n=1
Sarah E Ferguson et al,1963-2003	n=8	16 to 69	Vaginal bleeding	Not known	Recurrence in n=2 Death in n=2 Disease free in n=3
Brand E et al,1987	n=4	17 months to 48 years	Vaginal bleeding Distant metastasis in n=1	Not known	Death in n=1

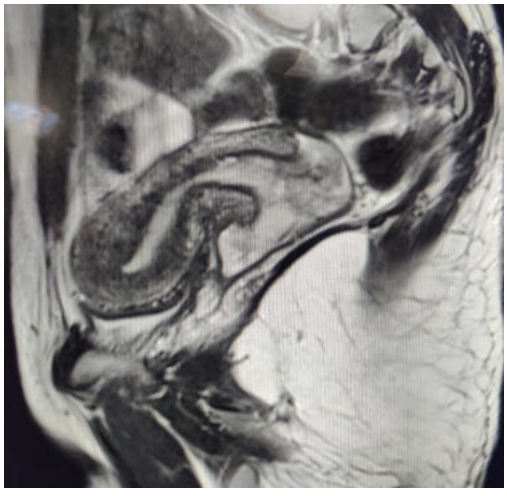

Fig.1.-MRI image showing the lesion arising from cervix; rest of the pelvis is unremarkable.

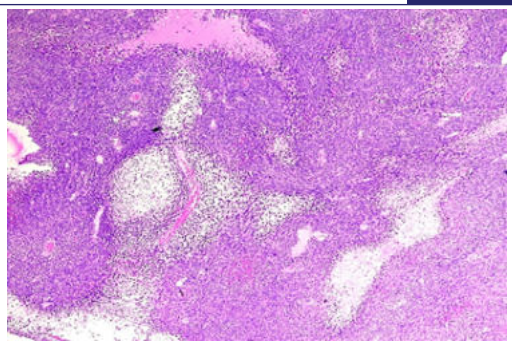

Fig.2-Hematoxylin & Eosin (H&E) stain (20x) showing the alternate hyper and hypocellular areas of arrangement of tumor cells

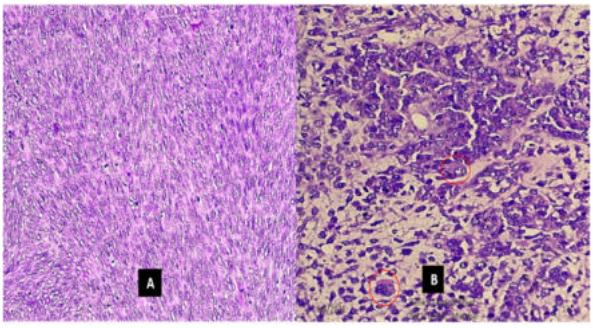

Fig.3A-H&E stain (40x) showing tumor cells; spindle in shape with eosinophilic cytoplasm elongated pleomorphic nuclei with high mitotic activity.

Fig.3B-H&E stain (40x) showing tumor cells with hyperchromatic pleomorphic nuclei; few showing presence of nucleoli; multinucleated tumor giant cell (encircled) also can be seen.

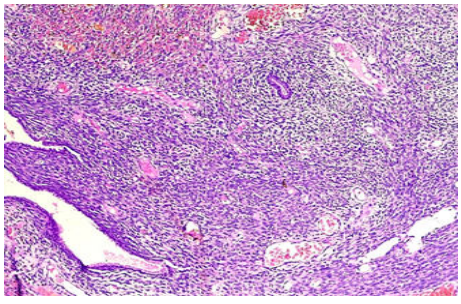

Fig.4-H&E(40x) stain showing benign entrapped epithelial glands below the overlying surface epithelium.

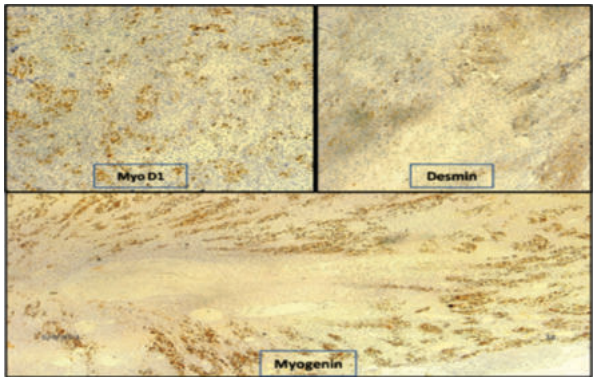

Fig.5- IHC image(20x) showing tumor cells positive for Myo D1, Desmin and Myogenin

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