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Original Contribution

Five rare cases of Ewing sarcoma, including with epithelial differentiation, involving the female genital tract, displaying *EWSR1* rearrangement: Diagnostic challenge and treatment implications

Bharat Rekhi[a,b,*], Radhika Agrawal[a], Omshree Shetty[b], Kedar K. Deodhar[a], Santosh Menon[a], Jaya Ghosh[c], Rajendra Kerkar[d], Amita Maheshwari[d]

[a] Department of Surgical Pathology, Tata Memorial Hospital, Parel, Mumbai 400012, India
[b] Division of Molecular Pathology and Translational Medicine, Tata Memorial Hospital, Parel, Mumbai 400012, India
[c] Department of Medical Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India
[d] Department of Surgical Oncology, Tata Memorial Hospital, Parel, Mumbai 400012, India

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ABSTRACT

We present clinicopathological and molecular cytogenetic features of five rare cases of Ewing sarcomas, occurring in the female genital tract.

A 40 year-old lady presented with a 5.4 cm-sized vaginal mass of 3 months duration, which was histopathologically diagnosed as ES. She defaulted chemotherapy and 8 months later, presented with a recurrence. She underwent chemotherapy and radiotherapy.

A 45 year-old lady presented with recurrent vaginal bleeding, for which she underwent total abdominal hysterectomy (TAH) and unilateral salpingo-oophorectomy (USO), 2 and 1/2 years back. Subsequent vaginal biopsy was reported inconclusively, elsewhere. Thereafter, a 5 cm-sized, residual cervicovaginal mass was reported as ES. She completed induction chemotherapy with a significant response.

A 35 year-old-lady was referred with a 4 cm-sized cervical mass, for which she underwent TAH-USO with pelvic and para-aortic lymphadenectomy.

A 39 year-old-lady presented with a right labial lesion, which recurred. She underwent initial excision, chemotherapy, wide excision and brachytherapy. A year later, she developed multiple metastases; received palliative radiotherapy and died-of-disease.

A 16 year-old girl presented with perineal swelling of 4 months duration. She underwent surgical excision of a recurrent right-sided labial cyst, followed by chemotherapy.

On histopathological review, all 5 cases were malignant round cell tumors. Immunohistochemically, tumor cells displayed MIC2/CD99 and Fli1 positivity, along with focal positivity for pan cytokeratin (AE1/AE3) (cases 1 and 2) and p63 (case 2). Furthermore, tumor cells in the 1st, 2nd, 3rd and 5th cases displayed *EWSR1* rearrangement.

Five uncommon cases of ES involving the female genital tract are presented with diagnostic challenges and therapeutic implications.

1. Introduction

Primary Ewing sarcoma (ES)/primitive neuroectodermal tumor (PNET) constitutes the Ewing sarcoma family of tumors; is a malignant round cell tumor, characterized by t(11;22) (q24;q12) chromosomal translocation leading to formation of *EWS-FLI1* transcript, in 85–90% cases [1]. Remaining cases are characterized by other fusion transcripts, including *EWS-ERG* [2]. Ewing sarcoma is a chemosensitive tumor, treated by a specific Ewing family of tumors (EFT) 2001 chemotherapy regimen at our Institution [3]. It is rarely reported in the female genital tract [4-9].

Immunohistochemically, invariably all cases of Ewing sarcoma display cytoplasmic membranous positivity for MIC2/CD99 and intranuclear positivity for Fli1 [1,3-7]. Rarely, such tumors have been reported, displaying immunostaining for epithelial markers, such as pan cytokeratin (AE1/AE3) and epithelial membrane antigen (EMA) [1].

* Corresponding author at: Room: AB818, Department of Surgical Pathology, Tata Memorial Centre, Dr E. Borges Road, Parel, Mumbai 400012, India.
E-mail address: rekhib@tmc.gov.in (B. Rekhi).

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This can cause a significant diagnostic challenge, especially with the existing lower index of suspicion for this diagnosis at relatively uncommon sites, such as the female genital tract. Therefore, it is imperative to utilize molecular and or cytogenetic techniques for a confirmatory diagnosis.

Herein, we describe clinicopathological and molecular cytogenetic features of 5 uncommon cases of Ewing sarcoma, involving the female genital tract, including diagnostic challenges and treatment implications.

2. Material and methods

Histopathologic sections including immunohistochemical (IHC) stains in all 5 cases were reviewed by BR with RA.

IHC staining was performed by polymer detection technique on 3 μm thick sections mounted on tissue bound coated slides.

Molecular cytogenetic analysis by fluorescence in-situ hybridization (FISH) study with LSI break apart, dual color EWSR1 probe (Zytolight SPEC EWSR1 dual color break-apart probe) was performed on 4 μ thick paraffin-embedded tissue sections.

Processed sections were finally stained with 4′-6-diamidino-2-phenylindole (DAPI) and examined under a fluorescent microscope (Carl Zeiss, Axio Imager Z1, Germany), using AxioCam MRc5 camera and Axio vision Rel 4.5 software. Tumor sample was considered positive if more than 15% of 100 cells analyzed showed rearrangement/"break-apart". A total of 50 (minimum) up to 100 cells were scored for analysis. Molecular test, by FISH technique in all cases were reported by BR and OS.

3. Results

3.1. Case 1

A 40 year-old lady presented with a vaginal mass of 3 months duration. She underwent radiologic imaging, followed by an excision of the mass, elsewhere, which was reviewed at our Institution. She defaulted the recommended chemotherapy (CT) and 8 months later, presented with a recurrent right-sided vaginal mass.

During local examination, a 5 cm × 5 cm-sized proliferative lesion was noted in the region of anterior vagina at introitus, involving periurethral area, along with bilateral labia minora. Cervix appeared free of tumor.

Pre-operative magnetic resonance imaging (MRI) showed an ill-defined mass lesion in the anterior vaginal wall at level of urethral opening, measuring 5.4 cm × 4.6 cm.

Post-operative positron emission tomogram (PET) scan showed an FDG avid right-sided ill-defined, hypermetabolic vaginal mass measuring 4.7 cm × 3.7 cm with an SUV max 11.7, indicative of recurrent tumor (Fig. 1).

She was induced on EFT 2001 chemotherapy protocol, followed by external beam radiation therapy.

3.2. Pathologic findings

Sections from the primary lesion revealed a malignant tumor comprising uniform population of small round cells arranged diffusely and focally, in a rosetting pattern with a focal area of tumor necrosis. By immunohistochemistry, tumor cells displayed diffuse cytoplasmic membranous positivity for MIC2/CD99, intranuclear positivity for Fli1, along with focal positivity for synaptophysin and pan cytokeratin (AE1/AE3), while negativity for desmin and LCA. Diagnosis of Ewing sarcoma was offered.

Subsequently, the tumor was tested for *EWSR1* rearrangement by fluorescence in-situ hybridization (FISH). Ninety-five percent cells displayed red-green 'split 'signals, indicative of *EWSR1* rearrangement (Fig. 2). Diagnosis of Ewing sarcoma was further confirmed.

3.3. Case 2

A 45 year-old lady presented with vaginal bleeding, for which she underwent total abdominal hysterectomy (TAH) and unilateral salpingo-oophorectomy (USO), 2 and 1/2 years ago. She had another episode of vaginal bleeding a year later, for which she underwent biopsy that was diagnosed as adenocarcinoma and a germ cell tumor, elsewhere, for which underwent chemotherapy. Thereafter, radiologic imaging disclosed a residual cervicovaginal mass, which was excised.

Local examination revealed a soft friable vault growth, measuring, 6 cm × 6 cm with deposits in the Pouch of Douglas.

CECT revealed a 5.7 cm × 4.7 cm-sized mass in the residual cervical stump and vaginal vault with loss of fat planes with bladder and rectum.

Post-operative MRI revealed a residual bulky, heterogeneous soft tissue mass measuring 4.9 cm × 2.7 cm × 3 cm, involving the posterior wall of vagina as well as the anterior wall of rectum and exhibiting post-contrast enhancement (Fig. 3).

She completed induction chemotherapy, with significant response and was subsequently recommended definite radiation therapy. Unfortunately, she was lost to further management and follow-up.

3.4. Pathologic findings

Sections from the primary lesion revealed a malignant round cell tumor with cells arranged in a characteristic acinar-rosetting pattern. By immunohistochemistry, tumor cells displayed diffuse cytoplasmic membranous positivity for MIC2/CD99, intranuclear positivity for Fli1, along with focal positivity for p63, AE1/AE3 and EMA, while negativity for CEA, chromogranin and CD56. Diagnosis of Ewing sarcoma was offered.

Thereafter, the tumor was tested for *EWSR1* rearrangement by fluorescence in-situ hybridization (FISH). Ninety percent cells displayed red-green 'split 'signals, indicative of *EWSR1* rearrangement (Figs. 4 and 5). Diagnosis of Ewing sarcoma was further reinforced.

3.5. Case 3

A 35 year-old-lady was referred with a 4 cm-sized cervical mass, for which she underwent TAH–USO, with pelvic and para-aortic lymphadenectomies, elsewhere.

Sections from the biopsy revealed a malignant round cell tumor. By immunohistochemistry, tumor cells displayed diffuse cytoplasmic membranous positivity for MIC2/CD99, intranuclear positivity for Fli1, along with focal positivity for synaptophysin, while negativity for CD10, ER, AR and cyclin D1. Diagnosis of Ewing sarcoma was offered.

Subsequently, the tumor was tested for *EWSR1* rearrangement by fluorescence in-situ hybridization (FISH). Eighty-six percent cells displayed red-green 'split 'signals, indicative of *EWSR1* rearrangement (Fig. 6). Diagnosis of Ewing sarcoma was further confirmed.

3.6. Case 4

A 39 year-old-lady presented with a right-sided labial lesion, for which she underwent an excision elsewhere. She was recommended wide excision of the scar and adjuvant radiotherapy, for which she defaulted. Later, she received 16 cycles of induction and maintenance chemotherapy, in the form of EFT 2001 protocol,

One year later, she developed recurrent lesions, for which she underwent wide local excision, followed by chemotherapy, including gemcitabine and irinotecan.

One month later, she developed another recurrence. On local examination, two lesions were noted, including a growth in her right-sided labia minora, near clitoris, measuring 2 cm × 2 cm sized, along with a firm nodular lesion measuring 1 cm × 1 cm in her right-sided labia majora, at the junction of upper one-thirds and lower two-thirds

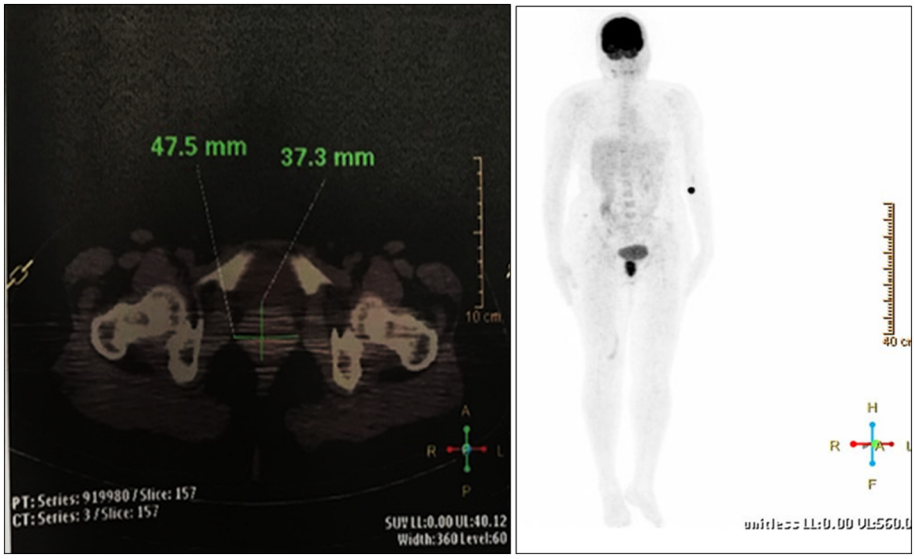

Fig. 1. Case 1. Post-operative positron emission tomogram (PET) scan showing a recurrent tumor in the vagina with high FDG uptake.

of the anterior margin.

She underwent another wide excision with interstitial brachytherapy and was planned for 6 cycles of adjuvant chemotherapy, including drugs such as vinblastine, cyclophosphamide, toptecan and adriamycin. After completion, she developed an ill-defined conglomerate nodal mass in the right groin region, focally abutting the right femoral vessels along with inguinal lymph node metastasis. Positron emission tomogram (PET) whole body revealed hypermetabolic lesions in the form of conglomerated right inguinal adenopathy, for which she underwent groin node debulking. Subsequently, she received external radiotherapy and cumulative dosage of doxorubicin.

Three months later, she developed multiple lung and vertebral (C1) metastasis, for which she received oral metronomic chemotherapy and palliative radiotherapy. However, three months later, she died of the disease.

3.7. Pathologic findings

Sections from the primary, recurrent and metastatic lesion revealed a malignant round cell tumor with cells. Areas of necrosis were noted in the excised recurrent lesion. By immunohistochemistry, tumor cells displayed diffuse cytoplasmic membranous positivity for MIC2/CD99, intranuclear positivity for Fli1, while negativity for AE1/AE3, CD34, EMA, BCL2, SMA and desmin (Fig. 7). Diagnosis of Ewing sarcoma was offered.

3.8. Case 5

A 16 year-old girl presented with perineal swelling of 4 months duration. She underwent a surgical excision of a right labial cyst, which recurred. On clinical examination, a 4 cm × 3 cm sized lesion was noted

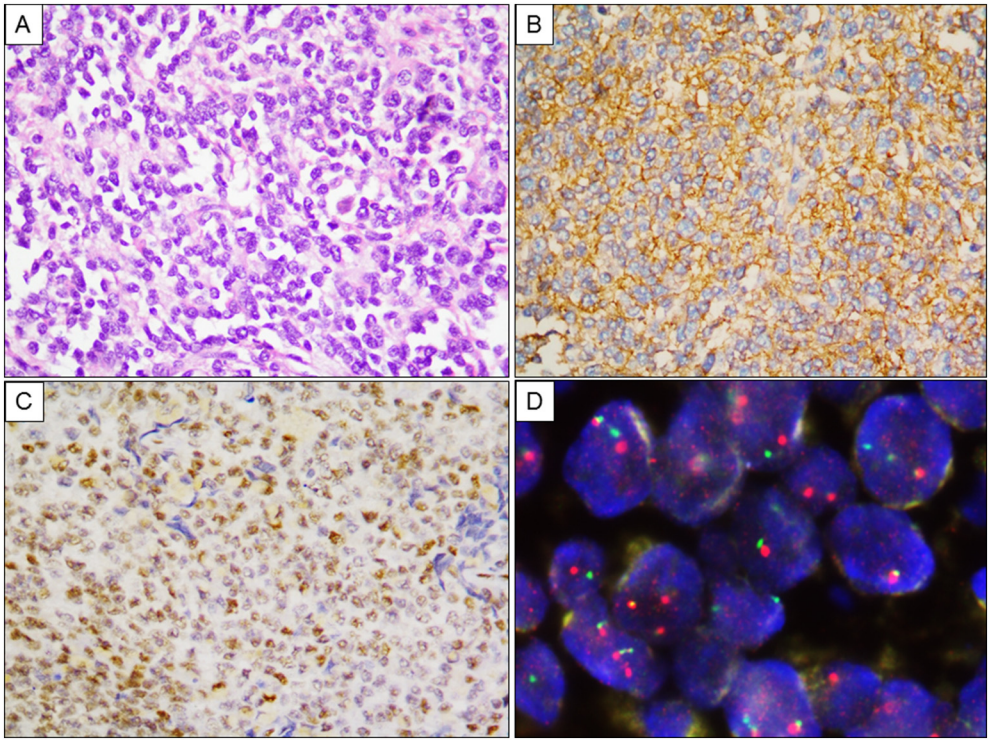

Fig. 2. Case 1. Microscopic features. Malignant tumor composed of uniform population of round cells arranged in a sheet-like/diffuse growth pattern. Hematoxylin and Eosin (H and E), ×400. By immunohistochemistry, tumor cells displaying diffuse cytoplasmic membranous positivity for CD99/MIC2. Diaminobenzidine (DAB) ×400. C. Intranuclear positivity for Fli1. DAB, ×400. D. Tumor cells displaying *EWSR1* rearrangement (re-green spilt signals in several cells), by FISH. DAPI, ×1000. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

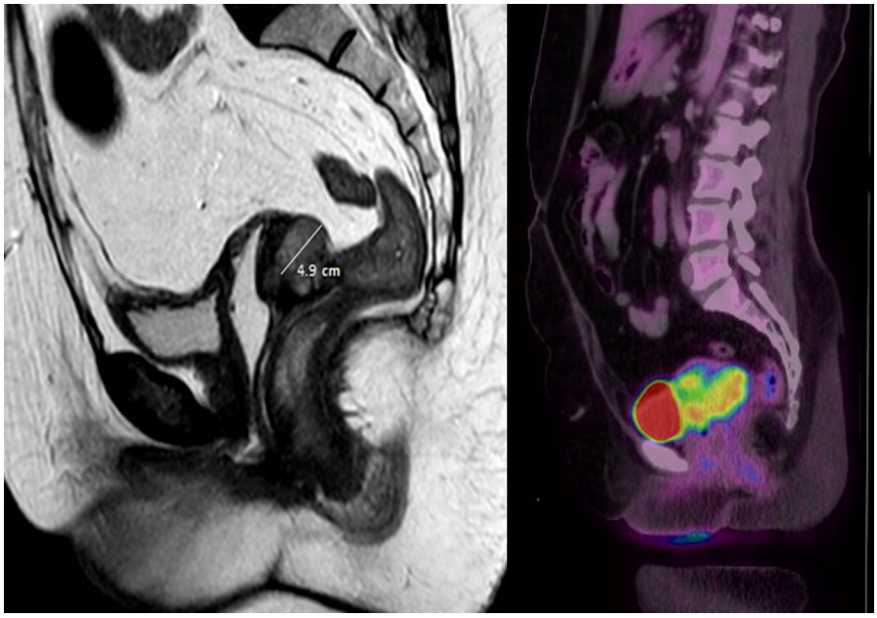

Fig. 3. Case 2. Post-operative MRI revealing a residual bulky, heterogeneous soft tissue mass measuring 4.9 cm, involving posterior wall of vagina, exhibiting post contrast enhancement.

over the lower border of her right labia majora, 2 cm away from the anal verge. Overlying skin was normal. Presently, she is on chemotherapy (EFT2001 protocol).

CECT further disclosed a mass measuring 5.6 cm × 4.4 cm × 2.6 cm in her right labia majora. PET scan showed an FDG avid, heterogeneously enhancing soft tissue mass involving right labia majora, extending into the perineal fat with an SUVmax = 7.6.

Biopsy showed a malignant round cell tumor. Immunohistochemically, tumor cells showed cytoplasmic membranous positivity for MIC2, intranuclear positivity for Fli1 and negativity for desmin. Diagnosis of Ewing sarcoma was offered.

By FISH for *EWSR1* gene rearrangement, 96% cells displayed red-green 'split 'signals, indicative of *EWSR1*positive rearrangement (Fig. 8). Diagnosis of Ewing sarcoma was further reinforced (Table 1).

4. Discussion

Ewing sarcoma of the female genital tract is a rare tumor, with 17 cases reported in vulva and 19 in cervix, including 11 cases confirmed by molecular testing. Few such cases have also been reported in the uterus, ovary and vagina [4-11]. The present study constitutes the largest series of Ewing sarcomas, involving the female genital tract from our subcontinent.

Median age of the patients harboring ES in vulva or cervix is

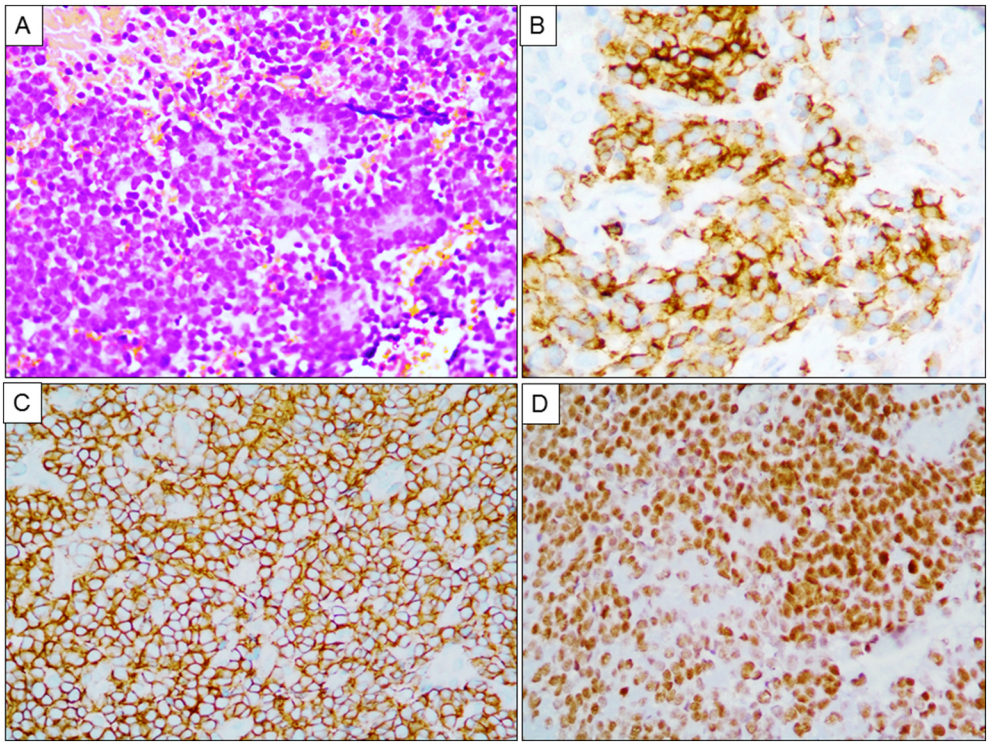

Fig. 4. Case 2. Microscopic features. A. Malignant tumor composed of small round cells arranged in a conspicuous acinar-rosetting pattern. H and E ×400. B. Immunohistochemically, tumor cells showing significant cytoplasmic membranous positivity for EMA. DAB, ×300.C. Diffuse cytoplasmic membranous positivity for CD99/MIC2. DAB, ×400. D. Intranuclear positivity for Fli1. DAB, ×400.

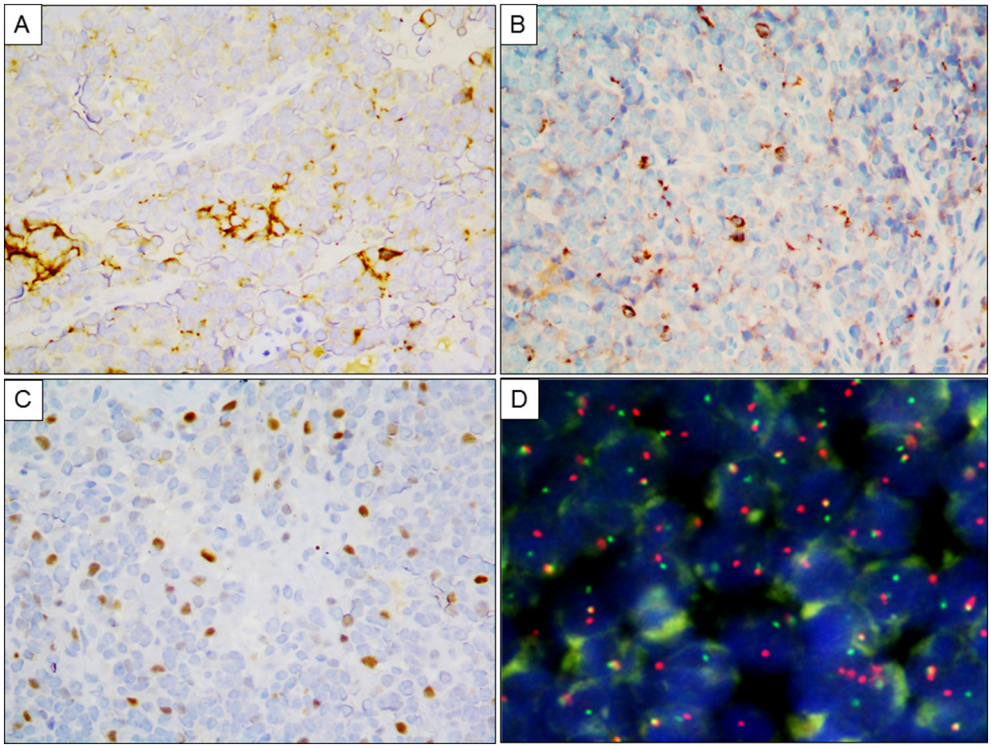

Fig. 5. Case 2. A. Focal synaptophysin positivity. DAB, ×400.B.Focal pan cytokeratin (AE1/AE3) positivity. DAB, ×400. C. Focal and distinct positivity for p40. DAB, ×400. D. Tumor cells displaying *EWSR1* rearrangement. DAPI, ×1000.

reported as 20 years and 39 years respectively. In our series, the average age of the patients was 40 years. The possible reasons include a delayed presentation at our referral centre. An exact diagnosis was made on histopathological examination, in all the cases.

Differential diagnoses considered in the various cases included poorly differentiated carcinoma (PDCa), including small cell carcinoma (SCC), synovial sarcoma (SS), rhabdomyosarcoma (RMS) and non-Hodgkin lymphoma (NHL). Immunohistochemistry was useful in ruling out these entities. AE1/AE3 and synaptophysin immunopositivity led to consideration of a PDCa, including a SCC in the first 2 cases. Epithelial differentiation is reported in 5–32% cases of Ewing sarcoma [12,13]. Lately, p40 (marker of squamous differentiation) immunoexpression, as noted in case 2 of the present study, has been reported in "adamantinoma-like" Ewing sarcomas [14] However, this has not been reported

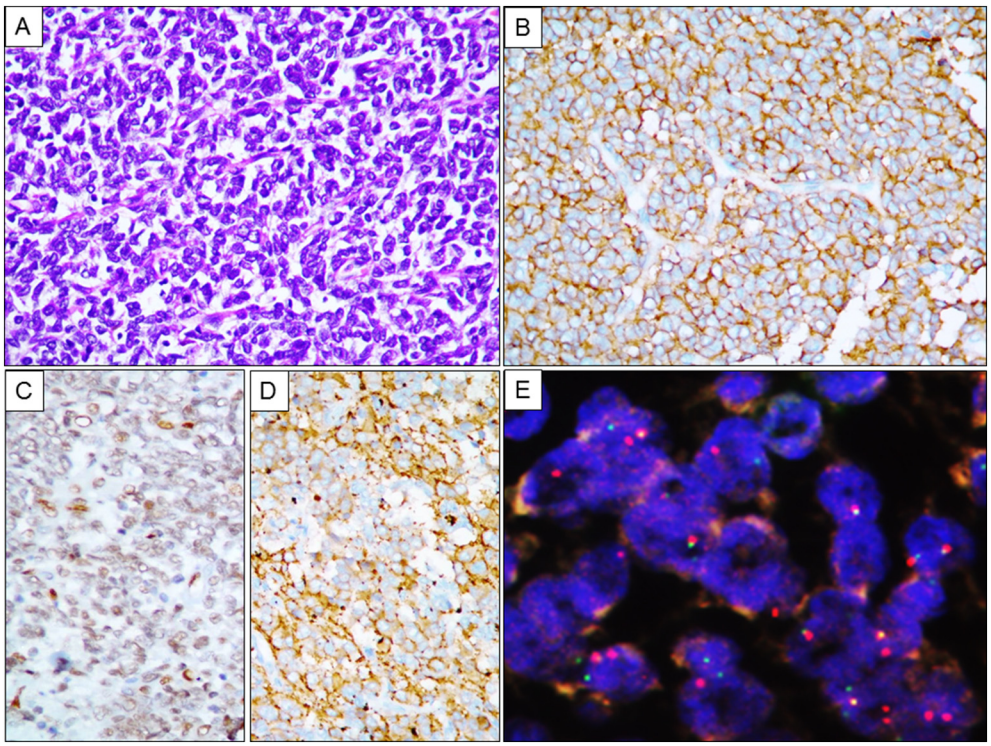

Fig. 6. Case 3. Microscopic features. A. Malignant round cell tumor with uniform cells arranged in a diffuse pattern and interspersed thin walled capillaries. H and E, ×400. B. By immunohistochemistry, tumor cells displaying diffuse cytoplasmic membranous positivity for CD99/MIC2. DAB, ×400. C. Tumor cells sowing focal intranuclear positivity for Fli1. DAB, ×400. D. Significant positivity for synaptophysin. DAB, ×400. Tumor cells displaying *EWSR1* rearrangement. DAPI, ×1000.

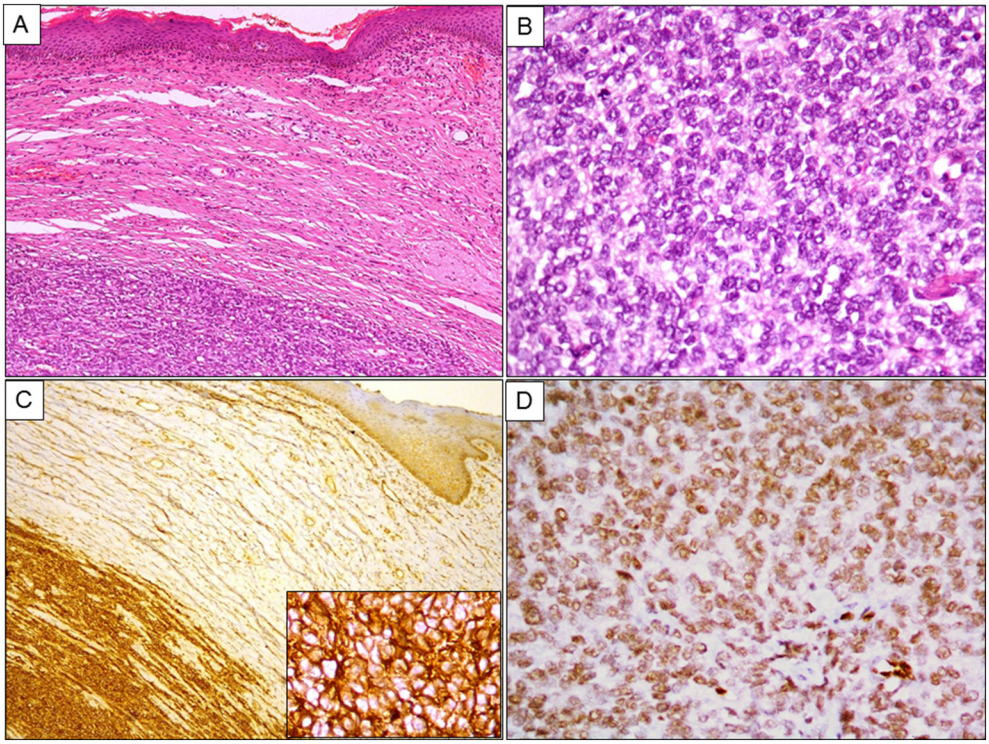

Fig. 7. Case 4. Microscopic features. A. Cellular tumor below epidermis. H and E, ×100. B. Malignant small round cells arranged in rosetting pattern. H and E, ×400. Diffuse, intense cytoplasmic membranous positivity for MIC2, in the tumor cells. DAB, ×100. Inset: tumor cells showing intense staining, on higher magnification. DAB, ×400.

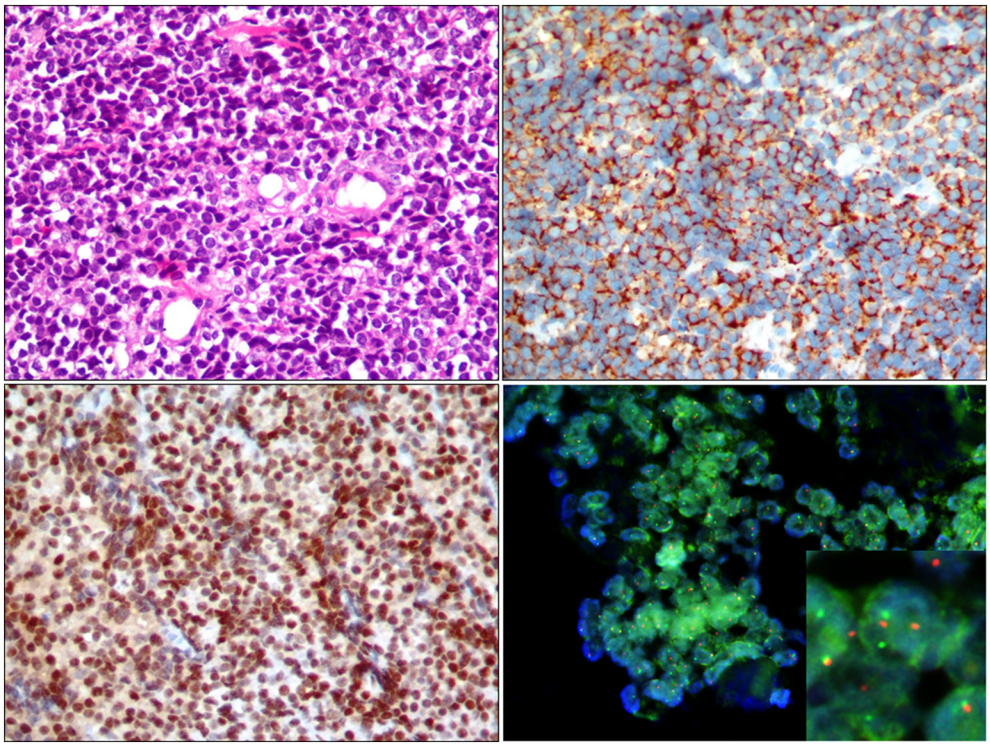

Fig. 8. Case 5. Microscopic features. A. Malignant round cell tumor. H and E, ×400. B. CD99/MIC2 positivity (incomplete to complete cytoplasmic membranous). DAB, ×400. C. Diffuse intranuclear positivity for Fli1. DAB, ×400. D. Tumor cells displaying *EWSR1* rearrangement. Inset: red-green split signals on higher magnification. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in any case of Ewing sarcoma, described in the female genital tract [4-11]. Epithelial immunoexpression was the reason of initial mistaken diagnosis of an adenocarcinoma in the second case.

Lack of LCA and Desmin with MyoD1 and myogenin immunostaining can help ruling out RMS and NHL. Diffuse, cytoplasmic membranous MIC2 along with FLI1 positivity were helpful in the diagnosis of ES in all five cases.

It is noteworthy that MIC2/CD99 is not specific for diagnosis of Ewing sarcoma, especially at unusual sites, such as the present cases [13,15,16]. Lately; NKX2.2 has emerged as another IHC marker for diagnosing Ewing sarcomas. However, this is also reported to have imperfect specificity [17]. Therefore, it is crucial to test such cases by molecular and or cytogenetic tests.

Four out of five cases in the present study, tested for *EWSR1* rearrangement by FISH technique, showed positive results. The remaining single case (case 4), which was referred from another laboratory was uninterpretable, in view of poor fixation. Nonetheless, in view of diffuse cytoplasmic membranous positivity for MIC2, coupled with

Table 1
Clinicopathological, immunohistochemical and molecular cytogenetic features of five cases of Ewing sarcomas involving the female genital tract.

Sr no.	Age	Site	T-size (cm)	IHC results	Molecular cytogenetic test result	Treatment	Outcome
1	40	Vagina	5.4	MIC2-P, Fli1-P, Synapto-FP, CD56-P, NSE-P, AE1/AE3-P	*EWSR1*-P (95% cells)	Surgical excision + CT + RT	Recurr (8 mo.) AWD (18 mo.)
2	45	Cervicovaginal	5.7(R)	MIC2-P, Fli1-P, P63-FP, AE1/AE3-FP, EMA-FP	*EWSR1*-P (90% cells)	TAH-USO + CT + RT (recommended)	AWD (20 mo.) Lost to FU.
3	35	Cervix	4	MIC2-P, Fli1-P, Synapto-FP.	*EWSR1*-P (86% cells)	TAH-USO + lymphadenectomies	NA
4	39	Vulva (labia)	2(R)	MIC2-P, Fli1-P, AE1/AE3-N, EMA-N	NW	Surgical excision + CT + RT	Recurr + Mets (lung and bone). DOD (15 mo.)
5	16	Vulva (labia)	5.6 (R)	MIC2-P, Fli1-P	*EWSR1*-P (96% cells)	Surgical excision + CT	On treatment

R: recurrent tumor, P: positive, FP: focally positive, N: negative, NW: not worked, CT: chemotherapy, RT: radiation therapy, TAH: total abdominal hysterectomy, USO: unilateral salpingo-oophorectomy, AWD: alive with disease, DOD: died of disease.

morphological features, this was considered as Ewing sarcoma. Subsequently, the first 2 cases received EFT 2001 chemotherapy, to which the 2nd case responded. Third was a referral case. Fourth case, despite surgical excision and adjuvant chemo and radiotherapy, died of the disease. Probably, incomplete resection of the primary tumor, managed elsewhere, defaulted and incomplete chemotherapy were factors that added to the aggressive clinical course. Earlier reported cases have been similarly treated [6,7,10].

Clinical outcomes have been variable in the various reported cases. While there are patients harboring Ewing sarcomas of the vulva, vagina and cervix, who underwent complete treatment, including chemotherapy, with relatively favorable outcomes; cases of Ewing sarcomas involving ovaries have been mostly associated with aggressive clinical course [4-10] Most of the cases in the present study were either not initially correctly diagnosed, from where they were referred, or were associated with a poor compliance to treatment. Therefore, an exact diagnosis, followed by timely treatment is crucial in such cases.

To conclude, five cases of Ewing sarcoma, involving female genital tract, confirmed by IHC and molecular cytogenetics, constitute as the first such series from our country. Epithelial differentiation can lead to a diagnostic challenge, especially for these tumors occurring in the genital tract. An index of suspicion is necessary for this diagnosis. It is ideal to test such cases by molecular or cytogenetic techniques, for a precise diagnosis. An exact diagnosis has significant treatment implications.

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Declaration of Competing Interest

None.

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