Case Report

Ewing's Sarcoma of Cervix: A Case Report and Literature Review

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Ewing's sarcoma [ES] is a rare cancer which usually presents in childhood or early adulthood. Most are found in osseous sites. Uterine cervix is an uncommon site for ES, with only 18 patients previously reported. Our patient was a 34 years old woman, who presented with abnormal vaginal bleeding. Pelvic examination showed an 8-cm mass prolapsed from cervix to vagina with purulent discharge in vagina canal. Uterus and adnexa were unremarkable. Pathology from biopsy showed only few tiny fragments of benign endometrial tissue admixed with blood component. Preoperative diagnosis was prolapsed submucous leiomyoma. Total hysterectomy was performed. Histologic features showed small blue round tumor cells with positive vimentin, neuron-specific enolase [NSE] and CD99 stains. Pancytokeratin and leukocyte common antigen [LCA] stains were negative. Fluorescence in situ hybridization [FISH] revealed ESWR1 gene rearrangement, establishing a diagnosis of Ewing's sarcoma. Recurrent tumors were experienced 2 months after operation as large pelvic masses. Subsequent lung metastases were evident. Then, she received palliative chemotherapy which yielded only partial response as the best response before progression. She died 10 months after diagnosis.

Keywords: Ewing's sarcoma, uterine cervix, ESWR1 gene rearrangement

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Ewing's sarcoma [ES] is a rare cancer among the Ewing sarcoma family of tumors [EFT]. It usually presents in childhood or early adulthood. Although it can occur anywhere in the body, the most common site is osseous structure and rarely at cervix. The correct diagnosis of this rare cancer is a challenge because the histologic features of small round cells may be found in several tumors of divert natures. We presents a patient with cervical ES who did not have a correct diagnosis preoperatively, experienced recurrence, and died within a year after diagnosis.

Case Report

A 34 years old woman, sought for medical consultation for abnormal vaginal bleeding for 4 days. She had good consciousness, pale, no jaundice, normal vital signs, without other pertinent findings. Pelvic examination showed an 8-cm mass prolapsed from cervix to vagina with purulent discharge in vagina canal. Uterus and adnexa were unremarkable. Biopsy was performed and showed only few tiny fragments of benign endometrial tissue admixed with blood component. Preoperative diagnosis was prolapsed submucous leiomyoma. The other differential diagnoses include endometrial polyp and malignant mixed Mullerian tumor.

Total hysterectomy [TAH] was done without bilateral salpingo-oophorectomy or lymph node dissection. Gross findings showed normal size of uterus. Cervix was enlarged with a gray white exophytic mass, measuring 8.2x5.0x4.1 cm, arising from upper cervix protruding into vaginal canal. The consistency was partly solid firm and friable with necrotic tissue. Upon sectioning, the mass also infiltrated into cervical stroma through the cervical fascia. The endometrium and myometrium were grossly unremarkable.

Histologic examination by hematoxylin and eosin (H&E) stain of the mass showed tumor cells

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arranging in loosely cohesive pattern, infiltrating into the stroma (Figure. 1A). These tumor cells were relatively uniform, small, round shape, scanty cytoplasm with hyperchromatic nuclei, and some visible nucleoli (Figure. 1B). Mitotic figures were 8 per 10 HPF (high-power field). Scattered areas of hemorrhage and necrosis were present. Differential diagnoses included poorly differentiated carcinoma, neuroendocrine carcinoma, malignant lymphoma, and Ewing's sarcoma. Special staining with Periodic acid-Schiff [PAS] demonstrated small amount of glycogen in cytoplasm. Immunohistochemical [IHC] study showed negative staining for cytokeratin (AE1/AE3), epithelial membrane antigen [EMA], leukocyte common antigen [LCA], synaptophysin, chromogranin, melanocytic antigen [Melan-A], S-100, smooth muscle actin [SMA] and desmin (Figure. 2). Stainings for vimentin, neuron-specific enolase [NSE] and CD99 were strongly positively and diffusely. We additionally performed the fluorescence in situ hybridization [FISH] which revealed ESWR1 gene rearrangement (27% of tumor cells), establishing a diagnosis of Ewing's sarcoma.

She had a diagnosis of cervical cancer stage IIB (extending to cervical fascia/possible parametrium) having incidental hysterectomy. Complete clinical evaluation including abdominal computerized tomography scan was performed 2 months after the operation. The scan demonstrated several matted masses ranging from 5 to 8 cm in the pelvic cavity. The masses compressed the ureters leading to bilateral hydronephrosis. After a thorough counseling, chemotherapy was planned but she had oliguria, rising of serum creatinine level and febrile illness from complicated urinary tract infection. During 2 months of medical and supportive treatment to convert the urine flow by percutaneous nephrostomy, new metastatic pulmonary lesions were discovered. She subsequently received palliative chemotherapy with vincristine, doxorubicin, and cyclophosphamide for 6 cycles. The tumors showed partial response during the courses of chemotherapy but progressed after the 6th cycle of chemotherapy. She died 10 months after the diagnosis.

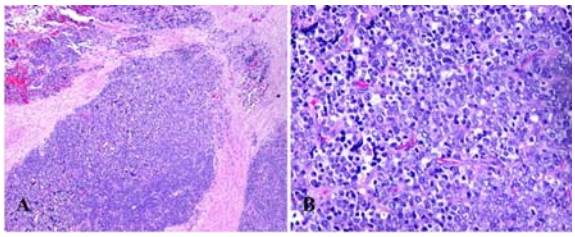

Figure 1. Histomorphology of the cervical mass: A. Sheets of tumor cells arranged in loosely cohesive pattern infiltrating into cervical stroma (H&E,100x); B. Tumor cells had round-shaped nuclei, visible nucleoli and scant cytoplasm. (H&E, 400x).

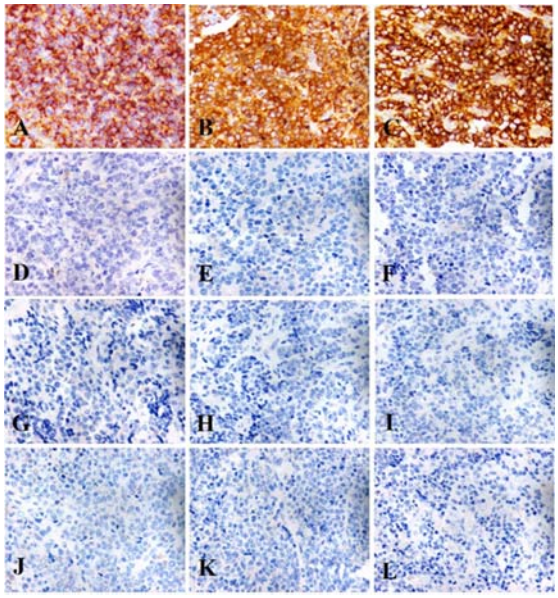

Figure 2. Immunohistochemical study (600x) showed cytoplasmic expression of vimentin (A), NSE (B), CD99 (C) and negative expression of cytokeratin (D), EMA (E), LCA (F), synaptophysin (G), chromogranin (H), Melan-A (I), S-100 (J), SMA (K), and desmin (L).

Discussion

Ewing's sarcoma is most commonly found at osseous structure. Uterine cervix is an unusual site of this rare cancer. To date, only 18 cases of cervical Ewing's sarcoma were previously reported[1-17] (Table 1). The average age of presentation was 32 years (12 to 57 years). Thirteen out of 18 patients (72%) presented with irregular bleeding per vagina, whether with lower abdominal pain or not[7,11,14,15,17]. The other symptoms included purulent or watery vaginal discharge[8] or dysuria[10]. Three cases were found during pregnancy[4,13,14]. One of them was discovered as a 5-cm fleshy mass immediately after expulsion of placenta during delivery[13].

From physical examination, all 18 patients had an irregular mass of cervix protruding into vaginal canal[1-17]. Preoperative diagnosis was correctly made in 13 patients[2,4,5,7-9,12,14-17]. Among 15 reports with

Table 1. Clinical presentation, treatment and outcome of case reports of uterine cervical Ewing's sarcoma and including our case

First Author/Year	Age	Symptoms	Stage	Pre-op Dx	TAH	Chemo therapy	Radio therapy	Outcome
Sato, 1996[1]	44	Irregular genital bleeding	IB2	Yes	Yes	Yes*	No*	Alive, NED 6 months
Horn, 1996[2]	26	Abnormal cervical smear	IB1	Yes	Yes	Yes**	Yes*,**	Recurred 3 yrs, DOD 4.2 years
Cenacchi, 1998[3]	36	Intermenstrual spotting	IB2	No	Yes	No	No	Alive, NED 18 months
Tsao, 2001[4]	24	Cervical mass (GA 8 weeks)	N/A	Yes	Yes	Yes*	Yes*	Alive, NED 24 months
Malpica, 2002[5]	35	Abnormal bleeding	IB1	Yes	Yes	Yes*	No	Alive, NED 5 months
Malpica 2002[5]	51	Abnormal uterine bleeding	IB2	Yes	Yes	Yes*	No	Alive, NED 18 months
Snijders-Keilholz, 2005[6]	21	Abnormal vaginal bleeding	IB2	N/A	Yes	Yes*	No	Alive, NED 27 months
Goda, 2007[7]	19	Vaginal discharge, abdominal pain	N/A	Yes	No	Yes*	Yes*	Alive, ongoing chemo- radiation therapy
Farzaneh, 2011[8]	45	Purulent vaginal discharge	IB2	Yes	Yes	Yes*	No	Alive, NED 4 years
Zenib, 2012[9]	25	Vaginal bleeding	IIB	Yes	Yes	Yes*	Yes*	Alive, NED 8 years
Arora, 2012[10]	23	Irregular vaginal bleeding, dysuria	N/A	No	Yes	Yes*	Yes*	Alive, NED 4 years
Masoura, 2012[11]	23	Abnormal bleeding, abdominal pain	IV	N/A	Yes	Yes*	No	DOD 12 days
Li, 2013[12]	27	Contact vaginal bleeding	IIIB	Yes	Unresectable	Yes*	Yes*	Alive, NED 6 months
Sonali, 2014[13]	27	Asymtomatic, expulsion with placental during delivery	IB2	No	Yes	Yes**	Yes**	Recurred 3 months, Alive, Ongoing radio-chemotherapy
Khosla, 2014[14]	28	10th weeks of pregnancy with vaginal bleeding and pelvic pain	IB2	Yes	Yes (pregnancy termination)	Yes*	No	Alive, NED 33 months
Nazia, 2015[15]	49	Vaginal bleeding, abdominal pain	IIB	Yes	Yes	Yes*	Yes*	DOD 10 months
B□lek, 2015[16]	57	Cervical mass	IIB	Yes	Yes	Yes*	Yes*	Alive, NED 18 months
Rastogi, 2016[17]	12	Vaginal bleeding, abdominal pain	IV	Yes	N/A	N/A	N/A	N/A
Our patient	34	Abnormal vaginal bleeding	IIB	No	Yes (for recurrence)	Yes**	No	DOD 10 months

*As adjuvant treatment after surgery or primary treatment, ** As salvage treatment for recurrence
DOD = died of disease; TAH = total hysterectomy; N/A = not available; NED = no evidence of disease

available data, more than of half of such patients had stage IB1 or IB2 (9 cases)[1-3,5,6,13,14] whereas the remaining were locally advanced or advanced stage (3 stage IIB, 1 stage IIIB, and 2 stage IV)[9,5,11,12,16,17].

The histologic feature from H&E staining of Ewing's sarcoma is sheets of small round and uniform cells. Generally, various differential diagnoses can be made for the small round cells tumors. These include malignant lymphoma, poorly differentiated carcinoma, metastatic carcinoma, neuroendocrine carcinoma, neuroblastoma, Ewing's sarcoma, malignant melanoma, alveolar rhabdomyosarcoma and other soft tissue sarcoma.

Special staining and IHC study play an important role for a correct diagnosis. PAS stain for glycogen is frequently demonstrated in the cytoplasm of Ewing's sarcoma cells and is generally negative for the other small round cell tumors. Hence, the positive PAS stain in our patient suggested the diagnosis. However, due to the unusual site of this rare cancer at cervix, IHC study was carried out to confirm the diagnosis. Our case showed negative IHC staining for pancytokeratin, LCA, synaptophysin and chromogranin which help excluding the diagnosis of carcinoma, lymphoma, and neuroendocrine tumor respectively. The positive stainings were demonstrated in NSE, vimentin and CD99. Although each stain may be positive in some of these tumors, a triple positive staining (NSE, vimentin and CD99) strongly supported the diagnosis of Ewing's sarcoma. Some reported positive cytokeratin in Ewing's sarcoma, however, they were generally focal and weak intensity[18]. Few other

studies also reported positive Ki-67 indicating high proliferative index (80 to 90%)[12,19] and Friend leukemia integration 1 [FLI-1][20] in some cases of Ewing's sarcoma. We did not evaluate the latter 2 stainings but proceeded to a confirmatory diagnosis with EWSR1 gene rearrangement. A molecular genetic characteristics of t(11;22)(q24;q12) chromosomal translocation of the EWS gene at 22q12.2 with FLI (friend leukemia virus integration 1), a member of the ETS transcription factor family at 11q24.1-q24.3, leading to EWS-FLI1 fusion, were reported in 85% of cases[21,22]. Some reported EWS-ERG translocation [t (21; 22) (q22; q12)] in 10 to 15% of cases[23]. The other translocations were uncommonly seen. The findings of a triple positive IHC staining and the genetic derangement confirmed a diagnosis of Ewing's sarcoma in our patient.

Although there had been no standard treatment for cervical Ewing's sarcoma because of its rarity, most had surgical treatment before adjuvant therapy. From the 18 cases reports with available data (including our patient), only 2 patients had chemotherapy and radiation without surgical treatment due to unresectable tumors[7,12]. Another had only hysterectomy without any further therapy (stage of disease not reported)[3]. Other 15 cases had postoperative chemotherapy with[2,4,9,10,13,15,16] or without radiation[1,5,6,8,11,14].

Among 19 case reports with available data, regarding clinical outcomes (including our patient), four died (including our case)[2,11,15]. All of them were treated by total hysterectomy and chemotherapy. The stage and survival duration were: stage IB1 (4.2 year)[2], stage IIB (10 months; 2 cases)[15], and stage IV (12 days)[11]. The other 14 patients were alive at the time of their reports[1,3-10,12-14,16]. The survival duration ranged from 5 months to 8 years. The patient who had lived for 8 years without evidence of recurrence had stage IIB and underwent hysterectomy followed by adjuvant radiation and chemotherapy[9].

Conclusion

Ewing's sarcoma rarely occurs as a primary cancer of cervix. The diagnosis is based on combination of histological features, IHC study and molecular genetic analysis. No specific treatment guidelines have been established for Ewing's sarcoma. The prognosis is generally poor. Here, we described a case involving the cervix in a 34-year-old woman. The patient was treated by total hysterectomy and chemotherapy. The patient had an overall survival of 10 months after diagnosis.

Potential conflicts of interest

The authors declare no conflict of interest.

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