Lymphoepithelioma-like Carcinoma of Endometrium; A Rare Case Report

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Abstract Lymphoepithelioma-like carcinomas (LELCs) are tumors with histological features similar to those of lymphoepithelioma of nasopharynx. They have been described in many organs including female genital tract. Their histology is characterized by sheets, nests and cords of large syncytial tumor cells containing round nuclei with prominent nucleoli and dense lymphoplasmacytic infiltrate in the stroma. The association of Epstein-Barr virus (EBV) with LELCs has not been observed in western patients. But a few Asian patients with these tumors in uterine cervix have shown positive association of EBV. Cervical LELCs harbor EBV more frequently than cervical squamous cell carcinomas. These tumors are rarer in endometrium. Only 3 cases have been reported and the association of EBV has not been observed. We present here a rare case of LELC in endometrial polyp from India, who presented with postmenopausal vaginal bleeding. The tumor cells were positive for cytokeratin and EBV Latent membrane protein-1.

Keywords Endometrial carcinoma · Lymphoepithelioma-like carcinoma · EBV · LMP 1

Introduction

Lymphoepithelioma is an undifferentiated non keratinizing type of nasopharyngeal carcinoma. Tumors with similar histology have been described as lymphoepithelioma-like

carcinomas (LELCs) in stomach, lung, salivary gland, thymus, urinary bladder, breast and a few in uterine cervix, vulva, vagina, and ovary [1–10]. They are very rare in endometrium. Only three cases have been described in the literature [11, 12]. They are characterized by large syncytial tumor cells seen in diffuse sheets, nests and trabeculae or scattered singly. Tumor cells contain round nuclei with prominent nucleoli. The stroma contains dense lymphoplasmacytic infiltrate. The association of Epstein-Barr virus (EBV) with lymphoepithelioma nasopharynx, Hodgkin lymphoma and Burkitt lymphoma has been well documented. Patients with these tumors in stomach, lung, breast and uterine cervix, have shown better prognosis than those with conventional carcinomas of the corresponding organs [1, 2, 6, 7]. Hence the pathologists and the surgeons in different specialties should be aware of this entity. We are reporting a first patient 63 year old woman from India, who presented with postmenopausal vaginal bleeding due to LELC in endometrial polyp. Tumor cells showed cytokeratin and EBV protein LMP 1 positivity.

Case Report

A 63-year-old woman presented with postmenopausal bleeding of 15 days duration. Initially she had 2 episodes of heavy bleeding followed by spotting. She attained menopause 3 years back. She was on medication for type 2 diabetes mellitus, hypertension and hypothyroidism for 6 years. She consulted the local doctor; biopsy was done and reported as adenocarcinoma endometrium. Thyroid, breast, spine examination, and systemic examination showed no abnormalities. Pelvic examination revealed bulky uterus, and tenderness in fornices. MRI pelvis revealed retroverted bulky uterus measuring 4.1 × 5.2 × 7.1 cm, with endometrial thickness of 21 mm and fluid

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in endometrial cavity. An ovoid hyper intense lesion in the anterior wall of the myometrium near the fundus and prominent right iliac lymph nodes were noted. Other organs showed no abnormalities. Features were suggestive of endometrial carcinoma. Endometrial biopsy done earlier was reviewed and opined as poorly differentiated adenocarcinoma- endometrium. Total abdominal hysterectomy with bilateral salphingo- oophorectomy and pelvic with paraaortic lymph node dissection was done. Ascitic fluid was negative for malignant cells.

Surgical specimen consisted of uterus, cervix, both ovaries and fallopian tubes, both side pelvic lymph nodes. Uterus, cervix measured 7×5×4 cm. Cut surface showed intramural fibroid of 2×2 cm, and endometrial polyp of 3×2.5 cm diameter. Cut surface of the polyp showed whitish solid and cystic areas (Fig. 1). Right fallopian tube measured 3 cm, and contained little hemorrhagic fluid. A total of 11 lymph nodes on left side and 7 on right side from pelvic dissection tissue were separated for study. Microscopy of cervix showed chronic endocervicitis with small foci of basal cell proliferation. Endometrium showed atrophic changes. Endometrial polyp showed tubular and cystic endometrial glands lined by hyperplastic epithelium, sheets and nests of large syncytial tumor cells having round nuclei with prominent nucleoli (Fig. 2). Tumor cell

Fig. 1 Endometrial cavity shows polyp cut surface with solid whitish tumor, small cystic spaces and intramural fibroid

Fig. 2 Histology of Polyp shows solid sheets of tumor cells, lymphoid infiltrate and compressed hyperplastic endometrial glands (H&E, ×400)

neests were surrounded by dense lymphoplasmacytic infiltrate (Fig. 3). Myometrium showed leiomyoma and small clusters of syncytial tumor cells rimed by lymphocytic infiltrate in paravascular area. Right fallopian tube showed dysplastic epithelium and tiny tumor deposits in subserosa. Four out of 7 pelvic lymph nodes from right side showed metastatic tumor deposits with similar morphology (Fig. 4) and all 11 lymph nodes from left side showed reactive changes. The immunohistochemical study showed strong cytokeratin AE1/AE positivity (Fig. 5) (Biogenex Anti cytokeratin cocktail clone AE1 and AE3) and EBV latent membrane protein -1 (LMP-1) positivity (Fig. 6) in the tumor cells (Dako FLEX monoclonal mouse Anti-Epstein-Barr Virus, LMP clones CS.(1–4) Paraffin embedded sections of Hodgkin lymphoma were used as positive

Fig. 3 Sheets of classical syncytial tumor cells, round nuclei with prominent nucleoli (H&E, ×400)

Fig. 4 Metastatic tumor cells in right pelvic lymph node (H&E, $\times 400$)

control. Stromal lymphoid cells showed CD3, CD20 positivity (not included in the panel). Hence the final diagnosis of lymphoepithelioma-like carcinoma endometrium with metastases in right fallopian tube and right pelvic lymph nodes was made. Patient was taken to regional cancer center and managed with adjuvant radiotherapy and chemotherapy details of which are not known. The patient is doing well without any fresh symptoms since 1 year.

Discussion

The term “lymphoepithelial carcinoma” may be applied when abundant lymphocytes and plasma cells infiltrate the tumor islands breaking them up into tiny clusters or single cells and obscuring the epithelial nature of the tumor. Lymphoepithelioma is a distinctive type of nonkeratinizing undifferentiated carcinoma nasopharynx, characterized by

Fig. 5 Tumor cells were positive for Cytokeratin AE1/AE3. (H&E, $\times 400$)

Fig. 6 Tumor cells were positive (arrow) for EBV LMP1.(H&E, $\times 400$)

large syncytial tumor cells with indistinct cell borders, round to oval vesicular nuclei, and large central nucleoli. Sometimes nuclei are chromatin rich. The cells appear crowded or overlapping, arranged in solid dyscohesive sheets, irregular islands, and trabeculae, intimately intermingled with variable numbers of lymphocytes and plasma cells [14]. Tumors with similar histological features have been described as lymphoepithelioma-like carcinomas (LELCs) in stomach, salivary gland, lung and female reproductive organs cervix, vulva, vagina, ovaries and endometrium [1–3, 7–12]. Patients with LELC in uterine cervix, like those in stomach, lung and breast, have shown a better outcome, than those with the usual squamous cell carcinoma in cervix [12, 13]. This may be because of pronounced host reaction to the neoplasm as well as the sensitivity of LELC cells to chemotherapy and radiotherapy.

They are said to be more common in Asian population. But LELC endometrium is rarely reported in Western as well as in Asian literature. Only three patients with LELC endometrium have been reported, 2 from University of California at Los Angeles, Torrance USA [11] and one from Rome Italy [12]. All were postmenopausal women aged 74, 55, and 57 years, and presented with bleeding per vagina. First was in FIGO Stage IVB and was alive free of disease for 9 months with chemotherapy, second was in FIGO Stage IIIC and died of disease one year after the diagnosis, and treated with radiotherapy and chemotherapy for 6 months and third was in FIGO stage IB and surviving 24 months after total hysterectomy with bilateral salphingo oophorectomy and pelvic abdominal lymphadenectomy. Our patient was also a postmenopausal woman presented for vaginal bleeding of short duration. Uterus showed classical LELC arising from the endometrial polypin addition to simple cystic hyperplastic endometrial glands and dense lymphoplasmacytic infiltration in the

Table 1 shows clinicopathological features of four cases of LELC endometrium

S. No	Age	FIGO stage	Tumor pathology	Treatment/follow up
1. (Ref [11])	74	IV B	Tan tumor 0.6 cm above endometrial surface, left adnexa, iliac, paraaortic and inferior mesenteric lymph nodes, serosa and mesocolon of sigmoid colon.	Total abdominal hysterectomy+systemic chemotherapy. Alive disease free 9 months after diagnosis.
2. (Ref [11])	55	III C	Ulcerated, haemorrhagic tumor in endometrial cavity, infiltrated half of myometrium Para-aortic lymph nodes	Total abdominal hysterectomy, radiotherapy and systemic chemotherapy. Died 1 year after diagnosis with extensive retroperitoneal tumor.
3. (Ref [12])	57	I B	Vegitant tan tumor involving half of posterior uterine wall. Cervix both adnexa, lymph nodes were free of tumor.	Total hysterectomy with bilateral salpingo-oophorectomy and pelvic-abdominal lymphadenectomy. Alive free of disease 24 months after diagnosis.
4. (Present case)	63	II B	Endometrial polyp contained tan tumor. Subserosal para-vascular and lymphovascular tumor emboli in uterus. Sub-serous deposit in rt tube. Metastases in 4/7 right pelvic lymph nodes.	Total abdominal hysterectomy bilateral salpingo-oophorectomy, pelvic paraaortic lymphadenectomy

stroma. The cystic glands in the polyp at places contained tiny clusters of epithelial cells in pseudo papillary pattern and some glands were lined by layer of syncytial cells. Both the patterns were having the cells morphologically similar to those of LELC. Rest of the uterine cavity showed atrophic endometrium. Tumor cell deposits were seen in outer myometrium, serosal layer of right fallopian tube and in right pelvic nodes Table 1.

The occurrence of LELCs and their association with EBV both vary in different geographic regions and different organs involved. The association EBV with LELCs stomach, lung, salivary gland, and thymus has been reported, [1, 3–5] but has not been reported with LELCs in renal pelvis, urinary bladder, breast or liver and in female genital tract such as vulva, vagina, cervix, ovary and endometrium [5, 7–12]. However the study from Taiwan reported the EBV gene sequences more frequently in cervical LELCs than in cervical squamous cell carcinomas [13].

The immunohistochemistry in all the three cases of endometrial LELCs revealed that the tumor cells were positive for cytokeratin (AE1/AE3) and epithelial membrane antigen (EMA) and negative for lymphoid markers. The association of EBV with LELC endometrium was negative in all the three cases [9, 10, 12, 13]. The tumor cells in the present case were also positive for cytokeratin (AE1/AE3), and the stromal lymphoid cells were positive for CD3 and CD20. The tumor cells were negative for both lymphoid markers. A few tumor cells in the present case showed positivity for EBV LMP1. The positive association of EBV with LELC uterine cervix has been shown in Taiwan patients [13, 14]. Systemic chemotherapy in patients with advanced ovarian LELC showed improved survival with no residual tumor in metastatic lymph nodes. Our patient was also referred to regional cancer center

for adjuvant radiotherapy and chemotherapy details of which are not known. However patient is doing well without any fresh symptoms.

We wish to conclude that both pathologists and clinicians should be aware of LELCs when they come across a case of undifferentiated or high grade carcinomas in endometrium and or sites in female genital tract. The recognition and long term follow up of large number of cases is needed to understand their biological behavior, their association with EBV and response to chemotherapy especially in patients of Asian countries. Thus it is important for both the pathologists and the attending physician to recognize this rare histological type to understand the role of EBV association and to study the effective treatment and the prognostic factors.

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