LYMPHOEPITHELIOMA-LIKE CARCINOMA OF THE CERVIX - DIAGNOSTICS, TREATMENT, MONITORING

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ABSTRACT

Lymphoepithelioma-like carcinoma of the cervix (LELC) is a rare subtype of squamous cell carcinoma.
This is a case report of a 40-year-old female patient diagnosed with LELC. The tumor is clinically presented as an exophytic mass on the front lip of the cervix. Magnetic resonance imaging (MRI) of the pelvis revealed a cervical tumor mass with a diameter of 21 mm. The findings of the preoperative pathohistological analysis of the biopsy tissue indicated LELC. The disease was clinically and radiologically staged as IB1 stage according to the 2009 FIGO classification, and the patient underwent surgical treatment. A total radical hysterectomy with pelvic lymphadenectomy was performed, followed by external beam radiotherapy.
The patient was regularly monitored with the last check-up on February 2024 (36 months) and MRI control of the pelvis and abdomen without signs of recurrence of the underlying disease. The patient is in good general condition, without subjective complaints and side effects of the applied therapy.
Key words: *lymphoepithelioma-like carcinoma of the cervix, LELC, cervical carcinoma, radical hysterectomy.*

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INTRODUCTION

According to the Global Cancer Observatory (GLOBOCAN), cervical cancer ranks fourth in incidence among malignant diseases in women, with a total of 570,000 new cases in 2018, accounting for 6.6% of all newly diagnosed cancers in women (1).

Lymphoepithelioma-like cervical cancer (LELC) is a very rare type of tumor, occurring in 0.7% of all cervical cancers (2). This histological type of tumor was first described in the nasopharynx, and then it was discovered in other anatomical locations, such as lungs, skin, salivary glands, gastrointestinal tract and urinary bladder (3). LELC typically occurs in younger women, more often in Asian and black women (4).

According to some authors, LELC is a variant of cervical squamous cell carcinoma that is associated with HPV infection (5,6).

Histologically, it is defined by infiltrative growth, poor differentiation and epithelial proliferation with abundant lymphocytic infiltrate. The proliferated epithelium forms nests that are surrounded by an intense inflammatory reaction with a predominance of lymphocytes, plasmocytes and eosinophils. Unlike other types of squamous cell carcinoma, LELC can sometimes be without a clinically evident mass or ulceration of the cervical mucosa. Morphologically, it is characterized by syncytial growth, mostly clearly delineated by a margin from healthy normal tissue (7).

Often, due to the localized nature of the lesion, inadequate cervical cytology and the small amount of tissue taken during cervical biopsy, preoperative diagnostics do not determine the LELC presence (3,8).

There are assumptions that LELC occurs associated with EBV (Epstein Barr Virus) infection, with the existence of concomitant HPV (Human Papilloma Virus) infection (4). This claim has been proven by some studies in patients of the Asian race, but not in other ethnic populations (5,9,10). Other studies did not determine the association of HPV infection of the cervix with the appearance of LELC, while some confirmed this relationship (11).

The prognosis of LELC has proven to be better compared to other types of cervical cancer, although the exact reasons have not been established (8).

CASE REPORT

A 40-year-old female patient was diagnosed with cervical cancer, without a previous history of malignant diseases.

From the medical history, it is learned that it is a subserous myoma of the uterine body that was operated laparoscopically in 2019 (two years before the diagnosis of cervical cancer), as well as that she had a breast segmentectomy due to fibroadenoma in 2009. Menarche occurred at the age of eleven. The patient had one cesarean delivery (twin pregnancy) and one spontaneous abortion in the first trimester of pregnancy. The family history is not burdened with malignant diseases.

During a regular gynecological examination, the existence of a tumorous change in the cervix was recorded, which was biopsied with an endocervical curettage (ECC).

The pathohistological findings of the sample were described as cervical cancer similar to lymphoepithelioma, and the patient was referred to the Oncology Commission for Gynecological Tumors at the Oncology Institute of Vojvodina (IOV) for a decision on further treatment and its implementation.

Clinically, an exophytic tumor mass with a diameter of about 3 cm was recorded at the 12 o'clock position, on the front lip of the cervix. The rest of the cervix, vaginal vaults, vaginal walls, and parametria were clinically tumor-free, according to speculum, bimanual and digitorectal examination.

The radiological evaluation of the disease with magnetic resonance (MR) of the pelvis and abdomen, as well as the radiogram (X-ray) of the chest in the anteroposterior projection is indicated for the patient.

The finding of the MRI of the pelvis and abdomen was described as an indistinctly limited ovoid infiltrative soft tissue change in the region of the anterior lip of the cervix, the largest diameter of 21 mm, without MR signs of infiltration of the parametrium, vaginal vaults, rectal wall, urinary bladder and without infiltration of the endometrium. The existence of altered lymph nodes in the pelvis and abdomen, as well as the existence of dissemination of the disease to the structures of the abdomen, were not described. No signs of dissemination of the underlying disease into the chest structures were described on the chest X-ray.

The patient was clinically and radiologically classified according to FIGO 2009 as IB1 or IB2 according to the new FIGO 2018 classification, and the decision was made to undergo surgical treatment.

The patient was admitted to the Gynecology Department of the Surgical Oncology Clinic of the Oncology Institute of Vojvodina for planned operative treatment.

SURGERY

Total radical hysterectomy type C2 was performed with left adnexectomy and right salpingectomy with preservation, elevation and fixation of the right ovary to the peritoneum above the level of anterior superior iliac spine. The place of the right ovary was marked with clips. Bilateral lymphadenectomy of the small pelvis was performed as well as the excision of the intraoperatively recorded change from the front wall of the rectum with placement of sero-serous sutures. The tissue specimens were sent for PH analysis.

HISTOPATHOLOGICAL FINDINGS

The macroscopic pathohistological finding is described as an exophytic white-gray tumor change in the cervix, measuring 25 x 20 x 13 mm, with the measured site of the deepest invasion of the cervical stroma of 13 mm.

Histologically, the tumor resembles a nasopharyngeal lymphoepithelioma-like carcinoma. The tumor is composed of poorly differentiated (G3) nests of squamous cells with uniform, vesicular and prominent nuclei and a moderate amount of cytoplasm, substantial nuclear and cellular pleomorphism and syncytial growth. There are no signs of the presence of keratinization and lack of intercellular bridges. Fibrovascular stroma was permeated by a dense lymphocytes infiltrate. There were no signs of lymphovascular invasion. The resection margins were negative for dysplasia or malignancy (R0 resection) (Figure 1).

The material of the lymph nodes contains a total of 22 lymph nodes in which there are no elements of malignancy. Reactive lymphadenitis is registered in all examined lymph nodes: right parailiac group - 7, left parailiac group -6, obturator right - 3, obturator left - 6.

In the excised specimen from the anterior wall of the rectum, described as muscularis propria tissue with subserosal and serosal layers of the rectal wall, two-millimeter endometriosis foci were found, without any elements of malignancy.

Other incidental findings indicate metaplasia of the planocellular epithelium of the cervical canal, supserosal and intramural uterine leiomyomas, bilateral paratubal cysts, corpus luteum cyst and endometriosis of the left ovary.

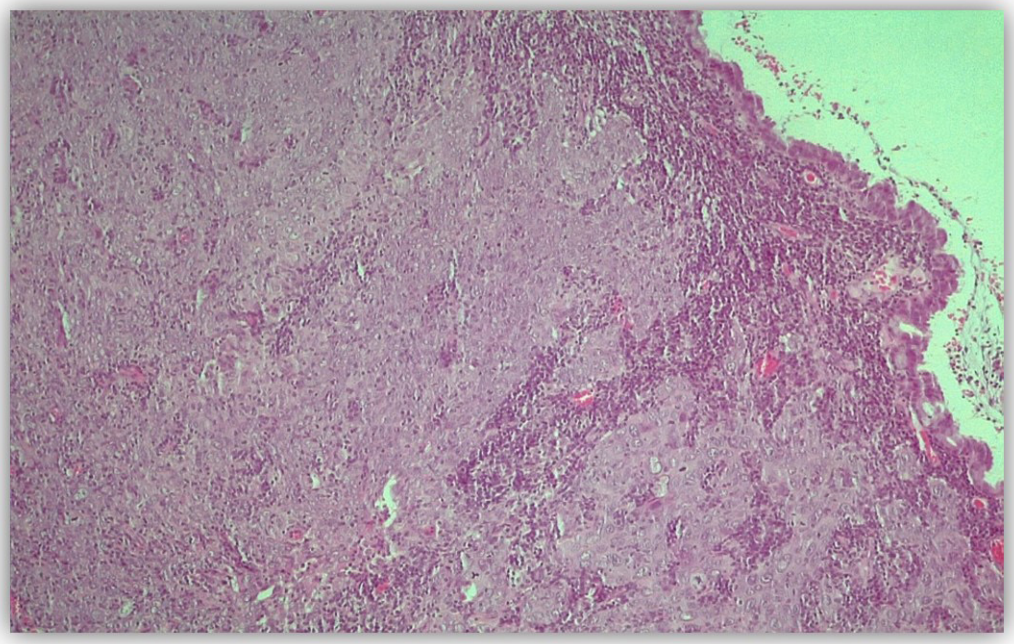

Figure 1. Pathohistological presentation of the surgically obtained tumor tissue preparation, stained with HE (hematoxylin-eosin) showing the presence of LELC.

The patient was presented to the Oncology Council for Gynecological Tumors of the IOV. Considering LELC as a rare subtype of squamous cell carcinoma, larger than 2 cm, FIGO IB2 and histologically poorly differentiated (G3), a decision was made to perform external radiation therapy with respect to the position of the preserved right ovary.

External beam radiation therapy (EBRT) was carried out five days a week for five weeks, according to the VMAT (Volume modulated arc therapy) protocol.

The patient was regularly oncologically monitored and controlled every three months for the first two years.

The last checkup was February 2024 (36 months) with MRI control of the pelvis and abdomen without recurrence of the underlying disease, as well as no deterioration of her general condition or local findings. The patient subjectively feels well and has no complaints or unwanted effects of the applied therapeutic modalities.

DISCUSSION

The LELC of the cervix is classified as a subtype of squamous cell carcinoma, which occurs very rarely in the general population. Considering such an epidemiological situation, there is a lack of information in the literature about the diagnosis and specifics of the treatment of this type of cancer. Much of the data comes from studies that studied the behavior of histologically identical tumor types in other anatomical locations, especially in the nasopharyngeal mucosa. Therefore, it is clear that there is not enough reliable data to set diagnostic standards for LELC, as well as official guidelines for its treatment.

Like most oncological diseases, the pathogenesis and etiology of LELC are unknown, and in the literature it has been found that EBV and HPV have an influence on its development. Several studies have established the existence of a connection between EBV infection and LELC, especially in Asian women, while some of the studies have determined that this connection is insignificant in white women, which shows the influence of specific racial and geographical factors on its occurrence (4,5,9,10). Some other studies have shown that there is no evidence that EBV is associated with LELC at all, but given the small number of samples, all these studies lack sufficient credibility. This implies that further research on this topic is necessary in order to reach the final scientific truth.

The biggest challenge in LELC is pathohistological diagnosis, which is the gold standard for diagnosing, given that the identification of microscopic parameters and characteristics that depict LELC is difficult and very demanding. There is a high chance of misdiagnosing the tumor as an inflammatory infiltrate in the tissue, especially when the inflammatory reaction is intense and obscures the tumor cells (7). In such situations, it is necessary to apply methods of immunohistochemical staining of cytokeratin and epithelial cell membrane antigens. These methods can also be useful for confirming the depth of cervical stromal invasion, especially when clusters of inflammatory cells are scattered in healthy tissue around cancer cells (3).

The problem of differentiation occurs in tumors that cause intense inflammatory response, as can be seen in adenosquamous carcinoma of the Glassy cell type (GCC), where proliferated tumor cells penetrate the cervical stroma, which is infiltrated by lymphocytes. The mentioned subtypes have completely different clinical behavior. Clear cell carcinoma is extremely aggressive and has a poor prognosis, while LELC is clinically more indolent and has a better prognosis, which indicates the importance of correct HP diagnosis (3).

The problem of diagnosing LELC can best be illustrated by the example of a study that took into account 59 reports and case series of patients with this type of cancer, conducted between 2001 and 2020 (12). The clinical examination of 59 patients revealed the presence of an exophytic cervical tumor mass in 11 of them, an endophytic lesion was seen in 5 patients, no clinically manifest change was found in 2, while no data on the clinical findings of the disease was given for 41 patients. These reports also demonstrate the fact that there are no macroscopic features that distinguish this subtype from other cervical cancers.

Out of 59 cases, cytological analyses of cervical smears were performed in 24 patients, which resulted in only 8 pathological findings, while the results of the remaining 16 findings were not even specified.

Only 18 out of 59 patients underwent preoperative tumor tissue sampling for a histopathological diagnosis. In only 7 of them (38.9%), preoperative PH was verified as LELC, in 4 patients from the material obtained by diagnostic conization and in 3 patients from the material obtained by biopsy. In the remaining 11 patients (61.1%), LELC was not proven, but the changes were described as high-grade intraepithelial lesion (HSIL), squamous cell carcinoma and unspecified poorly differentiated carcinoma (12).

In contrast to the above study, one case series showed that by colposcopically guided tumor biopsy, preoperative HP verified LELC in 11 out of 15 patients, while in the remaining 4 PH findings were described as undifferentiated carcinoma (4). In another series of cases, LELC was proven preoperatively after biopsy in only 38% of patients (in 7 out of 18), which further confirms the claims that preoperative diagnosis of LELC is insufficient and does not lead to an exact diagnosis for various reasons (13).

In a case series of 59 patients with LELC, the majority of patients had early-stage disease, with 48 of 59 being classified as FIGO stage IB. Out of a total of 59 women, 53 underwent radical hysterectomy, while 28 underwent adjuvant radiotherapy. After regular oncological controls and an average follow-up of 24 months (2-134), relapse was proven in 6 patients, 5 patients died due to disease progression, while in 48 (81.3%) the presence of disease was not proven (12). This epilogue of the follow-up of treated patients confirms the evidence presented by studies about the better progno-

sis of LELC in comparison with other types of cervical cancer, but it can be attributed to the fact that LELC is more often detected in the early stages and there is less lymphovascular invasion.

The study by Yordanov. et al. included 17 patients with LELC treated and monitored over a ten-year period, 13 of whom were in stage IB1, 3 in stage IB2 and one in IB3. A total of 16 out of 17 patients underwent total radical hysterectomy with bilateral lymphadenectomy, and then adjuvant radiotherapy was applied to all operated patients, just like our patient. The 5-year survival rate was 69% (14).

Considering the rarity of LELC in the general population and the consequent lack of experience in the treatment of this type of cervical cancer, as well as the lack of adequate literature data about the treatment, follow-up and outcomes of patients with LELC, new research on this topic, just like this study, can be useful in expanding and understanding the existing information and knowledge about this type of cancer and acquiring new ones.

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