

Case Report

Advance stage small cell neuroendocrine carcinoma of cervix: A case report

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Abstract. Neuroendocrine small cell carcinoma of the uterine cervix is an entity with very aggressive behaviour. The optimal initial therapeutic approach to this rare disease has not yet been clearly defined. These tumors are difficult to manage. It is often diagnosed at an advanced stage and its prognosis is generally poor. In this paper, a 44-year-old woman with small cell neuroendocrine tumor of the cervix presenting with widespread metastasis is reported. Literature provides limited research on the issue and the reported research involves only small series and case reports on neuroendocrine small cell cervical carcinoma. Neuroendocrine differentiation can be shown by several methods. The most important of all these methods is immunohistochemical study. Surgery, radiotherapy, and chemotherapy have been used either alone or in combination. The purpose of this case is to evaluate this rarely seen, aggressive, malignant cervical tumor with poor prognosis, and thus, make some contribution to the literature.

Key words: Chemoradiotherapy, immunohistochemical study, neuroendocrine small cell carcinoma

1. Introduction

Small cell neuroendocrine tumors of uterine cervix are rarely seen, but they are malignant tumors with poor prognosis and exhibit highly aggressive behavior (1). They constitute less than 3% of all uterine cervical cancers. Generally, they are divided into four categories: a) small cell; b) large cell; c) atypical cell; and d) classical carcinoid tumors (2). While the average age when the endocrine tumors are diagnosed is 44, it is 50 in small cell cancers. 80% of the neuroendocrine tumors are stained immunohistochemically. However, due to the existence of several pathological entities defined as small cell, dilemmas can be experienced in pathological diagnosis of these tumors. In the literature, there are very few reported studies and they involve

only small series and case reports on neuroendocrine small cell cervical carcinoma. Furthermore, the patients are at advanced stages in most of the reported cases. Yet, in the literature, there are a few small cell cancer cases which were diagnosed during pregnancy. As a result, the optimal treatment approach for these tumors still remains unknown. Even in early stage tumors, the death rate is higher than that of other histological types of cancers of the cervix. The purpose of this case is to evaluate this rarely seen, aggressive, malignant cervical tumor with poor prognosis and to underline the steps of the radiological and pathological diagnosis; thus, to make some contribution to the literature.

2. Case Report

A 44 year-old, gravida 3, parity 1 woman applied to the urology outpatient clinic in February 2009 with a complaint of suprapubic pain. Physical examination revealed tenderness and pain in the pelvic area. Ultrasonography showed thickening in the wall of left lateral bladder base and grade 1 widening in the left renal pelvis. Therefore, a bladder cold-cup biopsy was taken from the patient with sistoscopy, and subsequently, complete abdominal computed tomography (CT) was planned. The bladder cold-cup biopsy showed invasive carcinoma. Also, as a result of the subsequent immunohistochemical study on

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the biopsy samples, pancytokeratin, chromogranin and synaptophysin was found to be positive while cytokeratin 7, cytokeratin 20 and vimentin was negative. Thus, by the pathology, the pathology specimen was found to be compatible with "Small Cell Carcinoma" (SCC), made up of small round shaped cells which showed neuroendocrine differentiation. In the upper and lower abdominal spiral CT examination, not only a grade 1 widening in the left kidney collecting duct system was determined, but also at the infrarenal level, multiple lymph nodes, the biggest of which were 2x2cm were found. The cervix uteri was measured as 4.5x5.2 cm with a heterogeneous appearance. Thickening and contrast staining were observed in the left base of bladder and the left ureteropelvic junction. Additionally, myometrial heterogeneity was seen and there was some liquid in the endometrial cavity. There were lymph nodes, whose short axis reached up to 1 cm, in internal iliac chain.

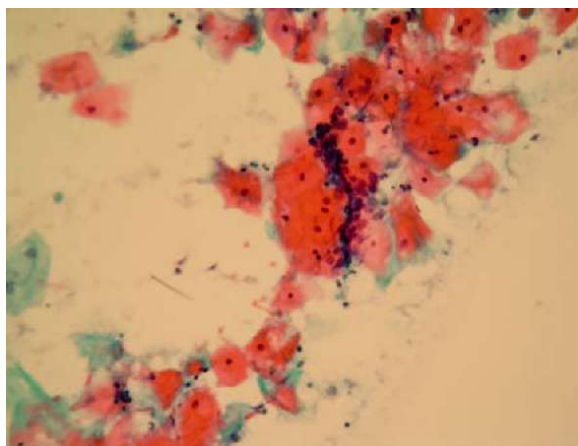


Fig. 1. Tumor infiltration seen in cervicovaginal smear (PAP x400).

These findings were compatible with the cancer of cervix uteri that showed invasion to left ureteropelvic junction. Then, in March 2009, the patient was referred to the obstetrics and gynecology outpatient clinic with a diagnosis of cervical cancer. In the speculum examination, there was an irregular ulceration in the cervix. In the manual examination, cervix was found to be bigger than normal and fixed. Vaginal walls were normal. Cervicovaginal smear, cervical punch biopsy and endometrial sampling were taken from the patient. The result of the cervicovaginal smear turned out to be positive in terms of malignancy (Figure 1). The result of the cervical punch biopsy was reported as "low grade small cell neuroendocrine carcinoma". In microscopy,

neoplastic infiltration made up of small round cells was seen, which started from mature squamous epithelium on the surface and advanced to the deeper levels in stroma. In some places, the tumor cells infiltrated the surface epithelium (Figure 2a). Mitotic activity was high in the tumor cells, which showed common crush artifacts and necrosis (Figure 2b). In the immunohistochemical study, the material was stained as P16 (+), synaptophysin (+) (Figure 3), chromogranin A (+), neuron specific enolase (+), pancytokeratin (+), cytokeratin 20 (-), cytokeratin 7 (-), CEA (-).

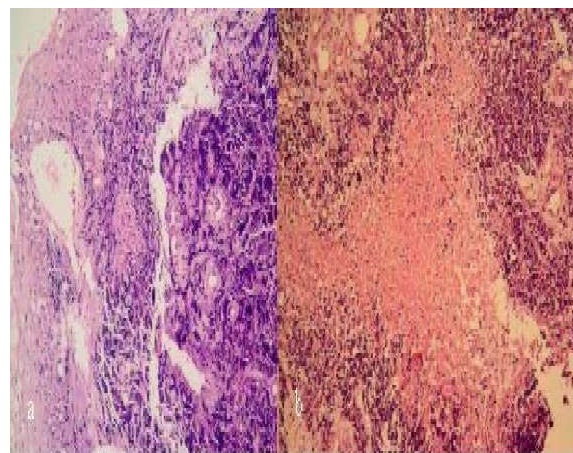


Fig. 2a. Cervical lesion infiltrating the surface epithelium (Hematoxylin-eosin x40), b. Common crush artifacts and necrosis with high mitotic activity tumor cells (Hematoxylin-eosin x40).

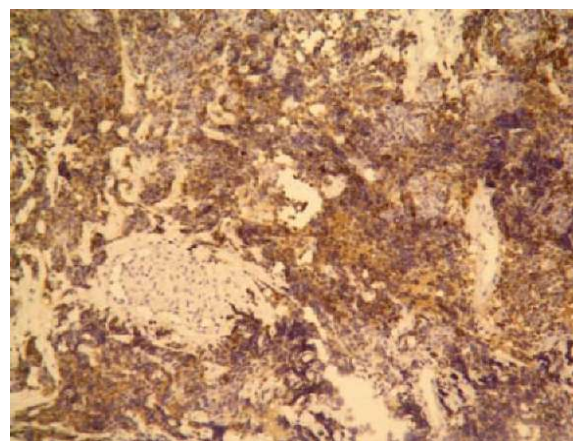


Fig. 3. Tumor cell stained synaptophysin positive (Synaptophysin x100).

Thorax spiral CT was performed to the patient, who was thought to have advanced stage cervical cancer, and no evidence could be found in favor of metastasis. In the biochemical results of the patient, no pathology could be seen except for the high LDH and creatinin values. Being regarded to

be inoperative, the patient was given chemoradiotherapy. After two courses of chemotherapy (cisplatin and etoposid combination), renal functions of the patient deteriorated. A single percutaneous nephrostomy and bilateral percutaneous nephrostomy 10 days later were performed to the patient. In the repeated thoraco-abdominal CT examinations, unlike the previous examinations, in the right hilar area and bilateral infraclavicular areas, lymph nodes over 1 cm were seen. In the liver, there were 7 hypodense lesions in accordance with the metastasis. There was also a progression in the cervical invasion of the lesion, found in the former CT, spread to the right parametrium and pelvic sidewall, and a new semi solid mass in the right adnexa, with a 70 mm diameter. It involved cystic areas, biggest of which was 45 mm. Whole body bone scintigraphy of the patient was found to be normal. At the beginning of the July 2009, thoracentesis was applied to the patient due to pleural effusion and no malignant cell detected in the liquid. The patient died as a result of cardiopulmonary arrest in July 2009.

3. Discussion

In this study, a 44 year-old women with small cell neuroendocrine differentiated tumor of the cervix presenting with common metastasis has been reported. In addition, surgical and medical treatment of neuroendocrine tumors with pathological diagnosis is emphasized. Neuroendocrine tumors originate from Kulchitsky cells which can be found in all parts of the body, and female genital area outside the cervix is naturally one of them. However research in this area is limited by only a number of case reports. The research for the etiology is still continuing. Normally, neuroendocrine cells can be observed in endocervix. It is asserted that this increases the development of neuroendocrine tumors. Furthermore, undifferentiated basal stem cells and mesoderm totipotent precursor cells are claimed to be the origin of neuroendocrine cells. Cervical tumors may originate from stem cells or totipotent precursor cells with glandular, squamous or neuroendocrine differentiation (3). In the frequently observed types of the cervical cancer, neuroendocrine cells are not rare, and there is published empirical evidence showing that this rate is 21% especially in adenocarcinomas. In a study of small cell neuroendocrine tumors, only human papillomavirus-18 was detected in all of the pure tumors and both the small cell neuroendocrine carcinoma and adenocarcinomatous components in the mixed tumors. Therefore, this viral agent

must also be considered while examining the etiopathogenesis. Also chromosomal deletions on 3p was found in small amount of endocrine tumors (4). Pathological diagnosis of neuroendocrine small cell tumors necessitates an experienced pathologist because there are many pathological entities which are described as small cell cancer, such as fully differentiated small cell non keratinizing squamous cell carcinoma, reserve-cell carcinoma and neuroendocrine carcinoma. Neuroendocrine differentiation can be shown by several methods. The most important of all these methods is immunohistochemical study with chromogranin A, neuron specific enolase (NSE) which was implemented in this study. Chromogranin A is a more specific stain on this issue. The case in this study was positive in terms of the two stains and of synaptophysin and P16. In the literature, there are studies that have been conducted to show the presence and significance of neuroendocrine differentiation in a specific tumor, especially on gastrointestinal tract and lungs, and these studies have concluded that this differentiation is related with poor prognosis and survival. For instance, in colorectal carcinomas, the patients with chromogranin A stained neuroendocrine cancer cells have been compared to those with unstained cells, and prognosis has been determined to be exceptionally poor in the patients with positive staining (5). The small cell carcinomas of cervix that show neuroendocrine differentiation have very poor prognosis. Race, age and stage of the tumor seem to be the prognostic factors. Of all these, the most important prognostic factor is lymph node metastasis (6). While the lymph node invasion in neuroendocrine tumors is 38%, it is 50% in small cell tumors. No significant difference could be found between neuroendocrine and small cell carcinomas in terms of estimated survival time and this duration is 30 months after the diagnosis (7). Another factor that results in the decrease of the survival time is a tumor's diameter which is larger than 4 cm. In our case, the patient had both lymph node and organ metastasis. Furthermore, tumor's diameter was larger than 4 cm in the patient; therefore, prognosis was very poor. The optimal treatment approach in these tumors is still unknown due to the rarity of the cases. However, they are extremely aggressive tumors and five year survival is 36,8% even in the early stage diseases. The literature indicates that systematic combinations are essential for this aggressive tumor. Chan et al. (8) showed that radical hysterectomy improved survival in local tumors, which are at early stages and which are smaller than 2 cm. Without doubt, surgical

approach should be staging surgery. Lee et al. (9) compared adjuvant chemotherapy, adjuvant chemoradiotherapy and neoadjuvant chemotherapy among patients who have diagnosis of stage IB-IIA small cell carcinoma of the cervix. The effectiveness of neither neoadjuvant chemotherapy nor adjuvant chemoradiotherapy could be proven. In their retrospective study, Cohen et al. (10) suggested that adjuvant chemotherapy or adjuvant chemoradiotherapy sustained longer survival rates. Briefly, neuroendocrine tumors of cervix are chemosensitive tumors. Cisplatin and etoposide are the most frequently used agents. It has been shown that platinum and etoposide (PE) or vincristine, adriamycin and cyclofosamide (VAC) chemotherapy protocols increased the estimated survival rates. However, the average survival duration after the diagnosis has still not been extended. There is a need for the systemic regimes for the treatment. However, in the presence of small series and a few case reports it is difficult to analyze the effects of a treatment. In this study, too, the patient was diagnosed at an advanced stage, and having not benefited from the systematic chemotherapy, the patient was consequently lost 5 months later.

4. Comments

As a result, the rarity of the neuroendocrine tumors of cervix has hindered the adequate amount of prospective clinical research on this type of tumors. Therefore, the optimal treatment standards have still not been set. The prognosis is still very poor and they are generally diagnosed at advanced stage. It is imperative that the rare cases similar to the current study continue to be published in order to be able to create universal diagnosis and treatment protocols.

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