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Neuroendocrine carcinoma of the cervix: Rare case report with review of literature

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Abstract
Small cell neuroendocrine carcinomas of the female genital tract are uncommon. They account for only around 2% of all the cervical cancers. Owing to their rarity and the lack of randomized trials, the diagnosis and treatment modalities of these tumors are unfamiliar and are mostly based on the neuroendocrine cancers of the lung. In spite of multimodal management strategy, the prognosis stays bad. We report a rare case of small cell neuroendocrine carcinoma of the cervix along with a brief literature review that is focused on the various aspects of this rare tumor.

Keywords: small cell neuroendocrine carcinoma, cervix, radiotherapy, chemotherapy

Introduction

Small cell carcinoma is a variant of neuroendocrine tumor that originates in the neuroendocrine cells seen throughout the body. It is known for its aggressiveness and is related to bad prognosis, even if caught at its initial stages. We received a rare and unusual neuroendocrine carcinoma of the cervix that encouraged us to do a brief literature review about this uncommon tumour in an unusual location.

Case report

Thirty-seven years old female patient presented with menorrhagia and dyspareunia. No urinary or digestive signs were noticed. Speculum examination of the cervix showed large polypoidal tumour arising from anterior lip of cervix approximately 6 cm long. Slight enlargement of the uterus is noticed at pelvic examination and the parameters were free. Gross examination of the excised tumor revealed grey brown soft tumour tissue. Microscopic examination showed tumor cells arranged in anastomosing trabeculae and nests [Fig 1]. Individual tumour cells were seen to exhibit moderate atypia and coarse chromatin. Mitotic activity was moderate [Fig 2]. Large areas of necrosis were seen. There was no sign of keratinisation. The tumour was seen to be infiltrating the cervical stroma. No normal cervical epithelium was noticed.

An initial diagnosis of small cell non keratinising squamous cell carcinoma of the cervix was made to be confirmed with immunohistochemistry. Immunohistochemical study with high molecular weight cytokeratin showed complete negativity. Further immunohistochemistry with synaptophysin showed strong positivity [Fig 4]. A final diagnosis of small cell neuroendocrine carcinoma of the cervix with extensive necrosis was made.

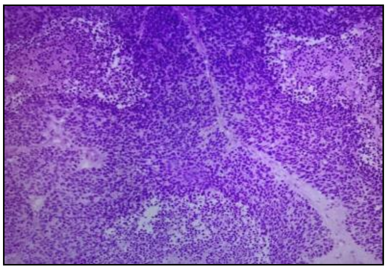

Fig 1

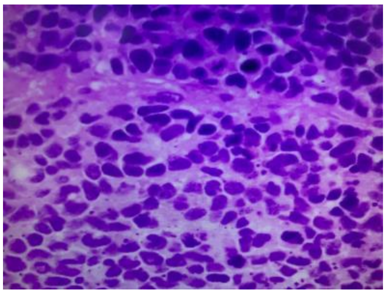

Fig 2

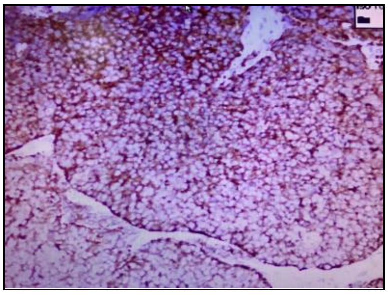

Fig 3

Discussion

Neuroendocrine carcinoma (NEC) is an uncommon malignant neoplasm with a bad prognosis, more commonly located at the lung and gastrointestinal system. NECs constitute only about 3% of all cancers of the cervix, the majority of which are squamous cell carcinomas [1, 2]. MEC was first described in 1957 [3]. The exact incidence of NEC is underestimated since it is known by various different terminologies such as carcinoid, oat cell tumour, small cell carcinoma, undifferentiated carcinoma and intermediate cell carcinoma [1, 3]. In an attempt of homogenising the NECs, Albores-Saavedra *et al*., rendered a proposal of classifying all NECs into 4 subtypes, that includes small cell neuroendocrine cancers, the most common subtype featured by high mitotic index, large areas of necrosis, invasion of the blood vessels and are often related to human papillomavirus infection. Rest of the subtypes include large cell neuroendocrine cancers and well differentiated neuroendocrine lesions that constitute atypical and typical carcinoid tumors [4]. Owing to the usage of this common classification by pathologists all over the world, there has been an increased incidence of NECs of the cervix during the past two decades. Retrospective studies done on cervical neuroendocrine cancers also highlighted many features of NECs that were unique to this unusual site.

The MECs are known to affect people of age between 20 and 87 with 42 years being the median affected age [2, 5], which seems to be a younger age group when compared with the age group affected by the squamous cell cancers of the cervix. The clinical presentation is frequently nonspecific, followed by metrorrhagia and leucorrhoea. Pelvic mass is often noticed on examination. Very occasionally, patients were seen to present with signs and symptoms of paraneoplastic syndrome (cushing's syndrome, hypoglycemia, syndrome of inappropriate secretion of antidiuretic hormone, carcinoid syndrome and hypocalcemia).

Owing to the inefficiency of cervical pap smears in identifying small neuroendocrine cells, unlike abnormal squamous cells, NECs are often diagnosed at their later stages [6, 7]. Diagnosis of NEC is based on histological examination and needs confirmation with immunohistochemical study with at least one neuroendocrine tumour marker (chromogranin A, synaptophysin, specific neuron enolase). Grossly, NECs of the cervix are mostly endocervical. Two major presentations are usually seen: large nodular mass with little attachment to the cylindrical epithelium and multiple small nodular basaloid tumors [8].

On microscopic evaluation, NECs present as a histological spectrum varying from typical or atypical carcinoid tumor to small cell neuroendocrine carcinoma. Neuroendocrine cells are very diverse in their size, argyrophilia, immunohistochemical nature and ultrastructure. They are recognised by means of Grimelius histochemical staining and in electron microscopy by identification of neurosecretory or argyrophilic granules, in immunohistochemistry by a positive synaptophysin, chromogranin, neuron specific enolase and antibodies for insulin or gastrin. Occasionally, neuroendocrine cells can be identified by their ability for ectopic production of adrenocorticotropic hormone, melatonin stimulating hormone, serotonin, histamine or amylose. Mannion *et al*. did a comparison study on the histologic features and the prognosis of the 4 subtypes of NECs; small cell NECs had the worst prognosis similar to the small cell carcinomas of the lung. They are characterized by extensive necrosis, high mitotic index, and enormous lymphovascular invasion with a close relationship with human papilloma virus strain 18 [8].

Owing to the strong propensity for local and distant spread, the evaluation of NEC patients must include radiological assessment of abdomen and pelvis, preferably by magnetic resonance imaging. Recently, and with the objective of enhancing NEC staging, positron emission tomography has been shown to have increased efficiency in identifying pelvic and lumbar-aortic lymph node involvement, permitting double evaluation of target lesions from a morphological point of view as well as metabolic point of view and hence it is considered as the best tool, especially when you wish to better monitor the efficiency of a treatment [9].

Staging is mandatory in all cervical cancers. However, it is essential to assert the elevated risk of lymphovascular involvement and the increased rate of recurrences in extra pelvic sites. For instance, the early lymph node involvement identified by locoregional lymphadenopathy was seen in 40% of stages IB NECs that are less than three cm in diameter. In 60% of these NECs lymphovascular involvement was noticed at initial diagnostic point. The average time of occurrence of recurrence is 19.9 months [10]. Metastatic spread is more frequently that of bone, lung and supraclavicular sites. The management of NECs of the cervix is designed on that of squamous cell carcinomas, also taking into consideration the features of NECs of the lung.

For low stage I-IIA cancers with limited local spread, regional treatment seems to be insufficient. Researchers reported disappointing data suggesting very low survival rates in patients who received local treatment even at their earliest stages [11, 12]. Hence systemic treatment seems to be essential at all stages which is being attributed to early lymphovascular involvement and frequent lymphovascular relapses [13]. Studies done to compare local treatment and systemic chemotherapy reported significant improvement in the overall patient survival rate with systemic chemotherapy. Some studies found neoadjuvant chemotherapy to be useful [14].

Because of the absence of clinical trials agreeing on the most effective treatment for NECs of the cervix, a multimodal approach is usually preferred. A better clinical outcome has been reported when a combination of radiotherapy, chemotherapy and surgery. The best outcome was recorded in patients with tumours less than 2cm treated with radiotherapy [15]. Tumors that are spread locally and inoperable, a combination of chemotherapy and radiotherapy is generally suggested [16]. In the case of metastatic or recurrent disease, chemotherapy, consisting of a combination of drugs, is recommended. Prognostic factors are tumor size, clinical stage, extent of metastatic lymphadenopathy, small cell type histology and tobacco use. The only predictive factor of survival seems to be the clinical stage of the disease. The most frequent sites of relapse are metastatic bone and lung lesions rather than local relapse [17].

Conclusion

Larger clinical trials conducted at multicenter levels are essential to try to identify and streamline a unanimous and efficient management protocol for small cell NECs of the cervix for the purpose of improving patient outcome.

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