ORIGINAL RESEARCH PAPER
Volume - 13 | Issue - 05 | May - 2024 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MIXED SQUAMOUS CELL CARCINOMA AND SMALL CELL NEUROENDOCRINE CARCINOMA OF CERVIX: REPORT OF A RARE CASE

Oncopathology

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ABSTRACT

Purpose: Mixed squamous cell carcinoma and neuroendocrine carcinomas are very rare and so far only two cases have been reported, one from Vietnam in a lady with primary breast cancer and the other recently diagnosed case from Malta. Here we are presenting a case report of a mixed squamous cell carcinoma and small cell neuroendocrine carcinoma of the cervix to highlight the fact that these types of cancers can exist together and hence we need to be more cautious while diagnosing such cases, so that ideal treatment can be started as soon as possible. **Method:** Relevant history was taken from a 65 year old postmenopausal female presented with complaints of acute retention of urine, bleeding per vagina for 1 week, white discharge per vagina for 3 months. There was no history of cancer in the family. USG whole abdomen reveals an irregular hypoechoic mass lesion in the cervix. CT whole abdomen also revealed the same with the presence of multiple intraabdominal and a single inguinal lymph node. FNA sample from the inguinal lymph node was taken and reporting was done accordingly. Simultaneously biopsy was taken from the growth and immunohistochemistry was performed to confirm the diagnosis. **Result:** The final diagnosis came out to be mixed squamous cell carcinoma and small cell neuroendocrine tumor of the cervix. She has been planned for palliative chemotherapy. **Conclusion:** Because of the rarity, such types of malignancies should be thoroughly discussed to know about the presentation, prognostic factors and treatment protocol.

KEYWORDS

Squamous, Neuroendocrine, Immunohistochemistry, Palliative, Chemotherapy.

INTRODUCTION: Squamous cell carcinoma accounts for approximately 70-80% of all cervical cancers [1], most of which are non-keratinizing squamous cell carcinoma. On the other hand, neuroendocrine carcinoma accounts for only 2% of the female genital tract [2]. But combined squamous cell carcinoma and neuroendocrine carcinomas are very rare and so far only two cases have been reported, one from Vietnam in a lady with primary breast cancer [3] and another recently diagnosed case from Malta [4]. Most non-keratinizing squamous cell carcinomas are associated with Human Papilloma Virus (HPV) 16 and 18 and similar etiology has been identified in most of the neuroendocrine carcinomas [5], hence a common pathway of development of both tumors can be considered. However, the neuroendocrine component is more aggressive, show early lymph nodal metastasis, and is associated with a poorer prognosis than concurrent squamous cell carcinoma and hence most treatment protocols are targeted against the neuroendocrine part [6].

Case Presentation:

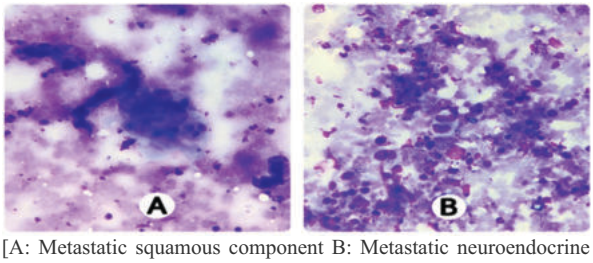
A 65 years old lady presented with complaints of acute retention of urine, bleeding per vagina for 1 week, white discharge per vagina for 3 months along with the presence of burning micturition. The patient was postmenopausal for the last 20 years and her previous cycle were regular. She has 4 living children and her last childbirth was 30 years ago. She had no history of addiction to any abusive substance neither she had significant history of any illness or any history of surgery. There is no history of cancer in the family.

On per vaginal examination, the cervix was found to be replaced by an infiltrative growth reaching up to the lower one-third of the anterior vaginal wall and upper two-thirds of the posterior vaginal wall. On per rectal examination, rectal mucosa was free from tumor. A single mobile right inguinal lymph nodes measuring 2.5x2.5 cm was present.

[Per vaginal examination showing infiltrative growth at cervix]

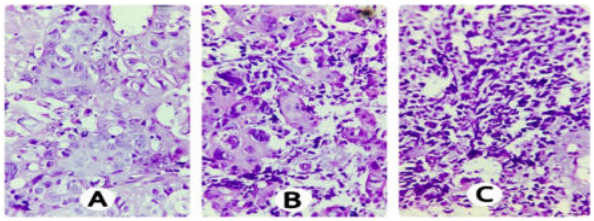
USG whole abdomen revealed an irregular hypoechoic mass lesion in the cervix infiltrating the urinary bladder wall. CT whole abdomen showed a large lobulated heterogeneously enhancing necrotic soft tissue mass involving the cervix, infiltrating the posterior wall of the urinary bladder and compressing the rectum, extending into bilateral parametrium. Inferiorly it involved the lower vagina and reached upto the level of the introitus. Prominent aortocaval, and paraaortic nodes were seen - the largest one measures approximately 14 x 10 mm. A few prominent mesorectal nodes were also seen. An enlarged node was seen in the right inguinal region measuring 27x24 mm. Enlarged external iliac nodes were seen bilaterally.

Fine needle aspiration cytology (FNAC) from the inguinal lymph node was reported as metastatic poorly differentiated squamous cell carcinoma. It showed presence of scattered and occasional clusters of atypical squamous cells along with a few atypical cells with irregular hyperchromatic nuclei, inconspicuous nucleoli and scant to absent cytoplasm in a background of necrotic material and hemorrhage.



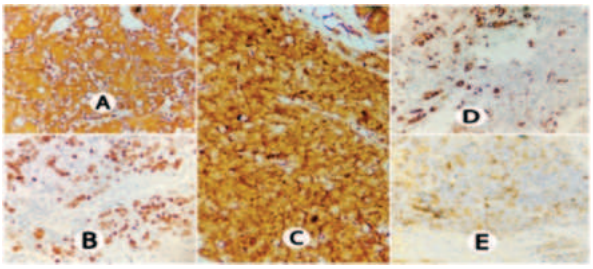
[A: Metastatic squamous component B: Metastatic neuroendocrine component]

Histopathological examination (HPE) of cervical growth showed features of poorly differentiated carcinoma consisting of areas resembling keratinizing squamous cell carcinoma admixed with small hyperchromatic cells with finely stippled chromatin and scant cytoplasm showing crush artifacts and areas of necrosis, probably suggesting neuroendocrine carcinoma.



[A: Squamous component B: Mixed squamous cell and neuroendocrine component C: Neuroendocrine component]

The immunohistochemistry report showed that the squamous cell components were strong and diffusely positive for CK, P40 and the atypical hyperchromatic cells were positive for synaptophysin and showed patchy positivity with CK. Both components were diffusely positive for P16. These findings confirmed the presence of mixed squamous cell carcinoma and small cell neuroendocrine carcinoma components in the cervical growth. Since both the components were positive for P16, an association with HPV can be considered.



[A: Squamous component showing diffuse and strong CK positivity. B: Squamous component showing nuclear staining for P40. C: Both squamous and neuroendocrine component are positive for P16. D: Neuroendocrine component showing patchy positivity for CK. E: Neuroendocrine component showing Synaptophysin positivity]

DISCUSSION:

Squamous cell carcinomas are common in the elderly age group, but neuroendocrine neoplasms can occur at ages ranging from 22 years to 87 years with a mean age of diagnosis of 45 years [7,8]. Their etiology of the concurrent occurrence of squamous cell carcinoma and neuroendocrine carcinoma is not clear but a multidirectional differentiation of origin from stem cells has been suggested in such tumors arising from the oral cavity. According to this study, both components can be differentiated from single stem cells by bidirectional proliferation or neuroendocrine carcinoma can arise secondarily from squamous cell component or vice versa [9,10]. Diagnosis of such tumors is possible only by having suspicious morphology in histopathological slide examination and doing confirmatory immunohistochemistry. Being very aggressive tumors, they show early dissemination and a similar picture has been noted in our case also. It was suggested that the treatment of primary neoplasms comprising of multiple histological types is tailored to the most histologically aggressive tumor [11]. Hence, the regimen for treatment is similar to neuroendocrine carcinoma alone. Although due to very less prevalence, there are no documented treatment guidelines for this type of concurrent carcinoma, but surgery is recommended, followed by adjuvant therapy in the early stage of the disease [12]. Treatment also depends on tumor dissemination, nodal status and the general health condition of the patient.

Some authors have therefore used multimodality approaches, comprising of the therapy of cervical cancer in general along with treatment protocol of neuroendocrine tumors of the lung in particular. In 2011, the Society of Gynecologic Oncology (SGO) published an article on the management of women with neuroendocrine carcinoma in cervix [13]. SGO recommends etoposide/platinum-based chemotherapies which should be managed similar to gastro-enteropancreatic neuroendocrine tumors. In 2014, the Gynecologic Cancer Inter Group (GCIG) recommended radical surgery for early stage disease, either primarily or after neoadjuvant chemotherapy and chemoradiation and systemic chemotherapy consisting of etoposide and cisplatin for advanced stage disease [14]. Various chemotherapy regimens have been used since ages, for example, Yin et al. used a combination of cisplatin and etoposide in 23 cases with high success rate [15]. Other chemotherapy regimens described in the literature are cisplatin/irinotecan, carboplatin/ paclitaxel, and cisplatin/ vincristine/ bleomycin.

CONCLUSION:

These cancers can behave very aggressively like small cell carcinomas of cervix and the prognosis is poor. Diagnostic pitfalls can lead to the identification of a single component and thus they can progress despite aggressive treatment against the known component. Here we are presenting a case report of a mixed squamous cell carcinoma and small cell neuroendocrine carcinoma of the cervix to highlight the fact that these types of cancers can exist together and hence we need to be more cautious while diagnosing so that ideal treatment can be started and better patient outcome achieved.

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