



Case Report

Carcinoid tumor of cervix with recurrence - a rare case report

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Introduction

Neuroendocrine tumors of the cervix are rare and are often under diagnosed or misdiagnosed. Because these tumors are very aggressive, early diagnosis and prompt treatment are warranted.

Neuroendocrine tumors of the uterine cervix describe cervical neoplasms that show the histological characteristics of carcinoid, including argyrophilia and/or argentaffinia and immunoreactivity for chromogranin, synaptophysin and neuron-specific enolase. Histologically carcinoid tumors are composed of monotonous sheets of small, round cells with uniform nuclei and cytoplasm¹.

Case report

A 30 year old Hindu woman G₄P₄A₀ presented on 22nd July, 2005 complaining of pain and swelling in left lower limb and vomiting. She had no diarrhea and no episodes of flushing. Her child birth was 9 years back.

She was non-alcoholic and non-smoker. Her family history was non-significant. She was having no past history of tuberculosis, diabetes mellitus and hypertension.

Her last childbirth was 9 years back. She had a total abdominal hysterectomy with bilateral salpingo-oophorectomy in a private hospital on 22nd January, 2005 for metrorrhagia. Histopathological examination of operated specimen showed adeno-squamous carcinoma of cervix. She had received no adjuvant treatment. She was not having any preoperative details. Patient did not have any complaints till June 2005, when she started complaining of pain in left lower limb with swelling. This pain was progressive in nature. She was having no symptoms of carcinoid syndrome. On clinical examination pallor and pitting edema on left lower limb were present. There was a diffuse tender mass in the left iliac fossa. On vaginal examination the vault was healthy. Rectal examination revealed a growth in the left parametrial region. Histopathological review of previous slides revealed a neuroendocrine type of tumor of the cervix (malignant carcinoid tumor). Her chest x-ray and skeletal survey showed no abnormality. CECT scan of whole abdomen and pelvis (Figure 1 and 2) revealed a large irregular malignant left adnexal mass at the left pelvic wall with iliopsoas muscle infiltration and with multiple enhancing ill defined polypoidal masses on left lateral wall of urinary bladder with left

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para-vesical stranding, and para-aortic and retrocaval lymphadenopathy. An ultrasound guided tru-cut biopsy was taken from the left adnexal mass. Immunohistochemistry was performed on this tru-cut biopsy specimen. Neuroendocrine differentiation was evident with 100% of cells reacting positively for chromogranin, synaptophysin and neuron specific enolase. Reactivity for keratin was also diffusely positive. Vimentin and S-100 protein were negative. Tru-cut specimen was compared with the original cervical tumor specimen, morphologically and immunohistochemically. Because of the phenotypic and immunophenotypic similarity, both cervical (Figure 3) and adnexal mass (Figure 4 and 5) was considered to be the same tumor viz., malignant carcinoid tumor.

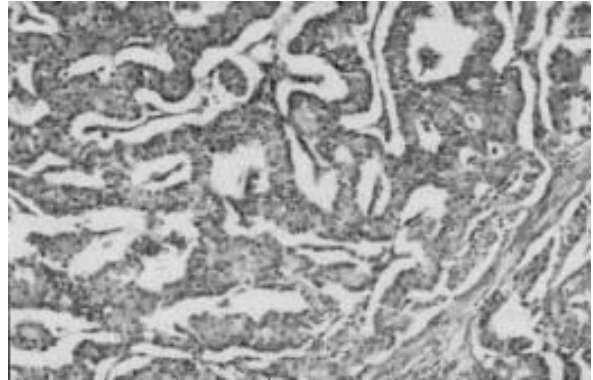


Figure 3. H & E section showing neoplastic cells arranged in solid nests, trabeculae anastomosing bands and rosette like pattern. Cytoplasm is vacuolated and mitotic activities are inconspicuous.

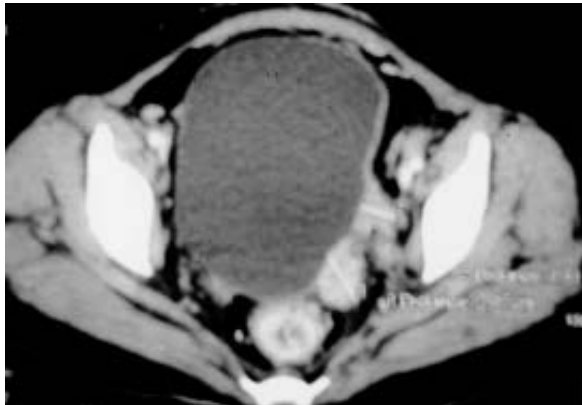


Figure 1. CT of pelvis showing soft tissue masses on the left lateral wall of urinary bladder.

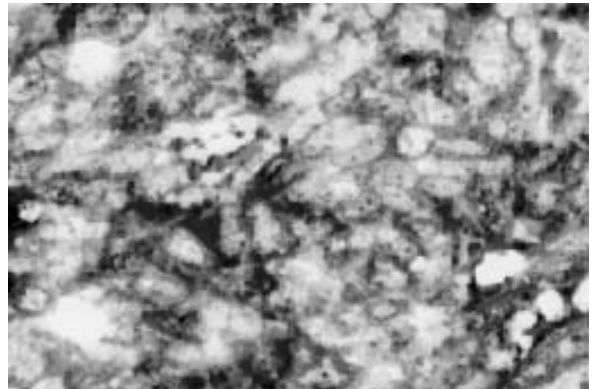


Figure 4. (Neurone specific Enolase (NSE) stained section showing neoplastic cells arranged in solid nests, bands and rosette pattern with goblet cells stained with the NSE.

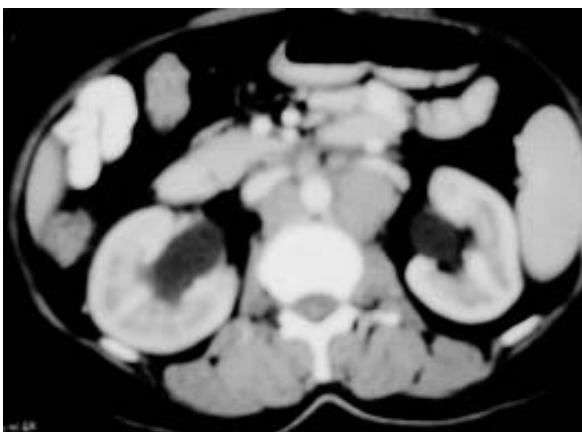


Figure 2. CT of lower abdomen showing multiple nodal masses in para-aortic and retrocaval region.

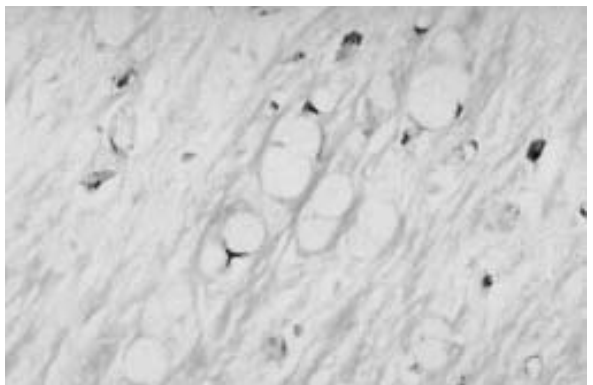


Figure 5. Immunoperoxidase staining with antisynaptophysin and antichromogranin antibody confirming neuroendocrine differentiation of the adnexal mass.

Urinary 5-HIAA was 24 mg/24 hour (normal, 0-10 mg). Plasma albumin was low at 2.9 g/dL (3.5-5.5 g/dL). Liver function tests were normal with an alkaline phosphatase of 105 U/L (39-117 U/L), aspartate aminotransferase of 42 U/L (0.65 U/L), alanine aminotransferase of 33 U/L (0-65 U/L) and total bilirubin of 1 mg/dL (0.3-1.1 mg/dL). Renal function tests were also within normal limit.

Because of the extensive metastasis, the patient was considered inoperable. She was given opioids for severity of pain. Subsequently, the pain went on worsening, for which a nerve block was considered but could not be given due to extensive involvement. She received palliative chemotherapy with adriamycin 5-fu and cyclophosphamide. She expired in October 2005.

Discussion

Neuroendocrine tumors of the uterine cervix are uncommon, with a range of frequencies from less than 0.5 to 5% of cancers of the cervix. The etiology of these rare neuroendocrine tumors remains unknown. Because the normal endocervix contains as may as 20% of argyrophilic cells resembling endocrine cells, neuroendocrine tumor formations may arise from these cells.

Neuroendocrine tumors of the cervix show expression of neuroendocrine markers, often argyrophilia, and characteristic morphological features defined by electron and light microscopy. Among the carcinomas of the endocervix with neuroendocrine differentiation, small cell carcinomas are well characterized². Non-small cell neuroendocrine carcinomas of the uterine cervix however have rarely been described and are probably under- or misdiagnosed.

Incidence, clinicopathological features, biological behavior and natural history of these tumors have been difficult to estimate because various descriptive terms have been used for their broad morphologic spectrum of the uterine cervix. Analogous to pulmonary neuroendocrine tumors, four general categories of neuroendocrine tumors of the uterine cervix have been suggested: typical (classical), atypical carcinoid tumors, large cell neuroendocrine carcinomas, and small (oat) cell carcinomas. Carcinoid tumors occur in diverse sites such as the lung, biliary tree, pancreas, stomach, duodenum, small intestine, colon, rectum, ovary, cervix, testis thymus, kidney and larynx.

Although an adenocarcinoma of the uterine cervix can be associated with all four aforementioned categories of neuroendocrine tumors of the cervix, a misdiagnosis as moderately or poorly differentiated adenocarcinoma instead of carcinoid tumor can easily be made if glandular differentiation within the neuroendocrine tumor, a separate component of non-neuroendocrine adenocarcinoma, adenocarcinoma in situ, or combinations thereof, are present. In our patient, the diagnosis of atypical carcinoid was based on the cervix and adnexal mass showing features such as- neoplastic cells arranged in solid nests, trabeculae, anastomosing bands and rosette like pattern. Cytoplasm was vacuolated and mitotic activities are inconspicuous, and there was a strong positive reactivity for chromogranin, synaptophysin and neuron specific enolase. In addition, our patient presented with urinary levels of 5-HIAA two times above normal. The specificity of urinary 5-HIAA for carcinoid is reported to be between 88 and 100%^{3,4}.

Electron microscopy and immunohistochemistry play an important role in the complete evaluation and diagnosis of less-differentiated cervical neoplasms in order to specifically identify the primary cell (cells) of origin. In our case, the initial diagnosis was adeno-squamous carcinoma, which after proper immunohistochemical examination turned out to be malignant carcinoid tumor.

Neuroendocrine carcinomas of the cervix are regarded as highly aggressive tumors⁵ with subclinical hematogenous and lymphatic metastasis frequently seen even in early disease. Neuroendocrine features in poorly differentiated carcinomas of the cervix indicate a poor outcome. Sixty-five percent of patients with cervical non-small cell neuroendocrine carcinomas die within 3 years of diagnosis³. Carcinoid tumor cells that stain positive for CEA indicate a poor prognosis and often contain features of adenocarcinoma⁶.

Treatment of neuroendocrine tumors of the cervix depends on the stage of the disease. In patients with inoperable metastatic carcinoid tumors, various chemotherapeutic regimens have been tried but none gives a good response. The average duration of remission is less than 1 year. Therapy with somatostatin analogs, such as octreotide and lanreotide, has resulted in reduction of the hormonal manifestations of the carcinoid syndrome⁶⁻⁷.

A neuroendocrine tumor of the cervix, such as an atypical carcinoid, should be considered when an adenocarcinoma of the cervix is diagnosed. Clinical signs and symptoms of the carcinoid syndrome should be pursued. If carcinoid syndrome is suspected, a urinary 5-HIAA level should be obtained. Treatment of a cervical neuroendocrine tumor should be aggressive and directed toward the adenocarcinoma element.

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