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NEUROENDOCRINE CARCINOMA OF THE UTERUS

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Abstract

Neuroendocrine carcinoma of the cervix and endometrium are very rare and aggressive tumours. The present case study is of a 52 year old female who was a known case of hypertension and diabetes mellitus and presented to Sir Ganga Ram Hospital with postmenopausal bleeding per vaginum with moderately differentiated adenocarcinoma reported on endometrial biopsy done outside. Patient underwent total Laparoscopic Radical Hysterectomy with staging and bilateral pelvic lymphadenectomy. Her final FIGO staging was stage Ib. Histopathology confirmed poorly differentiated endometroid carcinoma of fundus of uterus involving up to 2/3rd of myometrium with immunohistochemistry positive for cytokeratin, synaptophysin and 10-15% of tumour cells positive for Ki67, thus confirming the diagnosis of neuroendocrine carcinoma. So, it was concluded that the diagnosis of neuroendocrine carcinoma has to be kept in mind while treating patients with bleeding per vaginum especially in perimenopausal and postmenopausal group. A multispeciality approach is a key to the management on such a group of patients, to yield the best of results.

Introduction

Neuroendocrine carcinoma is most commonly found in lungs and rarely can be seen involving gastrointestinal tract.[1] The occurrence of these tumors in the female genital tract is very rare and have predilection to involve cervix and ovary and rarely endometrium.[2] It accounts for only 0.8% of all endometrial carcinoma.[1] Till now, approximately 80 cases of neuroendocrine endometrial carcinoma have been reported in the literature reviewed.[3,4]

The median age of presentation is 60 years with most common clinical symptom being perimenopausal and postmenopausal bleeding. These tumors behave aggressively and 5 year survival rate is 60 % for stage 1 tumor.[5] Most patients are in advanced stage at presentation, with a median survival of only 5 months.Surgical management includes hysterectomy with bilateral salpingooophorectomy and pelvic and paraaortic lymphnodes dissection followed by radiation and chemotherapy.[6]

Case

A 52 year old woman (para 4 live 4), postmenopausal since 15 years presented with complaints of bleeding per vaginum since 1 ½ month.She was a known case of hypertension and diabetes mellitus and was on treatment. On examination her vitals were stable, per abdominal examination was normal, per speculum examination revealed a normal cervix and vagina. Per vaginal examination was suggestive of a bulky uterus with bilateral fornices free. She underwent endometrial biopsyoutside which reported as moderately differentiated adenocarcinoma. So, patient came to our hospital for further treatment with histopathology report and an ultrasound suggestive of a hypoechoic mass in the endometrium of around 22.8×7mm with minimum vascularity.

All baseline investigations were normal. The tumor markers were CEA 3.17ng/ml, CA125 33.2 units/ml, and CA19-9 was 7.79 units/ml. The patient was planned for advanced imaging to map out the disease prior to procedding. MRI revealed a focal lesion of 1.1× 1cm in posterior wall with no evidence of extrauterine spread or lymph node enlargement. Patient and her relatives were explained about the need of radical surgery as the treatment of her condition and they agreed on laparoscopic approach. So, microhysteroscopy with laparoscopic radical hysterectomy

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with bilateral pelvic lymphnode dissection was done. Microhysteroscopy revealed a small ulcer on posterior wall of uterus below left ostia. Endometrium was sent for frozen section and was reported as adenocarcinoma. Intra operatively, uterus was bulky and bilateral adnexae were normal. All the specimens were sent for histopathological examination. Patient's postoperative hospital stay was uneventful and she was discharged on 4 th day in stable condition.

On gross pathological examination uterus measured 8×4×2cm. Endometrium was 0.1cm and myometrium was 1.5cm in thickness. Cervix measured 2.5cm in length and 1cm in diameter at external OS. Both ectocervix and endocervix were unremarkable. Bilateral ovaries and Fallopian tubes were unremarkable.Microscopically, (figure 1) sections from the uterus showed a malignant tumour in the endometrium with tumour cells,small round to polyhedral,arranged chiefly in nests and groups. Tumour was present in the fundus and upper half of body of uterus showing infiltration of more than 2/3rd thickness of the myometium with marked lymphovascular invasion.Lower half of body of uterus, isthmus, cervix and bilateral parametriae were free from the tumour. Both ovaries and fallopian tubes were free from tumour. Four pelvic lymphnodes excised were free from tumour and showed reactive changes. Immunohistochemical stains were strongly positive for cytokeratin (CK), synaptophysin (figure 2,3) and negative for ER, PR and vimentin. Ki 67 proliferation index was 10-15%(figure 4) in the tumour cells, thus confirming the diagnosis of neuroendocrine carcinoma. Patient was given complete course of post-operative chemoradiotherapy and is doing well till the time of reporting this case.

Discussion

Small cell neuroendocrine carcinoma of the uterus is a very rare and aggressive tumour of definite endometrial origin resembling small cell carcinoma of the lungs.Tumor has no known etiology, however heterotrophic nuclear localization of beta-catenin may play a role in invasion and its aggressive behavior. Usually patients present with perimenopausal or postmenopausal bleeding. The tumor usually originates at body of the uterus or isthmus with no cervical involvement.[5]WHO defines Small cell carcinoma as an undifferentiated carcinoma with cellular and nuclear features like small sized cells, scant cytoplasm , hyper chromatic finely granular and moulded nuclei ,inconspicuous nucleoli and high mitotic rate[6]. Immunohistochemistry staining in these cases are positive for synaptophysin, chromogranin A and cytokeratin.[7]Small cell carcinoma of endometrium may accompany other types of endometrial carcinoma, like endometrioid and adenosquamous.[8] This may be rarely associated with paraneoplastic syndrome as well. Treatment includes hysterectomy with bilateral salpingooophorectomy and pelvic and paraaortic lymphnodes dissection followed by radiation and chemotherapy[6].Prognosis of the disease is dependent on the stage of the disease at presentation. Majority of the cases reported were in stage III of IV at the time of presentation.

IsinUreyan et al[3], reported a case of a 52 year old patient who presented with postmenopausal bleeding, similar to our case. Her endometrial biopsy revealed a poorly differentiated adenocarcinoma. Her pre operative Ca 125 was 42. Total abdominal hysterectomy, bilateral salpingoopherectomy with bilateral pelvic and paraaortic lymph node dissection was done along with omentectomy. Final histologic examination of the specimen was SCC of the endometrium of stage Ic. This tumor was though negative for synaptophysin. She received chemoradiotherapy and the patient is without the evidence of disease for 58 months, prior to reporting.

In a clinicopathological study of six cases reported by Yu- Jin-Koo et al[4], it was found that the median age of all the patients was 60 years. Vaginal bleeding was the most common complaint. All underwent hysterectomy, bilateral salpingoopherectomy and systematic lymphadenectomy. Three were in stage I and stage II, and the other three in stage III as per FIGO classification. Pathologically, deep myometrial invasion was observed in five patients and all had lymphovacular invasion.One patient refused adjuvant treatment, 5 patients received chemotherapy and one chemoradiotherapy.

In another case reported by Hwang JH[9], a 59 year old women presented with postmenopausal bleeding. She underwent total abdominal hysterectomy, bilateral salpingoopherectomy and pelvic and paraaortic lymph node

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dissection followed by chemoradiotherapy, similar as in our case. The only major differentiation being laparoscopic management. Immunohistochemical study showed neuroendocrine differentiation with positive CD 56, chromogranin and synaptophysin markers.

Conclusion

Small cell Neuroendocrine carcinoma are very rare and aggressive tumors and can be confused with other histologic types.Hence the diagnosis has to be kept in mind while treating patients with bleeding per vaginum especially in perimenopausal and postmenopausal group women.The cancer can be managed laparoscopically provided it is in the hands of surgeons with good expertise and adequate knowledge. A multimodal approach, involving good laparoscopic surgeon, a trained pathologist, radiologist and well versed oncologist is thus a necessity in such cases, to ensure optimal management of the patient.

Acknowledgement

A team work is very important in any specialised care but specially so in minimally invasive surgeries.

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Figures:

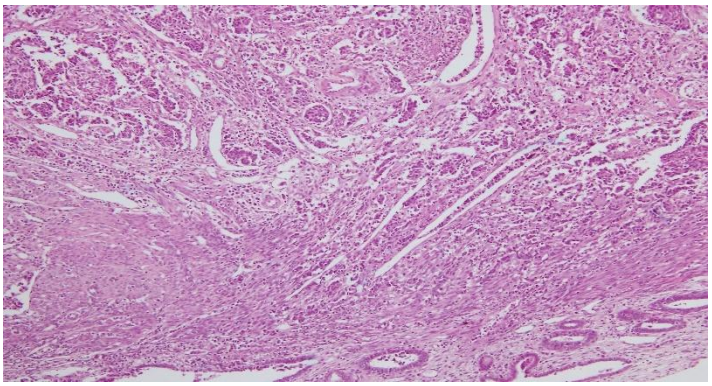

Figure 1: H and E stain showing arrangement of small round to polyhedral cells in nests and groups.

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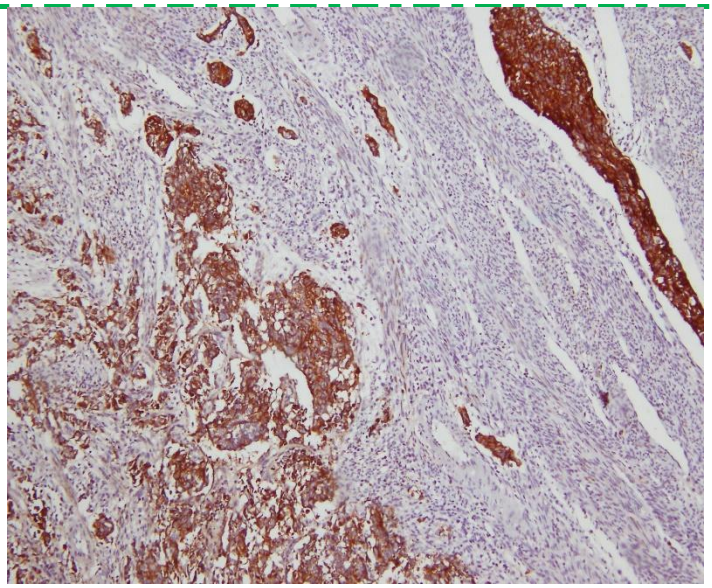

Figure 2: immunohistochemical stain showing cytokeratin positive

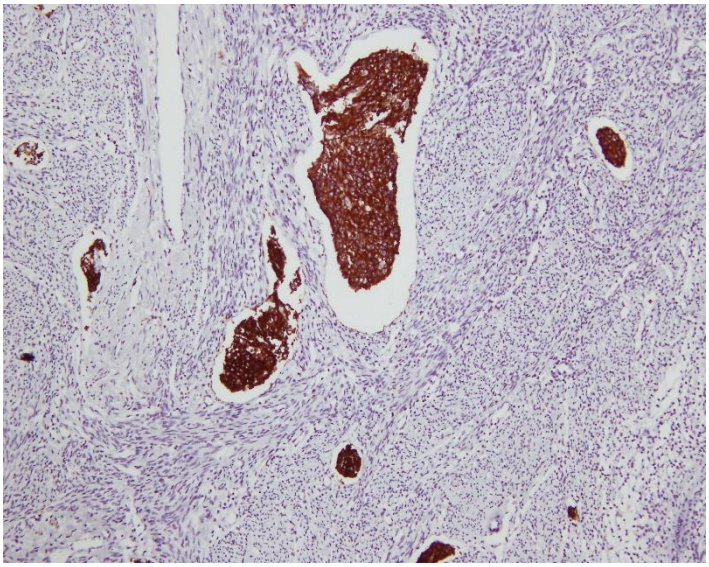

Figure 3: immunohistochemical stain showing synaptophysin positive

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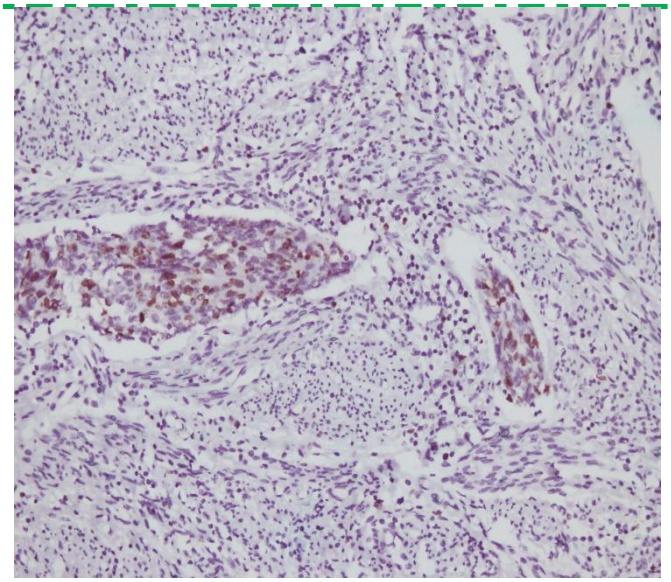

Figure 4: Ki67 proliferation

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