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REVIEW ARTICLE

Clear Cell Carcinoma of Endometrium: A Clinical Review

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ABSTRACT

Clear cell carcinoma of endometrium is a rare (1-6%) but aggressive malignancy with high propensity of early extra-uterine spread. The usual presentation is postmenopausal bleeding and discharge as with other endometrial cancers but it does not have preceding hyperplastic stage, instead it develops from thin atrophic endometrium, therefore impossible to identify by the screening measures like Pap smear and transvaginal sonography. First step for early diagnosis of such unfavorable endometrial cancer should be endometrial biopsy. Histopathological diagnosis is mandatory to confirm the clear cells present in the endometrial sample before planning the management. Clinical staging is highly erroneous in clear cell endometrial cancer and should not be taken into consideration in management plan. Being a rare cancer, there is lack of true evidence on its management protocol. Here, we had tried to provide the review about the clear cell endometrial (CCE) cancer diagnosis and management along with a case report for clinical perspective.

Keywords: Clear cell carcinoma, Postmenopausal bleeding, Endometrial malignancy, Chemoradiation.

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INTRODUCTION

Endometrial cancer is the most prevalent female genital tract malignancy and third commonest malignancy of women after breast and lung in developed countries, while the brunt of cancer cervix is high in developing countries like India. Continued increase in life expectancy suggest that prominence of endometrial cancer will be maintained or it perhaps will increase in developing countries. The most prevalent histological type is endometrioid endometrial carcinoma (75-80%), followed by papillary serous carcinoma (15-20%). Clear cell endometrial (CCE) carcinoma is very rare accounting for only 1 to 6% of cases.[1] Due to rarity, it is difficult to develop the evidence-based management. Therefore, consensus regarding management has been lacking.

First reported case of CCE was published by de Benneville in 1911. Clear cell endometrial cancer is considered as one of the most aggressive types of endometrial cancer with estimated survival rate of 71% at lower stages (I and II) as reported by University of Texas from retrospective review of 17 cases.[2] Another report of 686 endometrial cancer cases from University of Chicago found 38 (5.5%) cases had clear cell tumor, of which 18 were pure clear cell, while 20 had mixed clear cell pathology along with adenocarcinoma or other unfavorable histologies. All of those underwent staging laparotomy, hysterectomy with lymph node sampling and adjuvant therapy either in form of radiotherapy or chemotherapy. Actual disease free survival of entire group reported was 38.5% only.[3]

Typical clinical course of the clear cell endometrial cancer is presented here in form of a case report along with the review for the understanding the recommended management protocol till date. PubMed was used to search the English literature about the clear cell endometrial carcinoma to have this comprehensive review.

Typical Clinical Scenario

A 60-year-old postmenopausal north Indian women presented with complaint of excessive discharge per-vaginum, spotting and few episodes of bleeding per-vaginum since last 6 months. There was no past history of any long-term drug intake, hormone replacement therapy, contraception, chemotherapy or radiation exposure. Family history was also not suggestive of any cancer or related deaths in her family. Cancer antigen (CA-125) was found raised 92 IU/L suggesting malignancy. Ultrasound reported an enlarged uterus of 85 × 54 mm size with a vascular mass of 4.6 × 3.8 cm filling the entire endometrial cavity (Fig. 1). Presenting complaints, age, biomarker and imaging were highly suggestive of endometrial malignancy, and endometrial biopsy confirmed it as a case of clear cell endometrial carcinoma (CCE). Staging laparotomy was done along with hysterectomy and bilateral salpingo-opherectomy. Minimal peritoneal fluid was present in pouch of douglas which was negative for malignant cells. Anterior and posterior peritoneum was apparently normal

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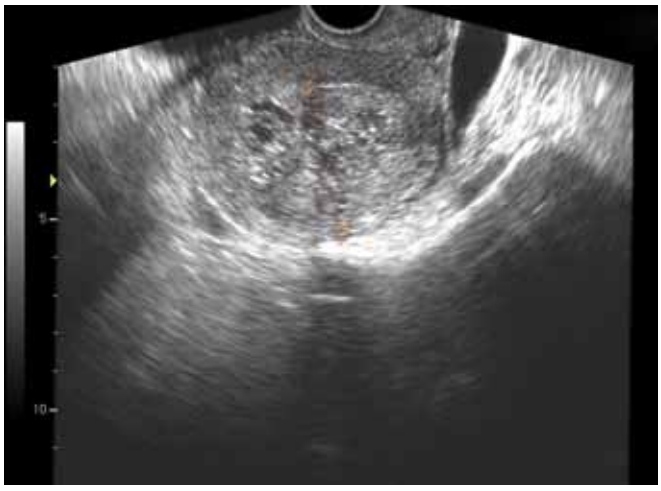

Fig. 1: Transvaginal sonography of the case of CCE

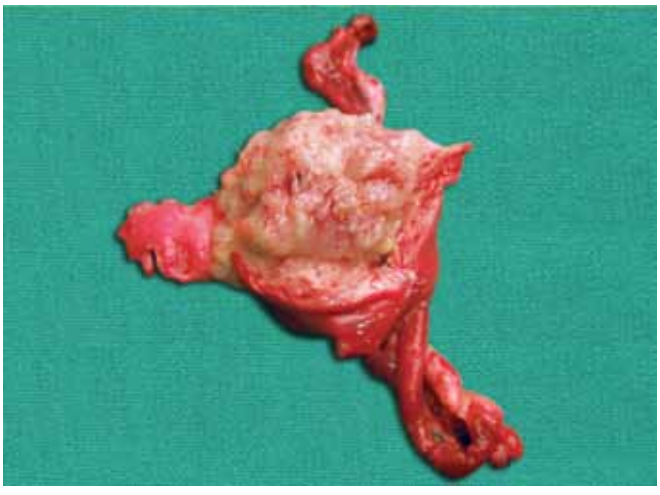

Fig. 2: Surgical specimen showing the fluffy growth filling the endometrial cavity

and free. Clinically, no pelvic lymphadenopathy was found during surgery. Uterus was enlarged 8 weeks plus size, globular and very soft in consistency. On resection, the uterine cavity was found to be filled with large fluffy greyish white mass of 4 × 4 cm size and some amount of thick discharge which on histopathology came out to be clear cell carcinoma of endometrium (Fig. 2).

Etiology

Etiology of CCE is not well understood, but appears to be unique from endometrioid histology. A recent study identified putative precursor lesion in 90% of uterine specimens. Clear cell carcinomas are more common in older women, among tamoxifen treated breast cancer patients, and women diagnosed with endometrial cancer following pelvic radiation for another condition.[4,5]

Screening

Clear cell endometrial carcinoma is rarely associated with endometrial hyperplasia. Routine screening for endometrial malignancy is neither cost effective nor warranted [American College of Obstetrician and Gynaecologists (ACOG)]. Transvaginal sonography (TVS) a commonly used non-invasive, simple and safe, tool for screening endometrial pathology in reproductive age can be misleading in clear cell cancer as it may not have preceding hyperplastic endometrium. Pap smear is not so reliable screening method for endometrial carcinoma as it can detect only the shed abnormal cells which are restricted in postmenopausal cases due to barricading of uterine cavity often with sclerotic endocervical canal.[6]

Diagnosis

History of unprovoked postmenopausal bleeding or spotting along with excessive vaginal discharge in an elderly women is harbinger of genital malignancy. On local inspection, per/speculum and bimanual pelvic examination if the vulva, vagina and cervix is apparently healthy on visualization and palpation then finding directly points toward the endometrial pathology. Initial evaluation is done by Pelvic sonography preferably transvaginal, to assess the endometrial lining and its thickness. Thickness more than 4 mm in postmenopausal women is predictive of endometrial pathology. But endometrial cancer specially the unfavorable histological varieties including CCE can develop within atrophic endometrium of <5 mm thickness, therefore, sonography results should be interpreted with caution.[7] Adding the Doppler flow helps out in identifying the vascular pattern of the endometrium and helps in differentiating benign from malignant growths.

Magnetic resonance imaging (MRI) is much better non-invasive imaging tool available to us to be done in suspicious cases as it gives clear idea about the growth, its consistency, myometrial invasion if present and the lymph node metastasis to some extent (Fig. 3).

An elderly case, having high probability of malignancy must alert clinician and endometrial sample should be histologically evaluated in all perimenopausal and postmenopausal women with abnormal uterine bleeding to rule out endometrial cancer. It is not wrong to say that any episode of postmenopausal bleeding represents endometrial cancer until proved otherwise. Traditional dilatation and curettage has now been abandoned as the premier means of endometrial sampling, but its outpatient version is still the gold standard for histological diagnosis. Numerous devices are available for obtaining samples as, endometrial brush or lavage, metallic Novak's endometrial curette, suction devices, like Vabra aspirator, Pipelle, or endoscopic techniques using hysteroscopy and guided biopsy. Some surgeon's avoid doing hysteroscopy in highly suspected cases of endometrial cancer as it may have chances of disseminating the malignant cells into the peritoneal cavity

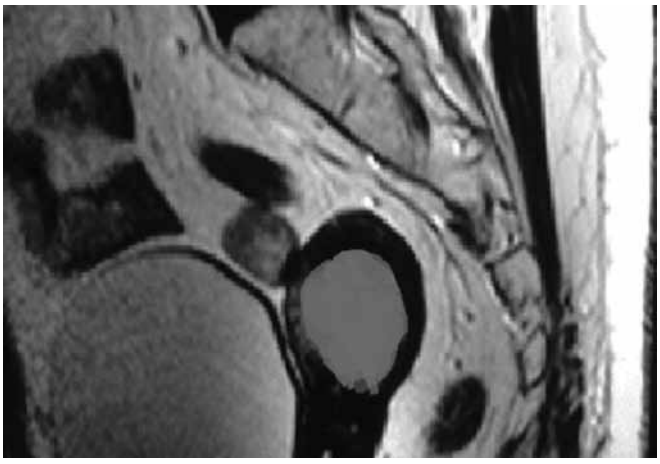

Fig. 3: MRI showing the endometrial growth

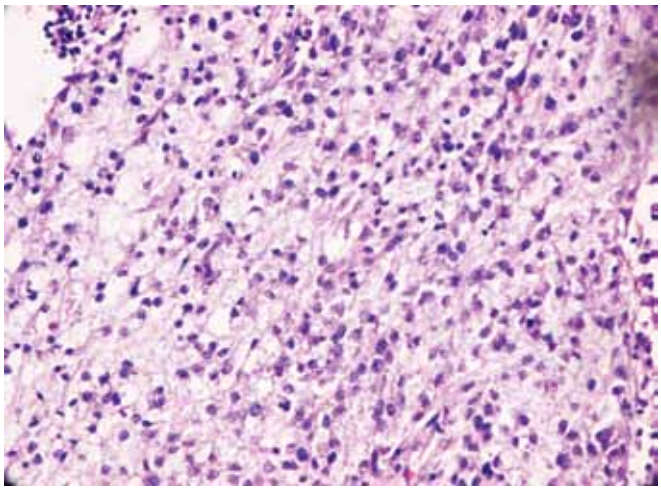

Fig. 4: Histology showing polygonal clear cells with large vacuole and eccentric nuclei

through fallopian tubes. Endometrial biopsy including those performed with endometrial pipelle or aspirator in office is minimally invasive procedure requiring no anesthesia and highly reliable in obtaining the diagnosis with sensitivity of 85 to 98%, with the rare possibility of missing out the early focal lesions of endometrium.

Histology

Clear cell endometrial can exist alone or in combination with endometrioid and other endometrial cancers.[1] Clear cell histology should comprise more than 50% of the tumor before the tumor can be designated as CCE. Histologically, it can have papillary, tubulocystic or solid patterns. The papillary pattern is the commonest with papillae being filiform and regular or irregular in size and shape with hyalinised or edematous core, or in a ring shape. The constituent cells of CCE cancer are polygonal with clear glycogen rich oxyphilic cytoplasm, having eosinophilic hyaline mucin containing vacuoles and eccentric nuclei (Fig. 4). Clear cell endometrial cells are periodic acid schiff stain and Best's carmine stain positive, but negative for mucin. Tumor nuclei are hyperchromatic, irregular in shape with numerous indentations and fragmented irregular nucleoli.

Most striking ultrastructural feature of CCE is massive accumulation of glycogen particles, in close association with prominent membranes of granular endoplasmic reticulum, free ribosomes, supranuclear Golgi and subnuclear Mitochondria.[8]

Differential Diagnosis

Histologically is important to distinguish secretory carcinoma of endometrium from clear cell carcinoma as both have cells with clear glycogen rich cytoplasm but papillary or cystic architecture and hobnail pattern is absent in secretory carcinoma. Former has excellent prognosis, while CCE cancer being aggressive requires adjuvant radiotherapy even in absence of myoinvasion.[9]

It is also sometimes difficult to differentiate papillary serous carcinoma with CCE by histology and requires the aid of 'Immunohistochemistry'. Clear cell endometrial has low reactivity to p53 and it is estrogen and progesterone receptors negative, while papillary serous carcinoma being just opposite have high p53 reactivity and usually estrogen and progesterone receptor positive. Clear cell endometrial has high Ki-67 proliferation index.[10] Hepatocyte nuclear factor – 1 beta (HNF-1b) expression is there in CCE. Rarely, clear cell cancer if seen with p53 overexpression tend to present at higher stage with peritoneal metastasis and pursue a aggressive clinical course as papillary serous carcinoma.

Histologist should clearly mention the pattern of clear cells present, other mixed histology if seen, atypia, depth of myoinvasion if there, peritoneal, omental and lymph node spread in the sampled specimen to identify the correct disease stage and prognosis can be predicted to some extent.

Origin

Proposed origins include coelomic epithelium, mesonephric rests, or direct metaplasia from endometrial epithelium. Coexistence of clear and nonclear cell types of endometrial cancer, and similarity of with the clear cell carcinoma of ovary, vagina and cervix, support the concept of mullarian histogenesis of CCE rather than mesonephric. Clear cell carcinomas frequently have PIK3CA and ARID1A mutations.

Treatment

Clear cell endometrial requires multimodal therapy in form of primary surgery with adjuvant radiotherapy or chemotherapy depending upon surgical staging. Alternatively if surgical staging results are not available adjuvant therapy can be decided based on pathological findings of surgical specimen.

Clinical staging is not sufficient as it carries high chances of error regarding extent of disease. In CCE importance of surgical staging laparotomy was emphasized in a recent review by Thomas et al.[11] In his study, 52% women with disease clinically confined to uterus were found to have extra uterine disease on surgical staging. Accurate identification of disease extent with CCE is must to plan the adjuvant radiotherapy thus avoiding unnecessary cost and potential morbidity. As CCE has high chances of extra uterine spread, so adjuvant therapy is usually recommended.

Preoperative Workup

Apart from detailed history and complete physical examination, careful evaluation of axillary, supra-clavicular and inguinal lymphnodes and rectovaginal examination to assess parametria, rectum and *cul de sac* are necessary. Imaging in form of chest X-ray, computed tomography of pelvis and abdomen and MRI (optional) be done to have an idea of extent of spread. Proctosigmoidoscopy, cystoscopy, barium enema and intravenous pyelography may be done if higher stage (III and IV) is clinically suspected. Complete hematology profile, liver and kidney function, clotting profile, electrolytes and CA-125 should be known before planning the major cytoreductive surgery.[6]

Surgery

Comprehensive surgical staging and optimal cyto-reduction is the first step in treatment program for the CCE. Staging laparotomy includes evaluation of peritoneal cavity with washing, smears and biopsies of suspicious looking areas, total hysterectomy with bilateral salpingo-opherectomy, pelvic and para-aortic lymphadenoectomy along with omentectomy. Saygili et al[12] found occult omental metastasis in 33% of cases with CCE. One should try to resect all the clinically visible extra uterine lesions (maximum cytoreductive effort). Completely cytoreduced cases had a better survival compared with patient with residual disease.

Adjuvant Therapy

Radiotherapy is utilized in postoperative adjuvant setting. Postoperative whole abdomino-pelvic radiation (WAPI) for high risk histology as clear cell carcinoma had been found to be 80 and 60% 5 years survival in surgical stage I and II respectively but with 12% long-term major complications. Mundt et al reported the outcome of different radiotherapy modalities as vaginal brachytherapy, extended field radiation therapy (EFRT), and WAPI in clear cell carcinoma stage I to IV. He found that there is less propensity of abdominal failure (13%) compared to distant failure (40%) in clear cell endometrial cancers. He concluded that CCE does not require routine use of WAPI, while extended field radiation therapy (EFRT) is sufficient, and distant site metastasis needs development of adjuvant chemotherapy protocols.[13]

Chemotherapy

Adriamycin, cisplatinum and paclitaxel have been identified to be the most active agents for the endometrial cancer. Thomas et al review suggest that adjuvant chemotherapy is not necessary in thoroughly surgically staged clear cell endometrial cancer confined to uterus (stage I and II).

Doxorubicin paclitaxel and cisplatinum (TAP) and carboplatin and paclitaxel (TC) regimens have been defined for the treatment of clear cell cancer with later having less toxicity, better tolerability and efficacy. Regimens are commonly used in treatment for distant metastasis and recurrent cancers.[14]

CONCLUSION

Although rare, clear cell histology is an independent predictor of poor prognosis and have worst outcome compared to same staged endometrioid endometrial cancer. Comprehensive surgical staging is the best approach to decide the complete treatment plan for all the types of endometrial carcinomas. Apart from lung, abdomen, disseminated bone and paranasal sinus metastasis had been reported in the past. Abdominal and pelvic failure rates leading to relapse are high without adjuvant radiotherapy. Considering propensity for early recurrence and aggressive behavious it is reasonable to have platinum-based adjuvant chemotherapy in women with distant metastasis and recurrent clear cell endometrial cancer. Careful long-term surveillance should be done, given the higher rate of recurrence compared to endometrioid endometrial cancer.

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