Case Report

Mixed Large Cell Neuroendocrine Carcinoma and Endometrioid Adenocarcinoma: A Rare Case Report with Review of Literature

Vinay N. Gowda, Meenakshi Rao, Shashank Shekhar[1], Parmod Kumar[2]

Departments of Pathology and Lab Medicine, [1]Obstetrics and Gynaecology and [2]Medical Oncology/ Haematology, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India

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Abstract

We report the case of a 60-year-old female who presented with postmenopausal bleeding after she underwent investigations followed by a total abdominal hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. A diagnosis of low-grade endometrioid adenocarcinoma admixed with large cell neuroendocrine carcinoma (NEC) was made based on the histomorphology and immunohistochemical profile. NEC of the endometrium is a rare and highly aggressive neoplasm requiring a multidisciplinary approach for its treatment. As treatment strategies are changing over time, preoperating imaging evaluation and histopathological examination with molecular characterization whenever possible are essential to follow, to offer the appropriate information to surgeons and/or oncologists for optimal management in these patients.

Keywords: *Endometrial carcinoma, endometrium, large cell neuroendocrine carcinoma, neuroendocrine carcinoma*

Introduction

Endometrial carcinoma makes up for the vast majority of uterine malignancies and is the sixth most diagnosed cancer in women and the second most diagnosed female genital organ cancer. Prolonged exposure to unopposed estrogen is a risk factor such as with early menarche, late menopause, nulliparity, obesity, tamoxifen, polycystic ovary syndrome, or estrogen-producing ovarian tumors. While the majority of primary uterine malignancies are endometrial endometrioid adenocarcinomas (EEC) (80%–90%), other significant tumor types are also noted (such as serous carcinoma, clear cell carcinoma, undifferentiated carcinoma, neuroendocrine carcinoma (NEC) as carcinosarcomas, and mesenchymal malignancies). The peak age incidence at the diagnosis is between the age group of 55 years and 64 years (median 62 years).[1,2]

NECs of the gynecologic tract are uncommon, comprising about only 2% of all gynecologic malignancies, while an endometrial primary is very rare, accounting for < 0.8% of endometrial carcinomas. The present guidelines suggest the incorporation of established molecular parameters characterizing biologically distinct EECs adding relevant prognostic information. These include *POLE*-ultramutated endometrioid carcinoma, mismatch repair–deficient endometrioid carcinoma, p53-mutant endometrioid carcinoma, and no specific molecular profile endometrioid carcinoma.[3]

The International Federation of Gynecology and Obstetrics (FIGO, 2023) grading system for carcinomas of the uterine corpus is followed. Pathological staging is done by the American Joint Committee on Cancer (AJCC 8th edition) and a parallel system formulated by FIGO.[2,4] We report the case of a 60-year-old postmenopausal female with mixed EEC and large cell NEC (LCNEC).

Case Report

A 60-year-old postmenopausal female presented with postmenopausal bleeding. Ultrasonography shows a bulky uterus with heterogeneous myometrium and mixed echogenic consistency within the endometrial cavity. The margin is indistinguishable from the endometrium, with internal vascularity present. Enlarged bilateral

Address for correspondence: Dr. Meenakshi Rao, Department of Pathology and Lab Medicine, All India Institute of Medical Sciences, Jodhpur - 342 005, Rajasthan, India.
E-mail: drmeenakshirao@gmail.com

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iliac and pre- and para-aortic lymph nodes suggest metastatic involvement. Magnetic resonance imaging reveals a large lobulated lesion in the uterus extending from the endometrial cavity to the serosal-subserosal margin, with metastatic lymphadenopathy. Biopsy suggests high-grade endometrial carcinoma with large areas of coagulative necrosis. She underwent radical hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. Grossly, the cut surface of the uterus showed a growth in the endometrial cavity involving the fundus, body, and lower uterine segment having a solid gray-white and firm appearance with areas of hemorrhage and necrosis. The tumor reached up to the serosal surface. On microscopy, the tumor comprised two components: a well-differentiated component, comprising 30% of the tumor, composed of back-to-back arranged glands with a complex branching pattern and focal loss of intervening stroma. The second poorly differentiated component comprised 70% of the tumor, composed of diffuse sheets and nests of medium to large cells with extensive geographical necrosis (40%). The individual tumor cells in the well-differentiated component showed moderate nuclear pleomorphism, had round-to-oval nuclei, coarse chromatin, 0–1 small nucleoli, and a moderate amount of cytoplasm. Calcification and a few psammoma bodies were also noted. The cells in the poorly differentiated component were dyscohesive, had moderate-to-abundant eosinophilic cytoplasm, round to oval large nuclei, and prominent nucleoli with many markedly pleomorphic and occasional bizarre cells. Mitosis was brisk in this component (35/2 mm^2), with numerous atypical mitotic figures. Karyorrhectic debris and apoptotic bodies were also seen interspersed within. Extensive extratumoral lymphovascular invasion was noted in both small and medium vessels. Focal areas of hyalinization were noted. The tumor reached up to the serosa with the presence of serosal deposits. The cervical stroma, parametria, and bilateral ovaries were involved in the tumor. Bilateral fallopian tubes were free of tumors; however, lymphovascular invasion was noted in the vessel of the right fallopian tube [Figure 1].

Immunohistochemistry (IHC) applied showed a varied IHC pattern in both components. The well-differentiated, low-grade component tumor cells were diffusely and strongly positive for Estrogen Receptor alpha (ER), Paired-box gene 8 (PAX8), Cytokeratin 7 (CK7), CAM5.2, and Epithelial Membrane Antigen (EMA); moderately positive for Progesterone Receptor (PgR); focally positive for vimentin; and negative for Wilms Tumor gene 1 (WT-1). Her2Neu expression was equivocal (score 2+, weak-to-moderate staining in >10% of the cells). The poorly differentiated component tumor cells were diffusely and strongly positive for chromogranin A and CD56, with neuroendocrine marker positivity seen in 98% of the tumor cells; focally positive for CAM 5.2, CK7, EMA, and PAX8; and negative for leukocyte common antigen, ER, PgR, and WT-1. Her2Neu expression was negative (score 0). p53 expression was abnormal/mutant type in both the components. MicroSatellite Instability (MSI) IHC was not performed due to the nonavailability of the marker in our laboratory and the patient was not affordable to get it performed at another laboratory [Figure 1]. Based on the findings, a diagnosis of carcinoma was admixed with NEC which included p53 mutant endometrioid carcinoma, low grade (FIGO Grade 1), and LCNEC. Right lymph nodes showed tumor deposits in two of six lymph nodes with extranodal extension. Left lymph nodes showed three lymph nodes, all free of tumor deposits. Soft-tissue tumor deposits were also present. Based on AJCC 8th edition guidelines, pathological pTNM staging of pT3aN1a was given with parallel FIGO 2023 stage of IIIC1. The patient received three cycles of adjuvant chemotherapy with paclitaxel and carboplatin, no clinical improvement was noted in the patient's condition and further, the patient had refused further treatment on subsequent follow-up.

Discussion

LCNEC is a poorly differentiated high-grade carcinoma composed of nonsmall cells. It can arise in any epithelium-containing organ, with the most common site being the lung, accounting for 15% of all neuroendocrine neoplasms. Outside the lung, these tumors are rare, aggressive, have poor prognosis, high mortality rate, and account for 2% of all primary malignancies occurring at each site. In the female genital tract, the cervix is the most common site, followed by the ovary and endometrium. In the cervix, association with high-risk human papillomavirus (HPV 18) is noted, although its status in other sites is still unknown. In endometrium, defects in mismatch repair system (MSI) are a common finding in LCNEC. Presentation is seen in the fourth to fifth decades of life and a predilection in both pre- and postmenopausal women is noted. Association with other carcinomas is seen which have the same prognosis and epidemiological factors.[5]

The WHO guidelines for the diagnostic criteria for endometrial LCNECs have not been proposed. Thus, the criteria proposed for lung LCNEC are considered which include a poorly differentiated neuroendocrine morphology displaying large cell (nonsmall cell) cytology, high proliferation rate (>10 mitotic counts in 2 mm^2 of viable tumor [10 high power field]), and immunohistochemical evidence of neuroendocrine differentiation, which includes IHC expression of chromogranin A, synaptophysin, CD56, or INSM1.[6]

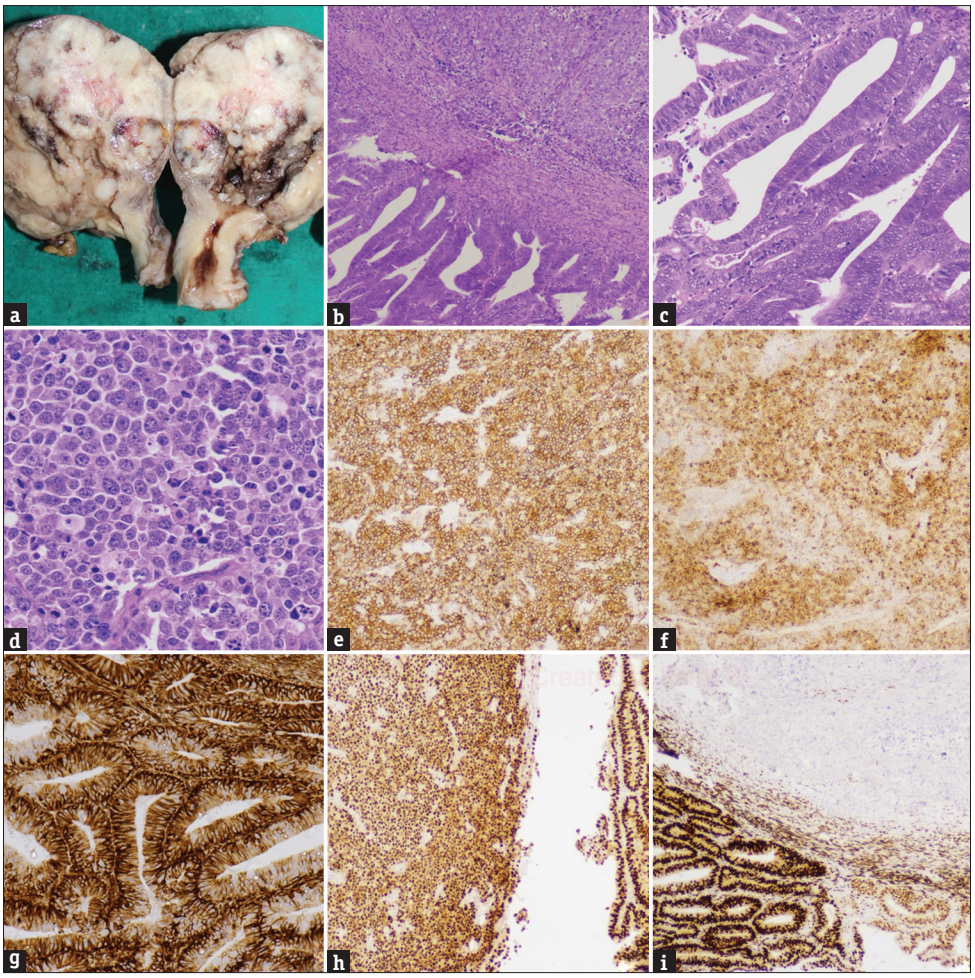

Figure 1: Gross, microscopy and immunohistochemistry profile. (a) Gross examination showing a gray-white firm growth in the endometrial cavity involving the fundus, body, and lower uterine segment reaching up to the serosal surface; Microscopy: (H and E stain); (b) Tumor comprises of two components (×100); (c) Well-differentiated component, composed of back-to-back arranged glands with complex branching pattern (×200); (d) Poorly differentiated component, composed of diffuse sheets and nests of tumor cells with extensive geographical necrosis (×100); Immunohistochemistry: Poorly differentiated component tumor cells are diffusely and strongly positive for (e) CD56 (×100) and (f) Chromogranin A (×100); (g) (×200): Well-differentiated component is focally positive for vimentin; (h) p53 expression is abnormal/mutant type (diffuse nuclear positivity) in both the components (×100); (i) Well-differentiated component is positive for ER (×100), while negative in the poorly differentiated component

Undifferentiated/dedifferentiated carcinoma of the endometrium is a malignant epithelial neoplasm with no overt cell lineage differentiation. Dedifferentiated carcinoma is composed of an undifferentiated carcinoma and a differentiated component (typically of FIGO Grade 1 or 2 endometrioid carcinoma). The diagnostic features supporting an undifferentiated carcinoma include a dyscohesive cell morphology and immunohistochemical lack of PAX8, reduced/lost keratin, and <10% reactivity for neuroendocrine markers. They are uncommon and account for around 2% of endometrial carcinomas. An association with Lynch syndrome has been suggested. Mixed carcinoma of endometrium is another entity, composed of two or more discrete histological types of endometrial carcinoma, where at least one component is either serous or clear cell. These account for about 10% of the endometrial carcinomas.

However, in our case morphologically, the major component is poorly differentiated with IHC expression of neuroendocrine markers, which is seen in more than 10% of the tumor, suggesting a diagnosis of an admixture of EEC with LCNEC. Due to its rare and uncommon presentation, we feel it is important to keep ourselves updated regarding various entities arising within the uterine endometrium, especially NECs arising as a primary. We reviewed a few previous case reports and studies performed [Table 1]. The literature showed the average age at presentation was 59 years and most patients were postmenopausal with complaints of bleeding per vaginum.[1,3,7-10]

Most cases adhered to the staging guidelines outlined by FIGO and AJCC. Numerous studies have explored the correlation between microsatellite instability (MSI) and germline mutations in MMR genes such as MLH1,

Table 1: Reported cases of large cell neuroendocrine carcinoma of the endometrium

Citation	Age	Presentation	Final diagnosis	FIGO stage
Nguyen *et al*. (2013)[10]	71	PMB	Pure LCNEC	IVB
Jenny *et al*. (2019)[8]	56	PMB	LCNEC+endometrioid adenocarcinoma	IVB
Inoue K *et al*. (2021)[3]	65	Symptomatic endometrial thickening	LC and SCNEC+endometrioid adenocarcinoma, grade 2, MSI high	IIIB
Yi-An Tu *et al*. (2018)[7]	51	PMB	Neoplastic metaplasia from low-grade endometrial carcinoma to malignant mixed Mullerian tumor and LCNEC	IVB
Joshua *et al*. (2021)[4]	61	PMB	High-grade neuroendocrine tumor with combined small cell and LC histomorphology	IIIC2
Our case	60	PMB	Endometrioid adenocarcinoma, low-grade admixed with LCNEC	IIIC1

TAH: Total abdominal hysterectomy, BSO: Bilateral salpingo-oophorectomy, FIGO: The International Federation of Gynecology and Obstetrics, PMB: Postmenopausal bleeding, LC: Large cell, LCNEC: LC neuroendocrine carcinoma, SCNEC: Small cell neuroendocrine carcinoma

MSH2, MSH6, and PMS2, finding a close association. However, a few studies, such as the one by Tu *et al*., have highlighted the adverse prognosis associated with p53, noting high recurrence rates and extrapelvic tumor spread even after debulking surgery and postsurgical chemotherapy. Molecular classification remains pivotal in guiding clinical decisions for high-grade or high-risk endometrial carcinomas, with *POLE*-mutant tumors demonstrating a favorable prognosis, while p53-abnormal neoplasms tend to have poorer outcomes.[3,7,11]

Nguyen *et al*. conducted a literature review of LCNEC cases in the endometrium, identifying 13 cases, with only three showing an admixture of LCNEC with well-differentiated EEC. They emphasized the need for more data to establish the incidence and optimal management of this rare and aggressive malignancy, particularly given its poor prognosis even in early-stage disease. Standard surgical management of endometrial carcinoma typically involves total hysterectomy with bilateral salpingo-oophorectomy and lymph node assessment. Both NCCN and European guidelines agree on a minimally invasive surgical approach, even in patients with high-risk endometrial carcinoma, by minimizing tumor spillage. Palliative hysterectomy may be an option for selected metastatic patients with symptomatic disease, while comprehensive surgical staging is recommended for serous and undifferentiated carcinoma cases due to the risk of omental metastases.[10,11]

Advanced-stage endometrial carcinomas, particularly undifferentiated and carcinosarcoma subtypes, have a 70% risk of brain metastasis. Traditional treatment includes whole-brain radiation therapy and stereotactic radiosurgery as primary therapies. Prophylactic cranial irradiation (PCI) was once recommended for small cell NEC (SCNEC) due to high rates of brain metastasis, but concerns about long-term neurocognitive effects have led to a reconsideration of its use. Recent evidence suggests that PCI may not be necessary, even for SCNEC patients, due to potential adverse effects on memory.[12]

Conclusion

Admixture of endometrioid carcinoma and LCNEC is a rare presentation. Most of the times, this diagnosis is missed due to a poorly differentiated morphology. Due to its prognostic implication, a timely and correct diagnosis is essential to characterize any poorly differentiated component arising within the uterine corpus for optimal management of patients. An immunohistochemical panel of neuroendocrine markers and epithelial markers is suggested with further molecular subtyping. Proper workup with subtyping of all EECs and regular follow-up is important in the management of these cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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