Endometrial neuroendocrine carcinoma frequently associated with mismatch repair deficiency

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Abstract

Background: Endometrial neuroendocrine carcinoma (NEC) is a uncommon histologic subtype of endometrial cancer. It is currently unclear if the endometrial NEC has any particular relationship with mismatch repair (MMR) protein expression patterns. Here we report 3 endometrial NEC cases showing loss of MMR expression.

Case presentation: The cancers had two components with one poorly differentiated or NEC component, accounting for 60–90% of the neoplasms and the other of well differentiated glandular component. The NEC cells mainly showed solid sheets and organoid patterns, whereas insular, trabecular and rosette/pseudorosette patterns were also found. The NEC component was composed of cells with large, polygonal, vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. In all cases, the NEC component was diffusely positive for p16 and at least 2 of the 3 neuroendocrine markers (CGA, SYN, CD56) reactive in > 10% of the cancer cells. Loss of MMR protein expression was found in all three cases with loss of MLH1 in cases 1 and 2 and loss of MSH2 and MSH 6 in case 3. No PMS2 loss was found. In addition, aberrant *TP53* and SMARCB1 (INI1) expression was found in case 3 only. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, and two of them received postoperative chemotherapy and/or radiation therapy. The patients remained alive with no disease for 51, 17 and 6 months, respectively.

Conclusion: Endometrial NEC is frequently associated with MMR deficiency, some of which may have a better prognosis than we expect.

Background

As recommended by the World Health Organization (WHO), the terminology for gastro-entero-pancreatic neuroendocrine tumors (NET) is applicable to neuroendocrine carcinoma (NEC) arising from the female genital tract [1]. NETs are classified as poorly-differentiated NEC and well-differentiated NET based on the tumor nuclear grade. Low-grade NET is extremely rare with only occasional reports in the English literature [2, 3]. Meanwhile, NEC with very high grade is also rare. It is well known that NECs such as small or the large cell NEC behave aggressively and patients with such cancers have a poor prognosis [4]. There are approximately 100 cases of NEC arising from the endometrium have been reported in the past [4]. However, there were few studies addressed the relationship between the endometrial NEC and the abnormality of mismatch repair (MMR) protein expression in these cancers. We herein delineated 3 cases of the endometrial NEC with MMR deficiency.

Material And Methods

Tissue samples

All three cases were retrieved from the archives of the Department of Pathology, the Women's Hospital, School of Medicine, Zhejiang University, China, in the last 5 years. We obtained clinicopathologic information from hospital informatics system. This study was approved by the ethics committee of above institution. Large cell NEC is diagnosed based on World Health Organization (WHO) criteria: 1) large cells with prominent nucleoli and abundant cytoplasm, 2) a neuroendocrine growth pattern (organoid, insular, trabecular, rosette/pseudo-rosette), and 3) > 10% of tumor cells reactive to at least one NET markers including chromogranin (CGA), synaptophysin (SYN) and CD56 [1]. Hematoxylin and Eosin (H&E) and immunohistochemistry (IHC) slides were reviewed by 3 gynecologic pathologists (FZ, XZ, and WZ) and the pathologic diagnosis of the cases was confirmed by consensus.

Immunohistochemical analysis

Additional 4- μ m paraffin sections were stained with a panel of antibodies using the 2-step Envision method according to the manufacturer's instructions and visualized with 3-diaminobenzidine tetrachloride (Sigma, St Louis, MO) as described previously (add a reference here). The sources and dilutions of the antibodies used in this study are detailed in Table 1. All primary antibodies and the detection kit were products of Dako Corporation (Glostrup, Denmark). The omission of primary antibodies with the same class non-specific IgG was used as the negative control. The IHC stained slides were scored as follows: negative (no cells stained), focally positive ($\leq 10\%$ cells stained), patchy positive (11–49% cells stained) and diffusely positive ($\geq 50\%$ of cells stained).

Results

Clinical findings

The main clinical findings of these cases are summarized in Table 2. Briefly, median age was 56 years (range, 54-59 years), and all patients presented with postmenopausal or perimenopausal vaginal bleeding/discharge. All patients denied familial history of endometrial or colon cancer. No any other history of malignancies were identified from patients' relatives. The diagnosis was made on endometrial biopsy and was followed by total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) and staging procedures. The tumors showed the FIGO stage as follows: case 1 with stage IIB, case 2 with stage IB, and case 3 with stage IIIC at the time of diagnosis. Patients of case 1 and 3 received both postoperative chemotherapy and radiation therapy, while case 2 received adjuvant radiation only.

Pathological findings

The main pathological findings of these cases are given in Table 2. Macroscopically, all tumors formed large, polypoid, intracavitary masses, ranging from 3 to 4.5 cm. The tumors were largely located in the uterine funds with no low uterine segment location was noted. The cut surface was soft, fleshy, and necrotic. Microscopically, the tumors showed a dominant NEC component ranging from 60-90% of the total tumor volumes of the cases. Small amount of well-differentiated endometrioid carcinoma with focal

areas of squamous differentiation were identified in case 3 only. Increased tumor-infiltrating lymphocytes at the tumor invading front or periphery were found in all 3 cases (Fig. A). Extensive geographic necrosis was present. The NEC components mostly showed solid sheets with organoid growth patterns, whereas insular, trabecular and rosette/pseudorosette patterns were found in about 30% cancerous areas in average (Fig. B-D). The NEC components were composed of cells with large, polygonal, vesicular nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm. The mitotic count was >20 per 10 high-power fields for each case. Lymphovascular space invasion was evident in case 1 and 3, but not found in case 2. Three para-aortic lymph nodes showed NEC metastasis by morphology in case 3. No nodal metastasis was seen in cases 1 and 2.

The immunostaining results of the tumors are given in Table 3. All NEC components of the cases were positive for p16 and at least 2 out of 3 neuroendocrine markers (CGA, SYN and CD56) with >10% of the tumor cells. SYN was the most commonly expressed biomarker (20% in case 1, 15% in case 2, 80% in case 3), followed by CGA (15% in case 2, 70% in case 3), and CD56 (20% in case 1, 80% in case 3). In case 3, there was strong and diffuse expression of all three neuroendocrine markers. The well-differentiated adenocarcinoma components were all positive for estrogen receptors, with only focally positive for CGA. p53 immunoreaction was aberrant (mutational type) in case 3 and wild type in the other two. Notably, p53 overexpression was exclusively limited to the NEC component. Loss of SMARCB1 (INI1) expression was found only in case 3, but loss of SMARCA4 (BRG1) or ARID1A expression was not found in any case. In terms of MMR biomarkers, MLH1 was lost in case 1 and 2, MSH2 and MSH6 was lost in case 3. No PMS2 loss was found in all cases. Representative pictures of the IHC staining results are shown in Figures E-I.

Based on the above findings, diagnosis of primary endometrial large cell neuroendocrine carcinoma (LCNEC) was made for all three cases.

Follow-up

Follow-up information was available for all patients. The three patients remained alive with no disease for 51, 17 and 6 months, respectively.

Discussion

LCNEC arising from the endometrium are rarer than those arising from the cervix and ovaries [4-14]. Based on published reports in English, the neoplasms are either “pure” LCNEC or admixed with other histologic components [5-16]. Among other histologic components of endometrial LCNEC, endometrioid carcinoma is the most common histologic type, followed by serous carcinoma. Based on prior reports and the findings of our cases, the most common clinical symptoms were postmenopausal or perimenopausal vaginal bleeding and/or abnormal vaginal discharge [5-16]. In current cases, the patients presented within the average age range and exhibited typical clinical presentations of the endometrial LCNEC.

When the tumor is poorly differentiated with morphologic suggestion of neuroendocrine differentiation, the IHC with neuroendocrine markers are deemed as the most useful method for diagnosing NEC. The most common markers used in this setting include SYN, CGA, and CD56. In our study, at least 2 out of 3 neuroendocrine markers are positive in at least 10% of the tumor cells. SYN was the most commonly expressed neuroendocrine marker, followed by CGA and CD56. However, neuroendocrine markers, especially positive CD56 expression is relatively common in endometrial cancers even without classic neuroendocrine histology [17]. Combined with morphological features, we would like to emphasize that at least 2 NE marker should be reactive in >10% of tumor cells as the diagnostic criteria of NEC.

In many situations, the endometrial NECs occur in association with a more typical form of endometrioid carcinoma [4]. The adenocarcinoma components were also low-grade endometrioid carcinoma in our cases. Hence, compared with the conventional adenocarcinoma components, the NEC was dominant in all these cases. It has been indicated that NEC originates from NE cells of the endometrium and may result from “divergent differentiation” [5]. Yasuoka et al. [18] found that both cervical adenocarcinoma and NEC showed identical clonality by using an X-chromosome clonality assay. Such observation suggests that the NEC may arise from the adenocarcinoma through a “dedifferentiation process”. Moreover, the overt continuity between the two components and focally positive expression of NE markers in adenocarcinoma component in one of our cases is of supportive of this hypothesis. In addition, loss of INI1 (one of those dedifferentiation markers) expression was found in both components (case 3) suggest that “dedifferentiation” from endometrioid carcinoma to form NEC may represent part of the mechanisms for the development of these cancers.

Differential diagnoses of endometrial NEC are extensive [4, 16]. One of the major differential diagnoses of the endometrial LCNEC is the dedifferentiated endometrial carcinoma [16]. Both of them share many histologic and immunophenotypic features including loss of MMR protein expression as well as positive for neuroendocrine markers [17, 19]. However, 3 cases presented here do not represent dedifferentiated carcinoma. This is mainly because of the following reasons. 1) the high-grade looking area of the cases morphologically show features of NEC without evidence of undifferentiated carcinoma such as sheet-like growth patterns; 2) immunophenotypically, the cancer cells are positive for at least 2 neuroendocrine markers; and 3) Among the three commonly used dedifferentiation markers (INI1, BRG1, and ARID1A), only INI1 was lost of expression in only one of the 3 cases we studied. The dedifferentiation markers of INI1, BRG1, and ARID1A belong to switch/sucrose non-fermenting protein complex. Loss of such protein complex expression has been widely applied for the diagnosis of dedifferentiated carcinomas [14, 20, 21]. Rosa-Rosa et al. [20] studied 10 dedifferentiated carcinomas, they found that 9 of 10 showed loss of ARID1A expression. Another study found that 15 of 30 (50%) of the dedifferentiated carcinomas showed either loss of BRG1 or INI1 or loss of both biomarkers [21]. In our cases, as mentioned earlier, there was only loss of INI1 expression in case 3, but both BRG1 and ARID1A expression were intact.

All the three patients aged < 60 years old, the tumor showed increased tumor-infiltrating lymphocytes at the tumor invading front or periphery, the tumor in case 1 located at the lower uterine segment. Such

morphologic findings may raise a suspicion of Lynch syndrome [21]. MMR protein panel (MLH1, PMS2, MSH2 and MSH6) IHC was implemented to screening for Lynch syndrome. Interestingly, abnormal MMR protein expression were found in all 3 cases. MLH1 was lost in case 1 and 2, MSH2 and MSH6 was lost in case 3. Only PMS2 was intact in all cases. However, germ line mutational analysis was not performed due to limitations of genetic counselling, accessibility of next generation sequencing analysis. Upon reviewing the literature, we found a few studies addressing abnormal MMR protein expression in endometrial NEC [12, 14, 23]. Combined loss of MLH1 and PMS2 is usually more common. One study by Pocrnich et al. [12] reported 6 of 18 endometrial NEC cases showing MLH1/PMS2 loss. In contrast, isolated MSH6 or MSH2/MSH6 loss is relatively rare in endometrial NECs. The same study by Pocrnich et al showed only 1 of 18 endometrial NECs with MSH2/MSH6 loss [12]. There is also isolated PMS2 loss found in 2 out of 4 endometrial NECs [14]. Compared to all those reported series, loss of MMR protein expression can be found in endometrial NECs. But it is rare for us to find all 3 cases with loss of the expression. It is quite uncommon that single MLH1 loss without loss of PMS2 in 2 of the 3 cases we show in this study.

Although NEC usually exhibits aggressive behavior, our patients are alive with no disease for 51, 17 and 6 months, respectively. Interestingly, case 3 (FIGO Stage IIIC) with para-aortic lymph nodes metastasis and case 2 (FIGO Stage IB) didn't receive either adjuvant chemotherapy or radiation therapy, though the follow-up time remains short. It is currently unclear what are the underlying reasons for patients with endometrial NECs having not very poor prognosis. Based on the findings from our cases and data presented elsewhere, we believe that loss of MMR protein expression in the tumor cells may illicit more immune responses due to incompetent repair those damaged DNA in the tumor cells. Such enhanced immune responses may contribute to a better prognosis compared to those NECs without MMR protein loss. Our observations were based on a relatively small number of follow-up samples, additional and systematic studies to address this issue are needed.

In summary, endometrial NEC frequently associated with MMR deficiency, some of which may have a better prognosis than we expect. It is important to emphasize that at least 2 NE markers should be reactive in >10% of tumor cells for the diagnosis of NEC in addition to morphologic support.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Women's Hospital, School of Medicine Zhejiang University, and the patient provided written informed consent to participate in the study.

Consent for publication

We obtained written informed consent of the patient for the publication of the case report and accompanying images.

Availability of data and material

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors state they have no competing interests.

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Authors'contributions

All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; ZF and XM involved in drafting the manuscript and revising it critically for important intellectual content; ZF gave final approval to the version to be published. All authors read and approved the final manuscript.

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Tables

Antibody Clones		Dilutions Sources	
p16	16P04/JC2	1:100	Zeta
p53	DO-7	1:600	Thermo
ER	1D5	1:300	Thermo
PR	1A6	1:500	Thermo
CGA	SP12	1:500	Thermo
SYN	SP11	1:200	Thermo
CD56	123C3	1:400	Thermo
MLH1	ES05	1:50	Leica
PSM2	A16-4	1:100	Epitomics
MSH2	25D12	1:100	Leica
MSH6	EP49	1:400	Epitomics
INI1	25/BAF47	1/100	BD Biosciences
BRG1	EPR3912	1:50	Abcam
ARID1A	HPA005456	1:400	Sigma
Ki67	MIB-1	1:400	Dako

Table 1 Antibody clones, sources, and dilutions

	Case 1	Case 2	Case 3
Age (yr)	54	59	55
History of pregnancy	G2P2	G2P2	G2P1
History of cancer	NO	NO	NO
Familial history of cancer	NO	NO	NO
Clinical presentation	Irregular menstruation	Postmenopausal vaginal bleeding	Postmenopausal vaginal bleeding and discharge
Serum tumor biomarkers	Normal CEA, CA125 and CA153	Normal CEA, CA125 and CA153	CA125:50.1 U/mL, Normal CEA and CA153
Imaging findings	A mass in the LUS and cervix canal	A mass in the endometrium	A mass in the endometrium
FIGO Stage	IIB	IB	IIIC
Tumor size	4 × 3 × 1.5 cm ³	4.5×4.4×1.8cm ³	3 × 2.5 × 1 cm ³
Pathological findings	LCNEC (90%) + EC G1 (10%)	LCNEC (60%) + EC G1 (40%)	LCNEC (70%) + EC G1 (30%)
Mitotic count	>20/10HPF	>20/10HPF	>20/10HPF
MI	<50%	>50%	>50%
Cervical interstitial infiltration	YES	NO	NO
LVS1	YES	NO	YES
Treatment	TAH-BSO+RT+CTX	TAH-BSO	TAH-BSO+CTX
Follow-up	Ned at 51 mo	Ned at 17 mo	Ned at 6 mo

Abbreviations: G, gravidity; P, parity; LCNEC, large cell neuroendocrine carcinoma; EC, endometrioid carcinoma; HPF, high power field; MI, myometrial invasion; ned, no evidence of disease; TAH-BSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; RT, radiation therapy; CTX, chemotherapy; mo, month.

Table 2 Clinical findings and pathological results of the tumours

	Case 1		Case 2		Case 3	
	LCNEC	EC	LCNEC	EC	LCNEC	EC
P16	+ (D)	+ (P)	+ (P)	+ (F)	+ (D)	+ (P)
P53	+ (P)	+ (F)	+ (F)	+ (F)	+ (D)	+ (F)
ER	-	+ (D)	+ (D)	+ (D)	-	+ (P)
PR	-	+ (D)	+ (D)	+ (P)	-	-
CGA	-	+ (F)	+ (P)	+ (F)	+ (D)	+ (F)
SYN	+ (D)	-	+ (P)	-	+ (D)	-
CD56	+ (P)	-	-	-	+ (D)	+ (F)
MLH1	Lost	Lost	Lost	Lost	+ (R)	+ (R)
PSM2	+ (R)	+ (R)	+ (R)	+ (R)	+ (R)	+ (R)
MSH2	+ (R)	+ (R)	+ (R)	+ (R)	Lost	Lost
MSH6	+ (R)	+ (R)	+ (R)	+ (R)	Lost	Lost
INI 1	+ (intact)	+ (intact)	+ (intact)	+ (intact)	Lost	Lost
BRG1	+ (intact)	+ (intact)	+ (intact)	+ (intact)	+ (intact)	+ (intact)
ARID1A	+ (intact)	+ (intact)	+ (intact)	+ (intact)	+ (intact)	+ (intact)
Ki67	+ (D)	+ (P)	+ (D)	+ (P)	+ (D)	+ (D)

Abbreviations: D, diffuse (≥50% labeling); F, focal (≤10% labeling); -, negative; P, patch (11-49% labeling); +, positive; R, retained nuclear staining.

Table 3 Immunostaining results of the tumours

Figures

Figure 1

A-I. Case 3: Well-differentiated EC with local squamous differentiation and increased tumor-infiltrating lymphocytes (A, 10×). LCNEC arranged in solid sheets and organoid with necrosis (B, 10×), trabecular (C, 20×) and rosette/pseudorosette (D, 40×). The immunochemical photograph of LCNEC: CGA (E, 20×), SYN (F, 20×), CD56 (G, 20×), MSH2 (H, 20×), MSH6 (I, 20×).