Collision Primary Tumor of the Endometrium: Large Cell Neuroendocrine Carcinoma and Endometrioid Adenocarcinoma

Wyatt Unger, Qian Tang, Danielle Summers and Wenxin Zheng*

University of Arizona College of Medicine Department of Pathology, Department of Obstetrics and Gynecology, and Arizona Cancer Center, 1501 N. Campbell Avenue, #5205 Tucson, AZ 85724, USA

Abstract: This is the first reported case, to our knowledge, of a true collision primary tumor of the endometrium. Neuroendocrine carcinoma of the endometrium is itself a rare tumor. In this case we present a collision tumor of neuroendocrine carcinoma with endometrioid adenocarcinoma of the endometrium. The unique morphologic and immunophenotypic features of these tumors in this case are discussed, justifying the classification of this case as a collision primary tumor of the endometrium.

Keywords: Collision, synchronous, tumor, endometrium, adenocarcinoma, neuroendocrine.

CLINICAL HISTORY

The patient was a 62-year-old woman, gravida 4 para 4, who initially sought medical attention for postmenopausal bleeding. She underwent menarche at age 14 and menopause at age 50. She had no history of oral contraceptive use, hormone replacement therapy, or abnormal pap smears. She had no previous cancer history and a recent colonoscopy and mammogram were both negative. Her mother had a previous diagnosis of Paget's disease of the breast, her maternal cousin had pancreatic cancer at age 65, and another maternal cousin had breast cancer at age 50. She had a 10-pack year history of smoking and was obese.

An endometrial biopsy showed a neuroendocrine carcinoma while a cervical biopsy and endocervical curettage were both negative. A CT scan of the abdomen and pelvis showed an abnormally thick endometrium (3 cm) without evidence of lymphadenopathy. A transvaginal ultrasound showed an 8.6 cm uterus with a 5 cm subserosal leiomyoma and a thickened endometrial stripe of 8 mm.

As a result of her biopsy and radiologic findings, she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection, omentectomy, and washings.

MATERIALS AND METHODS

Surgical specimens were fixed in 10% buffered formalin and representative sections were taken for routine microscopic examination.

*Address corresponding to this author at the University of Arizona College of Medicine Department of Pathology, Department of Obstetrics and Gynecology, and Arizona Cancer Center, 1501 N. Campbell Avenue, #5205 Tucson, AZ 85724, Tel: 520-626-2396, Fax: 520-626-1027;
E-mail: zhengw@email.arizona.edu

Immunohistochemical studies from the representative tumor sections, described previously [1] were performed using the avidin-binding-peroxidase method, with antisera to estrogen receptor (ER), progesterone receptor (PR), p53, IMP-3, Chromogranin, CD56, synaptophysin, CK7, PAX-8, and CD10.

PATHOLOGIC FINDINGS

The radical hysterectomy specimen consisted of a 150g uterus measuring 10.0 x 7.3 x 3.0 cm. The outer surface of the endometrium was red-tan and trabeculated. No masses were seen on the outer surface. The ectocervix had focal areas of red-brown discoloration. The endocervical canal was red-tan and trabeculated. There was a polypoid tan friable mass measuring 6.0 x 3.5 x 2.0 cm occupying the entire endometrial cavity (Figure **1**). A smaller polypoid lesion measuring 1.5 x 1.1 x 0.4 cm was located 2cm from the first described mass. This mass was yellow-tan, smooth and glistening, with a polypoid architecture and located in the superficial endomyometrium. The remaining myometrium showed multiple leiomyomata ranging in size from 0.3 cm to 1.6 cm.

On microscopic examination, the endometrial tumors consisted of two morphologically distinct regions, with abrupt margins. The 6 cm polypoid mass was mainly comprised by malignant neuroendocrine cells. It consisted of small blue cells, with many mitoses, growing in a sheet-like pattern. The mitoses were easily identifiable. The cell nuclei had salt and pepper chromatin. The neuroendocrine cells surrounded benign appearing endometrial glands (Figure **2**). The second mass, 1.5 cm in size, adjacent to the 6 cm mass showed mainly neoplastic glandular endometria. These neoplastic cells consisted of well-

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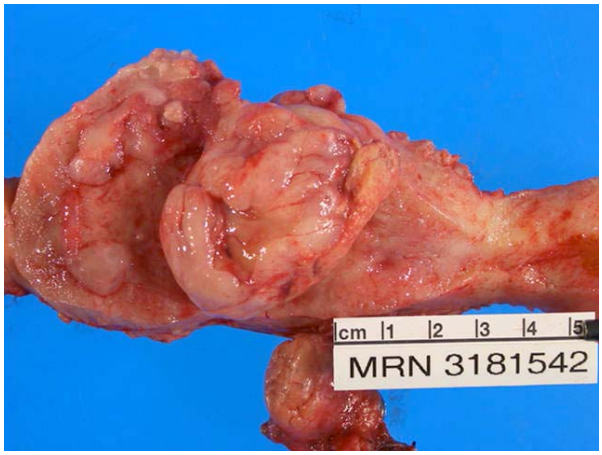


Figure 1: The radical hysterectomy specimen with a polypoid tan friable mass occupying the entire endometrial cavity. A smaller polypoid lesion measuring was located 2cm from the first described mass. The remaining myometrium showed multiple leiomyomata.

formed tubular glands, most of which were medium-sized (Figure **3**). Some of these glandular structures anastomosed together with partial fusion of the tumor cells forming a cribriform growth pattern. The cells lining these glands exhibited mild nuclear pleomorphism, and had mildly eosinophilic cytoplasm. There was a small area of squamous differentiation. The two neoplastic components were sharply demarcated without intermingling with one another. Tumor mass with neuroendocrine appearance showed no myometrial invasion, while the glandular part invaded through 20% of the myometrium. There was no lymphovascular space involvement identified for both tumor components.

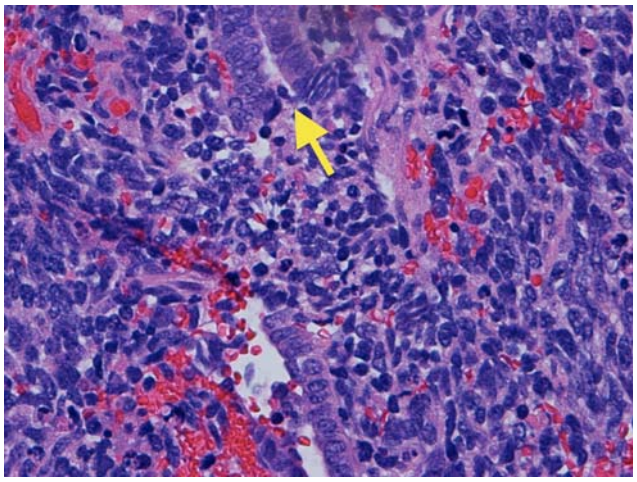


Figure 2: Neoplastic neuroendocrine cells surrounding benign appearing endometrial glands (arrowhead).

Immunohistochemical stains were performed to further differentiate these two focally abrupt regions of tumor. Based on tumor morphology, markers were selected to differentiate between neuroendocrine and endometrial endometrioid carcinomas. The results of the immunohistochemical stains are summarized in Table **1** and representative pictures are presented in Figure **4**.

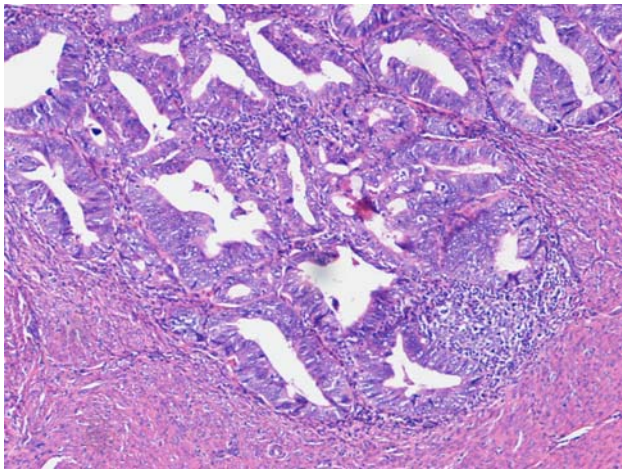


Figure 3: Typical low-grade endometrioid carcinoma component.

The final diagnosis in this case was a synchronous or collision carcinoma of the endometrium. One is a neuroendocrine carcinoma, which is a polypoid lesion without myometrial invasion. The other is adenocarcinoma of the endometrium, endometrioid type, which is located in the fundus with myometrial invasion of 40%. The morphologic and immunophenotypic patterns of each were distinct which supports the diagnosis.

COMMENT

Neuroendocrine carcinoma of the endometrium is an uncommon malignancy. There are approximately 60 reported cases of neuroendocrine carcinoma of the endometrium in the English literature [2-5]. The average age of onset for neuroendocrine carcinoma of the uterus is 60, where the average age for endometrial carcinoma is 50. A synchronous component of endometrioid adenocarcinoma has been found in one half to two thirds of reported cases of small cell neuroendocrine carcinoma of the endometrium [6]. There are several explanations that have been proposed for the co-occurrence of endometrioid adenocarcinoma with neuroendocrine tumors of the endometrium. These include divergent differentiation of a common progenitor tumor, dedifferentiation of a differentiated tumor, and a true collision tumor. We would argue that this case of synchronous endometrial primaries represents a true collision tumor, with unique

Table 1: Immunohistochemical Profiling of the Endometrial Tumor

Summary of Immunohistochemical Staining					
Marker	**Clone**	**Dilution**	**Source**	**Neuroendocrine Component;**	**Endometrioid Component**
ER	ER/SP1	Neat	VMS	Negative	90%
PR	PR/1E2	Neat	VMS	Negative	90%
P53	DO-7	Neat	VMS	100%	80%
IMP-3	69.1	1:125	Dako	100%	Negative
Chromogranin	LK2H10	Neat	VMS	Negative	Negative
CD56	123C3.D5	1:25	Cell Marque	100%	10%
Synaptophysin	RAB Poly	Neat	VMS	100%	Negative
CK-7	SP52	Neat	VMS	Negative	Positive
PAX-8	NA	1:50	PRO DES	Negative	Positive
CD10	SP67	Neat	Cell Marque	Negative	Negative

features not shared by previously reported synchronous primaries of the endometrium.

It has been suggested that synchronous endometrial primaries represent divergent differentiation from a common neoplastic pluripotent progenitor cell [7]. In contrast to previously reported cases of synchronous primaries of the uterus, the endometrioid carcinoma in this specimen was confined to one discrete focus. It was not surrounded by or comingled with the neuroendocrine component. In a previous case series including 3 cases of combined large cell neuroendocrine carcinoma and endometrioid adenocarcinoma, immunohistochemcial staining of the samples showed that the neuroendocrine component expressed CK-7 in each of these samples [5]. This suggests that the neuroendocrine component shared some common lineage with the endometrioid component in the cases from that series.

In another series of 16 cases, where 8 cases exhibited synchronous endometrioid adenocarcinoma, only 2 of these cases were described as having morphologically distinct areas of endometrioid adenocarcinoma. Eight of ten small cell carcinomas from this series expressed cytokeratins [3]. The endometrioid and neuroendocrine components coexpressed synaptophysin in this case series, which has been cited as molecular evidence for the theory that when synchronous these tumors are probably derived from a common progenitor cell [5].

Another case of small cell neuroendocrine carcinoma of the endometrium associated the cancer with HPV exposure and was strongly p16 positive. The endometrioid component in the case also coexpressed several IHC markers, including PR, synaptophysin, and p16 [6]. The coexpression of several markers in this case is probably related to the common origin of these two components from cells infected with the HPV, which then differentiated divergently. In our case, both the endometrioid and neuroendocrine components stained positive for p16. p16 positivity is common in neuroendocrine carcinoma, and is frequently associated with cervical canal adenocarcinoma associated with HPV infection, undifferentiated endometrial adenocarcinoma, as well as occasionally in endometrioid adenocarcinoma [8].

There is one previously reported case of small cell neuroendocrine carcinoma synchronous with endometrial serous carcinoma in which IHC staining was distinct. In that case there was no coexpression of immunohistochemical markers. However, the two tumor components were intimately intermingled with only a few foci of morphologically distinct areas [9]. In the case we present, save for p16, there is no coexpression of immunohistochemical markers across the neuroendocrine and endometrioid components.

Little data exists about the appropriate therapy for neuroendocrine carcinoma of the endometrium. This malignancy is sufficiently rare such that there are no published trials regarding optimal therapy. It has been suggested that a polypoid architecture may be associated with a favorable prognosis in neuroendocrine carcinoma of the endometrium and cervix. In the case series that proposed this however,

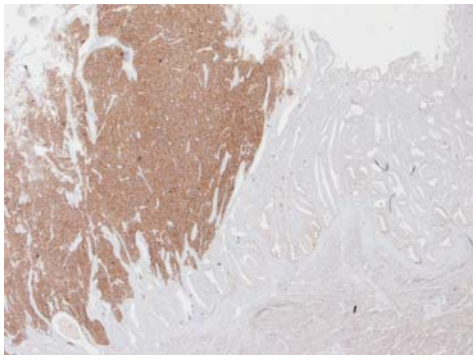
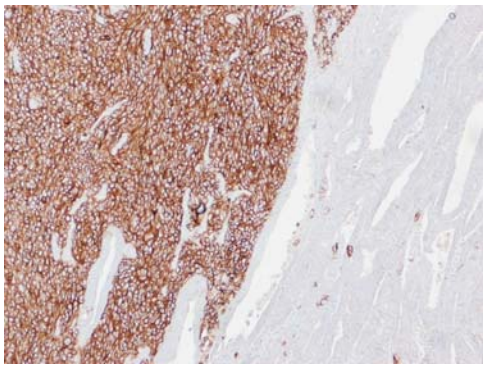
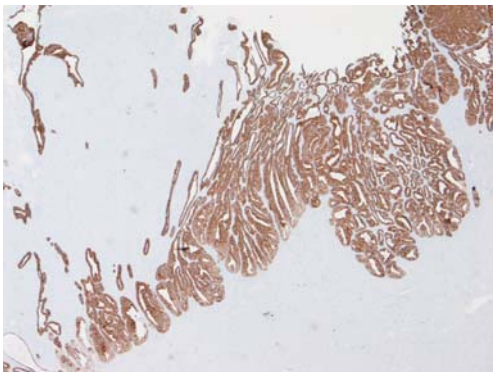
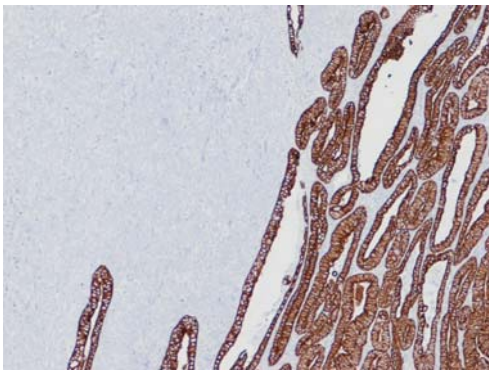
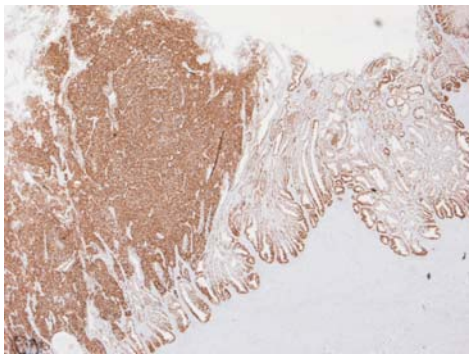
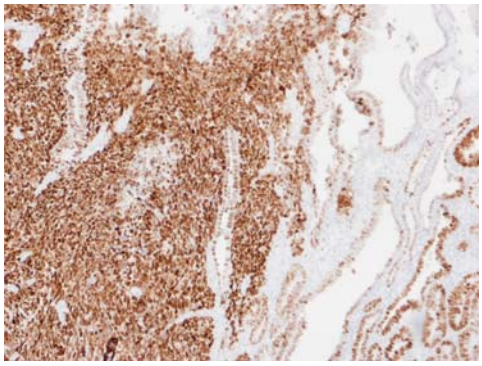
20 x Magnification	100 x Magnification	IHC Stain
		CD56
		CK7
		P53

Figure 4: IHC Profiling of the Endometrial Tumor.

The neuroendocrine component is on the left side of the pictured slides and the endometrioid component is on the right side. The neuroendocrine component stained strongly for CD56. The endometrioid component stained strongly positive for CK7. Both tumors stained strongly positive for p53.

none of the neuroendocrine cancers were synchronous with other regular endometrial cancers [10]. Although the architecture of the neuroendocrine cancer in our case may imply a favorable prognosis, neuroendocrine cancers are aggressive, and although low in stage, the neuroendocrine cancer warrants aggressive therapy, including chemotherapy and radiation therapy.

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