Undifferentiated Endometrial Carcinoma
A Diagnosis Frequently Overlooked

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*Undifferentiated endometrial carcinoma (UEC) is a relatively uncommon neoplasm with only few studies published thus far. It has always been a diagnostic challenge because of the lack of proper definition cited in most of the standard textbooks. Recently however, a few studies have highlighted the clinicopathologic features of UEC. The distinctive morphology of UEC was noted by the group from MD Anderson Cancer Center, which enabled them to establish the defining criteria. It appears to be more aggressive than endometrial endometrioid adenocarcinoma, FIGO (International Federation of Gynecology and Obstetrics) grade 3, its main differential diagnosis. Proper recognition of this entity is important owing to its aggressive behavior.*


**GROSS PATHOLOGY AND HISTOPATHOLOGY**

Undifferentiated endometrial carcinoma may present as large polypoid masses with evident necrosis. Involvement of and origin from the lower uterine segment is a frequent finding, as well as gross involvement of the cervix. Microscopically, it is defined as a tumor composed of medium or large-sized cells with complete absence of glandular differentiation and with absent or minimal (<10%) neuroendocrine differentiation. It usually displays a patternless solid, sheetlike growth, with total absence of nests, papillae, glands, or trabeculae. Occasional delicate fibrovascular septae that segregate tumor cells focally into an alveolar pattern (Figure 1) are described, as well as vague cords and trabeculae. Large areas of necrosis with viable perivascular tumor cells are seen. The cells are dysesive, mostly monomorphic and relatively uniform. The nuclei are vesicular with prominent eosinophilic nucleoli, although they can sometimes be hyperchromatic. Variation of cellular size from small cells with scanty basophilic cytoplasm to large cells with clear or vacuolated cytoplasm is also described (Figure 2), as well as variable percentage of tumor cells demonstrating rhabdoid cell morphology, often in a myxoid background (Figure 3). Numerous mitoses and also apoptosis are usually seen. Lymphovascular invasion is seen in more than half of cases. Further morphologic characterization was provided by a comprehensive study with equal contribution by 2 groups, one from Memorial Sloan-Kettering Cancer Center (New York, NY) and the other from Stony Brook University...
They have concluded that UEC can present in either pure or mixed forms, a finding that also applies to similar cases from the ovary. Association with differentiated components, more commonly of low-grade (FIGO grade 1 or 2) endometrioid carcinoma, but occasionally with endometrioid carcinoma FIGO grade 3, is the defining feature for the mixed forms. Defined as such, pure forms appear to be more common in some reports, while the mixed forms are more common in others. In the mixed forms, which are sometimes referred to as combined carcinoma or more appropriately, dedifferentiated carcinoma, the percentage of the undifferentiated component ranged between 20% and 90%, and the interface between the differentiated and the undifferentiated components was described as abrupt and sharply demarcated, with a more superficial location for the differentiated component and a deep location for the undifferentiated carcinoma. Occasionally, UEC may be detected asynchronously in the recurrences or metastasis of an otherwise previously confirmed and treated endometrial endometrioid adenocarcinoma. Other specific histologic details displayed by some UECs were marked nuclear pleomorphism and multinucleation, and prominent tumor-infiltrating lymphocytes. As originally described, this entity should not show squamous differentiation, mucinous differentiation, or spindled growth pattern. Later reports, however, allowed for foci of vague spindling, and abrupt keratinization.

ANCILLARY STUDIES

Immunohistochemical characteristics of UEC include focal staining (<10%) for keratin AE1/AE3, CAM 5.2, and epithelial membrane antigen (EMA). Others have reported focal (5%–10%) keratin staining (Figure 4) and focal (10%–20%) EMA staining in most cases. Special emphasis was given to cytokeratin 18 as being the most helpful stain to show epithelial differentiation, even if more than 1 tumor block needed to be stained to pick up the very focal diagnostic staining areas. Of note is the marked intensity of tumor cells staining for keratins and EMA, regardless of the percentage of positive cells. In addition, UEC showed reactivity for vimentin (Figure 5) and retained nuclear staining for BAF-47 (INI-1). One or more neuroendocrine markers including chromogranin, synaptophysin, and/or CD56 can be expressed focally in less than 10% to 20% of tumor cells. Focal staining for S100 protein, CD10, estrogen receptor, and progesterone receptor was also noticed. Completely negative staining for smooth muscle actin, desmin, and HMB-45 was reported.

PATHOGENESIS

Relation to Lynch syndrome has been suggested after testing of UEC for DNA mismatch repair (MMR) genes. Loss of 1 or more of these genes has been reported in 47% of the tested cases, most frequently, MLH1 and PMS2. The loss was demonstrated in both differentiated and undifferentiated components in tested combined cases, supporting the common origin of both components and thus the designation as dedifferentiated carcinoma. These results conferred the property of microsatellite instability to UEC, linking it to hereditary nonpolyposis colorectal carcinoma or Lynch syndrome. MLH1 promoter hypermethylation has been described in a subset of what appeared to be sporadic cases. The young age of presentation, presence of previous history of colorectal carcinoma, positive family history for
Lynch syndrome–associated tumors, localization to lower uterine segment, presence of tumor-infiltrating lymphocytes, and synchronous ovarian carcinomas\textsuperscript{10,14} should all mandate testing of UEC for DNA MMR genes.

**DIFFERENTIAL DIAGNOSIS**

**UEC Versus Endometrioid Adenocarcinoma FIGO Grade 3**

Undifferentiated endometrial carcinoma is most frequently misdiagnosed as endometrial endometrioid adenocarcinoma, FIGO grade 3. However, the latter is defined by the WHO as composed of 1% to 49% glandular areas. Although the presence of focal glandular differentiation can help in separating endometrial endometrioid adenocarcinoma, FIGO grade 3, from pure forms of UEC, this feature loses its power in cases of mixed forms of UEC or dedifferentiated carcinoma, where the UEC component is mostly seen admixed with lower-grade endometrioid carcinoma. The presence of cohesive sheets of neoplastic cells in solid areas (Figure 6), the comparable cytologic features in the glandular and solid components, the absence of rhabdoid features, and the diffuse immunoreactivity for keratins (Figure 7) and EMA can help to support the diagnosis of poorly differentiated endometrioid adenocarcinoma.\textsuperscript{3} The cytologic features of UEC and differentiated components in the dedifferentiated carcinoma are distinct.\textsuperscript{3} The Table summarizes the main differences between UEC and endometrioid adenocarcinoma FIGO grade 3.

**UEC Versus Neuroendocrine Carcinoma**

Neuroendocrine carcinoma is another important differential diagnosis. Tumors that usually had been referred to in the literature as small and large cell carcinomas should be regarded as neuroendocrine carcinomas rather than variants of UEC, as they do display a form of differentiation, which goes against the definition of undifferentiated carcinoma. Expression of 1 or more neuroendocrine markers, including

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**Figure 4.** Cytokeratin MNF immunostain showing focal intense reactivity (original magnification ×20).

**Figure 5.** The tumor is focally positive for vimentin immunostain (original magnification ×40).

**Figure 6.** Cohesive growth of the solid component of the poorly differentiated endometrioid adenocarcinoma, FIGO (International Federation of Gynecology and Obstetrics) grade 3 (hematoxylin-eosin, original magnification ×20).

**Figure 7.** Cytokeratin MNF immunostain showing diffuse and strong reactivity in poorly differentiated endometrial adenocarcinoma, FIGO (International Federation of Gynecology and Obstetrics) grade 3 (original magnification ×20).
synaptophysin, chromogranin, and/or CD56 in more than 20% of tumor cells, should support this diagnosis.5,9

**UEC Versus Serous Carcinoma**

Serous carcinoma with solid growth pattern tends to show distinctive high-grade cytoplasmic findings, in addition to the papillary and/or slitlike spaces. Frequent lymphovascular invasion with papillary formations is seen frequently in the advancing edge of the tumor. In addition, psammoma bodies are indentified in one-third of cases of serous carcinoma.15

**UEC Versus Carcinosarcoma**

Carcinosarcoma affects elderly females and would evidently display a biphasic pattern, typically spindle-cell sarcomatous component.

**UEC Versus Sarcoma**

Endometrial stromal tumors, especially undifferentiated endometrial sarcoma (UES), should be considered in the differential diagnosis. This is a high-grade tumor with marked pleomorphism, brisk mitosis, and necrosis. Although UES might show some staining with CD10, it is nonreactive for other markers, including epithelial markers,5 and extensive sampling to rule out the presence of focal areas of differentiation should always be performed. High-grade endometrial stromal sarcoma is a recently “revisited” entity, with intermediate features between low-grade endometrial stromal sarcoma and UES. It exhibits uniform cells with evidence of endometrial stromal differentiation.16

Epithelioid leiomyosarcoma is ruled out through negativity for muscle markers including desmin, smooth muscle actin, and h-caldesmon. Pancytokeratin staining should be cautiously interpreted in epithelioid leiomyosarcoma as it can show positivity.37

**Others**

The striking dyshesion of the UEC tumor cells makes lymphoma, plasmacytoma, and granulocytic sarcoma enter the list of the differential diagnoses. Nonetheless, immunophenotyping makes the distinction quite easy.

**CURRENT TREATMENT AND PROGNOSIS**

Undifferentiated endometrial carcinoma appears to pursue an aggressive clinical course with advanced stage at presentation and a median survival of 6 months. Disease-related death rate ranges from 41% to 75% of reported cases, which occurs mostly in the first 5 years after diagnosis. According to Altrabulsi et al,3 54% of UECs present as high-stage disease (stage III or IV), as compared to 30% of endometrioid endocarcinomas FIGO grade 3. Pelvic and paraaortic lymph nodes are the most common sites of metastasis. Silva et al4 and Tafe et al5 noted that in cases of combined histologic appearance, the presence of even a small undifferentiated component appears to carry a poor clinical outcome, while the presence of a better-differentiated component, irrespective of its extent, does not appear to confer improved clinical outcome. No association was found between age, stage, presence and number of tumor-infiltrating lymphocytes, rhabdoid cell morphology, and clinical outcome.5

Treatment modalities include total abdominal hysterectomy and bilateral salpingo-oophorectomy, as well as chemotherapy and radiotherapy, with regimens similar to those for endometrioid carcinoma FIGO grade 3. Hayashi et al18 reported a successful experience with a case of UEC that was treated by surgery in conjunction with a combination chemotherapy regimen consisting of tetrahydroprynyl-adiamycin, taxane (paclitaxel), and JM-8 (carboplatin), the TTJ regimen. The patient was treated with 6 cycles of TTJ and achieved complete response. She continued to be carefully followed up by clinical examination, magnetic resonance imaging, and bone scan. She was followed up for 41 months and remained alive without metastasis. Another example of long survival is that of a patient with advanced-stage disease who was treated exclusively with radiotherapy and showed no evidence of disease after a follow-up of 104 months.3

**Clinicopathologic Features of Undifferentiated Endometrial Carcinoma/Dedifferentiated Carcinoma and Endometrial Endometrioid Adenocarcinoma, FIGO Grade 3**

<table>
<thead>
<tr>
<th>Clinicopathologic Features</th>
<th>Undifferentiated/Dedifferentiated Endometrial Carcinoma</th>
<th>Endometrial Adenocarcinoma, FIGO Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at presentation, y</td>
<td>55</td>
<td>68</td>
</tr>
<tr>
<td>High stage (stage III/IV), %</td>
<td>45</td>
<td>30</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancytokeratin</td>
<td>Patchy/local</td>
<td>Diffuse* in 60% of cases</td>
</tr>
<tr>
<td>EMA</td>
<td>Patchy/local</td>
<td>Diffuse*</td>
</tr>
<tr>
<td>ER/PR</td>
<td>Focal in 12% of cases</td>
<td>Diffuse*</td>
</tr>
<tr>
<td>Morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growth pattern</td>
<td>Diffuse patternless sheets*</td>
<td>Solid and glandular</td>
</tr>
<tr>
<td>Myxoid matrix</td>
<td>May be present</td>
<td>Present (1%–49% of tumor area)</td>
</tr>
<tr>
<td>Rhabdoid cells</td>
<td>May be present</td>
<td>Cohesive squamouslike</td>
</tr>
<tr>
<td>Cords and trabeculae</td>
<td>Vague*</td>
<td>Intermingled components</td>
</tr>
<tr>
<td>Component demarcation</td>
<td>Sharp demarcation</td>
<td>Absent</td>
</tr>
<tr>
<td>Glands</td>
<td>Absent*</td>
<td>Absent</td>
</tr>
<tr>
<td>Cohesive growth</td>
<td>Dyshesive cells</td>
<td>Absent</td>
</tr>
<tr>
<td>Psammoma matrix</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Integration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EMA, epithelial membrane antigen; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; PR, progesterone receptor.

This applies only to pure forms of undifferentiated endometrial carcinoma, as glandular component can be seen in the lower-grade component of the dedifferentiated carcinoma.

Diffuse staining is defined as staining in more than 50% of tumor cells.
POUNTS OF CONTROVERSIES
Are UEC and Neuroendocrine Carcinoma the Same or Different?

The exact relation between neuroendocrine carcinoma and UEC needs further elaboration. Focal neuroendocrine differentiation, defined as less than 10% positivity of various intensities with 1 or more neuroendocrine markers, was reported in 41% of UECs by Taraif et al. 19 Interestingly, there was no difference in the prognosis and overall survival between both groups. 19 Within UEC, this focal neuroendocrine differentiation does not seem to affect the outcome either. 1

What Is the Difference Between Pure Forms of UEC and Mixed or Dedifferentiated Carcinoma Forms?

Microsatellite instability immunostaining performed in some cases is in support of a common origin of the better differentiated and undifferentiated components in the mixed tumors; thus, the suggested term dedifferentiated carcinoma. 4,5 Treatment protocols are similar in both scenarios, as pure and mixed forms of UEC are treated as endometroid carcinoma FIGO grade 3. Prognosis is reported to be poor regardless of the amount of undifferentiated component, irrespective of its extent, does not appear to confer an improved clinical outcome. Total engulfment of the better-differentiated component by the undifferentiated one might offer a reasonable possible explanation.

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References

CAP ‘13 Abstract Program Accepting Submissions

Abstract and case study submissions will be accepted beginning Monday, February 4, 2013 for the College of American Pathologists (CAP) 2013 meeting. CAP ‘13 will be held October 13 through the 16th in Orlando, Florida. Submissions for the CAP ‘13 Abstract Program will be accepted through Monday, April 1, 2013.

Accepted submissions will appear in the October 2013 issue of the Archives of Pathology & Laboratory Medicine. Visit the CAP ‘13 Website at www.cap.org/cap13 for a link to the abstract submission site and additional abstract program information as it becomes available.