

Commentary

Serous EIC as an early form of uterine papillary serous carcinoma: recent progress in understanding its pathogenesis and current opinions regarding pathologic and clinical management

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Uterine papillary serous carcinoma (UPSC) is an aggressive form of endometrial cancer, that has a dismal prognosis [1–3]. Since its etiology is virtually unknown, physicians and research scientists who battle this disease have tried to identify its precursor lesions in order to improve disease management through early detection.

The term endometrial intraepithelial carcinoma (EIC), as a putative ‘precursor lesion’ of UPSC, was first proposed by Sherman et al. in 1992 [3] and formalized by Ambros et al. in 1995 [4]. Almost at the same time, Spiegel described the same disease as endometrial carcinoma in situ (ECIS) [5]. EIC or ECIS was defined morphologically as replacement of endometrial surface epithelium and glands without myometrial or stromal invasion by frankly malignant cells identical to UPSC tumor cells [3–5]. The terms of EIC and ECIS, however, were challenged by Zheng et al. [6] by proposing a term called uterine surface carcinoma (USC) mainly because this putative precursor lesion is commonly associated with extrauterine serous carcinoma [3,4,7–12] and it does not just behave like intraepithelial carcinoma or carcinoma in situ although morphologically no myometrial invasion is associated. With similar reasons, Wheeler et al. proposed another term as minimal uterine serous carcinoma (MUSC, any non-invasive uterine serous carcinoma less than 1 cm in greatest dimension) [12]. This putative precursor lesion of UPSC is now being referred as serous EIC by the WHO classification [13]. The terminology of

this endometrial lesion causes confusion in terms of its behavior and management. This commentary recommends that serous EIC be considered an early form of UPSC and provides management guidelines based on our experience and that of others.

Does serous EIC behave like a truly intraepithelial carcinoma? The significant number of serous EIC or stage 1A UPSC presenting concurrently with extrauterine disease and its high recurrence rate argues strongly against serous EIC being an intraepithelial, that is, an in situ form of UPSC. Wheeler et al. [12] reported on 21 serous EIC cases without myometrial invasion. Of these 21 patients, 7 were associated with extrauterine disease. Silva and Jenkins [11] reported on 16 cases of non-invasive UPSC in endometrial polyps. Ten of them had clinical stage IA disease at presentation. Of these 10 patients, 6 experienced abdominal recurrences and 4 died of their diseases. Carcangiu et al. [7] reported 2 of the 13 stage IA UPSC cases died of disease with intra-abdominal carcinomatosis at 10 and 14 months after their initial complete surgical staging. Recently, Slomovitz, et al. reviewed 32 serous EIC or stage 1A cases. Among the 32 patients without uterine invasion, surgical staging revealed that 13 (40%) had stage III or stage IV disease [14]. It is currently unknown whether the size (less than one versus one cm or bigger) of non-invasive uterine serous carcinoma yields a prognostic difference.

We recently reviewed 9 serous EIC cases (lesion less than 1 cm in size) and 8 stage 1A UPSC (lesions equal or larger than 1 cm but no myometrial invasion) accessioned from the years 2000 to 2004 in the Department of Pathology of Yale-New Haven Hospital. All 17 cases had complete surgical staging including omentectomy. We found that 6

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(67%) of 9 serous EIC had extrauterine disease. These included 3 cases with serous carcinoma involving ovaries and omentum, 1 case with tubal serous carcinoma, 1 with endocervical mucosa involvement only and 1 with positive peritoneal washing only. Among the 8 stage 1A UPSC cases, 5 (63%) had extrauterine disease including 1 minimal ovarian involvement, 3 extensive ovarian and omental involvement, and 1 omental involvement only. There was no statistical difference between the serous EIC (lesions less than 1 cm) and non-invasive UPSC in terms of association with the extrauterine serous carcinoma involvement (Zheng and Schwartz, unpublished data). A similar high incidence rate of extrauterine disease and recurrence in non-invasive serous carcinoma has also been reported in other studies [3,9].

The mechanism of dissemination from serous EIC to extrauterine serous carcinoma or carcinomatosis has not been defined. There are basically two explanations, that is, transtubal metastasis and simultaneous “field effect”. These hypotheses may not be mutually exclusive. Hematogenous dissemination is unlikely since no case of serous EIC associated with distant organ metastasis has been reported, although UPSC commonly shows extensive lymphovascular space invasion when extensive myometrial invasion is present. At the molecular level, a few studies on this issue suggest that extrauterine serous carcinoma represents metastases of serous EIC. This is supported by the finding of identical clones of p53 mutations when comparing the intrauterine to extrauterine lesions in same patients [15,16]. If the extrauterine disease represents a true metastasis from serous EIC, it is logic to speculate that transtubal metastasis is likely to be the pathway. This is substantiated by occasional findings of so-called in transit deposits of serous carcinoma cells in the fallopian tubes in serous EIC cases. From the biologic point of view, transtubal metastasis makes a better sense than transmyometrial or transvascular metastasis simply because of easy access to the peritoneal cavity.

Soslow et al. studied CD44v6 expression in high-grade endometrial cancers and found that loss of this cell surface adhesion molecule is strongly associated with serous type malignant cells [17]. Alterations of other cell surface adhesion molecules, E-cadherin and Beta-catenin, in uterine serous carcinoma may also be associated with the tendency of malignant serous cells to dislodge and deposit in extrauterine sites [18,19]. However, in a study of BRCA-positive women with primary peritoneal carcinoma, tumors at different sites including UPSC were found to be polyclonal [20]. An occasional case of a serous EIC has been associated with a de novo carcinoma of the ovary in an ovarian serous adenofibroma [12]. Compared with the monoclonal origin of multifocal disease in metastatic serous EIC and UPSC, there is some evidence that peritoneal serous carcinoma may have multifocal independent primaries [21]. These findings are suggestive of a multicentric primary of extrauterine disease. Based on the cases we observed at Yale, the extrauterine disease can be divided

into two categories. One is with minimal microscopic involvement, and the other is with bulky extensive disease. It is unknown whether serous EIC with minimal extrauterine involvement is more likely derived from transtubal metastasis while serous EIC with extensive extrauterine disease represents independent primary cancers. This topic is currently being investigated in our group.

Considering the above observations it is reasonable to conclude that serous EIC is not a true intraepithelial carcinoma as it differs from carcinoma in situ at other sites. It has a capacity to spread even when myometrial invasion is not present. It has a unique association of a high incidence (up to 67%) of extrauterine serous carcinoma or even carcinomatosis. Therefore, serous EIC represents an early form of UPSC, given the fact that serous EIC and UPSC have morphologically identical malignant cells and share similar molecular alterations [10,22–25]. UPSC does not require a large amount of tumor volume to be associated with an aggressive course.

It is generally accepted that UPSC arises in atrophic or resting endometrium [1,2,4,5,10,12,26,27]. Morphologically, serous EIC shows indisputably malignant glandular cells within the endometrium. It is apparent that something is missing between the completely benign endometrium and obviously malignant endometrial glands. Zheng et al. recently described a new entity called endometrial glandular dysplasia (EmGD), which bridges benign resting endometrium and serous EIC [27]. Zheng et al. speculate that EmGD may represent the earliest morphologically identifiable intraepithelial precursor lesion in the process of UPSC development. EmGD as a true precursor lesion of serous EIC and therefore UPSC was based on the following observations. First, morphologic transitions between EmGD and serous EIC and between serous EIC and UPSC are frequent, but no direct transitional areas are identified between EmGD and UPSC. Second, in UPSC cases, EmGD is often multifocal and involves sites that are noncontiguous with the main tumor mass. In contrast, EmGD lesions are intimately associated with serous EIC. Third, in addition to a close association with serous EIC, the atypia of EmGD cytologically fall short of serous EIC. Fourth, EmGD p53 overexpression scores and MIB-1 proliferative indices are mostly less than serous EIC but more than benign resting endometrium. Fifth, EmGD frequently shows loss of heterozygosity (LOH) at multiple chromosomal loci, particularly at 17p (TP53) and 1p. In addition, significantly high concordant LOH frequency between EmGD and serous EIC or UPSC is observed in a paired molecular study [28].

A model of UPSC development from resting endometrium to EmGD and to serous EIC has now been proposed [27]. Based on this UPSC development model, alteration of the p53 tumor suppressor gene is an early event, which involves lesions of EmGD, serous EIC, and UPSC [10,23–25,28]. The p53 immunostaining and a mutation based p53 gene analysis assay will be useful in the early detection of UPSC. Since serous EIC has already been associated with a

high incidence of extrauterine disease, the diagnosis of serous EIC may not represent early detection. It is unknown whether EmGD is associated with extrauterine disease, the window period from EmGD to serous EIC and UPSC, the progression rate, and other molecular changes in addition to p53 in the process of UPSC development. Such studies are urgently needed and we are also investigating the issue intensively at Yale.

Recognition that some serous EICs behave aggressively, while others may have an uneventful outcome in many years, has led to confusion concerning the behavior and appropriate management of serous EIC. Most studies showed that serous EIC has a good prognosis if extrauterine disease is excluded by meticulous staging. However, the prognosis is poor if even minimal extrauterine disease is present. There are no standard guidelines regarding how to manage serous EIC in terms of pathology assessment and clinical treatment. We currently adhere to the following protocol to evaluate serous EIC or potential serous EIC specimens: serial sections are carefully reviewed when a serous EIC is present in a curettage specimen and the entire endomyometrium (3 to 5 mm interval) is examined when the lesion is in a hysterectomy specimen. To ensure the detection of extrauterine disease, we evaluate the entire ovaries and fallopian tubes (3 mm interval) and at least 10 omental sections when no gross tumor is identified. All lymph nodes are meticulously dissected and microscopically examined. When the diagnosis of serous EIC is in question, p53 (both clones of 1801 and DO7) and Ki-67 immunostainings are performed to aid the diagnosis [24,27]. Complete surgical staging including a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph nodes dissections, omentectomy, peritoneal biopsies, and pelvic washings) has been recommended and performed by multiple institutions in the United States when serous EIC is encountered to determine the prognosis [7,11,12,14,27,29,30].

It is the current practice at Yale-New Haven Hospital to observe patients with Stage IA UPSC or EIC when no residual disease is found in the hysterectomy specimen. No recurrences were noted among 7 patients with no additional therapy in this circumstance, nor in 3 patients who received brachytherapy with (two) or without (one) receiving chemotherapy [31]. In 6 patients who received radiation plus chemotherapy because there was residual UPSC in the hysterectomy specimen, no recurrences have been observed to date (median disease-free survival 52 months, range 22–65 months). Two of 7 patients who did not receive postoperative chemoradiation have now recurred when they were found to have residual disease remaining in the uterus following definitive surgery (median disease-free survival 26 months, range 6–80 months). Additionally, 7 patients with Stage IIIA disease all of whom received chemotherapy, 5 of whom received brachytherapy to the vaginal apex have remained clinically free of disease since the initial treatment

(Median disease-free survival 14 months, range 8–41 months).

Our current practice is to offer all patients who have residual disease, that is, serous EIC or UPSC limited to the endometrium in the hysterectomy specimen or found in association with any extrauterine disease, chemoradiation using carboplatin and paclitaxel given systemically and vaginal cuff radiation administered in 2 doses, one 1 week before and one 1 week after the second chemotherapy treatment. Patients whose hysterectomy specimens lack residual disease and have no extrauterine serous carcinoma receive no additional therapy. When vaginal cuff radiation is given, it is used to avoid the development of recurrent disease only at that one site. Systemic chemotherapy is given to control systemic disease.

In terms of EmGD, currently, we do not yet know the clinical relevance. Lesions of EmGD might be benign, might be low-grade malignant, and might be fully malignant. Prospective studies regarding its risk for UPSC development are needed. Until those data are complete, we will not know whether EmGD are true precursor lesions of UPSC.

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