Uterine Serous Carcinoma: Clinicopathological features, Precursor lesions and Molecular Alterations

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Abstract

Uterine serous carcinoma (USC), while only comprising 10-12% of all endometrial cases, accounts for nearly half the deaths caused by this disease. Its aggressive nature is highlighted by the high risk of recurrence seen even in patients with disease limited to the uterus. The biology of these tumors is underpinned by genetic and molecular features, which are clearly distinct from the endometrioid subtype. This dichotomy in clinical, pathological and molecular features validates a dualistic classification of endometrial carcinoma, which include Type I and Type II cancers. Type I lesions include endometrioid carcinoma and its subtypes, while serous carcinoma is a prototype of Type II. The clinical characteristics and biologic behavior of serous carcinomas generate constant interest and research to identify novel and potential therapeutic targets.

INTRODUCTION

It is estimated that approximately 52,630 endometrial carcinomas will be diagnosed in 2014 with 8,590 deaths [1]. USC, while comprising less than 10% of all endometrial carcinomas, paradoxically cause a high proportion of relapses and endometrial cancer related deaths, which is a testimony to its biologically aggressive nature [2,3]. Advanced stage disease (Stage III and IV) has a dismal prognosis with a 3-year survival of about 56% [4]. USC was first recognized by Lauchlan [5] and then described by Hendrickson as an endometrial carcinoma with histology similar to ovarian serous carcinoma [2]. Its defining histologic features and distinctive behavior have been validated in subsequent studies [6-8].

Clinico-pathological features

Uterine serous carcinoma (USC) usually occurs in postmenopausal women, in the milieu of an atrophic endometrium [9]. Although it was traditionally considered to be estrogen independent (as opposed to the endometrioid type), it has become increasingly evident that estrogen production continues after menopause from extra-ovarian sources, and therefore it is fair to say that USC are more likely estrogen deficient than estrogen independent (reviewed in [10]). High-grade histologic features characterize USC. These tumors exhibit severe nuclear pleomorphism, hyperchromasia, prominent nucleoli, increased mitotic activity and single cell apoptosis, akin to ovarian serous carcinoma. Additionally, the cells are dyshesive and lack cell polarity. Contrary to the high-grade cytology, these tumors tend to form glands (lined by these highly atypical cells). In addition, areas of papillary and solid architecture are also seen. Also seen are characteristic slit like spaces and budding/micropapillae. These tumors, diagnosed later in life, often arise in a background of atrophic endometrium [2,8,11]. Clinically, the aggressive biology of USC has been well established and this underlies the interest that has been generated in this disease. These tumors are biologically distinct with a poorer prognosis compared to stage-matched endometrioid carcinomas [3,12,13]. Sherman et al, had argued that a diagnosis of serous carcinoma is used when at least 25% of the tumor is serous in nature [8]; however, other investigators have reported that any serous component in mixed tumors will confer a worse prognosis compared to endometrioid carcinomas [14,15]. Also, it has been determined that the usual risk factors to predict recurrence in endometrioid carcinomas may not be useful to assess risk of recurrence in USC [15]. At clinical presentation, these tumors are more commonly diagnosed at a high stage with evidence of extra-uterine spread [16,17]. Slomovitz and colleagues have reported a significant frequency of extra-uterine disease (37%) and a poor prognosis [18] in patients with small endometrial lesions that.
Central

...may not be applicable in USC. Traditional risk factors associated with endometrial carcinomas in patients with uterine serous carcinoma without myometrial high risk of lymph node metastasis (ranging from 13% to 36%) stage IVB disease [21].

The association of serous carcinoma with endometrial polyps was first described by Silva and Jenkins [22]. In their study, they described 16 patients with USC involving a polyp with minimal or no myometrial invasion. Six of these 16 (37.5%) patients also had extra-uterine disease. Involvement of an endometrial polyp was also found in 30.9% of cases in series of USC limited to the endometrium, reported by Semaan et al; and of these 29.4% had stage IVB disease [21]. Numerous studies have also identified a high risk of lymph node metastasis (ranging from 13% to 36%) in patients with uterine serous carcinoma without myometrial invasion [12,18,23]. These findings underline the fact that the traditional risk factors associated with endometrial carcinomas may not be applicable in USC.

Precursor lesions

Serous endometrial intraepithelial carcinoma (EIC) also known as “endometrial carcinoma in situ”, “surface serous carcinoma”, “minimal USC”, is considered to be the precursor to USC, first recognized as intraepithelial carcinoma present adjacent to serous carcinoma [6,8,24]. This lesion is described as composed of cytologically malignant cells, similar to those seen in USC, lining the surface of the endometrium or endometrial glands without invasion of endometrial stroma, myometrium or lymphovascular spaces [25]. It is often seen in conjuction with USC, which raises the possibility that this might be a precursor lesion. Pure EIC is a rare disease. Although technically noninvasive in appearance, these tumors have been associated with extra-uterine disease, reflecting their aggressive biology [17-19,23]. Identical p53 mutations in EIC and the pelvic serous component have been described by various studies [26,27]. One of the mechanisms of spread that have been postulated is that there is dissemination of dysplastic neoplastic cells shed from the surface of the endometrium and glands through the fallopian tubes into the peritoneal cavity [28,29]. Another possibility is development of multifocal disease, as synchronous primaries involving various foci in the Mullerian epithelium [30].

Molecular signature

The concept of a dualistic model of carcinogenesis for endometrial carcinomas was first introduced by Jan Bokhman in 1982 [31] based on the widely varied clinical presentation and behavior of various types of endometrial carcinoma. This hypothesis has subsequently been validated by various studies, which have identified varying molecular aspects underlying the morphological and clinical differences between Type I, and Type II carcinomas. Type I endometrial carcinomas comprise close to 80% of all endometrial cancers and are related to unopposed estrogen stimulation. Common molecular alterations seen in those tumors are PTEN mutations, microsatellite instability, K-ras and β-catenin mutations [32-37]. Type II tumors include serous and clear cell carcinomas. Chromosomal instability, characterized as extensive genetic alterations which include loss or gain of chromosome arms and/or whole chromosomes [38], is frequently seen in serous carcinoma [39], while microsatellite instability is reportedly uncommon [11]. The most frequently detected genetic alterations are p53 mutations, Her-2/neu amplification, negative or reduced E-cadherin expression and inactivation of p16. Below is a review of these common genetic alterations encountered in USC.

a) TP53: The most common mutations seen in uterine serous carcinomas are those involving the p53 gene and include mis-sense mutation followed by insertion mutation. Majority of the mutations in the p53 gene occur in exons 5-8 [40]. These mutations lead to an accumulation of abnormal intra-nuclear protein, which is more stable than the normal protein and therefore easily identified by immunohistochemistry. Rarely, a nonsense mutation may result in a truncated protein, which is not compatible with immunohistochemistry and therefore results in a negative staining pattern [41,42]. Loss of the normal protein prevents apoptosis and promotes tumor progression.

Mutations in the p53 gene have been reported in up to 90% of serous carcinomas [42]. Additionally, these mutations have also been documented in EIC adjacent to uterine serous carcinoma and EIC without associated USC, implying that these mutations occur early in the pathogenesis. The similarity in mutations between EIC and co-existent USC supports the hypothesis that EIC is linked to the development of USC. It has been postulated that the p53 mutation occurs early in one gene resulting in EIC; this is then followed by loss of heterozygosity affecting the remaining wild-type gene and resulting in progression to USC [42]. There exists a strong correlation between strong p53 protein expression (strong immunohistochemistry) and p53 mis-sense mutations. Rarely insertion mutations may result in a more unstable protein, which may not be stained by immunohistochemistry. Identical mutations have also been reported in USC and extra-uterine serous carcinoma, supporting a monoclonal origin for these tumors [26,27].

There are reports in the literature, which have attempted to establish “pre -precursors” of USC. Zheng et al have reported an entity, “endometrial glandular dysplasia” (EmGD), composed of single or a group of atypical appearing glands or surface epithelium, with enlarged, hyperchromatic nuclei and rare mitoses. The nuclear atypia described is less than that seen in EIC. These glands have an “intermediate’’ level of p53 and Ki-67 expression [44]. In subsequent molecular studies [45], approximately a third of the foci of EmGD identified showed LOH at TP53 in a pattern concordant with the co-existent EIC and USC. Concordant p53 mutations have also been reported in EmGD and co-existing EIC and USC lesions [46].

The identification of the “p53 signature” in the fallopian tube in association with in situ carcinoma [47] has generated a search for a similar lesion in the endometrium. Jarboe et al reported the increased expression of p53 in cytologically benign appearing glands adjacent to EIC involving endometrial polyps and in benign

endometrial polyps. The Ki-67 labeling index in these foci ranged from 0-20% (often <5%), akin to the p53 signature described in fallopian tubes. Concurrent mutation analysis of the p53 gene from both the "p53 signature" and the adjacent EIC, showed similar mutations in a subset of cases, suggesting biological clonality [48]. Based on these findings, the authors suggest that there might exist a latent precursor of EIC in the endometrial lining, similar to the "p53 signature" lesions seen in the fallopian tube. Multiple such events with varying mutations might occur early on with only a subset progressing to malignancy [48].

It has been postulated that the hypoxic environment of atrophic endometrium promotes selection of cells able to overcome apoptosis, thereby selecting for cells with p53 mutations.

b) Her-2/neu: Her-2 receptor is membrane bound protein encoded by the Her-2/neu gene, located on chromosome 17p. It belongs to the Her family of tyrosine kinase receptors which include Her-1, Her-3 and Her-4. It is a tyrosine kinase receptor with an extra-cellular ligand binding domain, a transmembrane component and an intracellular component related to tyrosine kinase enzyme [49,50]. There is no known ligand for the Her-2 receptor; activation occurs by homodimerization or heterodimerization with other her family receptors with Her-2/Her-3 heterodimer forming the most potent combination for mitogenesis [51]. Her-2 receptors are normally present on the cell membrane of non-neoplastic epithelial cells, but not in enough numbers to result in dimerization and activation of the tyrosine kinase enzyme. Her-2/neu gene amplification results in over-expression of the receptors with homo and heterodimerization and ultimately in activation of the tyrosine kinase enzyme and related pathways resulting ultimately in increased cell proliferation, survival and migration [52].

Variable levels of Her-2/neu protein expression have been reported in uterine serous carcinomas [35-36] and the concordance level with Her-2/neu gene amplification by Fluorescent in Situ Hybridization (FISH) assay has also been variable. While Santin et al found a high level of concordance between protein expression and gene amplification [53], Mentrikoski and colleagues reported concordance between protein expression and gene expression in about 1/3rd of the cases. This is far short of the concordance level of > 95%, that is mandated in breast carcinoma for this marker to be clinically relevant. The heterogeneity of Her-2/neu protein expression reported in the above studies might be attributed to small sample size, lack of standardized Her-2/neu scoring system, different histologic subtypes of cancer included and variation in the antibodies used.

Over expression of Her-2 protein has been associated with poor prognosis and shorter overall survival [54,57,58]. Santin and colleagues have also reported a significantly shorter survival in patients with Her-2/neu gene amplification, compared to those without [59]. However, other studies have failed to show such a correlation [60]. One of the explanations for this could be that the cases included in this study were already high stage or recurrent.

Interest in the role of Her-2/neu gene in endometrial carcinoma increased after the discovery of successful targeted therapy in patients with Her-2/neu positive breast carcinoma. The same efficacy has not been established in endometrial carcinoma yet. The utility and therapeutic efficiency of Her-2/neu targeted therapy in endometrial carcinoma may follow accurate and optimal patient selection.

c) EGFR: Epidermal Growth Factor Receptor (EGFR/Her-1) is a trans- membrane tyrosine kinase receptor (belonging to her family receptors). Similarly composed of an extracellular ligand binding domain, intracellular tyrosine kinase activity and a portion spanning the cell membrane. Ligands associated with EGFR are EGF and transforming growth factor α. Mutant variants of EGFR, while do not bind a ligand have activated tyrosine kinase resulting in increased cell progression and inhibition of apoptosis. Although the studies are limited in the literature, EGFR over-expression has been reported in a significant subset of serous carcinomas; however, concomitant EGFR mutations in these cases were not documented [61,62]. Down-stream PIK3CA mutations were identified in a small proportion of these cases [62].

d) E-Cadherin: This is a cell-adhesion molecule, which is present on the cell membrane and is Calcium dependent. This molecule maintains the cell-to-cell adhesion by interacting with the actin cytoskeleton of the cell and β-catenin. Reduced or negative expression of E-Cadherin has been attributed to loss of heterozygosity of the CDH1 tumor suppressor gene in serous carcinomas [63]. Decreased or aberrant E-Cadherin function has been implicated in the epithelial to myoepithelial transformation pathway [64], which results in disorganization of the affected neoplastic cells, increased invasive and metastatic potential with tumor dedifferentiation. Decreased E-Cadherin expression has been associated with higher grade endometrial carcinoma, increasing depth of invasion and increased lymph node metastasis [65]. Aberrant E-Cadherin protein also results in cytosolic accumulation of β-catenin with subsequent its translocation to the nucleus. β-catenin is a key player in the Wnt signaling pathway. By immunohistochemistry, E-Cadherin and β-catenin expression is membranous, in non neoplastic epithelium. Defective expression of the E-Cadherin protein results in aberrant staining pattern described as reduced and patchy or negative; while β-catenin is seen to be cytosolic or nuclear. In uterine serous carcinoma, authors have shown decreased E-Cadherin expression in at least a proportion of serous carcinoma [36,63,66,67], suggesting that dysfunction of this molecule may at least in part contribute to the aggressive behavior of these tumors. Increased expression of E-Cadherin in Stage I-III endometrial carcinomas has been associated with a better prognosis [63]. A concurrent nuclear localization of β-catenin is not observed in serous carcinomas, suggesting that the abnormalities of this molecule are more relevant in the Type I carcinogenesis.

e) P16 (INK4a): This is a tumor suppressor gene present on the 9p21 gene locus. It controls the G1-S transition of the cell cycle via the pRB pathway. Any damage to p16 by mutation or hypermethylation will result in defective tumor suppressor function of the pRB gene and this may result in over-expression of p16 protein, presumed due to an aberrant negative feedback mechanism. Loss of p16 function in various neoplasms has been well documented including head and neck squamous cell carcinoma, pulmonary neuroendocrine carcinomas and
pulmonary squamous and adenocarcinomas. High expression of p16 is also seen in cervical adenocarcinoma and adenocarcinoma in situ, in these cases being used as a marker for high risk HPV infection. Although limited, studies have shown that a significantly higher proportion of USC are diffusely positive for p16 by immunohistochemistry when compared to non-serous USC [68,69]. These studies also demonstrated a lack of high risk HPV DNA in these cases of USC, suggesting alternate molecular mechanisms might be involved in carcinogenesis.

Genomic characterization of USC

Most recently, The Cancer Genome Atlas Research Network published its findings from the genomic characterization of 373 endometrial carcinomas, which included 66 cases of USC. By unsupervised hierarchical clustering, they found that endometrial carcinomas could be grouped into 4 distinct clusters. USC (along with a subset of the FIGO 3 endometrioid carcinomas) formed a separate cluster which was characterized by a high frequency of TP53 mutations (90%), fewer PTEN mutations (11%) and MSI (6%). This cluster also included other gene amplifications, which included ERRB2, MYC, CCNE1, FGFR3 and SOX17. Tumors in this “serous-like” cluster had a worse prognosis compared to the “endometrioid-like” tumors [70].

CONCLUSION

USC is an aggressive variant of endometrial carcinoma with poor prognosis in even seemingly limited or early stage disease. This highlights the need to understand the pathogenesis of this disease and identify novel therapeutic treatments. Continued appraisal of its molecular alterations may help identify precursor lesions that may be easier to cure. Furthermore, such understanding will identify specific changes that can be targeted with novel approaches and drugs.

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