

Endometriosis Associated Ovarian Malignancies-Update of Risk and Phenotype Variability

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Received Date: September 23, 2017 Accepted Date: September 26, 2017 Published Date: September 28, 2017

Citation: Cornelia Amalinei (2017) Endometriosis Associated Ovarian Malignancies-Update of Risk and Phenotype Variability. *Matern Complicat Womens Health J* 1: 1-3.

Introduction

Endometriosis, defined as ectopic (ovarian or extra-ovarian) implants of endometrium, is a challenging diagnosis and its complications are severe (chronic pelvic pain, infertility, dyspareunia, dysmenorrhea, and tumors development) [1]. Since the first description of the disease and the launching of the hypothesis of malignancy development within endometriosis, more and more clinicopathological and epidemiological evidences have been highlighting this possibility, mainly for ovarian location. Regarding their possible association, either they share similar molecular pathways, which tend to become later divergent, either cancer develop from endometriosis [1]. Molecular biology has been very useful by detecting similar molecular mutations in both entities, along with endometriosis monoclonality (similar to malignancies) [2]. Moreover, a transitional phase, named atypical endometriosis, has been identified by several teams of research in 60-80% of cases of Endometriosis-Associated Ovarian Cancer (EAOC) [3] or Endometriosis-Related Ovarian Neoplasm (ERON) [4]. ; Cervical cancer; Trachelectomy; Abdominal cerclage.

Which are the entities more likely to be associated with endometriosis? In the effort to give an answer to this question, several types of ovarian carcinomas have been identified as the most prevalent malignancies to occur in association with endometriosis. Their behavior is less aggressive and their prognosis is consequently better when compared with similar subtypes without associated endometriosis [5]. These mostly belong to endometrioid tumors, clear cells carcinoma, seromucinous tumors, and rarely to endometrial stromal sarcoma and adenosarcoma. A brief description of the most encountered histopathological type characteristics and their

risk of development in association with endometriosis are highlighted in the following section.

Endometrioid carcinomas are typically associated with endometriosis, both entities being correlated to hormonal stimulation [6], possibly in the context of Tamoxifen therapy [7]. Endometriosis-associated endometrioid carcinomas show Wnt/ β -catenin pathway defects, somatic mutations of Catenin (Cadherin-Associated Protein), Beta 1 (CTNNB1), Phosphatase and Tensin Homolog (PTEN), and Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) [8], and altered AT-Rich Interaction Domain 1A (ARID1A) tumor suppressor gene expression [9,10]. The high occurrence of synchronous endometrioid endometrial carcinomas (around 50%) supports the common genetic and microenvironmental background [11]. Atypical proliferative or borderline endometrioid tumors also belong to this spectrum, being characterized by a good prognosis [12].

Clear cell carcinomas associated with endometriosis show non-cystic (adenofibroma-derived) and cystic types (endometriotic cyst-derived) [13] and exhibit a specific gene expression or "signature" [14], consisting of Hepatocyte nuclear factor-1 β (HNF-1 β) over expression, along with versican, and several genes involved in oxidative stress [4]. Endometriosis-associated clear cell carcinoma also shows PIK3CA and ARID1A mutations [15].

Seromucinous tumors (borderline and carcinoma) are frequently associated to endometriosis (30-70%) [16], showing a mixed Mullerian phenotype [4] and exhibit similar ARID1A mutations as endometrioid and clear cell carcinomas [17]. Due to the multiple histological patterns, possible admixture of clear cells component, there is a poor morphologic reproducibility and interobserver confidence of diagnosis [18]. Moreover, non-specific immunophenotype and molecular features, along with limited available data on prognosis, proposals of its withdrawn from the current WHO classification have been claimed [18].

Considering the dualistic model of ovarian carcinogenesis [19], EAOs belong to type I, showing Tumor Protein P53 (TP53), PTEN, ARID1A, along with Kirsten Ras Oncogene Homolog (KRAS), CTNNB1, microRNAs (miRNAs), and microsatellite instability [20]. There is a strong support for the hypothesis that endometriosis is a neoplastic process which may undergo malignant transformation, possibly by transition through an atypical phase [3]. Atypical endometriosis is associated to 23% of endometrioid and 36% of clear cell carcinomas [21], while very rare in endometriosis without associated malignancy [22], being considered as a precancerous lesion [11].

However, due to the high probability of underscoring the associated endometriosis with or without transition histopathological proof in ovarian carcinoma reports, the real prevalence may be achieved by corroborating histology with sonography [23]. Another current issue is that of exploring the possibility of association to pain management, hormone and surgical therapy, of several targeted anti-cancer drugs in endometriosis therapy, by considering their analogous characteristics and molecular pathways involved in their pathogenesis. In perspective, the application of modern molecular therapies, such as aromatase inhibitors [24], anti-angiogenic [25], immunomodulators [26], antiproliferative [27] and anti-inflammatory agents [28], might prevent and cease the development of full spectrum endometriosis, improving the fertility and quality of patients' life.

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