Ovarian Carcinoma: The Challenge of Early Diagnosis

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General Considerations

Ovarian Cancer (OC) is the most lethal gynecologic tumor, notorious for being diagnosed in late stages. About 14.000 women in the USA and 160.000 women worldwide die every year of OC. In the USA approximately 23.0000 new cases are predicted to be diagnosed in 2016. Morbidity and mortality due to OC have changed very little over the past 5 decades, despite extensive basic research efforts, identification of risk factors, chemotherapy and cytoreductive surgery. This is in contrast with other gynecologic malignancies which underwent spectacular declines of their mortality rates, such as cervical cancer, due to the identification of precursor lesions and of etiopathogenic infections (HPV). OC results in more deaths than all other gynecologic cancers combined in the USA.

The reason for this dismal outcome is the fact that the vast majority of cases (about 80%) are diagnosed in advanced stage of disease when the tumor is spread beyond the ovary (ies). This is due to the lack of specific early symptoms a notion recently challenged [1] and of reliable sensitive and specific tumor markers in the serum. Ca 125 is a marker used for follow-up of advanced stage OC treated with chemotherapy but is not effective in early stage OC. Anatomic characteristics of the ovaries such as their hidden location in the pelvis/abdomen and paucity of sensorial nerves (early tumors are painless and clinically mute) preclude an early diagnosis despite the current sophisticate technologies of pelvic visualization. The risk for developing OC is still poorly understood: a small percentage (about 10%) of women with inherent mutated BRCA 1 and2 genes are known to be at risk, while most cases of OC are considered to be sporadic.

Recent Classification of OC

Based on identification of tumor markers correlated with phenotypical structural characteristics OC are now classified into low-grade and high grade tumors, the latter unfortunately representing the majority. Low-grade OC are growing slowly and are amenable to an earlier diagnosis while high-grade OC are growing fast and aggressively and are diagnosed mostly in late stages when spread beyond the ovaries; they are highly lethal. The most common entity is the serous papillary adeno carcinoma arising in the surface ovarian epithelium, an extension of the peritoneal serosal mesothelium, and much more often than previously thought, in the secretary cells lining the Fallopian tube fimbria [2]. Less common high-grade OC are some Endometrioid Carcinomas and Malignant Mixed Muellerian Tumors High grade OC are frequently associated with perturbations in the P53 pathway resulting in P53 nuclear over expression in the tumor cells. The common simultaneous involvement by high-grade serous carcinoma of ovaries are Fallopian tubes, uterus and pelvic/abdominal peritoneum justifies the term "high-grade pelvic tumor" (potentially of multicentric origin, possibly monoclonal), presently used when the primary origin is not identifiable [3].

Low-grade OC are less common and include rare and often controversial low-grade serous papillary carcinoma, probably derived from borderline serous papillary tumors, endometrioid, mucinous and clear cell carcinomas also presumed to develop from the respective borderline tumors. They have a slower and more indolent growth pattern, are more often unilateral and less often associated with an extraovarian spread. The immunophenotype of the two categories of OC is also different: low-grade OC are associated with mutations of K-RAS, B-raf, Beta-catenin, PTEN, AIRD1, while high-grade serous and endometrioid tumors are frequently associated with P53 nuclear overexpression and BRCA1,2 WT1, p16 positivity. The genetic alterations on the molecular level are different as well: microsatellite instability is more frequent in the high-grade type.

Precursors of OC

The successful decline in morbidity and mortality due to many neoplasms can be attributed to the identification of precancerous lesions, the removal of which intercepts their progression to invasive cancer. This is the case of uterine cervical,

breast, colon, skin and many other precancerous lesions, known as carcinoma-in-situ or dysplasia of epithelial tissues. In the case of the ovaries the detection of such lesions is difficult and even controversial because of the complicated access to the organ and the often difficult interpretation of the subtle nature of the histologic structural and molecular changes. Precursors of the low-grade OC are presumed to be the borderline serous tumors (especially the micropapillary variant), the borderline mucinous tumors and atypical endometriosis. Endometriosis is a frequent ovarian lesion and is fortunately benign in most cases. It seems however that endometriotic cysts lined by atypical epithelium may progress to endometrioid carcinoma and rarely, to clear cell carcinoma. Ovarian cystadenofibromas with endometrioid and clear cell atypia also represent potential though uncommon cancer precursors.

The precursors of high-grade OC are tubo-ovarian dysplasia defined by histologic, morphometric, immunohistochemical and molecular characteristics. Dysplastic cells are irregularly stratified and display loss of polarity and nuclear atypia consisting of enlargement, irregular nuclear membranes and especially an abnormal texture reflecting abnormal chromatin and DNA distribution. Positive immune stain for P53 in phenotypically unremarkable cells is also described as "P53 signature" that may precede the dysplastic change [2,3]. The finding of dysplastic changes in specimens removed preventively in women at high risk for OC (Prophylactic salpingo-oophorectomy) similar to those seen in the vicinity of overt invasive OC validates their carcinogenic potential [4]. Unfortunately no follow-up as in cervical, breast, colon pr other dysplastic lesions is possible for tubo-ovarian dysplasia unless the ovarian surface could be examined directly and repeatedly as proposed tentatively (confocal "optic" biopsy), a method practiced for evaluation of cancer precursors in the gastro-intestinal tract [5,6].

Early Stage OC

Ovarian Serous Papillary Carcinomas (OSPC) represent about 80-87% of all OC. They are diagnosed mostly in advanced stages (Stage III-IV) when spread to the pelvic and to the peritoneal cavity. In a study of Stage I OC [7] only a minority of less than one third was OSCP while the majority were non-Serous Ovarian carcinomas (NSOC). The few Stage I OSPC were mostly diagnosed fortuitously in patients under close surveillance for personal or family high risk for breast cancer and/or BRCA positivity; one patient had surgery for vaginal bleeding associated with Tamoxifen therapy for breast cancer end endometrial cancer coexisting with an asymptomatic clinically "mute" Stage I OSPC.

NSOC represented the majority of Stage I OC although overall, in all Stages, they are by far the less common. They were diagnosed at an early stage because of their association with symptomatic pathologic lesions, in other words while the ovarian tumor itself is mute (asymptomatic) the associated pathologic changes such as endometriosis, uterine polyps, endometrial hyperplasia and/or neoplasia are symptomatic and bring the patient to medical attention. Pelvic and ovarian endometriosis often cystic, adherent to neighboring organs is manifested as painful masses. At surgery the occasionally detected OC in the endometriotic cyst is usually Stage I with a better prognosis than the asymptomatic OC not associated with endometriosis. Uterine pathologic lesions, benign (leiomyomas, adenomyosis, endometrial polyps with or without hyperplasia) or malignant (endometrial carcinoma) manifested with vaginal bleeding and pelvic masses also bring the patient to medical attention; occasionally during hysterectomy an asymptomatic Stage I OC is discovered. The patients in the study diagnosed with NSOC were younger on average, had often a clinical background of hyperestrogenic syndromes (infertility, endometriosis, irregular menses). None of the patients with NSOC was BRCA positive out of 7 tested, while 5 of the OSPC patients were BRCA! and one patient was BRCA2 positive, out of 17 tested.

Challenges and Conclusion

The mystery of ovarian carcinogenesis is far from being solved and early detection is still elusive The presently accepted classification into low- and high-grade OC is not an absolutely one since some endometrioid and clear cell carcinomas can behave as highly aggressive tumors. OC is presently rarely diagnosed in early stages because of paucity of symptoms and a still elusive reliable tumor marker. Efforts should be directed to identify associated symptomatic gynecologic pathology, most commonly endometriosis, now considered as a potential precancerous condition, often detected at a work-up for infertility. Low-grade OC are more amenable to early diagnosis because of their slower growth and frequent origin in associated cystic lesions, symptomatic as pelvic masses.

Precursors of OC evolve through a multistep and multifactorial progression from tubal-ovarian dysplasia the study of which is facilitated by the availability of specimens obtained from women at risk who had prophylactic salpingo-oophorectomies. The reports on Fallopian tube involvement in ovarian and pelvic serous carcinogenesis indicate the need for careful study of early potentially carcinogenic changes in both ovarian and fallopian tube epithelium. The surgical accessibility of pelvic structures by advanced laparoscopic techniques, the discovery of efficient biomarkers, the implementation of systematic follow-up of women with associated gynecological pathology may open possibilities for intercepting a neoplastic growth before it reaches its lethal course.

References

1. Curtin C, Gordon PS, Fishman D (2013) Early detection of Ovarian cancer. Altchek's Diagnosis and Management of Ovarian Disorders, (3rd edn). In: Liane Deligdisch, et al. (Eds.), Publisher Cambridge University Press, UK, pp. 357-358.

2. Crum CP (2009) Intercepting pelvic cancer in the distal Fallopian tube: theories and realities. Mol Oncol 3(2): 165-170.

3. Folkins AK, Jarboe EA, Roh MH, Crun C (2009) Precursors to pelvic serous carcinoma and their clinical implications. Gynecol Oncol 113(3): 391-396.

4. Deligdisch L, Gil J, Kerner H, Wu HS, Beck D, et al. (1999) Ovarian Dysplasia in Prophylactic oophorectomy specimens: Cytogenetic and morphometric correlations. Cancer 86(8): 1544-1550.

5. Tanbakuchi AA, Udovich JA, Rouse AR, Hatch KD, Gmitro AF (2010) In vivo imaging of ovarian tissue using a novel confocal microscope. Am J Obstet Gynecol 202(1): 90-97.

6. Deligdisch L (2011) Optic biopsy in gynecologic pathology: anatomic pathology consideration. Bull Acad Matl Med 195: 135-141.

7. Deligdisch L, Penault-Llorca F, Schlosshauer P, Peiretti M, Nezhat F, et al. (2007) Stage I Ovarian Carcinoma : different clinical-pathologic patterns. Fertil Steril 88(4): 906-910.