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 23,000 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 sophisticated 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 adenocarcinoma 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 extraneous 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 or 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 OSCP 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 OSCP.

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 BRCA1 positive out of 7 tested, while 5 of the OSPC patients
were BRCA1 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.

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