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1. The place of gynaecologic cancers in peritoneal surface oncology concept

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Abstract. The locoregional progression of gynecological cancer usually results in peritoneal carcinomatosis, condition that may confer a poor prognosis.

Peritoneal carcinomatosis is a common metastatic manifestation of digestive-tract malignancies and gynecological carcinoma. Primitive peritoneal carcinoma is a rare condition. Tissue of the genital tract plays a definite role in its pathogenesis.

Indeed serous ovarian, Fallopian tube and peritoneal carcinomas share histologic characteristics, natural history and maybe the same tissue origin.

Recent studies shed light on the role of distal Fallopian tube in pelvic serous carcinogenesis, including peritoneal serous papillary carcinoma.

Among gynaecological malignancies, ovarian cancer is responsible for most of peritoneal carcinomatosis. Two ovarian carcinoma groups are distinguished, considering molecular pathogenesis and propensity for peritoneal dissemination.

Embryology and the secondary mullerian system can account for the mullerian-like morphology of ovarian carcinoma and the presence of tumors, histologically identical to ovarian carcinoma, in peritoneal surface, outside the ovary.

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Role of tissue of genital tract and embryology

Epithelial ovarian cancer is a highly heterogenous group of cancer and contain 4 subtypes: serous, mucinous, endometrioid and clear cell. Ovary is made up of cortex and inner medulla, ovarian surface epithelium (OSE) is a single layer of cells in continuity with the peritoneal mesothelium.

The Fathalla's theory of incessant ovulation underline the role of repeated ovulatory mechanical action over a prolonged period of three or four decades [1]. Repeated ovarian epithelial surface disruption and recurrent exposition to oestrogen-rich follicular fluid, are suspected to enhance mitotic activity [2] and consequently increase the risk of unrepaired DNA damages. Epidemiologic data and animal models support this hypothesis: pregnancy, lactation and oral contraception use, that inhibit ovulation, reduce the risk of developing ovarian carcinoma. It has been demonstrated, so, that poultry hens with hyperovulation are likely to develop peritoneal carcinoma [3].

However, the Fathalla's theory has been unchallenged for a long time in spite of its inconsistencies. Indeed, it fails to explain the mullerian-like morphology of some ovarian carcinoma whereas ovarian surface epithelium consist of two types of modified mesothelial cells: the first is cuboidal with abundant microvilli and the second is flat squamous [4].

Ovarian carcinomas are more differentiated than OSE, they are made up of cells more specialised than the tissue of origin and express more markers. This feature distinguishes ovarian carcinomas, since in other solid tumors cells are generally less differentiated than those of normal tissue [5].

Dubeau formulated an hypothesis based on an intermediate step: invasive carcinoma may arise from an ovarian surface epithelial that has undergone a mullerian metaplasia [6].

However, early ovarian neoplastic changes are rarely, if ever, found in OSE, but usually observed in ovarian inclusion cysts lined by a mullerian-like epithelium [7].

Inclusion cysts are a frequent histological feature observed in normal ovaries. Many hypothesis can account for the cysts origin: ovarian surface epithelium is entrapped within the stroma during post-ovulatory reparing process [8], more merely it can be the result of an epithelium invagination that eventually lose its connections with the surface. Lining epithelium cysts contain flat-to-cuboidal cells and sometimes a Fallopian tube –like architecture is observed. Authors have assumed that tubal epithelium cells seeded on ovary surface are entrapped into an ovulation stigma and give rise to a cyst [9].

There are evidences that inclusion cysts are not directly related to the number of ovulation: polycystic ovaries known for low ovulatory activity, present though a high frequency of inclusion cysts. Moreover, mullerian-

lined cysts can be observed far from ovarian surface, in the deep cortex, in the medulla, in the hilum, in paraovarian and paratubal areas and also in lymph nodes, where there are called endosalpingiosis [6].

This disseminated mullerian tissue, is reffered to as secondary mullerian system [10].

It is essential to shed light on organogenesis of genital tract to understand pathogenesis of pelvic carcinoma.

During the seventh week the canal system of the female genital organ differentiates. The mesonephronic ducts atrophy and the future fallopian tube, the uterus, the upper part of the vagina arise out the paramesonephronic ducts of Mullerian ducts. Primary Mullerian system is composed of upper part of vagina, cervix, uterus and fallopian tubes. The epithelia of mullerian origin can take on different appearances: endometrioid (endometrium), ciliated (fallopian tube) or stratified squamous non cornified (vagina exocervix) or secreting (endocervix), it can express oestrogen and progesterone receptor.

The secondary mullerian system consist of peritoneum, mesothelial inclusions in pelvic lymph nodes and ovarian surface cell layer [10]. It is found outside the mullerian ducts path.

The simple cubic ovarian mesothelium arise out a thickened coelomic epithelium. One describes two type of modified mesothelial cells, one is cuboidal with abundant microvilli and the other is flat squamous with fewer microvilli [11]. This shared origin can explain the mullerian morphology of tumors arising from organs not of mullerian origin.

The metaplastic theory can not be definitely ruled out, but it supposed a pre-existing epithelium, which seems improbable inside lymph nodes for instance [6].

The role of secondary mullerian system in ovarian carcinoma has been little explored. And yet, this hypothesis reaches to explain two main inconsistencies: first, the mullerian morphology of most ovarian carcinoma and second, the presence of carcinomas, clinically and histologically indistinguishable from ovarian carcinoma outside the ovary and even in women with previous oophorectomy.

The common localisation of ovarian carcinoma support the theory of inclusion cysts carcinogenesis. Indeed, at early stage ovarian tumors are frequently found inside ovary stroma and not at the surface.

Role of environmental factors

The female peritoneum presents a determining particularity: it is exposed to external environment. Most human cancers arise from epithelial surfaces that are exposed to carcinogen agents. Whereas male peritoneum is a closed

cavity, in women, fallopian tubes open the peritoneum and connect it to uterine cavity and vagina.

Thus, peritoneum and ovaries are exposed to external agents by vaginal route. Talc use, particularly when contamined with asbestos was suspected to be a valid carcinogen agent of ovary. One found a relationship between talc use and increased risk of developing ovarian carcinoma [10, 12]. Even if asbestos and fiber exposure is known to be associated with higher risk of serosal cancer, the role of talc even fiber-contamined in ovary carcinogenesis is still controversial [13, 14].

The particularity of the female peritoneum must be taken into account, and the role of external agents in peritoneal and ovarian carcinogenesis not definitely ruled out.

Two pathologic categories of ovarian cancers

Among gynaecological malignancies, ovarian cancer is responsible for most of peritoneal carcinomatosis. Two pathologic categories have been recently distinguished, considering molecular pathogenesis and trend to extraovarian spread [15].

The type I include borderline malignancy, low grade serous carcinoma, endometrioid and mucinous ovarian carcinoma. Pathologic observation shed light on a pathologic continuum from benign to malignant lesion. This group is genetically stable and present shared mutations including KRAS, BRAF, PTEN and beta catenin [15]. Studies show that mutation of KRAS is the most frequent genetic alteration found in mucinous tumor [16, 17].

Among mucinous tumors: 80% of advanced stage are associated with pseudomyxoma peritonei. Mucinous carcinoma are often unilateral, well differenciated and grow slowly. An increased rate of KRAS mutation is described respectively in cystadenoma, mucinous borderline and mucinous carcinoma. This data support the theory of a continuum from a benign lesion to a frankly invasive form of mucinous carcinoma [15].

Pseudomyxoma peritonei (PMP) is a condition characterised by an abundant intraperitoneal mucinous material. PMP is from appendiceal origin in more than 90% of cases but also may be due to colonic mucinous tumors [18]. In women, the origin of PMP represent a greater stake since ovary can give rise to mucinous tumor, and further, secondary localisation on ovary can mimic primitive ovarian tumor. Another dilemma is whether the peritoneal localisations associated with PMP are metastasis of the primary mucinous tumor, whether they are expression of a multifocal neoplastic process involving peritoneum and ovarian surface [19].

Secondary ovarian localisations generally involve both ovaries and when unilateral the tumor is right-sided. Like in peritoneum, implants are confined to the surface epithelium and are never observed deeper than superficial stroma [19]. On contrary, ovarian mucinous low malignant potential is generally unilateral, with the same frequence in each side and involve the entire ovary. Survival for women with stage I MBT is 100% [19], death occur in advanced stage MBT, mostly associated with PMP. These data taken into account, we can assume that MBTs, unlike serous border line tumors, rarely spread beyond the ovary. Authors assume that MBT never spread beyond ovary

The type II includes mainly, ovarian serous carcinoma. This entity is aggressive, genetically instable and present TP53 mutations [15]. High grade serous carcinoma is poorly differentiated and display a papillary architecture, the cells have large pleomorphic nuclei, often multinucleated. Mitosis are numerous and abnormal mitotic figures are frequent. Concerning serous carcinoma, several grading system exist [20], the FIGO uses a three-tier classification (poorly, moderately and highly differentiated) based on the amount of solid growth. This classification mean there's a continuum from well to poorly differentiated sub-type [21]. However, a two-tier system is consistent with the epidemiologic data: the 5-year survival rates ranged from 40% to 56% for low-grade serous carcinoma and 9% to 34% for high grade serous carcinoma [22-24]. As seen above, the molecular characteristics of poorly and well differenciated serous carcinoma are completely different. It seems that low-grade micropapillary serous carcinoma arise from serous borderline tumor, whereas, no precursor lesion for high-grade serous carcinoma has been yet identified [21]. Regarding molecular and genetic data, the pathway of tumor development are necessarily different. A recent study has shown there is no difference in extreme drug resistance and TP 53 mutation, between poorly and moderately differentiated serous carcinoma. These results provide strong evidence for a two-tier classification.

Patterns of peritoneal diffusion

The ovarian metastatic process consist of cell dissociation, cell seeding and eventually invasion of the peritoneum [25]. At the molecular level, peritoneal seeding is related to impaired cell-cell adhesion. Indeed, tissular cohesion is due to cell adhesion with extracellular matrix and to direct cell-cell contact. There are three type of cell junction: tight-junction, adherens-junction and gap-junction. E-Cadherin is a calcium-dependent adherens junction molecule [5]. The invasiviness is the result of a progressive loss of epithelial phenotype and gain of mesenchymal features, also named epithelial-

mesenchymal transition. Endothelin A receptor/ Endothelin 1axis induces proliferation, survival and loss of intercellular communication. This axis drive EMT by inducing down-regulation of E-Cadherin [26].

Place of tubal in situ carcinoma

Serous ovarian carcinoma, fallopian tube carcinoma and primitive peritoneal serous carcinoma display numerous similarities in their morphology and natural history. Insomuch it is often impossible to determine the organ of origin at late stage, when ovaries, abdominal cavity and fallopian tubes are all involved.

Recently, Fallopian tube has been suspected to be original site of pelvic serous carcinoma [27]. Indeed, tubal in situ carcinoma (TIC) shares the same p53 mutation than the synchron associated ovarian carcinoma, suggesting monoclonality and so, a common origin.

Fallopian tubes have three functions: pick up the ovum, transport it and facilitate the fertilisation. The tubal epithelium structure varies with hormonal status and with the tubal segment. Three types of cells are described, ciliated, serous and intercalary.

Few is known about tubal surface epithelium carcinogenesis. In analogy with OSE, we can assume that incessant variation in hormonal levels induce incessant mitotic activity and consequently higher the risk of unrepaired DNA damaged. Even in Fallopian tube removed prophylactically, chromosomal abnormalities are noticed. This may suggest that genetic alterations occur early in the carcinogenesis process of pelvic serous carcinoma. Women with BRCA mutations present an increased risk of developing any form of pelvis serous carcinoma [28]. In this population, TIC is often the only neoplasm diagnosed, which led to assume that TIC is a precursor to pelvic serous carcinoma. However, TIC may be a frequent lesion, under-diagnosed, so it could also coexist with the primitive lesion of ovary or primitive peritoneal carcinoma. Kindelberger and al examined ovaries and fallopian tubes from salpingo-oophorectomy in unselected population. TIC was found coexisting with all forms of pelvis serous carcinoma. The tubes were entirely sectioned, extensively examined according and screened twice. Fimbria where thouroughly examined since it is site of early serous carcinoma in BRCA+ women [29, 30]. Before making a diagnosis of tubal intraepithelial carcinoma pathologist had to ensure that: there was not any site of invasive carcinoma, this lesion was actually primitive and not a secondary localisation or a remote tumor (even if fallopian mucosa is rarely the site for implants of serous neoplasms) [31].

Uterine serous carcinoma (USC)

Uterine serous carcinoma is an aggressive histological type of endometrial carcinoma. It spreads to peritoneal cavity rapidly. Ambros and colleagues have proposed the term of Endometrial intraepithelial carcinoma (EIC) to define a USC without endometrial invasion. Mostly, EIC is associated to USC [32]. USC present loss of heterozigosity at the p53 locus and most EIC contain only one mutated p53 allele [33]. These data suggest that USC originate from EIC. Authors hypothesize that patients with EIC and concomitant pelvic serous carcinoma present actually peritoneal metastasis of a primitive endometrial carcinoma (even non invasive). The p53 data support strongly this hypothesis. The natural history of peritoneal carcinomatosis from endometrial malignancy is unique. Endometrial carcinoma metastasizes by vascular and lymphatic invasion similar to other gynaecological malignancies. However retrograde transtubal spread is another potential mode of tumor spread. Transtubal spread has been proposed as a mechanism of tumor dissemination in Uterine Serous Carcinoma (UCS). 62 % of patients with UCS had extrauterine disease at hysterectomy, of which 20% was peritoneal disease without myometrial or lymphatic-vascular invasion [34]

Alteration in adhesion molecule expression account for serous carcinoma seeding [35, 36]. Peritoneal deposits of endometrial serous carcinoma and peritoneal serous carcinoma are morphologically similar. However, differences exist: USC typically occur in seventh to eighth decade whereas patient with PSC are one decade younger [37, 38].

Ovarian carcinoma: Paradigm for locoregional treatment?

Ovarian carcinoma is the most lethal gynaecological malignancy, 70% of patient present peritoneal metastasis at diagnosis. OC disseminate preferentially in peritoneal cavity rather than lymphatic and venous route. Even at recurrent stage, ovarian cancer is often a locoregional disease involving only the peritoneum and adjacent intrabdominal organs, making it ideally suited for locoregional therapy. Two therapeutic tools have largely demonstrated their efficiency in the management of peritoneal carcinomatosis: systemic chemotherapy and optimal cytoreductive surgery (CRS) [39]. But despite the high rate of remission obtained following this therapeutic strategy, more than 50% of patients will recur [40].

A new strategy has emerged during the last 20 years: the hyperthermic intraperitoneal chemotherapy (HIPEC). The rationale for locoregional treatment combining CRS and HIPEC is based on the high rate of ovarian cancer recurrence, the results of CRS for recurrent ovarian cancer [41, 42] those of

CRS with HIPEC in the management of peritoneal carcinomatosis from gastrointestinal cancer [43], and those of intraperitoneal chemotherapy in the first line of treatment [44]. The CRS allows treatment of macroscopic disease and HIPEC is used to treat microscopic diasease. Small phase II studies have already reported interesting survival results with the use of CRS and HIPEC for the treatment of recurrent or chemoresistant ovarian cancers [45-47]. Cisplatinum appears to be the molecule of choice for the treatment of ovarian cancer regarding its cytotoxicitys enhancement by hyperthermia and its pharmacokinetics advantages [46, 48]. But of course this new strategy need to be evaluate into phase III trials.

Conclusions

Ovarian, Tubal and endometrial carcinomas natural history leads to peritoneal carcinomatosis. A recent theory assumes that all pelvic carcinomas have a common origin in fimbrial epithelium. Tubal in situ carcinoma, an underrecognised condition, comes out as a consistent precursor of so-called primitive peritoneal carcinoma.

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