THE PERITONEUM AND SECONDARY PERITONEAL TUMORS – A REVIEW

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THE PERITONEUM AND SECONDARY PERITONEAL TUMORS – A REVIEW (Abstract) : Peritoneal carcinomatosis represents the dissemination of a primary tumor on the surface of the peritoneum. It has been considered a stage in the natural evolution of digestive tract and genital cancers with a poor prognosis and beyond medical or surgical resources. It is now considered a loco-regional extension of the primary tumor and not a systemic disease, thus the possibility of a curable treatment.Treatment possibilities include citoreduction surgery followed by intraperitoneal chemotherapy with very high success rate for genital and colorectal cancers. The present paper reviews the different peritoneal dissemination processes and the host tissue- tumor cell interactions. The emphasis will be on anatomical factors involved, both macroscopically and microscopically, rheology of the peritoneal fluid and types of invasion of the mesothelial layer, and the role of surgery, each presented with their unique patterns. Also presented is the polyclonal theory, which emphases on possible embryological origin of peritoneal carcinomatosis. **Key words** : CARCINOSIS, PERITONEAL CARCINOMATOSIS, GASTRIC, COLORECTAL, PSEUDOMYXOMA, CANCER

INTRODUCTION

Peritoneal carcinomatosis represents the dissemination of a primary tumor on the surface of the peritoneum. It has been considered a stage in the natural evolution of digestive tract and genital cancers with a poor prognosis and beyond medical or surgical resources. Therefore, little has been studied about carcinomatosis and few data exists until 1980s. At this point, there was a paradigm shift : carcinomatosis was considered a loco-regional extension of the primary tumor and not a systemic disease, thus the possibility of a curable treatment (1). This directed the focus of many studies trying to uncover the mechanism of peritoneal dissemination. Present day treatment possibilities include citoreduction surgery followed by intraperitoneal chemotherapy with very high success rate for genital and colorectal cancers. This paper reviews the role of the peritoneum in carcinomatosis from a primary tumor and the mechanism of dissemination.

ANATOMY

The peritoneum is the largest serous membrane of the human body, with an approximate surface of 1.8 m^2. The parietal peritoneum lines the inner surface of the abdominal wall then reflects itself and becomes the visceral peritoneum covering the intraperitoneal organs to different extents, thus becoming their serous layer.

The parietal peritoneum draws its blood supply from the arteries of the abdominal wall and from the parietal pelvic arteries and for the visceral pleura the blood supply is derived from the superior and inferior mesenteric arteries, celiac trunk and the visceral pelvic arteries. The venous blood drains in the inferior cava vein, whereas the venous blood from the visceral peritoneum drains in the portal vein. Approximately 80% of the lymphatic circulation drains in the thoracic duct and the right lymphatic duct (2).

Macroscopically, there aren't differences between the peritoneum regarding anatomical

region, with the particularity of the serous adjacent to the internal female genitalia. Along the full length of the fallopian tubes, the peritoneum forms deep folds called the broad ligaments, stretching from the uterus to the pelvic wall. Also at this site, the visceral peritoneum is called mesoovarium, mesosalpinx and mesometrium (3). The ovaries are not covered by the peritoneum, but are embedded in the ovarian bursa and are attached to the fallopian tubes through the mesoovarium. The ovarium bursa is a membranous sac composed of a single layer of epithelial cuboid cells, which continues itself with the visceral peritoneum of the broad ligaments (2). Unlike the peritoneal cavity of males which is a closed cavity, in females, the peritoneum is discontinuous at the fimbrilar opening of the fallopian tubes.

The microscopic structure of the peritoneum is still a matter of debate regarding the number of layers. Thus, it is described as a single-layer of mesotelial cells or having a tri-layered structure consisting of mesotelium, basal lamina and submesotelial stroma.

The mesotelial cells are approximately 25 μm in diameter, have mesodermal origin and they possess both epithelial and mesenchymal features. In certain situations, they can lose their epithelial features during a mezotelial-mesechymal transition (2). Between the mesotelial cells there are lymphatic portals known as stomata which are connected directly to the lymphatic drainage system. These portals have an important role in the active absorption of fluid and enabling the bidirectional migration of immune cells. These peritoneal stomata are organized around the milky spots, which consist of the stomata and macrophage-lymphocyte aggregation. It is also considered that the macrophages found in the milky spots are resting macrophages that migrated from the lymphatic subperitoneal spaces and play an important role in the innate immune system of the peritoneal cavity.

DISSEMINATION FROM A PRIMARY TUMOR

The peritoneal dissemination from a primary tumor begins with the spontaneous exfoliation of tumor cells in the abdominal cavity, thus being an important independent prognostic factor. This occurs when the primary tumor invades the serous layer and is also dependent on the down-regulation adhesion molecules like Epithelial (E)-cadherines in the neoplasic cell (4). This down-regulation, which reduces intercellular bonds, has been proven in the case of colo-rectal, ovarian and gastric cancers with peritoneal carcinomatosis (5,6,7). At the same time it is an up – regulation of N(neural) – cadherines, that enable the tumor cell to attain migratory and invasion traits, through a complete reorganization of the actin cytoskeleton (8). This process is called epithelial-mesenchyme transition and it is a dynamic reversible process, proving that tumor progression is not solely achieved through gene alteration but also regulated by the tumor microenvironment (9). Other ways of tumor cells gaining access in the peritoneal cavity are preoperative rupture, cut into manipulation of the primary tumor or through the transection of lymph and blood vessels. Also there is a third theory called tumor cell entrapment in which, in the peritonectomizated areas or the places where the peritoneal barrier was disrupted by the dissection, tumor cells are entrapped in the fibrin network, only to be exposed to the influence of growth factors during the healing process (10). Once in the peritoneal cavity, depending on the site of the tumor, viable tumor cells will be distributed following the circulation of the peritoneal fluid, influenced by the negative pressure in the supramezocolic space created by the diaphragm movements, bowel peristaltic and gravity. These factors create a clockwork circuit starting in the pelvis, right paracolic gutter, subdiaphragmatic space then back to the pelvis. Considering only the physical forces and rheology of the peritoneal fluid, it is explained why certain sites- the rectouterine or rectovesical pouch, greater omentum (omentummajus), subphrenic region, diaphragm, mezentery are predisposed for tumoral secondary implants (4). The implant sites are also predisposed because of their morphology, in regard of the great concentration of peritoneal stomata and milky spots. It can be concluded that the location of peritoneal metastasis are dependent both on the specific features of the tumor cells and the particularities of the host tissue. The exception is pseudomixomaperitonei, which, because of the mucinosascitis has different spread patterns (11).

The next stage of peritoneal metastasis is the attachment and invasion of the mesotelial layer.

This can be achieved following two paths : transmesothelial or translymhatic.

The transmesothelial path begins with the adhesion of viable tumor cells to the mesotelium. This adhesion is facilitated by several adhesion molecules such as adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) located on the mesothelial cell (12). The expression of these molecules are mediated by several pro-inflamatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6 and interferon-γ, cytokines which are released in the abdominal cavity during the surgery or secreted by the circulating neoplasic cells (13). Tumor expressed CD44 is also a ligand for the hyaluronan, which is a glycosmainoglycan coating of the innermost layer of the peritoneum (14). After the tumor-mesothelial adhesion is achieved, under the effect of tumor-released cytokines, the mesothelial cells will contract thus exposing the basement membrane (15). The cascade of events which follow include the invasion of the blood-peritoneal barrier, proliferation and neoangiogenesis, all these mechanisms being the subject of extensive research.

The second path is the translyphatic dissemination, process which is stil unclear. In theory the loose tumoral cells gain acces to the subperitoneal lymphatic spaces through the stomata and the milky spots.The exact mechanism involved is still unclear but the milky spots appear to be a preferential site for implantation of the tumoral cell. These structures have a very rich capillary network, with signs of active angiogenesis caused by the hypoxic mesotelial cells situated adjacent show, which in turn generates the release of vascular endothelial growth factor – A (16). Also, colorectal and ovarian tumor cells have been shown to recruit elements of the immune system, especially macrophages (Tumor associated macrophages – TAM) in releasing cytokines and promoting angiogenesis (17). All these factors contribute to making these structures an ideal implantation site. From this point the cells follow the same path as in the transmesothelial invasion, but also having access to the lymph vessels, the cells will metastasize in loco-regional lymphnodes (4).

Depending on the histological type of the tumor, the dissemination process will be more likely to use one of the stated paths then the other, without exclusion of the other. Gastric and colorectal tumors for example use both transmesothelial andtranslymphatic processes. The exception is a particular form of tumor which causes mucinous ascites : pseudomyxomaperitonei, either from appendiceal, ovarian or colorectal orgin. In this particular case, the disease progression process is characterized by the redistribution phenomenon, meaning that large volumes of tumor will be found in predetermined anatomical sites, whereas in the rest of the abdominal cavity there will be minimal or no tumor present. This is due to the lack of specific adhesion molecules, making for example the intact visceral peritoneum of the small bowel an impossible dissemination site, due to the continuous peristaltic activity. Deposits of free tumor cells will be found in fluid reabsorption sites and distributed according to gravity and peritoneal fluid rheology, unique distribution pattern consistent with the classical view of carcinomatosis pathogenesis (18).

FOCAL POLYCLONAL THEORY

The traditional theory of carcinogenesis and peritoneal carcinomatosis is not without controversy. This theory states that genetic mutations in a normal somatic cell cause increased proliferation, reduced apoptosis and progressively gaining dedifferentiation and regressing to a primitive phenotype. Cancer stem cell theory states that tumor have an hierarchy similar to normal tissue with a small amount of proliferative cells capable of self-renewal and differentiation into multiple lineages(a reversed mirror image of the traditional model of carcinogenesis). Considering that the stem cells gain the mutation during the embryonic period and then remain dormant until activation by environmental factor, it could explain the different evolution of the peritoneal metastasis and of the primary tumor (19). This model could explain the behaviorof two tumors which can present peritoneal dissemination : ovarian tumors with low malignant potential and extraovarian papillary serous carcinoma of the peritoneum (15).

CONCLUSIONS

The peritoneal carcinomatosis represents a highly dynamic process in which the homeostasis of the abdominal cavity is severely altered. With the new concept that it is a loco-

regional extension of the primary tumor and therefore, a treatable condition, the peritoneum has become the focus of multidisciplinary research. The molecular interactions between host and tumor cell explain unique features for each type of tumor disseminated in the peritoneal cavity but also bring new prospect regarding the role of surgery as first in the treatment chain of peritoneal carcinomatosis. With all light being shed of the subject, certain intimate processes remain unclear. For example, according to the polyclonal theory, there exists a heterogeneity of tumor cells proportionate to the tumor volume. These distinct cell populations will present with different genetic alteration and because of this, different response to chemotherapeutic agents and different pathogenesis patterns. The tumor cells which disseminated were subject to certain genetic alteration like endothelial-to-mesenchymal transition.

This new acquired phenotypegrants them resistance to systemic chemotherapy.The intratumoral clonal heterogeneity opens new treatment perspectives such as site- specific chemotherapy (20).

The subject of peritoneal carcinomatosis is by far a closed topic, but recent discoveries in the peritoneum serous and tumor cells as described in this paper, help explain some unique traits of the disease and confirm the peritoneal carcinomatosis as an loco-regional process which requires a complex multidisciplinary approach.

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