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Abstract

Due to low symptomatology, a lack of screening, and relatively complicated diagnostic procedures of ovarian carcinoma, more and more women are believed to visit their doctors in advanced stage of the disease, complicated with ascitic fluid. There is an increasing evidence that peritoneal cytology is a subjective assessment with certain percentage of false-positive and false-negative results that may cause application of unnecessary chemotherapy or nonapplication of necessary chemotherapy. Maximal cytoreductive surgery followed by intraperitoneal or systemic chemotherapy remains to be the gold standard in preventing ascites. Ascites is not only a symptom of a disease, but a specific microenvironment for formation and mediation of protumorigenic signals that control ovarian cancer progression, proliferation, invasion, anti-apoptosis, chemoresistance and tumor heterogeneity. Acellular cytokines and immunological factors influence ovarian cancer progression and its ability to prevent immune responses of the body and tumor reaction to chemotherapy. Ascites contributes to disease dissemination, changing its course and final outcomes. Management of patients with ascites and ovarian carcinoma is complex and often the goal of the treatment is to target palliative procedures. Multidisciplinary approach is necessary in the management of these patients. Further investigations of new drugs and immunomodulators are needed aiming at prolonged periods between relapses.

Keywords: ovarian carcinoma, ascitic fluid, treatment, cytological findings, immunohistochemical markers

1. Introduction

Ascitic fluid is the presence of large volumes of fluid accumulated in the abdominal cavity. Normally, several liters of peritoneal fluid are produced and it is not accumulated, but
effectively absorbed. This fluid continuously circulates in a clockwise direction helping in the lubrication of intestines.

Malignant ascites accounts for about 10% of all cases of ascites [1]. Causes of nonmalignant ascites are: liver diseases (cirrhosis), congestive heart failure, and occlusion of the inferior vena cava or the hepatic vein occlusion, as well as benign tumors of the genital tract (ovarian fibromas). Malignant ascites are most commonly found with gynecological neoplasms (primarily ovarian and endometrial cancer), gastrointestinal malignancies, and breast cancer. In 15–30% of cases, the ascites is associated with carcinomatosis of the endometrium [2].

According to traditional classification, ascites is divided into exudative and transudative types. Ninety percent of ascitic fluids are transudates resulting from nonmalignant conditions, such as congestive heart failure or liver cirrhosis. Physical characteristics include clear appearance of the fluid with the presence of few cells (acellular) and low albumin level. On the other hand, exudates are most commonly malignant (ovarian carcinoma), with usually cloudy appearance of fluid, increased cellular count, and higher albumin level in comparison to transudates [3].

A new term used to assist in determining such a classification is the serum-ascites albumin gradient (SAAG).

This gradient is defined like the difference between albumin concentration of serum and ascitic fluid. If the gradient is >1.1, it indicates transudates due to portal hypertension, cirrhosis, hepatic congestion, portal vein thrombosis, etc. If SAAG <1.1, it indicates exudates not related to portal hypertension, but mostly malignant etiology (ovarian carcinoma), peritoneal carcinomatosis, chronic peritoneal infection, nephrotic syndrome, or hypoalbuminemia [4].

Besides protein concentrations, ascitic fluid may additionally be analyzed by macroscopic and microscopic testing.

Macroscopic testing means the analysis of appearance and color of ascites. Cloudy physical characteristics indicate the presence of leukocytes, infection, or malignancy. Yellow color is more common in liver diseases, greenish results from the bile, and reddish color may indicate the presence of hemorrhage.

Chemical tests, in addition to albumin concentration, include glucose level concentration (lower with infection), amylase (increased with pancreatitis), and lactate dehydrogenase (increased in carcinomas). If an infection is suspected, Gram stain analyses may be performed, as well as bacterial culture testing, viral testing, and microbacterial testing (tuberculosis).

Microscopic examination is performed if infectious or malignant ascites is suspected. Total cell count or leukocyte counting and differentiation are performed to determine infectious etiology more precisely. If malignant etiology is suspected, the most important thing is to determine the presence or absence of the cells with atypical morphological characteristics or malignant cells.
2. Pathophysiology

The pathophysiology of malignant ascites is multifactorial and is related to a combination of two basic pathogenic mechanisms, increased vascular permeability and obstructed lymphatic drainage.

Five microscopic barriers prevent movement of proteins away from vascular space: capillary endothelium, capillary basement membrane, interstitial stroma, mesothelial basement membrane, and mesothelial cells. In 1922, Putnam described the peritoneal membrane as a living, dynamic membrane through which the electrolytes pass between the peritoneum and serum. The movement of colloid solutions from serum is not clear enough and presents the relative impermeability through intercellular spaces based on Starling’s law of osmotic gradient. The exchange of fluid between the plasma and interstitium is based on the hydraulic and osmotic pressure. Oncotic pressure is based on fluid reabsorption from the interstitial space and edema prevention. Macromolecules, proteins, and cells that accumulate in the peritoneal cavity may return to the systemic circulation by means of peritoneal lymphatic system and lymphatic stomata to lymphatics that lead to the diaphragm and the thoracic duct [5].

In 1953, Holm and Nielson demonstrated the importance of lymphatic obstruction in pathogenesis of malignant ascites. The basic characteristics of malignant ascites include increased ascitic fluid protein concentration, increase of lactate dehydrogenase, large number of leukocytes, and positive cytology regarding the presence of malignant cells. High protein concentration in the peritoneal cavity results from vascular permeability due to increased vascular endothelial growth factor (VEGF) levels. The concentration of VEGF is significantly higher in malignant ascites than in nonmalignant ascites (cirrhosis). Splanchnic hyperemia and tumor necrosis factor dominate in nonmalignant ascites.

The complete pathogenic mechanism of malignant ascites is still not well understood. The events that are definitely happening and that we are familiar with include an increase of net filtration and accumulation of ascitic fluid resulting from increased capillary permeability, increased surface area for filtration, increased hydraulic pressure difference, and decreased oncotic pressure difference [6].

A two-way permeability of blood vessels is necessary for tissue normal supply with nutrients, gases, minor proteins, and waste removal. It can be basal, acute vascular (a consequence of short exposure to VEGF) and chronic, characteristic of pathological (malignant) angiogenesis.

Apart from the most important aforementioned VEGF that stimulates vascular permeability, other factors responsible for stimulation include basic fibroblast growth factor (bFGF), angiogenin, transforming growth factors (TGF α and β), and interleukin-8. All these factors lead to neovascularization and angiogenesis, starting with endothelium stimulation and resulting in hyperpermeability and degradation of endothelial membrane, followed by migration and proliferation of endothelial cells and the development of new capillaries. VEGF has been identified in ovary tumor cells, with its overexpression reported in ovarian carcinoma.


