

Malignant Ascites: A Review of Pathogenesis and Management



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Abstract

Malignant ascites is an ominous sign that indicates peritoneal metastasis of the primary malignancy. The average survival after development of malignant ascites is only about 5 months. Malignant ascites may be associated with a variety of neoplasms including, ovarian, breast, colorectal, gastric, hepatobiliary and pancreatic carcinomas. The ascites per se and need for repeated paracentesis adversely affect the quality of life and also increase the risk of morbidity. Management of malignant ascites is essentially palliative. Conventional first-line approach to a patient with tense ascites includes paracentesis, diuretics or combination of both. Peritoneovenous shunts have also been utilized in selected patients with such situation. However, these approaches have limited efficacy and associated with high morbidity rates. Although effective options for the management of malignant ascites are limited, newer modalities like targeted therapy, immunotherapy, radioisotopes and hyperthermic intraperitoneal chemotherapy (HIPEC) have shown promising outcomes in their preliminary evaluation. This article reviews the pathophysiology and recent developments in the management of malignant ascites.

Keywords: Malignant; Ascites; Paracentesis; HIPEC

Abbreviation: HIPEC: Hyperthermic Intraperitoneal Chemotherapy; PC: Peritoneal Carcinomatosis; USG: Ultrasonography; CT: Computed Tomography; LDH: Lactate Dehydrogenase; VEGF: Vascular Endothelial Growth Factor; SAAG: Serum Ascites Albumin Gradient; DIC: Disseminated Intravascular Coagulation; EpCAM: Epithelial Cell Adhesion Molecule

Introduction

Malignant ascites is defined as an accumulation of excess fluid in the peritoneal cavity secondary to a disseminated malignancy [1]. Apart from being a poor prognostic indicator it also adversely affects the patient's quality of life [2]. According to an estimate, it affects around 3.6-6% of patients admitted in the palliative care unit [3]. Malignant ascites is an ominous sign with an average survival of around 20 weeks from its diagnosis [4]. Around 95% of patients have metastatic disease involving peritoneum, liver, bone and lungs [5]. Ovarian malignancy is the most common cause (37%) followed by pancreatobiliary (21%) and gastric malignancy (18%) [5]. Around 20% patients have unknown primary malignancy [6].

Discussion

Pathophysiology

Pathophysiology of malignant ascites is multifactorial. It originates from an imbalance between fluid secretion and absorption by peritoneum. This is secondary to increased fluid production by tumor cells lining peritoneal cavity in cases of peritoneal carcinomatosis (PC), alteration in vascular

permeability, release of inflammatory cytokines and decreased lymphatic drainage due to tumor involvement and increased portal pressure due to tumor metastasis [7,8]. Obstruction of lymphatics is believed to be the main pathogenic mechanism for malignant ascites. It has also been demonstrated that there is an abnormal accumulation of various osmotic macromolecules in the peritoneal cavity of subjects with malignant ascites [4]. Alteration in the vascular permeability allows larger molecules to accumulate in the peritoneal cavity, leading to the shift of fluid balance towards net filtration which overwhelms the drainage capacity of the peritoneal membrane. The combined effect of lymphatic obstruction and abnormal macromolecule concentration in the peritoneal cavity is thought to produce refractory ascites in cases of PC. Role of matrix metalloproteinase-9 has also been implicated in the pathophysiology of malignant ascites [8].

Presentation

Symptoms are non-specific and may range from abdominal distension, early satiety to dyspnea, orthopnea and peripheral edema. Diagnosis is made by clinical examination,

ultrasonography (USG) or Computed Tomography (CT) scan. Ascitic fluid analysis is considered the gold standard investigation [4]. Tumor markers are not diagnostic for malignancy but may help in identifying primary malignancy. Low glucose levels (<100mg/dl) and high fluid to serum lactate dehydrogenase (LDH) levels (>1) are suggestive of peritoneal carcinomatosis (PC) [9]. Laparoscopy and tissue sampling may be utilized to confirm the diagnosis [4].

Prognosis

It is associated with a strong negative prognostic value. Survival is poor when ascites is secondary to GI malignancy as compared to ovarian malignancy. Other prognostic factors include low serum albumin, liver metastases and elevated serum bilirubin levels [4]. High level of Vascular endothelial growth factor (VEGF) have been found to be independent poor prognostic factor for overall survival [10].

Management

The aim of management is to provide symptomatic relief and specific treatment of the primary pathology. Management options may be classified into conventional methods and newer modalities.

a) Conventional management: General management includes low salt diet and diuretic therapy. Response is better with diuretic therapy in patients with increased renin values, massive liver metastases and elevated serum ascites albumin gradient (SAAG) [1,5,6]. Therapeutic paracentesis can be used for rapid symptom control. Large volume paracentesis (upto 5 litre) can be done without undue complications. However, it may lead to secondary peritonitis and pulmonary embolism [1]. Tunnelled catheters like permanent peritoneal catheter drainage system have been tried. They are placed subcutaneously under local anesthesia. Process involves attaching vacuum bottle to catheter and draining fluid. Advantages include greater flexibility, frequent episodes can be done, reduced infections and reduced resource usage [6,11,12]. However, they are not widely available. Peritoneovenous shunts have been utilized for malignant ascites [5,6,13]. They are recommended if life expectancy is more than 3 months. Symptom palliation is seen in 70% of patients. Complications include shunt occlusion, fever, cardiopulmonary compromise, disseminated intravascular coagulation (DIC). Contraindications are fulminant hepatic failure, ascites with positive malignant cytology, hemorrhagic or chylous ascites and life expectancy less than one month.

b) Hyperthermic Intraperitoneal Chemotherapy (HIPEC): As PC is one of the most important cause of malignant ascites, specific treatment may yield better survival results. Systemic chemotherapy is rarely effective and more toxic in PC due to poor blood supply. CRS with intraperitoneal chemotherapy has been effectively utilized for GI malignancies associated with PC [14]. Rationale behind this procedure includes cytoreduction with

prolonged contact on tumor nodules, selective cytotoxicity due to protein denaturation, impaired DNA repair due to hyperthermia and hyperthermia induced vasodilatation with improvement in tumor oxygenation. Improved survival has been achieved with this technique as compared to systemic chemotherapy [5,6,8,15]. Combination with intravenous chemotherapy has been tried along with HIPEC. Due to high morbidity rates with CRS and HIPEC, laparoscopic HIPEC has been tried in patients not fit to undergo cytoreductive surgery. Intraperitoneal chemotherapy is administered via infusion trocar and table is tilted for effective contact. It has been found to be a safe and effective modality for palliation of malignant ascites [4].

c) Newer modalities: Newer drugs have been tried for malignant ascites. OK-432 is a preparation from *Streptococcus pyogenes*. Intraperitoneal instillation reduces ascites in 60% of patients. Mechanism of action is not clear. Improved mean survival has been reported with this therapy [5,6]. Metalloproteinase inhibitors like Batimastat have been studied in early phase trials with good results [5,6]. However, larger trials are needed to conclusively define their benefits. Anti VEGF therapies like Bevacizumab have been shown to inhibit ascites formation in animal models and human trials are ongoing [5,6,8]. Various cytokines like Interferon alpha, Interleukin 2 and Tumor Necrosis factor have been reported with variable effectiveness in small pilot studies [5,6]. Antibodies against cellular adhesions molecules like Epithelial cell adhesion molecule (EpCAM) like Catumaxomab after therapeutic paracentesis are associated with prolonged paracentesis-free survival, improved quality of life and prolonged overall survival [5,7,8]. Mechanism of action includes decreased proliferation, migration and invasion of cancer cells. Photosensitisers have also been tried. They act by stimulating antitumor response and selective destruction of cancerous tissues [5]. However, further studies are needed to conclusively recommend the therapy.

Conclusion

Malignant ascites remains a difficult condition to treat. It portends an uniformly grim prognosis. Multiple treatment options have been tried with variable results. CRS with HIPEC promises better survival rates at the cost of increased morbidity. Newer drugs are being developed but evidence is lacking to recommend one drug over another.

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