Supplemental Online Case Discussion:
Management of Malignant Ascites in the Acute Oncology Setting

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Case History
A 57-year-old female presented to her local hospital with a 2-month history of retrosternal discomfort that was initially diagnosed as esophageal spasm. She had progressive symptoms, had regurgitation of food, and underwent upper gastrointestinal endoscopy. The stomach appeared grossly abnormal and had the morphological appearances of linitis plastica. Staging computed tomography (CT) showed a thick-walled stomach, omental nodularity, and large volume ascites. Biopsy found HER2-negative signet ring adenocarcinoma of gastric origin. Cytological analysis of her ascitic fluid was consistent with metastatic adenocarcinoma. She was staged as T3NXM1. She was seen in the oncology clinic and assessed as suitable for systemic treatment (performance status 1). Palliative epirubicin, cisplatin, and 5-fluorouracil (ECF) chemotherapy was commenced. She developed nausea, abdominal discomfort, and constipation and was admitted for therapeutic paracentesis. A total of 8 liters was removed; midprocedure, the drain was temporarily clamped at 5 liters to allow for hemodynamic adjustment. During the course of chemotherapy, the fluid re-accumulated rapidly, requiring repeat drainage. Consequently, to avoid repeated admissions for drainage, she underwent insertion of a PleurX peritoneal catheter (Becton Dickinson Global, CareFusion, San Diego, CA, http://www.carefusion.com/our-products/interventional-specialties/drainage/about-the-pleurx-drainage-system/pleurx-drainage-system). This allowed weekly drainage by the district nursing team at home. Despite four cycles of ECF, she had disease progression, as evidenced by repeat accumulation of ascites. She generally deteriorated and was admitted to her local hospice, where she passed away 7 months from diagnosis.

Current Knowledge
Ascites is the abnormal accumulation of fluid within the peritoneal cavity, the commonest cause being benign liver cirrhosis with portal hypertension. Approximately 10% of cases are due to malignancy, and other than in the context of ovarian cancer, the condition is associated with a poor prognosis [1]. The average median survival once malignant ascites is diagnosed is approximately 1 to 4 months (varying according to primary cancer). It is a significant contributor to poor quality of life for those patients in the terminal phase of their illness, due to symptom burden and frequent hospital attendance for drainage of ascites [2].

Symptoms usually relate to the pressure effect on the gastrointestinal and genitourinary tract. These include nausea, vomiting, anorexia, distension, discomfort, constipation, and urinary frequency. Gross ascites can also cause breathlessness due to diaphragmatic pressure [3].

The pathophysiology of ascites is not completely understood; it is complex and multifactorial. In carcinomatosis, neovascularization of the peritoneum contributes to increased vascular permeability and subsequent release of peritoneal fluid. Vascular endothelial growth factor (VEGF) has been implicated in ascites production. It plays a role in altering vascular permeability, being 50,000 times as potent as histamine, and increased levels have been found in malignant ascitic fluid [4].

Another major factor is the blockage of lymphatics channels by tumor cells, which obstructs drainage from the peritoneum [5]. It is also hypothesized that cancer cells produce matrix metalloproteinases, which disrupt the extracellular matrix, contributing to tumor spread, and influence vascular permeability [3]. Table 1 lists the most common causes of malignant ascites and the different mechanisms involved [6, 7].

Differential Diagnosis
In patients who present acutely with ascites, a high index of suspicion for underlying malignancy should be entertained. Benign causes should be excluded, including ascites secondary to liver cirrhosis (approximately 80% of cases), congestive cardiac failure, portal hypertension, and chronic pancreatitis.

Investigations
In general, physical examination is of limited value in the assessment of malignant ascites. Ultrasound scan is a quick screening test and can detect as little as 100 cc of fluid [3]. Blood tests for full blood count, liver function test, and urea plus electrolytes are helpful to exclude anemia, infection, hypoalbuminemia, and liver and renal dysfunction. A coagulation screen is useful if paracentesis is planned. Studies have shown that a serum-ascitic albumin gradient (SAAG) of >1.1 g/dL is a useful test when the etiology is in doubt, as it can identify patients with benign portal hypertension who may benefit from diuretic therapy [8]. Conversely, a lower gradient (due to an exudate ascites) is possibly secondary to malignancy.

If infection is suspected, ascitic fluid can be analyzed for cell counts and culture of microorganisms. Cytology of ascitic fluid has a specificity of 100% and is the gold standard for the diagnosis, but because not all tumors shed cells into the peritoneum, biopsy of a solid tumor may prove useful in confirming the diagnosis [3].

Imaging with CT can help identify the primary tumor. It provides diagnostic accuracy in 55% of cases, although this varies between tumor groups [9]. Furthermore, positron emission tomography CT is a helpful modality, particularly in lung, head and neck cancers, and the detection of occult metastatic spread [10].
Tumor markers such as CA125 and CEA have poor sensitivity and specificity [11], and their use in evaluation of new onset ascites is generally discouraged unless there is a strong diagnostic suspicion of a neoplasm of ovarian or colonic etiology.

**Management**

**Acute Oncology**

From an acute oncology perspective, the aim of management of ascites presenting as a hospital emergency is to alleviate the physical symptoms of ascites and, during this process, to assess the patient’s overall condition and suitability for further systemic treatment such as chemotherapy, bearing in mind that treatment will be of palliative intent. If the patient is unsuitable for active treatment, as assessed by performance status, comorbidities, and patient choice, then the clinical focus should be in providing the best supportive care, and not pursuing unnecessary investigations such as further imaging and biopsy.

However, if the patient is fit for treatment and keen to pursue this avenue, the acute oncology team is in a prime position to advise on best management as regards diagnostics, multidisciplinary team (MDT) referral, and liaison with other teams, including cancer nurse specialists (CNS) and appropriate MDT referral, in addition to providing psychological support to patient and caregivers until a tumor-specific CNS has been identified for the patient.

Up to 5% of invasive cancers can present as a cancer of unknown primary (CUP). The diagnostic process can be complex, and biopsy of malignant tissue and pathological analysis is key, assuming the patient is fit enough, considering performance status, nutritional status, and comorbidities, to undergo systemic chemotherapy. In the presence of poorly differentiated cancer, light microscopic analysis has limitations. Immunohistochemical staining may suggest a likely primary, but in some cases, this is not specific [9]. Gene expression profiling is an emerging molecular technique that can identify subgroups of CUP patients with treatable tumors and therefore guide treatment [12].

**Table 1. Common causes of malignant ascites and the underlying pathophysiological processes involved [6, 7]**

<table>
<thead>
<tr>
<th>Causes of malignant ascites</th>
<th>Proportion caused</th>
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<tbody>
<tr>
<td>Ovarian cancer</td>
<td>37.7%</td>
</tr>
<tr>
<td>Pancreatobiliary cancers</td>
<td>21%</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>18.3%</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>4%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>3.7%</td>
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<tr>
<td>Breast cancer</td>
<td>3%</td>
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</tbody>
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**Pathophysiology of malignant ascites**

<table>
<thead>
<tr>
<th>Pathophysiology of malignant ascites</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>53%</td>
</tr>
<tr>
<td>Massive liver metastases causing portal hypertension</td>
<td>13%</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis plus massive liver metastases</td>
<td>13%</td>
</tr>
<tr>
<td>Hepatocellular carcinoma plus cirrhosis</td>
<td>13%</td>
</tr>
<tr>
<td>Chylous ascites, usually due to lymphoma</td>
<td>7%</td>
</tr>
<tr>
<td>Budd-Chiari syndrome due to malignancy occluding hepatic veins</td>
<td>Rare</td>
</tr>
</tbody>
</table>

**Paracentesis**

Paracentesis provides quick and effective symptom control in 90% of patients [1]. Unlike in patients with nonmalignant liver disease, there is not a high risk of hypotension and renal failure. Studies have demonstrated up to 5 L can be drained safely; however, for larger volume paracentesis, it is advisable to clamp the drain every 4–5 L to allow for hemodynamic adjustment [13].

It is important to emphasize that, unlike benign ascites, there is no evidence to indicate that intravenous fluid or albumin replacement is required to prevent hypotension in patients undergoing paracentesis for malignant ascites (who do not also have portal hypertension). Generally, this is a safe and well-tolerated procedure although there is a low risk of infection, loculation of the ascites, bowel perforation, and development of adhesions.

**Diuretics**

Diuretics are commonly used; however, according to the literature, there are no randomized trials to assess efficacy and the response rate is at best 44% [3]. Diuretics are more effective if the patient has a SAAG greater than 1.1, indicating a degree of nonmalignant liver disease may be implicated.

**Peritoneovenous Shunts**

Peritoneovenous shunts have been used effectively in patients with a longer prognosis but need specialist surgical input and have significant side effects, such as pulmonary embolism, coagulation disorders, infection, and shunt blockage.

**New Developments**

The PleurX peritoneal catheter and drainage system (Becton Dickinson Global, CareFusion) has recently been approved by the National Institute for Health and Care Excellence [14] for use in patients with recurrent malignant ascites. The device consists of a silicone peritoneal catheter that is permanently placed inside the abdominal cavity with a cuff that is placed subcutaneously with a safety valve on the abdominal wall of the patient. A vacuum bottle can be intermittently attached to the port to enable drainage of ascitic fluid by the patient.
or their caregiver and hence reduce hospitalization. When not in use, the valve is covered with a cap and a simple dressing. This is a cost-effective device that reduces the need for repeated hospital admissions and, in relieving this burden, improves the patient’s quality of life.

A series of case reports in ovarian cancer have reported reasonable benefit of 2–6 months symptomatic improvement with intraperitoneal bevacizumab. Aflibercept, the fusion protein VEGF-Trap, has been reported to improve ascites, although also associated with a significant risk of intestinal perforation [15]. Batimastat is a metalloproteinase inhibitor. It was recently assessed in a small phase I study, in which more than half the patients treated demonstrated no reaccumulation of their ascites after drainage [3]. Hyperthermic intraperitoneal chemotherapy has been proposed as a palliative treatment for malignant ascites; small number case series have reported positive results, but more work is needed to establish this as a potential therapeutic option [16].

Recent research has focused on immune modulation as a novel approach to treating malignant ascites. Epithelial cell-adhesion molecule (EpCAM), expressed in normal epithelium, is overexpressed in most carcinomas. Catumaxomab is a rat/murine hybrid trifunctional monoclonal antibody to EpCAM. It binds with EpCAM and CD-3 on T cells through its two binding arms. It also binds accessory cells (e.g., macrophages and dendritic cells) via the fragment crystallizable (Fc) region leading to immune activation and tumor cell death (Fig. 1) [16]. Recent clinical trials have shown that patients with malignant ascites have experienced sustained improvement with intraperitoneal catumaxomab, and in a subgroup with gastric cancer, this has translated into a survival benefit [17].

**Patient Management**

In the cited case, the patient was referred to the acute oncology (AO) team when she was admitted from clinic for drainage of ascites. When she then re-presented within 30 days, again requiring ascitic drainage, the AO team advocated referral for insertion of the PleurX peritoneal catheter (Becton Dickinson Global, CareFusion). This advice was based on the fact that the ECF chemotherapy was not benefiting her, as evidenced by repeated accumulation of ascites; second-line chemotherapy in this setting has a low response rate; hence, she was likely to be troubled by ongoing ascitic fluid collection. A PleurX peritoneal catheter (Becton Dickinson Global, CareFusion) was inserted by the interventional radiologist, and the patient was instructed in how to care for the device by the acute oncology CNS and discharged home later that day. She had community follow-up with the district nurses to help empty the drain, and she was referred to the community palliative care team. She did not require further hospital admission for management of her ascites.

**Conclusion**

The presence of ascites represents a symptom of serious underlying pathology. The aim of management is to establish the underlying cause in addition to providing rapid symptomatic relief with urgent paracentesis. For many patients the symptom burden and frequent hospital attendances can represent a serious deterioration in quality of life during the terminal phase of their illness.

To address this, drainage should occur on the day of admission, preferably under ultrasound-guided control. For those patients in whom the underlying disease is considered resistant to systemic treatment, insertion of the PleurX peritoneal catheter (Becton Dickinson Global, CareFusion) enables management within the community. The local AO team is invaluable in advising on best management for such patients and should be involved from point of admission. New approaches such as targeted therapies (anti-VEGF) and immunological treatments appear to be promising options albeit with more work needed to fully establish their safety and role in clinical practice.

![Figure 1. Schematic of the structure and mode of action of catumaxomab.](https://example.com/figure1.png)

**Abbreviations:** CD3, cluster of differentiation 3; DCs, dendritic cells; EpCAM, epithelial cell-adhesion molecule; Fc, fragment crystallizable; IgG, immunoglobulin; NK, natural killer; IL, interleukin; INF, interferon; GM-CSF, granulocyte macrophage colony-stimulating factor; ADCC, antibody dependent cell mediated cytotoxicity; DC-Ck1, dendritic cell CK1.
References