Pseudomyxoma peritonei (PMP) is an uncommon clinical condition that typically originates from a perforated epithelial neoplasm of the appendix. The clinical presentation is variable, often with non-specific symptoms and is associated with abdominal distension in advanced cases. Whilst traditionally considered benign, it is apparent that PMP represents a spectrum of disease and, at best, should be considered a “border-line” malignancy. The condition is characterised by the development of mucinous ascites. Tumour cells and mucin accumulate at characteristic sites within the peritoneal cavity according to the redistribution phenomenon, usually sparing the mobile small bowel. In advanced cases, high volume disease and mucinous ascites lead to compression of the gastrointestinal tract, bowel obstruction, and ultimately, starvation. Controversy still exists over the pathological classification of PMP and its prognostic value. Computed tomography remains the optimal preoperative staging investigation. Elevation of serum tumour markers correlates with a worse prognosis. Optimal treatment involves cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC). With complete cytoreduction and HIPEC an 80% 5 year survival can be achieved in patients with low grade disease. Maximal tumour debulking can produce good palliation and long term survival in a small number of patients. Initial high morbidity and mortality is seen to decrease with increasing experience and this is likely to represent improvement in patient selection and postoperative management as well as surgical expertise.

Key words: appendiceal mucinous tumour, cytoreductive surgery, HIPEC, jelly belly, peritoneal malignancy, pseudomyxoma peritonei

Introduction

Pseudomyxoma peritonei (PMP) is an uncommon clinical condition characterized by mucinous ascites and predominantly originates from a perforated epithelial neoplasm of the appendix [1,2]. The clinical presentation is variable, often with non-specific symptoms and is associated with abdominal distension in advanced cases [1,2]. Whilst traditionally considered benign, it is apparent that there is a spectrum varying from slowly progressive to aggressively malignant disease such that pseudomyxoma peritonei, at best, should be considered a “border-line” malignancy [2]. Similar clinical, radiological and pathological features may originate from any abdominal mucinous tumour, in particular the ovary in females or colorectal pathology in males or females. PMP of non-appendiceal origin tends to be at the adverse end of the spectrum. The primary tumour is more likely to be a mucinous adenocarcinoma with a worse prognosis than that in classical PMP of appendiceal origin.

The incidence of PMP is unknown as there is no substantial information on the true incidence of either appendiceal mucinous tumours or of PMP. Estimates of an incidence of PMP of 1 per million per year had been proposed [3], though this was based on a figure with no scientific evidence. An epidemiological analysis by Smeenk et al in 2008 of a population based study in the Netherlands [4] reported an incidence of mucinous epithelial ne-
Pathophysiology of PMP and the Concept of the “Redistribution Phenomenon”

PMP arises from mucin secreting peritoneal and omental implants secondary to a perforated mucinous neoplasm, typically originating in the appendix. The initiating appendiceal neoplasm progresses and gradually occludes the lumen, causing the appendix to become distended with sterile mucin, eventually perforating, and spilling mucous and mucinous tumour cells into the peritoneal cavity. Following the initial rupture there is often a continued slow leak of mucus.

Although some cases present as acute appendicitis, many occur without symptoms. It is hypothesized that the gradual occlusion of the lumen prevents significant bacterial contamination of the mucin distended distal appendix.

Once free within the peritoneal cavity, epithelial cells continue to proliferate and can produce significant volumes of mucus. This culminates in the characteristic accumulation of gelatinous mucus in the peritoneal cavity, also commonly referred to as “jelly belly” [6]. Whilst the classical PMP appearances originate from an appendiceal tumour, the clinical, radiological and indeed image guided biopsy appearances of “jelly belly” may also originate from a true adenocarcinoma of the appendix, of the colon or rectum, primary peritoneal or ovarian malignancies, and there are indeed case reports and small series of PMP cases originating from most intra-abdominal organs, including the stomach, pancreas, liver, gallbladder, urinary bladder and urachus [2,7].

The distribution of mucinous tumour implants within the peritoneal cavity is determined by what has been termed “the redistribution phenomenon” [2,8]. Rupture of the primary tumour results in release of free floating cells and mucin which disseminate throughout the abdominal cavity. The epithelial tumour cells have either none, or low, adhesion properties and consequently distribute within the peritoneal fluid [8]. Characteristically cellular deposits accumulate, and proliferate, in predetermined sites by two main mechanisms, absorption of peritoneal fluid and gravity. The physiology of the peritoneal cavity involves production, circulation and absorption of peritoneal fluid. The main sites of fluid reabsorption are the greater and lesser omentum (accounting for the classical “omentum cake”, Figure 1) and the undersurface of the diaphragm, particularly the right side, resulting in tumour accumulation in the subdiaphragmatic and suprahepatic regions (Figure 2).

The second main mechanism is by gravity with cell accumulation in dependent sites, such as the recto-vesical pouch, the right retro-hepatic space and the paracolic gutters [2,8].

Mobile organs such as the small bowel and its mesentery are usually spared, particularly early on in the course of the disease. In contrast the less mobile, partially retroperitoneal, ascending and sigmoid colon, as well as the fixed points of...
the stomach in its distal portion and the duodenjejunal flexure at the ligament of Treitz can be heavily involved by disease and may warrant bowel resections such as colectomy and distal gastrectomy to remove troublesome deposits (Figure 3 and 4).

The relative sparing of the motile small bowel and its mesentery allows complete removal of tumour in most patients without the need for substantial small bowel resection.

Extensive small bowel involvement can occur at an early stage in more aggressive tumours and even in less invasive tumours when the disease is at an advanced stage. Prior attempts at tumour removal, particularly where extensive abdominal surgery has been performed, can lead to tumour proliferation in scar tissue and may involve the small bowel at the sites of adhesions. Extensive small bowel involvement, particularly if the disease involves the serosa or infiltrates at the junction of the small bowel with its mesentery, may prevent a complete tumour removal.

In advanced cases, high volume disease and mucinous ascites lead to compression of the gastrointestinal tract, bowel obstruction, and ultimately, starvation. More aggressive tumours can lead to the involvement of the bowel at an earlier stage.

Clinical presentation

In the early stages of PMP, many patients have no symptoms. Even when the disease burden is marked, abdominal symptoms can be vague. Some patients may have been investigated with luminal endoscopy and labelled with irritable bowel syndrome.

The initial appendiceal tumour is commonly asymptomatic, even when perforated, but suspected appendicitis is a common mode of presentation. Management of an unexpected appendiceal neoplasm has been summarised elsewhere [9].

In 2000, Esquivel and Sugarbaker [10] looked at 410 patients with appendiceal tumours. Overall the most common presentations were suspected appendicitis (27%), increasing abdominal distention (23%) and a new onset hernia (14%). In women, the diagnosis was most commonly diagnosed after gynaecological investigation revealed an ovarian mass. Computed tomography (CT) now plays an increasingly important role in diagnosis. We examined the mode of presentation of 222 patients undergoing surgery for PMP in Basingstoke in 2012 and 2013 [11]. Overall 36.5% of patients were diagnosed by preoperative CT alone.
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and 14.4% by an abnormal CT that led to operative confirmation. 20.7% were diagnosed at laparoscopy or laparotomy with acute symptoms or on histology after appendicectomy. An incidental finding at surgery for a new onset hernia accounted for 5%.

Many reports suggest an increased incidence in women but his may result from a lower threshold for abdominal imaging in women on suspicion of ovarian pathology resulting in both more frequent and earlier diagnosis. In addition progressive ovarian involvement may lead to earlier onset of symptoms.

In advanced cases, physical examination may detect important clinical signs. Shifting dullness of ascites suggest serous rather than mucinous ascites. Mucinous ascites may be too dense to redistribute when the patient is repositioned. Large ovarian masses and an omental cake are sometimes palpable. Disease in the rectovesical pouch may be felt on digital rectal examination.

Investigations

A CT of the chest, abdomen and pelvis with intra venous and oral contrast is the investigation of choice [12]. Mucinous disease is typically represented by areas of low attenuation with islands of high attenuation due to solid material within the mucinous ascites. Tumour deposits on the visceral surfaces of the liver and spleen lead to the classical appearances of “scalloping” on CT, distinguishing it from fluid ascites (Figure 5).

A striking feature of PMP is the relative sparing of the small bowel and its mesentery. In more advanced cases this may lead to compartmentalisation of the small bowel in the central abdomen, surrounded by a massive omental cake and mucinous ascites. Sparing of the small bowel and mesentery are essential for complete tumour removal. Contrast enhanced CT can help predict the likelihood of successful cytoreductive surgery. Adverse radiological features associated with small bowel involvement include segmental obstruction and tumour masses greater than 5cm on the small bowel and its mesentery. When both features are present there is an 88% probability of incomplete resection compared with a 92% probability of complete resection when both are absent [12].

Magnetic resonance imaging (MRI) in the assessment of PMP has been proposed [13,14] and appears promising but requires further evaluation. Positron emission tomography (PET) and PET-CT have a limited role in the investigation of low grade mucinous disease but may be of value in detecting extra-abdominal disease or liver metastases in patients with adenocarcinoma [15].

Serum tumour markers can provide useful prognostic information in patients undergoing surgery for PMP. CEA, Ca 125 and Ca 19.9 have been found to have both diagnostic and predictive value in some patients [16-18]. In a study of 519 patients who underwent complete tumour removal in Basingstoke, patients with normal tumour markers had significantly higher disease free and overall survival compared with patients with elevated tumour markers [19]. The number of elevated markers (0–all three) correlated with a worse outcome.

Tumour markers appear to provide prognostic information independent of histopathological grading and may have a role in determining consideration of post-operative systemic chemotherapy and timing and frequency of follow-up.

When cross sectional imaging is equivocal or tissue is required for histological confirmation, laparoscopy and biopsy can be useful. Wherever possible, laparoscopic ports should be positioned in the midline, such that these sites can be excised by a midline laparotomy wound to reduce the risk of tumour seeding. With advanced or recurrent disease, laparoscopic access and visualisation of the peritoneal cavity can be difficult and dangerous and for PMP adds little in most cases.

Treatment

The optimal management of pseudomyxoma peritonei is complete cytoreductive surgery (CRS) in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). The aim of this strategy is to remove all visible disease within the peritoneal cavity. The intraoperative HIPEC then targets any residual microscopic disease, or small volume macroscopic tumour nodules (<2.5mm) [20-22]. Completeness of cytoreduction has been shown to be the most important prognostic factor.

With an average operating time of 9 hours [23], CRS and HIPEC is a major surgical intervention. Specialised anaesthetic and perioperative management is required. Positioning of the patient on the operating table requires experience in order to allow full access to the abdomen and perineum whilst minimising the risk of neurological compression and compartment syndrome.

The operation starts with a midline incision from xiphisternum to symphysis pubis, excising the umbilicus and any previous midline scar. Once the abdomen is open a full assessment of the disease can be made. We usually commence...
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with a right parietal peritonectomy and mobilisation of the right colon identifying the right ureter and gonadal vessels. Providing there is widespread disease, peritonectomy is continued to perform a right diaphragmatic peritonectomy with full mobilisation of the liver. If required, a liver capsulectomy is performed with the help of a ball tipped diathermy at maximal setting. A high power smoke extraction system is essential to remove the resulting smoke. The same procedure is repeated on the left side with a left parietal peritonectomy, identification of the left ureter and gonadal vessels and left diaphragmatic peritonectomy if required.

A radical greater omentectomy is performed inside the gastro-epiploic arcade and the spleen is assessed. If the spleen is involved with disease a splenectomy is performed after full mobilisation. Care is taken not to damage the tail of the pancreas. Dissection into the pelvis starts with mobilisation of the rectum in the mesorectal plane posteriorly. Anteriorly the peritoneum is dissected off the bladder. The rectum and sigmoid colon can usually be spared but in advanced disease, and following prior pelvic surgery, an anterior resection may be required. In the female, the ovaries are routinely removed. A hysterectomy may also be necessary. An appendicectomy may be all that is required to remove the primary tumour. If there is extensive disease around the caecum or terminal ileum or if there is a likelihood of adenocarcinoma then a right hemicolecction is performed.

In the upper abdomen, the lesser omentum is removed from the lesser curve of the stomach preserving the left gastric vessels. The dissection continues to the porta hepatis, taking care to take only the peritoneum and preserve the common bile duct, hepatic artery and portal vein. Identification of the portal anatomy is aided by retrograde cholecystectomy. After mobilisation of the liver, disease in the aorto-caval groove is removed. The peritoneum between the caudate lobe, right crus of the diaphragm and inferior vena cava is removed. When there is a high volume of upper abdominal disease a distal gastrectomy may be necessary. In the series from Basingstoke this was necessary in almost 10% of patients with PMP who had a complete cytoreduction [22].

Once all visible tumour has been removed, HIPEC is administered by a continuous infusion of Mitomycin C (10mg/m², with dose adjustments for patients with renal impairment, significant abdominal distention, recent chemotherapy and older age) heated to 42 degrees for one hour. We use an open method to administer the chemotherapy utilising a “coliseum” technique.

After HIPEC the abdomen is washed out and any gastrointestinal anastomoses are performed. If an anterior resection has been required a stapled colorectal anastomosis is performed and routinely defunctioned with a loop ileostomy. Up to four abdominal drains are inserted. It is our routine practice to place chest drains if the diaphragmatic peritoneum has been removed. Patients are managed post-operatively on an intensive care unit. In some units early post-operative intra-peritoneal chemotherapy (EPIC) is used. In Basingstoke selected patients receive 5-fluorouracil at 15mg/kg for up to 4 days post-operatively via a tenckhoff catheter.

If complete cytoreduction is not possible, maximal tumour debulking (MTD) is performed. MTD usually involves a greater omentectomy and either an ileocolic anastomosis or a total colectomy and ileostomy.

**Histopathological classification**

The classification of pseudomyxoma peritonei has been confusing. There have been a number of different terminologies and classification systems used for epithelial appendiceal neoplasms. In addition, the clinical presentation of PMP can also result from high grade colonic mucinous neoplasms, adenocarcinoma of the appendix and mucinous adenocarcinomas originating from other intra-abdominal organs. PMP of appendiceal origin is a best a borderline malignant condition but more accurately represents a spectrum of disease from low to high grade.

Different pathological classifications of PMP have led to difficulties in the interpretation of treatment outcomes. Some series include all cases including those originating from adenocarcinoma while some report only those arising from low-grade appendiceal tumours.

In 1995, Ronnet et al. [24] produced the first internationally recognised classification system based on patients who had undergone cytoreductive surgery in Washington by Sugarbaker’s group. They divided PMP into three categories: Disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) and an intermediate group. Bradley et al. [25] proposed classification into two distinct categories, mucinous carcinoma peritonei low grade and mucinous carcinoma peritonei high grade. The former incorporating DPAM and the intermediate group, the latter PMCA, including cases that are moderately to poorly differentiated and those with sig-
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A classification by the WHO in 2010 [26] divided PMP of appendiceal origin into low and high grade. A review of over 270 cases by Carr et al. [27], correlating histology with clinical findings and survival data found that categorisation as either low grade or high grade correlated well with prognosis. The Peritoneal Surface Group International is working with the leading pathologists on appendiceal tumours to reach a consensus on this classification.

The pathological classification is important as it provides an indication of prognosis following CRS and HIPEC. Patients with low grade PMP appear to gain maximal benefit.

Outcomes of CRS and HIPEC

Surgery for pseudomyxoma peritonei traditionally involved repeated debulking for symptomatic relief with limited expectation of long term survival and no prospect of cure. The lack of a successful treatment strategy and the rarity of PMP meant that historical series were small and selective. In a series from the Mayo Clinic, between 1957 and 1983, Gough and colleagues [28] reported a 52% 10-year survival in 56 patients who underwent serial debulking and selective intraperitoneal radiotherapy or chemotherapy.

The modern management strategy of CRS and HIPEC was developed and popularised by the work of Paul Sugarbaker and colleagues at the Washington Cancer Institute [29]. In 1999 Sugarbaker et al. [21] published a series of 385 patients, 205 of which received HIPEC. Complete cytoreduction was associated with 5 year survival of 80% compared to 20% in whom macroscopic tumour removal could not be achieved. What has come to be known as the “Sugarbaker procedure” is now the accepted standard of care with subsequent series confirming the efficacy of CRS and HIPEC. Disease or progression free survival of 75%, 56-70% and 67% at 1 year, 5 years and 10 years respectively and overall survival of 69-75% at 5 years, 57% at 10 years have been reported [22,30-33].

Completeness of cytoreductive surgery is a major predictor of outcome independent of histological grade. The completeness of cytoreduction is assessed after surgery with no visible tumour is graded as CC-0 and residual disease and with no nodule greater than 2.5mm as CC-1. Residual disease nodules between 2.5mm and 2.5cm correspond to CC-2 and greater than 2.5cm CC-3 [34]. Scores of CC-0 and CC-1 are taken to represent complete cytoreduction with significantly better reported outcomes than seen in patients with CC-2 or CC-3 residual disease.

With an incomplete cytoreduction (CC-2 and CC-3), or major tumour debulking, the 5 year survival was 24%. This is compared with 85% in patients with CC-0 and 80% with CC-1 complete cytoreduction [23]. The ability to achieve a complete cytoreduction may depend upon the extent of disease and histological grade. As previously discussed, involvement of the small bowel and mesentery remain the major limiting factors. Previous surgery, particularly attempts at partial debulking, can reduce the chances of complete cytoreduction with compromise of the natural peritoneal barrier and entrapment of tumour within scar tissue and adhesions [35].

Although complete cytoreduction is the optimal treatment, where it is not possible, maximal tumour debulking, usually involving a greater omentectomy, colectomy and end ileostomy can produce good palliative results and even long term survival in a small number of patients. In a recent series, Dayal et al. [5] reported 748 consecutive patients who underwent surgery for PMP in Basingstoke, 205 of whom received maximal tumour debulking. Overall survival was 47%, 30% and 22% at 3, 5 and 10 years compared with 90%, 82% and 64% in those who received complete cytoreduction.

Morbidity and mortality

CRS and HIPEC is a complex surgical intervention and carries a significant risk of complications including anastomotic leakage, intra-abdominal abscesses, small bowel and pancreatic fistulae, respiratory infections and venous thromboembolism. Operating times are long, averaging around 9 hours and can result in significant blood loss. Neutropenia and associated sepsis are recognised complications of intraperitoneal chemotherapy.

Reoperation rates for post-operative complications have been reported to range from 11% [56] to 21% [57] and 30 day mortality from 0% to 14% [58].

It is now clear that the learning curve for surgical units performing complex procedures like CRS and HIPEC can have a major impact on outcomes [39]. Initial high morbidity and mortality is seen to decrease with increasing experience and this is likely to represent improvement in patient selection and postoperative management as well as surgical expertise.

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Follow-up

The rational for active follow-up is the ability to detect and treat recurrent disease. Elective reoperation for recurrent disease is beneficial for selected patients. Esquivel and Sugarbaker [40] reported 5 year survival of 74% in selected patients with recurrent PMP of appendiceal origin who underwent repeat CRS and HIPEC. Mohamed et al. [41] reported 5 year survival of 70% from the initial operation in selective patients who had 3 or more attempts at CRS and HIPEC.

Our practice involves CT scanning and serum tumour markers at one year post-operatively and annually thereafter for 10 years. Earlier imaging can be employed if symptoms develop or a high suspicion of recurrence exists. This strategy has developed due to the fact that early recurrence after complete cytoreduction is likely to represent aggressive, rapidly progressive disease, unlikely to be amenable to salvage surgery. In early recurrent disease and particularly in high grade PMP, systemic chemotherapy is advocated by some although strong evidence is lacking.

Patients likely to benefit from further CRS and HIPEC are those with slowly progressive disease. As such, a policy of watch and wait can be employed with low volume or stable recurrence with the option of reoperation with evidence of progression or development of symptoms.

The optimal strategy for follow-up has yet to be defined and as the experience from large international units develops and the follow-up data matures this will provide fertile ground for future research.

Conclusions

Pseudomyxoma peritonei is an uncommon condition that classically originates from a ruptured mucinous appendiceal neoplasm. It is, at best a borderline malignancy and with a spectrum of disease from low grade to high grade and adenocarcinoma. The optimal treatment for PMP is complete cytoreduction combined with hyperthermic intra-peritoneal chemotherapy. This is a major surgical intervention and requires careful patient selection and perioperative management to minimise morbidity and mortality and should be performed in experienced centres.

The treatment PMP has become a model for other peritoneal malignancies, particularly peritoneal mesothelioma and selected patients with colorectal peritoneal metastases.

References

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