Reminder of important clinical lesson

Perforated mucinous cystadenoma of the vermiform appendix: an overview in reasoning clinical decisions

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Summary

Recent advances in the management of appendiceal mucinous neoplasms (AMN) such as peritonectomy combined with hyperthermic intraperitoneal chemotherapy have introduced new standards of care. However, many dilemmas are encountered in decision making as in the following patient. A 74-year-old woman was admitted with an appendiceal cystadenoma found in a preadmission CT scan. However, the tumour was not documented by the in hospital investigation due to its perforation and its reduction in size. Consequently, a series of management dilemmas were encountered that were solved by cautious evaluation of the pre and peroperative findings. She was submitted to a right hemicolectomy. A spontaneous perforation was suspected, but the accurate diagnosis was documented postoperatively by histopathology. This paradigm motivated this review which concluded that reasoning clinical decisions in the light of recent advances and appropriate care based on the disease-stage are essential for an optimal outcome in the management of AMN.

BACKGROUND

The biology of appendiceal mucinous neoplasms (AMN) as well as the appropriateness with respect to operative procedures used in the treatment of AMN have both been controversial issues for a long time.¹ However, recent advances in the management of AMN have indicated prognostic factors and suggested new standards of care.²

The age-adjusted incidence of primary malignant appendiceal neoplasms including colonic-type adenocarcinoma, carcinoid, signet ring cell carcinoma and mucinous adenocarcinoma, is 0.12 patients per 1 000 000 people per year.³ The primary malignant appendiceal neoplasms represent 0.63% (196 of 31,341) of all colon malignancies.⁴

In a series of 198 patients with appendiceal adenocarcinomas, approximately 40% were mucinous and 60% were non-mucinous.⁵ Mucinous adenocarcinomas of the appendix represent 0.14% of a total 31 341 of colon malignancies.⁴

AMN are often presented as a mucocele which is a dilation of the appendix due to an intraluminal accumulation of mucoid material. In a retrospective study of 43 000 appendectomies performed from 1914–1938, the collective frequency of the so-called 'cystic tumours' of the appendix including 'mucoceles', 'adenomas' and 'mucoid cysts' was 0.3%.⁶ In another study of 50 000 appendiceal specimens from surgical appendectomies including postmortem samples of appendices published in 1955, the rate of 'mucoceles' was found to be 0.2%.⁷ Causes of obstruction of the appendiceal lumen in 'mucoceles' are mucosal hyperplasia (25%), mucinous cystadenoma (63%) and mucinous cystadenocarcinoma (12%).⁸

Despite its rarity, surgeons may encounter an AMN a few times, because appendectomies are common operations.

Moreover, AMN may present by a variety of signs and symptoms, at an early or advanced stage and in different clinical settings. Hence, many dilemmas in making clinical decisions are encountered in practice. An overview on reasoning clinical decisions is presented herein by the paradigm of a patient with AMN.

CASE PRESENTATION

A 70-year-old woman suffered an episode of acute lower abdominal pain accompanied with vomiting and diarrhoea which subsided spontaneously after 2–3 days. A residual pain associated with episodes of diarrhoea persisted and an investigation was begun by her family physician. She was referred to this surgical unit for treatment of a tumour mass of the right iliac fossa 3 months after the onset of symptoms. On admission, she was nearly asymptomatic with a mild tenderness on deep palpation of the right lower abdominal quadrant. A mild bilateral angle pitting oedema was also present.

Her medical history included hypertension over the previous 15 years and compensated chronic renal failure that were attributed to benign nephrosclerosis and focal glomerulonephritis diagnosed by two renal biopsies 5 and 4 years earlier, respectively.

INVESTIGATIONS

On admission, haemoglobin was 12.1 g/l, white blood cells $6.1 \times 10^9/l$, platelet count $239 \times 10^9/l$, C-reactive protein was normal (0.19 mg/l), blood urea nitrogen 110 mg/dl, creatinine 2.4 mg/dl, serum albumin 2.6 g/dl, and the 24-h loss of protein in the urine was 6.4 g. She also had metabolic acidosis with HCO_3^- at 21.2 mmol/l and a base excess of -5.6 mmol/l. The serum carcinoembryonic antigen (2.99 ng/ml) and carbohydrate antigen (CA) 19-9

Figure 1 CT scan showing a round, thin-walled, encapsulated mass, at the expected site of the appendix (arrows).

(2U/ml) were normal, but the CA-125 had risen to 87.1 U/ml (normal values are less than 35 U/ml).

An abdominal axial contrast material-enhanced tomography (CT scan) was performed 2 weeks after the onset of pain (3 months prior to admission) and showed a smooth round mass 3 cm in diameter and 5.3 cm long in the right iliac fossa tapering towards the pelvic brim that was interpreted as an appendiceal mass due to a 'mucocele', (figures 1 and 2).

A colonoscopy performed nearly 2 months prior to admission had shown an approximately 1.5 cm smooth and round projection at the expected origin of the appendix resembling the so-called endoscopic sign of a 'trapped balloon', (figure 3). An endoscopic biopsy showed inflammation with cryptitis and rare micro-abscesses. Incidental findings were three sigmoid polyps of 1 to 2 cm in size and multiple sigmoid diverticula.

On admission, the first dilemma was to interpret the vague clinical findings, CT scan, endoscopic and biopsy findings. To ascertain the initial diagnosis of a mucocele an ultrasound (US) scan was performed which showed a short (3 cm) appendix with a thickened wall but markedly reduced in relation to its size as was indicated by the CT scan (figure 4). The disparity between the US scan and CT scan findings led to performing MRI which did not show any tumour mass or distension of the appendix.

DIFFERENTIAL DIAGNOSIS

There were no clinical or imaging findings to support a pathology of the ovaries, tubes, uterus or an inflammatory bowel disease. The presentation was not typical of acute appendicitis. The colonoscopy and biopsy results were not typical of a caecal carcinoma.

The initial diagnosis was of appendiceal mucocele but a dilemma was raised by the reduction of its size. The endoscopic finding of 'trapped balloon' as well the initial findings of the CT scan in association with the residual abdominal pain were the arguments to proceed to surgery.

TREATMENT

The patient was submitted to an elective laparotomy by a midline incision. Less than half a litre of crystal-clear, free ascitic fluid was aspirated from the abdominal cavity. Its nature raised the next dilemma. The liver appeared normal and the ascitic fluid was attributed to her chronic renal failure. The collected fluid was sent for cytology and flow cytometry; however, we did not obtain the results until a few days later.

Peroperatively, the appendix appeared short with a thick wall and a few palpable intramural nodules at its base of less than 0.5 cm each in size, (figure 5). The appendiceal mesentery had moderately shrunk and thickened as was the ileo-caecal mesentery. A safe appendiceal stump could

Figure 2 CT scan showing distension of the appendix and projection of its tip to the pelvis (arrows).

not be achieved. Given that a mucocoele had initially been found by the CT scan which had substantially reduced in size, a preceding spontaneous perforation of the mucocoele was hypothesised. The extent of required resection was the next dilemma. A right hemicolectomy was performed in the presence of the described findings.

Cytology as well as flow cytometry of the ascites did not show any pathology. The formalin-fixed appendix was 3 cm long and 1 cm wide. At its base, a circumferential 0.7 cm tumour was found obstructing the appendiceal orifice, (figure 6). Microscopy showed that this was a cystadenoma of the appendix with low-grade and focal high-grade intraepithelial neoplasia with abandoned extracellular mucus

and without infiltrative invasion of the appendiceal wall, (figure 7). Interestingly enough, a focal covered microscopic perforation of the appendix was confirmed and was associated with findings of localised peritonitis at its mesentery, (figure 8). Reactive changes but no metastases were found in the 14 lymph nodes of the resected specimen.

OUTCOME AND FOLLOW-UP

Postoperative recovery was uneventful and the patient was discharged after 6 days. A week later, she was readmitted with non-specific abdominal pain, remained for a 5-day observation and was discharged again. The multidisciplinary oncology meeting recommended a long-term

Figure 3 Colonoscopy: smooth round projection of the base of the appendix previously described as a 'trapped balloon' which is an endoscopic sign of a mucocoele (arrows). The blood clot resulted from a biopsy.

follow-up. The endoscopically resected colonic polyps, 2 months following the laparotomy, were histologically confirmed as adenomas. She has remained well over the last year.

DISCUSSION

Histological typing of AMN by the World Health Organisation includes mucinous cystadenoma and mucinous cystadenocarcinoma,⁹ but controversy still exists with respect to the biology and prognosis of AMN. Nevertheless, their management has been highlighted over the last two decades.

PRESENTATION

The presentation of AMN is variable.¹⁰ In a series of 45 patients with AMN, 37.8% presented as acute appendicitis, 20% were an incidental finding, 17.8% presented with non-specific tumour-related symptoms and 24.4% were referred for additional surgery for advanced AMN.⁴ AMN are often presented as mucocoeles caused by cystadenomas or cystadenocarcinomas and are usually large, measuring up to 6 cm in width.¹¹ Cystadenomas are often presented as mucocoeles with a diameter greater than 2 cm.¹⁰ A high incidence of perforation (55%) is reported in appendiceal adenocarcinoma.⁵ Spontaneous perforation with resolution of the 'tumour mass' of the right iliac fossa was the main pitfall in the management of the presenting patient. Synchronous abdominal metastases at presentation are encountered in 28.9% of patients with mucinous appendiceal adenocarcinoma.⁴

Mucinous appendiceal adenocarcinomas are also associated with synchronous colonic adenocarcinomas with reported rates at 8.9%⁴ and 11%.¹⁰ Interestingly enough, the patient presented in this study had three sigmoid adenomas.

In addition, patients with mucinous tumours of the ovaries often have mucinous tumours of the appendix, and it has been reported by some authors that ovarian tumours are probably secondary to an appendiceal tumour.¹²

PREOPERATIVE IMAGING

Preoperative imaging may help in the differential diagnosis of a mucocoele of the appendix from acute appendicitis. It also helps to plan the surgical approach in advanced stages of AMN.

Abdominal plain radiography may indicate a soft-tissue mass in the right lower abdominal quadrant.

Abdominal US scan may show a cystic appendiceal distension with fluid content of variable echogenicity attributable to contained mucus. A 'chicken drumstick' stratified appearance¹³ or 'onion skin-like' circles are considered characteristic signs of a mucocoele.¹⁴ An appendiceal outer diameter more than 1.5 cm documented preoperatively by ultrasonography is highly predictive of a mucocoele rather than of acute appendicitis.¹⁵

CT scan or MRI is needed for evaluating the extent of the disease. An appendiceal mucocoele may appear as a round, low-density, thin-walled encapsulated mass, in continuity with the caecum.¹³ Curvilinear mural calcification is highly suggestive of this diagnosis but is seen in fewer than 50% of cases.¹³

Figure 4 Ultrasound scan indicating the thick wall of the appendix (arrows).

Colonoscopy may show a smooth, mucosal projection at the expected base of the appendix that follows the patient's respiratory movements, a sign known as a 'trapped balloon'¹⁶ as was evident in the presenting patient, or the 'sign of the volcano', consisting of a soft mass with a central crater discharging mucus,¹⁷ (figures 3 and 6).

SURGICAL MANAGEMENT

Surgeons often have to treat a patient with AMN without knowing of its presence preoperatively and in the absence of any histology, cytology or imaging findings. Hence, clinical dilemmas may arise because proper management is critical to avoid iatrogenic peritoneal dissemination.¹⁰ The morbidity and mortality associated with both cystadenoma and cystadenocarcinoma arise from spontaneous or perioperative rupture and intraperitoneal spread of mucin-producing epithelium. It is recommended that mucocoeles with a diameter greater than 2 cm should be removed to eliminate premalignant lesions.¹⁰ A complete surgical excision of an intact mucocoele presents no future risk for the patient.¹⁸

Patients with benign neoplastic mucocoeles have shown 5-year survival rates of 91–100%, even in cases with extension of mucus into the extra-appendiceal spaces.¹⁹ It has also been reported by other authors that the presence of perforation does not necessarily lead to a poor prognosis.⁵

Open laparotomy and not a laparoscopic procedure is recommended by some authors²⁰ to minimise the risk of rupture, to thoroughly explore the peritoneal cavity, to harvest any fluid from the peritoneal cavity or to perform lavage for cytological examination.

An earlier study recommended a right hemicolectomy for the treatment of AMN.²¹ However, prospective data have shown²² that there is no survival advantage by performing a routine right hemicolectomy in treating appendiceal mucinous carcinomas. AMN can metastasise to regional lymph nodes, but this is not a common event.

Peri-appendiceal, meso-appendiceal or ileocolic lymph nodes are involved in 20.8% of nodes assessed histologically throughout the course of the patients' disease.²² Right hemicolectomy should be performed if it is necessary to clear the primary tumour or achieve complete cytoreduction and if lymph node involvement is demonstrated by histopathological examination of the appendiceal or ileocolic lymph nodes. Another indication for a right colectomy is the tumour positive margin at the appendectomy site.²² It seems that haematogenous spread does not occur.

PSEUDOMYXOMA PERITONEI

Perforation of 'mucocoeles', may result in the dissemination of cells with low-grade dysplasia or with high-grade dysplasia in the peritoneal cavity despite the fact that appendiceal mucinous neoplasms frequently lack classic, infiltrative invasion of the appendiceal wall yet manage to seed the peritoneum.²³ In a series of 19 patients with pseudomyxoma peritonei, confirmed by malignant epithelium in peritoneal implants, 75% had mucinous cystadenomas of the appendix as the primary lesion.²⁴ With respect to pseudomyxoma peritonei, controversy as to whether the epithelium is adenomatous or carcinomatous (i.e. derived from a ruptured adenoma or an invasive carcinoma) still persists.²⁴

Improved long-term survival is reported in patients with pseudomyxoma peritonei of low-grade tumours.²⁵

Progression to pseudomyxoma peritonei is often indolent and not readily diagnosed. Approximately one third of patients with pseudomyxoma peritonei presented as appendicitis (20–34%), increasing abdominal girth (19–27%), ovarian mass (39% of women), ascites (4–5%) and abdominal pain (3–5%).²⁶

It has been reported that appendiceal adenoma with peritoneal seeding in the absence of specialised treatment is eventually fatal.²⁷ AMN primarily involve the parietal and visceral peritoneal surfaces. The greater omentum is

Figures 5 A segment of the freshly opened surgical specimen showing opaque globules of mucous in the lumen of the appendix, a flat and atrophic appearance of the mucosa, a thick and fibrotic wall and a nodular appearance at the base of the appendix (arrows).

Figure 6 Photograph of the opened specimen focusing on the base of the appendix and showing obstruction of its stoma. Compare to the endoscopic view of figure 3 and CT scan of figure 1.

commonly and extensively thickened by tumour invasion that is described as ‘omental cake’. Although a large volume of mucinous neoplasm fills the peritoneal cavity, it does not invade the liver and spares the small bowel. Sparing of the small intestine has been attributed to its

constant mobility. This pattern of spreading often permits aggressive locoregional surgical treatment.²⁸

The advocated standards of treatment strategy of pseudomyxoma peritonei consist of cytoreductive surgery with peritonectomy to eliminate all visible tumour

Figure 7 Photomicrograph showing the deeply-stained appendiceal cystadenoma (arrows), haematoxylin–eosin x 200.

Figure 8 Photomicrograph showing mucoid material (blue asterisks) in the surrounding the appendix fatty tissues (red asterisks), and reactive type changes indicating microscopic perforation, haematoxylin–eosin x 40.

in the abdomen and pelvis combined with perioperative hyperthermic intraperitoneal chemotherapy.² Long-term survival of patients with pseudomyxoma peritonei can be achieved by combined surgery and hyperthermic intraperitoneal chemotherapy with acceptable morbidity and

mortality.^{27–31} Cytoreductive surgery and peritonectomy combined with perioperative intraperitoneal hyperthermic chemotherapy are not readily feasible in many surgical settings. Hence, regionalised multi-disciplinary specialising centres should be established. Despite recent advances,

the biology²⁷ of AMN is still not completely understood and guidelines for long-term follow-up are sparse.

In conclusion, awareness of recent advances, clinical reasoning and preparedness to individualise care remain important factors for a good outcome in patients with appendiceal mucinous neoplasms.

Learning points

- ▶ Appendiceal mucinous cystadenoma:
- ▶ A futureless presentation, highly diagnostic CT scan, colonoscopic sign of 'trapped balloon', coexistence of distinct sigmoid adenomas and obstruction of the base of the appendix by the cystadenoma were documented.
- ▶ Consecutive radiological imaging showed a reduction of the size of a 'mucocoele', due to its perforation. Microscopic perforation was documented by histology.
- ▶ Spontaneous rupture of the cystadenoma was the main pitfall in decision making.
- ▶ Clinical decision reasoning and preparedness to individualise care according to recent advances remain important factors for a good outcome.

Competing interests None.

Patient consent Obtained.

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