“The Jelly Belly”: Diagnostic Dilemmas and Current Concepts

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Abstract

Background Pseudomyxoma peritonei (PMP) is a rare and poorly understood clinicopathological entity characterized

by gelatinous ascites with neoplastic or non-neoplastic mucinous implants in the peritoneum. Although its origin was debated, current evidence in literature favours the appendix as the origin of the disease, over the ovaries. The changing terminologies in the classification of this entity pose diagnostic and management challenges.

Case Reports Herein, we report three cases of PMP in postmenopausal women, their clinical presentation, pathological staging based on the peritoneal tumor deposits and the treatment administered. Two patients recovered uneventfully, while one had recurrence of adenocarcinoma. **Conclusion** The rarity of this disease and the diagnostic challenges associated with it are discussed with an emphasis on the current concepts in its origin and management. Appropriate classification and complete removal of the tumor is mandated to prevent disease-related mortality.

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Introduction

Pseudomyxoma peritonei (PMP) is an enigmatic intra-abdominal disease characterized by epithelial implants secreting extracellular mucin resulting in dissecting gelatinous ascites [1]. PMP is a clinical terminology rather than a pathological diagnosis. The primary neoplasms producing PMP may be benign or malignant and their origin has been debated, until recent studies have attributed it to primary appendiceal mucinous neoplasms [2–4]. It may also originate from other mucinous neoplasms throughout the gastrointestinal tract [5]. The ovaries usually represent secondary involvement. The pathological diagnosis and classification of PMP has posed much debate. It was classified into disseminated peritoneal adenomucinosis (DPAM) and peritoneal mucinous carcinomatosis (PMCA) based on cellularity, epithelial atypia and mitotic activity which presented much subjective ambiguity [6, 7]. According to the current AJCC and WHO classification, any neoplastic mucinous epithelium in the appendiceal wall and beyond is a mucinous adenocarcinoma. This can be further classified as invasive, low grade or high grade, based on the WHO AJCC 2010 classification [6]. The treatment options range from cytoreductive surgery to hyperthermic intraperitoneal chemotherapy (HIPEC) with varied prognosis [7, 8].

Case Reports

Case 1

A 75-year female presented with abdominal distension and loss of appetite for 2 months. On ultrasonography, a large, multiloculated cystic lesion measuring $15 \times 12 \times 16$ cm was noted in the pelvis. Investigations revealed an elevated CEA (923 ng/ml) and mildly elevated CA 125 (51 U/ml). Intraoperatively, the peritoneal cavity was filled with gelatinous material, a large mucinous tumor (with ruptured capsule) replacing the left ovary and an enlarged appendix. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, retro peritoneal lymph node dissection was done along with appendectomy. The samples were sent for histopathological examination.

Histopathology of the left ovarian mass revealed a mucinous tumor with borderline features composed of multiple mucin filled cysts lined by multilayered mucinous epithelium. There was no evidence of atypia or invasion. The intervening fibroblastic stroma showed dissecting pools of mucin (Fig. 1). The right ovary was atrophic. The cut surface of the appendix revealed mucinous material. The sections of the appendix revealed a mucinous neoplasm with minimal atypia. The mucin was dissecting

between muscularis propria and extending up to the serosa, suggestive of rupture (Fig. 2). The omentum showed mucin pools with scanty epithelial fragments (Fig. 3). Hence, a diagnosis of low-grade mucinous adenocarcinoma of the omentum, secondary to a low-grade mucinous neoplasm of the appendix along with borderline mucinous tumor of the left ovary, was rendered. This was called diffuse peritoneal adenomucinosis of appendiceal origin, according to the earlier classification by Ronnett et al. The retroperitoneal lymph nodes showed no metastasis. The uterine cervix, endometrium and right ovary showed no mucin, although the parametria, serosal aspect of the uterus and right fallopian tube showed mucoid material with inflammation. The postoperative period was uneventful, and the patient was put on adjuvant chemotherapy.

Case 2

A 54-year female presented with loss of appetite and abdominal distension. Ultrasonogram revealed bilateral ovarian cystic masses. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy was performed after an intraoperative frozen section biopsy which revealed borderline mucinous ovarian tumors of both ovaries. The omentum and uterine serosa had mucinous deposits with epithelial cells. This was consistent with a diagnosis of PMP. A history of appendectomy was not recovered from the medical records, nor was the specimen of appendix received; therefore, the status of the appendix was unknown. The patient returned 2 years later with abdominal distension, deposits on the intestinal wall, highly suspicious for a recurrent malignancy. The deposits were sent for histopathological analysis which showed a high-grade mucinous adenocarcinoma. On immunohistochemistry, the epithelial cells displayed diffuse strong positivity for CK 20 and focal positivity for CK7 supporting gastrointestinal origin as the primary.

Case 3

A 44-year female patient presented with abdominal discomfort and severe backache since 3 months. Blood investigations revealed elevated CEA (153 ng/ml) and CA125 (94 U/ml). Radiological investigations showed a large, well-defined, multiloculated, cystic lesion with internal septations arising from the pelvis and extending intra-abdominally with free fluid in the abdomen and multiple omental nodules. Intraoperatively, there was a right adnexal mucinous tumor with breached capsule (Fig. 4). The appendix had a ruptured base and was distended with mucinous material (Fig. 5). Multiple peritoneal mucinous deposits were present in the greater and lesser omentum, liver, lesser sac and hilum of spleen, the

Fig. 1 Ovary showing a mucinous tumor with borderline features and multilayered mucin-secreting epithelial cells

Fig. 2 Appendix showing a low-grade mucinous neoplasm with mucin dissecting through the muscularis propria

largest deposit measuring 3 × 4 cm. Surgical debulking was done with residual disease of about 2 cm in greatest dimension, around the liver and inferior vena cava. Histopathology analysis revealed a mucinous neoplasm of the right ovary and mucinous cystadenoma of the appendix, both with evidence of rupture. Peritoneal deposits with dissecting mucin and islands of benign mucinous epithelium compatible with a diagnosis of DPAM (Ronnett [3]) and low-grade mucinous adenocarcinoma of the appendix (AJCC/WHO [6]). The patient is on adjuvant 5-FU chemotherapy.

The clinicopathological characteristics of the three patients are summarized in Table 1.

Fig. 3 Mucin pools dissecting through the omentum with low-grade neoplastic epithelial cells

Fig. 4 Ovary showing a mucinous tumor with capsular breach

Fig. 5 Cut surface of the distended appendix showing mucinous material. *Inset* appendix distended with mucin before sectioning

Table 1 Clinicopathological characterization of the three patients with PMP

Case and year of diagnosis	Age in years	Symptoms	Histopath of ovary	Appendix status	Peritoneum	Treatment	Tumor recurred	Ronnett (1995)	WHO AJCC (2010)
1. 2009	75	Abdominal distension Loss of appetite	Mucinous tumor with borderline features, left ovary	Low-grade mucinous neoplasm	Mucin with low-grade epithelium	Surgical Debulking	No	DPAM	Low-grade mucinous adenocarcinoma
2. 2001	54	Loss of appetite Abdominal distension	Borderline mucinous cystadenoma, bilateral ovaries	Not known	Mucin with low-grade epithelium	Surgical Debulking	Yes, in 2003, metastatic mucinous adenocarcinoma deposits on intestinal wall	PMCA	High-grade mucinous adenocarcinoma
3. 2013	44	Abdominal discomfort Severe backache	Mucinous neoplasm right ovary with evidence of Pseudomyxoma ovarii	Mucinous cystadenoma	Dissecting mucin with islands of benign mucinous neoplasm	Surgical Debulking and postoperative chemotherapy	No	DPAM	Low-grade mucinous adenocarcinoma

Table 2 Classification of appendiceal mucinous neoplasms and pseudomyxoma peritonei [6]

	Ronnett et al. [3]	AJCC and WHO [6]
Tumor confined to appendix		
Limited to mucosa	NA	Adenoma
Low-grade/high-grade cytology	NA	Adenoma
Positive surgical margin	NA	Adenoma
Neoplastic epithelium in appendix wall	NA	Invasive Mucinous Adenocarcinoma
Tumor beyond appendix		
Low-grade epithelium in peritoneal mucin	Disseminated peritoneal adenomucinosis (DPAM)	Low-grade mucinous adenocarcinoma
High-grade epithelium in peritoneal mucin	Peritoneal mucinous carcinomatosis (PMCA)	High-grade mucinous adenocarcinoma

Discussion

PMP is a diagnostically challenging disease with poor response to chemotherapy and frequent recurrences [7, 8]. The term introduced by Werth [1], meaning a “false mucinous tumor of the peritoneum,” is characterized by mucinous ascites with peritoneal and omental neoplastic implants. It is discovered incidentally intraoperatively in about 1 in 10,000 laparotomies [9]. The origin of PMP was much debated due to the involvement of both ovaries and appendix in a majority of female patients, but the appendiceal origin of most PMPs is undoubtedly confirmed [2–4]. Firstly, as most studies involved a fraction of male patients who developed PMP and in females, the ovarian involvement was usually right-sided in the vicinity of the appendix or bilateral. One of our cases was right-sided, one was bilateral and one was left-sided but with an atrophic right ovary suggesting the possibility of mucinous degeneration/postrupture atrophy of the right ovary. Secondly, immunohistochemical evidence proves

that the peritoneal tumor and ovarian tumors had an immunoprofile similar to that of appendiceal mucinous tumors. A study revealed that expression of CK7, CK 18, CK 20, CEA, HAM-56 of the ovarian neoplasms with PMP was similar to the appendiceal tumors but were unlike the control group of ovarian mucinous tumors without PMP [10]. Further studies show that the extra-cellular mucin-secreting goblet cells in PMP express MUC-2 which is similarly expressed by mucinous tumors of the appendix further supporting an appendiceal origin [11]. Molecular analysis of the neoplastic cells demonstrated identical K-ras mutations in both the ovarian and appendiceal neoplasms. Further, loss of heterozygosity occurred in both the appendiceal and ovarian neoplasms in all cases except for one where there was preservation of both alleles in the appendix [12, 13]. This was attributed to a loss of heterozygosity as a part of tumor progression by the ovaries. Appendiceal primaries can be neoplastic or non-neoplastic [6]. Ovarian involvement is usually secondary.

PMP was originally classified by Ronnett et al. as DPAM and PMCA [6–9]. It is currently classified as mucinous adenocarcinoma: low grade and high grade (WHO and AJCC 2010) [6] (Table 2).

Prognostication is based on the following factors:

1. Histological type [4, 6, 7, 14] with low-grade tumors (DPAM according to older classification) having a better prognosis than high-grade tumors (PMCA).
2. Completeness of cytoreduction (CCR) score [7, 8], i.e., removal of all gross disease, as assessed by Chua et al. study [15]. When no residual disease remained, the CCR score was 0. When no nodule >2.5 mm in diameter remained, score 1 was assigned. When gross residual disease remained, it was score 2 or 3. The 5-year overall survival revealed patients with CCR score 0 had significantly better disease-free survival.

Surgical debulking remains the main stay of treatment with role of hyperthermic intraperitoneal chemotherapy (HIPEC) being assessed in terms of morbidity, mortality, efficacy and long-term survival [7, 8, 16, 17].

Conclusion

PMP still remains a difficult disease entity to diagnose both clinically and histopathologically. With recent evidences in the literature suggesting appendiceal origin for PMP, a thorough search should be made and appendix removed for histopathological examination in all cases of PMP. Although the grade of malignancy can be assessed on hematoxylin- and eosin-stained slides, the immunohistochemical origin confirmation with markers specific to appendix should be attempted wherever feasible. Appropriate classification with the recent terminology proposed by AJCC/WHO is mandated to get uniformity in disease classification across the globe. Although the role of HIPEC in disease management is controversial, an attempt at complete removal of the tumor to achieve CCR score 0 is mandated to prevent disease-related mortality.

Compliance with Ethical Standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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