Review Article

Pseudomyxoma peritonei usually originates from the appendix: a review of the evidence

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Summary

Pseudomyxoma peritonei (PMP) is a rare condition, said to be more common in females during the fourth or fifth decade of life with an incidence believed to be in the region of one per million per year. Although PMP has been reported as originating from many intra-abdominal organs, in the majority of cases an ovarian or appendix cystadenoma or cystadenocarcinoma has been implicated as the primary site. Our experience suggests that most cases arise from the appendix. We have reviewed the clinical and scientific evidence. In the four largest reported series of 393 patients, 181 (46%) were males. Immunohistochemistry techniques in women with both appendical and ovarian tumours favour an appendiceal primary in most cases. The distinction between "benign" adenomucinosis and mucinous adenocarcinoma is important in both treatment and prognosis. Experience suggests that there may well be a spectrum of disease and possibly an "adenoma carcinoma sequence".

Key words: Pseudomyxoma peritonei; Origin; Gender distribution.

Introduction

Pseudomyxoma peritonei (PMP) is a rare condition, with a reported incidence of approximately one case per million per year, in which diffuse collections of gelatinous fluid are associated with mucinous implants on the peritoneal surface. The term "jelly belly" has been used to describe the large accumulation of mucinous ascites so typical of this condition. Despite its relatively benign behaviour and a better understanding of its aetiology and prognostic features, the long-term survival in most patients with PMP remains poor with a reported five to ten year survival rate of 50% and 10-30%, respectively [1]. Controversy has always existed as to the precise origin of PMP.

Werth [2] in 1884 coined the term pseudomyxoma peritonei when he described the condition in association with a mucinous carcinoma of the ovary. The term pseudomyxoma referred to chemical differences from other types of mucin that had been histologically analysed. In 1901 Frankel [3] described a case of Pseudomyxoma peritonei in association with a cyst of the appendix. Since these early reports there has been ongoing uncertainty as to the primary origin of this rare tumour in women. While most authorities acknowledge that the condition predominantly originates in the appendix in men [4], debate remains as to whether the origin of most cases in females is the ovary or the appendix. Synchronous disease is found at these two sites in most females with the condition, and the disease is reported to be more prevalent in females [1].

The most common mode of presentation is progressive abdominal distension and appendicitis in males, while females often present with abdominal distension and ovarian masses [4]. In addition to the association of PMP with appendiceal and ovarian tumours, there are case reports suggesting occasional origin from other intra-abdominal organs such as the colon and rectum [5], small intestine and urinary bladder [5], lung [6], breast [7], gallbladder and bile ducts [8], stomach [9], fallopian tube [10], and pancreas [11]. These are rare and account for less than 5% of the total cases. A similar clinical, radiological and surgical presentation can be seen in disease originating from colonic adenocarcinoma, particularly of mucinous type. Indeed this adds to many of the difficulties in managing this condition. It would appear that mucinous peritoneal deposits, in the absence

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of other systemic spread to the lymphatics or liver via the blood stream, is not uncommon and can simulate pseudomyxoma peritonei. This clinical presentation has led to ongoing confusion and it becomes impossible to interpret many reports in the literature, often with small numbers of cases being reported.

Paul Sugarbaker, one of the leading authorities on this condition, has stated that 'the term pseudomyxoma peritonei syndrome be strictly applied to a pathologically and prognostically homogeneous group of cases characterised by histologically benign peritoneal tumours that are frequently associated with an appendiceal mucinous adenoma' [4]. Ronnett *et al.* [12] have categorized the tumours into three broad groups, namely adenomucinosis, a hybrid group and a mucinous adenocarcinoma, with operability and prognosis heavily dependent on the histological type. In our opinion, there is a spectrum of disease ranging from adenomucinosis to adenocarcinoma, and we have found it difficult to categorize most patients with this disease into distinct groups. We believe that pseudomyxoma peritonei usually originates as an adenoma in the submucosa of the appendix. The adenoma ruptures and results in the release of mucin and cellular material into the peritoneal cavity. In many cases appendicular adenoma perforation is an occult event which is not diagnosed clinically, with the rupture resealing. This phenomenon of repeated perforation and resealing often results in scarring of the appendix which can sometimes be detected histologically. In women with synchronous tumours of the appendix and ovary, there are a number of theoretical possibilities. The appendiceal tumour could be a secondary from an ovarian primary; the ovarian tumour could originate from the appendix (Figure 1) or both tumours could be synchronous individual primaries. In an attempt to elucidate the origin of pseudomyxoma peritonei, particularly in women, we present a review of the available scientific and clinical evidence.

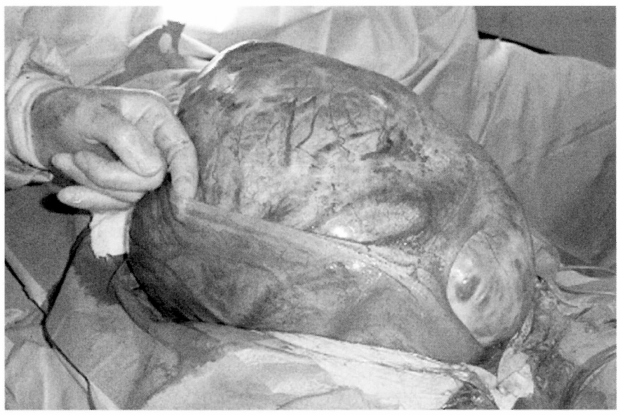

Figure 1. — A 38-year-old woman who had had a right hemicolectomy for ruptured mucinous cystadenoma of the appendix in 1999 presented three years later with progressive abdominal distension. Laparotomy revealed a huge ovarian mass and classical distribution of pseudomyxoma peritonei. Complete cytoreduction was achieved in eight hours.Histology and immunohistochemistry suggests that the ovarian tumour was secondary to an appendiceal primary.

Scientific evidence

Women with PMP often have synchronous ovarian and appendiceal tumours. There has been considerable debate as to whether the ovarian tumours are secondary to the appendiceal tumour or are independent primary ovarian tumours; the latter are usually classified as mucinous tumours of low malignant potential. Various studies using immunohistochemistry and molecular genetic techniques have recently attempted to clarify the origin of PMP. Ronnett *et al.* [12] used immunohistochemistry techniques in an attempt to identify the origin of PMP in females. The scientific basis for the study was that nearly all ovarian mucinous low malignant potential (MLMP) tumours and mucinous carcinomas stain positively for cytokeratin (CK) 7, 18 and 20, as well as CEA and human alveolar macrophage 56. Most colorectal adenocarcinomas are positive for CK20 and CEA but negative for CK 7 and human alveolar macrophage 56. In a total of 13 cases of PMP, appendiceal mucinous adenomas and ovarian tumours from the same patients were stained for these antigens. They concluded that most ovarian tumours in PMP are immunophenotypically identical to the associated appendiceal tumours and distinct from ovarian MLMPs. Young *et al.* [13] undertook a similar study analysing clinical and histological features in 22 cases of PMP with both appendiceal and ovarian disease.

They concluded that ovarian tumours are often

Table 1. — *Sex distribution in published clinical services.*

Centre	Number of cases with PMP	Males	Females
Washington Hospital Cancer Centre [4]	217	105 (48%)	112 (52%)
Pseudomyxoma Unit Basingstoke [18]	74	37 (50%)	37 (50%)
Amsterdam Centre Series [16]	46	19 (41%)	26 (59%)
Mayo Clinic Series [17]	56	20 (36%)	36 (64%)

secondary to primary appendiceal lesions. Prayson *et al.* [14] reached the same conclusion from their analysis of 17 cases. In contrast, Chuaqui *et al.* [15] using similar techniques, concluded that in women with synchronous appendiceal and ovarian mucinous tumours, the ovarian disease represented second primaries.

Clinical evidence

While it has generally been stated that PMP is much more common in women, it is impossible to know whether this simply represents under-diagnosis in men. Our experience has been that women tend to have an earlier diagnosis due to the awareness that painless abdominal distension could represent ovarian pathology and therefore there is a low threshold for abdominal imaging in females. Men often present later and are often categorized as diffuse carcinomatosis of unknown primary. Anecdotally many have negative gastroscopy and colonoscopy and it is quite remarkable that practically all who undergo surgery have a primary tumour, often adenocarcinoma, of the appendix. It would be reasonable to speculate that there is unlikely to be huge differences in the pathological behaviour of the appendix in females as compared to males. An analysis of the male/female distribution of case series might shed some light on the subject. Esquival and Sugarbaker [4] recently reported their experience with 217 cases of PMP, where 105/217 (48%) were males. Similarly, in Basingstoke, of 74 cases of PMP undergoing cytoreductive surgery, 37/74 (50%) were males and the majority of female patients had appendiceal adenomas either removed at prior surgery or during their cytoreductive surgery [18].

Series from Amsterdam [16] and the Mayo Clinic [17] report similar sex distributions. Although the Mayo group had a higher proportion of females (64%), when resected specimens were subjected to histological examination, over half of these had a primary tumour originating in the appendix.

Conclusion

There is increasing evidence, both scientific and clinical, to suggest that pseudomyxoma peritonei predominantly originates as an adenoma in the submucosa of the appendix. The presentation of PMP in females with ovarian masses most likely results from transcoelomic spread to the fertile environment of the ovary.

Most detailed scientific studies have shown that when appropriate staining techniques are employed, the appendix is the most likely primary site of origin for pseudomyxoma peritonei. The reported case series support the theory of an appendiceal origin in that the male/female distribution is similar. As the ovary cannot be responsible in males, logic would suggest that the appendix might well account for most cases in females also.

From a practical viewpoint, all females undergoing surgery for pseudomyxoma peritonei should have the appendix removed, even if it is macroscopically normal. Histological analysis will usually confirm an appendiceal adenoma and immunohistochemical staining and genetic analysis may then elucidate the origin.

References

[1] Hinson F.L., Ambrose N.S.: "Pseudomyxoma peritonei". *Br. J. Surg.,* 1998, 332.
[2] Werth R.: "Klinische and Anastomische Untersuchungen Zur Lehre von der Bauchgeschwullsten and der Laparotomie". *Arch. Gynecol. Obstet.,* 1884, *24,* 100.
[3] Frankel E.: "Uher das sogenanute Pseudomyxoma peritonei". *Med. Wochenschr.,* 1901, *48,* 965.
[4] Esqviel J., Sugarbaker P.H.: "Clinical presentation of Pseudomyxoma peritonei syndrome". *Br. J. Surg.,* 2000, *87,* 1414.
[5] Costa M.J.: "Pseudomyxoma peritonei. Histologic predictors of patient survival". *Arch. Pathol. Lab. Med.*, 1994, *118*, 1215.
[6] Kurita M., Komatsu H., Hata Y., Shiina S., Ota S., Terano A. *et al.*: "Pseudomyxoma peritonei due to adenocarcinoma of lung: case report". *J. Gastroenterol.*, 1994, *29,* 344.
[7] Hawes D., Robinson R., Wira R.: "Pseudomyxoma peritonei from metastatic colloid carcinoma of the breast". *Gastrointest. Radio1.*, 1991, *16*, 80.
[8] Young R.H., Scully R.E.: "Ovarian metastasis from carcinoma of the gall bladder and extra hepatic bile ducts simulating primary tumour of ovary. A report of six cases". *Int. J. Gynecol. Pathol.*, 1990, *9,* 60.
[9] Ikejiri K., Anai H., Kitmura K., Yakabe S., Saku M., Yoshida K.: "Pseudomyxoma peritonei concomitant with early gastric cancer: report of a case". *Surg. Today,* 1996, *26*, 923.
[10] McCarthy J.H., Aga R.: "A fallopian tube lesion of borderline malignancy associated with pseudomyxoma peritonei". *Histopathology,* 1988, *13,* 223.
[11] Chejfec G., Rieker W.J., Jablokow V.R., Gould V.E.: "Pseudomyxoma peritonei associated with colloid carcinoma of pancreas". *Gastroenterology,* 1986, *90,* 202.

[12] Ronnett B.M., Shmookler B.M., Diener-west M., Sugarbaker P.H., Kurman R.J.: "Immunohistochemical evidence supporting the appendiceal origin of Pseudomyxoma peritonei in women". *Int. J. Gynaecol. Pathol.,* 1997, 16, 1.
[13] Young R.H., Gilks C.B., Scully R.E.: "Pseudomyxoma peritonei". *Am. J. Surg. Pathol.,* 1993, *17,* 1068.
[14] Prayson R.A., Hart W.R., Petras R.E.: "Pseudomyxoma peritonei: A Clinopathologic study of 19 cases with emphasis on site of origin and nature of associated ovarian tumours". *Am. J. Surg. Pathol.*
[15] Chaqui R.F., Zhuang Z., Emmert-Buck M.R., Bryant B.R., Nogales F., Tavassoli F.A. *et al.*: "Genetic analysis of synchronous mucinous tumours of ovary and appendix". *Hum. Pathol.,* 1996, *27,* 165.
[16] Gough D.B., Donohue J.H., Schutt A.J., Gonchoroff N., Goellner J.R., Wilson T.O. *et al.*: "Pseudomyxoma peritonei. Long term patient survival with an aggressive regional approach". *Ann. Surg.,* 1994, *219,* 112.
[17] Witkamp A.J., de Bree E., Kagg M.M., Van Slooten G.W., Van Coevorden F., Zoetmulder F.A.N.: "Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with Pseudomyxoma peritonei". *Br. J. Surg.,* 2001, *88,* 458.
[18] Parvaiz A., Amin A.I., Howell R., Sexton R., Moran B.J.: "First one hundred referral predominantly of Pseudomyxoma peritonei to a peritoneal surface malignancy unit: Operability and early outcome". *Br. J. Surg.,* 2002, *89,* 3.

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