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**History of pseudomyxoma peritonei from its origin to the first decades of the twenty first century**

Morera-Ocon FJ *et al*. History of pseudomyxoma peritonei

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**Abstract**

Pseudomyxoma peritomei (PMP) is a disease wrapped up in misunderstanding and controversies. The terminology of that disease becomes ambiguous unless knowledge about the etimology is offered. Pseudomyxoma stands for pseudomucin, a term used to design a type of mucin. PMP was first described in a case of a woman alleged to have a ruptured pseudomucinous cystadenoma of the ovary, an old term now in disuse to refer to ovarian cysts. Today we know that in the majority of cases the origin for PMP is an appendiceal neoplasm, often of low grade histology. Ovarian tumors as important etiology of pseudomyxoma remain recognized coming to the end of the second decade of 2000’s, even if this notion is completely wrong. Its classification is maintained under discussion, and experts’ panels strive for consensus. Malignancy of PMP is another point in discussion, and as it is shown in this review that discussion has a long-standing historical reason. Surgery is the main type of treatment for PMP, and the only therapy with potential curative option.

**Key words:** Pseudomyxoma peritonei; Pseudomucin; Appendiceal neoplasm; Hyperthermic intraperitoneal chemotherapy

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**Core tip:** The fact thatPseudomyxoma peritonei is an orphan disease explains a certain ignorance ab**o**ut this nosologic entity. It continues to be involved in controversy, starting with its classification. It is thought that mucinous c**y**stadenocarcinoma of the ovary is an important etiology for genesis of Pseudomyoma. Nevertheless, this statement is completely wrong. This review is aimed at providing~~-~~clarifications around some of the misconceptions surrounding this disease, and explaining the historical sources from which such misconceptios have been drawn.

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**INTRODUCTION**

The National Library of medicine terminology defines Pseudomyxoma Peritonei (PMP) as “A condition characterized by poorly-circumscribed gelatinous masses filled with malignant mucin-secreting cells”, definition which may be considered correct. The definition follows explaining the etiologies: “Forty-five percent of pseudomyxomas arise from the ovary, usually in a mucinous cystadenocarcinoma (cystadenocarcinoma, mucinous), which has prognostic significance. PMP must be differentiated from mucinous spillage into the peritoneum by a benign mucocele of the appendix (Segen, Dictionary of Modern Medicine, 1992)”, statements that is wrong. It has been demonstrated that PMP arises from appendiceal neoplasms, rarely from other tumors such as neoplasms from colon, urachus, or pancreas; and mucocele is a terminology which bears a great amount of ambiguity. So, this definition needs to be amended.

Today the knowledge about etiology and epidemiology of PMP has been elucidated, even if some points keep a certain ambiguity. Nevertheless, the Peritoneal Surface Oncology Group International (PSOGI) endeavored to clarify concepts about PMP, and published a consensus for classification of PMP and associated appendiceal neoplasia in 2016[1].

This manuscript deals with the history of this rare disease, from the origin of the terminology to the current notions that have been elucidated.

**ORIGIN OF THE TERM**

Myxoma refers to a benign tumor of connective tissue containing mucous material, the most common primary tumor of the heart. This histology is not related at all with that pertaining to what is call PMP. The term pseudomyxoma in PMP stands for pseudomucin. The prefix myxo-, Latin form for muxa from the Greek, and meaning *mucus*, use to be employed when mucus was present in the nosological condition. The term “Pseudomyxoma peritonei” was introduced by Werth[2] in 1884 when he described a case of a woman with gelatinous masses in the peritoneal cavity from alleged ruptured pseudomucinous cystadenoma of the ovary, and which he found to be pseudomucin instead of mucin. The term pseudomucin was originally used to describe the content of the locules present in ovarian pseudomucinous cystadenoma, which was thought to differ from mucin. Mucin and pseudomucin were known as composed of glycoproteins, and they were differentiated by certain physical characters[3,4]. Years later Frankel[5] recovered the term for describing a case in a man with ruptured cyst of mucinous content from the cecal appendix, the second traditional etiology for PMP, and the terminology became established in the medical literature.

Several descriptions of the disease were reported thereafter. The cause of the disease was identified in rupture of a pseudomucinous ovarian cystoma, the bursting of the appendix vemicularis, or sometimes it was thought that simultaneous process of disease was going on in the two organs, so two distinct causes were responsible in the same clinical case[6].

In classical descriptions two theories were proposed for explaining the condition of PMP. A German gynecologist, discussed the hypothesis that the epithelial cells from the lining of the ruptured cyst were transplanted to the peritoneum, where they took root and continued to secrete gelatinous material[7]. This theory of implantation had to be confronted with the theory of inflammation, where the gelatinous material irritates the peritoneum and causes it to react increasingly to further production of similar masses[8]. Unquestionably, it is the former theory the one which has remained, but both were considered plausible even until the late 1950’s.

What it was the real nature of the condition named Pseudomucinous Cystadenoma of the ovary, or Pseudomucinous cystadenomata is not clear. The expression was still employed in the 1950’s[9,10], less frequently in the 1970’s[11] and absolutely abandoned today. This former terminology could encompass the mucinous cystadenoma of the ovary but also the metastatic secondary tumors. Currently the mucinous tumors of the ovary are classified in cystadenoma, borderline tumor, mucinous carcinoma, and a new entity named seromucinous tumors[12]. None of them, as stated, are origin of PMP.

Pseudomucin and paramucin are terms in disuse, and mucin is the remaining nomenclature. Mucins, or MUC glycoproteins, are a family of high molecular weight, glycosylated proteins, divided into membrane-associated type and secreted type. The secreted MUC type are subdivided into gel-forming and non-gel-forming subtypes[13,14]. In PMP, mucin around tumor cells allows them to disseminate and redistribute within the peritoneal cavity. MUC2, a gel-forming mucin, is the most common type of mucin found in PMP gelatinous matter, and is associated with appendiceal neoplasms[15].

In brief, Pseudomyxoma refers to the production of mucus free in the peritoneal cavity or in cystic gelatinous masses. The etimology of Pseudo-myxoma derives from pseudomucin, being pseudomucin an obsolete terminology in molecular biology.

**ETIOLOGY OF PMP**

PMP is a clinical syndrome arising most commonly from the intraperitoneal spread of a mucinous appendiceal neoplasm[16] (supplemental digital content, video). Studies based on immunohistochemical analysis and molecular biology have demonstrated the appendiceal origin of nearly all cases of PMP, being ovarian involvement a secondary feature[17].

Mucocele is not a histopathological diagnosis but as in PMP terminology, it is a clinical description. It was first recognized as a pathological entity by Rokitansky in 1842, who described it under the term “hydrops of the appendix”. Later, Virchow also described the mucocele and considered it a colloid degeneration of the appendix.

When PMP is originated from the appendix, which it is in most cases, the primary lesion of PMP is not a mucocele of the appendix. Instead, the etiology is a mucinous neoplasm of the appendix, which may occasionally show the appearance of mucocele.

The ovary as a significant etiology of PMP has been refuted. PMP does not arise from mucinous epithelial ovarian carcinoma[18]. When mucinous ovarian lesions are present in PMP, better recognition by pathologist of histological features help distinguish between primary mucinous ovarian tumors and tumors which are metastatic to the ovary. The only retained origin from ovarian tumor is the infrequent case of PMP arising from a mature ovarian cystic teratoma[19,20].

In our experience, over some 100 appendiceal mucinous tumors with peritoneal spread, clinical PMP (*i.e.*, increase in abdominal girth) was present in less of 20% of the cases. Between the etiologies of the clinical PMP presentation of our series, the origin was appendiceal in all but one rectal cancer, 2 colon cancers, and one urachal cancer. A woman of 37 years was operated on of a ruptured giant mucinous cystadenoma of the pancreas (Figure 1) and was referred to us because of residual peritoneal lesions which did not cause a clinical PMP. This picture may be debatable when allocating the case under PMP diagnose, but it was a gelatinous belly with epithelial cells into the peritoneum. Ovarian tumor was not responsible in any case of our series. Nevertheless, more than half of the female patients referred to us with peritoneal metastases from mucinous appendiceal neoplasm had previously been operated on with the misdiagnosis of primary ovarian cancer.

In spite of all this data, it is difficult to erase the concept of ovarian origin in this pathology, concept being strengthened by the first historical reports and kept until the earlies 2000’s.

**CLASSIFICATIONS**

The first classification of this disease that we have found is attributed to Oscar Polano[6] , who in 1901 divided the condition into two classes: the cystadenoma mucinosum peritonei simplex, representing simple superficial metastasis produce by implantation; and the cystadenoma malignum pseudomucinosum peritonei, with sharply progressive and destructive character. Almost 100 years later the classification of Ronnett *et al*[21], and later the classification of Bradley *et al*[22] share striking similarities with that of Polano, keeping the ambiguous features that turn the PMP in an elusive condition to define.

A variety of different classifications have been proposed, leading to confusion among this condition. PMP still appears as a histologic diagnosis in the 2010 World Health Organization classification of tumors of the digestive system[23], even it is defined as a description of the macroscopic appearance of mucinous ascites.

It is said that PMP has been classified according to the histology of the peritoneal disease rather than the primary tumor. When metastases from colorectal cancer are found in liver or lung, the classification of the condition continuous to be colorectal adenocarcinoma stage IV with specific site metastases. When those metastases are involving the peritoneum, the adenocarcinoma continuous to be stage IV with peritoneal metastases. Confusion may originate from the persistent effort in classifying PMP as a distinct condition from the originating cancer. When a mucinous appendiceal neoplasm has metastasized to the peritoneum it is a stage IVa mucinous appendiceal neoplasm, and may or may not acquire the PMP appearance.

This issue probably emerges from the classic questioning of the malignancy of mucinous appendiceal neoplasms. In historical medical literature it was thought that “the condition is not malignant in the sense that a carcinoma has developed, but is malignant clinically in that the condition tends toward the death of the patient”. Opinions from several authors revisited by Krivsky[6] in his review in 1917 were in the same line of reasoning, such as “According to the pseudomyxoma of peritoneum is in the pathological sense benign, but clinically is not an innocent disease *etc*. Much the same opinion considering the pseudomyxoma of the peritoneum arising from the appendix to be a benign process. Bailey says that ‘there is no record to my knowledge of malignancy following a pseudomucin cyst of the appendix, but by the plastic peritonitis and mechanical interference which follow such an extravasation equally dangerous conditions may develop’”.

Today, peritoneal involvement of a mucinous neoplasm of the appendix is considered a malignant disease, and systemic metastases may occur. In our series we found two patients having systemic lung metastases from low-grade appendiceal mucinous tumors (Figure 2), distinct from pleural metastases which may arise the suspicion of dissemination from diaphragmatic surfaces, mainly during surgical procedure. This kind of metastases have been describe by others[24].

To dispel controversies in the PMP classifications, the PSOGI published a consensus for classification of PMP and associated appendiceal neoplasia. They arrive at this terminology for the peritoneal disease component: low-grade mucinous carcinoma peritonei, high-grade mucinous carcinoma peritonei, and high-grade mucinous carcinoma peritonei with signet ring cells. Broadly, there are not so much differences between this classification and that of Ronnet or even, that of Polano’s. It maintains the problem of classifying the syndrome rather than the original tumor. This classification not considers that PMP origin may be in other malignancies such as colorectal cancers, fact which nullify any effort of classifying PMP as a distinct pathological condition.

**TREATMENT**

In the article stated that “the only correct treatment of this disease is the removal of the ruptured cystoma by surgical operation and of the colloid matter which has escaped from it into the peritoneum”. This assertion has not changed in our days. PMP is a surgical disease, with no indication for systemic chemotherapy as in other abdominal malignant conditions. Systemic Chemotherapy should only be considered for patients who have no other options[25].

It had been proposed that radiotherapy should be offered to patients with PMP, and it has been eventually employed until the 1990’s[26]. Nevertheless, this therapeutic option is not currently considered.

The natural selection in PMP therapeutic armamentarium kept surgery as the most reliable treatment to cure or prolong survival in those patients. Nevertheless, it was not until the coming of the cytoreductive surgery (CRS) concept, coupled with the administration of hyperthermic intraperitoneal chemotherapy (HIPEC), that this surgical treatment took its principal role in the management of PMP. The procedure of CRS was based in complete removal of the visible disease employing peritonectomy techniques, based on the redistribution phenomenom. This phenomenom was hypothesized by Paul Sugarbaker[27] in the 1990’s, and means that large amounts of tumor will be found at some predetermined anatomic sites within the abdominal cavity, sparing other sites. The anatomic sites target of this redistribution event are the greater omentum which the highest extend being the omental cake (Figure 3), the undersurface of the right diaphragm, the Douglas pouch, the Morison pouch, the left colonic gutter, and the Treitz ligament. The limitation for complete CRS is the massive involvement of the small bowel, mainly due to iterative procedures with creation of scars where tumors infiltrate.

Even when the tumor volume is high, the cytoreduction may result in benefit for overall survival[28].

The introduction of chemotherapy agents locally applied into the peritoneum goes back to the experience reported by Economou *et al*[29]in 1957. This author employed nitrogen mustard in 36 patients with tumor of breast, colon, rectum, and stomach, and injected the agent into a branch of the portal vein, or was left in the peritoneal cavity at the end of the operation, or both.

Spratt in the 1980’s renewed the practice of intraperitoneal chemotherapy, and Sugarbaker[27] developed it in the 1990’s.

Nevertheless, the PMP is usually derived from cells of low-grade malignancy, with poor aggressive behavior in terms of growth rate and systemic metastasis, so theoretically they show poor response to chemotherapy agents which the mechanism of action is over cellular cycle. This raise doubts of the effect of HIPEC in the treatment of this pathology. Another question to solve is the effect of the hyperthermic component of the therapy, which has demonstrated a direct effect on cytolysis.

In the rare cases when PMP originates in mucinous colon adenocarcinoma, the cytotoxic drugs may enhance the radically of the procedure. Nevertheless, the PROGIDIGE 7 randomized trial, a multicenter French study analyzing the effect of Oxaliplatin as HIPEC drug in colon cancer showed nor benefits in the median overall survival when compared with CRS only. However, the impressive mean overall survival of more than 40 mo in each branch of the study must be emphasized (results in ASCO 2018)[30].

**CONCLUSION**

The etymology of PMP derives from the presence of mucin and mucin neoplastic cells spreading in the peritoneal cavity. The origin of the disease is a leaking or ruptured neoplasm of the appendix in the majority of cases. When mucinous metastases in the peritoneal cavity are thought to arise from an ovarian neoplasm, appendiceal and gastrointestinal mucinous adenocarcinoma must be rule out. The cytoreductive techniques described in the CRS/HIPEC procedure has become of extreme value in the management of patients with manifest PMP.

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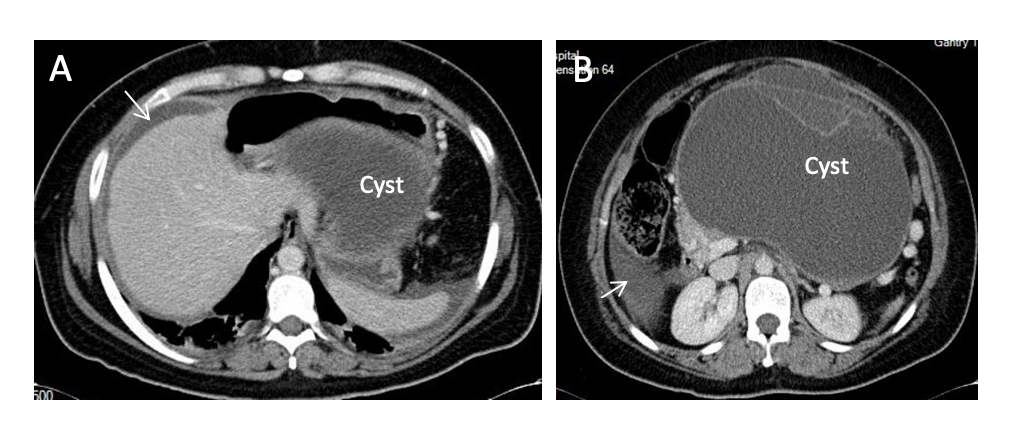
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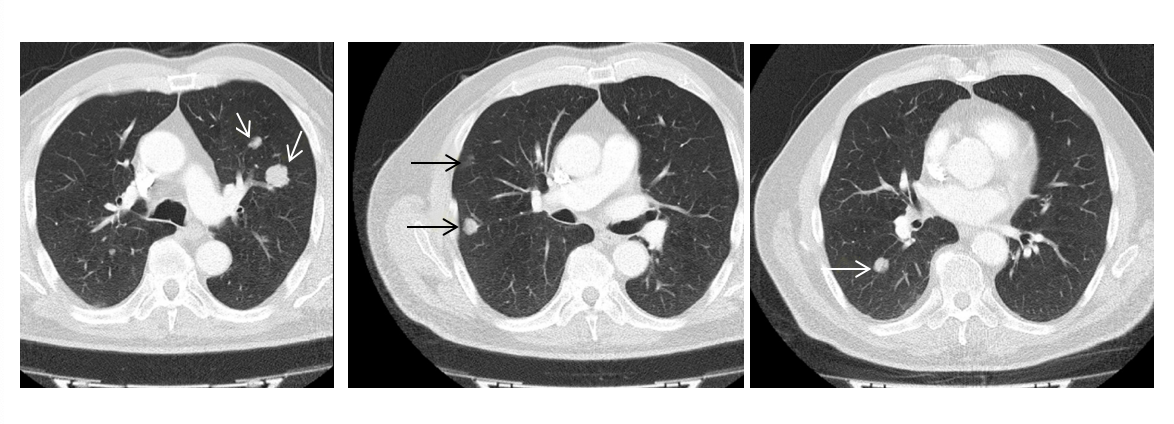
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Grade D (Fair): 0

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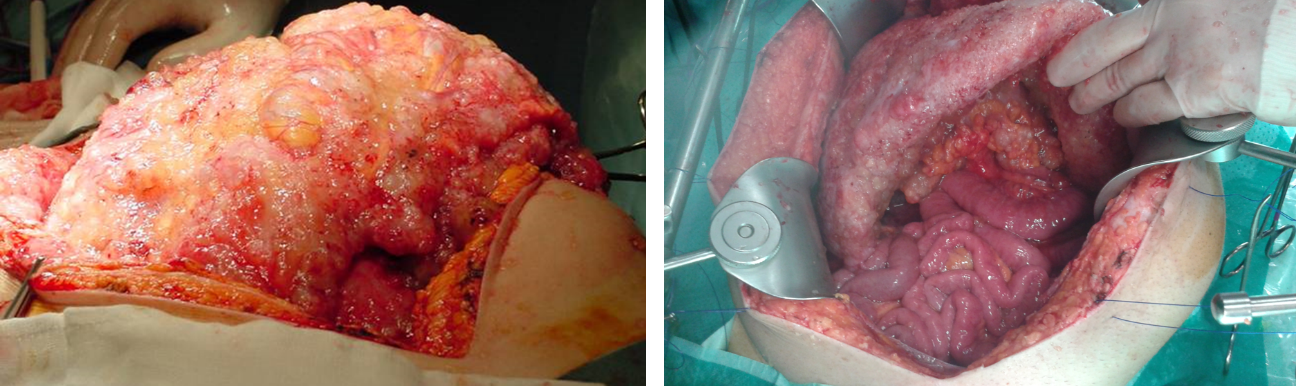


**Figure** **1 A woman of 37 years was operated on of a ruptured giant mucinous cystadenoma of the pancreas.** A: Computed tomography slide showing free mucinous ascites (arrows) and the dome of the pancreatic cystic lesion (mucinous cystadenoma with focal adenocarcinoma) in retrogastric area; B: Peritoneal fluid in right paracolic gutter (arrow) and corporal cystic lesion with septa.



**Figure 2 Thoracic computed tomography slides with bilateral nodular metastases (arrows) from a low grade appendiceal mucinous neoplasm.**

A B



**Figure 3 Two forms of omental cake in two patients with peritoneal dissemination of low grade appendiceal mucinous neoplasm.** Note sparing of the small bowel in the right picture.