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Review Article

Pseudomyxoma Peritoneii – A Review

Dr Jayati Nath.[1]. Dr Mehak Manocha.[2]

[1]Professor Ob Gyn Sgt Medical College Gurugram Mmimsr Ambala Haryana-122003 India.
[2]PG Trainee Ob Gyn Sgt Medical College Gurugram Mmimsr Ambala Haryana-122003 India.

*Corresponding Author
Dr Jayati Nath

Abstract: Pseudomyxoma peritoneii remains an enigma- a rare malignant condition with poorly understood etio-pathogenesis, characterized by progressive accumulation of mucin secreting tumour cells inside the abdomen and pelvis, the site of origin might be appendix or the ovary. This review is being done to have a better understanding of the disease process along with the diagnostic modalities and treatment options so as to formulate appropriate management strategies to ensure the best outcome for the patients.

Keywords: Pseudomyxoma peritoneii, mucinous tumour of the ovary, malignant ovarian tumour, appendix.

Pseudomyxoma peritoneii is a poorly understood condition characterized by massive accumulation of mucinous material inside the peritoneal cavity, associated usually with mucin producing adenoma or adenocarcinoma of the appendix, colon or the ovaries, first described by Werth (Thanasak, S. *et al.*, 2013; Werth, R. *et al.*, 1884). This condition is rare, often accidentally discovered during surgery for ovarian tumour, seen as gelatinous ascites and diffuse implants involving the peritoneal surfaces and omentum (Werth, R. *et al.*, 1884). Due to the rarity of the condition along with poorly understood pathophysiology, researches are still searching for the best treatment options available to ensure the best outcome in patients diagnosed with this condition. This article reviews the current clinical profiles and the best currently available management options of patients with pseudomyxoma peritoneii.

The term 'Pseudomyxoma peritoneii' means literally – "false mucinous tumor of the peritoneum", and is most commonly refers to a slowly progressive disease process which is characterized by excessive amounts of mucin, which over time, gradually fills the entire peritoneal cavity. Such tumor is not considered biologically much aggressive as it neither invades nor metastasizes, though it is a deadly process which involves the whole intraperitoneal space of the abdomen and pelvis being filled up with the mucinous tumour tissue.

Most oncologists & pathologists apply the term 'pseudomyxoma peritoneii' for any condition, which leads to extensive mucous accumulation within the abdominal cavity and pelvis (Thanasak, S. *et al.*, 2013). Therefore, a clear understanding of the natural history of pseudomyxoma peritonei has not been possible due to the fact that tumours of various primary sites with significantly different biological behaviors have been clumped together as one clinical entity (Thanasak, S. *et al.*, 2013).

Pseudomyxoma peritoneii that originates from the primary appendicular adenoma was named Disseminated Peritoneal Adenomucinosis, as against the more biologically aggressive primary mucinous carcinoma of the appendix named Peritoneal Mucinous Carcinomatosis (Thanasak, S. *et al.*, 2013). Therefore, pseudomyxoma peritoneii of ovarian origin should be classified as either Benign or Malignant, for proper management stratification (Thanasak, S. *et al.*, 2013).

Incidence:

It is a rare condition, with a reported incidence of approximately 1-2 per 10,000 laparotomies & 3-4 times more common in women (Campbell, J.S. *et al.*, 1973; Mann W. J. *et al.*, 1990), occurring mostly in the 5th& 6th decades of life & in about 2.5% of ovarian mucinous tumors (Michael, H. *et al.*, 1987).

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Pathogenesis:

There lies considerable disagreement regarding the origin of pseudomyxoma peritoneii, though it is most commonly associated with benign, borderline or malignant mucinous ovarian tumours & also those of the appendix (Jones, D.H. *et al.,* 1965; Fernandez, R.N. *et al.,* 1980; Long, R.T. *et al.,* 1969; and Smith, J.W. *et al.,* 1987), and also of the urachus, bowel, pancreas and common bile duct (Mann W.J. *et al.,* 1990; Sugarbaker, P.H. *et al.,* 1992; Chefec, G. *et al.,* 1986). Many investigators believe that the appendix is the primary origin in most of the cases while the peritoneal and ovarian lesions are actually metastatic (Merino, M.J. *et al.,* 1985). Many researchers also advocate that pseudomyxoma peritoneii might originate from implants of a primary mucinous tumour or as a part of a multifocal neoplastic process thereof (Sumithran, E. *et al.,* 1992). Therefore, the actual knowledge about the pathogenesis of this entity still remains elusive (Sumithran, E. *et al.,* 1992).

Although the tumour cells spread widely throughout the peritoneal cavity, they do not usually invade past the peritoneal surface. On the contrary, the tumour cells do not progress exuberantly on the surface. This could explain why ascites & implants are usually extensive but visceral invasion is relatively uncommon (Mann W.J. *et al.,* 1990). Another hypothesis being considered statis pseudomyxoma peritoneii as a result of an agent in the mucinous ascitic fluid, which includes a mucinous metaplasia in the peritoneal mesothelium (Sanderberegh, H.A. *et al.,* 1977).

CLINICAL PRESENTATION& IMAGING:

The commonest presenting symptoms are symptomatic pelvic or abdominal mass and gradual increase in the abdominal girth (Wertheim, I. *et al.,* 1994). Some patients might complain of painful sensation in the abdomen, fever, anorexia, dyspepsia, nausea, vomiting and unaccountable weight cachexia (Wertheim, I. *et al.,* 1994).

Diagnosis is made when a laparotomy is done, because presence of a distended abdomen with non-shifting ascites as physical signs is inconclusive by themselves. Radiological aids might be helpful especially in advanced diseases, example plain films used when the abdomen is distended with mucous may show central displacement of the bowel with obliteration of the psoas muscle shadow (Crough, D.B. *et al.,* 1994), sometimes, small calcified lesions may be visible widely disseminated all throughout the abdomen. With the progression of the disease process, there appear more and more signs of bowel obstruction & might warrant urgent emergency debulking (Green, N. *et al.,* 1975). When used in adjunct to barium studies, the proximal extent of the disease is assessable and a possible extrinsic tumour causing large gut obstruction can be ruled out with conviction.

Ultrasonography, on the contrary, is more useful and has similar features to CT images showing abdominal echogenic masses with gross evidence of ascites with multiple septations and scalloping of the liver and spleen (Beller, F. K. *et al.,* 1986; Roy, W. J. *et al.,* 1997).

CT usually shows any of the following 4 basic patterns:

- Posterior displacements of the intestines along with numerous low-density masses & calcifications.
- Diffuse infiltration of the peritoneum appearing similar to ascites with septations and fluid pockets filling the pelvic cavity.
- Low density intrahepatic attenuated lesions.
- Scalloping of intra-abdominal organs due to extrinsic pressure of the adjacent peritoneal implants.

TREATMENT:

The mainstay of treatment of pseudomyxoma peritoneii has always been primary cytoreductive surgery, removing the primary disease i.e. oophorectomy and /or total abdominal hysterectomy, followed by removal of all the mucinous implants and nodules from the omental and peritoneal surfaces along with appendicectomy followed by histopathological analysis.

Earlier, radical surgeries using ball-tip electrode with a high –cutting current was used to destroy as much of the tumour implants possible but it produced large intraperitoneal burns, many a times resulting in prolonged ileus requiring prolonged total parenteral nutrition of approximately 3-4 weeks.

Newer techniques eg. Argon beam coagulator are used nowadays which spread over the tissue surface with a more homogenous distribution of energy and much less tissue injury than seen with standard electrocautery.

Since the mucinous tumours associated with pseudomyxoma peritoneii are minimally invasive and yet extensively coat the parietal peritoneal surfaces, a series of peritonectomy procedures have been developed for the same. These include stripping the parietal peritoneum & resecting structures at fixed sites, which contain visceral peritoneum with the use of electrocautery to obtain maximal cytoreduction in peritoneal carcinomatosis (Crough, D.B. *et al.,* 1994).

The 6 different peritonectomy procedures – greater omentectomy-splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, lesser omentectomy –cholecystectomy with stripping of the omental bursa, pelvic peritonectomy with sleeve

reduction of the sigmoid colon & antrectomy, can be performed separately or all together.

An objective scoring system for the presence & size of macrosomic tumours in 13 different abdominal regions was developed by **Sugarbaker (Peritoneal Cancer Index)** before and after primary cytoreductive surgery (Sugarbaker, P. H. *et al.,* 1997). This score not only helps in estimating the likelihood of complete cytoreduction in peritoneal surface carcinomatosis to prevent unnecessary surgery in very high-risk patients but also in prognosticate the patients and thus decrease postoperative morbidity in such patients.

ADJUVANT TREATMENT

Though primary cytoreductive surgery aimed at surgical debulking and removal of the mucinous ascites remains the cornerstone of the treatment of pseudomyxoma peritoneii, many a times, complete removal of the tumour tissue implants becomes impossible. For this reason, many adjuvant treatment modalities have been developed.

Mucolytic Agent Therapy:

Many regimens have been developed to prevent the re-accumulation of the mucinous implants – including intraperitoneal and systemic chemotherapy.

Many researchers advocate intraperitoneal irrigation or percutaneous lavage with Dextrose and water to expedite the removal of the mucin and prevent its re-accumulation though the exact mechanism of action is still not understood (Green, N. *et al.,* 1975; Haid, M. *et al.,* 1981).

Beller *et al.,* (1986) reported instillation of intraperitoneal mucolytic agents eg. Dextran sulphate (5% concentration) for treating recurrence and also prevention of the same when used along with plasminogen activators eg. Urokinase (Beller, F. K. *et al.,* 1986). Side effects include dangerous hyperglycemic coma, which requires stringent blood glucose monitoring during and after the irrigation procedures.

Chemotherapy:

Pseudomyxoma peritoneii especially due to ovarian carcinomatosis calls for vigorous postoperative intraperitoneal and also intravenous chemotherapy (Niwa, K. *et al.,* 1995; Jones, C.M. *et al.,* 1985).

Until the mid-1980's Melphalan was the first line chemotherapeutic agent used for pseudomyxoma peritonei (Mann W.J. *et al.,* 1990).Today, cisplatin-based regimens have become the standard chemotherapy for the same –either single drug regime with cisplatin or ciplatinum-based combination chemotherapy (Mann W.J. *et al.,* 1990; Michael, H. *et al.,* 1987).

Radiotherapy:

Fernandez *et al.,* advocated the use of postoperative radiotherapy for betterment of prognosis and prolonging the five-year survival rates as compared to chemotherapy in patients of pseudomyxoma peritoneii (75% versus 44%) (Fernandez, R.N. *et al.,* 1980).

New modalities of treatment in Pseudomyxoma Peritoneii:

- Intraoperative heated chemo-perfusion of the peritoneal cavity has been utilized for the prevention and treatment of peritoneal surface malignancies. Hyperthermia itself due to its inherent direct cytotoxic effect caused by impaired DNA repair along with denaturation of cell proteins, introduction of heat –shock proteins serving as receptors for NK (natural killer) cells, apoptosis induction and inhibition of angiogenesis has a very favorable outcome in cases of pseudomyxoma peritoneii (Pisharodi, L. R.*et al.,* 1997; Beller, F. K. *et al.,* 1986; Roy, W. J. *et al.,* 1987). Ultimately, increased permeability of the cell membranes at higher membranes at higher temperatures also increases the drug uptake by the tumour tissues (Dahl, O *et al.,* 1999). Many studies of clinical experience with aggressive primary surgical cytoreduction combined with hyperthermic intraperitoneal chemotherapy have been reported by various workers with various degrees of success and favorable outcomes in patients with pseudomyxoma peritoneii (Roy, W. J. *et al.,* 1997; Dahl, O *et al.,* 1999) and also advanced ovarian carcinomatosis. It has been observed that patients who received a combination of cytoreductive surgery and intraperitoneal chemotherapy have had better five-year survival rates (Dahl, O *et al.,* 1999).

- Incomplete and inadequate chemotherapy course, abdominal discomfort and pain, seizures, neutropenia, thrombocytopenia and agranulocytosis have been reported with the use of intraperitoneal chemotherapy (Dahl, O *et al.,* 1999; Storm, F.K.*et al.,* 1989). Apart from these hematologic toxicities, many patients demonstrated non-hematologic morbidities eg. Intestinal obstruction, perforations,anastomotic and bile leaks ,fistulae—gastrointestinal and urogenital, bleeding, dehiscence,pancreatitis & venous and pulmonary thrombo-embolism (Sugarbaker, P. H. *et al.,* 1997; Sanderberegh, H.A. *et al.,* 1977).

- Photodynamic therapy is another modality of alternative treatment used in pseudomyxoma peritoneii, which aims at selective destruction of malignant cells with the prevention of normal tissue destruction (Crough, D.B. *et al.,* 1994). Thistherapy destroys malignant tumours through

the selective uptake of photosensitizing compounds, which then are activated by exposure to light of a particular intensity and wavelength thereafter (Sugarbaker, P.H. *et al.,* 1999).The patients might develop cutaneous photosensitivity, transient liver function derangements, postoperative haemorrhage, necrotizing pancreatitis,intestinal and urinary fistulae (Vander, V. N. *et al.,* 2000).

PROGNOSIS:

Literature cites the five-year survival rate of pseudomyxoma peritoneii at approximately 50% (range 11-75%) (Fernandez, R.N. *et al.,* 1980; Smith, J.W. *et al.,* 1987) with patients who had ovarian tumours of low malignant potential having significantly better prognosis than those with adenocarcinoma (Smith, J.W. *et al.,* 1987; Sugarbaker, P.H. *et al.,* 1992).The cited overall 5 -year & 10-year survival rates in patients with borderline ovarian tumours are 85-90% & 75-80% respectively. **Kem** *etal.,* reported pseudomyxoma peritoneii as one of the prognostic factors negatively affecting the survival rates (Kaern, *et al.,* 1993). **Wertheim** *et al.,* reported 40% of patients with borderline tumours had either died or had a recurrence after a median follow-up interval of 3 years (Wertheim, I. *et al.,* 1994).

Another controversial subject of interest is the significance of epithelial cells in peritoneal specimens of pseudomyxoma peritoneii, which has been associated with disease recurrence and poor prognosis.

CONCLUSION:

Pseudomyxoma peritoneii, a rare condition, most commonly arising from mucinous tumours of the ovary and appendix. Timely and aggressive primary cytoreductive surgery including total abdominal hysterectomy with bilateral salpingo-oophrectomy,appendicectomy along with omentectomy,removal of all visible mucinous implants & nodules from the peritoneal surfaces is the mainstay of the treatment.Though optimal cytoreduction could be difficult, however,proper preoperative evaluation and surgery in a well equippedcenter at the hands of a skilled surgical team could benefit the patient to the maximum.Postsurgical adjuvant therapies in the form of mucolytic agent administration intraperitoneally are recommended to prevent disease recurrence. Adjuvant noble modalities of treatment in the form of chemotherapy, radiotherapy etc. may prove to be useful in selected patients and further studies are required and recommended for ensuring the best prognosis and survival rates in patients suffering from pseudomyxoma peritoneii.

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