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## CASE STUDY

# MUCINOUS CYSTIC NEOPLASM PANCREAS WITH CARCINOMA PANCREAS INVADING SPLEEN AND MUCINOUS CYSTADENOMAS BOTH OVARIES: A CASE REPORT AND REVIEW OF LITERATURE

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**ABSTRACT**

A 37-year-old lady presented with a recurrent cystic lump in left hypochondrial region. It was initially thought to be of renal origin and marsupialized. Recurrence of the lesion after three years prompted a repeated surgery in the form of a sub-total excision wherein the "renal cyst" was noted to be densely adherent to the tail of the pancreas. The histopathology was reported as a "benign intestinal duplication cyst". During post-operative period a collection was noted in left hypochondrial region, which was drained under ultrasound guidance. Further serial sonograms revealed progressive increase in its size as well as appearance of cysts in the ovaries; first in the left and then in the right ovary. Follow up CT Scan revealed a cystic lesion in the spleen with extra splenic extension into the tail of the pancreas. Large thin walled cysts were noted in both ovaries. Tumour markers like CA 125, CEA, AFP and BHCG were all within normal limits. The huge cystic masses of both ovaries and the spleen were distending the abdomen. She was taken up for exploratory Laparotomy and a Total Abdominal Hysterectomy with Bilateral Salpingoophorectomy, with Splenectomy and Distal Pancreatectomy was done. Her post-operative recovery was uneventful. Final histopathology examination revealed a Mucinous Cystic Neoplasm Pancreas with a Well Differentiated Adenocarcinoma Pancreas with extra Pancreatic Extension involving Spleen and Bilateral Ovarian Mucinous Cystadenomas. The rare lesion was difficult to label accurately because of its nebulous connection and origin from the tail of the pancreas. Once excised completely and accurately labelled she has been offered adjuvant chemotherapy which she is continuing, despite a stormy first pulse, which was complicated by a recurrence of collection in left hypochondrial region causing features of sub-acute intestinal obstruction, but managed successfully with ultrasound guided pig tail drainage. In view of propensity of metastases from pancreas to simulate primary mucinous tumours of the ovary a close watch is being maintained while continuing adjuvant chemotherapy.



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## INTRODUCTION

Abdominal left upper quadrant cystic lesions pose an interesting conundrum. The differential diagnosis includes lesions of the pancreas, spleen, adrenal gland, kidney and mesentery. Rarely, Mullerian cysts, intestinal duplication cysts, teratomas and lymphangiomas too have been reported (Momosaka *et al*., 2016; Jung *et al*., 2014; Yang *et al*., 2004; Yohendran *et al*., 2004; Hruban and Klimstra, 2014; Garcea *et al*., 2008; Upadhyay *et al*., 2006). We describe an unusual case of a Mucinous Cystic Neoplasm of the Pancreas with Adenocarcinoma Pancreas invading Spleen with Bilateral Ovarian Cystadenomas, which was initially mimicking a renal cyst and later an intestinal duplication cyst. The final diagnosis could be established only when the entire mass was resected. Non-inflammatory cystic lesions of the pancreas are more common than perceived. Advances in cross-sectional imaging are helping detect them with increasing frequency in the primary care setting. Autopsy series have detected pancreatic cystic lesions in a quarter of the patients studied. Some of these have little or no risk for developing a malignancy while others have a high malignant potential. Pancreatic cysts may be one of several types of nonneoplastic cysts or may be intraductal mucinous neoplasms, mucinous cystic neoplasms, serous cystadenomas, solid pseudopapillary neoplasms, cystic variant of pancreatic neuroendocrine tumors or a pancreatic ductal adenocarcinoma. The major challenge in the management of pancreatic cystic lesions is the distinction between these, the understanding of the underlying pathology, the risk for concurrent or later development of malignancy and the risk from adjacent organ involvement (Crippa *et al*., 2008; Farell, 2015; Lennon *et al*., 2014; Naveed *et al*., 2014). Accurate prognostication is vital since Carcinoma of the Pancreas is a calamitous disease with a dire prognosis. Fortunately, in India, the incidence of pancreatic cancer is low (0.5 – 2.4 per 100, 000 men and 0.2 – 1.8 per 100,000 women) but the prognosis

remains dismal, at par with the world. Only 15 -20% of patients have resectable dismal, at presentation and of this only 20% survive five years (Shrikhande *et al*., 2009). Worldwide, pancreatic cancer is the fourth most common cause of cancer related mortality. Exocrine pancreatic cancer has an overall survival rate of less than 6%. The diagnosis of Pancreatic Cancer remains enigmatic because there are no characteristic signs or symptoms, especially in the early stages as the organ remains hidden behind other organs, is difficult to visualize on imaging tests, and tumor markers like CA 19.9 have low specificity. Further, accurate characterization of biopsy specimens is difficult because the neoplastic glands are remarkably well-differentiated making it difficult to tell them apart from non-malignant, reactive glands (Hruban and Klimstra, 2014). The increased availability of non-invasive imaging modality to evaluate non-specific abdominal complaints has led to, more and more pancreatic lesions being diagnosed. Of these, true pancreatic cysts comprise only 10-15% of all pancreatic cystic lesions. Two well defined entities have been seen to largely make up this group of non-inflammatory, true cystic lesions of the pancreas namely, Intraductal Papillary Mucinous Neoplasm (IPMN) and Mucinous Cystic Neoplasm (MCN).

The presence of ovarian-type stroma surrounding the tumor and an inner epithelial layer with tall mucin producing cells are pathognomonic and a characteristic feature which distinguishes MCN from IPMN (Farell, 2015, Tanaka *et al.,* 2006). When ovarian type stroma is used as a "sine qua non"; MCN it is found to occur almost exclusively in females (95%) and restricted to body and tail region of the pancreas (95-98%). 25% are incidentally discovered and overall show a prevalence of cancer in 6-36% of resected specimens. The 5-year disease specific survival for benign MCN is 100% but for those with invasive cancer, usually a tubular / ductal carcinoma, it is 57-62% (Crippa *et al*., 2008; Farell, 2015; Testini *et al*., 2010; Pusateri and Krishna, 2018). Due to close histopathological and immunohistochemical resemblance to ovarian mucinous cystadenomas, stromal luteinization, co-location during embryogenesis of the buds of the genital tract and dorsal pancreas, which forms the pancreatic body and tail (the usual site for MCN), has led to the hypothesis that MCN arise from ovarian rests in the pancreas (Naveed *et al*., 2014). Symptomatic cysts, increasing age, multilocular cysts, thickened wall with peripheral calcification, solid component, papillary proliferation, vascular involvement and hypervascular pattern predict a malignant diagnosis. Raised cyst aspirate CEA, CA-19.9, Mucin content and abnormal cytology can also help in making the distinction between benign and malignant cysts.

In spite of comprehensive preoperative evaluation, the surgeon's preoperative diagnosis is correct in one-third of cases, incorrect in another third and non-specific in the remaining and above all a high index of suspicion is necessary especially if dealing with rare presentations (Farell, 2015; Naveed *et al*., 2014; Smith *et al*., 2004). Invasive Pancreatic Adenocarcinoma are defined by an intense desmoplastic reaction especially within the pancreas such that non neoplastic cells may outnumber the neoplastic cells and though neoplastic glands are often extremely well differentiated application of established criteria can help distinguish benign from malignant glands like the presence of: haphazard arrangement of glands, perineural invasion, vascular invasion, a gland adjacent to a muscular artery, luminal necrosis, incomplete lumina, variation in size of nuclei in a gland by more than four to one, "naked" glands in fat (Hruban and Klimstra, 2014). Malignant MCN are associated with activating point mutations in the K-ras, BRCA 1, BRCA2, SMAD4 (DPC4) and TP53 gene as also the overexpression of EGFR. The mostly negative p53 status and the known association of high-risk HPV targeting p53 for proteasomal degradation, keeping p53 at a low level, and the reported series of ovarian mucinous cystadenomas occurring synchronously with MCN suggests the possibility of a link between HPV and MCN. Case reports have identified HPV-16 in MCN (Pusateri and Krishna, 2018; Gagne *et al*., 2000; Tong *et al*., 2007). Currently treatment recommended is surgical resection, since majority of these patients with MCN are young, and would otherwise face a lengthy and comprehensive surveillance, additionally most of these lesions are located in the body and tail region of the pancreas, where competent resection carries negligible morbidity and low mortality. The prognosis after complete resection is excellent unless concurrent invasive carcinoma is detected (Garcea *et al*., 2008; Crippa *et al*., 2008; Farell, 2015; Naveed *et al*., 2014; Tanaka *et al*., 2006; Testini *et al*., 2010).

## CASE REPORT

A 37 years old lady, G5 P2 A3 L2, had been symptomatic for last four years, with pain in left hypochondrium. Initially hospitalized at another hospital where USG Abdomen revealed small GB Polyps, Large cyst in upper pole of Left Kidney. Uterus and Ovaries, NAD. CT Abdomen done at that time revealed benign morphology cyst 11.5 x 13.5 x 15 cm, between Adrenal medially, Kidney Inferiorly, pancreatic body and tail anteriorly, reported as "probably of upper renal pole origin" (Figure 1). Pancreas was reported normal. No Adnexal Mass was seen. She was operated and Lap Cholecystectomy with Marsupialization of "Left Renal Cyst" was done. She remained relatively well for three years but her symptoms recurred and follow up Ultrasonography of the abdomen, revealed a large left hypochondriac region cystic lesion. She was seen at a tertiary referral centre and CT Abdomen was done which was reported to reveal a thin-walled cyst 16.7 x 14.4 x 19.4 cms (Figure 2 & 3), reported as Benign Cyst "probably of Renal origin". Pancreas was again reported normal. No Adnexal Mass was seen. She was operated and a Laparoscopic Left Renal Cyst sub-total excision done as the cyst wall was found densely adherent to tail of pancreas and spleen but easily dissected off the kidney and adrenal. Histopathological Examination of the cyst wall revealed features suggestive of a Benign Intestinal Duplication Cyst (Figure 4). During follow up a collection was detected in left hypochondrium and an ultrasound guided aspiration was done. The collection suggestive of a recurrent cyst reappeared and further serial sonograms revealed progressive increase in its size as well as the appearance of a thin-walled cyst in the left ovary and over a period of three months a similar cyst was noted in the right ovary. A CT scan revealed a Cystic lesion in the spleen measuring 8.1 x 7.4 x 6 cm. with an Extra Splenic extension into tail of Pancreas 4.2 x 4.9 x 5.3 cm (Figure 5). Few foci of calcification noted along walls of lesion. Rest of pancreas normal. The lesion was noted to abut the adrenal gland with effaced fat planes.

A Right Ovarian Cyst measuring 9.3 x 12.2 x 13.1 cms and a Left Ovarian Cyst measuring 8.4 x 12.7 x 11.7 cm was also noted (Figure 6). There was no significant adenopathy and the Right adrenal gland was normal. An MRI of the Pelvis

delineated a multicystic lesion in both adnexa with thin walls. No solid component was seen (Figure 7). Her CA 125 was 31.5 U/ML, AFP was 1.68IU/ml, CEA was 4.13ng/ml, and Beta HCG was 0.3. She had been detected to have hypertension four months earlier and had been started on anti-hypertensive medication. Her General Exam did not reveal any abnormality. Her Abdomen was distended and two Cystic masses were palpable filling the entire abdomen. She was taken up for surgery and during preliminary exploration no ascites, no serosal nodules, no hepatic metastases or para aortic lymphadenopathy was detected.

Distal Pancreatectomy with Splenectomy (Figure 8) and Total Abdominal Hysterectomy with Bilateral Salpingoophorectomy done to excise both Adnexal masses, Splenic Cyst and Cyst in Tail of Pancreas. Her Post-operative recovery has been uneventful. The final histopathology has revealed Mucinous Cystic Neoplasm with Well Differentiated Adenocarcinoma Pancreas (Figure 9 & 10) with extra Pancreatic extension involving Spleen with Bilateral Ovarian Mucinous Cystadenoma and Chronic Cervicitis.

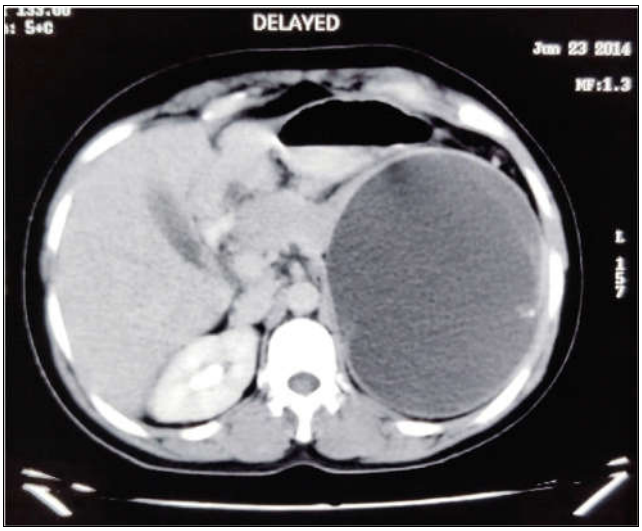


**Figure 1. CECT Axial pane showing cyst at presentation (June 2014)**

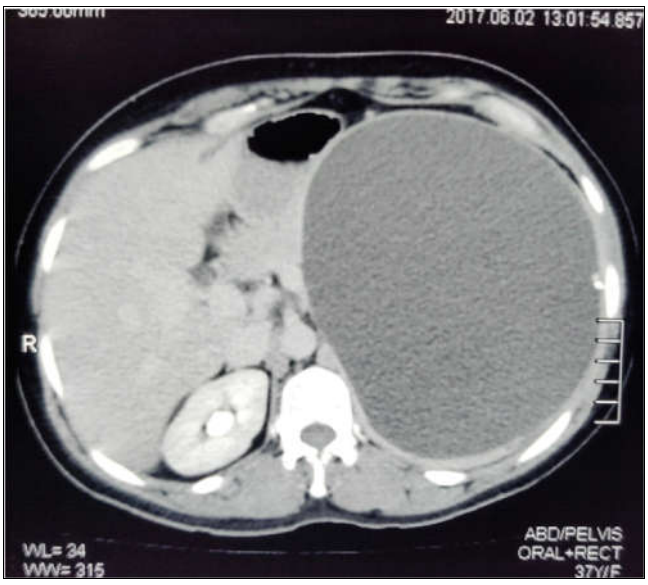


**Figure 2. CECT axial pane showing cyst recurrence after 3 years (June 2017)**

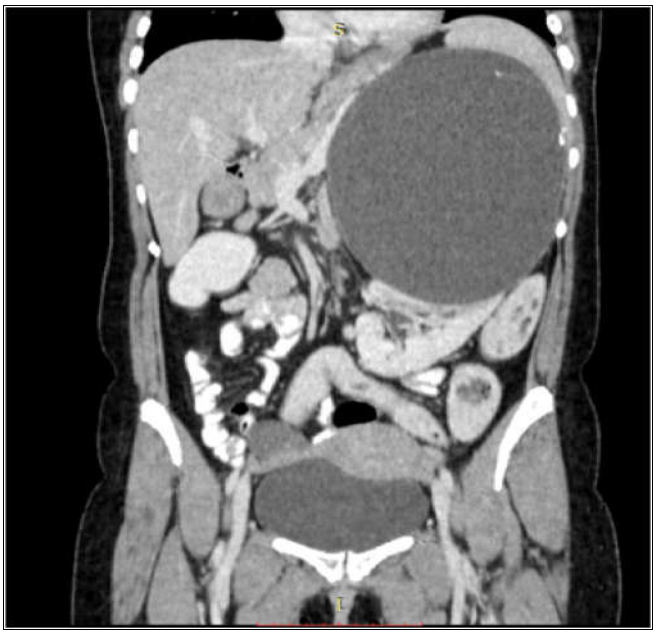

**Figure 3. CECT Coronal pane showing cyst recurrence (June 2017)**

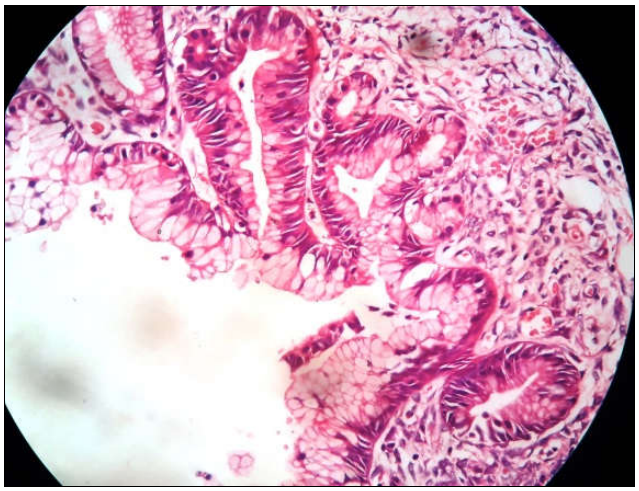

**Figure 4. Cyst wall lined by intestinal type epithelium and focal aggregates of mature glands with morphology favoring benign intestinal duplication cyst**

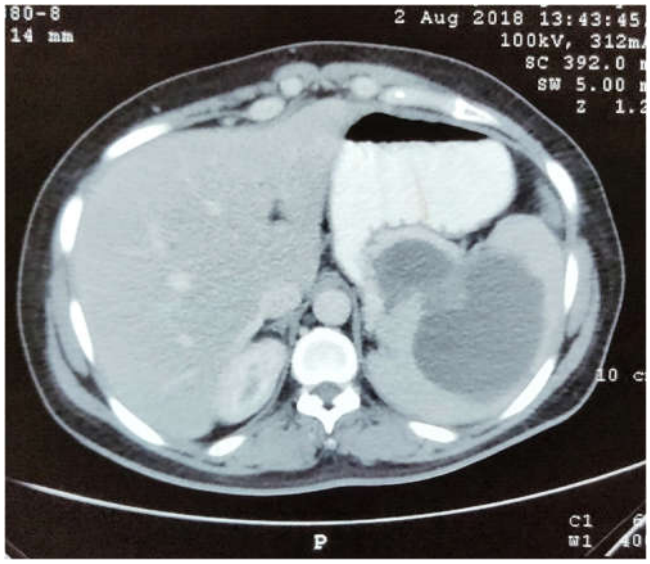


**Figure 5. CECT axial pane showing cyst recurrence (August 2018)**

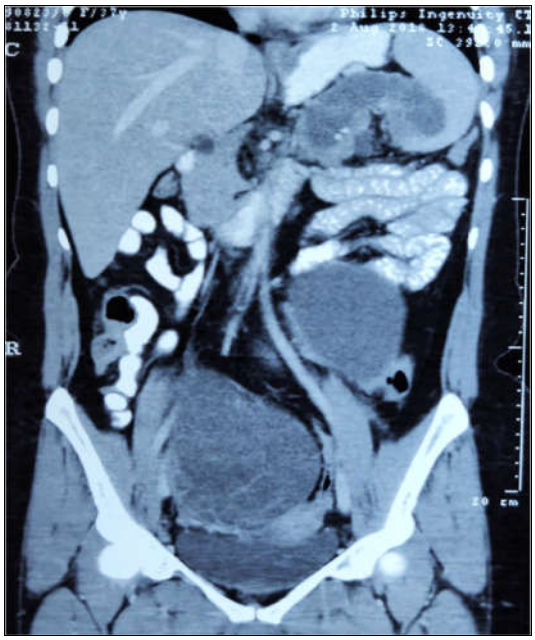

**Figure 6. CECT Coronal pane showing recurrent cyst involving pancreas and spleen and bilateral ovarian cysts (August 2018)**

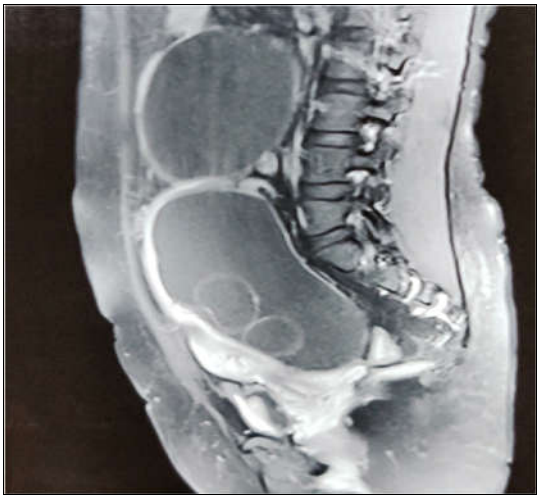

**Figure 7. MRI showing thin walled ovarian cysts in both ovaries**

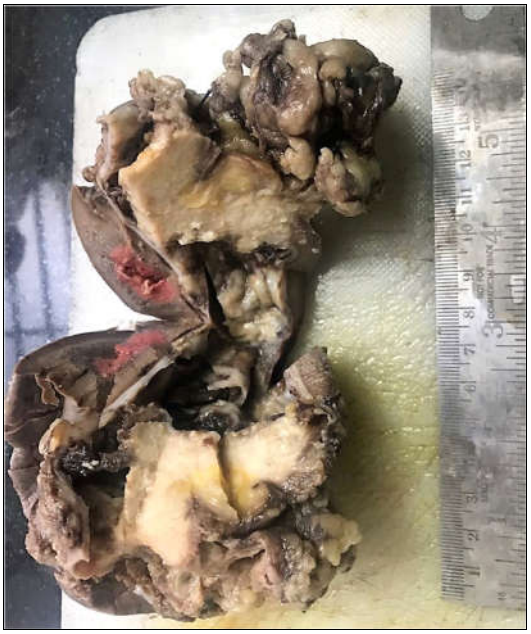

**Figure 8: Thick inferior wall of Splenic Cyst**

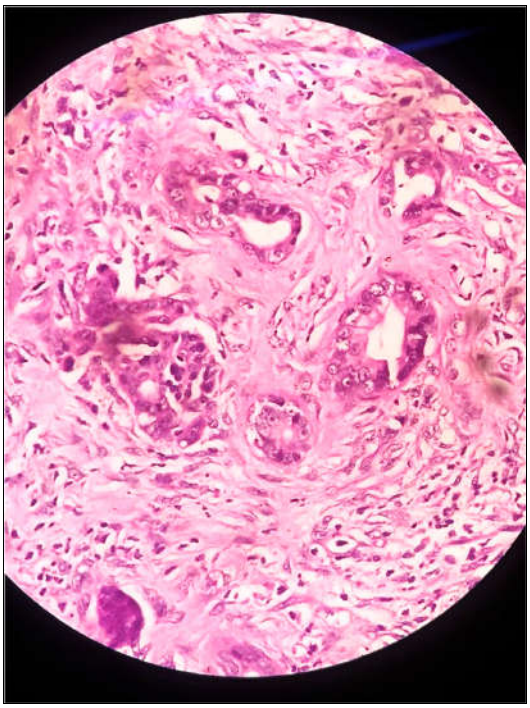

**Figure 9: Irregular malignant glands in pancreatic parenchyma (40 X)**

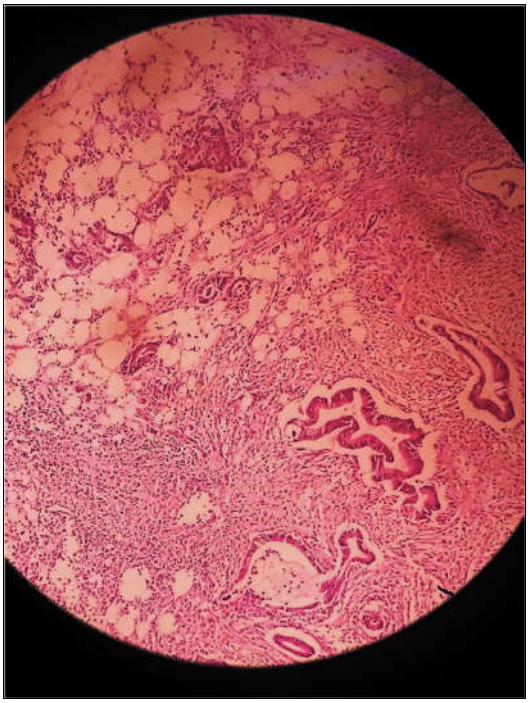

**Figure 10. Isolated malignant pancreatic acinar glands in adipose tissue (10 X)**

## DISCUSSION

Due to improvements in imaging modalities, cystic lesions in the abdomen do get picked up frequently but, exact diagnosis often remains a challenge. Cystic lesions in the left upper abdomen are particularly challenging as lesions of the pancreas, adrenal gland, kidney, mesentery, Mullerian cysts, intestinal duplication cysts, teratomas, lymphangiomas are all to be considered, ranging from completely benign, through to premalignant and malignant lesions. This 37-year-old lady presented with a left upper quadrant cystic mass lesion with symptoms due to mass effect. The cyst of apparent large size

and benign morphology was localized on CT Scan as lying between the adrenal medially, the kidney inferiorly and the pancreatic body and tail anteriorly. It was reported as a renal cyst and was operated 4 years ago wherein marsupialization was done. She remained relatively well for three years when a swelling was again noted in the left upper abdomen, was diagnosed as a recurrence of the renal cyst and was excised. During surgery it was found to be easily dissected off the renal parenchyma and the adrenal but densely adherent to the pancreas and the spleen, the cyst was decompressed by needle aspiration of 1700 ml of clear mucinous fluid but still only subtotal excision could be done safely. The indolent nature of the lesion was in keeping with behavior of benign lesions which are incompletely excised. The histopathological picture of a cyst wall containing benign appearing intestinal glands was reported as an intestinal duplication cyst and a good outcome was expected after the subtotal excision but the lesion recurred and progressively involved the spleen and both ovaries.

The course now was more ominous and radical surgery in the form of distal pancreatectomy, splenectomy, total abdominal hysterectomy and bilateral Salpingoophorectomy was offered to tackle all the concurrent pathologies. There were no pointers to indicate a sinister pathology either in the history in the form of anorexia, weight loss, chronic pancreatitis, diabetes, obesity, smoking or chronic alcohol consumption. There was no history of back pain or migratory thrombophlebitis. No pointers to a malignant diagnosis were elicited in routine serology as CEA, CA19.9, BHCG and CA125 were within normal limits. The imaging too could add nothing more than cystic involvement of pancreas, spleen, and both ovaries, with no regional nodal involvement or hepatic metastases. The etiology remained inconclusive prior to surgery as is usual for more than 6o% of cystic lesions in this region (Naveed *et al*., 2014). Following surgery, the grossing revealed large septated thick walled cysts filled with mucinous material involving spleen and pancreas. The pancreatic cyst wall was at one place white-grey, thick and sclerotic. Histopathological evaluation revealed an inner epithelial layer composed of tall mucin secreting cells and a dense cellular, ovarian type stroma suggestive of mucinous cystic neoplasm of pancreas.

MCNs as in this case are characterized by septated cysts forming epithelial neoplasms which produce mucin and have a distinctive ovarian type stroma which is not found in other pancreatic neoplasms. The origin of ovarian type stroma identified is under debate, and a stimulation of endodermal immature stroma left behind during gonad-genesis by female hormones is suggested as a possible etiology. Approximately a third of such cases of Mucinous Cystic Neoplasms of Pancreas have an associated invasive adenocarcinoma of the tubular or ductal type. Invasive adenocarcinoma of the pancreas was identified in our case too. Additionally, blocks from the pancreatic lesion revealed haphazard arrangement of glands, perineural invasion, vascular invasion, infiltration of spleen, gland immediately adjacent to a vascular artery, luminal necrosis, incomplete lumina, nuclear size variation in a single gland by more than 4:1 between ductal epithelial cells, naked glands in fat as well as metastatic deposit in one of three nodes included in the specimen, which all confirmed well differentiated adenocarcinoma of pancreas with extra-pancreatic extension to involve the spleen and metastasis in one of three nodes. Both ovaries showed features consistent with mucinous cystadenoma, with no features suggestive of malignant change, however it is known that metastases to ovaries may simulate primary mucinous ovarian tumors. On checking back with the patient, it was reconfirmed that there was no family history of any of the cancer hereditary syndromes, like Lynch syndrome, FAP, familial breast cancer, Peutz Jeghers Syndrome or familial atypical multiple mole melanoma. It is known that occasionally metastases to ovaries may simulate primary mucinous ovarian tumors and this fact is being kept in mind as adjuvant therapy is being continued (Young and Hart, 1989; Meriden *et al*., 2011).

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