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Case Report

Malignant Epithelioid Peritoneal Mesothelioma Recurring after 5 years, Case Report and Literature Review

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Abstract

Malignant Peritoneal mesothelioma is a rare disease of the peritoneal lining and its aggressiveness vary depending on the biology of the tumor and the risk factors of the patient. We are reporting in the following case the history of a 69 years old gentleman working in a petrochemical area in Saudi Arabia, who developed an epithelioid malignant peritoneal mesothelioma with a peritoneal carcinoma index (PCI) of 26 and who had a completeness of cytoreduction of 0 (CC0) after neoadjuvant chemotherapy, sequential chemotherapy (SIC) cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), only to witness and survive a recurrence of his cancer 5 years after, revealing itself in a severe intestinal obstruction. Epidemiology, causes, diagnosis, pathology, risk factors, treatment and prognosis of this disease will be discussed in our discussion, insisting on the importance of regular surveillance to detect an early relapse of the disease and improve survival.

Keywords: Malignant Peritoneal mesothelioma; Cytoreductive surgery; Chemotherapy

1. Introduction

Malignant peritoneal mesothelioma (MPM) is a rare tumor presenting many challenges in diagnosis and treatment [1]. We will discuss a case of malignant peritoneal mesothelioma recurring after 5 years of cytoreductive surgery with completeness of cytoreduction 0 (CC0), and the challenges in the

diagnosis and management of this disease. We will insist on the importance of follow up imaging to detect an early recurrence of the disease and treat it promptly for a survival benefit [2].

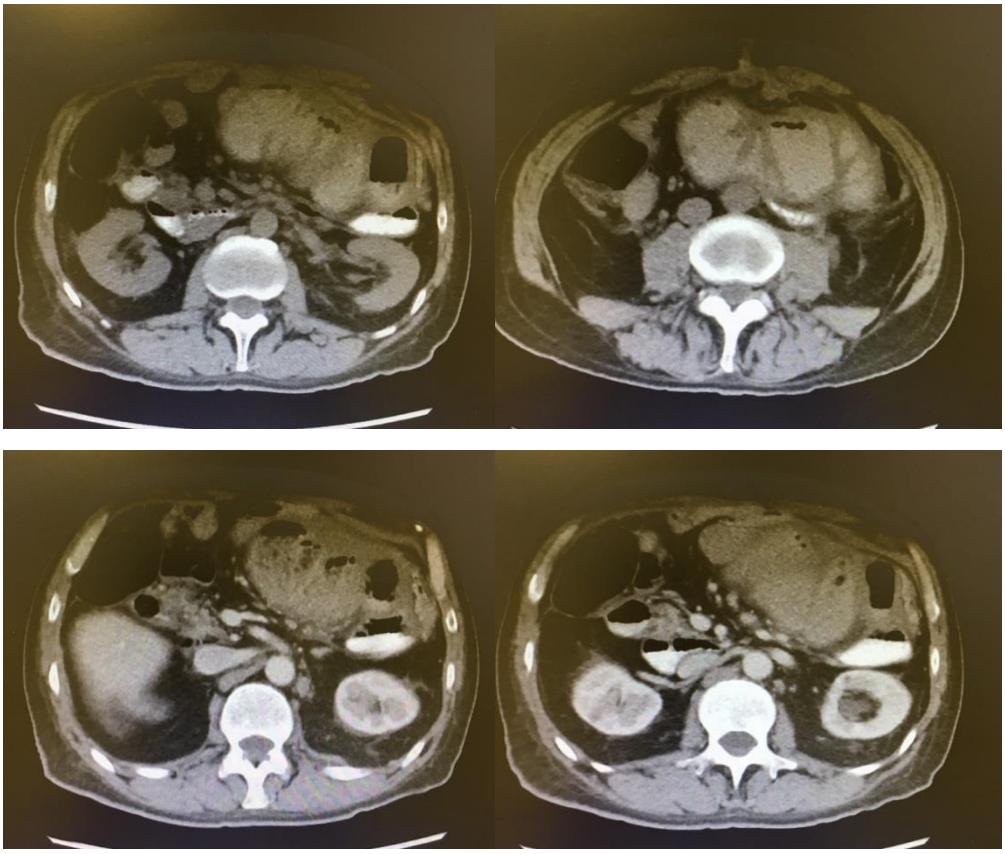
2. Case Presentation

It's a 69 years old gentleman with a history of HTN since 2005 on coveram 10/5 mg daily, non-smoker non-alcoholic, living and working as engineer in an industrial petrochemical area in Al-Jubayl, Saudi-Arabia. In November 2014, the patient was found to have moderate ascites on abdominal ultrasound done for intermittent dysuria. He came to Lebanon for investigation. Meanwhile he begins to develop symptoms of abdominal pain, bloating, nausea, vomiting and decrease appetite. Imageries were done and reveal ascites, omental caking, splenomegaly and no liver metastasis. CT guided biopsy was done and malignant peritoneal mesothelioma was found. Pet done in December 2014 and showed right iliac hyperfixation. He was started on neo-adjuvant intravenous chemotherapy, cisplatin and alimta, on January 2015, and was advised to go to France for an exploratory laparoscopy and HIPEC. The patient was getting better on chemotherapy. He had no more abdominal pain and the amount of ascites was decreasing. Exploratory laparoscopy was done on July 2015 showing extended lesions all over the peritoneal cavity. All abdominal quadrants were involved. Ascites was drained and some of the peritoneal nodules were resected and sent for pathology. PCI was estimated. An Intraperitoneal catheter was inserted during the laparoscopy for sequential chemotherapy (SIC). So the chemotherapy was switched to alimta intraperitoneal 500mg/DT associated to systemic cisplatin. The histology came back few days after, revealing: tubular and trabecular architecture and cubic cells and desmoplastic stroma, fat tissue infiltrate, calcospherites in middles of fibrosis, paucity of anisocaryosis and rare mitosis. On immunohistochemistry (IHC): calretinin positive, CK5/6 positive, D2-40 positive, WT positive, ACE and BerEp4 negative compatible with a diagnosis of peritoneal mesothelioma.

ACE: 2, Ca19-9 <1, Hb:11.3, plt: 114 000, leucocytes: 6.4, GFR: 56 creat: 117 umol. Cisplatin was switched to carboplatin AUC 5, due to a borderline kidney function.

After 4 cycles of SIC, another exploratory laparoscopy was done on November 2015 revealing a potentially resectable disease with a PCI of 26. Pathology revealed diffuse fibrosis and necrosis. In february 2016, a Complete Cyto-Reductive Surgery (CRS) was done followed by a HIPEC. Anterior resection of the rectum, and ileo-colectomy, splenectomy, omentectomy, cholecystectomy, multiple peritonectomies and Glisson capsule destruction were accomplished. PCI was at 30. Oxaliplatin IP 600 mg/m^2 was given. 12 Lymph nodes were extracted all came back negative. No sarcomatoid component was found. Diffuse fibrosis was noted on pathology. No postoperative complications. The ileostomy was closed later on. There was no indication to an adjuvant CT. He was cured from his disease and came back to Saudi-Arabia where he lives with his wife. He was doing well until June 2020, when he began to have severe abdominal pain, bloating, nausea and vomiting. He presented to a local hospital and underwent an ultrasound of the abdomen revealing a moderate amount of turbid fluids more in the center of the abdomen, and dilated bowel loops. CT scan of the abdomen and pelvis revealed mild ascites with left paraumbilical hernia containing mesenteric fat and bowel loops, with partial small intestinal obstruction.

The small bowel wall was thickened with multiple fluid level with mild dirty mesenteric fat, contrast seen in rectum indicating partial intestinal obstruction. He was scheduled for a laparoscopic repair of his ventral hernia with mesh under general anesthesia. Unfortunately, the operation was converted to an open exploration and adhesiolysis due to intestinal adhesions. Small bowel resection was done due to the presence of two suspicious grayish firm ill-defined masses infiltrating the whole wall thickness and immediate mechanical anastomosis was decided. The pathology came back as follows: the two masses detected at the larger intestinal segment and the numerous subserosal nodules have the picture of infiltrative moderately differentiated carcinoma with glandular differentiation, in favor of metastatic disease, with recurrence of mesothelioma as differential diagnosis. Two mesenteric LN were free of tumor deposits. Other LN were positive. The surgical resection margin showed subserosal tumor deposits. CT scan done on September 2020 showed irregular soft tissue thickening of the upper abdominal and parietal peritoneum with ill-defined soft tissue density along the stomach bed, the inferior aspect of Left diaphragm; mid and distal portions of transverse colon also showed luminal narrowing. Markedly dilated fluid filledjejuinal loops reaching a diameter of 5 cm, with mild diffuse mural thickening.



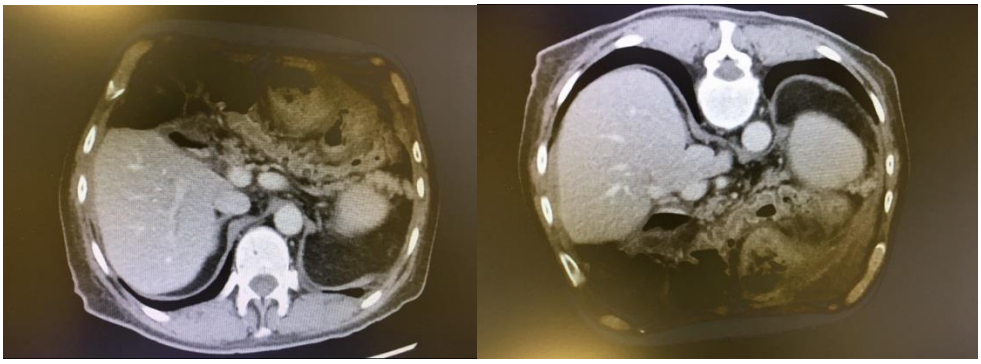
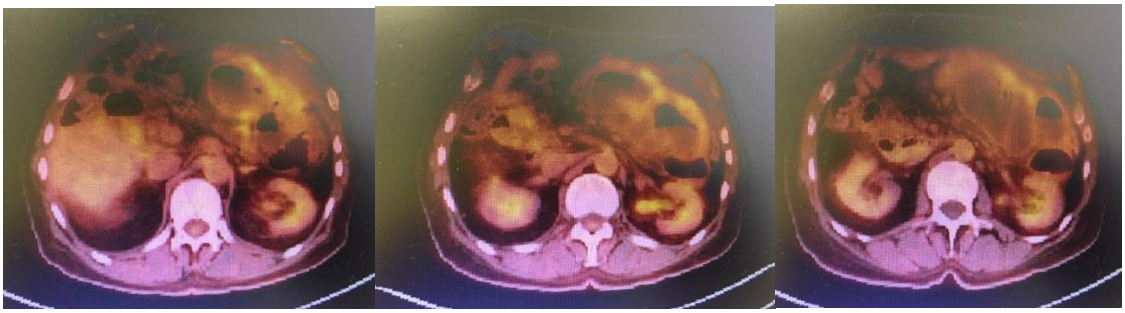


Figure 1: CT scan showing irregular soft tissue thickening of the upper abdominal and parietal peritoneum with ill-defined soft tissue density along the stomach bed, the inferior aspect of Left diaphragm; mid and distal portions of transverse colon also showed luminal narrowing. Markedly dilated fluid filled jejuinal loops reaching a diameter of 5 cm, with mild diffuse mural thickening

Pet-Ct done in September 2020 reveals diffuse irregular area of increase FDG uptake (SUV=3) corresponding to CT findings of peritoneal and omental thickening, focal area of increased FDG uptake (SUV=3.7) corresponding to CT scan findings of peritoneal deposits, its active component measures 1.7*1 cm just anterior to the head of pancreas, focal area SUV 4.2 within the colon anterior to the level of R renal pelvis, likely physiologic FDG accumulation. Few sclerotic bone lesions within both iliac bones with no FDG uptake. So a hypermetabolic active malignant peritoneal and omental thickening with deposit denoting a disease recurrence was concluded.



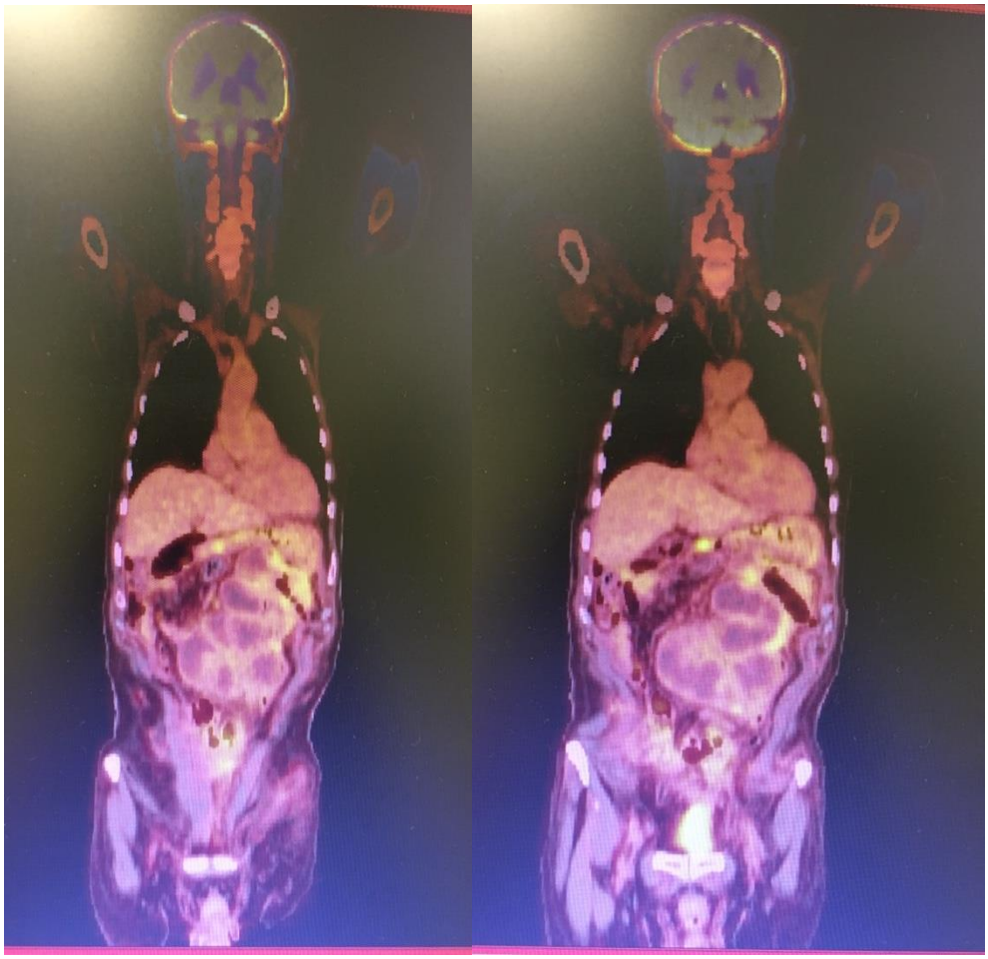


Figure 2: Pet scan showing diffuse irregular area of increase FDG uptake (SUV=3) corresponding to CT findings of peritoneal and omental thickening

The patient came to Lebanon in October 2020 for care and management. An exploratory laparoscopy was done on October 2020. Major adhesions all over the abdomen between the small bowels and the parietal peritoneum were found with recurrence of the disease in the R and L upper quadrants and midline. A peritoneal catheter was inserted.

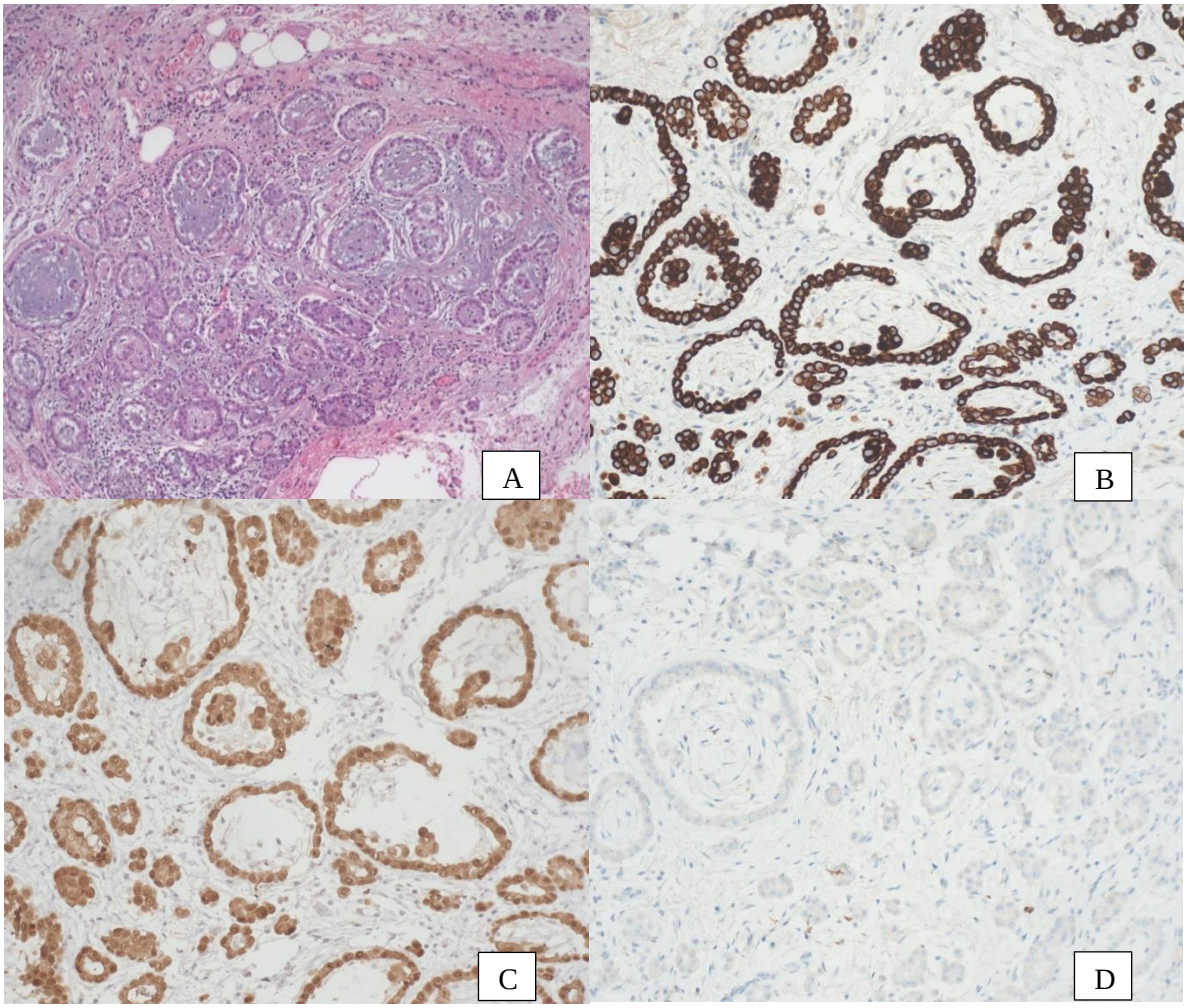


Figure 3: A: Epithelioid mesothelioma (H&E x200); B: CK7 immunostain highlighting the mesothelioma cells; C: Calretinin immunostain highlighting the mesothelioma cells; D: B72.3 immunostain negative in the mesothelioma cells.

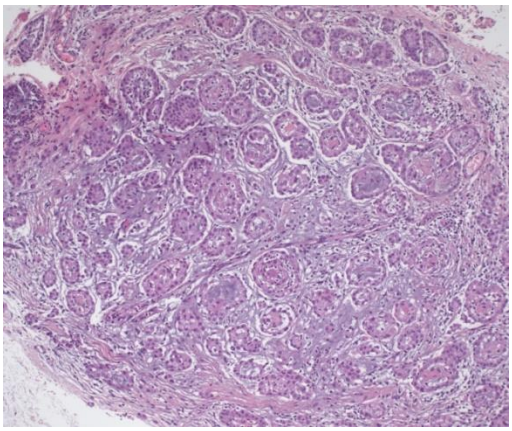


Figure 4: Epithelioid mesothelioma: Nests of mesothelioma are present in a desmoplastic stroma. (H&E x200)

A 1.4cm x 1.2cm fragment of membranous tissue was sent to pathology. Histopathologic examination showed nests of mesothelioma involving peritoneal tissues. Immunohistochemistry performed with adequate controls show that the tumor cells expressed CK7 and Calretinin (a mesothelial cell marker), while negative for B72.3. This immunostaining profile was consistent with a diagnosis of mesothelioma.

3. Discussion

Mesothelioma is a malignancy of the mesothelial cells and can occur in pleura, peritoneum, pericardia and tunica vaginalis [1]. Peritoneal Mesothelioma is a rare disease of the peritoneal lining and its aggressivity vary depending on its biology [3]. Its epidemiology vary worldwide between 2 to 30 per million by population, and constitutes 10 to 30% of all mesotheliomas (4). Statistical data show that MPM will reach its peak at 2030 [1] and in 2040, asbestosis will no more be linked to new cases of mesothelioma in US [2] Malignant peritoneal mesothelioma (MPM) differ from pleural mesothelioma. We summarized in table 1 the principle differences [1,2,3]. MPM is the most common primary peritoneal cancer [5]. It was first described in 1908 by Miller & Wynn in a 32 years old gentleman [6]. Its pathogenesis especially in those without clear risk factors remain unclear. Studies show recurrent mutations in tumor suppressor genes, DNA repair, cell cycle regulation and epigenetic regulators including BAP1, NF2, SETD2, p53. EWSR1-YY fusion, EWSR1-ATF1 fusion and FUS-ATF1 fusion genes are seen but their implication in the pathogenesis of MPM is still poorly understood [7]. Its presentation is atypical, that's why most often there is a delay in the diagnosis [8]. It presents usually with a symptomatology of diffuse abdominal pain, girth due to ascites, bloating, nausea, vomiting, weight loss, dyspnea, chest pain, dysuria, new onset of an abdominal wall hernia and can be the cause of bowel obstruction and cachexia [9,10]. We rely on Computed Tomography (CT) scan with iv contrast for diagnosis [11]. On CT we usually find enhancing heterogenous and irregular soft tissue masses, omental caking, thickness of peritoneum. There is no discrete primary site of the disease. Lymph nodes positivity and liver metastasis are found in very rare cases when the disease is in a very advanced stage. Cystic masses can also be detected. We summarized in table 2 the favorable and unfavorable findings on CT [3,8]. There is not a well-defined role of Positron emission tomography (PET) scan and Magnetic resonance imaging (MRI) in initial diagnosis [3,8]. We don't measure markers as Ca 125 routinely [2]. Gastro-colonoscopy and gynecologic exam needs to be done to rule out GI and gynecologic source of the peritoneal disease [2]. Three histologic subtypes are mainly seen at pathology but many variants exist. It's important to know the histology because it can alter the management. Epithelioid histology is the most frequent subtype and constitutes 75 to 90% of cases and has the best prognosis. We see normal mesothelial cells with predominance of tubulo-papillary and trabecular pattern. Sarcomatoid subtype is rare and aggressive and presents in lightly arranged spindle cells with malignant appearing osteoid, chondroid and muscular features. Biphasic subtype is a mixture of epithelioid and sarcomatoid elements. Other variants like pleomorphic, decidual, small and clear cells do occur [3,12,13]. It's so difficult to diagnose a MPM based only on cytology [14]. The results are usually inconclusive and the malignant character of mesothelial cells is not always obvious and IHC tests

demonstrating absence of BAP1 (BRCA associated protein 1) are needed to confirm MPM pathology [15]. We note that Loss of BAP1 expression exists in 60% of MPM and does not have a prognostic significance. So a CT-guided biopsy or biopsy via diagnostic laparoscopy is imperative to assess invasiveness for diagnosis [9]. Even with a biopsy, the diagnosis is incorrect in 44% of cases because of specimen insufficiency and physician inexperience [1]. IHC and genetic studies are indispensable to rule out the differential diagnosis like a metastatic carcinoma, peritoneal serous carcinoma or a benign mesothelioma [1]. In fact, there is no specific biomarker to Rule out or rule in a mesothelioma, rather there is a panel of mesothelioma markers (calretinin, Wilm's Tumor WT, cytokeratin 5/6, mesothelin, fubulin, D2-40) and a panel of carcinoma markers (human mesothelial C-1, thrombomodulin, CEA, TTF1, B72.3, MOC 31, Ber.Ep4, LeuM1, Bg8, ER, CD15, PAX8, PR, CD138, CK20) [1,9]. CK 7 is usually positive in MPM. The patient needs to have 2 positive mesothelioma markers and 2 negative carcinoma markers to consider a diagnosis of mesothelioma rather than carcinoma [9]. GLUT1, member of glucose transporter isoform family, is another marker important in differentiating a reactive mesothelioma from neoplastic tissue [5]. MPM tends to spread locally in an expansive way and not in an infiltrative way. Rarely it metastasizes to lymph nodes (LN) and distant locations [9]. That's why we don't use the typical TNM staging system for MPM. The peritoneal carcinoma index (PCI) is widely used and it serves for prognostication of the disease [16]. It measures disease spread and was first described for all kind of peritoneal carcinomatosis. It can be calculated by CT or diagnostic laparoscopy. There is no statistical difference between the 2 approaches. To calculate it, the abdomen is virtually divided to 9 segments and the bowel and mesentery to 4 segments. Each segment gets a score from 1 to 3 depending on the size of the largest lesion present in this segment. So the PCI score will vary between 0 and 39. Yan et al established a TNM stage based on PCI quartiles and survival [11], (table 3). PCI help also in making the decision to do a CRS [8]. There is a Dutch simplified version of PCI (SPCI) with a score from 0 to 21 that asses also disease spread across the abdomen [17]. For a CRS to be successful, the completeness of cytoreduction (CC) has to be 0 (no visible residual disease) or 1 (residual disease <2.5 mm) [18]. Historically, the treatment was by chemotherapy with a poor response rate (RR) [19]. The standard of care for this disease nowadays is cytoreductive surgery and HIPEC combined with a huge survival benefit; 6 months without treatment to more than 5 years survival with CRS and HIPEC [9]. Favorable and unfavorable risk factors exist, and they help in selecting patients who can undergo a curative surgery [5]. We summarized them in table 4. We note that in academic and specialized center, high risk patients tend to undergo cytoreductive surgery [4]. For example, in patients who have biphasic histology, there is a survival benefit when CRS-HIPEC is done (20). Patients with unfavorable risk factors tend to have a reserved prognosis. They also tend to have early recurrence and rapid progression after a surgical intervention, if an intervention were to be done [21]. In patients with severe cardiac, hepatic or renal function, poor PS, extensive involvement of small bowel and mesentery, extra-abdominal disease or para-aortic LN, CRS-HIPEC is contra-indicated [22]. A bi-cavitary mesothelioma is a relative contra-indication for surgery. In some instances, a bi-cavitary surgery with diaphragm resection with bi-cavitary chemoperfusion may be used [19]. Trials have also studied other forms

of delivering chemotherapy like normothermic early post-operatory CT (EPIC) of paclitaxel or alimta anytime between d1 and day 7, or sequential CT (SIC), IP or systematically or both IP and iv in post op setting or anytime and results were all promising [23]. But CRS-HIPEC is the preferred combination. And the RENAPE study demonstrated that patients extract the most benefit from a platinum based combined CT. cisplatin and pemetrexed confer a 71% disease control rate [24]. Often than not, if the tumor is not resectable, patients undergo an induction CT iv and/or IP in the hope that the tumor become resectable in the future [9]. There is no data on if 2 steps CRS is beneficial in cases difficult to resect [19]. 60% of patients may not receive surgery [25]. For inoperable cases, systemic therapy is used with an OS of 13 months. almost all the available data about Chemotherapy treatment are retrospective or by extrapolation of pleural mesothelioma data. For example, the latest ASCO guidelines cites that the efficacy of cisplatin -alimta is same in pleural and peritoneal mesothelioma. So the treatment plan should be individualized as the role of CT in the neoadjuvant and adjuvant setting is not well established [19]. There are several ongoing studies on the place of targeted therapy in the treatment of MPM. Alk rearrangement is prevalent in young patients who were not exposed to asbestosis. Thus the questionable role of alk inhibitors in this setting [26]. First generation EGFR inhibitors have been proven not to have any role in MPM. But studies show that nintedanib, an angiokinase inhibitor targeting VEGF, FGF, Src and Abl kinase signaling has a Progression free survival PFS benefit when combined to cisplatin and alimta [27]. Studies also show that bevacizumab has an overall survival OS benefit when combined to cisplatin and alimta. But its use may complicate any planned operation intervention [28]. Studies are also ongoing on the place of phosphoinositide 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) in the management of MPM [29]. There are ongoing trials on immunotherapy, CTLA4 inhibitors and anti PD1 antibodies and their role in treatment of MPM. No results exist yet. Mesothelin, a cell surface glycoprotein and tumor differentiation antigen which stains along cell membrane in MPM contrary to adenocarcinoma where it stains only focally and in cytoplasm, is an attractive candidate for immunotherapy. Anti-mesothelin Antibody: amatuximab, has been studied in vitro and has promising results [1]. Surveillance of the disease by bi annual physical exam, symptom review and CT with po and iv contrast for the first 5 years then annually is indispensable. An early detection of recurrence of MPM while the patient is asymptomatic is correlated with better prognosis. Studies show that repeating CRS-HIPEC is associated with long term survival, although we have less chance to achieve a complete CRS in subsequent operations [21].

4. Conclusion

We are reporting this case of MPM to shed light on this rare disease and to consider it as differential diagnosis in any patient with diffuse malignant process in the peritoneal cavity. Its correct management has a survival benefit. Regular Surveillance and follow up imageries help in the detection of an early recurrence and initiate prompt treatment and thus has a survival benefit. Ongoing trials are promising, but more prospective and multicentric trials have to be done on this disease.

	Pleural mesothelioma	**MPM**
Frequency	More common	
Male to female ratio	More in men	More in women
Mean age at diagnosis	64	Yonger age than in men
		Non-Hispanic whites, black
Causes	Asbestosis++	Other mineral fibers: silicate fiber irionate ++ therapeutic RT, thorostat dye, Germline genetic alteration++, unknown causes
Time from exposure to diagnosis	30 years	20 years
Genetic alteration	No alk rearrangement	Alk rearrangement, germline BAP mutation++
IHC+	PAX8-	PAX8+

Table 1: Differences between Malignant peritoneal mesothelioma (MPM) and pleural mesothelioma

Favorable findings	**Unfavorable findings**
Ascites	No ascites
Minimal soft tissue mass	T>5cm in lesser omentum, sub-pyloric spaces and jejunal regions
Normal small bowel and mesentery	Anatomic distortion of the bowel, bowel obstruction
	hydroureter
No lymph nodes	Mesenteric and para-aortic lymph nodes

Table 2: Favorable and unfavorable findings on CT

PCI	**T**	**Stages**	**5 years survival**
1-10	T1	Stage I	87%
11-20	T2	Stage II (N0M0)	53%
21-30	T3		
31-39	T4	Stage III (N0 orN1 M0 or M1)	29%

Table 3: PCI quartiles and TNM stage

Favorable risk factors	**Unfavorable risk Factors**
Women	Men
<60 years old	More than 60 years old
Ki67<10%	High grade, Ki 67>10%, mitotic rate
Epithelioid histology	Biphasic or sarcomatoid histology
In favor for CC0 or CC1 CRS	Large burden of disease at presentation
No positive Lymph nodes	Positive Lymph nodes
Good PS	
Absence of pretreatment thrombocytosis	Thrombocytosis
	Deep tissue invasion, T on small bowel or mesentery
Low level of Osteopontin (OPN) on IHC	High level of OPN on IHC

Table 4: Favorable and unfavorable risk factors

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