



Localized Biphasic Malignant Peritoneal Mesothelioma: Two Case Reports in Atypical Location and Literature Review

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Abstract

Background: Peritoneal mesothelioma is a rare tumor of serosal membranes. Mesothelioma peritonei imaging is poorly described and the correlation between imaging pattern and histologic subtype is quite limited. Under a common name, mesothelioma peritonei is actually composed of five histologic subgroups (2 benign and 3 malignant) with quite different behavior and prognosis. Among these five subtypes, Biphasic mesothelioma is the rare subtype with dismal prognosis, often presenting as a bulky mass pattern (localized form).

Case presentation: We report two cases of localized biphasic malignant peritoneal mesothelioma initially presented on imaging as gastro intestinal stromal tumor and as adenocarcinoma of the head of the pancreas, respectively. The initial pathological analysis after biopsy remained unclear with diagnosis of undifferentiated carcinoma.

Conclusion: Malignant mesothelioma peritonei may have different imaging features depending to their histology subtypes. Most of sarcomatoid and biphasic subtypes are localized presenting as one or a few bulky peritoneal masses without ascitis, involvement of the greater omentum and extraperitoneal sites.

Keywords: Biphasic mesothelioma; Localized mesothelioma; Peritoneal mesothelioma

Abbreviations: CRS: Complete Cytoreduction Surgery; CT: Computed Tomography; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; MPM: Malignant Peritoneal Mesothelioma

Introduction

Mesotheliomas are rare neoplasms that arise from the mesothelial cells lining the serosal membranes of body cavities. Most frequently mesotheliomas arise from the parietal or visceral pleura and less commonly in the peritoneum and pericardium. Peritoneal mesotheliomas are divided into 3 sub-groups with

very different presentation and prognosis; from the best to the worse prognosis: multicystic mesothelioma, benign papillary mesothelioma and malignant peritoneal mesothelioma (MPM) [1]. The last subtype is divided into 2 presentations, diffuse and localized, and 3 pathological categories: epithelioid, sarcomatoid and biphasic, which is composed by epithelioid and sarcomatoid cells in varying proportions [2-4]. Localized and biphasic subtypes are the least common forms. Only 9 cases of localized biphasic MPM have been reported in the literature and most of them were localized intrahepatic or within the abdominal wall [5-13]. Herein, we report two rare cases of extra hepatic localized biphasic MPM. We then discuss the different patterns of MPM focusing on correlation between histopathology and imaging.

Case Presentation

Case 1

A 35-years old woman presented with new-onset increasing abdominal pain that appeared first during a trip to Sri Lanka. The patient had no personal history of asbestos exposure but a positive family history (grandmother) of peritoneal cancer of undetermined origin. Clinical examination was unremarkable and laboratory data revealed an inflammatory syndrome. Computed tomography (CT) examination showed, on axial portal phase with coronal and sagittal reconstruction images, a voluminous abscessed mesenteric mass with fistulisation into the small bowel (Figure 1a-e). In addition, three supracentimetric peritoneal masses (between 2 and 3 cm) were localized in the left sub-phrenic region with heterogeneous contrast enhancement and central necrosis, as well as the presence of ascites and a right cardiophrenic angle lymph node. An 18F-FDG PET/CT was then performed showing a strong hypermetabolism of all peritoneal lesions (Figure 1f-h).

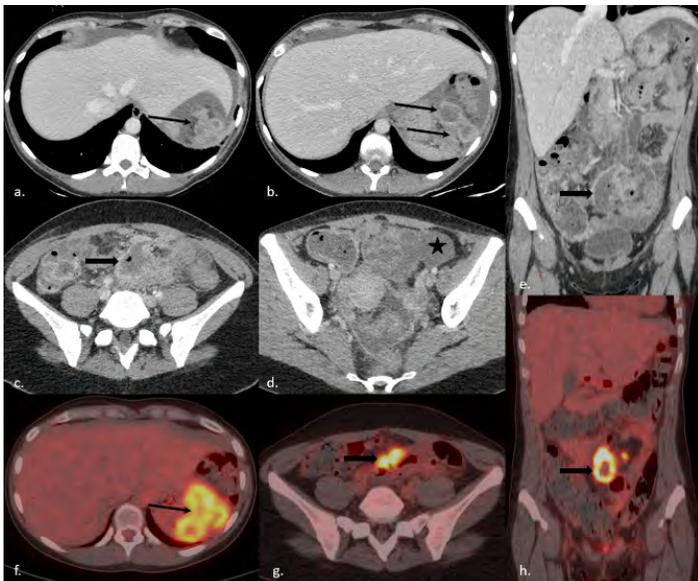


Figure 1: CT scan and PET-CT of case 1, CT scan in axial (a, b, c and d) and coronal (e) plan showing well defined peritoneal masses into the left hypochondrium (thin arrow) with peripheral enhancement and central necrosis, mesenteric mass with small bowel fistula recognizing by the air bubble (thick arrow) and ascites (star). Peritoneal and mesenteric masses were hypermetabolic on 18FDG PET-CT (f, g, h).

Given these imaging features, a broad differential diagnosis was proposed. Based on the small bowel impairment with necrotic mass associated with large and heterogeneous peritoneal nodule, a gastro-intestinal stromal tumor (GIST) was first advanced. Other differential diagnosis included adenocarcinoma of the small bowel

with peritoneal carcinomatosis (with unusual large and necrotic peritoneal implants) and a desmoplastic small-round-cell tumor (with unusual clinical presentation as most of these tumors occur in male children or young men). An ultrasound-guided biopsy of a left sub-phrenic lesion was finally performed with histopathological diagnosis of undifferentiated carcinoma. The patient received 4 cures of neo-adjuvant chemotherapy with cisplatin regimen allowing partial response according to RECIST 1.1 criteria. A surgery was then performed including a complete cytoreduction surgery (CRS) with ileo-colic, gall bladder, omentum and parietal peritoneum resection followed by a hyperthermic intraperitoneal chemotherapy (HIPEC). The final pathology revealed a malignant tumor infiltrating the intestinal wall, consisting predominantly of trabeculae and bundles of cohesive, round or polygonal cells with eosinophil cytoplasm and severe atypia admixed with more spindled, fusocellular atypical cells disposed in sheets (Figure 2a,b). The immunohistochemical analysis revealed a mixed immunophenotype, disclosing a diffuse immunoreactivity for mesothelial markers like calretinin and podoplanin (Figure 2c) and partial immunoreactivity for epithelial markers as CKAE1/AE3 and CK5/6. No adjuvant treatment was proposed. Patient died 32 months after diagnosis.

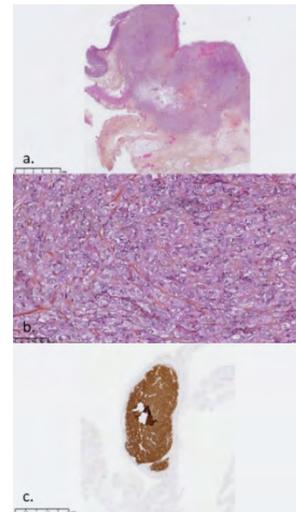


Figure 2: CRS procedure specimen pathology images. a,b. Hematoxylin and eosin stain (HE) showing atypical biphasic proliferation infiltrating intestinal wall with epithelioid and sarcomatoid cells admixed (x2, a. and x20, b.). c. Immunohistochemistry (IHC) slide showing diffuse calretinin immunoreactivity (x20).

Case 2

A 75 years-old man presented with a recent history of increasing abdominal pain without further complaints. The patient had personal history of tuberculosis treated in

childhood, no asbestos exposure and no family history. Clinical examination was unremarkable and laboratory data revealed an inflammatory syndrome. CT scan showed, on axial portal phase, a poorly defined mass centered on the duodeno-pancreatic sulcus extended over 7cm with circumferential thickening of the second duodenum (Figure 3). The mass was heterogeneous with moderate enhancement. No vascular involvement was observed. There was a mass effect on the Wirsung canal with consecutive dilatation upstream but normal bile ducts. There were no other findings on CT. Secondly, an 18F-FDG PET/CT was performed finding a marked hypermetabolism of the mass. Adenocarcinoma of the head of the pancreas was suspected. A biopsy was performed under echo-endoscopy guidance and histopathological examination of biopsy samples revealed an undifferentiated carcinoma. Patient underwent duodenopancreatectomy. Final pathology analysis reported a 9 cm-large ulcerative mass centered on the papilla, invading duodenal wall, without invasion of the pancreas (Figure 4). The mass consisted histologically of a biphasic proliferation of epithelioid, cohesive cells with abundant eosinophilic cytoplasm and sarcomatoid cells, spindle or round shaped, pleomorphic, with indistinct borders and mitotically active. There were no vascular or nervous invasion and no lymph node metastasis. The immunohistochemical analysis on tumor cells disclosed a strong immunoreactivity to epithelial markers such as CK7 and CK5 and to mesothelial markers as podoplanin. Tumor cells were also immunoreactive to WT1, partially. No loss of BAP1 was observed. Tumor cells were negative for others markers. Resection was considered as complete and no adjuvant treatment was proposed. Patient had been doing well without recurrence for six months after surgery.

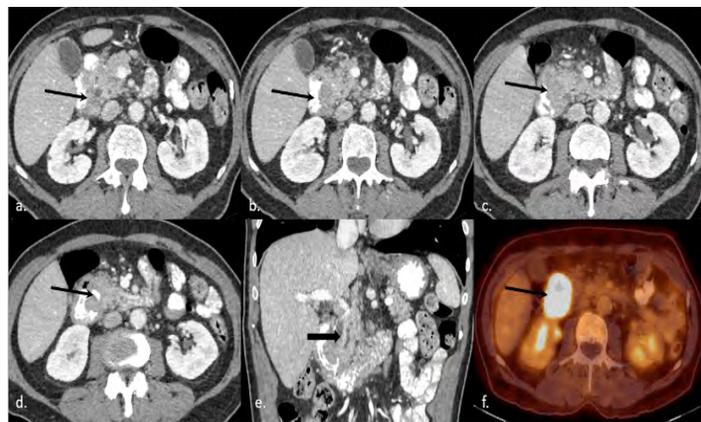


Figure 3: CT scan and PET-CT of case 2, Axial CT scan (a, b, c, d, e) and PET-CT (f) showing mass syndrome of the head of the pancreas with circumferential thickening of the second duodenum (thin arrow). Wirsung is moderately dilated (thick arrow). This mass is heterogeneous with poorly delimited wall. On PET-CT mass is clearly hypermetabolic.

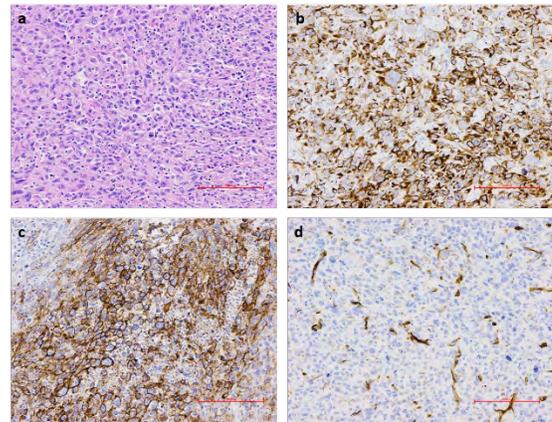


Figure 4: Whipple procedure specimen pathology images. a. HE slide showing atypical biphasic proliferation with epithelioid and sarcomatoid cells admixed (x20). b. IHC slide showing CK7 immunoreactivity (x20). c. IHC slide showing Podoplanin immunoreactivity (x20) d. IHC slide showing partial WT1 immunoreactivity (x20).

Discussion

Mesothelioma peritonei imaging is poorly described and the correlation between imaging pattern and histologic subtype is quite limited. Under a common name, mesothelioma peritonei is actually composed of five histologic subgroups (2 benign and 3 malignant) with very different behavior and prognosis. On imaging, mesothelioma peritonei is characterized by 3 different patterns:

- A multicystic mass: this pattern is very specific for multicystic mesothelioma. It appears as multiple and translucent cysts forming a confluent mass with bunch of grapes appearance and thin septation classically found in the pelvis [14]. This is a benign tumor with a low risk of malignant transformation and an excellent prognosis. It occurs mainly in young to middle-aged women. Thanks to the combination of complete cytoreduction surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC), recurrence free survival at 5 years is about 84% [15]. Its major differential diagnosis on imaging is the lymphangioma.

- A peritoneal carcinomatosis-like pattern: both, benign papillary mesothelioma [16] and malignant epithelioid mesotheliomas may have this nonspecific pattern. The peritoneal involvement is often diffuse, featuring predominant ascites and involvement of the greater omentum. Peritoneal plaques or nodules, sometimes calcified, peritoneal thickening, or solitary mass can also be observed [17]. Epithelioid mesothelioma is the only form linked to asbestos exposure, occurring typically 20-50 years after exposure. Well-differentiated papillary mesothelioma most commonly occurs in young women and has no association

with asbestosis exposure. No key imaging feature allows for the differential diagnosis between the benign and malignant subtype and a biopsy is generally necessary for diagnosis. Lymph node involvement is present in about 10% of patients with epithelioid subtype and has a poor prognosis [18]. The solid subtype has been shown as an independent risk factor for worse overall survival [19]. Patient with the epithelioid histological type have a median overall survival of 18 months whereas the benign papillary subtype has favorable outcome [20].

- **Bulky mass pattern:** This pattern is most commonly depicted in the sarcomatoid and biphasic MPM subtypes occurring in younger patients than other histologic subtypes. Peritoneal involvement is characterized by peritoneal masses that are often multiple but not diffuse, large in size and with necrotic appearance like in our first observation (Figure 1). The greater omentum and peritoneal surface and no extraperitoneal sites are observed.

On microscopy, MPM are classified depending on their morphological aspects into 3 variants with prognostic and therapeutic implications. The most common variant is the epithelioid MPM (75%), followed by the biphasic MPM (25%), the pure sarcomatoid variant [21,22] being extremely rare. The biphasic subtype is composed of epithelioid and sarcomatoid cells in varying proportions (each comprising at least 10% of the tumor) and histologic patterns. Prognosis mainly depends on the sarcomatoid part. Thus, the sarcomatoid subtype had a median survival of 7 months and the biphasic subtype 10 months [20].

Currently, only few case reports with localized biphasic MPM have been reported in the literature. Interestingly, their imaging and clinical presentations are variable. In our two cases, both were discovered through abdominal pain investigation. The detailed characteristics from relevant publications and from our present cases are summarized in Table 1. Localized biphasic MPM seems to affect both men and women (6 men versus 5 women) even if, for all MPM, literature described higher incidence in men [23]. It seems that incidence increases with age since 9/11 patients (82%) were over 50 years old. While asbestos exposure is a recognized risk factor for pleural mesothelioma [24] and the epithelioid subtype of mesothelioma peritonei [25], the risk factor was in 2 of the 11 reported cases of localized biphasic MPM. Location is variable, with frequent sites in the abdominal wall (4/11) or in the liver (3/11). Biologically, the most frequently found abnormalities are anemia (4/11) and inflammatory syndrome (4/11). In our review, tumoral markers (CEA, Ca 19.9, Ca 125)

were normal. Literature reports that high serum levels of CA-125 could be observed in case of peritoneal mesothelioma [26,27]. It was suggested that CA-125 might be helpful in the diagnosis and follow-up of MPM especially in women, and MPM should be included in the differential diagnosis in a woman with high level of CA-125 and diffuse peritoneal spread. In our review, no patients presented elevated CA-125 level. However, this biological data was available only for 3 women patients including our first case [6,11].

Imaging features are not specific. Patients often have a large mass (from 40mm to more than 200mm) with central necrosis (7/11) and well defined boundaries (7/11). Enhancement is often peripheral (8/11) with possible septas. Calcification is rare but possible. Finally, ascites is sometimes observed (3/11). In imaging, there is no difference between different histological type of localized MPM (epithelioid and sarcomatoid) and final diagnosis is made by pathology. Pathological diagnosis can be established based on different types of sample but remains challenging overall: ascites fluid, fine needle aspiration or tumor biopsy. Ascites cytological analysis has a very low diagnostic yield, due to a usual small number of tumor cells in the fluid, having a varied range of morphological aspects, that can be hard to distinguish from reactive mesothelial cells [21]. However, preoperative diagnosis of MPM remain challenging, as the broad variety of morphological aspects of MPM, bring up many differential diagnoses of carcinomas, sarcomas, spindle cell neoplasms and mixed or biphasic tumors. Most MPM are also heterogenous and can disclose in the same tumor several patterns that can be very focal and a biopsy may not be representative of the whole tumor or lead to misdiagnosis depending on the portion biopsied. Immunohistochemical analysis is very helpful in diagnosis of MPM, but no single marker is specific. It is recommended to use two different positive mesothelial markers (for instance calretinin, WT1, podoplanin) and two positive epithelial markers (for instance broad spectrum keratins, CK5/6, EMA) for diagnosis of MPM [28]. Other markers will be used for excluding differential diagnosis depending of the MPM morphology. Furthermore, molecular analysis can be interesting in some cases as a diagnosis or prognosis marker (in particular alterations regarding CDKN2A, BAP1, NF2 genes). In our two patients, the initial pathological analysis after biopsy was unclear with diagnosis of undifferentiated carcinoma. It is in agreement with others cases for which needle biopsy was moderately contributive and the final histological analysis was made in the on the surgical base or during the autopsy [5,8,12].

Autor study	Year	Gender	Age	Asbestos exposure	Location	Size (mm)	Clinical findings	Biological findings	Tumoral markers	Boundaries	Central necrosis	Enhancement	Calcification	Ascitis	Treatment	Outcomes
Sasaki (5)	2009	Male	66	Yes	Intrahepatic	40	.	Normal	Normal	Well delimited	No	Peripheral	No	No	Surgical Resection	Alive without recurrence at 6 months
Shao (6)	2011	Female	77	No	Right abdominal wall	very large	Palpable mass	Normal	Normal	Poorly delimited	No	Moderate and late	No	Yes	Symptomatic	Died six months later due to gradual deterioration
Kohno (7)	2012	Male	69	Yes	Left abdominal wall	107	Abdominal pain	Normal	.	Well delimited	Yes	Peripheral	No	No	Surgical Resection	Alive without recurrence at 7 months
Takehara (8)	2014	Male	72	No	Transverse colon	100	Palpable mass	Inflammatory syndrom	Normal	Poorly delimited	No	Peripheral	No	No	Surgical Resection	Peritoneal metastasis at 7 months and death at 18 months
Serter (9)	2015	Male	66	No	Intrahepatic	220	Abdominal pain	Anemia	Normal	Well delimited	Yes	Peripheral	No	No	Surgical Resection	.
Haji (10)	2016	Female	41	No	Intrahepatic	210	Abdominal pain	Anemia	.	Well delimited	Yes	Peripheral with septas	Yes	No	Surgical Resection	.
Hassan (11)	2018	Female	69	No	Right abdominal wall with liver and colon invasion	90	Abdominal pain and fatigue	Inflammatory syndrom and anemia	Normal	Poorly delimited	Yes	Peripheral	No	No	Surgical Resection + adjuvant chemotherapy	Disease recurrence (hepatic and peritoneal). Death within 6 months
Saisho (12)	2019	Female	84	No	Rectum	80	Bloody stool	Anemia	Normal	Well delimited	Yes	Peripheral	No	No	Palliative chemotherapy	Death at 4 months
Liu (13)	2020	Male	79	No	Right pelvic wall	80	Constipation	Normal	.	Well delimited	Yes	Moderate and late	No	Yes	Surgical Resection	Local recurrence at 4 years. Death at 6 years
Present case 1	2020	Female	35	No	Mesenteric and peritoneal mass	50	Abdominal pain	Inflammatory syndrom	Normal	Well delimited	Yes	Peripheral	No	Yes	Surgical resection (CRS/HIPEC)	Death at 32 months
Present case 2	2020	Male	75	No	Duodeno-pancreatic sulcus	90	Abdominal pain	Inflammatory syndrom	Normal	Poorly delimited	No	Moderate and late	No	No	Surgical Resection	Alive without recurrence at 6 months

Table 1: Literature review of localized biphasic malignant peritoneal mesothelioma.

MPM treatment is complex. The combination of complete cytoreduction surgery with hyperthermic intraperitoneal chemotherapy (CRS / HIPEC) is a fundamental step in the management of diffuse mesotheliomas [16]. Since the biphasic subtype is exceedingly rare and has a poor prognosis (due to its sarcomatoid component), it has long been considered a contraindication to surgery. Nevertheless, Votanopoulos et al. [29] specifically assessed the impact of CRS/HIPEC on the biphasic subtype and concluded that CRS/HIPEC was an acceptable option in limited disease if complete cytoreduction could be achieved. In addition, Allen et al. [30] evaluated the outcome after surgical resection of isolated pleural and peritoneal mesothelioma and showed that these isolated tumors recurred in the form of a loco-regional mass and not as pleural or peritoneal carcinomatosis. Thus, like in the 2 patients presented, we can propose, in case of localized biphasic MPM, a complete surgical resection without HIPEC; in case of biphasic MPM extended to peritoneum we suggest to perform a CRS/HIPEC if complete resection can be obtained. If surgery is possible and using this algorithm, early survival is acceptable. However, if patients are not eligible for complete surgery, the short-term prognosis is poor (death within 6 months). In all cases, and even if surgery is complete, long-term survival is moderate with a 5-years survival of about 50% (29).

Conclusion

In conclusion, localized biphasic MPM is rare without specific character on imaging. However, some characteristics should alert the radiologist to localized MPM: large tumor well delineated with central necrosis and peripheral enhancement centered on a location of peritoneum (abdominal wall, around peritoneal folds).

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