Diffuse malignant biphasic peritoneal mesothelioma with cystic areas
A rare case


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We report a case of peritoneal biphasic mesothelioma with cystic areas in a patient with professional exposure to asbestos. It showed focal epithelial glandular and papillary proliferations, also presenting fluid filled cysts, whose wall consisted of a proliferation of spindle cells. Atypia and mitoses were very scanty. EMA, vimentin, CK5/6, D2-40, calretinin and P53 were positive and desmin was negative in both epithelial and spindle areas, including the ones surrounding the cystic spaces. These findings gave an essential aid in the differential diagnosis with a benign cystic mesothelioma and with a cystic epithelial mesothelioma with secondary pseudosarcomatous myofibroblastic proliferation. The presence of cystic areas in a malignant mesothelioma could make difficult the diagnosis. A large amount of tumour tissue is necessary for confirming the biphasic histotype, an aggressive histotype, even in the presence of mild histological features and of some others favourable clinical prognostic indices as in this case. To our knowledge this is the first case of malignant peritoneal biphasic mesothelioma with cystic features reported in the literature.

KEY WORDS: Cystic Mesothelioma, Immunohistochemistry, Malignant Mesothelioma, Peritoneal Diseases, Mesothelial Neoplasms

Introduction

Diffuse malignant peritoneal mesothelioma is a rare entity. It is difficult diagnose due to its different clinical and morphological presentations. The relation with exposure to asbestos is 33%, less marked than in the pleural disease. The prognosis is still considered extremely unfavorable with a mean survival of 5.4 months. The introduction of cytoreductive surgery and intraperitoneal chemotherapy has brought improvements in terms of prognosis in selected cases in referral centers.

We describe a biphasic peritoneal mesothelioma in a patient with a thickening in the parietal peritoneum and with cystic areas filled of fluid. The patient who was clinically diagnosed as a Crohn's disease in another hospital showed bowel loops with thickened walls. Due to the cystic features of the neoplasia, the true nature of malignant biphasic mesothelioma was not obvious; it came out only through the histological and immunohistochemical analysis. It is important to note that cystic areas in malignant mesothelioma had been very rarely reported. To our knowledge, this is the first case of biphasic mesothelioma with such histological features.
Case Report

The patient, a 73-years-old man, with an anamnesis of professional exposition to asbestos, was urgently admitted in a peripheral hospital with pain in the inferior abdominal quadrant, vomitus, constipation and ileus. The initial clinical assumption was appendicitis with peritonitis, therefore the appendectomy was performed. The histological examination of the appendix didn't show any inflammation. Furthermore, due to the intra-operative presence of edema and thickening of the wall of pre-terminal and terminal ileum (40-50 cm), easy to bleed (previously evidenced by computerized tomography (CT), the examination brought to an acute phase of Crohn's disease. Consequently, the patient started a medical therapy with Mesalazina and Betamethasone.

Occasionally, the patient kept showing abdominal pain in the right quadrant, constipation and a progressive weight loss (10 Kg). These symptoms drove him to our observation 1 year later. A thoracic CT highlighted the presence of partially calcified diffuse bilateral thickenings, radiologically identified as pleural plaques, in keeping with the history of exposure to asbestos. The CT-enterography revealed regular distension, thickness and contrast enhancement of the ileum and colon walls. A colonoscopy, performed to assess the Crohn's disease previously hypothesized, showed regular colonic and ileal mucosa; the intestinal biopsies revealed only slight aspecific inflammation. So the medical therapy for Crohn's disease was stopped due to lack of signs of disease.

The clinical examination evidenced diffuse abdominal pain without signs of peritonitis and with regular bowel sounds. Blood count, metabolic panel and liver function tests were within normal limits. Albumin was 3.2 g/dL. Tumor markers were in the normal ranges (carbohydrate antigen 19.9 (CA19.9) = 6 U/mL, carcinoembryonic antigen (CEA) = 1.08 ng/mL, cancer antigen 125 (CA125) = 12.2 U/mL). Tests for tuberculosis,
cytological and bacteriological analysis of the ascitic fluid and blood culture resulted negative. Conversely, the abdominal CT showed a diffuse and irregular thickening of the parietal peritoneum in the left quadrant, a cystic capsulated area with a fluid collection (2.3 cm x 1.6 cm) behind the superior part of the spleen (Fig. 1 arrow) and fluid filled areas in the rectus-bladder space. Abundant presence of ascites was evidenced. The mesentery showed hyper-density and centmetric lymph nodes. The wall of the right colon was thick, with irregular enhancement and with hyper-density of the perivisceral fat. Therefore, a peritoneal carcinosis of undetermined origin was suspected. Consequently, an explorative laparoscopy with the use of a three port technique was performed and it showed the presence of abundant red-brown ascitic fluid and many, firm, visceral-parietal adherences which thwarted the access to the abdominal cavity.

Conversely, the stomach and spleen were normal. While the liver presented a thickened capsule with widespread nodular lesions. The lesion in the sub-diaphragmatic left area, behind the spleen, suspected to be an abscess by the CT, was removed. Interestingly it was surrounded by fat yellow tissue (Fig. 2) and after cutting a large cystic area emerged. The lower quadrants were explored through a laparotomic access. The distal portion of the ileum was resected as it was surrounded by a thick and fibrotic capsule, the ileal loops were adherent each other and showed a thickened wall with diffuse lesions on the peritoneum and the mesentery, ranging from few mm to 2, 5 cm, on the peritoneum and the mesentery; the larger lesions were translucent and whitish in color (Fig. 3) and after cutting they showed a large central area of cavitation (Figs. 3, 4, 5).

Histologically the cystic formations were present in the peritoneum, mesentery and in the sub-serosa layer of the bowel. No alterations in mucosal, sub-mucosal and muscular layers were present in the bowel wall. The cystic lumen was partially filled of fibrous and sometimes necrotic material.

Fig. 5: Cystic formations in the sub-serosal layer of the bowel. No alterations in mucosal, sub-mucosal and muscular layers were present in the bowel wall. The cystic lumen was partially filled of fibrous and sometimes necrotic material.

Fig. 6: (A) Nodule with a large central cystic area with a wall lacking of epithelial lining and consisting of a proliferation of spindle cells among which were present focal glandular-like proliferations (arrows). HE stain X40. (B) Spindle cells in wall of the cyst, with mild atypias and scanty mitoses (arrow). HE stain X400. (C) Mildly atypical small glands in the sub-serosal layer. HE stain X100. (D) Multiple, small papillary projections in the serosal lining. HE stain X200.

Fig. 7: Positive immunostaining for CK5/6 in epithelial component (A) and in spindle cell component (B-C) including spindle cells surrounding the cystic areas (C). Positive immunostaining for D2-40 in epithelial component (D) and in spindle cell component, including spindle cells surrounding the cystic areas (E). A,B,C) CK5-6 X200; D) D2-40 X400; E) D2-40 X200.
subserosal layer and multiple small papillary projections in the serosa lining (Fig. 6 C, D).

The immunohistochemical assay showed positive immunostaining for epithelial membrane antigen (EMA), cytokeratin (CK) 5/6 (Fig. 7 A, B, C), podoplanin (D2-40) (Fig. 7 D, E), vimentin (Fig. 8 A, B), calretinin (Fig. 8 C, D, E), focal nuclear positivity for P53 and negative immunostaining for desmin (Fig. 9 A, B) both in epithelial areas and in spindle cell areas, including the ones surrounding the cystic areas. Finally, other immunohistochemical markers, such as CEA, B72.3, thyroid transcription factor 1 (TTF-1) and Ep-CAM/epithelial specific antigen (Ber-EP4) stained negatively.

The histological and immunohistochemical findings confirmed the diagnosis of malignant biphasic mesothelioma. Noteworthy, both components of the tumor (epithelial and spindle cells component) showed very few atypia and very few mitoses, keeping with a low histological grade. The ascitic fluid was negative for neoplastic cells. The Peritoneal Carcinomatosis Index (PCI) according to Sugarbaker classification was 8 (right upper: 1; left upper: 1; left flank: 1; right lower: 1; right flank: 1; upper ileum: 1; lower ileum: 2) 7. The stage of disease was stage I according to the staging system proposed by Yan 8. Patient recovery was slow, characterized by prolonged ileus and low serum albumin levels. Discharge occurred in the thirteenth post-operative day.

The patient was referred to oncology and due to the histological subtype, the advanced age of the patient and the bowel involvement, underwent systemic combined chemotherapy with a Pemetrexed and Cisplatin, without any other surgical treatments. Six months later the patient is still alive and in good clinical conditions. The control CT showing only a little fluid collection in the bladder-rectus space.

**Discussion**

Few surgical case reports and relatively small series of peritoneal mesothelioma are reported in the literature 2,5,7,9-14. Although its incidence is still low, it will increase in the next years due to the natural history of the disease and its correlation with asbestos, even if less marked than the pleural mesothelioma. Accordingly, La Vecchia stated that the peak is expected in Italy from 2012-2024 15.

It has been proved that the classical symptoms are weight loss, anorexia; abdominal distension, cachexia and ascites, but omentum thickenings mimicking omental infarction, intestinal obstruction, bowel perforation, acute abdomen and recurrent adhesional obstruction have been reported too1. Sometimes the initial diagnosis is not clear and not it is often unrecognized in the hospital where patients have had the first admission 16.

De Pangher Manzini suggests a classification based on clinical presentation: classical type, characterized by abdominal swelling with ascites and/or abdominal mass often associated with pain and weight loss; surgical type presenting as a surgical emergency; medical type characterized by fever, diarrhea, weight loss and acute phase changes resembling an intestinal inflammatory bowel disease 17.

Following Manzini’s classification, our patient had a first presentation as a surgical emergency (surgical type) when he underwent appendectomy without the correct diagnosis, an intermediate course as an inflammatory bowel disease and finally a presentation as a classical type, when despite the unusual presence of cystic features the right diagnosis was done.

Differential diagnosis regards peritoneal carcinomatosis, primary peritoneal carcinoma, ovarian carcinoma, lymphoma, tuberculous peritonitis and cocoon syndrome18-21. Diffuse malignant peritoneal mesothelioma is characterized by thousands of whitish tumor nodules varying in size and consistency; these nodules may form plaques, masses or layers that cover part or the whole peritoneal surface; although ascites is the most common finding.
Histologically it is categorized into three subtypes: epithelial (56%), sarcomatous (32%) and mixed or biphasic (13%) 1,4. Both epithelial and mesenchymal malignant components coexist in biphasic malignant peritoneal mesothelioma, sometimes intimately mixed but more frequently in different parts of the same tumour. Therefore, there is a high degree of subjectivity in the diagnosis of pure sarcomatoid versus the biphasic one, which depends also on the amount of tissue available and on the extent of the sampling 16.

Cystic lesions are typical of the benign cystic peritoneal mesothelioma and they are unusual in the malignant form 22. To our knowledge only one case of malignant peritoneal mesothelioma presenting cystic lesions has been previously reported and it belonged to the epithelial subtype 6. Recently a case of “multicystic peritoneal mesothelioma” with a progression of disease has been reported. It showed multiple well-defined cystic spaces separated by a loose and myxoid spindle-celled stroma that also with the aid of the immunohistochemical results was interpreted as reactive myofibroblastic proliferation 23. To our knowledge, this is the first case of true biphasic peritoneal mesothelioma with cystic areas.

Immunohistochemistry represents a very important diagnostic tool. Since one specific marker for mesothelioma has not yet been recognized, the immunohistochemical diagnosis of this tumor is done using a panel of markers including positive Markers (thrombomodulin, calretinin, CK 5/6, D2-40, mesothelin, and Wilms tumor 1 protein) and negative markers (desmin, CEA, B72.3, and Ber-EP4) 1. Calretinin appears to be one of the most sensitive and most specific markers for mesothelioma 9,17, 22-24. We found a positive immunostaining for EMA, vimentin, CK5/6, D2-40, calretinin and P53 and a negative immunostaining for desmin, both in epithelial areas and in spindle areas, in particular in those around the cystic spaces.

It is interesting to note that, these immunohistochemical findings were opposite from the ones reported by Singh, who found positive cysts lining cells for EMA and cytokeratins, while the stromal cells were both negative for these antibodies and calretinin, but positive for desmin, leading to the diagnosis of "multicystic peritoneal mesothelioma with secondary pseudosarcomatous myofibroblastic proliferation" 23.

On the contrary, in our case the same immunohistochemical findings were evidenced in both components. That, together with the negativity for desmin and the focal positivity for P53, despite the relatively uniform appearance of the spindle cells, brought to the diagnosis of malignant biphasic mesothelioma.

As previously stated, the low reliability of cytological results warrants an invasive procedure to obtain a generous sample of peritoneal tumor in patients with peritoneal surface cancer of uncertain etiology. In these cases the use of laparoscopy could be recommended, a three port-technique could be the choice 21-23, even though the samples are sometimes not enough 16, 25-28.

The palliative use of systemic chemotherapy has been the only therapy for this uncommon disease for long time. Pemetrexed and platinum compounds or gemcitabine are the current therapy established by the Food and Drug Organization 28. New targeted therapies have demonstrated some promise and are being addressed in clinical trials 29-30. Palliative therapy ensures a median survival of about 12-14 months with a combined treatment; however in elderly and unfit patients one single-agent (Pemetrexed) may be considered 1.

Since 1995 several groups of experts introduced a new combined surgical and oncological approach, through an aggressive cytoreductive surgery and a hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) with an improvement in median survival, reaching 40-92 months, and a cure rate of 43.6% 9,17, 22-23, 32. However, for a better management before any aggressive surgical decision, Sugarbaker suggested to assess the PCI that, combining lesion size with tumor distribution, quantifies the extent of the disease with a value ranging from 0 to 39 7. In this regards, Yan proposed a staging system that includes PCI, lymph node involvement and extra-abdominal metastasis to stratify the survival by stage (5-year survival: I stage 87%; II stage 53%; III stage 29%). He reported also that a PCI score above 20 is a negative prognostic factor for survival (119 vs 39 month) and the chance of achieving complete cytoreduction is small especially if the small bowel and its mesentery or crucial anatomic sites, as the epigastric region, are involved 8.

Magge reported as predictors of poor survival: older age (>65 years), low preoperative albumin level, high PCI, incomplete cytoreduction, estimate of high blood loss, high grade tumor histology, aggressive histology (sarcomatous and biphasic), major wound infection, postoperative sepsis, prolonged ileus > 3 weeks, low albumin level at discharge and reoperation due to complications. Finally he stated that patients with aggressive histology have minimal benefit from CRS/HIPEC with a short survival (10.5 months), a disease control rates and a long-term survival similar to historical controls receiving systemic therapy 9.

Similarly, Deraco affirmed that biphasic/sarcomatoid histology and lymph-node involvement are correlated to poor prognosis and that a combined treatment seems to be effective only if there is a small disease volume and a good response to preoperative systemic chemotherapy 9.

Our patient showed a PCI of 8, normal levels of preoperative albumin and disease in first stage, but he was 75 years old, showed a large involvement of bowel and mesentery, a prolonged ileum and his serum albumin at the discharge was 2.2 g/dL. Moreover, though the histological grade of both components of the tumor was low (very few cell atypia and rare mitoses), he showed a malignant biphasic subtype, that is considered a more aggressive histotype. A palliative therapy...

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was chosen due to the age, the biphasic histotype and the bowel involvement. The patient is still in oncological management and in good clinical conditions six months after the diagnoses.

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Riassunto

Il mesotelioma peritoneale maligno è una patologia rara la cui diagnosi è resa particolarmente difficile dalla molteplicità delle possibili presentazioni cliniche e morfolologiche. A differenza della patologia pleurica, questa sembra avere una minore correlazione con l’esposizione all’asbesto. La prognosi è sfavorevole con una sopravvenza media di 5,4 mesi.

Riportiamo un caso di mesotelioma peritoneale in un paziente di 73 anni con esposizione professionale all’asbesto. La diagnosi è verosimilmente avvenuta dopo diversi inquadramenti clinicis che hanno compreso addominalgie attribuite ad IBD, poi non accertate istologicamente, e ad un’appendicite acuta. Per ultimo il paziente è giunto alla nostra osservazione con un quadro subocclusivo che l’indagine TC attribuiva ad una verosimile carcinosi peritoneale a primitiva sconosciuta.

La laparoscopia esplorativa, poi convertita in approccio laparotomico, ha mostrato un quadro di peritonite incaussante che coinvolgeva estesamente l’intestino tenue. È stata eseguita una resezione intestinale del tenue coinvolto ed una asportazione di un’area nodulare peri-spleatica.

L’esame istologico con l’integrazione di indagini immunostoichimiche ha permesso la diagnosi di mesotelioma peritoneale cistico maligno con istotipo bifasico che risulta essere il primo descritto in letteratura. Le aree cistiche avevano inizialmente fatto propendere per una diagnosi di mesotelioma multicistico benigno o di mesotelioma cistico con secondaria proliferazione miofibroblastica pseudosarcomatosa.

Negli ultimi anni la prognosi di questa patologia ha trovato nell’utilizzo della chirurgia citoriduttiva e della chemioterapia intraperitoneale un miglioramento prognostico, queste nuove tecniche sono disponibili in centri di riferimento e trovano ad oggi indicazione solo in casi selezionati e in istotipi poco aggressivi.

Il nostro paziente a causa dell’estensione della malattia, dell’istotipo non favorevole e dell’età avanzata è stato riferito al servizio di oncologia per il prossimo delle cure. È stato sottoposto a chemioterapia con Pemetrexed e Cisplatino e dopo sei mesi presenta soddisfacenti condizioni cliniche generali e la TC di controllo non ha mostrato progressione di malattia.

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