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Our experience and review of the literature

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Giuseppe Santangelo*, Marina Accardo**, Ferdinando De Vita***, Santolo Del Giudice*, Federica Gallucci*, Alessio Fabozzi***, Massimo De Falco*

Second University of Naples, Naples, Italy
**U.O.C. of General and Geriatric Surgery (Director: Prof. S. Canonico)*
***Department of Pathological Anatomy*
****Department of Medical Oncology*

Malignant transformation in non-recurrent peritoneal cystic mesothelioma. Our experience and review of the literature

AIM: *Cystic peritoneal mesothelioma is commonly regarded as a benign neoplasm at its first manifestation. It can only seldom show malignant transformation, and only after repeated postoperative recurrences.*
MATERIAL OF STUDY: *We hereby represent a unique case of peritoneal cystic mesothelioma, malignant since its first presentation. We observed a 73 year-old man presenting with intermittent abdominal pain and periumbilical swelling. At surgery, we found an extensive, oval-shaped, multi-lobed cystic formation that was surgically removed.*
RESULTS: *Histopathology was consistent with a malignant peritoneal cystic mesothelioma. In agreement with oncologists, we decided not to give any further therapy because of the few possibilities offered by systemic chemotherapy and the paucity of published data from the literature. We planned periodical follow-up including US scan every six and CT-scan every 12 months.*
DISCUSSION: *Several cases of malignant transformation occurring after repeated recurrences of peritoneal mesothelioma have been reported. To our knowledge, this is the first case showing "ab initio" histological features of malignancy, typical of an active, proliferating and infiltrating lesion. In addition, advanced age and male gender of our patient are extremely peculiar*
CONCLUSION: *Our observation suggests the possibility, although very rare, that peritoneal cystic mesothelioma may present as malignant since its first manifestation.*

KEY WORDS: Peritoneal cystic mesothelioma

Introduction

Peritoneal Cystic Mesothelioma is a rare tumor (0.15/100000 persons) [1-4] usually considered benign, although a trend toward local recurrence without distant metastases is documented (> 50% of cases) [5,6].
Several cases of malignant "transformation" occurring after repeated episodes of postoperative recurrence have been recently described [7,8]; indeed, some authors are questioning the current terminology "benign" (Benignant Peritoneal Cystic Mesothelioma – BPCM) [3].
The present case shows evident peculiarities because of the baseline characteristics of the patient (age, sex) and the malignant pathological features "*ab initio*".

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Correspondence to: Massimo De Falco, U.O.C. of General and Geriatric Surgery, Second University of Naples, Piazza L. Miraglia, 2 Napoli, Italy. (e-mail: massimo.defalco@unina2.it)

Case Report

A 73-year-old man was admitted to our Surgical Unit on June 2004 because of intermittent abdominal pain and periumbilical swelling lasting since 3 months. At clinical examination we observed a mass with elastic consistency and smooth surface, movable on superficial and profound levels, and slightly painful on palpation.
US revealed a multilocular intra-peritoneal cystic formation, with a maximum diameter of 16 centimeters.
Abdominal contrast-enhanced CT and MR-scan (Fig. 1 A-C) confirmed the presence of an "oval-shaped multilocular lesion with fluid content, having diameters of 16 and 10 centimeters, with well defined, multilobed contours, located in submesocolic position"
In consideration of these data, we decided to schedule the patient for surgery.
After median xipho-pubic incision, we found free intraperitoneal serosanguineous fluid and an extensive multilobed cystic formation (similar to a rugby ball) located within the omentum. The top of the mass was adherent to the stomach wall and its bottom to some ileal loops. The adherences were sectioned and the mass was completely removed (Fig. 1D).

Histopathological analyses

Samples were fixed in 10% formalin diluted with a 0.1 M phosphate buffer, pH 7.2, and were embedded in histowax after dehydration. Hematoxylin & eosin (h.-v.Gieson, P.A.S) stain was used. For immune-histochemical analyses the following antibodies were used: ker 5/6 - 1:75, Leu M1 (CD15) - 1:50, Ber EP4 - 1: 50, Vimentin -1: 100, and MOC 31 - 1: 100 (Dako, UK); calretinin - 1:8000 (Zymed, USA); B72.3Mab - 1:300 (Biogenex, USA).
Samples for electron microscopy were fixed in Karnovsky's solution, post-fixed in 1% osmium tetroxide, dehydrated in alcohol and embedded in Epon 812 resin. Semi-fine sections were hence cut and stained with toluidine blue. Ultra-fine sections were obtained and contrasted with lead citrate and uranyl acetate.

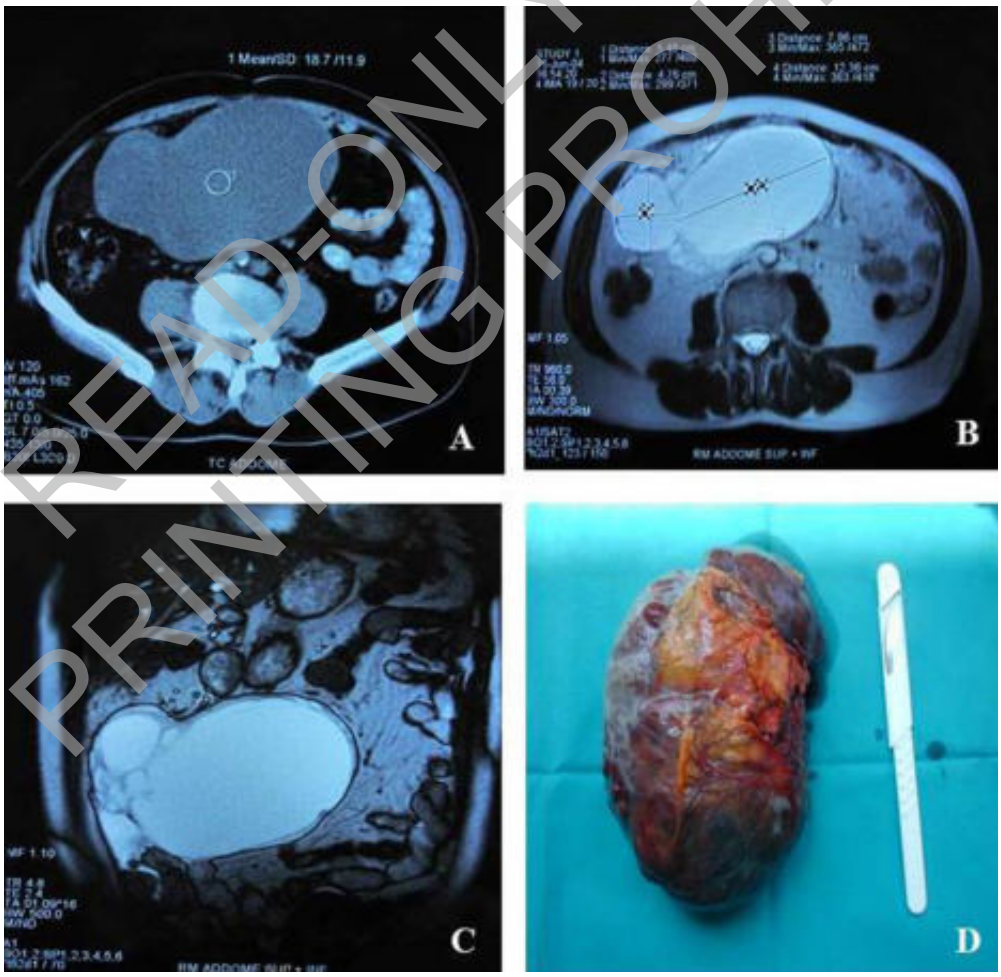

Fig. 1: The contrast enhanced-CT (A) and the MR (B-C) of the abdomen showed the oval multilocular mass containing fluid without signs of local infiltration. (D) Surgical specimen: multi-lobed cystic formation similar to a "rugby ball".

Results

Postoperative course was uneventful and the patient was discharged on post-operative day eight.

At pathology, the material was macroscopically multicystic. The mass was delimited by a fibrotic capsule, locally infiltrated by lympho-monocytes; the cystic cavities appeared interconnected and filled with a dark fluid.

Low magnification revealed in the sub-capsular area of a wide, sub-capsular, microcystic band with a multilocular structure. At the center of the formation variously orientated compact cellular cords were observed (Fig. 2A).

With greater magnification, the sub-capsular microcystic component showed an empty pluricystic reticulum; the internal walls of any single cysts were covered with mono-stratified flat cubic cells, characterized by low cytoplasm and normochromic nuclei (Fig. 2B). These cellular threads were lying on a thin fibrillar stroma.

In many areas multi-layered aggregates of these elements were observed, typical sign of proliferative hyperplastic activity.

The compact area filling the central part of the neoplasm consisted of cells beams massed together and cohering (Fig. 2C). The component elements were of medium size, with a clear eosinophilic cytoplasm and irregular and vesicular nuclei; among this population we found elements with atypical nuclei or in mitotic activity (Fig. 2D). In this area, a conspicuous vascular component was observed, represented by capillaries and post-capillary veins that infiltrated by lymphocyte aggregates.

In many fields various regressive processes were noted, consisting of hemorrhagic areas, intercellular edema, inflammatory infiltration sustained by immune-competent cells, and foci of micro and macro- necrosis.

Lastly, a tissue band interposed between the above described structures was found.

This showed transitional morphological characteristics along with microcystic formations that tended to collapse under the proliferative thrust of atypical cells (Fig. 2E).

Histopathological report was implemented with the following immune-histochemical markers: ker5/6, Calretinin, MOC31, B72.3, Ber-EP4, LeuM1 (CD15), and Vimentin. As expected, ker5/6, Calretinin and Vimentin were positive, whereas MOC31, B72.3, Ber-EP4, LeuM1 were not expressed.

Ultra-structural investigation was carried out on samples obtained from areas with atypical mesothelial elements. Thin microvilli were observed on the free surfaces of cells, confirming the mesothelial nature of this cell population, with no organelles and evidence of few ribosome in the cytoplasm, sign of cellular immaturity.

Immune-histochemical diagnosis and ultra-structural investigation (Fig. 3) together with the morphological features, allowed for making the definitive diagnosis of multicystic mesothelioma, with malignant features.

According to the oncologists' opinion, considering the few possibilities offered by systemic chemotherapy and the minimal experience reported in medical literature, it was decided not to follow any further complementary therapy but to start a periodical follow-up (US scan every six months and CT-scan every 12 months.).

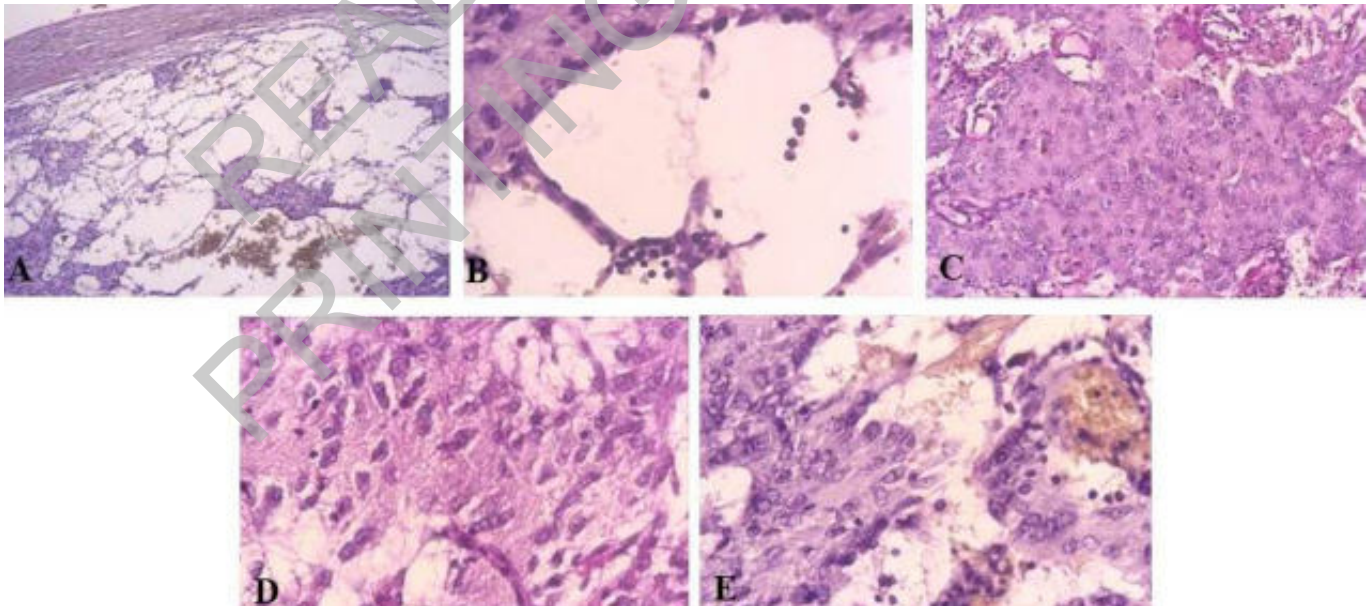

Fig. 2: (A) The neoplastic peripheral portion shows a micro-macrocystic structure with apparent empty spaces [Hematoxylin-eosin (HE) 100X]. (B) The single cystic cavities are covered by well-differentiated monostratified flat cells [Periodic acid-Shiff (PAS) 400X]. (C) The thickened area is constituted by cell cords (PAS 200X). (D) The cell cords are constituted by adherent cells that show irregular and atypical nuclei (PAS 400X). (E) Microcysitc areas delimited by atypical pluristratified cells showing proliferative activity (HE 400X).

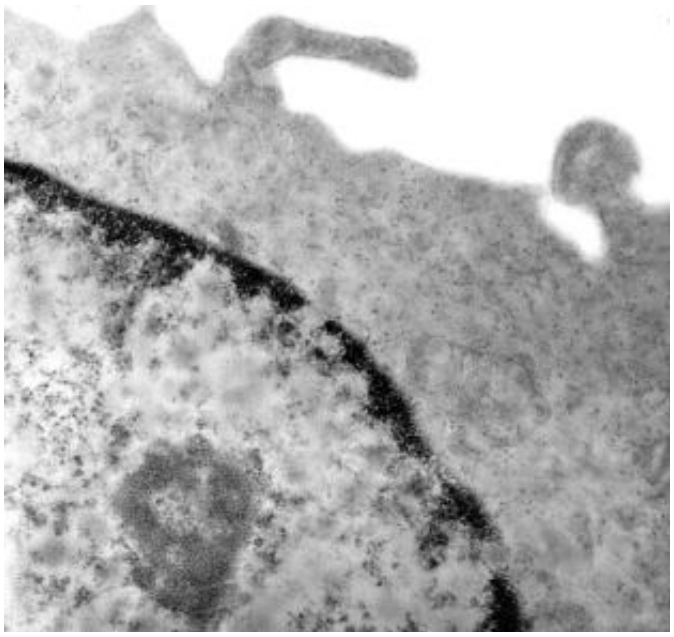

Fig. 3: Mesothelial cell: the cytoplasm appears compact, without organelles and containing microvilli (TEM 12.000X).

At 10-year follow-up after surgery no signs of either local or distant relapse have been observed with clinical, serological, and imaging examinations. The patient did not need any additional treatment and has good Performance Status (0 according to ECOG scale).

Discussion and Comments

Three entities are described among tumors originating from the peritoneal mesothelium [9]. The BPCMs are classified as intermediate between "benign adenomatoid tumors" (usually small and asymptomatic, without postoperative recurrence) and malignant mesothelioma (tubular-papillary and symptomatic, with extremely negative prognosis), with clinical and biological characteristics falling between these two forms.

Although they have a high rate of postoperative relapse (over 50%), the term "benign" refers to the clinical course, i.e. the almost total absence of malignancy and the positive prognostic evaluation [1,2,10].

BPCM prevalently affects female subjects (F/M ratio 4-5/1), and the average age is 60 years [5,11]. The advanced age and gender of our patient represent two uncommon findings.

BPCM etiology is unknown [2], and different hypotheses have been proposed: the reactive-inflammatory cause [12], especially in cases associated with chronic intestinal inflammation, and/or prior abdominal surgery; primitive neoplastic processes [13]; the possible but not yet demonstrated hormone-sensitivity (suggested by response to Tamoxifen) [14]. No definitive data support a relation with exposure to asbestos [10,15].

BPMCs are often asymptomatic and are only occasionally diagnosed (18% of cases) [16]; they often cause non-specific symptoms of diffuse abdominal pain, until they cause visceral compression [10,11,17] with abdominal swelling, due to their intra-abdominal enlargement.

Instrumental diagnosis is extremely difficult because the imaging techniques (US, CT, MR) are not able to differentiate between BPCM and other intra-peritoneal cystic lesions (especially cystic lymphangioma) [18,19], even if they ensure a correct vision of the spatial ratio of the cystic tumefaction. Fine-needle aspiration cytology (FNAC) does not commonly provide useful information due to its low specificity.

Histological and immune-histochemical examinations of the specimen allow for obtaining definitive diagnosis [20-22]. Hence, surgery plays a crucial role both for diagnosis and therapy. Surgical excision should be as radical as possible. Taken into account the high frequency of relapse, extensive surgical demolition may be needed to resect the mass en-bloc with involved, sacrifiable structures [2].

Neo-adjuvant therapies (Tamoxifen; Gn-RH agonists) have been evaluated in few studies [23], with an inconstant reduction of the size of the cyst and growth deceleration. Neither adjuvant chemo- nor radio-therapies provide any therapeutic advantage.

Relapses occur in over 50% of patients [5,6], usually within two years, and can be attributed to an effective disease recurrence, but often results from incomplete removal owing to disease persistency. A careful and active instrumental follow-up is therefore mandatory for a period of at least six years, starting early after surgery. In fact, relapse has been recorded even after 48 months. In the absence of histological features of malignancy, the recurrence tendency has not impact on postoperative relapses rerelapses. Recently, cases of malignant transformation occurring after repeated relapses have been reported [7,8] and this led to the reconsideration of the term "benign" that is usually associated with the definition of the peritoneal cystic mesothelioma.

The peculiarity of our case relies on the presence of histological features of malignancy "ab initio", which are typical of an active, proliferating and infiltrating lesion. The absence of relapse over ten years from radical surgical removal, and an accurate periodical follow-up with radiological examination (US, CT, MR) suggest that our case could be enlisted among the BPCM, because of its favorable outcome.

Conclusions

The histo-pathological data and the biologic features that we herein describe reinforce the aforementioned perplexities about the correct classification of the biological

behaviour of this neoplasia. The possible removal of the term "benign" from the medical definition of this disease is attractive, according to authors who recently documented a malignant transformation of the original lesion. Moreover, it is advisable to seek for uniformity in diagnostic approach, treatment, and short/long term follow-up of this rare affliction with uncertain biological behaviour.

Riassunto

Il mesotelioma peritoneale cistico è un tumore raro. Si tratta di un tumore benigno, che tuttavia va incontro a recidive locali post-chirurgiche in oltre il 50% dei casi. È proprio a seguito di recidive ricorrenti che si possono determinare trasformazioni maligne di questa neoplasia, come descritto in Letteratura.

Nel Giugno del 2004 un paziente di 73 anni è giunto presso la nostra struttura con una tumefazione addominale causa di dolore gravativo: si trattava di una massa di 16 cm, la cui struttura, agli esami strumentali (ecografia, TC con m.d.c. e RMN), appariva pluricistica. Attraverso una laparotomia mediana si è provveduto alla sua rimozione e il paziente è stato dimesso in VIII giornata post-operatoria senza complicanze. L'esame istologico, corredato da studio immunoistochimico e di microscopia elettronica, ha consentito di porre diagnosi di mesotelioma peritoneale pluricistico in trasformazione maligna.

D'accordo con gli oncologi, in considerazione della scarsa efficacia dei trattamenti adiuvanti e della scarsità dei dati riportati in Letteratura sull'argomento, si è deciso di sottoporre il paziente unicamente ad uno stretto follow-up, con esecuzione di ecografia addominale ogni sei mesi e TC addominale ogni anno. Ad oggi, dieci anni dopo il trattamento, il paziente, di 83 anni, gode di un discreto stato di salute e non si sono verificate riprese o recidive di malattia, né locali, né a distanza.

Oltre al fatto di essere risultato maligno alla sua prima manifestazione e non dopo ripetute recidive, il caso presenta altre particolarità: il mesotelioma peritoneale cistico, infatti, solitamente colpisce soggetti di sesso femminile (con un rapporto F:M di 4,5:1) ad un'età media di 60 anni, mentre il caso descritto riguarda un soggetto di sesso maschile di 73 anni.

La nostra osservazione dimostra la possibilità che il mesotelioma peritoneale vada incontro a trasformazioni maligne già alla sua prima manifestazione e non esclusivamente dopo ripetute recidive locali, come è invece documentato in Letteratura; dimostra inoltre che la radicalità della rimozione chirurgica, senza la rottura della capsula di rivestimento, quando la patologia è ancora localizzata, garantisce la possibilità che non si verifichino recidive.

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