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Direttore Nicola Picardi

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Case report

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Ioan Şimon*/**, Ovidiu Fabian*/**, Emilia Maria Pătruţ */**, Iacob Domşa***, Adriana Zolog***, Gianluca Garigale**, Răzvan Dan Togănel */**, Gabriel Emil Petre*/**, Lorena Ciumărnean*/****, Olga Hilda Orăşan*/****

Ioan Simon, Ovidiu Fabian and Emilia Maria Patrut have contributed equally
**Iuliu Haţieganu University of Medicine and Pharmacy Cluj-Napoca, Romania*
***CF Clinic Hospital Cluj-Napoca, 4th Surgical Clinic, Romania*
****CF Clinic Hospital Cluj-Napoca, Laboratory of Anatomopathology, Romania*
*****CF Clinic Hospital Cluj-Napoca, 4th Medical Clinic, Romania*

Cystic malignant peritoneal mesothelioma of the abdominal wall. Case report

We present the clinical observation of a female patient with cystic peritoneal malignant mesothelioma developed *in the thickness of the abdominal wall. The diagnosis included several steps: tumor classification as mesothelioma, tumor differentiation from reactive mesothelial hyperplasia, establishment of the malignant nature and differentiation from other malignant peritoneal tumors. Relapse in about one year after surgery and about six months after the end of chemotherapy also claim malignancy of the tumor. The particular tumor location in the thickness of the abdominal muscles, seemingly without involvement of the parietal peritoneum, in a patient with a history of caesarean operation, questions its development out of ectopic tissue embedded in scar from previous surgery.*

KEY WORDS: Abdominal wall, Caesarian operation Cystic malignant peritoneal mesothelioma, CK5/6, p53

Introduction

Malignant peritoneal mesothelioma is a rare tumor originating from the mesothelial or submesothelial layer of the peritoneum. It is estimated that peritoneal mesothelioma represents 20-33% (in between one fifth and one third) of all mesotheliomas [1]. The main confirmed etiological factor is asbestos [2], but the tumor can exist in patients without asbestos exposure.
Peritoneal multicystic mesothelioma usually occurs in the pelvic peritoneum, sometimes after previous pelvic surgery [3-5]. However, retroperitoneal location of the tumor was also described [6]. It is generally considered benign, but it can have invasive behavior and recurrent character [7]; some multicystic peritoneal mesotheliomas are actually malignant.
Treatment of primary peritoneal tumors combines surgical resection with intraperitoneal chemotherapy and systemic chemotherapy [8].
The diagnosis is usually based on postoperative immunohistochemical staining, even if it may sometimes be suspected on preoperative imaging appearance.

Case report

A 55-year-old patient was admitted for pain in the lower abdomen, increase in volume of the hypogastric region and identification by autopalpation of a subumbilical tumor. The patient has given birth by cesarean section 27 years ago. She reports having discovered the tumor six months ago, which has increased in volume since

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Correspondence to: Gianluca Garigale, CF Clinic Hospital, 4th Surgical Clinic, Republicii street 18, Cluj-Napoca, 400015, Romania; (e-mail: gianlu.gari@outlook.it)

then. On physical examination a tumor of approximately 10 cm in maximum diameter was found, well-defined, with smooth surface, solidary with the anterior muscular abdominal wall, of elastic consistency, covered by normal skin. On percussion: dullness on the tumor, timpanism in the rest of the abdomen.
Common laboratory examinations showed no significant change. Tumor markers CA 125 (30.9 U/mL), and CEA (2 ng/mL) had both normal values. Abdominal CT scan with IV contrast showed a multiseptated polilobulated cystic mass, with peripheral solid component, located in the abdominal wall, with maximum dimensions of 13/8 cm (Fig. 1).

During surgery a multicystic tumor was found in the thickness of the abdominal wall (Fig. 2), which was excised with 3-5 cm of the adjacent muscle tissue and underlying parietal peritoneum (Fig. 3).
The defect in the abdominal wall muscle was replaced with a mesh.
Macroscopic examination revealed a polycystic mass containing sero-hemorrhagic cysts with size from a few millimeters up to 3 cm, with thin, smooth internal wall. In the periphery, striated muscle tissue and adipose tissue were present (Fig. 4).
On microscopic exam the tumor had architecture (pattern) of a multicystic tumor with cystic spaces of dif-

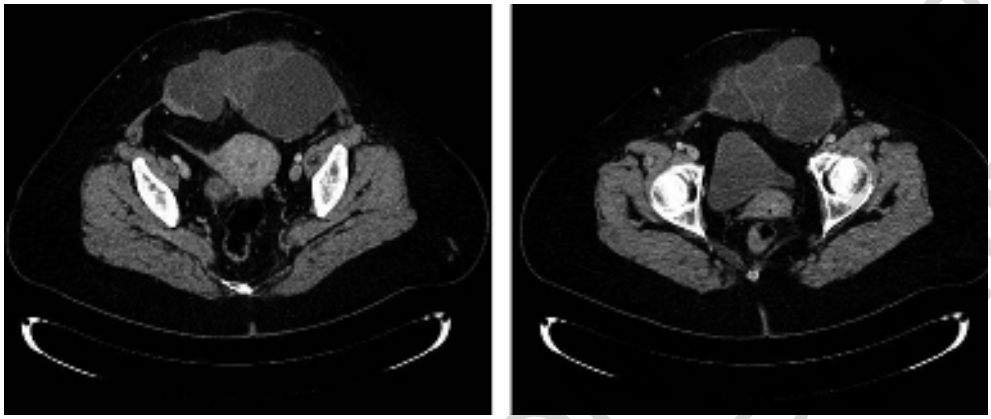

Fig. 1: Abdominal CT scan: multiseptated polilobulated cystic mass located in the muscular abdominal wall.

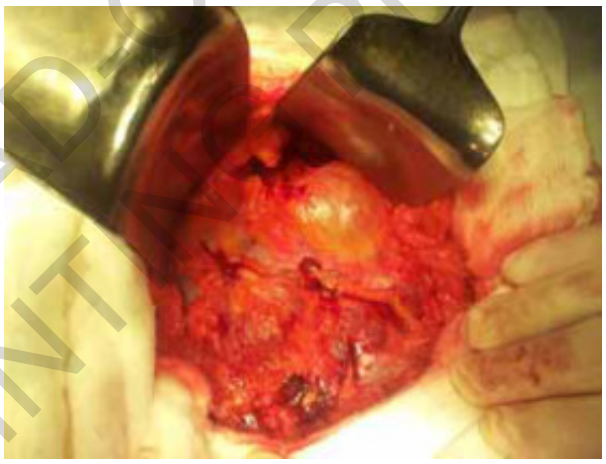

Fig. 2: Cystic tumor in the muscular layer of the abdominal wall.

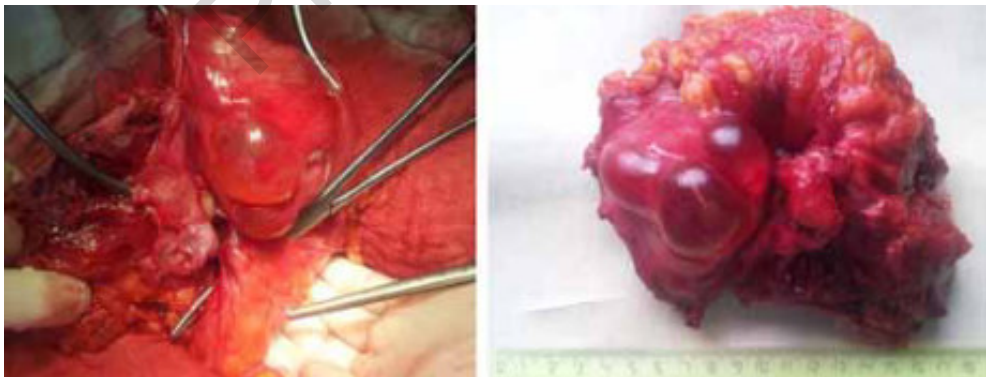

Fig. 3: Parietal cystic tumor. Intraoperative aspect and appearance of the removed tumor.

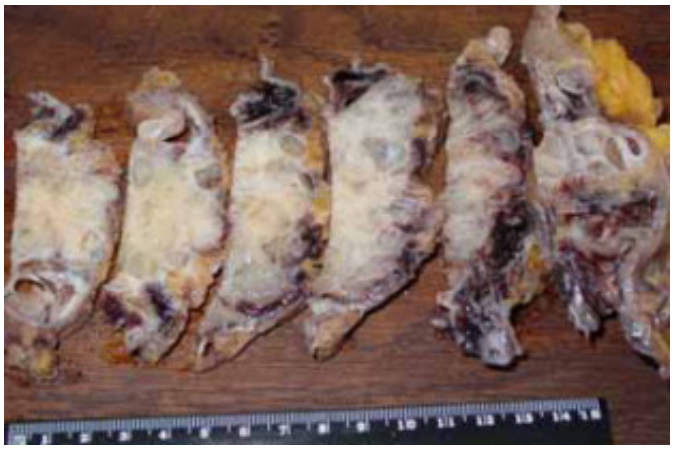

Fig. 4: Macroscopic appearance of tumor sections, after fixation.

ferent sizes (millimeter to centimeter), lined by a single layer of cells, flattened cubic or high with "hobnail" aspect. There were small areas in which the cells had clear cytoplasm, with nuclei situated centrally or peripherally, with signet ring aspect. Most cells lacked atypia, but there were small areas in which the cells had nuclei slightly atypical or bizarre. There were no mitoses present. Focally, the cells formed papillary structures or small solid nests or with cribriform appearance. Very rare microcalcifications (psammomatous bodies) could be observed. Septs were made up of loose fibrovascular connective tissue, lacking muscle fibers with a reduced chronic inflammatory lymphocyte infiltrate and small areas of bleeding. Vascular invasion or invasion of the connective stroma was not observed in the examined material. Tumor growth had an expansive model. Striated muscle tissue and fat located at the periphery was compressed but not invaded. Tumor was tangent to the resection margin.

Immunohistochemical staining: negative calretinin, positive CK5/6 (Fig. 6), negative CA19-9, negative CEA. P53 protein was positive on approximately 75-80 % of tumor cells (Fig. 7), and desmin was negative.

The aspect was interpreted as a multicystic peritoneal mesothelioma (inclusion peritoneal cyst), but because of p53 positivity on tumor cells it was classified as a malignant peritoneal mesothelioma.

Postoperatively the patient underwent systemic chemotherapy with Carboplatin and Gemcitabine (6 cycles). At one year follow-up the abdominal CT-scan revealed a 2 cm recurrent tumor in the abdominal wall.

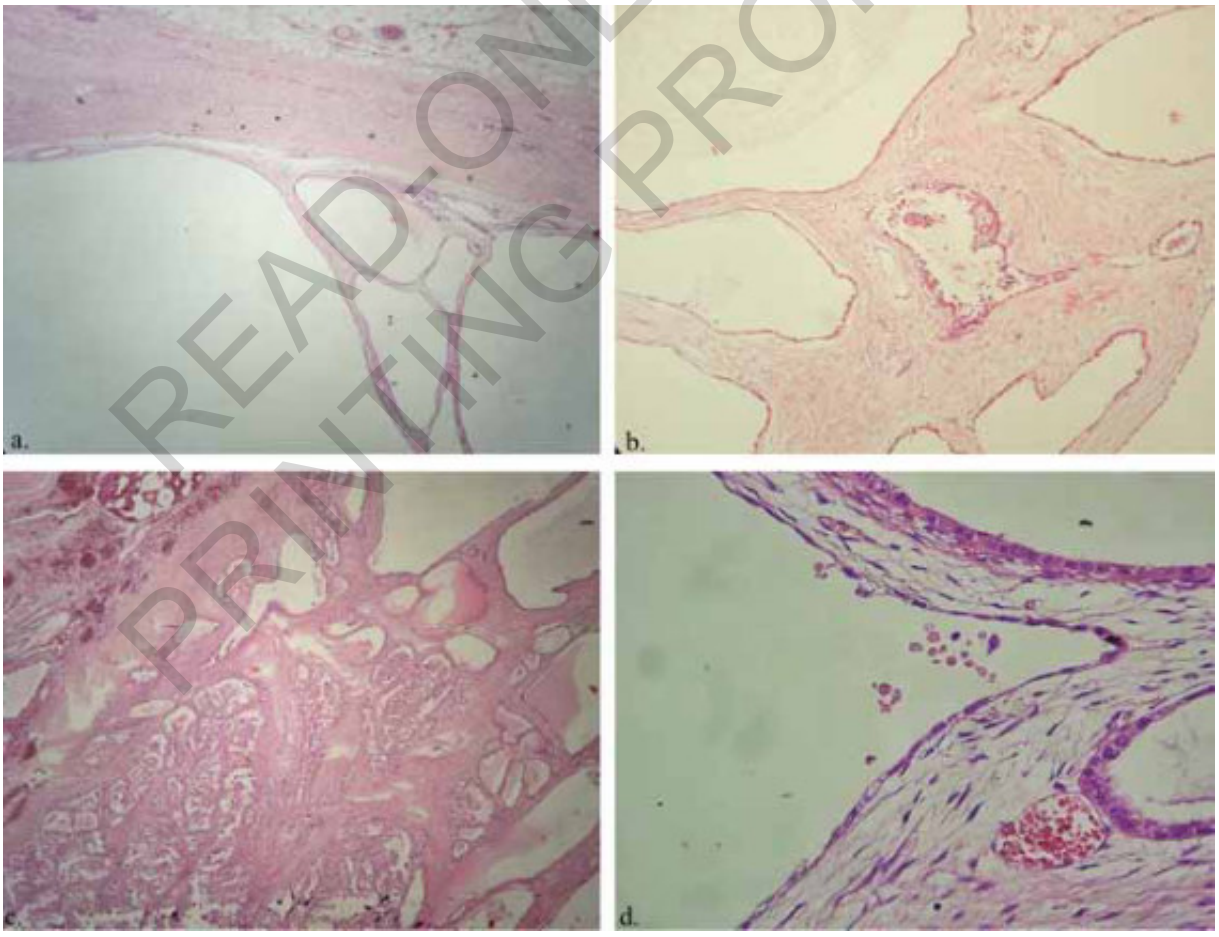

Fig. 5: A) multicystic architecture; B) simple cysts separated by connective septa; central cyst with cribriform epithelial architecture; C) cubic or flattened epithelium; D) complex papillary structures.

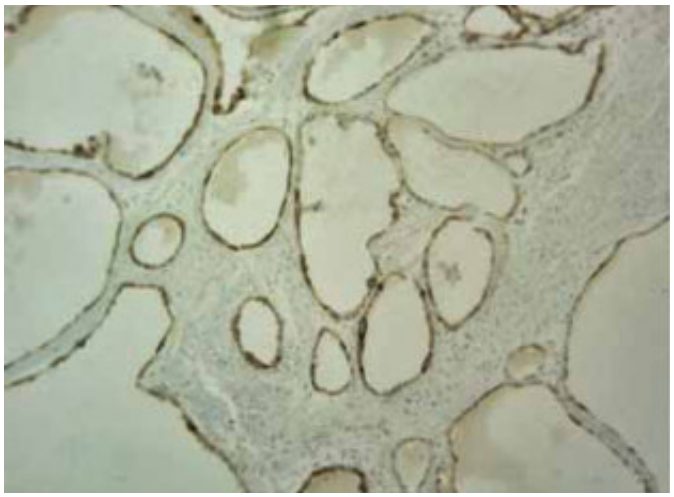

Fig. 6: Positive cytokeratin 5/6.

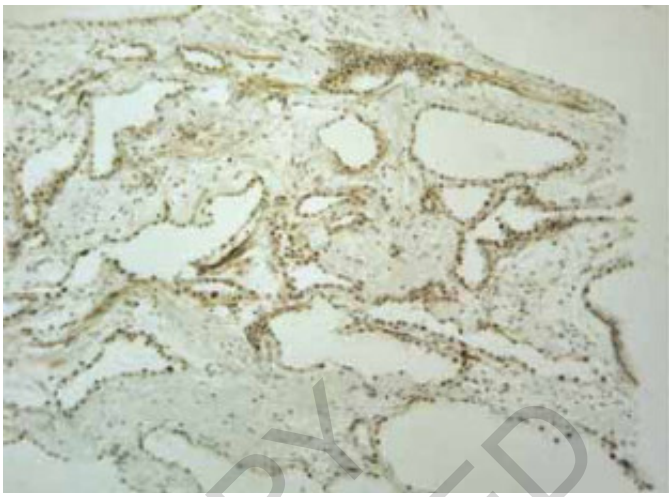

Fig. 7: Positive staining for p53 protein.

Discussions

Most malignant mesothelial tumors affect the pleura; about 9% affect the peritoneum and rarely the pericardium and tunica vaginalis [9]. Malignant peritoneal mesothelioma usually develops from parietal or visceral peritoneum of the pelvis, although it can also occur in the intestinal serous membrane [10], the large omentum[11] or retroperitoneum [12,13]. It is associated with endometriosis or exposure to asbestos, erionite or Thorotrast [15]. Peritoneal multicystic mesothelioma is a borderline tumor that includes benign but also malignant, rapidly lethal, forms [1,16].

Malignant peritoneal mesothelioma diagnosis is virtually impossible to establish preoperatively, firstly because symptoms are nonspecific. The most common symptoms are abdominal pain, ascites or presence of a tumor; other symptoms are anorexia, weight loss [17] or night sweats [9]; none of them is specific for the diagnosis. There is no specific serum tumor marker. However the increased level of mesothelin and normal level of CEA and CA 19.9 may suggest the diagnosis; osteopontin could be a prognostic marker [1,18]. Ultrasound can show thickening of the peritoneum or omentum, the presence of cystic tumors, the presence and volume of ascites, local invasion (into the mesentery, intestine etc.)[19]. Computer tomography differentiates between three types of malignant peritoneal mesothelioma: bulky disease (single or multiple) without ascites (dry-painful type); ascites with multiple nodules and plaques, but without solid tumor mass, intestinal distention (wet type) and mixed type [1,17]. Imaging examinations have shown a tumor located in the abdominal wall, muscle and subcutaneous fat respectively.

Specific features can't be identified during surgery. A peritoneal cystic tumor can have multiple origins and histological aspects. In the case of the discussed patient parietal peritoneum was free, the tumor developed intramuscularly and subcutaneously.

The first stage of tumor diagnosis is recognition as mesothelioma. Malignant peritoneal mesothelioma has three histologic subtypes: epithelioid type, sarcomatoid type and mixed type (biphasic), each with several patterns [20]. Polygonal, oval or cubical cells are predominant in the epithelioid type; spindle cells are predominant in the sarcomatoid type; the mixed type has areas with epithelioid cells and sarcomatoid cells [20].

Further differentiation from reactive mesothelial hyperplasia, which can mimic an epithelioid malignant mesothelioma, is necessary. In both cases there is a rich cellularity, presence of atypia and mitotic figures, but there are guiding criteria for the two pathologies (Table I). The key in malignant mesothelioma recognition is to demonstrate stromal invasion that may show the immunohistochemical staining for pan-cytokeratin or calretin [20,21].

Assessment of malignant or benign mesothelioma is done using a set of immunohistochemical staining, some of which tend to be positive in benign proliferations and others in malignant proliferations (Table I - Immunohistochemical markers section) [20,22-25].

Differentiation of a papillary serous carcinoma or peritoneal carcinomatosis may sometimes be difficult. Various immunohistochemical stainings may be necessary depending on the suspected tumor: carcinogenic embryonic antigen, estrogen receptors, progesterone receptors, CA-19-9[26], WT-1[27], MOC31[28], BER-EP4[29] and others.

In the case of the presented patient calretinin was negative, CK5/6 positive, CA19-9 negative, CEA negative. Although most mesotheliomas are calretinin positive, there is a rate of 20% negative mesotheliomas. Positive CK5/6 and negative CEA sustain the mesothelial origin of the proliferation, negative CA 19-9 excludes a papillary serous peritoneal carcinoma and negative CEA excludes a metastasis of adenocarcinoma.

The presence of nuclear atypia, although possible in reac-

TABLE I - *Differentiating between mesothelioma and reactive mesothelial hyperplasia* [20, 22-25]

	Mesothelial hyperplasia	Mesothelioma
Stromal invasion	Absent	Present*
Cellularity	Prominent , but limited to surface	Dense, cells surrounded by stroma
Papillae	Simple, with one cellular layer	Complex, multilayer
Inflammation	Present	Absent of minimal
Growth**	Uniform	Uneven, nodular
Immunohistochemical markers		
Desmin	Usually positive (80% positive)	Usually negative (90% negative)
EMA	Usually negative (80% negative)	Usually positive (80% positive)
P53	Negative	Frequently positive (45% positive)
Glut-1	Usually negative (97% negative)	Usually positive (67% positive)
IMP3	Negative	Usually positive (73% positive)

* Highlighted at the stain for pan-cytokeratin
** Highlighted at the stain for cytokeratin
Abbreviations: EMA = epithelial membrane antigen; Glut-1 = glucose transporter 1; IMP3 = insulin-like growth factor II messenger RNA-binding protein 3

tive mesothelial changes have imposed performing of additional immunohistochemical staining (p53, desmin) to assess the malignant or benign tumor character. Immunohistochemical staining result - p53 positive on about 75-80% of tumor cells and desmin negative - supports the malignant nature of the tumor proliferation.
A peculiarity of the presented case is its location in the thickness of the abdominal wall; the parietal peritoneum subjacent to the parietal tumor was intact, free of tumor. An explanation of the origin of this tumor could be the patient's history; it is possible that mesothelial fragments embedded in the scar following caesarean section surgery (28 years ago) have evolved into tumor degeneration. History of previous surgery, particularly gynecological, is seen quite often in patients with benign cystic peritoneal mesothelioma [3-5]. But in these cases the tumors usually develop in the pelvis, or in any case in the peritoneal cavity; tumors with this histology that develop outside the peritoneal cavity are exceptional. Malignant transformation of benign cystic peritoneal mesothelioma is possible[30,31], although no explanation for this process has been advanced so far. We cannot decide if the presented tumor is primarily malignant or originated in the malignant transformation of a benign cystic peritoneal mesothelioma, but in the latter case it is possible that atypical location plays a role in the malignant transformation.
The treatment of malignant peritoneal mesothelioma combines the aggressive surgical resection with hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy [16,32]. In the presented patient the tumor developed completely into the abdominal wall. The internal aspect of the parietal peritoneum during the operation was unremarkable, without tumors. Therefore hypertermic intraperitoneal chemotherapy (HIPEC) was not considered necessary.

Conclusion

Cystic peritoneal malignant mesothelioma diagnosis can be difficult in atypical localization of the tumor. Diagnostic reasoning must take into account a set of immunohistochemical staining and their inspired choice ensures correct diagnosis. Recurrent tumor character justifies an aggressive surgical attitude, but surgery alone is not enough. The addition of systemic or intraperitoneal chemotherapy to surgery improves the therapeutic outcome. Tumor location in the thickness of the abdominal wall, without affecting the parietal peritoneum, can be explained by the development from post-surgery peritoneal tissue inclusions.

Riassunto

Presentiamo il caso clinico di una paziente con un mesotelioma peritoneale cistico maligno sviluppatosi nello spessore della muscolatura della parete addominale. La diagnosi ha seguito diverse tappe: classificazione del tumore come mesotelioma, differenziazione dall'iperplasia mesoteliale reattiva, identificazione della malignità del tumore e diagnosi differenziale con altri tipi di tumori peritoneali maligni. La recidiva del tumore a circa un anno dall'intervento chirurgico, e a 6 mesi dalla fine del trattamento chemioterapico conferma la sua malignità. La localizzazione atipica del tumore nello spessore della muscolatura della parete addominale, con il peritoneo parietale adiacente apparentemente indenne, in una paziente con antecendente intervento cesareo, suggerisce lo sviluppo del tumore da tessuto peritoneale ectopico inglobato nella cicatrice chirurgica.

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