# Peritoneal mesotheliomas mimicking adnexal tumors. Clinicopathological characteristics of four cases and a short literature review

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**Summary**

Three cases of peritoneal benign cystic mesotheliomas in women 32-34 years of age and one case of peritoneal malignant mesothelioma in a 47-year-old woman are reported. All cases presented with abdominal discomfort and/or pain and the physical and radiological diagnostic methods showed adnexal tumors. The cystic mesotheliomas developed in the cul-de-sac and the right pelvic sidewall, presented as multiple small cysts or large multilocular cystic mass. The malignant mesothelioma showed extensive infiltration of the omentum the intestinal loops and the surface of the uterus and adnexa, with bilateral hydrosalpinx and ascites. All cases presented histological and immunohistochemical characteristics consistent with tumors of mesothelial origin. No history of asbestos exposure was reported. The correct diagnostic and therapeutic approaches to these neoplasms are discussed.

*Key words:* Mesothelioma; Peritoneum; Immunohistochemistry.

## Introduction

Peritoneal mesothelioma is a rare disease, with an incidence approximately one per million, and accounts for about 20% to 30% of all cases of mesothelioma [1]. Benign cystic mesotheliomas generally affect women of reproductive age and have a benign biological course, but local recurrence is possible [2]. On the other hand malignant mesothelioma is a diffuse tumor arising most commonly in the pleura (> 90%), secondly in the peritoneum (6-10%), but also in other serosal surfaces. Asbestos is believed to be the main causative agent, but also other factors such as radiation, peritonitis and SV40 have all been implicated [3, 4]. We present our institution experience over the last 15 years, where three cases of benign cystic mesotheliomas and one case of malignant mesothelioma in female patients, all of which affected the peritoneal cavity and mimicked ovarian tumors, were documented.

The aim of this study is to highlight the special features and immunohistochemical characteristics that lead to the correct diagnosis and treatment.

## Case Reports

*Case 1*

A 36-year-old female was operated laparoscopically due to acute abdomen related to a multicystic lesion of the right adnexa. During surgery a small amount of ascitic fluid was found and multiple cysts measuring 0.5-2 cm were observed, loosely attached to the cul-de-sac wall. The cysts were filled with serous fluid. Conversion to an open approach was decided and the cystic lesions were resected en bloc. The ovaries, uterus and appendix were normal and the patient had no asbestos exposure history. She was discharged on the fourth postoperative day. She was followed for five years and was free of disease clinically and by transabdominal sonography (TAS) yearly.

*Case 2*

A 33-year-old female was admitted to our hospital suffering abdominal discomfort for the last three months. Physical examination revealed a palpable mass on her left lower abdominal quandrant which was smooth and soft. Computed tomography scanning (CT scan) of the abdomen and transvaginal ultrasound (TVS) revealed a large cystic mass probably arising from the left adnexa. During exploratory laparotomy a 19 cm cyst with a thin, semi-translucent wall filled with serous fluid was revealed, loosely attached to the peritoneal surface of the pelvic sidewall. Frozen section biopsy of the tumor was negative for malignancy. The uterus and adnexa were normal. The patient had no history of asbestos exposure. She underwent an uneventful postoperative period and she was discharged on the fifth postoperative day. Seven years later she remains disease free.

*Case 3*

A 32-year-old woman with a cystic mass probably arising from the right adnexa, found incidentally by TAS and TVS, and no other findings from the abdominal CT scan underwent exploratory laparotomy. Many small cysts 0.5-3 cm with thin translucent walls attached to the right pelvic sidewall were revealed and were carefully resected en bloc. Once again the patient had no history of asbestos exposure. She had a urinary tract infection postoperatively and received antibiotics so she was discharged on the seventh postoperative day. In her follow-up visits every year for three years she had no complaints and TAS showed no findings consistent with disease recurrence.

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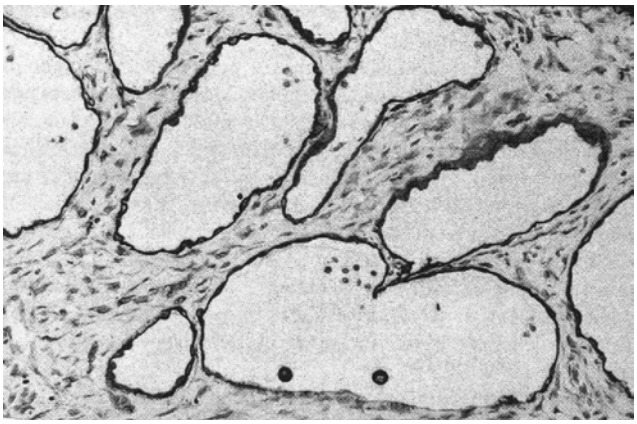
Fig. 1



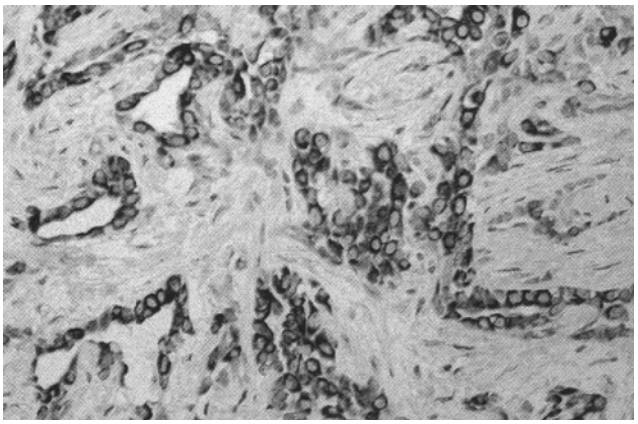


Fig. 2

Figure 1. — Histological section of a benign cystic mesothelioma, showing positive calretinin immunostain of the mesothelial cells that line the cystic spaces (immunostain x 25).
Figure 2. — Histological section of the malignant mesothelioma showing positive calretinin immunostain of the malignant cells forming glandular spaces (immunostain x 120).

*Case 4*

A 47-year-old woman was admitted to our hospital due to severe hypogastric pain and fluctuating fever and she was already under per os antibiotics for four days without any improvement of the symptoms. Physical examination showed diffuse abdominal tenderness and gynecological examination revealed pain on palpation of both adnexa. Laboratory exams showed mild anemia (Hb 10.5 g/dl). TAS and TVS revealed bilateral adnexal masses and the diagnosis of pelvic inflammatory disease was made. She was treated with intravenous antibiotics and she was discharged five days later after great clinical improvement, continuing orally administrated antibiotic therapy.

Three months later the patient was re-admitted suffering from severe hypogastric pain once again. An abdominal CT scan was performed, which demonstrated findings consistent with bilateral hydrosalpinx and a mild ascitic fluid collection with no further findings. Tumor markers were within normal range. Cytological examination of the ascitic fluid proved the existence of malignant cells. Exploratory laparotomy was decided and numerous neoplasmatic foci were found among the intestinal loops, which were adherent, while the omentum was infiltrated by a large number of brownish-white nodules. The pelvic cavity was full of neoplasmatic masses of brownish color, soft and friable in consistency, covering the outer surface of the uterus and adnexa. Total hysterectomy and bilateral oophorectomy as well as epiploectomy were performed. She underwent an uneventful postoperative period and she was discharged on the fifth postoperative day.

*Histopathological examination*

All specimens were fixed in buffered formalin. A special histochemical study was undertaken to exam the presence of proteoglucans and epithelial mucous (PAS and mucicarmine stains). Immunostains were performed to investigate the presence of high and low molecular weight keratins (MoabAE), CA-125, CEA (Monosan), EMA, (Monosan) factor VIII, vimentin, secretory component (Dako monoclonal antibodies) and calretinin (Invitrogen), with appropriate positive and negative controls.

Histological examination showed that the walls of the cysts in the first three cases were formed of loose connective tissue. The interior surface was smooth and covered by cuboidal or flattened mesothelial cells (negative to mucin stain and negative to immunostains for factor VIII, CA-125, vimentin, CEA and secretory component. There was a positive reaction only to keratin, both high and low molecular weight (Figure 1). The diagnosis was benign cystic mesothelioma.

*Fourth case:* Histopathological examination revealed a malignant mesothelioma. Microscopy showed the development of a malignant neoplasm with a papillary and partially solid arrangement of the neoplastic cells. The cells were relatively small, uniform, cuboid and showed moderate nuclear atypia with moderate mitotic activity. Focal necrosis and hemorrhagic infiltration of the tumor but no psammomma bodies were noted in the multiple histological sections examined. Small papillary neoplasmatic nodules were growing on the serosal surface of the tubes and the uterine corpus and minute papillary nodules were observed on the ovarian surface. The resected omentum was also extensively invaded from the neoplasm.

The differential diagnosis considered an extra-ovarian peritoneal serous carcinoma and malignant mesotheliomas. Immunostains for high and low molecular weight cytokeratins (moAb-Immunon) were highly positive in all cells and also to normal mesothelial cells (Figure 2). Staining for vimentin (V-9), moAb (Immunon, CEA moAb (Monosan), CA-125 (moAb-CIS Diagnostics), factor VIII, secretory component (poly-DAKO) and WF1 (Immunon) were negative in neoplastic cells.

The total morphology of this neoplasm in combination with the immunohistochemical study was consistent with a malignant mesothelioma. Postoperatively the last patient received two cycles of chemotherapy but she refused the rest of the treatment protocol and was lost to follow-up after a 7-month period.

## Discussion

Mesotheliomas are mesenchymal neoplasms originating from the serous lining of the pleural, pericardial or peritoneal space.

Benign cystic mesotheliomas (BCMs) are well described tumors of unknown etiology. These lesions tend to occur in young women of reproductive age, as in our cases, and the most common predisposing factors are pre-

vious surgery, pelvic inflammatory disease, or endometriosis. These conditions interfere with peritoneal re-absorption, so origin via reactive and inflammatory response is proposed rather than neoplastic. The ovary and uterus are the most common sites affected, and rarely do BCMs arise in the pleural cavity [5]. The presence of epithelial hyperplasia and/or atypia may create problems in the differential diagnosis from malignant mesothelioma (MM).

MM is a rare malignancy with increasing incidence worldwide [6]. It mostly affects adults over 40 years of age. In contrast to BCM, these lesions mainly affect the pleura and only 20% are noted in the peritoneum. MM has been proven to be related to chronic exposure to asbestos, as well as has been reported following radiation therapy, mica exposure, recurrent peritonitis and administration of thorium dioxide [7, 8]. The mechanism through which asbestos offends the peritoneum is unknown and usually the time interval between exposure and diagnosis of the disease is quite long, estimated approximately in 25-40 years [9]. Three major histological subtypes of MM are recognized: epithelial, fibrous (sarcomatous) and mixed. The first type predominates among series and is characterized by papillary and tubular patterns of growth. The tumor cells are usually cuboidal or polygonal, with moderate cytoplasm and central nucleus. Fibrous mesotheliomas have a sarcomatous appearance and in most cases are made up of malignant appearing spindle cells that grow in fascicles within a relatively scant amount of fibrous stroma. The mixed type, which is easily recognized, is identified under the term biphasic MM and consists of a mixture of epithelial and sarcomatous components.

The clinical symptoms and signs of mesotheliomas are not specific to the disease, and the level of clinical suspicion is relatively low due to the rarity of the condition. Diffuse abdominal or pelvic pain, an incidental clinically or radiologically demonstrated mass lesion and/or increased abdominal girth due to ascites, are the most common initial findings [10]. Also MM can produce symptoms of partial or complete bowel obstruction, like nausea, vomiting, malaise and abdominal distention.

Diagnostic modalities include US and CT, but preoperative diagnosis is often not conclusive and there are no protocols for diagnostic imaging. Prompt diagnosis is often established postoperatively, after extensive histopathological examination. Routine laboratory tests have not proven useful and cytology after needle aspiration of the ascitic fluid might be positive for malignant cells in MM, but with no further information and high rate of false-positive and false-negative results [11]. Among tumor markers CA-125 could be elevated and new tumor markers are being investigated like mesothelin, soluble mesothelin related proteins (SMRP) and osteopontin [12].

The invasive techniques available for final diagnosis are laparoscopy and exploratory laparotomy with an adequate tumor biopsy.

BCMs are managed with complete surgical resection either laparoscopically or in an open fashion. The laparoscopic approach has been described, but due to the danger of rupture and seeding of a thin walled cyst without confirmed preoperative diagnosis, open surgery seems the safer approach. Aggressive surgical approaches including cytoreductive surgery with peritonectomy are recommended. Anti-estrogens and gonadotrophin-releasing analogues, sclerotherapy with tetracycline and latelly hyperthermic peritoneal perfusion with intra-peritoneal chemotherapy have also been attempted in individual cases with varied degrees of success [13]. Because these tumors tend to recur, follow-up management of these patients is difficult but necessary and includes physical examination and abdominal US or CT scan, without any established guidelines.

On the other hand, treatment of MM requires a multidisciplinary approach combining surgery, chemotherapy and irradiation. Diffuse MM of the peritoneum remains in the peritoneal cavity throughout its clinical course and morbidity and mortality arises from complications of disease progression inside the abdomen and pelvis. Combined locoregional treatment consisting of aggressive cytoreductive surgery and intraperitoneal chemotherapy has strong rationale. Hyperthermal intraperitoneal chemotherapy (HIPEC) has shown promising results and immunotherapy using the target mesothelin and other agents is under investigation [14]. Radiotherapy is added to the management plan after HIPEC and systemic chemotherapy in the form of whole abdominal irradiation with limited success [15]. Prognosis of MM is severe, with a median reported survival between six to nine months [16].

## Conclusion

Peritoneal mesotheliomas are rare clinical entities with no specific symptoms or laboratory and imaging characteristics. A high index of clinical suspicion and lastly surgical exploration and histopathological examination set the correct diagnosis in order to provide the most appropriate management. A multidisciplinary approach is promising when dealing with MMs, which makes many physicians have a nihilistic attitude towards the disease.

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