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Recurrent Struma Ovarii with Incidental Peritoneal Inclusion Cysts: A Potential Pitfall

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Abstract

Objective: Peritoneal Inclusion Cysts (PICs) is the formation of multicystic abdominal masses. They are associated with previous abdominal surgery. Struma ovarii can be accompanied by ascites and raised CA-125. We present a case of recurrent struma ovarii, associated with incidental PICs.

Methods: A 22 year-old woman was admitted to our hospital with ascites. She was diagnosed with a right ovarian mass and raised CA-125 (2761.3 U/ml). Her surgical history included a prior laparoscopic cystectomy, for struma ovarii, with preservation of the right ovary. The association of pelvic mass, ascites and elevated CA-125, was highly suspicious of malignancy. The woman underwent right salpingo-oophorectomy.

Results: At operation, numerous cystic structures were incidentally found. The ovarian mass was a pure struma ovarii. Pathological examination of the cystic structures was consistent with PICs.

Conclusion: PICs are rare cystic structures that arise from the abdominal peritoneum and can mimic gynecologic malignancies. Past histological diagnosis should always be reviewed. CA-125 can be elevated in both benign and malignant ovarian tumors, including struma ovarii. The co-existence of a second pathology, not diagnosed preoperatively, like PICs should be borne in mind in cases of ascites after previous surgery.

Keywords: Struma ovarii; Recurrence; Benign cystic mesothelioma; Peritoneal inclusion cysts; CA-125; Pseudo-Meig's syndrome

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Introduction

Peritoneal Inclusion Cyst (PIC) (also known as a peritoneal pseudocyst and benign cystic mesothelioma) is a type of cyst-like structure that appears in relation to the peritoneum and results from a non-neoplastic reactive mesothelial proliferation. Peritoneal inclusion cysts occur almost exclusively in premenopausal women with a history of previous abdominal or pelvic surgery, trauma, pelvic inflammatory disease or endometriosis [1]. Most patients with PICs present with pelvic pain or a pelvic mass and very rarely with ascites [2]. About 10% are discovered incidentally [3]. Peritoneal inclusion cysts range in size from several millimeters in diameter to bulky masses that may fill the entire pelvis and abdomen [4]. Struma ovarii is a rare type of monodermal teratoma containing more than 50% thyroid tissue and accounts approximately 2% to 3% of all teratomas. It is most common between the ages of 40 and 60 years, but has been reported in patients as young as 10 years old [5]. In most of the cases there are no definite symptoms and the presence of an ovarian tumor is incidentally noted on ultrasonography performed for other reasons. It can also present with abdominal or pelvic pain and a palpable lower abdominal mass and less frequently with ascites and raised CA-125 serum levels [6].

We report a case of recurrent struma ovarii presented with ascites and raised CA-125 serum levels in a 22 year-old woman with the concomitant incidental intraoperative finding of PICs.

Material and Methods

A 22-year old woman entered our hospital after being diagnosed with ascites in another hospital. During clinical investigation she was diagnosed with a right ovarian mass. She had undergone a prior laparoscopic cystectomy in the past, with preservation of the right ovary. The outside hospital pathology report from the initial ovarian cystectomy indicated a cystic teratoma with a component of thyroid tissue, consistent with struma ovarii. The patient did well post-operatively

and was asymptomatic until four years later, when she complained of abdominal pain and an enlarged abdomen due to ascites. Abdominal Computed Tomography (CT) scans revealed an increased amount of ascites. Minor fluid collection was also found in the Douglas space. A very small cyst of 6 mm under the liver capsule in the V compartment of the right lobe was also recognized. CT scan also revealed a complex mass with solid and cystic components of 6.9 cm × 3.9 cm, arising from the right ovary. Rare cystic elements were also found in the left ovary.

Biochemical tests revealed raised tumor markers, like CA-125: 2761.3 U/mL (<35), CA19-9: 94.48 (<34 U/mL), Ca 15-3: 47.96 (<30 U/mL), CEA: 0.49 (<5 ng/ml). Preoperatively, the association of the pelvic mass, ascites and an elevated serum level of CA-125 was highly suspicious of malignancy.

The woman underwent right salpingo-oophorectomy. At operation, numerous cystic structures, many in grape-like clusters, containing clear fluid, were incidentally found involving the small bowel surface and omentum. Solitary cysts were also identified. A complete excision was not possible. Nine cystic structures of 0.6 cm to 1.5 cm were excised and sent for pathologic examination.

Her postoperative course was uneventful. Her symptoms had resolved during follow-up assessment 6 months after surgery. Serum CA-125 levels have shown a substantial decrease post-surgically, with the last measurement being 38.5 U/mL. The patient was put on drospirenone and ethinylestradiol.

Results

Pathologic specimen comprised a tumor mass of 7.5 cm × 4.5 cm × 4 cm, with nodular surface and mostly solid and occasional cystic gelatinous cut surface (Figure 1).

Sections from the ovarian mass showed histologic features of pure struma ovarii without any associated dermoid components. The struma composed of thyroid tissue with variably sized thyroid follicles filled with colloid (Figure 2).

Pathological examination of the cystic structures revealed thin-walled cysts with smooth walls, separated by thin septa composed of connective tissue (Figure 3). The cysts were lined by uniform low cuboidal or flattened cells, with cytologic and immunohistochemical features of mesothelial cells, consistent with peritoneal inclusion cysts. No mitotic figures were seen. Immunohistochemical stains with monoclonal antibodies to cytokeratins AE1-AE3, calretinin (Figure 4), Ker5/6, WT1 (Figure 5), D2 40, ER (Figure 6) and PR, were strongly positive in the cytoplasm of the cells lining the cysts.

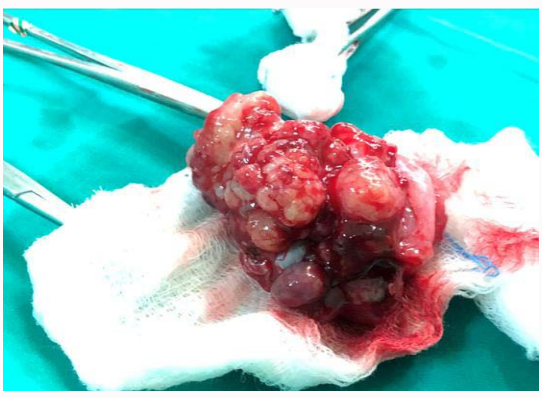

Figure 1: Pathologic specimen comprised a tumor mass with nodular gelatinous surface.

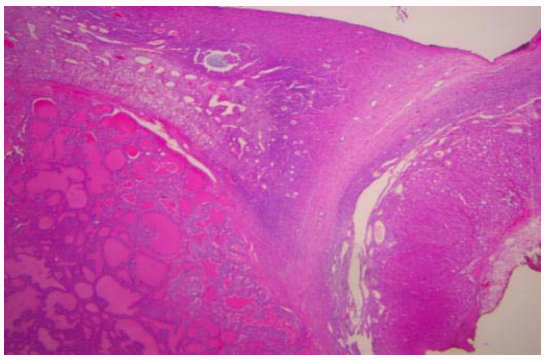

Figure 2: Histologic appearance of ovarian mass consisting of pure struma ovarii. The struma is composed of thyroid tissue with variably sized thyroid follicles filled with colloid (on the left). Evident corpus luteum (on the right) (H&E stain, x50 magnification).

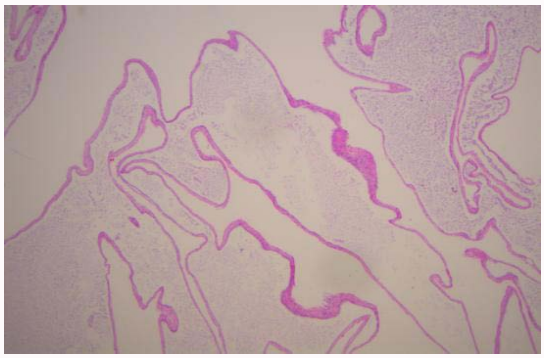

Figure 3: Pathological appearance of the cystic structures shows thin-walled cysts, lined by uniform low cuboidal or flattened cells, with cytologic and immunohistochemical features of mesothelial cells (H&E, x100 magnification).

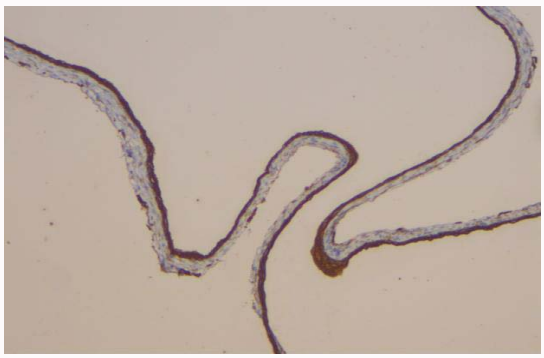

Figure 4: Peritoneal cyst lining with positive immunohistochemical staining in calretinin (Figure 4, x100 magnification).

Discussion

Primary peritoneal tumors are uncommon lesions that arise from the mesothelial or submesothelial layers of the peritoneum. Benign Multicystic Mesothelioma (BCM) is an unusual, multilocular cystic tumor that can arise from peritoneal, pericardial, or pleural mesothelial lining, with most cases commonly arising from the pelvic surfaces of the peritoneum. These proliferations of mesothelial origin are usually confined to the pelvis, but they can also been found in the upper abdomen and the retroperitoneum. They primarily adhere

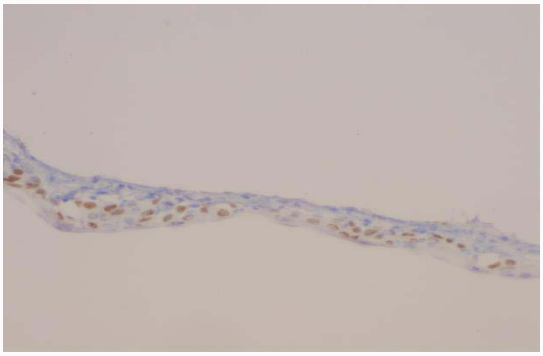

Figure 5: Peritoneal cyst lining with positive immunohistochemical staining in WT1 (Figure 5, x400 magnification).

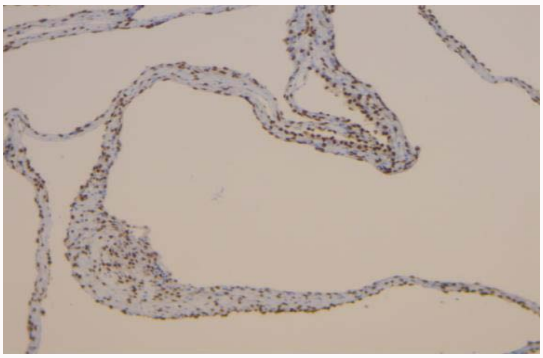

Figure 6: Peritoneal cyst lining with positive immunohistochemical staining in ER (Figure 6, x200 magnification).

to the peritoneum and ovaries, but may also be attached to the mesentery, omentum and gastrointestinal organ surfaces. Benign multicystic peritoneal mesothelioma (BCM) was first described in 1979 by Menemeyer and Smith [7]. Benign Cystic Mesothelioma (BCM) is a very rare disease characterized by proliferative lesions of the peritoneal mesothelial cells mainly in the pelvic or abdominal cavity. However, it can also be found in the pleura, pericardium, tunica vaginalis and spermatic cord. Multicystic mesothelioma has many alternative names, including peritoneal inclusion cyst, multilocular inclusion cyst and benign multicystic mesothelioma [1]. It is characterized by the formation of multiple multilocular thin-walled cysts, which may form large intra-abdominal masses. The BCM mostly affects women in 80% of cases, with an average age of 34 years old. It occurs most frequently in women of reproductive age and has a benign or indolent biologic behavior. There different arguments regarding the neoplastic or reactive nature of these lesions [8-10]. The clinical presentation is nonspecific: It is usually with abdominal pain, increase abdominal girth and constipation. Physical examination reveals abdominal distention, abdominal tenderness or a palpable mass. Worldwide, only 5 cases of BCM accompanied by ascites have been described so far [11].

BCM can be classified into three types: 1) the solitary type, when the boundary is clear, 2) the localized type when the multiple masses are found in the localized part of the abdominal membrane and 3) the diffuse type when the masses are widely spread across the abdominal membrane.

They are usually caused by accumulation of ovarian fluid that is contained by a peritoneal adhesion. The development of a PIC depends on the presence of an active ovary and peritoneal adhesions. The normal peritoneum absorbs fluid easily. However, the absorptive capacity of the peritoneum is greatly diminished in the presence of mechanical injury, inflammation and peritoneal adhesions.

Prior intraperitoneal surgeries are associated with peritoneal inclusion cyst formation, irrespective if they are laparoscopic or of open approach. Reported (past) surgical procedures related with PIC formation include ovarian cystectomy, oophorectomy, Unilateral or Bilateral Salpingo-Oophorectomy (UO or BSO), hysterectomy, caesarean section, myomectomy, tubal ligation, colectomy, appendectomy, cholecystectomy, partial pancreatectomy, hernia repair, partial gastrectomy, congenital urinary tract anomaly repair [12]. The reported interval between original surgery and detection of PICs ranges from 6 months up to 20 years [13]. Intra-abdominal inflammation is also related with PIC formation, with most common associated conditions being endometriosis, Pelvic Inflammatory Disease (PID), Crohn's disease and ulcerative colitis. Other conditions related with PIC formation are peritoneal tuberculosis, appendicitis, diverticulosis, peritonitis, the formation of tubo-ovarian abscess and appendiceal abscess, hepatitis, gastritis and peptic ulcer [12].

In addition there is a strong predilection for women of reproductive age that points to a hormonally driven process. However, the search for receptor positivity has not proven to be rewarding, with few patients testing positive for estrogen and progesterone receptors [14]. There are very few reports of genetic predisposition of BCM and an association with Mediterranean Familial Fever [15], as well as a family with BCM and several malignancies, including ovarian and colon cancer [16].

There is no consensus regarding the evaluation, treatment or follow up of patients with PICs. Patients with PICs have minimal mortality but high morbidity. Diagnosis is possible by clinical history, ultrasound imaging and CA-125 correlation.

It is difficult to diagnose preoperatively. There are no clinical pathognomonic signs or symptoms or laboratory results that can point to the diagnosis. Most clinical presentations are of peritoneal symptomatology mimicking acute abdomen, appendicitis, pelvic inflammatory disease, endometriosis and others. As such, the gold standard of diagnosis remains histologic (multiple, thin-walled cysts lined with mesothelial cells, filled with serous fluid). Occasionally, it can be diagnosed incidentally at surgery, laparoscopy, or cross-sectional imaging. In favor of the non-neoplastic nature of the disease is the fact that women with multicystic mesothelioma often have a history of prior pelvic surgery, endometriosis, or pelvic inflammatory disease (which some authors consider support for a non-neoplastic origin of the lesion). Imaging modalities that can be used for diagnosis are abdominal Ultrasound (US), CT scan or Magnetic Resonance Imaging (MRI). They permit the visualization of the lesion, but not its distinction from other cystic lesions of the peritoneum. Laparoscopy is the most reliable method as it enables the biopsy and (to establish the) final definitive diagnosis.

Cytology of peritoneal inclusion cyst fluid is usually non-diagnostic, as it demonstrates non-specific reactive mesothelial cells.

Multicystic mesothelioma has an indolent course in the majority of patients, with 50% of the cases having recurrences 1 to 27 years after the initial diagnosis. The average time to first recurrence is 32.2 months (range, four months to seven years). There are no specific factors for the prediction of recurrence. Recurrences are independent

of tumor size at initial or recurrent presentation, adequacy of tumor resection, or use of adjunctive chemotherapy [3].

Multicystic mesothelioma is composed of multiple, translucent, fluid-filled cysts that grow along the pelvic peritoneum in grapelike clusters. Usually, it is already of large size when diagnosed (mean diameter, 13 cm). Multifocal, freely floating cysts and unilocular cysts have been reported. In women, the tumor is typically located in the cul-de-sac and along the peritoneal surfaces of the uterus and rectum. Microscopically, the cysts are thin walled and may contain eosinophilic fluid. The mesothelial cells lining the cysts vary from flattened to endothelial-like to cuboidal. Foci of mesothelial hyperplasia may be present.

(Multicystic mesothelioma is not often considered in the differential diagnosis of a complex pelvic or abdominal cystic mass) (Omitted). The incidence of this disease is extremely rare, accounting for 0.15/100,000 annually, a fact that it makes it very challenging to diagnose and treat. From the limited cases reported in the literature, the prognosis appears to be very good and only one death has been reported, concerning a 47-year-old patient who died 12 years after diagnosis and refusing any surgical intervention [17].

Evaluation of complex pelvic masses usually includes examination of serum CA-125 level. A prospective evaluation by Guerriero et al. [18] revealed no appreciable difference between mean CA-125 levels of peritoneal inclusion cysts (23 IU/mL) and benign ovarian masses (22 IU/mL). In contrast, ovarian malignancies demonstrated a markedly elevated level (197.5 IU/mL). However, elevated CA-125 level may be seen in peritoneal inclusion cysts with associated endometriosis [18].

There are no evidence-based treatment strategies for BCM. Given the need for histological diagnosis, resection is most commonly used, but with recurrence rates up to 50% [19]. Peritoneal inclusion cysts have been observed to spontaneously regress in menopause [20]. Combined hormonal oral contraceptive may decrease or stabilize the size of the cyst and control associated symptoms by decreasing the production of cyst fluid. Medical treatment is suppressive, not curative. Long term use of these medications is obviously undesirable in patients desiring fertility. Discontinuing hormonal contraception may result in re-accumulation of peritoneal fluid and rapid growth of PICs as a hyperestrogenic state may precipitate their growth [21,22]. Antiestrogen, Gonadotropin-releasing hormone agonists and systemic chemotherapy have been used on a case-by-case basis in women with intraperitoneal masses [23,24]. Conservative treatment with the use of GnRhH analogs or oral contraceptives for the suppression of ovulation and pain medication is the first line of treatment [20]. There is no correlation of risk of recurrence with extent of resection [12]. This finding, together with the indolent course of the disease, makes less aggressive surgery attractive in the treatment of PICs. Therefore, minimizing the extent of surgery and the number of laparatomies may be appropriate when a correct diagnosis of benign lesion can be made [19]. There is only one case of malignant transformation of peritoneal cystic mesothelioma [25]. This fact supports the systematic clinical follow up of these patients for prolonged periods, perhaps for life. The accepted standard of treatment remains complete surgical resection with careful long-term follow-up.

The goal should not be a cure but symptomatic relief through individualization of (tailored) treatment [10]. Follow-up imaging should be considered, although no established follow-up guidelines exist because of the rarity of the disease.

Indications for surgical excision include an elevated CA-125, ultrasound appearance consistent with malignancy, persistence or recurrence of cysts or symptoms despite hormonal therapy, and infertility with an otherwise negative evaluation.

Given the young age and the decision to be conservative with imaging and tumor marker testing, our patient was clinically monitored with antiestrogen therapy.

Struma ovarii is a rare type of monodermal teratoma containing more than 50% thyroid tissue. In most of the cases there are no definite symptoms and the presence of an ovarian tumor is incidentally noted on ultrasonography performed for other reasons. It can also present with abdominal or pelvic pain and a palpable lower abdominal mass and less frequently with ascites and raised CA-125 serum levels [6]. Ascites occurs in about 10% of women and in some cases this can be combined with a pleural effusion (modified Meig's syndrome). About 17% of the patients develop pseudo-Meig's syndrome with pleural effusion and ascites [26]. The precise mechanism of the formation of ascites in struma ovarii patients are unclear to date, but it has been suggested that ascites, if present, usually regresses spontaneously after surgical removal of struma ovarii. High preoperative CA-125 levels can potentially lead to a misdiagnosis of a malignant ovarian carcinoma.

CA-125 is not a direct consequence of the presence of a malignant tumor, but rather a secondary effect due to the presence of ascites [27]. Tumor markers are of little clinical value. Although, (The) CA-125 levels may be raised in some patients, especially those, with ascites, this finding is not reliable in women of reproductive age, therefore is of little value in patients with struma ovarii.

Conclusion

BCM is a rare tumor that arises from the abdominal peritoneum with a predilection to the pelvic peritoneum and can often mimic gynecologic malignancies.

Diagnosis of a pelvic mass in a reproductive age female can be difficult and often requires surgical exploration and pathologic diagnosis. BCM requires a high index of suspicion for diagnosis.

BCM is generally considered a benign process; however given the high rate of recurrence and possible malignant transformation, close follow-up is important.

Although its recurrence is high after surgical resection, it does not present a tendency to transform into malignancy.

A prolonged systematic follow up of these patients, perhaps for life, is required since the lesion usually reappears and further resection, or another therapy may be indicated.

Although struma ovarii is rare, a high index of suspicion and relevant preoperative testing may facilitate the diagnosis, allow appropriate surgery to be performed and spare women from unnecessary morbidity. Past histological diagnosis should always be reviewed and compared with the present findings. If struma ovarii is suspected, thyroid functions should also be tested.

Increase of CA-125 levels in the serum can potentially lead to a misdiagnosis of a malignant ovarian carcinoma preoperatively.

The mechanism behind the raised cancer antigen levels in cases of pseudo-Meig's syndrome is still not well explained. However, CA-125 can be found to be elevated in both benign and malignant ovarian tumors, which means this clinical phenomenon is of little value in struma ovarii patients.

The co-existence of a second pathology, not diagnosed preoperatively, like BMC should be borne in mind in cases of ascites after previous surgical procedures.

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