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Challenges in the diagnosis and treatment of peritoneal mesothelioma: a case study and review of the literature

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ABSTRACT

Peritoneal mesothelioma is a rare neoplasm that is associated with multiple diagnostic and therapeutic challenges. Therapeutic guidelines are scarce and based on extrapolative data. Histopathological diagnosis is difficult as neither the morphological finding nor the immunohistochemical stains are specific. The mainstay treatment for resectable disease is cytoreductive surgery with intraperitoneal chemotherapy being a valuable addition. Treatment of non-resectable cases includes platinum-based chemotherapy, immune checkpoint inhibitors, and bevacizumab. We present a case of a 49-year-old woman suffering from inoperable peritoneal mesothelioma, which was initially diagnosed as ovarian cancer and treated accordingly.

Key words: differential diagnosis, ovarian cancer, peritoneal mesothelioma

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Introduction

Mesothelioma is a rare neoplasm associated with a poor prognosis and a high mortality rate. It originates from the serous membranes of the pleura, peritoneum, and pericardium.

The incidence rate in Europe is 0.36 per 100 000 per year. The peritoneum is the second most commonly affected organ, comprising 10–15% of cases [1, 2]. In Poland, 336 cases of mesothelioma were diagnosed in 2019, with an incidence rate of 0.6 cases per 100 000 inhabitants [3, 4]. The incidence is declining worldwide, especially among men. Poland remains one of the countries where the incidence is increasing.

Peritoneal mesothelioma is rare and, therefore, not well investigated. Most of the data are based on studies of more common pleural mesothelioma. The differences and similarities between these two diseases are not well understood. Although asbestos exposure is a significant

and predominant risk factor in both conditions, those cancers differ in gene expression and possibly also in molecular pathogenesis [5–7].

The symptoms of peritoneal mesothelioma are largely dependent on the extent of tumor spread in the abdominal cavity and the presence of distant metastases. The most common initial symptom is abdominal distension (30–80% of patients) and abdominal pain (27–58% of patients). Malignant bowel obstruction or perforation can also develop. Frequent symptoms also include poor appetite, early satiety, nausea or vomiting, weight loss, night sweats, fever, new-onset hernia, or urinary complaints. Due to the lack of characteristic symptoms, diagnosis is often delayed. Although symptoms of gastrointestinal involvement are the most common clinical presentation, patients sometimes present with distant metastases to the liver, spleen, thyroid, or brain, or the neoplasm is an incidental diagnosis found at laparoscopy [5, 8].

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Novel immunohistochemical and molecular markers have improved the accuracy of diagnosis. However, in about 14% (high-resource countries) to 50% (developing countries) of mesothelioma, diagnoses are incorrect and result in inadequate treatment and confounding epidemiological studies [6]. We aim to present the case of a patient with primary peritoneal mesothelioma which was misdiagnosed as ovarian cancer.

Case presentation

Clinical history

A 49-year-old woman was referred with a suspicion of ovarian cancer due to abdominal pain, bloating, and ascites. The previous medical history included: obesity, arterial hypertension, and appendectomy. Computed tomography (CT) revealed a solid cystic lesion of the right ovary (32 mm) with accompanying peritoneal implants involving the omentum, liver capsule, and sigmoid, and two lesions (up to 71 mm) in the enlarged spleen. No thoracic lesions were reported. The patient underwent laparotomy with hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and splenectomy. The procedure was performed in a clinical center with extensive experience, but, not in a tertiary center.

Histopathological examination and initial treatment

The histopathological result described numerous foci of adenocarcinoma within both ovaries and the omentum. The involvement of the ovary with small malignant foci and the presence of psammoma bodies resembled a serous papillary adenocarcinoma. Lesions in the omentum were classified as metastases, based on morphology and immunophenotypic examination [CK7 (+), CK20 (–), WT-1 (+)]. The pathological stage was established as pT3cN1. The spleen lesions were found to be vascular malformations. The International Federation of Gynecology and Obstetrics (FIGO) IV ovarian cancer was diagnosed.

The patient underwent six cycles of adjuvant therapy with paclitaxel, carboplatin, and bevacizumab. Post-treatment CT showed stable liver capsule lesions and partial remission in lesions located at the post-splenectomy site. A prominent epigastric hernia was also present in the laparotomy scar. Maintenance bevacizumab had continued but ended prematurely due to the development of a peritoneo-cutaneous fistula.

Further treatment

Three months later, follow-up CT revealed progression of diaphragmatic lesions, pathological common

iliac lymph nodes, ascites, consolidations in the left lung and contralateral hydrothorax. The patient was referred to a tertiary center and second-line chemotherapy with carboplatin and gemcitabine was initiated.

A histopathological reevaluation of the initial surgical specimen was ordered. Low-grade serous carcinoma (LGSC) was confirmed with the estrogen receptor (ER) expressed in <1%, progesterone receptor (PR) in < 1%, and Ki67 in 3% of tumor cells. Somatic and germline *BRCA1* and *BRCA2* mutations were excluded by the next-generation sequencing (NGS) test. The concentration of cancer antigen 125 (Ca-125) and human epididymis protein 4 (HE4) was within the normal range. Subsequent CT after 3 months showed stable disease. After further 3 months, CT was stable and both Ca-125 and HE4 levels normalized. After further 4 and 9 months, CT and Ca-125, and HE4 marker levels were stable. Meanwhile, postoperative hernia significantly reduced the patient's quality of life. She was referred for hernia surgery; however, due to the presence of the malignancy, numerous centers refused to operate.

Hernia surgery, clarification of the diagnosis

After confirming the stable disease on positron emission tomography (PET) in combination with a CT scan (PET-CT), a hernia removal was finally performed. The hernial sac contained ingrown intestinal loops and numerous malignant implants. Segmental resection of the ileum was necessary. Histopathological examination revealed neoplastic infiltrations of epithelioid cells with slight atypia, forming solid and papillary structures with metastases to the peri-intestinal lymph nodes. The immunophenotype included calretinin +/+, D2-40 +/+, CK5/6 +/+, and PAX8 -/-. The result contradicted the diagnosis of the ovary as primary cancer and established a new diagnosis of epithelioid mesothelioma. Repeated evaluation of the archival samples yielded results consistent with the new diagnosis. The newly obtained cancer sample expressed ER 3%, with no expression of PR or androgen receptors. Ki-67 was 12.5%. The mitotic index was 2 mitoses per 10 high-power fields. Subsequent CT showed low-grade progression of the peritoneal implants. Metronomic chemotherapy with continuous oral vinorelbine (40 mg 3 times a week) was administered. Treatment did not control the progression; therefore, cisplatin-pemetrexed chemotherapy was initiated. The therapy yielded good disease control. Cisplatin was discontinued after 6 cycles. Since then, the patient has enjoyed good general condition, with improved quality of life after hernia plastic surgery. The maintenance pemetrexed is continued.

Discussion

Peritoneal mesothelioma is a very rare neoplasm with nonspecific symptoms and a poor prognosis [8, 9]. It is likely to be misdiagnosed, especially if it coexists with peritoneal dissemination and other abdominal comorbidities. The literature describes cases of peritoneal mesothelioma resulting in small bowel obstruction [10] or infertility [11]. Other reports call attention to the simultaneous appearance of peritoneal mesothelioma along with endometriosis [12, 13] or breast cancer [14]. In a study of 164 women diagnosed with peritoneal mesothelioma, the mean age of diagnosis was 49 years, and the most frequently reported symptom was abdominal or pelvic pain. Some patients were asymptomatic and had paraneoplastic syndromes or cervical lymphadenopathy. In most cases, a personal or family history of other tumors was present [15].

Few therapeutic guidelines aimed specifically at MPM exist and are largely based on studies of more common pleural mesothelioma [16]. The recommended therapy for resectable disease is typically cytoreductive surgery (CRS). Small studies showed excellent results with hyperthermic intraperitoneal chemotherapy (HIPEC) following CRS [17]. The limitation of HIPEC is patient selection, toxicity, and lack of data from prospective randomized trials [18].

The standard first-line palliative treatment for unresectable disease is based on cisplatin or carboplatin combined with pemetrexed or raltitrexed. The combination of platinum and gemcitabine is considered a valuable alternative [1, 16]. The addition of bevacizumab to the cisplatin-pemetrexed doublet offers a modest survival benefit [19]. The latest National Comprehensive Cancer Network (NCCN) guidelines consider the combination of ipilimumab and nivolumab as another standard first-line therapy in advanced peritoneal mesothelioma. The recommendation is based on a recent phase 3 trial of nivolumab combined with ipilimumab in pleural mesothelioma showing significant improvement in overall survival (OS) compared to standard first-line chemotherapy (median OS — 18.1 vs. 14.1 m; HR = 0.74; 96.6% CI 0.60–0.91; $p = 0.0020$) [20]. Other checkpoint inhibitors were also investigated in mesothelioma. Pembrolizumab demonstrated an objective response rate (ORR) of 20% and a disease control ratio (DCR) of 72%. Atezolizumab combined with bevacizumab showed an ORR of 40% and DCR of 95% in a small study [21].

Vinca alkaloids demonstrated activity in patients with mesothelioma in a single or combined therapy; therefore, they are a reasonable option in subsequent lines [21]. As data on second- or third-line therapy are sparse, it is recommended that patients with peritoneal mesothelioma should be enrolled in clinical trials.

The histopathological diagnosis of peritoneal mesothelioma is challenging and, therefore, prone to diagnostic errors, especially in patients with involved ovaries [5, 6]. Most ovarian tumors are composed of epithelial cells, arranged in solid and tubulopapillary patterns. Low-grade serous carcinoma (LGSC) is characterized by a high architectural variety, including the presence of micropapillae and macropapillae that are usually surrounded by clefts or clear space. Psammoma bodies are a common finding. LGSC cells show mild to moderate nuclear atypia, and the nucleoli are sometimes visible. Mitotic activity is usually less than 2–3 mitotic figures per 10 HPF and necrosis features are seldom seen. The Ki-67 index is relatively low. LGSC cells express epithelial markers, including cytokeratin (AE1/AE3, CAM 5.2) PAX8, WT1, EMA, CA-125, and BER-EP4. The ER expression is high, while PR is approximately 50% positive. Cancer cells exhibit a wild-type p53 pattern. However, there is no diffuse expression of p16 [22–25].

Peritoneal mesotheliomas are made up of cells that are generally similar to mesothelium cells, with an eosinophilic cytoplasm and a cuboidal shape. They usually show mild to moderate nuclear atypia and have noticeable nucleoli; the mitotic figures are usually only slightly visible. About one-third of the cases show the presence of psammoma bodies. The typical patterns of peritoneal mesothelioma are tubular, papillary, and solid. In many cases, they coexist with each other, especially solid and papillary. Unlike LGSC, the papillary pattern is less complex and inconspicuous. In immunohistochemistry, mesothelioma cells are usually positive for CK7, Calretinin, EMA, WT-1, HBME1, CK5/6, and D2–40. What is characteristic of them, however, is the lack of expression of ER, PR, CEA, Leu M1, B72.3, MOC31, claudin-4, and BER-EP4 [22, 23, 26, 27].

The presented case posed many diagnostic challenges which made it difficult to differentiate between these two neoplasms. The examined tumor was composed, among others, of papillary structures with the presence of psammoma bodies, showing features of slight atypia, mitotic index of 2/10 HPF (Fig. 1), and Ki67 that ranged in various measurements from 3 to 12.5%. Tumor cells were positive for calretinin, D2-40, and CK5/6. The immunoreactivity for PAX-8 was negative (Fig. 2). This picture could indicate both of the discussed neoplasms.

A common diagnostic problem is a distinction between peritoneal mesothelioma and adenocarcinoma with diffuse peritoneal involvement or primary peritoneal adenocarcinomas, which are morphologically identical to ovarian or fallopian adenocarcinomas. Immunohistochemically, in most cases, MPM shows the expression of calretinin, WT-1, cytokeratin 5/6, and D2–40, while the presence of positive PAX-8 and ER favors the diagnosis of LGSC. High expression of ER and PR is observed in most LGSCs

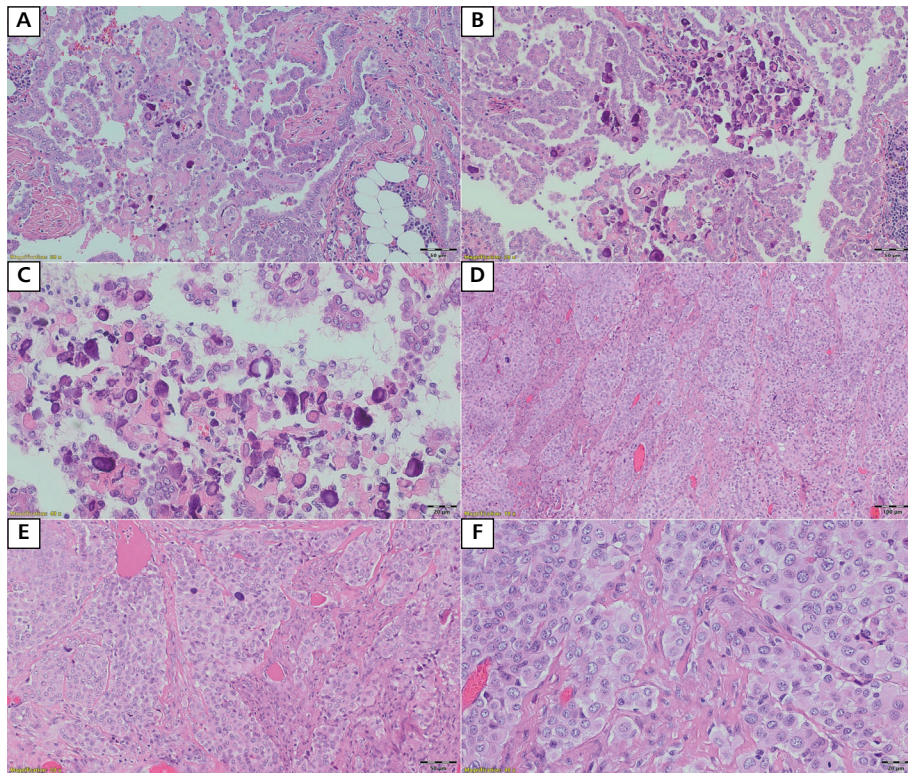


Figure 1. A–C. Papillary pattern of peritoneal mesothelioma with psammoma bodies; D–F. Solid pattern of peritoneal mesothelioma. Cells are epithelioid, with eosinophilic cytoplasm and moderate nuclear atypia

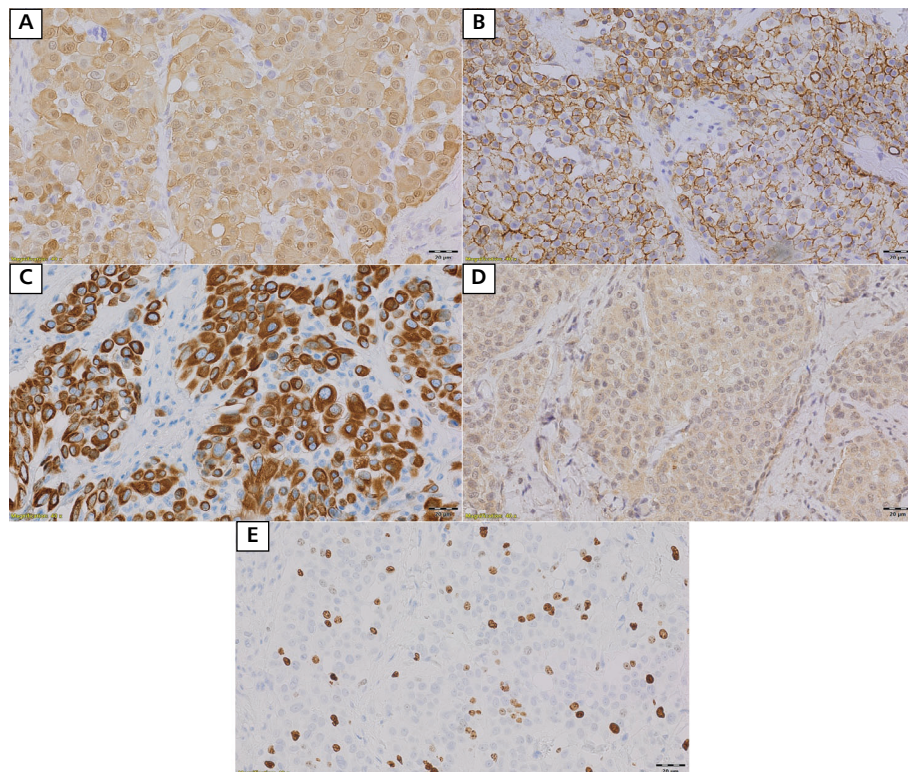


Figure 2. Immunohistochemical examination of peritoneal mesothelioma. Tumor cells are positive for calretinin (A), D2–40 (B), and CK5/6 (C); D. The immunoreactivity for PAX-8 was negative; E. Ki-67 expression was evaluated as 12.5%

while they are commonly absent in MPMs [22, 23]. Important in understanding the key pathogenetic mechanisms of cancer was the discovery that germline BRCA1-associated protein 1 (BAP1) mutations cause mesothelioma and other cancers (BAP1 cancer syndrome), which distinguishes malignant mesothelioma from benign mesothelial lesions and serous tumors of the ovary [27, 28]. Boussios et al. [29] claim that the PAX-8 gene negativity is a useful diagnostic marker that could be employed for the differential diagnosis of ovarian carcinoma. It was used in the evaluation of the histological preparation of the second surgery in our patient, giving a conclusive diagnosis. However, diagnosis may be hampered by the fact that most patients have an elevated Ca-125 level [30]. It should be noted that CA-125 is produced by mesothelial cells of the pleura and peritoneum, hence its increased level may be present in many diseases related to peritoneal damage, e.g., liver cirrhosis or previous surgery. Although CA-125 is often recognized as a marker of gynecological malignancies, its elevated level may also be present in mesothelioma or even benign conditions such as endometriosis. Therefore, the elevated level of CA-125 should encourage a wide-ranging differential diagnosis [30–35]. Radiological criteria for discrimination of the characteristics of adnexal masses, such as the simple ultrasound rules of the International Ovarian Tumour Analysis (IOTA), should form the basis for the diagnosis of adnexal mass. If the clinical picture is ambiguous, more precise indicators adapted to the clinical situation should be used, such as, e.g., the FDA-approved ROMA and OVA1 algorithms.

Another important aspect in our case described was the use of surgery for the treatment of persistent postoperative epigastric hernia after extensive surgery. It is known to negatively affect quality of life, and this topic is widely described [36]. In the study by Baucom et al. [37], it has been shown that in patients without prior ventral incisional hernia (VIH) who underwent abdominal malignancy resections, the incidence of VIH is high and can impact cancer survival, with pain and the need for additional operation. In the case of our patient, despite the ongoing remission of palliatively treated cancer, many surgical centers refused to remove the hernia. However, recent research shows that VIH repair after abdominal malignancy surgery can improve quality of life, functionality, social function, and satisfaction [38, 39]. More research is needed to assess which patients will benefit most from the procedure, but surgical correction of the treatment complication in cancer patients seems obligatory.

Conclusions

Despite the use of new immunohistochemical and molecular markers, mesothelioma can be misdiagnosed. Therefore, tumors in the abdominal cavity should be carefully evaluated as no single immunohistochemical stain differentiates between LGSC and PMM. In ambiguous cases or treatment failure, resampling and reevaluation of the tumor should be considered. Performing surgical procedures to reduce the discomfort associated with neoplasm in patients with stable neoplastic disease may significantly improve their quality of life. In palliative patients, the time of anticancer treatment interruptions can be used to tackle their remaining health problems.

Conflict of interest

Authors declare no conflict of interest.

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