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Single Case

Primary Peritoneal Mesothelioma: Diagnostic Challenges of This Lethal Imposter

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Abstract
Primary Peritoneal Mesothelioma is a rapidly aggressive and rare neoplasm that arises from the lining of mesothelial cells of the peritoneum and spreads extensively within the confines of the abdominal cavity. The pathogenesis of all forms of mesothelioma is strongly associated with industrial pollutants, of which asbestos is the principal carcinogen. Characteristically, asbestos exposure has a strong relationship with mesothelioma of the pleura, but the peritoneal cavity is the second most commonly affected site. Additionally, in contrast to pleural mesothelioma, which has a male predominance (male-female ratio of between four and five to one), women comprise approximately one-half of all cases of malignant peritoneal mesothelioma. A thorough history of occupational/paraoccupational exposure along with histopathology is the key to timely diagnosis and treatment.

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Introduction

Malignant peritoneal mesothelioma (MPM) is a highly lethal malignancy of the serosal membranes of the pleura, peritoneum, pericardium, or tunica vaginalis testes. Only 10–15% of the approximately 3,300 cases of mesothelioma diagnosed in the USA every year are peritoneal, resulting in about 600 new cases annually, making this a rare occurrence [1]. The peritoneum is the second most frequent site of origin of mesothelioma, following the pleura [2]. The pathogenesis of all forms of mesothelioma is strongly associated with industrial pollutants, of which asbestos is the principal carcinogen associated with the disease. In contrast to pleural mesothelioma, which has a male predominance (male to female ratio of 4-5:1), women comprise approximately one-half of all cases of MPM [3].

Presentation of MPM usually includes abdominal distention as the most frequent initial symptom, with pain as the second most common initial symptom [3]. Other common symptoms include early satiety, dysphagia, shortness of breath, weight loss, and overall lethargy.

Computed tomography (CT) with intravenous (IV) contrast is an indispensable study for any patient with ascites, increasing abdominal girth, and abdominal pain. Unfortunately, even with IV contrast, CT underestimates the burden of disease [3, 4]. Here, we present a case of primary MPM in a patient who may have only had paraoccupational exposure and whose nonspecific complaints complicated our path to his final diagnosis.

Case Presentation

A 67-year-old male with a past medical history of hypertension, benign prostatic hyperplasia, and childhood asthma presented to the emergency room with a 4-week history of progressively worsening dull, generalized abdominal pain. Associated symptoms consisted of bloating, decreased oral intake, shortness of breath, and fatigue. He also reported no bowel movement in the last 3 days, which was unusual for him. He denied any fever, chills, cough, trauma, weight loss, nausea, vomiting, diarrhea, sick contacts, recent travel, hematuria, and/or hematochezia. He did not report any new diet or unusual foods. He had never had similar symptoms in the past.

The patient was a retired office manager, former smoker, and reported drinking two to three beers every day for the last 20 years. Although a migrant from Cuba, he had been living in the USA for about 20 years. Home medications included finasteride, omeprazole, and tamsulosin.

On initial presentation, the patient was afebrile, with 102/47 mm Hg blood pressure, a heart rate of 149 beats per minute, and was saturating well on room air. Physical examination revealed bilateral decreased breath sounds with wheezing at bases, tachycardia, irregularly irregular pulse, trace bilateral pedal edema, soft, mildly distended abdomen, with diffuse tenderness.

Electrocardiogram revealed atrial fibrillation with rapid ventricular rate (afib RVR) with no evidence for ischemia. Laboratory values showed an elevated white blood count at 16 × 10^3/μL, ProBNP of 11,442 pg/mL, negative COVID-19 test, creatinine of 1.84 mg/dL, and elevated D-dimer of 6.45 mg/L. Chest X-ray showed minimal infiltrates, cardiomegaly, and mild pleural effusion bilaterally. An echocardiogram revealed a normal ejection fraction with no right heart strain. Due to his shortness of breath coupled with the elevated D-dimer, CT angiography was done on admission and was positive for right lower lobe pulmonary embolism (PE) and mild abdominal ascites. CT abdomen without PO/IV contrast reported extensive abdominal and pelvic ascites with no bowel obstruction and otherwise unremarkable liver morphology. The patient was prophylactically started on antibiotic coverage pending confirmatory diagnosis of sepsis and admitted to the intensive care unit. Urine and blood cultures drawn on admission did not show any micro-organisms.

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Abdominal discomfort persisted in the presence of afib RVR and PE. The patient's afib RVR was managed per hospital protocol, and he was anticoagulated for his PE. Due to worsening abdominal distension, paracentesis was completed twice during his stay. Initial abdominal ultrasound-guided paracentesis yielded 4250 cc of dark straw-colored fluid. Ascitic fluid analysis showed no evidence suggestive of spontaneous bacterial peritonitis. Preliminary ascitic fluid pathology showed atypical epithelioid cells most consistent with reactive mesothelial cells. Viral hepatitis serologies, liver function tests, Alpha -fetoprotien (AFP), CA 19-9, CEA, ANA, anti-smooth muscle antibody, and anti-mitochondrial antibody, were all noncontributory. Serum ascites albumin gradient (SAAG) was calculated and was found to be 0.8.

Due to the preliminary pathology report's high suspicion for malignant mesothelioma, family and social history were reviewed again with the patient and his family. They remained consistent with no history of work in shipping yards, construction, mining, mechanical work, or significant asbestos exposure. However, upon further discussion, it was discovered that the patient worked in a rum factory in an administrative capacity over 20 years ago while living in Cuba.

By day 7, the patient continued to deteriorate and developed new-onset nausea, vomiting, and diarrhea. A repeat CT abdomen/pelvis with PO contrast was ordered and revealed multiple dilated loops of the small bowel, consistent with high-grade small bowel obstruction as well as thickened omentum and questionable peritoneal carcinomatosis. The patient was expedited to the operating room for an exploratory laparotomy, which revealed the extensive spread of the disease. Biopsies were collected of what appeared to be advanced carcinomatosis with matted visceral structures and probable malignant ascites.

Unfortunately, by day 15, the patient rapidly decompensated and expired. The final pathology report then returned and confirmed the presence of primary MPM. Abdominal fluid revealed scattered and markedly atypical mesothelial cells suspicious for malignant mesothelioma in a background of mixed inflammation and numerous histiocytes. Immunohistochemistry was consistent with a mesothelial phenotypic expression. Peritoneum excision returned positive for malignant epithelioid mesothelioma with rhabdoid features.

Discussion

The lifetime risk of developing mesothelioma among asbestos workers is thought to be as high as 10%. The latency period between exposure and the development of mesothelioma is approximately 20–40 years [5]. Other possible factors include direct abdominal radiation and exposure to other mineral fibers, namely erionite, a substance found in volcanic ash.

A case-controlled study based on telephone interviews of mesothelioma patients found that the attributable risk for asbestos exposure was 58% for men and 23% for women. The reason for this gender difference is unclear, but misclassification of exposure history in women may be in part responsible [5]. This may be the case for our patient, whose family indicated that he had never been exposed to asbestos.

Additionally, paraoccupational exposure is yet another recognized risk factor for asbestos-related disease. A literature review of over 200 published articles was evaluated focusing on asbestos-related disease among household contacts of workers occupationally exposed to asbestos. Over 65% of these cases were in persons who lived with workers classified as miners, shipyard workers, insulators, or others involved in manufacturing asbestos-containing products. For our patient, it is possible that his position as glass-manufacture administrator put him at an indirect risk that was then compounded over time. However, there is currently a paucity of published data connecting workplace asbestos exposure to the development of malignancy in their associated household contacts.

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The pathogenesis underlying asbestos-induced carcinogenicity has not been understood in its entirety. Asbestos fibers can be broadly classified as follows – serpentine, which includes chrysotile (white asbestos), and amphibole, which includes crocidolite (blue asbestos), amosite (brown asbestos), anthophyllite, actinolite, and tremolite. The association between amphibole fibers and mesothelioma is well-established, with crocidolite fibers having the most oncogenic potential. In vivo studies have shown the asbestos fibers exert dose-dependent toxicity. In tissue cultures, doses equal to or higher than 5 μg/cm^2 or higher induce 100% cell death within a week [6]. Given that all cells die on exposure to crocidolite fibers, the question of tumorigenesis emerges as one of extreme importance.

The mechanism of this paradox is explained by a complex interlay of autocrine and paracrine effects exerted by human mesothelial cells in response to asbestos exposure. Studies have revealed that there is a predominant mononuclear phagocytic response in reaction to asbestos fibers. On differentiation of these cells to macrophages, the asbestos fibers are phagocytized, resulting in the release of TNF-α. In the same instance, there is upregulation of TNF- R1 (TNF receptor). On binding to its receptor, TNF-α induces the NF-κβ pathway, enhancing the survival of human mesothelial cells [6, 7].

Also, asbestos is known to cause breaks in the DNA of mesothelial cells secondary to reactive oxygen species and reactive nitrogen species formation. These breaks result in a wide variety of mutations in the mesothelial cells, thereby aiding the tumorigenesis [7–11]. In addition to TNF-α, other growth factors and cytokines that have been implicated in the pathogenesis of MPM are – platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factors (VEGF), IL-6, and IL-8 [7, 12]. This interplay of NF-κβ pathway activation and reactive oxygen species/reactive nitrogen species induced DNA breaks with subsequent mutations to allow the mesothelial cells to continue proliferation and at the same time accumulate harmful mutations. Furthermore, several tumor suppressors and oncogenes have been implicated in the pathogenesis of MM, including CDK2NA/ARF, p16, p14, p53, NF2, and BRCA1 [1, 12–15]. However, their contribution to the overall disease burden is yet to be determined.

Abdominal distention is usually the primary presenting feature (30–80%) and is usually followed by or coupled with pain (27–58%) [3, 16, 17]. In most cases, the pain is diffuse and nonspecific, similar to this patient's presentation. Paraneoplastic phenomena are rare and include fever, thrombocytosis, venous thromboembolism, hypoglycemia, and coombs-positive hemolytic anemia.

In 20% of cases, MPM metastasizes to the abdominal and pelvic lymph nodes [16, 17]. The mode of spread is by direct invasion, lymphatic permeation, peritoneal seeding, or hematogenous. The imaging patterns include fibronodular stranding, nodules, plaques, and masses [16, 17]. Mesenteric thickening may produce pleated or stellate patterns. Spiral CT is the most useful modality in the diagnosis and follow-up of these peritoneal tumors [1–3, 7]. Due to our patient's impaired renal function, initial CT was limited by lack of contrast; therefore, it was not until later that his carcinomatous was able to be clearly identified.

MPM is histologically classified into three forms/subtypes: epithelial, sarcomatoid, and biphasic [17]. The most common subtype is epithelioid, encompassing approximately 75% of the cases. Biphasic is the second most common subtype, contributing to approximately 25% of the cases, while sarcomatoid is seldom encountered [18]. The epithelioid subtype has the best prognosis, with a median survival of 55 months. Biphasic and sarcomatoid variants, on the other hand, are highly aggressive, like their pleural counterparts, with a median survival of 13 months [18]. Of note, the postmortem biopsy and histopathology showed a mix of solid epithelial cells with spindle cells and rhabdoid interspersed rhabdoid differentiation, classifying it into the biphasic subtype (shown in Fig. 1–3) [18, 19].

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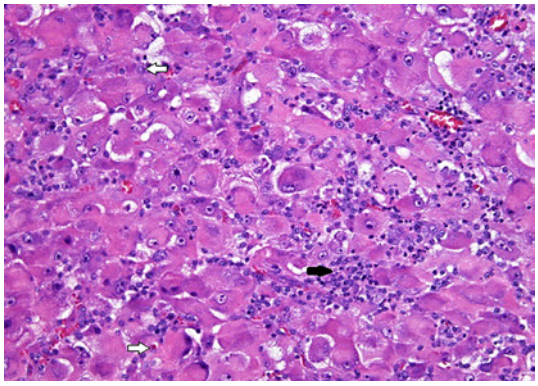

Fig. 1. Solid epithelial cells (white arrow) and rhabdoid differentiation (black arrow) in a background of mesothelial cells.

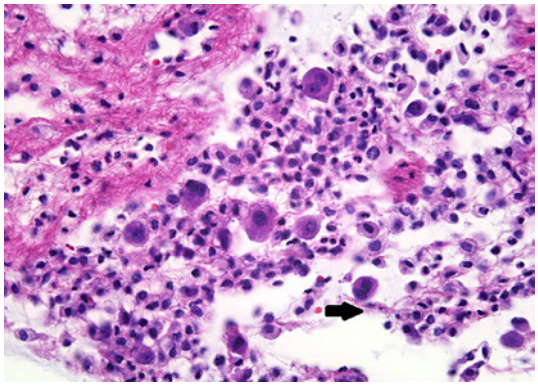

Fig. 2. Spindle cell differentiation (black arrow).

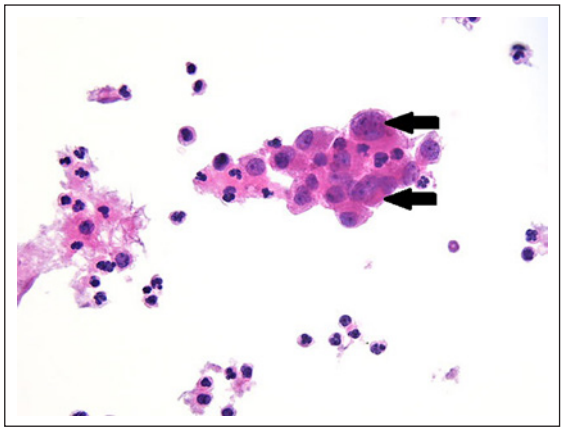

Fig. 3. Malignant mesothelial cells (black arrow).

To conclude, there is no consensus as to the optimal treatment for MPM. Due to its rarity, most of the available clinical information about treatment has been derived from retrospective singlecenter series, which have inherent selection biases. Prospective clinical trials are few and small, and there are currently no randomized studies that compare one treatment with another. As such physicians should maintain a high index of suspicion for abdominal malignancy in cases of new-onset ascites with prior history of unprovoked venous thromboembolism. Delay in diagnosis should be avoided with rapid diagnostic paracentesis and calculation of serum ascites albumin gradient to further elucidate etiology.

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Statement of Ethics

This study protocol was reviewed and the need for approval was waived by the Office of Human Research at Lakeside Medical Center. A written informed consent was obtained from the next of kin (patient's daughter) for publications of the details of their medical case and images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

1. Sonya K. Dusseault, DO – patient care and Drafting of the manuscript.
2. Okelue Edwards Okobi, MD, M.Sc, and Vignesh Sankar, BS – drafting of the manuscript.
3. Nimish Thakral, MD – drafting of the manuscript and literature research.
4. Ishan Gunawardene, MD; Bryan Dawkins, MD; Yaw Abu, MD; and Barry Davis, MD – patient care

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be sent to Dr. Sonya Dusseault.

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