

From Ascites to Malignant Peritoneal Mesothelioma: The Diagnostic Workup of a Rare Tumor

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Abstract

Background/Aim: Ascites is a common clinical manifestation of a wide spectrum of heterogeneous underlying conditions. All possible causes of ascites should be considered in the differential diagnosis to ensure an appropriate diagnostic workup. Among the rare causes, malignant peritoneal mesothelioma must be considered, as its diagnosis is particularly challenging.

Case Report: We present the case of a 77-year-old female who developed ascites and lower-quadrant abdominal pain. She had no prior history of cancer and no documented occupational exposure to asbestos or other known carcinogens. After exclusion of the principal benign and malignant causes of ascites, we performed a biopsy and ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT). The final diagnosis was primary malignant peritoneal mesothelioma, an extremely rare tumor.

Conclusion: This case highlights the complexity of the differential diagnosis. The diagnostic work-up for peritoneal mesothelioma must integrate the patient's clinical history, physical examination, tumor markers, and imaging findings. Biomarkers such as mesothelin and advanced imaging modalities including PET/CT assume an increasingly important role in staging and in distinguishing peritoneal disease entities.

Keywords: Malignant peritoneal mesothelioma, ascites, differential diagnosis, rare tumor, FDG-PET/TC, tumor markers.

Introduction

Ascites arises from a variety of causes, most commonly benign conditions such as heart failure or chronic liver disease. Nevertheless, a small subset of patients

with ascites may have an underlying malignancy (1). Approximately 5% of patients have multiple coexisting causes of ascites, which are the most difficult to diagnose, as each cause contributes to the fluid accumulation, but none seems severe enough on its own (2).



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Physical examination and abdominal imaging play a key role in the assessment of ascites, but abdominal paracentesis is crucial to determine its cause (3). Initial investigations should target the major causes and should include a general physical exam, determination of the serum-to-ascites albumin gradient (SAAG), ascitic fluid cell count (especially neutrophils), and total protein concentration. Since these tests may be normal in patients with rare causes of ascites, additional tests are recommended. These include for example microbiological culture and Gram stain (for infections and spontaneous bacterial peritonitis), glucose and lactate dehydrogenase concentrations, amylase (in pancreatic ascites or bowel perforation), triglycerides (elevated in chylous ascites), serum N-Terminal-pro brain natriuretic peptide (NT-proBNP, in heart failure), and cytology with carcinoembryonic antigen (CEA) levels (in malignancy).

Cytology is critical for identifying peritoneal carcinomatosis; nearly 100% of patients with this condition have a positive cytology for malignant cells in the ascitic fluid. However, not all malignancy-related ascites are due to peritoneal carcinomatosis (4). In the diagnostic work-up of malignant ascites, it is important to consider rare pathologies in which cytology may be negative. One such tumor is malignant peritoneal mesothelioma, a very rare and aggressive pathology whose diagnosis can be difficult and is often associated with negative cytology (5). Epidemiology can be useful for identifying areas with high rates of asbestos exposure, the main risk factor for this tumor (6). The most common clinical features of malignant peritoneal mesothelioma are abdominal distension and pain (6). Less common is the focal variant, where patients may present with a circumscribed mass and localized abdominal pain (7). The typical disease progression is confined to the peritoneal cavity, but it can also extend into the pleural cavity, causing a pleural effusion (8).

Tumor markers are not definitive to detect peritoneal mesothelioma. Cancer antigen 125 (Ca-125), alpha-fetoprotein (AFP), CEA and mesothelin can be elevated in some patients, and their levels may correlate with

disease progression, but their specificity is low during the diagnostic process (9).

Computed tomography (CT) is one of the first imaging modalities used to investigate the cause of ascites. Malignant peritoneal mesothelioma may appear on CT scan as irregular peritoneal thickening, with or without nodules and masses, which these finding may be further delineated with intravenous contrast. Positron emission tomography (PET) also plays a very important role as a predictor of malignancy (10), and in certain cases may help predict the histological subtype (11).

Despite clinical and radiographic evaluation, the definitive diagnosis remains histological. Fluid cytology is often inconclusive because this tumor sheds very few cells (5). In such cases, a CT-guided core needle biopsy or a laparoscopic biopsy can provide sufficient material for histopathological diagnosis (12). We report the case of a woman with ascites in whom the diagnosis of malignant peritoneal mesothelioma was challenging; in these patients, a delayed diagnosis leads to a worse prognosis. This report aims to highlight the diagnostic challenges presented by malignant peritoneal mesothelioma, particularly in cases with negative cytology and non-specific imaging findings.

Case Report

The patient is a 77-year-old female patient. She was admitted to the Internal Medicine ward of Rivoli Hospital for multiple episodes of emesis and diarrhea. She reported also occasional dyspnea without other associated symptoms. Written consent for publication of anonymized details has been obtained from the patient.

Her family history was positive for malignancy: her father died of hepatocellular carcinoma, and her mother was affected by renal cancer, though clinical reports were unavailable. The patient reported no history of smoking or alcohol use. No specific occupational exposures, including asbestos, were identified.

On admission her vital signs were: SpO₂ 96% on room air, blood pressure 125/75 mmHg, heart rate 80 bpm, afebrile; Glasgow Coma Scale score 15/15. Physical

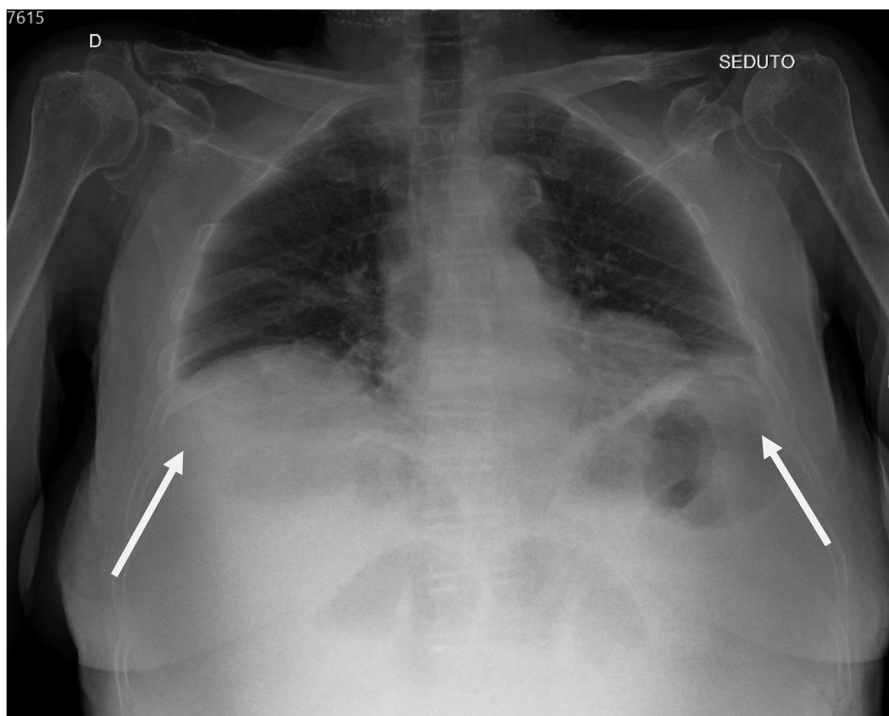


Figure 1. Chest X-ray in anteroposterior projection demonstrates bilateral elevation of the diaphragmatic domes. This is associated with increased opacity in the costophrenic recesses, findings suggestive of bilateral pleural effusion.

examination revealed reduced vesicular murmur with crackles at the lung bases. The abdomen was globose with pain in the lower quadrants. No other relevant features.

Initial investigations included an electrocardiogram showing sinus tachycardia; blood tests revealing a white blood cell count of $16,200/\text{mm}^3$, with neutrophils at $14,240/\text{mm}^3$, platelets at $509,000/\text{mm}^3$, and C-reactive protein (CRP) at 26.1 mg/dl ; a chest X-ray (Figure 1), which showed elevated diaphragmatic domes with an associated pleural effusion, more pronounced on the left side; and abdominal ultrasonography, which confirmed the presence of ascites throughout the peritoneum. In addition, the ultrasound identified hyperechoic formations in the left hepatic lobe consistent with liver angiomias, as well as a 35 mm renal cyst in the right kidney.

The patient was treated with empiric antibiotic therapy (ceftriaxone) due to elevated inflammatory markers suggesting an underlying infection, but her CRP level remained persistently high.

An evacuative paracentesis was performed, and eight liters of citrine fluid were drained. The fluid analysis revealed $1,200 \text{ leukocytes}/\text{mm}^3$, lactate dehydrogenase (LDH) of 151 U/l , and a protein level of 4.7 g/dl , with a SAAG of 0.74: these results were consistent of an exudate not caused by portal hypertension. Microbiological cultures of the fluid were negative, as cytology.

The negative ascitic fluid cytology is a key finding, reducing the likelihood of peritoneal carcinomatosis and guiding the diagnostic work-up toward alternative etiologies.

Further tests were performed to determine the cause of ascites: serological screening for hepatitis B and C was negative. Urinalysis showed no proteinuria, with a 24-h urine protein of 442 mg/day . Fecal occult blood was positive. Stool cultures and Quantiferon test were negative, ruling out infectious causes. Thyroid-stimulating hormone was normal. CEA, CA 19-9, and alpha-fetoprotein were negative. Only CA-125 was

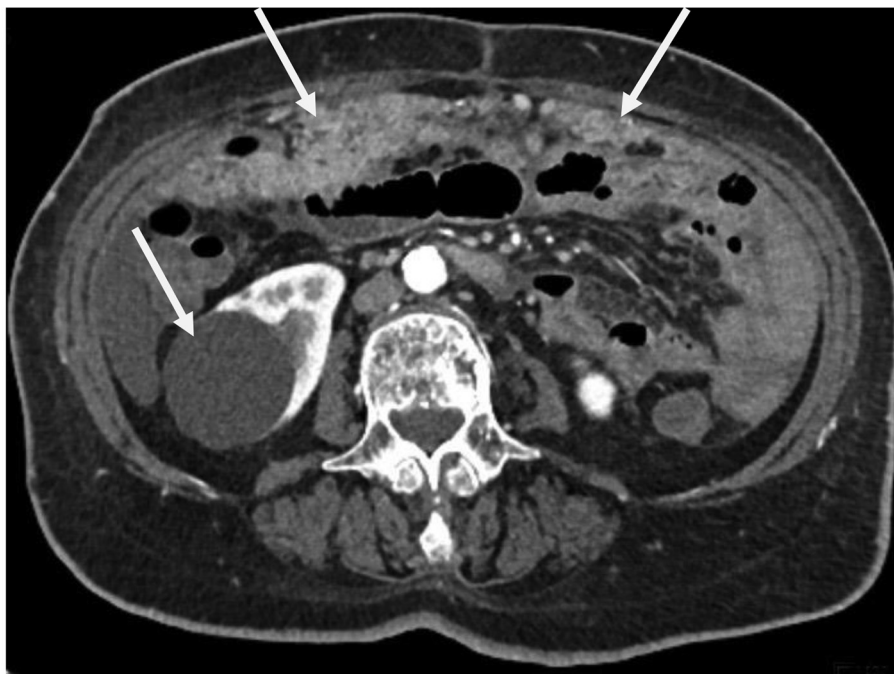


Figure 2. Contrast-enhanced CT scan of the abdomen, axial section. This imaging modality allowed identification of a suspected pathological tissue at the omental level. It demonstrates high arterial phase enhancement. A large simple renal cyst is also detected, but with no clinical relevance in the context of the patient's ascites.

elevated at 164 UI/ml (cut-off 0-35 UI/ml). Antinuclear antibody (ANA) screening was positive (1:640), which was later associated with a monoclonal gammopathy of undetermined significance (MGUS).

A contrast-enhanced abdominal CT scan (Figure 2) detected peritoneal thickening with high contrast enhancement and a solid tissue mass (40 mm) in the pararectal region of the pelvic cavity, suggesting a parietal intestinal *versus* a peritoneal lesion. These features were suggestive of malignancy-related ascites, but did not distinguish between peritoneal carcinomatosis and a rarer primary peritoneal tumor. A total-body CT scan confirmed the peritoneal thickening and the 40 mm pelvic lesion, as well as bilateral pleural effusion.

The patient underwent colonoscopy, which revealed a benign 5 mm sessile polyp in the ascending colon, thus ruling out colorectal cancer as the primary cause. A gynecological examination was performed to investigate the 40 mm pelvic node. Transvaginal ultrasonography

located the lesion near to the rectum, but the biopsy was technically impossible.

Subsequently, a fine-needle biopsy (FNB) of the omental tissue and an ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET/CT) scan were performed to determine the tissue's histological nature and metabolic activity. The FNB, performed with an 18G tru-cut needle under ultrasound guidance, showed morphological features suggestive of malignant peritoneal mesothelioma, but the sample was paucicellular, precluding a full immunohistochemical analysis.

The FDG-PET/CT detected no significant metabolic activity in the abdominal tissue, which would typically suggest a non-malignant process. However, some rare malignant lesions do not show high glucose uptake. In addition FDG-PET/CT can be useful to differentiate with high accuracy primary peritoneal tumors from peritoneal carcinomatosis.

Given the high suspicion for malignant peritoneal mesothelioma and after excluding the most common causes of ascites (heart failure, cirrhosis, nephrotic syndrome, infections, and gastrointestinal or gynecological tumors), a second FNB was performed. The second histological exam confirmed epithelioid subtype of peritoneal mesothelioma. The patient was then referred for oncological assessment to plan the optimal therapeutic strategy.

Discussion

This case report exemplifies the complex diagnostic workup of ascites caused by a rare tumor, requiring over five weeks to reach a definitive diagnosis. The time to diagnosis is critical for patients with malignant peritoneal mesothelioma because it directly affects staging accuracy, management, and prognosis. This rare tumor typically presents with non-specific symptoms such as abdominal pain and ascites (6), making its differential diagnosis challenging and often leading to diagnostic delay.

Early diagnosis is essential for accurate staging, and advanced imaging modalities such as FDG-PET/CT can support physicians. FDG-PET/CT can detect both intra-abdominal and extra-abdominal disease, assess metabolic activity, and guide biopsies (10). However, our case underscores a key limitation: some subtypes of malignant peritoneal mesothelioma, particularly epithelioid or multicystic variants, may exhibit low FDG uptake, resulting in false-negative scans. In contrast, biphasic and sarcomatoid subtypes more commonly show FDG avidity (11).

The different behavior of this tumor, linked to its epidemiology, make the diagnosis difficult. To detect and differentiate the subtypes of malignant mesothelioma, other imaging techniques are needed. A recent study evaluated the role of 68-Ga-fibroblast activation protein inhibitor (FAPI)-PET/CT in patients with FDG-non-avid malignant peritoneal mesothelioma and showed encouraging results (13). In the future, FAPI-PET/CT may play a key role in simplifying the diagnosis of this rare tumor.

In our case tumor markers were not relevant, only CA-125 was elevated. The most specific biomarker to detect malignant peritoneal mesothelioma from other malignancies is mesothelin, which has demonstrated higher specificity than CA-125 and osteopontin in recent studies (14).

An elevated mesothelin level, combined with a low CA19-9 level, strengthens the diagnostic suspicion of malignant peritoneal mesothelioma over other peritoneal malignancies. CA-125 and osteopontin have low specificity, their levels are high in different malignant and benign pathologies (15). Osteopontin may have a prognostic value (15) and CA-125 is often used for monitoring disease burden and response to treatment (14).

A key challenge in this case was the paucicellular nature of the first biopsy, which was insufficient for a complete immunohistochemical analysis. This raises the question of whether the low cellularity was due to the radiological procedure or the intrinsic nature of the tumor. In such conditions, a repeat biopsy or a diagnostic laparoscopy is necessary to obtain adequate sample (16).

Once an adequate sample is obtained, immunohistochemical markers remain essential to confirm mesothelial origin. Calretinin, Wilms-tumor 1 (WT1) and podoplanin are usually positive markers in malignant peritoneal mesothelioma (17). Negative markers such as anti-Epithelial Cell Adhesion Molecule (like Ber-EP4) and claudin-4 are crucial to exclude other malignancies like gastrointestinal carcinomas (17, 18). Finally, differentiating malignant mesothelioma from benign mesothelial proliferations requires assessing for the loss of BRCA-1 associated protein-1 (BAP1) expression and the deletion of p16/CDKN2A, which are hallmarks of malignancy (19). All of these markers lose sensitivity and specificity if mesothelioma has low cellularity: false-negative or equivocal staining are not so rare (17, 19).

Lastly, the patient's medical history can be a crucial clue. Asbestos exposure remains the primary risk factor for mesothelioma (20). Our patient did not report a clear history of exposure, although indirect exposure cannot be ruled out.

In conclusion, the diagnosis of malignant peritoneal mesothelioma remains difficult due to its rarity, non-specific clinical presentation, and complex differential diagnosis. The absence of a clear exposure history made this case particularly challenging. In the future, more specific biomarkers and advanced imaging techniques will hopefully facilitate a more rapid diagnosis, leading to improved treatment and prognosis.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Mirko Nastasi together with Giuliana Michelis and Enrica Branca conducted the diagnosis workup of the case report. Mirko Nastasi wrote the manuscript with the help of Chiara Ferrante and Emanuela Laurita. Silvia Novello and Manuel Ventura were responsible for supervising the study.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis or presentation of this manuscript.

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