

Case Report

Unusually Aggressive Presentation of Malignant Peritoneal Mesothelioma: Two Case Reports

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Keywords

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Abstract

Malignant peritoneal mesothelioma is a rare disease. Patients mainly present with abdominal distension, pain, nausea, and weight loss with or without an exposure history of asbestos. Diagnosis may be difficult from a clinical and histopathologic perspective. Treatment options are surgery in early stages, radiotherapy and/or intraperitoneal or systemic therapy. Prognosis depends on TNM stage and histologic subtype with epithelioid subtype being the most favorable one but in general remains poor. We present a 59-year-old male (patient 1) and a 79-year-old female (patient 2) with progressive dyspnea. PET-CT of patient 1 revealed metastatic spread in the pleura and extensive peritoneal carcinomatosis. PET-CT of patient 2 displayed FDG-avid lymph nodes on both sides of the diaphragm, polyserositis, and FDG uptake along the peritoneum. Both patients were eventually diagnosed with malignant peritoneal mesothelioma. Patient 1 was treated with carboplatin and gemcitabine, and patient 2 received no systemic therapy. Even though the epithelioid subtype was found, both patients succumbed due to rapid tumor progression in a matter of a few weeks only. Presentation with polyserositis even in the absence of relevant asbestos exposure may represent malignant peritoneal mesothelioma if ascites is present, and rapid invasive diagnostic (excision biopsy) should be performed. These two unusual cases emphasize that even in epithelioid subtype, clinicians ought to be aware of possible rapid clinical deterioration, and timely diagnosis with initiation

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of therapy is crucial. Further research is necessary to better understand tumor biology, establish predictive markers, and develop new treatment options.

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Introduction

The incidence of mesothelioma varies across Europe from 8.8–0.6/100,000 in men with hotspot regions such as Trieste with an incidence of 17.2/100,000 [1]. Female incidence rates are typically much lower. Prognosis of patients with mesothelioma remains poor with a median survival of approximately 12 months [2]. Malignant peritoneal mesothelioma (MPM) represents 10–30% of all mesotheliomas and therefore is an extremely rare disease [3]. Asbestos remains the best studied risk factor, especially at higher doses, and represents an attributable risk of peritoneal mesothelioma in 58% of men and 23% of women [4]. The median age at diagnosis is 63 years which is younger than in pleural mesothelioma (71 years) [5].

Pathological diagnosis may be difficult [6]. Diagnosis usually requires adequate biopsy and may be challenging particularly in small specimens, such as body fluid cytology and small tissue biopsies [7]. Using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) is essential in the separation of benign reactive mesothelial proliferations from malignant mesotheliomas. Based on sensitivity and specificity, calretinin (both cytoplasmic and nuclear staining), cytokeratin 5 or 5/6 (cytoplasmic staining), Wilms tumor-1 (WT1, only nuclear staining), and podoplanin (D2-40, membranous staining) are the most useful markers [6]. Recent studies demonstrated that homozygous deletion in the region 9p21 (p16) by FISH or the loss of BRCA-associated protein 1 (BAP1) by IHC are highly specific but not very sensitive markers for mesotheliomas [6].

Uncontrolled studies demonstrated longer disease control with surgery and intraperitoneal chemotherapy leading to 70% 5-year survival in selected patients with MPM treated at large-volume cancer centers [8]. Prognosis of mesothelioma depends on TNM stage as well as histologic subtypes with the epithelioid subtype being the most frequent and more favorable subtype followed by biphasic subtypes and sarcomatoid histology [9].

Standard systemic therapy of MPM is derived from pleural mesothelioma, typically consisting of a platinum doublet with pemetrexed which has shown to improve survival compared to cisplatin alone [10]. The activity of immunotherapy in MPM is largely unknown as only small subsets of patients with MPM were enrolled in clinical mesothelioma trials [11].

Our center manages approximately 20–25 mesothelioma patients per year; this includes 3–4 peritoneal mesothelioma cases. We present 2 cases from our hospital with unusually aggressive courses of MPM, illustrating the need of a rapid diagnostic workup and treatment initiation.

Case Presentation

Patient 1

A 59-year-old previously healthy male never-smoker was admitted as an inpatient because of a rapid onset of dry cough since 10 days, dyspnea on exertion, and intermittent abdominal pain. Exposure history was significant for work with asbestos in construction industry for 45 years. Diagnostic drainage of a right-sided pleural effusion detected on an external CT scan demonstrated an exudate with cells suspicious for mesothelioma. PET-CT surprisingly revealed a metastatic spread with multiple fluoro-deoxy-glucose (FDG)-avid lesions not only in the

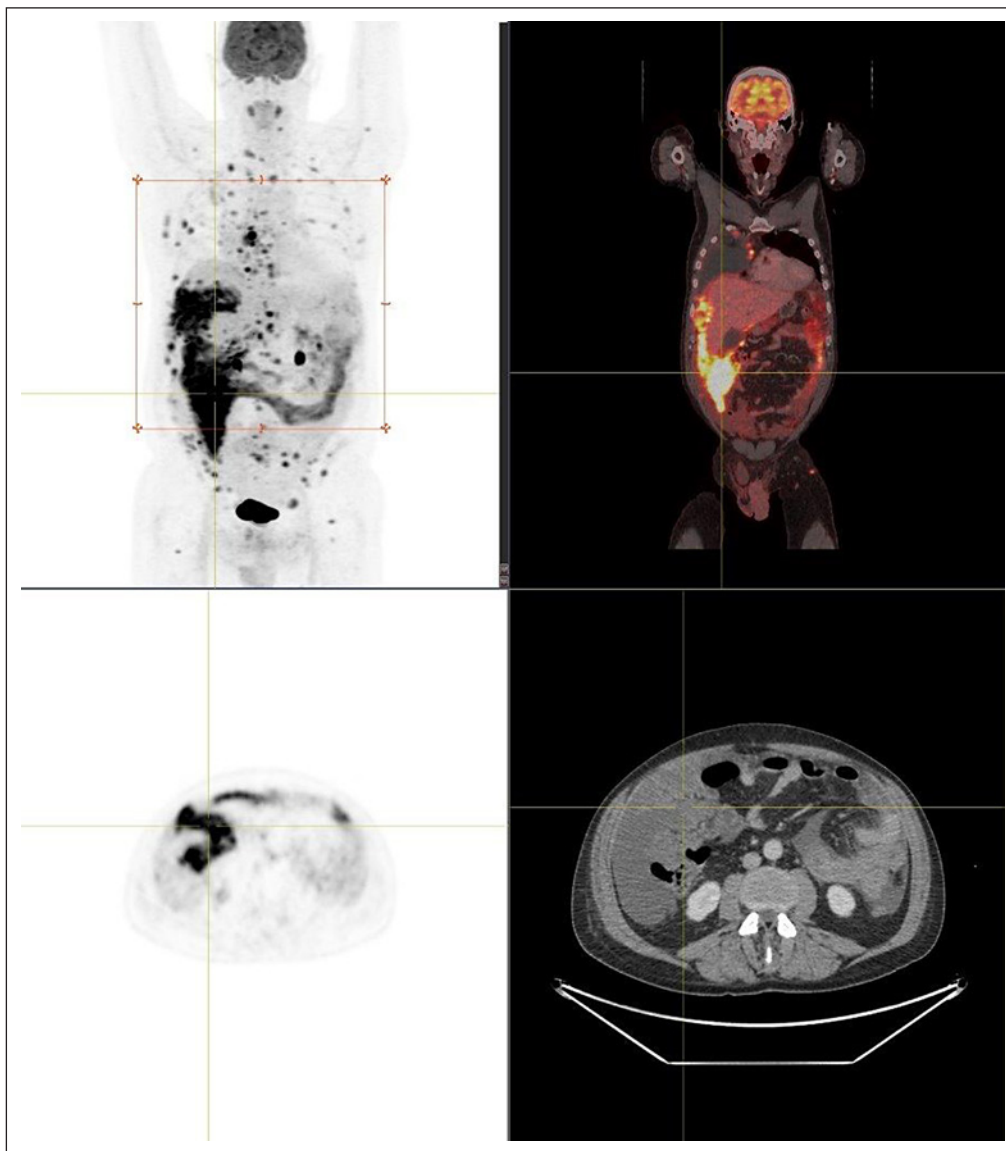


Fig. 1. PET-CT of patient 1 demonstrating large tumor burden in the abdominal cavity with intensive FDG uptake (standardized uptake value maximum 15.7).

pleura, lymph nodes in the mediastinum, and upper abdomen but also extensive peritoneal carcinosis with ascites (shown in Fig. 1) and disseminated lesions throughout the spine. Thoracoscopic biopsies revealed a highly proliferative (Ki-67 70%) and poorly differentiated neoplasia with immunohistochemical positivity for calretinin (shown in Fig. 2, 3), CK5/6, D2-40, and WT1 and negativity for desmin, suspicious for mesothelioma. Under assumption of an aggressive spread of the more prevalent pleural mesothelioma or lung cancer, we administered carboplatin and gemcitabine. On the basis of next-generation sequencing a pathogenic TP53 mutation (p.P177R [c.530C>G]) was found which is uncommon in the epithelioid subtype of mesothelioma but occurs in both biphasic as well as in sarcomatoid subtypes with a frequency of less than 10% [12]. No targetable driver mutation was detected. FISH for the deletion of p16 was negative, and no deletion of BAP1 was found to confirm the diagnosis. The patient's overall status deteriorated rapidly with massive abdominal distension and

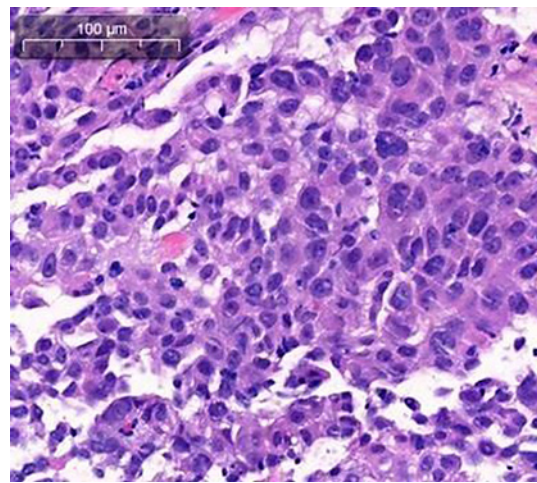


Fig. 2. Hematoxylin-eosin stain of pleural biopsy of patient 1 with infiltrates of the mesothelioma.

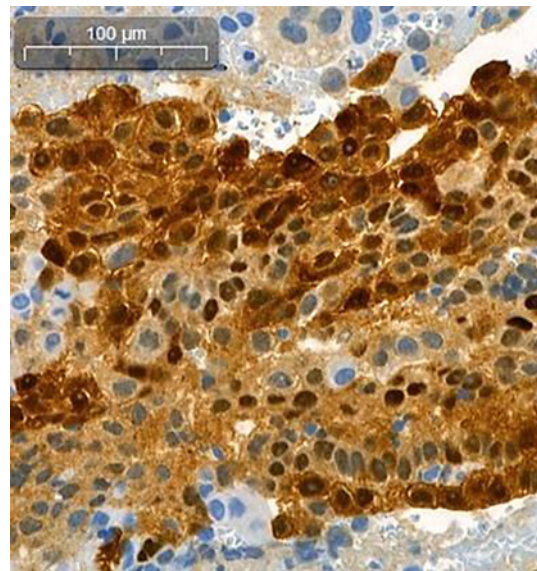


Fig. 3. IHC stain for calretinin of pleural biopsy of patient 1 (same section as Fig. 2).

constipation (shown in Fig. 4). Recurrent large-volume therapeutic ascites drainage only provided short-term relief. Four weeks after initial admission and despite administration of one chemotherapy cycle, the patient died due to rapid tumor progression. Autopsy diagnosed an MPM of the epithelioid subtype with a large abdominal tumor burden weighing 4 kg (shown in Fig. 5) accompanied by multiple metastases (pulmonary, osseous, lymphogenic, pleural, adrenal). As the most possible primary the funiculus spermaticus was discussed. The extent of the disease at autopsy with the bulk occurring in the abdominal cavity was surprising because it was not seen on the initial CT scan and underestimated in the PET-CT. No regressive tumor changes from chemotherapy were evident; death resulted from acute cardiovascular failure.

Patient 2

A 79-year-old female with a past medical history of diffuse large B-cell lymphoma treated with R-CHOP 17 years ago presented with lymphadenopathy and progressive shortness of breath. There was no history for asbestos exposure. PET-CT revealed multiple FDG-avid lymph nodes on both side of the diaphragm, anasarca, pleural effusion left > right, pericardial effusion, and ascites as well as



Fig. 4. CT abdomen of patient 1, 3 weeks after PET-CT, demonstrating massive tumor progression of the omentum (measuring 12.5 cm in the right hemiabdomen and 6.5 cm in the left hemiabdomen).

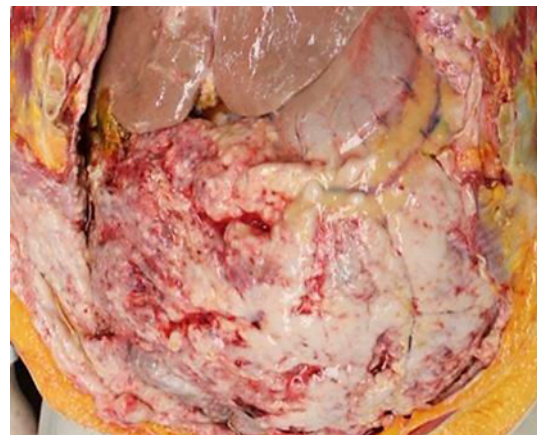


Fig. 5. Abdominal cavity upon autopsy of patient 1.

homogenous FDG uptake along the peritoneum (shown in Fig. 6). In order to rule out recurrent lymphoma, axillary lymph node excision was performed, where a proliferation of dense mesothelial cells was evident (shown in Fig. 7). IHC was positive for calretinin (shown in Fig. 8), BAP1, CK5/6, D2-40, and WT1 and negative for desmin. The proliferative index (Ki-67) was 10%. Pleura-centesis demonstrated atypical mesothelial cells, and IHC was positive for calretinin, BAP1, and WT1. Next-generation sequencing revealed a pathogenic TERT mutation (c.-57A>C) but no specific mutation suspicious for a neoplastic origin of the mesothelial cells. The final diagnosis took several weeks and was difficult because of the differential diagnosis of a benign lymph node mesothelioma inclusion which was considered due to the low proliferative index of 10%. The patient's clinical status deteriorated rapidly with recurrent hospitalizations. Progressive dyspnea, fatigue, and worsened performance status prohibited initiation of palliative chemotherapy. The patient also succumbed in a matter of weeks to the underlying disease, and autopsy was not performed.

Discussion and Conclusion

These 2 cases illustrate the existence of very aggressive clinical courses of MPM and the difficulties in obtaining the correct diagnosis from a clinical as well as from a histopathologic perspective. Both patients initially presented with pulmonary symptoms due to malignant

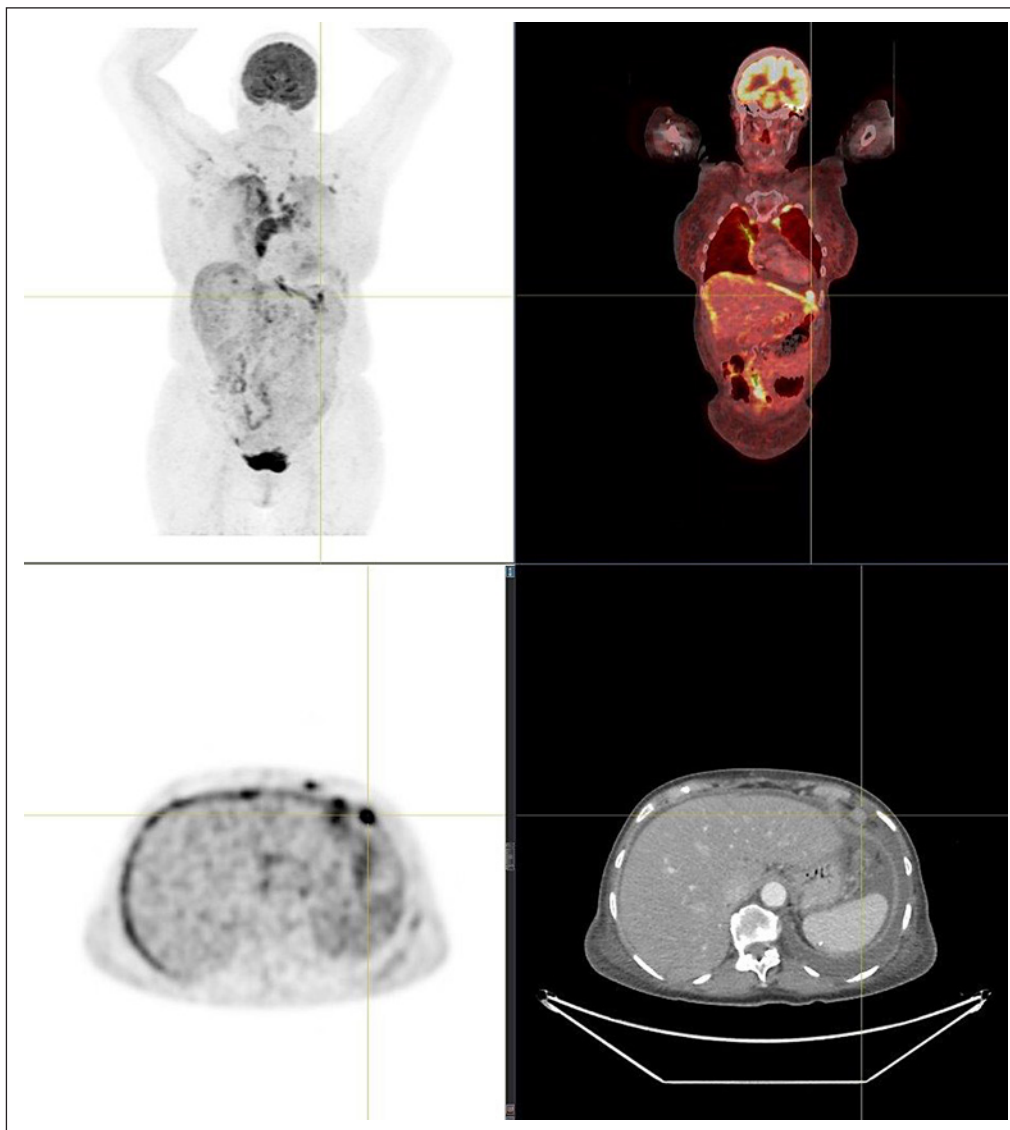


Fig. 6. PET-CT of patient 2 demonstrating FDG-avid lymph nodes on both sides of the diaphragm as well as uptake along the prominent peritoneum.

pleural effusion without visible pleural disease, obscuring the diagnosis of peritoneal mesothelioma. IHC and FISH normally distinguish between benign and malignant mesothelioma, which was challenging in both cases presented herein. The deletion of p16 by FISH is most frequently inactivated in malignant mesothelioma and has been shown to be associated with shorter patient survival and with non-epithelioid histology [12]. However, only 25% of peritoneal mesotheliomas demonstrate a loss of p16 by FISH, whereas many peritoneal mesotheliomas show BAP1 loss detected by IHC [6], which is not observed in benign reactive mesothelial cells [7]. Both FISH for the p16 deletion and IHC loss of BAP1 could not be shown in either case and were therefore not helpful in making the final diagnosis. From a clinical viewpoint, presentation with polyserositis should prompt a thorough exposure history, but even the absence of relevant asbestos exposure may represent MPM if ascites is present, and rapid invasive diagnostic (excision biopsy) should be performed in order to not delay the diagnosis of this very rare disease. Both cases impressively demonstrate that even in the epithelioid

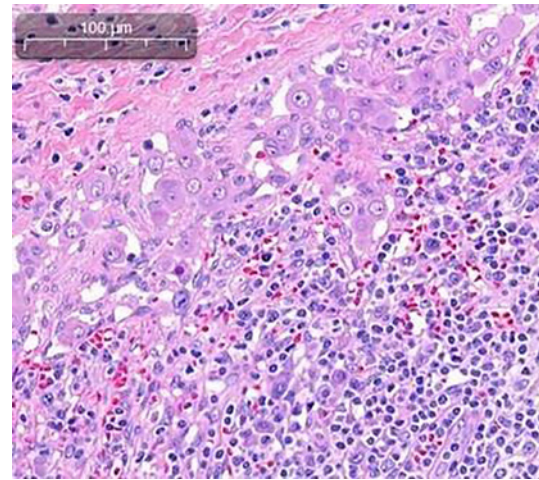


Fig. 7. Hematoxylin-eosin stain of axillary lymph node of patient 2 with mesothelial cells in the subcapsular sinus (upper left) and lymph node portion (lower right).

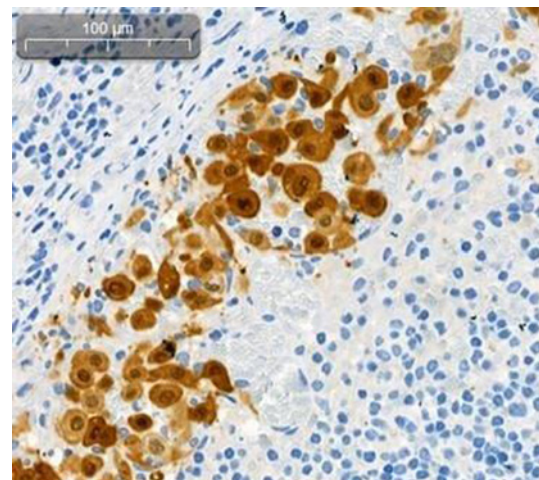


Fig. 8. IHC stain for calretinin of axillary lymph node of patient 2 (same section as Fig. 7). Aggressive MPM.

subtype, MPM may present as extremely aggressive with widespread bone metastases, large-volume pleural effusion, and ascites and may lead to death within a few weeks or less. To our knowledge, such rapid clinical courses of peritoneal mesothelioma have not been reported before, and previous series of patients with MPM from eight international institutions reporting a median overall survival of 26 months in patients with metastatic MPM would suggest a more favorable disease course compared to pleural mesothelioma [9]. In our opinion, the awareness of possible rapid clinical courses of MPM, timely diagnosis, and start of therapy are crucial and may improve prognosis [13, 14]. Further research is needed to better understand tumor biology, explore predictive markers, and eventually develop novel effective treatments in this rare malignancy.

Statement of Ethics

Written informed consent was obtained from both patients' next of kin for publication of this case report and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

Conflict of Interest Statement

Martin Früh received unrestricted grants to institution from BMS and AstraZeneca and has an advisory role for BMS, MSD, AstraZeneca, Boehringer Ingelheim, Roche, and Takeda. All the other authors have no conflicts of interest to declare.

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Author Contributions

All the authors wrote and approved the manuscript. Dominik Neff, Barbara-Christina Padberg Sgier, and Martin Früh were responsible for the study concept. Autopsy of patient 1 was performed by Hannah Dietze and Barbara-Christina Padberg Sgier. PET-CT was interpreted by Joachim Müller, who also provided the images from the PET scan.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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