Malignant Peritoneal Mesothelioma in the setting of a Ventriculo-Peritoneal Shunt: A novel clinical presentation

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ABSTRACT: We report a case of malignant peritoneal mesothelioma (MPM) in a 31-year-old male with history of cerebral palsy, hydrocephalus, and ventriculoperitoneal shunt (VPS) placed since infancy. He presented with fever, abdominal pain and distension. Computed tomography scan revealed a thick-walled rim-enhancing fluid collection, interpreted as pseudocyst. Intraoperatively, diffuse nodular peritoneal thickening with adhesions was demonstrated. The resection specimen consisted of multiple membranous fragments displaying firm nodules. Microscopic examination revealed a tumefactive malignant-appearing epithelioid proliferation involving the peritoneum, focally invading the underlying fat. Immunohistochemically, the tumor cells expressed keratin AE1/AE3, CK7, CK5/6, Calretinin, WT1 and D2-40, and were negative for CEA and MOC31. The findings were consistent with MPM, epithelioid type. The patient's condition continued to decline with increasing abdominal distension during the month following the original diagnosis. While atypical mesothelial hyperplasia has been described in association with long standing VPS, well-documented cases of MPM have not been previously reported in such context.

KEYWORDS: Mesothelioma, peritoneal, ventriculoperitoneal shunt

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Introduction

Malignant peritoneal mesothelioma (MPM) is a rare, insidious and aggressive neoplasm that arises from the mesothelial lining of the peritoneum. MPM accounts for 20% to 30% of all cases of mesothelioma. Mesotheliomas are strongly associated with asbestos exposure. Cases of mesothelioma have also been reported following exposure to erionite, Thorotrast and radiation therapy as well as in patients affected by familial Mediterranean fever and lymphomas.[1] Unlike their pleural counterpart, mesotheliomas arising in other locations, such as peritoneum and tunica vaginalis[2] have a less strong association with asbestos exposure.[3] The pathogenesis in these cases is not very clear.[2] Furthermore, while pleural mesothelioma is more frequent in males, MPM does not have gender predilection.[4]

MPM are most commonly diagnosed during the fifth to seventh decades of life.[1] Patients with MPM usually present with relatively insidious non-specific symptoms. The most common presentation is abdominal distension with ascites, followed by abdominal pain.[5] Due to this non-specific nature of presentation, most patients with MPM harbor an advanced disease burden by the time of presentation.[4] The radiologic findings in MPM vary from widespread nodularity over the peritoneal surface with ascites, to multiple masses or a single dominant localized mass with minimal or no ascites.[3,4]

We report the case of a MPM presenting in a young male with a long standing ventriculoperitoneal shunt (VPS) and no previous history of exposure to asbestos or radiation therapy.

Case Report

The patient was a 31-year-old Caucasian male with a medical history significant for cerebral palsy, spina bifida, seizure disorder and hydrocephalus, with a VPS placed since infancy. The patient presented with fever and diffuse abdominal pain and distension. Physical examination did not reveal any mass. Computed tomography scan revealed a large localized intra-abdominal fluid collection, with a rim-enhancing wall of variable thickness, in which the tip of the VPS catheter was embedded. The findings were interpreted as infected peritoneal "pseudocyst" in association with VPS. The patient was placed on antibiotics, and a surgical excision and drainage of the intra-abdominal process was scheduled. Intraoperatively, nodular peritoneal thickening was demonstrated with adhesions and pseudocyst formation. Only a portion of the lesional tissue was amenable to surgical excision. The fluid was sent for culture that grew *Pseudomonas stutzeri*.

The received resection specimen consisted of multiple membranous fragments lined by serosal surface, and displaying multiple areas of nodular thickening. The nodules were variable in size with firm gray-white cut surface. Microscopic examination of sections from these nodular areas demonstrated a dense, expansile and tumefactive proliferation (Figure 1A) of medium-sized to large atypical epithelioid cells arranged predominantly in solid sheets, with focal nests and trabeculae formation (Figure 1B). The neoplastic proliferation focally invaded the underlying adipose tissue (Figure 1C). The neoplastic cells had pale to eosinophilic cytoplasm

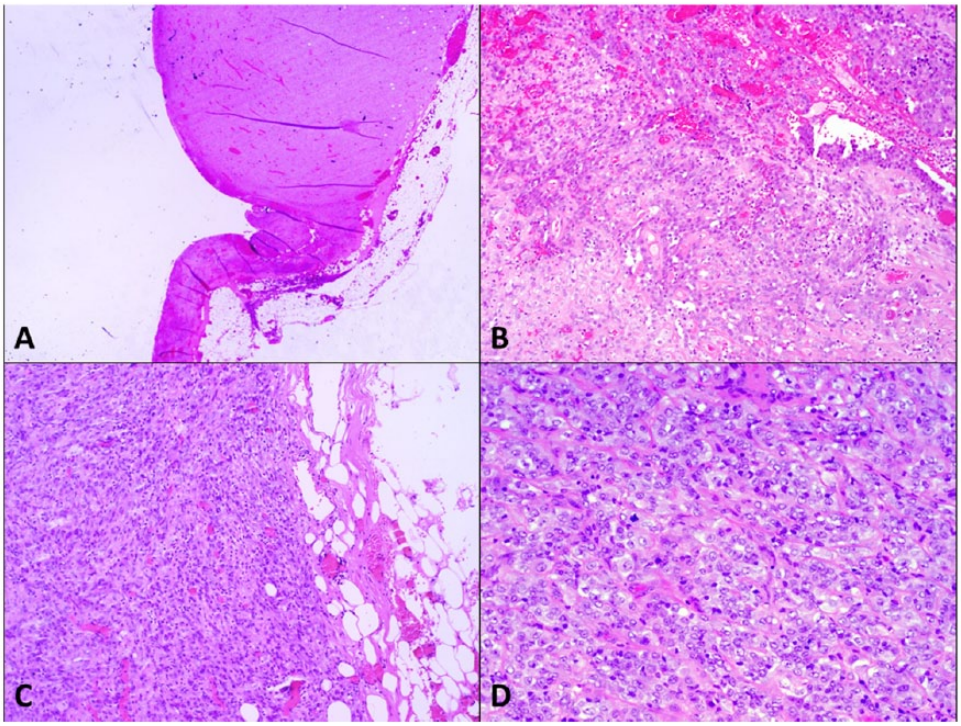

Figure 1. (A) Tumor mass showing a tumefactive neoplastic growth in continuity with the mesothelial lining (H&E, 20X). The neoplastic cells formed (B) diffuse sheets, nests and trabeculae (H&E, 100X) with (C) focal areas of infiltration into the underlying adipose tissue (H&E, 100X). (D) The neoplastic cells showed vesicular nuclei with nuclear atypia and frequent mitoses (H&E, 200X).

and vesicular nuclei with prominent nucleoli (Figure 1D). Frequent mitotic figures were identified, without necrosis. The findings were consistent with a malignant appearing epithelioid neoplasm.

Immunohistochemical studies revealed the neoplastic cells to be strongly immunoreactive for pankeratin AE1/AE3, CK7 (Figure 2A), CK5/6 (Figure 2B), and Cam5.2, with partial, strong expression of mesothelial markers, including nuclear-cytoplasmic staining for Calretinin (Figure 2C), nuclear expression of WT-1 (Figure 2D), and D2-40 positivity (Figure 2E). EMA showed membranous staining in the neoplastic cells. The neoplastic cells were positive for p53 and negative for MOC-31, monoclonal CEA, TTF-1, CD34, desmin, CDX2, PAX8, CD31, PLAP, S-100, CD68, PSA, CD43, CK20 and CD117. The findings were consistent with malignant peritoneal mesothelioma (MPM), epithelioid type.

Retrospectively, a history of environmental or domestic exposure to asbestos was not identified in this case. The patient continued to decline with increasing abdominal distension during the month following the original diagnosis. Due to the rapid decline in the patient's condition with multiple comorbidities, and due to the unresectable nature of the peritoneal disease, the patient was discharged to hospice care without further aggressive therapy.

Discussion

Beside the rarity of the disease, this case of MPM is unusual in several aspects, including the young age of the patient and the association with long standing VPS. The diagnosis of MPM in this case was established based on the mesothelial nature of the proliferation and on morphologic features of malignancy.

The mesothelial nature of the proliferation was confirmed by the immunohistochemical expression of CK5/6 and mesothelial markers (calretinin, WT1 and D2-40), and the negative staining with adenocarcinoma markers (MOC31, CEA) or other lineage and site-specific markers tested.[6] Melanoma, hematolymphoid processes or epithelioid sarcomas were unlikely in this case, given the diffuse expression of keratins. In particular, epithelioid sarcoma (typically CD34 and desmin positive)[7] and epithelioid angiosarcoma (usually CD31 positive)[8] were unlikely. Furthermore, no other neoplastic process was identified in the patient to suggest a metastatic disease. The tumefactive and nodular expansile growth pattern and the focal invasion of underlying adipose tissue are in keeping with the malignant nature of this mesothelial proliferation.[6]

The definitive diagnosis of MPM rests on pathologic evaluation. Epithelioid mesothelioma is the most common subtype (75%) of MPM. The growth patterns of epithelioid mesothelioma include tubulo-papillary, adenomatoid (microglandular), and solid sheet-like. Less commonly, small cell, deciduoid and acinar patterns may occur, and rarely pleomorphic and lympho-histiocytoid.[6] The occasional presence of desmoplastic response, signet ring cells and adenoid cystic configuration may mimic adenocarcinoma.[4] Although histologic grading has not traditionally been performed, nuclear grading (degree of

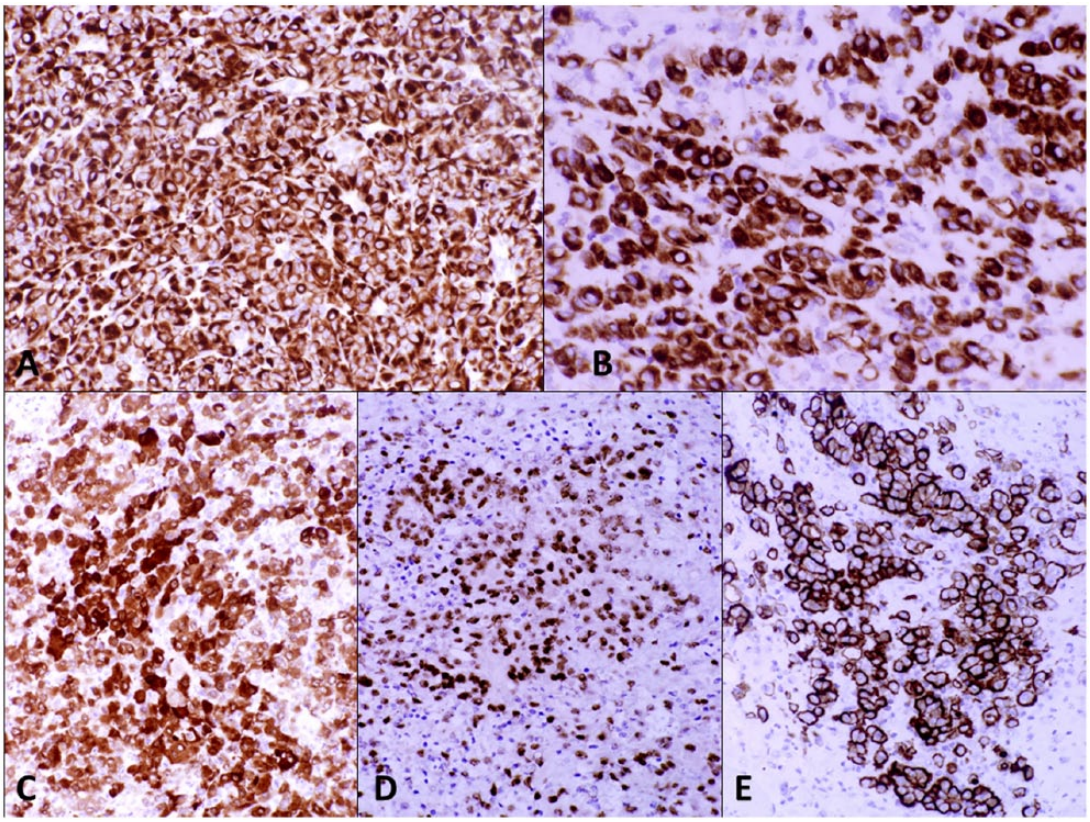

Figure 2. Immunohistochemically, the neoplastic cells were strongly reactive for (A) CK7 and (B) CK5/6. The neoplastic cells showed partial but strong expression of mesothelial markers, including (C) nuclear/cytoplasmic staining for calretinin, (D) nuclear expression of WT1, and (E) D2-40 positivity (Immunoperoxidase, 200X).

nuclear atypia and mitotic count and/or Ki67 labeling index) has been shown to be a strong predictor of overall survival in diffuse pleural and peritoneal mesothelioma. The non-epithelioid subtypes (biphasic, sarcomatoid and desmoplastic) of MPM are less common and have a worse prognosis.

The diagnosis requires evidence of mesothelial differentiation including at least two positive mesothelial markers (Calretinin, WT-1, Cytokeratin 5/6, D2-40) and two negative adenocarcinoma markers (CEA, CD15, B72.3, MOC-31, Ber-EP4 and BG-8). In women, the differential diagnosis of MPM and carcinoma may be more challenging, given the immunohistochemical overlap with serous carcinoma. Sarcomatoid MPM may lose some of the more specific mesothelial markers.[6]

The differentiation between benign and malignant mesothelial processes may also be problematic. A tumefactive growth pattern and invasion into the adjacent tissues are hallmarks of malignant mesotheliomas. Entrapment of mesothelial cells, well-differentiated papillary mesothelioma and benign multicystic mesothelioma should be distinguished from malignant mesothelioma by careful examination. Immunostains for p53, desmin, glut1 and EMA are often not helpful in an individual case.[6]

More recently, detection of p16 deletion by FISH and loss of BAP1 nuclear immunohistochemical expression seem to emerge as promising markers of malignancy in pleural mesothelial proliferations.[9] While most MPM do not show a loss of p16 by FISH, many show loss of BAP1 by immunohistochemistry.[6] These adjunct tests were not performed in our case, since the malignant nature of the disease was not questionable. Of note, these markers may be positive in the malignant mesothelioma, regardless of the presence or absence of germline mutation.[9]

Multiple complications are known to be associated with VPS placement. These include mechanical complications (such as blockage, disconnection or migration of the shunt components), intestinal volvulus, viscus perforation, infection, ascites and peritoneal "pseudocyst."[10] Mesothelial proliferations may also occur in this setting. In fact, a case of exuberant mesothelial hyperplasia mimicking malignant peritoneal mesothelioma was reported in association with long standing VPS.[11] Only one case of malignant mesothelioma in a child with a previous and remote history of VPS was reported, but histopathologic findings were not documented.[12] The underlying pathogenesis of this MPM in our case is not clear. There was no exposure history or previous radiation. Genetic testing for germline mutations was not performed. Chronic irritation and inflammation secondary to the long-standing VPS, with progression from mesothelial hyperplasia to malignant mesothelioma is a conceivable hypothesis.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy represents the standard treatment of resectable MPM.[13] The tumor in our patient was not amenable to further surgical treatment. For this reason, and due to the comorbidities of this patient and the rapid decline within the month after the initial diagnosis, an aggressive therapy was not undertaken.

The overall survival rate for MPM is poor with modest gain achieved from systemic therapy.[4] The median survival is 6 to 12 months.[1] Females have a better prognosis as compared to males. In addition to the histologic type and nuclear grade, variables that confer a poor prognostic effect on the overall survival are older age, higher stage, molecular alterations of the CDKN2A locus (9p21.3) and homozygous deletion of p16. Germline BAP1 mutations appear to give a favorable prognostic effect.[6,4] Mutational or germline testing was not performed in our case. Early clinical trials have identified a soluble mesothelin-related protein (SMRP) as a tumor marker of mesothelioma, which may be useful for monitoring the tumor response to therapy.[5]

To the best of our knowledge, this is the first reported case of a well-documented MPM developing in association with a long standing VPS in the absence of exposure history, with a rapid decline in the patient's condition within a month following the initial diagnosis. MPM can be a challenging diagnosis, and a carefully integrated thorough approach incorporating morphologic and immunohistochemical findings is necessary to establish the correct diagnosis.

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Author Contributions

Conceived and designed the experiments: MH, EC & WSM. Wrote the first draft of the manuscript: MH. Contributed to the writing of the manuscript: NH & CTP. Agreed with manuscript results and conclusions: MH, NH, CTP, EC & WSM. Jointly developed the structure and arguments for the paper: MH, EC & WSM. Made critical revisions and approved final version: MH & WSM. All authors reviewed and approved of the final manuscript.

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