Epithelioid Malignant Mesothelioma Metastatic to the Skin: A Case Report and Review of the Literature

Short Title: Metastatic Malignant Mesothelioma

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Introduction

Mesothelioma is a rare form of cancer arising from a monolayer of mesothelial cells that form the lining of the internal body cavities and organs, with the vast majority of cases arising from the pleura (65-80%), less commonly from the peritoneum (10-30%), and rarely from the pericardium and tunica vaginalis testis (1-2%).(1-3) Malignant mesothelioma (MM) is aggressive and is known to be locally invasive and have a propensity for metastasis to distant organs, rarely including metastasizing to the skin. Cutaneous involvement by MM can occur through three main routes: regional spread via lymphatics, direct extension within surgical scars, and distant metastasis via hematogenous spread.(4, 5) The most common route, direct extension in the form of needle track metastasis (NTM), can occur after placement of intraperitoneal catheters in the treatment of MM or through the contamination of surgical sites.(5-10) Few reports have noted true cutaneous metastasis of MM, with less than twenty cases found in the literature.(1, 2, 4, 6-9, 11-27)

Case Report

A 75-year-old retired automobile mechanic who specialized in brake repair presented to the Emergency Department with rapidly progressive dyspnea. A chest radiograph was performed, which showed a large left-sided pleural effusion. Evaluation of thoracentesis fluid showed reactive mesothelial cells without evidence of malignancy. Over the next few months, he experienced increasing dyspnea, hemoptysis, anorexia, and persistent hemorrhagic pleural effusions. A video-assisted thoracoscopic surgery (VATS) was performed, and multiple biopsies showed marked pleural thickening with a mixed infiltrate of tumor nests and necrotic debris. Immunohistochemical stains were positive for cytokeratin (CK) 5/6, CK7, Calretinin, D2-40
(podoplanin), p53, GLUT-1, with focal positivity of MOC-31, and negative for thyroid transcription factor (TTF)-1, CK20, caudal-related homeobox gene 2 (CDX2), BerEP4, and Napsin A (Fig. 1). The diagnosis of malignant mesothelioma of the pleura, stage II, was made. Due to his significant co-morbidities, he was not a candidate for systemic chemotherapy.

Four months later, he presented with a new single firm, pink cutaneous nodule measuring 6 x 8 mm on his upper back (Fig. 2). A shave biopsy was performed, which revealed a reasonably well-circumscribed nodular dermal proliferation of atypical epithelioid tumor cells forming pseudoglandular structures with numerous mitoses. The well-circumscribed and nodular growth pattern within the dermis as well as lack of surgical scars in the surrounding area favored metastasis over direct extension. Immunohistochemical stains showed immunoreactivity for CK5/6, CK7, Calretinin, and D2-40 and negative staining for TTF-1, CK20, GLUT-1, and prostate-specific antigen (PSA) (Fig. 3). The collective findings supported a diagnosis of epithelioid malignant mesothelioma metastatic to the skin. Unfortunately, the patient succumbed to his disease within a week following his biopsy.

Discussion

The results of a literature search of cases of cutaneous metastasis of malignant mesothelioma are summarized in Table 1.(2, 4, 6-9, 11, 12, 17-21, 23-27) There were nineteen previously reported cases of MM metastatic to the skin, three of which predated the availability of immunohistochemical stains. We excluded cases in which the cutaneous presentation was due to direct extension or regional spread. Importantly, as the umbilicus is an embryological remnant of the vitelline duct and retains a connection to the peritoneal cavity (22), we excluded cases of umbilical presentations of MM as we consider it to be a direct extension.(14, 16, 22) The average
age at presentation of cutaneous metastasis was 56.5 years (range: 25-77). Excluding one outlier (12), the average time from original diagnosis of MM to presentation of cutaneous metastasis was six months, with seven individuals receiving their diagnosis of MM at or shortly after the time of their cutaneous biopsy. MM primary to the pleura accounted for 85% of reported cases of cutaneous metastases, and peritoneal MM accounted for 15% of reported cases. The most commonly reported site of cutaneous metastasis was the face, followed by the scalp and chest. All peritoneal MM cases were of the epithelioid subtype. Approximately 60% of cases of pleural MM were of the epithelioid subtype, 23% were of the sarcomatoid subtype, and 17% were of the biphasic subtype. The majority of reports demonstrated positive staining with calretinin, cytokeratins (especially CK 5/6 and CK 7), vimentin, epithelial membrane antigen (EMA), thrombomodulin, HMBE-1, and Wilms’ Tumor (WT)-1. Commonly used negative stains included carcinoembryonic antigen (CEA), S100, TTF-1, Leu M1, Factor VIIIRA, cluster of differentiation (CD)-31, CD34, B72.3, and human melanoma black (HMB)-45.

The diagnosis of MM can be challenging for several reasons, including delayed and non-specific presentation, relative paucity of sensitive diagnostic techniques, and histologic similarity to other neoplasms. Primary MM has a very long latency period, often presenting up to four or five decades post-exposure, and is linked to asbestos exposure (including automobile brakes, which formerly contained asbestos) in up to 90% of cases of pleural MM.(1, 5, 6, 20, 28-31) Due to the delay from exposure to onset of symptoms, the disease is typically far progressed at the time of diagnosis, with metastases typically appearing at a late stage of the disease.(3, 9, 25, 32, 33) Additionally, diagnosis can be delayed because the symptoms for both pleural and peritoneal MM are vague and non-specific, including chest pain, dyspnea for pleural MM and abdominal pain, weight loss, and increased abdominal girth for peritoneal MM.(1, 3, 20, 26) Recurrent
pleural effusions and ascites are common in pleural and peritoneal MM, respectively. However, sampling of body cavity fluid cytology is oftentimes non-diagnostic, with reports estimating the sensitivity to be between 33 and 84%.(21, 32) Clinically, cutaneous metastases of MM can appear as violaceous nodules or papules (as is seen in the present case), erythematous eruptions, or inflammatory and infiltrative plaques.(5, 9)

There are three main histologic subtypes of MM: epithelioid (60%), sarcomatoid (10-20%), and biphasic or mixed (20-30%), which has both epithelioid and sarcomatoid components.(3, 5, 8, 29) The epithelioid subtype is comprised of trabecular cords of cuboidal, oval, or polygonal cells that are usually clumped together with visible, elongated nuclei and abundant eosinophilic cytoplasm and may have various secondary patterns, including tubulopapillary, micropapillary, acinar, adenoid cystic, clear cell, signet ring, solid, small and large cell patterns, and pleomorphic.(1, 5) The sarcomatoid subtype, the least common yet most aggressive subtype, is comprised of spindle cells arranged in fascicles with enlarged and elongated nuclei, which may have desmoplastic, lymphohistiocytic, fibrosarcomatous, chondrosarcomatous, osteosarcomatous, and malignant fibrous histiocytoma-like secondary patterns.(5, 34, 35) MM can be difficult to diagnose histologically, as the tumor can resemble features of benign reactive mesothelial proliferations, metastatic adenocarcinoma (especially neoplasms from the gastrointestinal tract, breast, lung, prostate, kidney, or thyroid), sarcoma (especially epithelioid angiosarcoma, which can develop from prior radiation exposure), lymphoma, and melanoma (adenoid or pseudopapillary subtypes).(1, 6-9, 12, 20, 23, 24, 26, 28) As such, immunohistochemistry plays a pivotal role in diagnosis. However, no specific unique immunohistochemical or genetic marker has been elucidated to allow for prompt, efficient
diagnosis. Therefore, the diagnosis of MM is typically one of exclusion and relies heavily on patterns of positive and negative stains. (3, 28, 35)

Calretinin is considered to be one of the most specific stains for MM, as it strongly and diffusely stains both the nucleus and cytoplasm, is frequently expressed in all histologic subtypes of MM, and stains positively in less than ten percent of adenocarcinoma. (1, 5, 12, 36, 37) Other less specific markers for MM are considered to be WT1, CK 5/6, thrombomodulin, and HBME-1. (5, 24, 27) Pertinent negative stains for MM include CEA, CA-125, Leu M1 (CD15), BerEP4, MOC-31, TTF-1, B72.3, which stain positively in adenocarcinoma, S100 and HMB-45, which stain positively in melanoma, Factor VIII, vimentin, and CD31, which stain positively in angiosarcoma, and PSA, which stains positively in prostatic adenocarcinoma. (5, 21, 23, 24, 28) Current recommendations for diagnosing MM suggest initial screening panels to include positive staining for at least two MM markers (such as calretinin, WT1, CK5/6) and negative staining for at least two carcinoma markers (such as CEA, Leu M1, BerEP4, TTF-1). (28, 38) More recent research has shown promising results using fluorescence in situ hybridization (FISH) analysis to detect homozygous deletion of p16 and immunohistochemistry to detect loss of nuclear staining of BRCA1-associated protein 1 (BAP1), independently or in combination, for difficult cases of MM. (38-40) This is especially useful in differentiating between malignant pleural mesothelioma and benign reactive mesothelial hyperplasia, which have cytologic and histologic similarities. (39, 41)

Though not approved for use at present, two serum markers, serum mesothelin-related protein (SRMP) and osteopontin, have been proposed to aid in diagnosis and monitor progression of MM. (26, 31, 42-44). Diagnosis can be challenging, but a thorough workup
including histologic, immunohistochemical, and molecular investigations, in combination with clinical and radiologic correlation, can aid in diagnosis.
References


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33. Lester T, Xu H. Malignant pleural mesothelioma with osseous metastases and pathologic fracture of femoral neck. Applied immunohistochemistry & molecular
Fig. 1. Hematoxylin and eosin staining of the pleural biopsy revealed marked thickening and a fibroblastic reaction to infiltrative tumor nests and pseudoglandular structures (A: x40). The tumor cells are mildly pleomorphic with increased mitotic activity (B and C: x100 and x200). Immunohistochemical staining showed positivity for calretinin (D: x200), CK 5/6 (E: x200), and CK7 (F: x200).
Fig. 2. A clinical image shows a single firm, pink cutaneous papule on the upper trunk.
Fig. 3. Hematoxylin and eosin staining of the cutaneous nodule shows a fairly well-circumscribed nodular proliferation of epithelioid cells within the dermis (A: x40). The tumor forms pseudoglandular structures with cytologic atypia and mitoses (B and C: x200 and x400). Immunohistochemical stains with positive results include calretinin (D: x200), CK 5/6 (E: x200), and CK7 (F: x200).
<table>
<thead>
<tr>
<th>Case</th>
<th>Year of Publication</th>
<th>Age (years)</th>
<th>Location of cutaneous mets</th>
<th>Time from original diagnosis of MM to met presentation</th>
<th>Positive Stains</th>
<th>Negative Stains</th>
<th>Type of Mesothelioma</th>
<th>Subtype of Cutaneous Metastasis</th>
<th>Treatment</th>
<th>Outcome/follow up</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1968 11</td>
<td>65/M</td>
<td>Scalp</td>
<td>2 mths</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Pleural</td>
<td>Sarcomatoid</td>
<td>Not Reported</td>
<td>Deceased within 23 mths</td>
</tr>
<tr>
<td>2</td>
<td>1980 17</td>
<td>50/M</td>
<td>Chest, face</td>
<td>16 mths, 21 mths</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Pleural</td>
<td>Biphasic*</td>
<td>Chemotherapy (cyclophosphamide, doxorubicin, MTX x 4 mths), Radiation</td>
<td>Deceased within 23 mths</td>
</tr>
<tr>
<td>3</td>
<td>1983 24</td>
<td>54/M</td>
<td>Neck, thorax, flank, abdomen</td>
<td>3 mths</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Peritoneal</td>
<td>Epithelioid*</td>
<td>Chemotherapy (4 cycles: Cycles 1 &amp; 2: vincristine, dacarbazine, cyclophosphamide Cycle 3: doxorubicin, dacarbazine, cyclophosphamide Cycle 4: (2 doses): MTX, Cycles 1, 2, 3 &amp; 4: CEA, CD34, Factor VIIIIRA, CD31, CD34, S100, S100, MTX), Radiation</td>
<td>Deceased within 11 mths</td>
</tr>
<tr>
<td>4</td>
<td>1992 7</td>
<td>60/M</td>
<td>Cheek</td>
<td>At time of biopsy</td>
<td>Cytokeratin, Vimentin, EMA, Orthokeratin Cytokeratin (AE1/AE3, MNF116, CAM 5.2), EMA Calretinin, Cytokeratin (CK19 &amp; AE1/AE3), HBME-1 Cytokeratin (MNF116)</td>
<td>Leu M1, CEA, S100, Factor VIIIRA, UE Leu M1 (CD15), CEA, CD34, Factor VIIIIRA, UE Leu M1, CEA, BerEP4, B72.3, S100, HMB-45, MART-1, Not Reported</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Not Reported</td>
<td>Deceased shortly after biopsy</td>
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<tr>
<td>5</td>
<td>1997 9</td>
<td>50/M</td>
<td>Chest wall</td>
<td>12 mths</td>
<td>Cytokeratin</td>
<td>Leu M1, CEA, S100, Factor VIIIRA, UE Leu M1, CEA, BerEP4, B72.3, S100, HMB-45, MART-1, Not Reported</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Radiation</td>
<td>Not Reported</td>
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<tr>
<td>6</td>
<td>2003 4</td>
<td>64/M</td>
<td>Lip, flank, pubis, calf</td>
<td>9 mths</td>
<td>Calretinin, Cytokeratin (CK19 &amp; AE1/AE3), HBME-1 Cytokeratin (MNF116)</td>
<td>Leu M1, CEA, S100, Factor VIIIRA, UE Leu M1, CEA, BerEP4, B72.3, S100, HMB-45, MART-1, Not Reported</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Radiation</td>
<td>Not Reported</td>
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<tr>
<td>7</td>
<td>2003 21</td>
<td>64/M</td>
<td>Chin</td>
<td>At time of biopsy</td>
<td>Calretinin, Cytokeratin (MNF116), CK5/6 (weak), CK7</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Sarcomatoid</td>
<td>Radiation</td>
<td>Not Reported</td>
</tr>
<tr>
<td>8</td>
<td>2005 4</td>
<td>25/F</td>
<td>Back, upper &amp; lower extremities</td>
<td>3 mths</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Sarcomatoid</td>
<td>Surgery, chemotherapy (6 cycles), radiation</td>
<td>Progressive disease on subsequent imaging</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2006 23</td>
<td>53/M</td>
<td>Flank</td>
<td>At time of biopsy</td>
<td>Calretinin, Cytokeratins (MNF116), CK5/6 (weak), CK7</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Chemotherapy, radiation, pleural sclerotherapy</td>
</tr>
<tr>
<td>10</td>
<td>2006 25</td>
<td>60/F</td>
<td>Chest wall</td>
<td>6 mths</td>
<td>Not Reported</td>
<td>Not Reported</td>
<td>Peritoneal</td>
<td>Not Chemotherapy</td>
<td>Not Reported</td>
<td>Not Reported</td>
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<tr>
<td>Case (year)</td>
<td>Age</td>
<td>Sex</td>
<td>Location</td>
<td>Duration</td>
<td>Immunostains</td>
<td>Tumor Type</td>
<td>Treatment</td>
<td>Survival</td>
<td></td>
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<tr>
<td>11 2007</td>
<td>67/M</td>
<td>Lip, scalp</td>
<td>12 years</td>
<td>Calretinin, CK5/6, CK7, EMA, HBME-1</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Chemotherapy (pemetrexed, cisplatin, gemcitabine)</td>
<td>Alive at 31 mths, but with progressive disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 2007</td>
<td>77/M</td>
<td>Lip</td>
<td>At time of biopsy</td>
<td>Calretinin, Cytokeratin (CAM 5.2, AE1/AE3), CK7</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Not Reported</td>
<td>Deceased within 6 mths</td>
<td></td>
<td></td>
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<tr>
<td>13 2007</td>
<td>47/M</td>
<td>Scalp, finger</td>
<td>Not Reported</td>
<td>Calretinin, CK5/6, Vimentin</td>
<td>Pleural</td>
<td>Biphasic</td>
<td>Chemotherapy (3 cycles vinorelbine before stopping treatment due to progressive disease)</td>
<td>Deceased within 6 mths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 2009</td>
<td>61/M</td>
<td>Face, posterior auricular</td>
<td>4 years</td>
<td>Calretinin (focally), CEA, TTF-1, Vimentin, CD10, Cytokeratin (CAM 5.2), SMA (focally)</td>
<td>Pleural</td>
<td>Sarcomatoid</td>
<td>Chemotherapy (6 cycles: pemetrexed, cisplatin), Radiotherapy</td>
<td>&gt;37 mths disease free</td>
<td></td>
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<tr>
<td>15 2009</td>
<td>54/M</td>
<td>Scalp</td>
<td>8 mths</td>
<td>Calretinin, CK5/6</td>
<td>Pleural</td>
<td>Epithelioid*</td>
<td>Chemotherapy (pemetrexed, cisplatin x5 mths)</td>
<td>Not Reported</td>
<td></td>
<td></td>
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<tr>
<td>16 2009</td>
<td>65/M</td>
<td>Face, scalp, trunk</td>
<td>At time of diagnosis</td>
<td>Cytokeratin (MNF116), Vimentin, CD10, Cytokeratin (CAM 5.2), SMA (focally)</td>
<td>Pleural</td>
<td>Biphasic</td>
<td>Not Reported</td>
<td>Deceased shortly after biopsy</td>
<td></td>
<td></td>
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<tr>
<td>17 2010</td>
<td>72/M</td>
<td>Abdomen</td>
<td>At time of biopsy</td>
<td>Calretinin, Pan-cytokeratin, WT1, CK7, CK20 (focal, weak)</td>
<td>Peritoneal</td>
<td>Epithelioid</td>
<td>Not Reported</td>
<td>Deceased shortly after biopsy</td>
<td></td>
<td></td>
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<tr>
<td>18 2011</td>
<td>75/M</td>
<td>Chest wall</td>
<td>8 mths</td>
<td>Calretinin, Pan-cytokeratin, CK5/6, thrombomodulin, vimentin, HMBE-1, EMA, WT1, BerEP4</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Chemoradiation</td>
<td>Deceased within 19 mths</td>
<td></td>
<td></td>
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<tr>
<td>19 2013</td>
<td>55/M</td>
<td>Abdominal wall</td>
<td>At time of biopsy</td>
<td>Calretinin, CK5/6, CK7, WT1</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Chemotherapy (6 cycles: pemetrexed, cisplatin)</td>
<td>Not Reported</td>
<td></td>
<td></td>
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<tr>
<td>20 Current Case (2017)</td>
<td>75/M</td>
<td>Upper back</td>
<td>4 mths</td>
<td>Calretinin, CK5/6, CK7, D2-40</td>
<td>Pleural</td>
<td>Epithelioid</td>
<td>Not Reported</td>
<td>Deceased within a week following cutaneous biopsy</td>
<td></td>
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</table>

*Subtype was inferred based on histologic description

Abbreviations: EMA, Epithelial Membrane Antigen; SMA, Smooth Muscle Actin; WT, Wilms' Tumor; CEA, Carcinoembryonic Antigen; UE, Ulex Europaeus lectin; HMB, Human Melanoma Black; MART, Melanocytic Antigen Recognized by cytotoxic T lymphocytes; TTF, Thyroid Transcription Factor; CDX, Caudal-related homeobox gene; PAX, Paired-box; CA, Cancer Antigen; PSA, Prostate-Specific Antigen; MTX, methotrexate; FU, fluorouracil

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