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Cutaneous Presentation of Mesothelioma With a Sarcomatoid Transformation

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Abstract

Malignant pleural mesothelioma is a rare neoplasm of mesodermal origin. Cutaneous involvement of malignant pleural mesothelioma is a very rare entity, with only 11 cases reported in the literature. Here, we describe the case of a 75-year-old man with stage IV epithelioid pleural mesothelioma, presenting with a cutaneous eruption 5 months after initial diagnosis, which revealed sarcomatoid features on skin biopsy. Histological analysis of malignancy progression through immunohistochemical staining of the pleural, lymph node, and skin tissue revealed gradual loss of calretinin and gain of desmin, supporting a transformation from epithelioid to sarcomatoid tissue. To our knowledge, this is the first reported case of an epithelioid to sarcomatoid transformation of malignant pleural mesothelioma manifesting in a cutaneous presentation.

Keywords

malignant mesothelioma; sarcomatoid transformation

INTRODUCTION

Mesothelioma is a neoplasm derived from cells of mesodermal origin, which comprise the pleura, peritoneum, pericardium, and tunica vaginalis of the testis. Asbestos exposure is the predominant etiological risk factor for mesothelioma, with a global 80% attributable risk of malignant pleural mesothelioma to asbestos in male patients.¹

Cutaneous involvement of malignant pleural mesothelioma is an extremely rare phenomenon, with only 11 cases previously reported in the literature.^{2–12} The involved

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location often correlates anatomically with the region of the primary tumor, and most cases were attributed to seeding in the skin at procedure sites or by direct infiltration through scars. Distant cutaneous metastases are rare, seen late in the disease course, and usually present as subcutaneous nodules or tumors. Less frequently, the cutaneous metastases present with warmth or erythema suggesting an inflammatory process or carcinoma erysipelatoides. Only 2 such cases have been identified in the literature.^{4,6}

We present an extremely rare case of a malignant epithelioid pleural mesothelioma in association with a chest wall eruption mimicking carcinoma erysipelatoides. Skin biopsy demonstrated sarcomatous cell morphology and markers associated with mesenchymal cells, supportive of an epithelioid to sarcomatoid transformation of the malignancy.

CASE REPORT

A 75-year-old male retired construction worker with a history of stage IV mesothelioma presented with minimally tender confluent red nodules and plaques on his chest wall of 3-week duration. He was diagnosed with epithelioid mesothelioma by pleural biopsy 5 months before and underwent 4 cycles of chemotherapy with pemetrexed/carboplatin. Within a month of his last cycle of chemotherapy, he experienced worsening pulmonary symptoms and was subsequently found to have progression of disease on computerized tomography imaging; a left axillary lymph node biopsy confirmed metastatic epithelioid mesothelioma. Within several weeks, he developed a new rash on the left chest (Fig. 1). He was initially treated with 2 weeks of valacyclovir for presumed herpes zoster with no improvement. He was then admitted for antibiotics because of concern for superimposed cellulitis.

On admission, the patient had numerous confluent red nodules and firm indurated plaques predominantly on his left chest wall (Fig. 1). Skin biopsy of a nodule demonstrated a diffuse and dense infiltrate of spindle cells extending from superficial to deep dermis on low magnification (Fig. 2A), and a dense proliferation of atypical spindle cells in a storiform pattern was revealed on higher magnification (Fig. 2B). Immunohistochemical analysis of the skin biopsy showed a strong positivity for desmin and a focal positivity for WT1, whereas calretinin, CK7, and carcinoembryonic antigen (CEA) were negative.

The microscopic and immunohistochemical findings were suggestive of a sarcomatous malignancy in the skin, without evidence of malignant epithelioid cells classically seen in mesothelioma. Based on this initial evaluation, it was not possible to delineate a conclusive diagnosis, as we considered whether this could be a new primary sarcomatoid neoplasm or a transformation of the previously diagnosed epithelioid mesothelioma.

For further clarification, we reanalyzed the pleural biopsy obtained 5 months before. Dense collections of large atypical cells can be seen on low magnification of the pleural tissue (Fig. 3A), and numerous large malignant epithelioid cells with micropapillary features are revealed on higher magnification (Fig. 3B); of note, there are no atypical spindle cells present on pleural biopsy. These findings are consistent with the classic histological presentation of epithelioid mesothelioma. Immunohistochemistry of the pleural tissue was positive for calretinin, WT1, and CK7; and negative for CEA and desmin (Fig. 3C).

We also reviewed the imaging studies which were obtained during the course of the patient's malignancy. At the time of pleural biopsy, computed tomography (CT) of the thorax depicted pleural thickening consistent with initial epithelioid mesothelioma (Fig. 4A). At the time of skin biopsy 5 months later, repeat CT imaging revealed malignant infiltration of the entire left intrathoracic cavity (Fig. 4B).

Finally, we tracked the progression of the patient's malignancy by reviewing an interval left lymph node biopsy obtained after chemotherapy failure, approximately 4 months after the pleural biopsy and 1 month before the skin biopsy. On low-power view (Fig. 5A), there is a pronounced infiltration of pink malignant cells on the left side of the node; the thin strand of blue lymphocytes on the right side represents normal lymphatic tissue. Higher magnification (Fig. 5B) reveals a mixed pattern with numerous large malignant epithelioid cells, consistent with epithelioid mesothelioma, as well as strands of atypical spindle cells in a storiform pattern, consistent with the beginning of a sarcomatous transformation. Desmin staining of the lymph node biopsy revealed new focal positivity, consistent with the new appearance of atypical spindle cells noted on H&E stain. Meanwhile, calretinin positivity, although still present, is much weaker when compared with the initial pleural biopsy. Last, the skin biopsy displayed strong positivity for desmin and was negative for calretinin (Fig. 5C).

Because of impending intubation for worsening respiratory status and lack of effective treatment options for an extremely aggressive malignancy, the patient elected for comfort measures only and died 8 days after dermatology consultation.

DISCUSSION

The pathologic diagnosis of malignant mesothelioma relies on identifying characteristic cellular morphology and supportive immunohistochemistry findings. The histologic pattern of malignant mesothelioma can present as epithelioid, which is the most common type, sarcomatoid, or mixed. Epithelioid mesotheliomas display cuboidal or polygonal cells that may appear similar to benign reactive cells, whereas sarcomatoid mesotheliomas usually present with spindle cells or sometimes other heterologous sarcomatoid cell variants.¹³ Although an epithelioid histological appearance suggests a differential diagnosis that includes malignant mesothelioma, other carcinomas may present with similar histologic features, and thus, immunochemistry is crucial for making a definitive diagnosis.

Currently, there is no single marker with sufficiently high sensitivity or specificity for diagnosis of malignant mesothelioma. The current gold standard is to obtain 2 positive markers suggestive of mesothelioma and 2 negative markers for other lung tumors that are under consideration given the overall histological pattern.¹³ The 3 most frequently used markers which are commonly expressed in epithelioid mesothelioma are calretinin, Wilms tumor gene (WT1), and low molecular weight cytokeratins. Calretinin is an intracellular calcium-binding protein normally expressed in central and peripheral nervous systems, and it frequently displays strong and diffuse staining in epithelioid mesothelioma.¹³ Its sensitivity and specificity have been reported at 95% and 87%, respectively.¹⁴ Wilms tumor gene, WT1, is an intranuclear transcription factor expressed in small round cell tumors and leukemia and has an estimated sensitivity of 78% and a specificity of 62%.¹⁴ Last,

cytokeratins are intracytoplasmic intermediate filaments found in many normal and malignant epithelial and mesothelial cells and are negative in breast and lung adenocarcinomas. They are positive in 75%–100% of mesothelioma.¹³ Mesothelioma is characteristically negative for the markers CEA and TTF1, which are associated with adenocarcinoma, as well as for the markers desmin and vimentin, which are suggestive of mesenchymal cell origin and are often expressed in sarcoma.

Epithelioid-sarcomatoid (or mesenchymal) transformation of mesothelioma is a process in which a morphologic transdifferentiation of malignant cells occurs. It is reported to occur in 5%–10% of mesothelioma. This transition is associated with loss of markers of adhesion and polarity, and in a variety of cancers, this mesenchymal transition is one of the key factors involved in apoptosis resistance, drug resistance, and increase in aggressive behavior, with the epithelioid type having the best prognosis, biphasic/ mixed having intermediate prognosis, and the purely sarcomatoid type conferring the worst survival.^{13,15} Two-thirds of sarcomatoid mesothelioma have distant metastases at the time of diagnosis, compared with one-third of epithelioid, further suggestive of increased aggressiveness.¹⁶ In vitro studies implicate various growth factors in the mechanism for this transdifferentiation, such as epithelial growth factor, insulin-like growth factor-1 (IGF-1), and transforming growth factor-beta (TGF- β).¹⁷ On sarcomatoid transformation, epithelial cells have been shown to switch expression from markers suggestive of epithelial cell origin, in particular E-cadherin and low molecular weight cytokeratins, to markers associated with mesenchymal cells, particularly desmin, vimentin, and α -smooth muscle actin.¹⁵

In this particular case, the epithelioid-sarcomatoid transformation involved the loss of calretinin expression and an increase in desmin expression, whereas the expression of the proto-oncogene/transcription factor WT1 was maintained during transformation. Clinically, this resulted in a profound increase in tumorigenesis and invasive potential, as demonstrated by serial CT imaging showing marked progression of the malignant infiltration (Fig. 4).

The immunohistochemical staining which revealed sarcomatoid features is highly suggestive of transformation in a patient with a known diagnosis of pleural epithelioid mesothelioma. However, there is a possibility that the malignancy noted on the skin may be a new primary neoplasm, such as a high-grade primary pleural sarcoma infiltrating the chest wall to skin. In the literature, rare pulmonary sarcomatoid neoplasms, such as pleuropulmonary blastoma and pulmonary leiomyosarcoma have been described to exhibit this behavior, and are often indistinguishable on immunohistochemistry.^{18,19} The gradient of increasing desmin staining and decreasing calretinin staining (Fig. 5) gives further evidence in support of a true epithelioid- sarcomatoid transformation, possibly involving transformation of the mesothelioma cells, as they progressed through lymph node metastasis.

In summary, to the extent of our knowledge, this is the first reported case of a cutaneous presentation of an epithelioid to sarcomatoid transformation of mesothelioma. All types of mesothelioma are currently associated with a poor prognosis; however, it is important for clinicians to be aware of the possibility of an epithelioid to sarcomatoid transformation, which confers an even more aggressive course and a worse prognosis.

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FIGURE 1. Photograph of the left chest wall showing numerous confluent red nodules and firm, indurated plaques in a dermatomal distribution. There are also few scattered red papules on his medial right chest.

FIGURE 2.

Histology of a left chest nodule. A, Diffuse and dense infiltrate of spindle cells proliferating from the superficial through the deep dermis ($\times 2$). B, Dense proliferation of atypical spindle cells arranged in a storiform pattern ($\times 100$). C, Immunohisto-chemical analysis revealing focal positivity for WT1 and strong diffuse positivity for desmin, as well as negative staining for calretinin, CK7, and CEA.

FIGURE 3. Histology of left pleural biopsy. A, Dense collections of large atypical cells ($\times 2$). B, Numerous large malignant epithelioid cells displaying micropapillary features ($\times 100$). C, Immunohistochemistry positive for calretinin, WT1, and CK7; negative for CEA and desmin.

FIGURE 4.

Computerized tomography of the thorax. A, Pleural thickening consistent with epithelioid mesothelioma. No evidence of extrapleural involvement. B, Pronounced malignant infiltration occupying the entire left intrathoracic cavity.

FIGURE 5.

A, H&E stain of left axillary lymph node biopsy at low power ($\times 2$). Dense collections of large atypical cells are seen on the left side of the node. Thin strand of blue lymphocytes on right side of node is consistent with normal lymphatic tissue. B, Numerous large malignant epithelioid cells consistent with epithelioid mesothelioma. There are also strands of atypical spindle cells in a storiform pattern, consistent with the beginning of a sarcomatoid transformation ($\times 100$). C, Immuno-histochemistry showing initial pleural biopsy strongly positive for calretinin, lymph node biopsy 4 months later more weakly positive, and finally skin biopsy 5 months later negative for calretinin. Desmin negative on initial pleural biopsy, weakly positive on lymph node biopsy, and strongly positive on skin biopsy.