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Metastatic squamous cell carcinoma with pseudoangiosarcomatous features and aberrant expression of vascular markers

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ABSTRACT

Squamous cell carcinoma with pseudoangiosarcomatous features is a rare but well-recognized variant of squamous cell carcinoma. These tumors exhibit complex anastomosing channels lined by neoplastic cells, histologically mimicking a vasoformative mesenchymal tumor. Immunohistochemically, the published cases expressed epithelial markers and were consistently negative for vascular markers. Squamous cell carcinoma with pseudoangiosarcomatous features and aberrant expression of vascular markers has never been reported. Herein, we report two cases of metastatic poorly-differentiated squamous cell carcinoma with pseudoangiosarcomatous morphologic features which showed immunoreactivity for vascular markers (CD31, Fli-1, and ERG). One case (left thigh skin squamous cell carcinoma with abdominal wall metastasis) showed strong and diffuse positivity for vascular markers, and the final diagnosis was confirmed with electron microscopy. The second case (squamous cell carcinoma of unknown primary site with bone metastasis) showed patchy positivity for both squamous and vascular markers. This is the first report of squamous cell carcinoma with pseudoangiosarcomatous features and aberrant expression of vascular markers, which resembles angiosarcoma both morphologically and immunohistochemically, and may represent a potential diagnostic pitfall. It is of crucial importance for pathologists to be aware of metastatic squamous cell carcinoma with such unique features, so that misdiagnosis and inappropriate treatment will be avoided.

1. Introduction

Morphological studies based on hemotoxylin and eosin stains remain the cornerstone of surgical pathology practice, and can provide extensive initial diagnostic information about tumor type and line of differentiation. The advent of tissue specific (through appropriate validation) immunohistochemical markers has improved our ability to correctly assess tumors, especially the poorly differentiated ones. But diagnostic challenges still exist when epithelial malignancies mimic mesenchymal/sarcomatous tumors, as well as when mesenchymal/sarcomatous tumors mimic epithelial neoplasms.

One well-recognized example is squamous cell carcinoma with pseudoangiosarcomatous features, which has been described under the names of pseudoangiosarcomatous squamous cell carcinoma (PASCC), pseudovascular squamous cell carcinoma, pseudovascular adenoid squamous cell carcinoma, pseudoangiosarcomatous carcinoma, and acantholytic squamous cell carcinoma [1–8]. This rare variant of squamous cell carcinoma has been noted in a variety of sites such as the skin, oral mucosa, lung and uterine cervix [1–8]. Few cases of other types of carcinoma with pseudoangiosarcomatous features have also been reported in the literature, such as two cases of poorly differentiated breast ductal carcinomas [1], and one case of metastatic adrenal carcinoma in the scalp [9]. These tumors exhibit complex anastomosing channels and pseudovascular spaces lined by neoplastic cells, histologically mimicking a vasoformative mesenchymal tumor. Immunohistochemically, the published pseudoangiosarcomatous carcinomas express epithelial markers such as cytokeratin and/or p63, and are consistently negative for endothelial cell markers, thus differentiating them from a true vascular tumor of endothelial origin [1–7].

In this study, we presented two cases of metastatic PASCC. These tumors show at least patchy expression of endothelial markers in the areas with pseudoangiosarcomatous features, therefore resembling angiosarcoma both morphologically and immunohistochemically. The histological features and unconventional sites for metastatic squamous cell carcinoma may lead to misdiagnosis and inappropriate treatment, particularly when the relevant history was not provided and the tumor was under-sampled.

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2. Materials and methods

This study was approved by the Institutional Review Board. Routine hematoxylin and eosin stained slides were reviewed on both cases. Pseudoangiosarcomatous features were defined as anastomosing channels and pseudovascular spaces lined by neoplastic cells. Immunohistochemical studies performed at the time of diagnosis were reviewed and additional markers were performed if necessary.

Immunohistochemistry for p63, p40, pan-cytokeratin, CD31, ERG, and Fli-1 were performed. Formalin-fixed, paraffin-embedded tissue blocks were sectioned at 4 µm and mounted on positively charged slides. p63 antibody (Dako North America, M7247) was used at 1:100 dilution. Antigen retrieval was performed using a Tris/EDTA solution for 20 min, and detection of antibody antigen reaction was accomplished using an EnVision + kit (Agilent Technologies). p40 antibody (EMD/Calbiochem, PC373) was used at a 1:2000 dilution. Antigen retrieval was performed with Epitrope Retrievel Solution 2 for 20 min (Leica Biosystems, Inc., AR94640) and detected using Bond Polymer Refined Detection (Leica Microsystems, DS9800). Pan-cytokeratin includes a cocktail of cytokeratin AE1/AE3 (Leica Biosystems, Inc., NCL-L-AE1/AE3, at 1:800 dilution), CAM5.2 (Becton Dickinson & Company, 349205, at 1:100 dilution), and MNF116 (Dako North America, M0821, at 1:400 dilution). The antigen retrieval was achieved using a Proteinase K for 5 min, and detected using Bond Polymer Refined Detection (Leica Microsystems, DS9800). CD31 antibody was used in a ready to use format (Leica Biosystems, Inc., clone JC70 A, PA0414) with antigen retrieval performed using Epitope Retrieval solution 2 (Leica Biosystems, Inc., AR94640) for 20 min. Antibody antigen reaction detection was accomplished with Bond Polymer Refined Detection (Leica Microsystems, DS9800). ERG pre-dilute antibody (Dako North America, EP111) was used with antigen retrieval performed using a Tris/EDTA solution, pH 9.0, on a Link PT module for 20 min. Antibody antigen reaction detection was accomplished using EnVision Flex + with Linker for 15 min. Fli-1 antibody (Thermo Fisher Scientific, RB-9295-P) was used at 1:100 dilution. Antigen retrieval was performed using EnVision Flex high pH for 20 min. Antibody antigen reaction detection was accomplished using EnVision Flex+. The sections were counterstained with hematoxylin.

3. Results

3.1. Case report 1

The patient was a 72-year-old male with a history of squamous cell carcinoma in the left anterior thigh which was resected. He had metastatic squamous cell carcinoma in the left external iliac lymph nodes, and subsequently underwent lymph node dissection 4 months after his initial diagnosis. He was also treated with proton radiation with concurrent chemotherapy. A year after his primary diagnosis he developed left lower lobe lung and mediastinal/hilar lymph node metastases, and was treated with left lower lobectomy, lymph node dissection, and subsequent chemoradiation. Approximately two years after his initial diagnosis and resection, he noticed pain in left abdominal wall. A CT scan revealed a 3.3 cm mass in the superior left rectus musculature, and a 7.2 cm mass in the inferior left rectus. The two masses were resected separately.

Microscopically, the two abdominal wall masses exhibited similar morphological features. The tumors consisted of solid sheets of malignant cells with infiltrative growth into skeletal muscle. The tumor cells were polygonal to spindle, with oval to spindle nuclei, eosinophilic cytoplasm and brisk mitotic activity. In areas, the tumor cells formed anastomosing blood-filled spaces lined by neoplastic cells, resembling vascular channel formation (Fig. 1**A and B**). The specimens were generously sampled and there was no evidence of keratinization or intercellular bridges. The overlying skin was unremarkable with no evidence of dysplasia or squamous cell carcinoma in situ. The specimens of iliac lymph nodes and lung mass were retrospectively reviewed. The metastatic squamous cell carcinoma in the iliac lymph nodes was moderately to poorly-differentiated with conspicuous areas of keratinization. The squamous cell carcinoma in the lung was predominately poorly differentiated, but foci of keratinization were easily identified. The specimen of the left anterior thigh squamous cell carcinoma was not available for review, a potential limitation in this case.

Immunohistochemically, the tumor cells in the abdominal wall metastasis exhibited immunoreactivity for both epithelial/squamous markers (p63, p40 and pancytokeratin) and endothelial/vascular markers (ERG, Fli-1, and patchy CD31) (Fig. 1**C–G**). The morphologic features and immnohistochemical features raised possibility of a de novo angiosarcoma versus metastatic squamous cell carcinoma. Electron microscopic examination demonstrated bundles of tonofilaments encircling the nucleus in many tumor cells. The tumor cells also exhibited scattered well-formed desmosomes joining their cell membranes (Fig. 1H). Pinocytotic vesicles or Weibel-Palade bodies were not identified. The electron microscopic evidence of squamous differentiation confirmed a diagnosis of metastatic squamous cell carcinoma. Immunohistochemistry was retrospectively performed on the metastatic squamous cell carcinoma in the iliac lymph node. Despite of areas of keratinization (Fig. 2**A and B**), the tumor cells exhibited immunohistochemical reactivity for vascular markers CD31, Fli-1, and ERG in the poorly differentiated, non-keratinizing areas (Fig. 2**C – H**), with the expression pattern similar to that in the abdominal wall tumor. These findings further support the conclusion that the abdominal wall tumor represents metastasis from the left anterior thigh squamous cell carcinoma.

3.2. Case report 2

The patient was a 74-year-old male who presented with a pathologic fracture of the right proximal humerus secondary to minimal trauma. Imaging at that time demonstrated a lytic lesion suspicious for a malignant process. Curettage of the humerus lesion demonstrated nests and solid sheets of malignant cells invading bone and surrounding soft tissue. The tumor cells were epithelioid with eosinophilic to amphophilic cytoplasm, large nuclei and prominent nucleoli. There was acute inflammation and hemorrhage, which gave rise to an appearance of tumor cell-lined, blood-filled spaces in areas (Fig. 3**A and B**). There was no evidence of keratinization or intercellular bridges. The tumor cells were strongly and diffusely positive for cytokeratin CAM5.2 (Fig. 3C), and showed partial reactivity for p63 (Fig. 3D). Immunoreactivity for cytokeratin 5/6 showed a similar distribution as p63. Immunohistochemistry for p40 was negative. There was patchy immunoreactivity for endothelial markers (Fli-1, ERG, and CD31), although it was weaker than that in vascular endothelial cells (Fig. 3**E–G**). No tissue was available for ultrastructural evaluation via electron microscopy in this case. Notably, the patient did not have any prior diagnoses of malignancy and subsequent radiographic studies did not demonstrate lesions in any other organs. The patient was noted to have hoarseness and a sore throat; however, a laryngoscopy was not performed because of his general poor performance status. The absence of morphologic comparison of the primary tumor to the humerus lesion is a potential limitation in this case. Similarly, the absence of a definitive primary site of origin for the patient's malignancy raised the possibility of primary osseous angiosarcoma. However, given the patchy vascular marker staining in the tumor along with strong and diffuse CAM5.2 expression, a metastatic squamous cell carcinoma, likely of the head and neck origin, was favored.

4. Discussion

PASCC is an uncommon but well-recognized histopathological variant of squamous cell carcinoma characterized by pseudoluminal or pseudovascular spaces lined by neoplastic cells, histologically