Pseudoangiosarcomatous squamous cell carcinoma: a rare subtype of squamous cell carcinoma that needs to be differentiated from angiosarcoma and has a poor prognosis

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ABSTRACT

This study aimed to investigate the formation mechanism of Pseudoangiosarcoma squamous cell carcinoma (PASCC). The researchers reviewed ten cases of PASCC and summarize their clinical outcomes, pathological morphological traits, immunophenotypes, treatment plans and the corresponding follow-up data. Results showed that the pathological morphology revealed complex reticular structures, where numerous tracts of anastomose, and lacunar structures lined with atypical neoplastic cells, which resembles the histopathological appearance of angiosarcoma. Particularly, we observed pathologic patterns that resemble Sclerosing Epitheliod Fibrosarcoma (or Myxoid Fibrosarcoma) in the patients who suffered a relapse. All cases present negative results for vascular markers (CD31, ERG) and positive results for epithelial markers (CK-pan, p40).

The average age of the participants is 60 years old (range: 48-79), relative aged, and there is no significant difference between male and female participants (6 men and 4 women). The locations of neoplasms involve face (n=3), upper limbs (n=1), waist(n=1), cervix uteri (n=1), lungs (n=2), thyroid (n=1), and breasts (n=1). All participants had received clinical follow-ups that range from 4 to 47 months, during which the researchers observed Lymph Node Metastases developed in three participants (out of 10; 30%); Distant Metastases in five participants (out of 10; 50%); two local recurrences at the site of surgical resection; and four deaths due to disease (out of 10; 40%), with 9.5 months estimated median survival time and 9 months mean survival time. It was concluded that PASCC presents the tendency for recurrence and metastasis. Accurate pathological diagnosis and standardized medical procedures are crucial to the treatment of PASCC. Epithelial-Mesenchymal Transformation (EMT) and P53 gene mutation are involved in the formation of PASCC.

Introduction

Pseudoangiosarcoma squamous cell carcinoma (PASCC) is a rare type of squamous cell carcinoma that is prone to recurrence and metastasis (1). The lack of pathological diagnosis and standardized clinical treatment plan are the important factors affecting the poor prognosis (2). In our retrospective analysis of PASCC cases, it was found that the pathological morphology of a patient with two relapses of PASCC changed from spindle cell squamous cell carcinoma to pseudoangiosarcoma type squamous cell carcinoma and poorly differentiated squamous cell carcinoma (similar to epitheliod fibrosarcoma and myxoid fibrosarcoma) during initial, relapse-recurrence and recurrence. This prompted us to study the formation mechanism of PASCC (3-4).

According to the World Health Organization (WHO), PASCC (also known as pseudoangiomatoid or pseudo-vascular adenoid SCC) is an uncommon original disease entity and a highly aggressive variant of SCC (1-3). The disease was first introduced by Nappi et al. in 1992 (4). It is such a rare condition that it only accounts for 0.2% of SCC approximately. To the researchers’ knowledge, less than 20 PASCC cases have been documented so far in international literatures.

PASCC mostly develops in body areas exposed to the sun. Clinically, the typical symptoms of PASCC are cutaneous ulcers that appear as tan-pink nodular crust (6-8), usually found in aged patients. When examining such skin lesions, there are often clear foci showing the transition of spindle cells (or well-differentiated SCC) into pseudovascular spaces. Tumors can spread to sweat glands, adipose tissues, or striated muscle tissues. Acute and chronic inflammatory cell infiltration and lymph follicle formation would be substantial in the background, while other regions usually feature a slit-like structure and, occasionally, sinusoidal patterns fringed with atypical, irregular-shaped pleomorphic epithelioid cells. In some cases, lesions may have a hobnail appearance and lack cohesion and lysis along the complex anastomosed channels (or reticular structure). Meanwhile, in the dissected lymph node tissues, the metastatic tumor tissues still retain the
pseudovascular structure, suggesting that the components of pseudovascularoid SCC have a higher chance to metastasize than well-differentiated SCC. There have been reports of PASCC in skin, breast, lung, and cervix uteri so far, but to the best of our knowledge, thyroid is an exception (5).

In this article, the Pseudoangiosarcomatous squamous cell carcinoma as a rare subtype of squamous cell carcinoma that needs to be differentiated from angiosarcoma and has a poor prognosis has been investigated.

Materials and Methods

The researchers retrieved ten cases recorded during 2015-2020 from the database maintained by the Pathology Center of the First Affiliated Hospital of Nanchang University and the Affiliated Cancer Hospital of Nanchang University. The cases were filtered with the keywords “Sarcomatoid Carcinoma” in the field of “final diagnosis”. The researchers examined the biopsies and surgical specimens of each case studied the associated clinical data and conducted follow-ups with the patient and his/her family. The processing of biopsies follows these standards: formalin-fixed and paraffin-embedded; sectioned to 4µm blocks; mounted on positively charged slides. Table 1 shows the immunohistochemical antibodies and the dilution ratios used for immunostaining. The immunohistochemical staining adopted the Ventana Benchmark XT System (Ventana Medical System, Benchmark ULTRA), and the results were interpreted as positive and negative based on staining intensity. However, one special case received AB-PAS staining in addition.

Results

Clinical features

Table 2 summarizes the clinical and follow-up details for the ten cases focused. The average age of the participants is 60 years old (range: 48-79), relatively aged. The results show no significant differences between male and female participants (6 men and 4 women). The locations of neoplasms involve face (n=3), upper limbs (n=1), waist (n=1), cervix uteri (n=1), lungs (n=2), thyroid (n=1), and breasts (n=1). Seven participants (out of 10; 70%) received surgical excisions, among which one had chemotherapy in addition after lung and bone metastases; another had radiotherapy after tumor recurrence. The other three patients (out of 10; 30%) received chemotherapy, among which two had neoadjuvant chemotherapy only; the other had both neoadjuvant chemotherapy and immunotherapy. All participants had received clinical follow-ups that range from 4 to 47 months, during which the researchers observed Lymph Node Metastases developed in three participants (out of 10; 30%); Distant Metastases in five participants (out of 10; 50%); two local recurrences (out of 10; 20%) at the site of surgical resection; and four deaths due to disease (out of 10; 40%), with 9.5 months estimated median survival time and 9 months mean survival time.

Table 1. Antibodies used for immunohistochemical analysis.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Vendor</th>
<th>Clone</th>
<th>Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratin (pan)</td>
<td>ZSGB-BIO</td>
<td>AE1/AE3</td>
<td>1:150</td>
</tr>
<tr>
<td>P63</td>
<td>ZSGB-BIO</td>
<td>B18</td>
<td>1:200</td>
</tr>
<tr>
<td>P40</td>
<td>ZSGB-BIO</td>
<td>BC28</td>
<td>1:100</td>
</tr>
<tr>
<td>CD31</td>
<td>ZSGB-BIO</td>
<td>UMAB30</td>
<td>1:100</td>
</tr>
<tr>
<td>CD34</td>
<td>ZSGB-BIO</td>
<td>10C9</td>
<td>1:200</td>
</tr>
<tr>
<td>ERG</td>
<td>ZSGB-BIO</td>
<td>UMAB78</td>
<td>1:200</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>ZSGB-BIO</td>
<td>EP6</td>
<td>1:100</td>
</tr>
<tr>
<td>Vimentin</td>
<td>ZSGB-BIO</td>
<td>UMAB159</td>
<td>1:150</td>
</tr>
<tr>
<td>Ki-67</td>
<td>ZSGB-BIO</td>
<td>MIB-1</td>
<td>1:100</td>
</tr>
<tr>
<td>Pax-8</td>
<td>ZSGB-BIO</td>
<td>EP298</td>
<td>1:150</td>
</tr>
<tr>
<td>P53</td>
<td>ZSGB-BIO</td>
<td>EP9</td>
<td>1:200</td>
</tr>
</tbody>
</table>

Table 2. Clinical features of the eight cases of PASCC.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age</th>
<th>Site</th>
<th>Specimen type</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>M /66</td>
<td>Face</td>
<td>Excision</td>
<td>Surgery</td>
<td>Alive, two recurrences were followed by surgical excision</td>
</tr>
<tr>
<td>Case 2</td>
<td>M /70</td>
<td>Face</td>
<td>Excision</td>
<td>Surgery</td>
<td>Dead, 4 months later</td>
</tr>
<tr>
<td>Case 3</td>
<td>F /67</td>
<td>Face</td>
<td>Excision</td>
<td>Surgery</td>
<td>Dead, 8 months later</td>
</tr>
<tr>
<td>Case 4</td>
<td>M /79</td>
<td>Lower Limb</td>
<td>Excision</td>
<td>Surgery</td>
<td>Alive, Recurrence occurred 13 months after surgery, further surgical resection and radiotherapy were performed</td>
</tr>
<tr>
<td>Case 5</td>
<td>M /59</td>
<td>Lung</td>
<td>Biopsy</td>
<td>Chemotherapy</td>
<td>Dead, 11 months later</td>
</tr>
<tr>
<td>Case 6</td>
<td>F /71</td>
<td>Thyroid</td>
<td>Excision</td>
<td>Surgery</td>
<td>Dead, 13 months later</td>
</tr>
<tr>
<td>Case 7</td>
<td>F /72</td>
<td>Cervix Uteri</td>
<td>Biopsy</td>
<td>Chemotherapy</td>
<td>Alive, 20 months after Chemotherapy</td>
</tr>
<tr>
<td>Case 8</td>
<td>F /48</td>
<td>Breast</td>
<td>Excision</td>
<td>Surgery</td>
<td>Alive, 12 months after surgery</td>
</tr>
<tr>
<td>Case 9</td>
<td>M /72</td>
<td>Lung</td>
<td>Biopsy</td>
<td>Chemotherapy and immunotherapy</td>
<td>Alive, 7 months after surgery</td>
</tr>
<tr>
<td>Case 10</td>
<td>M /71</td>
<td>Waist</td>
<td>Excision</td>
<td>Surgery and post-metastatic Chemotherapy</td>
<td>Alive, 4 months later, lung and bone metastases</td>
</tr>
</tbody>
</table>
displayed pathological traits similar to signet ring cells or adipoblast cells surrounded by mucus masses, instead of PASCC observed the histological similarity to a vasofor-mative mesenchymal tumor, which features well-differen-
tiated anastomoses of complex channels or reticular struc-
tures lined with hobnail cells without cellular cohesion. Some lesions are fringed with tumor cells and contain
blood, like vascular channels (Figure 1C), and the pseudo-
luminal spaces inside are filled with malignant epithelioid
cells, involving eosinophilic or amphophilic cytoplasm,
expanded nuclei, and clear nucleoli. In the thyroid, irreg-
ular lacuna lines with atypical, pleomorphic epithelioid
cells (Figure 1D). For all specimens, cytokeratin (Figure
2E), P40 (Figure 2F), and P63 are expressed, while CD31,
CD34, and ERG are unexpressed. The diffusion of P53
protein through nuclear is positive or unclear, indicating
P53 gene mutation (Figure 2G). The expression of E-cad
decreases significantly and sometimes becomes negative
(Figure 2H). The average number of mitoses is 8 (4-16)
per 10 HPF, and the average Ki-67 proliferation index is
51% (20%-80%). Table 3 provides the major immunohis-
tochemical staining scores of the specimens.

Pathological features and immunophenotypes of EMT
In addition to the above common features, one case of
PASCC recurred twice, showing some special morpho-
logical features. After the first relapse, tumor cells were
typically polygonal shaped, scattered around clusters of
collagen fibers, and positioned independently or as rows,
similar to the sclerosing epithelioid fibrosarcoma in soft
tissue (Figure 3I). After the second relapse, tumor cells
displayed pathological traits similar to signet ring cells or
adipoblast cells surrounded by mucus masses, instead of

Table 3. Immunohistochemical findings in pseudovascular squamous cell carcinoma case.

<table>
<thead>
<tr>
<th>Case</th>
<th>Cytokeratin</th>
<th>P40</th>
<th>P63</th>
<th>CD31</th>
<th>E-cad</th>
<th>P53</th>
<th>Ki-67</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20%+</td>
</tr>
<tr>
<td>Case 2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>70%+</td>
</tr>
<tr>
<td>Case 3</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>20%+</td>
</tr>
<tr>
<td>Case 4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>80%+</td>
</tr>
<tr>
<td>Case 5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>30%+</td>
</tr>
<tr>
<td>Case 6</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>80%+</td>
</tr>
<tr>
<td>Case 7</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%+</td>
</tr>
<tr>
<td>Case 8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>70%+</td>
</tr>
<tr>
<td>Case 9</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>70%+</td>
</tr>
<tr>
<td>Case 10</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>40%+</td>
</tr>
</tbody>
</table>
sclerosing epithelioid fibrosarcoma. The pathologist confused the scenario with tumor cells scattered over a mucous lake and, therefore, misdiagnosed the case as myxoid fibrosarcoma (Figure 3J). The case was later corrected with immunohistochemistry as SCC, as the neoplastic cells tended to be positive for cytokeratin (Figure 3K) and P40 (Figure 3L) but negative for P53 (Figure 3N), CD31, CD34, and ERG. Meanwhile, with the histochemical examination, AB-PAS was positive, and there existed acidic mucosubstance nearby.

Discussion

Our report of PASCC in the thyroid gland with trachea infiltration is the first in history, and one of our cases also concerns the classic pseudohemangiomatoïd area.

The prognosis of PASCC is less optimistic than other SCC variants, as recurrences and metastases are more likely to happen (9-11). The patient follow-up data in our study supports the evidence in four other cases, which shows PASCC develops in body areas exposed to the sun. The average age of our participants is 60 years old (range: 48-79), relative aged. All participants had received clinical follow-ups that range from 4 to 47 months, during which the researchers observed Lymph Node Metastases developed in three participants (out of 10; 30%); Distant Metastases in five participants (out of 10; 50%); two local recurrences at the site of surgical resection; and four deaths due to disease (out of 10; 40%), with 9.5 months estimated median survival time and 9 months mean survival time. Despite the lack of studies on the exact benefits of adjuvant therapy for PASCC, our observations suggest that PASCC, as a highly aggressive form of cancer, warrants radical treatment, which may include adjuvant radiotherapy and even chemotherapy (12-15). PASCC is prone to be misdiagnosed and even neglected if no immunohistochemical marker test was applied, especially to biopsy samples. It is thus important for pathologists to accurately describe PASCC and for surgeons to be more aware of this variant, including its symptoms and aggressive characteristics, to enable appropriate control strategies (16-19).

Over time, the SCC-like vascular lesions have been sorted into several different classes, and there are various interpretations of the basic etiopathological mechanisms. Some researchers believe that epithelial-to-mesenchymal transition (EMT) occurs in PASCC, while other theories support that tumor cells adopt EMT mechanisms to alter cellular properties (e.g., cytoskeletal structure, cell-cell junctions within epithelia, and tumor-microenvironment interactions) and thus to invade and metastasize. In support of the latter view, recent reports have shown that some EMT marker patterns are indicative of poorer outcomes (10,20,21), e.g., increased vimentin along with reduced E-cadherin (12,15). PASCC is prone to be misdiagnosed and even neglected if no immunohistochemical marker test was applied, especially to biopsy samples. It is thus important for pathologists to accurately describe PASCC and for surgeons to be more aware of this variant, including its symptoms and aggressive characteristics, to enable appropriate control strategies (16-19).

Data Availability

Case data were provided by the two pathology centers, and all patients had hospitalization numbers, case data, pathological reports and other information for inquiry and verification.

Conflicts of Interest

There is no conflict of interest regarding the publication of this paper.

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