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

Yuan Zhan[1#*], Hongping Wan[1#], Liqing Wu[2*], Xian Ge[1], Xinhua Xie[1], Luoyan Wu[2], Yong Cai[3]

[1] Pathology Center, The first affiliated hospital of Nanchang University, Nanchang, Jiangxi 330006, China
[2] Department of Pathology, First hospital of Nanchang city, Nanchang, Jiangxi 330008, China
[3] Department of Pathology, Jiangxi Cancer Hospital, Nanchang, Jiangxi 330029, China

#They contributed equally to this work.

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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 Epithelioid 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.

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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 epithelioid 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 pseudovascular 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

* Corresponding author. Email: 2461200391@qq.com

pseudovascular structure, suggesting that the components of pseudovasculoid 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.

Classic pathomorphism and immunophenotype of PASCC

The researchers observed skin ulcers in some patients, and pseudo-hemangiosarcoma cells in the surrounding areas of these ulcers shift and intermingle with spindle cells.

Table 1. Antibodies used for immunohistochemical analysis.

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

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

Case	Sex/Age	Site	Specimen type	Treatment	Follow-up
Case 1	M /66	Face	Excision	Surgery	Alive, two recurrences were followed by surgical excision
Case 2	M /70	Face	Excision	Surgery	Dead,4 months later
Case 3	F /67	Face	Excision	Surgery	Dead,8 months later
Case 4	M /79	Lower Limb	Excision	Surgery	Alive, Recurrence occurred 13 months after surgery, further surgical resection and radiotherapy were performed
Case 5	M /59	Lung	Biopsy	Chemotherapy	Dead,11 months later
Case 6	F/71	Thyroid	Excision	Surgery	Dead,13 months later
Case 7	F/72	Cervix Uteri	Biopsy	Chemotherapy	Alive,20 months after Chemotherapy
Case 8	F/48	Breast	Excision	Surgery	Alive,12 months after surgery
Case 9	M/72	Lung	Biopsy	Chemotherapy and immunotherapy	Alive, 7 months after surgery
Case 10	M/71	Waist	Excision	Surgery and post-metastatic Chemotherapy	Alive,4 months later, lung and bone metastases

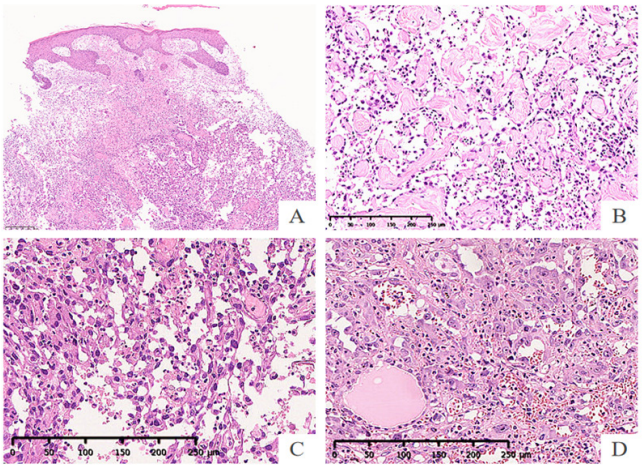

Figure 1. Pseudoangiosarcomatous squamous cell carcinoma comprising lacuna structures in the skin (A), Anastomosing complex slit-shaped channels (B), The cells had poor adhesion and were scattered through the lacunae (C), reticular structures in the thyroid (D).

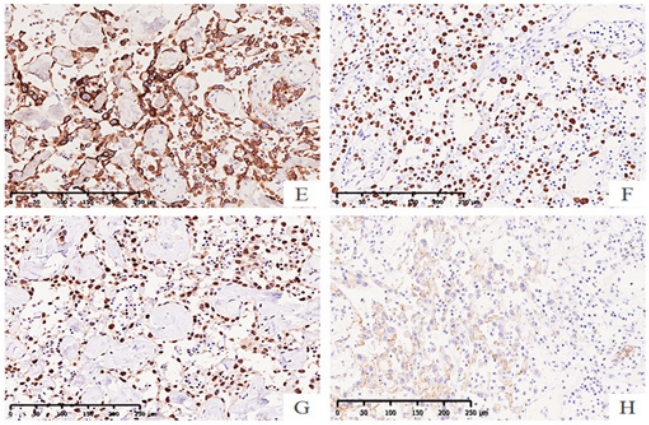

Figure 2. CK staining (E),P40 staining (F),P53 staining (G), E-cadherin staining (H).

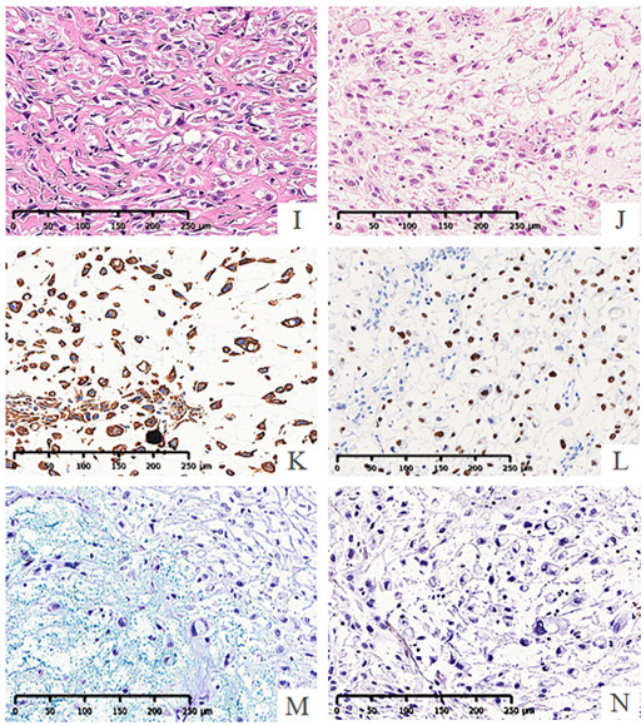

Figure 3. Tumor cells were scattered among a large number of collagen fibers, like sclerosing epithelioid fibrosarcoma in soft tissue (I). The tumor cells looked like signet ring cells or adipoblast cells, and masses of mucus accumulated in the cytoplasm and interstitium, resembling myxoid fibrosarcoma (J); CK staining (J), P40 staining (I), AB staining (M),P53 staining (N).

PASCC observed the histological similarity to a vasoformative mesenchymal tumor, which features well-differentiated anastomoses of complex channels or reticular structures lined with hobnail cells without cellular cohesion. Some lesions are fringed with tumor cells and contain blood, like vascular channels (Figure 1C), and the pseudoluminal spaces inside are filled with malignant epithelioid cells, involving eosinophilic or amphophilic cytoplasm, enlarged nuclei, and clear nucleoli. In the thyroid, irregular 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 immunohistochemical 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 morphological 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.

Case	Cytokeratin	P40	P63	CD31	E-cad	P53	Ki-67
Case 1	+	+	+	-	-	-	20%+
Case 2	+	+	+	-	+	+	70%+
Case 3	+	+	+	-	-	+	20%+
Case 4	+	+	+	-	-	+	80%+
Case 5	+	+	+	-	+	+	30%+
Case 6	+	+	+	-	-	+	80%+
Case 7	+	+	+	-	-	-	50%+
Case 8	+	+	+	-	+	+	70%+
Case 9	+	+	+	-	-	+	70%+
Case 10	+	+	+	-	-	+	40%+

sclerosing epithelioid fibrosarcoma. The pathologist confused the scenario with tumor cells scattered over a mucus 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 pseudohemangiomatoid 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, but how these patterns relate to the changes in morphology remains uncertain. One opinion suggests that reduced E-cadherin expression leads to the disruption of cell-cell adhesion and acantholysis, and some researchers propose that apoptosis and adhesion loss leads to cell dissociation and desquamation and that lysis could underpin the generation of pseudosarcomatous patterns in other organs (22-25).

In this study, one case of PASCC, developed in a 66-year-old man, is characterized by frequent recurrences and aggressiveness. Spindle tumor cells and vascular-like patterns were observed in the first and the second surgical specimens of this case, while in the third one, tumor cells were scattered around clusters of collagen fibers, in a polygonal shape, and distributed throughout the stroma as single cells or rows with low adhesion, similar to sclerosing epithelioid fibrosarcoma in soft tissue. Some tumor cells resemble signet ring cells or adipoblast cells and were scattered over the interstitium. In addition, there is a significant amount of mucus accumulation and many small blood vessels were observed in the interstitium, resembling myxoid fibrosarcoma. Hyaluronic acid, as colored by Alcian-blue staining, was found in most cystic spaces within tumors and intracytoplasmic vacuoles. The cells appear to be atypical keratinocytes, as they react positively to cytokeratin and P40 and negatively to vascular markers. With these pathological indications, we hope to demonstrate the connection between EMT and PASCC's mechanism of formation and thus performed E-cad immunohistochemistry in all cases. The results of E-cad are either sharply decreased or negative, which suggests that EMT is involved in the development of PASCC. Meanwhile, immunohistochemical detection of P53 protein consistently delivered strong expression or loss expression, indicating the mutation of the p53 gene and offering valuable clues for our future research into the mechanism.

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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