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Primary Signet-Ring Cell and Histiocytoid Carcinoma in the Axilla: A Case Report with Clinicopathology, Immunohistology, and Genetic Analysis

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Abstract

Signet-Ring Cell/Histiocytoid Carcinoma (SRCHC) is a very rare skin adnexal cancer that has been to occur mainly in the eyelid and axilla. SRCHC is characterized by composed of signet-ring cells and histiocytoid epithelial cells pathologically. We report a 55-year-old man who was diagnosed with SRCHC. A 55-year-old Korean male visited the hospital with a growing axillary mass that had appeared two years ago. Computerized tomography and positron-emission tomography showed a skin-involved mass and regional lymph node in the axilla. Signet ring cell and histiocytoid epithelial cell were found in his biopsy tissue. Immunohistology examination showed a decrease in E-cadherin, estrogen receptor/progesterone receptor negative, and androgen receptor positive. Based on the above findings, SRCHC was diagnosed. Genetic analysis using next-generation sequencing revealed mutations in PIK3CA (c263G>A, pR88Q), CDH1 frameshift (c1570_1574 del CGGAT, pR524fs), and TP53 (c329G>T, pR110L). The patient underwent surgical resection and adjuvant radiotherapy. Given the limited number of known cases, further clinicopathological and genetic analyses are needed.

Keywords: Signet-ring cell and histiocytoid carcinoma; Axilla; Clinicopathology; Next generation sequencing

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Introduction

Signet-Ring Cell/Histiocytoid Carcinoma (SRCHC) is a rare tumor newly classified in the 5th edition of the World Health Organization's skin tumor classification in 2023 [1]. It is characterized by the presence of signet-ring cells and histiocytoid epithelial cells in the dermis, subcutaneous tissue, and collagen bundles of the epidermis. SRCHC typically manifests on the eyelid and less commonly in the axilla [2-4].

To the best of our knowledge, there are only limited case reports and case series documenting SRCHC in the axilla. In this report, we aim to present a case of SRCHC originating in the axilla, providing detailed histopathological findings and results from next-generation sequencing.

Case Presentation

A 55-year-old Korean male presented to Inha University Hospital with a palpable mass in the left axilla that had its onset two years prior. Initially measuring approximately 1 cm in size, akin to the dimensions of a common bean, the mass exhibited a steady and worrisome growth pattern, ultimately reaching a diameter of 9.5 cm (Figure 1a). Concurrently, the patient experienced progressively worsening pain localized around the axillary mass, prompting his visit to our facility for a thorough evaluation. The patient presented with no known underlying medical conditions and was not currently undergoing any medical treatments. The sole noteworthy familial medical history pertained to the patient's sister, who had a previous diagnosis of breast cancer.

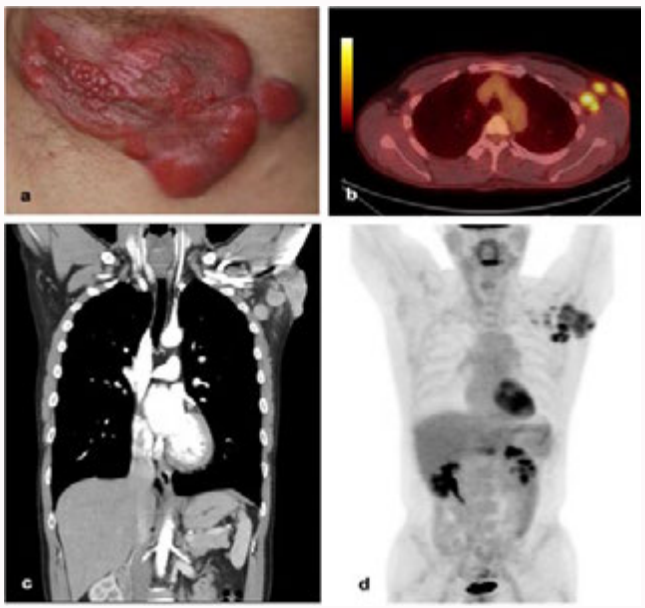

Figure 1: (a) Clinical appearance of the patient's mass located in the left axilla. The advanced nodular lesion was reddish in color and circumscribed. (b) Chest CT shows a skin mass measuring approximately 6.8 cm in the left axillary region, enlarging the adjacent lymph nodes. (c) PET/CT findings: Abnormal hypermetabolic lesion in left axillary LN level I and II.

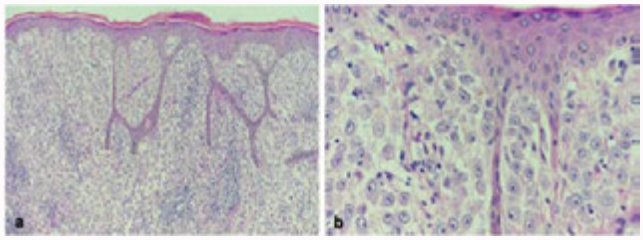

Figure 2: Histopathological findings of signet-ring cell/histiocytoid carcinoma of the patient.
(a) Diffuse infiltration of malignant epithelioid cells with extension to the subcutaneous.
(b) Histiocytoid neoplastic cells contain a sizeable hyperchromatic nucleus and eosinophilic granular cytoplasm. In addition, signet ring cells with mild atypia are also identified.

Computed Tomography (CT) of the chest revealed skin mass and adjacent lymph node enlargement in the axilla (Figure 1b). A positron-emission tomography/CT scan showed an abnormal hypermetabolic lesion in the left axillary lymph node levels I and II (Figure 1c). A skin biopsy was performed for pathologic diagnosis.

Histopathologic examination revealed diffuse infiltration of malignant epithelioid cells with extension to the subcutaneous tissue (Figure 2a). Furthermore, the signet ring cells with mild nuclear atypia were identified (Figure 2b).

An immunohistochemical study revealed a loss of E-cadherin. The tumor cells also showed diffuse immunohistochemical expression of Cytokeratin 7 (CK7), Androgen Receptor (AR), and GATA binding protein 3 (GATA3) (Figure 3a-3c) but negative for Progesterone Receptor (PR), Estrogen Receptor (ER), Human Melanoma Black 45 (HMB45), Melan A, CD34, Vimentin and Her-2 (c-erbB2) (Figure 3d).

Next-generation sequencing was analyzed using Archer Fusion

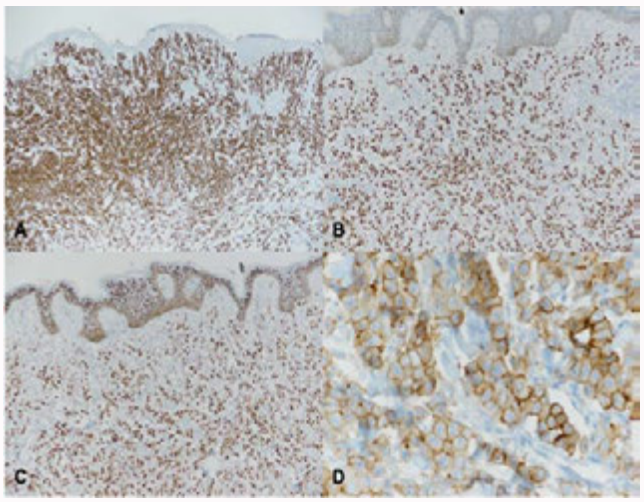

Figure 3: Immunohistochemical study
(a) Cytokeratin 7 is diffusely expressed. (original magnification x200)
(b) Androgen receptor is diffusely expressed. (original magnification x200)
(c) GATA3 is diffusely expressed. (original magnification x200)
(d) Her2 is not expressed in the neoplastic cells. (original magnification x200)

Plex Lung SK0133 v1.0 Assay Targets. Gene mutations were found in PICK3CA (c263G>A, pR88Q), CDH1 frameshift (c1570_1574 del CGGAT, pR524fs), and TP53 (c329G>T, pR110L).

We performed wide excision, axillary lymph node dissection, and reconstruction with ipsilateral latissimus dorsi myocutaneous flap. Thirty-six axillary lymph nodes were resected, twenty-six of which showed tumor metastasis. After surgical treatment, he received postoperative radiation therapy and has been following up for 6 months with no evidence of disease state.

Discussion

Signet-Ring Cell/Histiocytoid Carcinoma (SRCHC) in the axillary region is exceptionally rare, resulting in limited available data. This unique malignancy predominantly afflicts males and is characterized by distinctive morphological features, typically presenting as circumscribed plaques or nodules. Its clinical behavior can range from indolent to aggressive, with documented cases occasionally demonstrating lymph node metastasis [2-4,8]. The reported cases of SRCHC in the axilla are summarized in Table 1, 2 [3-16]. All but one case involved male patients, and among the total of 16 cases, which includes our own, comprising both male and female individuals, regional lymph node metastases were observed.

Due to the histopathological similarity between SRCHC and lobular carcinoma of the breast, SRCHC is sometimes misdiagnosed as a metastatic lesion of breast cancer. In this case, our initial assessment leaned towards the possibility of skin and lymph node metastasis of breast cancer, leading us to diligently search for the primary breast mass. However, no abnormal findings were detected upon physical examination and magnetic resonance imaging of the breast. While SRCHC typically presents with a characteristic nodular lesion, its clinical evaluation can be challenging, underscoring the critical importance of pathological examination in achieving an accurate diagnosis [3,4,7,17].

Histopathologically, SRCHC, as the name implies, is characterized by histiocytic cells containing a large hyperchromatic nucleus, slightly eosinophilic granular cytoplasm, and signet ring cells with an

Table 1: Summary of all published cases of axillary signet-ring cell/histiocytoid carcinoma.

Case No.	Country	Age	Gender	Side	Lymph node metastasis	Distant metastasis	Other neoplasm	Treatment	Outcome	Reference
1	Japan	85	Male	Left	Present	Absent	Absent	Local excision + radiotherapy + chemotherapy	SD	Goto et al. [3]
2	Japan	81	Male	Left	Present	Present (skin)	Absent	Local excision + radiotherapy + chemotherapy	PD	Goto et al. [3]
3	Japan	81	Male	Right	Absent	Absent	Absent	Local excision + radiotherapy	NED	Goto et al. [3]
4	Japan	72	Male	Right	Absent	Absent	Absent	Local excision	NED	Goto et al. [3]
5	Japan	53	Male	Right	Absent	Present (skin, bones, pleural)	Absent	Local excision + radiotherapy	DOD	Goto et al. [3]
6	Japan	88	Male	Left	Present	Present (skin)	Absent	Local excision	PD	Goto et al. [3]
7	Japan	81	Male	Left	Present	Absent	Absent	Local excision + radiotherapy	NED	Goto et al. [3]
8	Japan	64	Male	Left	Present	Present (bones, peritoneum, adrenal glands)	Absent	Radiotherapy + chemotherapy	DOD	Goto et al. [3]
9	Japan	80	Male	Left	Present	Absent	Absent	Local excision + radiotherapy	NED	Goto et al. [3]
10	Japan	74	Male	Right	Present	Present (bones)	Absent	Chemotherapy	PD	Goto et al. [3]
11	Japan	77	Male	Left	Present	Absent	Absent	Local excision	NED	Goto et al. [3]
12	Japan	85	Male	Left	Present	Absent	Absent	Chemotherapy	NED	Ito et al. [4]
13	Canada	71	Male	Right	Present	Present (bones)	Present (prostate)	Local excision	DOD	Berdugo et al. [5]
14	USA	58	Male	Left	Absent	Absent	Absent	Radiotherapy	ND	Philips et al. [6]
15	USA	63	Male	Left	Present	Absent	Present (non-Hodgkin lymphoma)	Local excision + radiotherapy	NED	Droubi et al. [7]
16	Japan	61	Male	Right	Present	Absent	Absent	Local excision	NED	Ishida et al. [8]
17	Japan	59	Male	Right	Absent	Absent	Absent	Local excision + radiotherapy + targeted therapy	NED	Miyake et al. [9]
18	Japan	55	Male	Left	Present	Absent	Absent	Local excision + radiotherapy + targeted therapy	NED	Misago et al. [10]
19	India	55	Male	Right	Present	Absent	Absent	No information on therapy	ND	Pai et al. [11]
20	Austria	71	Male	Right	Absent	Absent	Absent	Local excision	NED	Zelger et al. [12]
21	Japan	62	Male	Right	Absent	Absent	Absent	Chemotherapy	DUL	Kiyohara et al. [13]
22	Japan	74	Male	Right	Present	Absent	Present (prostate)	Local excision + radiotherapy + chemotherapy	DUL	Kuno et al. [14]
23	Japan	59	Male	Left	Absent	Absent	Absent	Local excision	NED	Kuno et al. [15]
24	Japan	68	Female	Right	Absent	Absent	Absent	Local excision	ND	Kuno et al. [15]
25	Spain	42	Male	Left	Absent	Absent	Absent	Local excision + radiotherapy	NED	Cameselle et al. [16]
Present case	Korea	55	Male	Left	Present	Absent	Absent	Radiotherapy	NED	

Abbreviation: SD: Stable Disease; PD: Progressive Disease; NED: No Evidence of Disease; DOD: Died of Disease; DUL: Died of Unrelated Cause; ND: Not Described

eccentric, slightly abnormal nucleus replaced by cytoplasmic vacuoles that typically contain mucin. These histopathological features can pose challenges in distinguishing SRCHC from other metastatic cancers with signet-ring cells or histiocytoid cells, necessitating a meticulous approach to differentiation [7,10,18].

Immunohistochemically, the tumor cells exhibited positivity for CK 7, cytokeratin 8 (CAM 5.2), MOC-31 (Epi-CAM), AR, and GATA3, while they tested negative for ER, PR, and Her 2. Notably, the absence of ER and PR expression is a distinguishing characteristic that sets SRCHC apart from other metastatic breast cancers, as ER and PR are often positive in male breast cancer [19]. Additionally, our case, like others with SRCHC, displayed a loss of E-cadherin, a pivotal regulator of tissue homeostasis governing multiple cellular functions and development [20]. Hence, an immunohistological approach is imperative for an accurate diagnosis.

Table 3 represents four cases, including our own, all of which underwent next-generation sequencing analysis. The analysis revealed PIK3CA mutations in all four cases. In our case, we identified PIK3CA mutations, TP53 mutations, and CDH1 frameshift mutations. Notably, prior to our case, only one case in the table exhibited a TP53 mutation. Furthermore, when comparing our case to another case with a PIK3CA mutation characterized as E545K, our case exhibited a distinct PIK3CA mutation, specifically R88Q. Mutations in the p110α subunit of PI3K, called PIK3CA, are found in a variety of cancers and play a role in promoting carcinoma formation and cancer progression [21]. The TP53 mutation is localized in the region encoding the DNA binding domain of p53. p53 plays an essential role in causing senescence, which may be an important mechanism for the

Table 2: Clinicopathological features and genetic analysis of primary signet-ring cell/histiocytoid carcinoma of the axilla.

Case No.	Age	Gender	Histopathological findings	Immunohistochemical findings	Reference
1	85	Male	Signet-ring cells and histiocytoid cells	Cytokeratin 7 (+, 11/11) Cytokeratin 19 (+, 5/5) Cytokeratin 20 (-, 0/4) P63 (-, 0/11) MUC1 (+, 10/10) MUC2 (-, 0/10) MUC5AC (+, 11/11) MUC6 (+-, 4/11) BerEP4 (+, 8/8) E-cadherin (+-, 8/11) GCDFP15 (+, 11/11) Mammoglobin (+-, 9/11) GATA3 (+, 10/11) Oestrogen receptor (-, 0/11) Progesterone receptor (-, 0/11) Androgen receptor (+, 11/11)	Goto et al. [3]*
2	81	Male	Signet-ring cells and histiocytoid cells Tubular pattern		Goto et al. [3]
3	81	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
4	72	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
5	53	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
6	88	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
7	81	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
8	64	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
9	80	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
10	74	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
11	77	Male	Signet-ring cells and histiocytoid cells		Goto et al. [3]
12	85	Male	Single cells cord histiocytoid cells signet-ring cells	Cytoeratin 7(+) Cytokeratin 20(-) GCDFP-15(a few+) GATA3 (+) AR(+) ER(-) PR(-)	Ito et al. [4]
13	71	Male	Signet-ring cells and histiocytoid cells	Cytokeratin 7(+) Cytokeratin 20(-) GATA3 (+) GCDFP-15 (+) AR(+) E-cadherin(+) ER(-) PR(-) HER2(-)	Berdugo et al. [5]
14	58	Male	Signet-ring cells and histiocytoid cells	Cytokeratin 7(+) Cytokeratin 19 (+) GATA3 (+) GCDFP-15 (+) Cytokeratin 20(-) AR(+) E-cadherin(+) ER(-) PR(-)	Philips et al. [6]
15	63	Male	Individual and small cords of tumor cells signet-ring cells	Cytokeratin 7(+) GCDFP-15 (+) ER(-) PR(-)	Droubi et al. [7]
16	61	Male	Single-file pattern histiocytoid cells signet-ring cells	Cytokeratin 7(+) Keratin 20(-) GCDFP-15 (+) ER(-) PR(-)	Ishida et al. [8]
17	59	Male	Trabecular pattern histiocytoid cells	Cytokeratin 7(+) Cytokeratin 20(-) GCDFP-15 (+) ER(-) PR(-)	Miyake et al. [9]
18	55	Male	Single-file pattern histiocytoid cells pagetoid spread(+)	Cytokeratin 7(+) GCDFP-15 (+) ER(-) PR(-)	Misago et al. [10]
19	55	Male	Signet-ring cells and histiocytoid cells	ND	Pai et al. [11]
20	71	Male	Reminiscent of invasive lobular carcinoma	Cytokeratin 7(+) Cytokeratin 20(+) GCDFP-15 (-), ER(+) PR(+)	Zelger et al. [12]
21	62	Male	Trabecular pattern signet-ring cells	Cytokeratin 20(+) GCDFP-15 (+)	Kiyohara et al. [13]
22	74	Male	Single-file pattern signet-ring cells	GCDFP-15 (+)	Kuno et al. [14]
23	59	Male	Single-file pattern signet-ring cells	Cytokeratin 20(-) GCDFP-15 (+)	Kuno et al. [15]
24	68	Female	Signet-ring cells	GCDFP-15 (+)	Kuno et al. [15]
25	42	Male	Pagetoid spread(+), signet-ring cells histiocytoid cells	GCDFP-15 (+)	Cameselle et al. [16]
Present case	55	Male	Signet-ring cells histiocytoid cells	Cytokeratin 7(+) GATA3 (+) AR(+) ER(-) PR(-)	

ND: Not Described

*The following references do not show immunohistochemical findings for individual cases, so the results are combined into one

Table 3: Genetic alterations detected in axillary signet-ring cell/histiocytoid carcinoma.

Case No	Age	Gender	Gene	Alteration	Reference
1	85	Male	PIK3CA	E545K	Goto et al. [3]
			TP53	E336X	
			TP53	E285K	
4	72	Male	PIK3CA	E545K	Goto et al. [3]
13	71	Male	PIK3CA	E545K	Ito et al. [4]
Present case	55	Male	PIK3CA	R88Q	
			CDH1	c1570_1574	
			TP53	R110L	

antitumor effects of agents that inhibit CDK4 or CDK6 [22]. Studies have shown that PIK3CA and TP53 mutations are the most frequent mutations found in skin adnexal cancers [23,24]. The frameshift mutation of the CDH1 gene also identified in our case. Loss-of-function mutations targeting CDH1 are known to cause a lack of cell-cell cohesion, which is often associated with tumor invasion and metastasis in several tumors [4,20,22].

Due to the rarity of this cancer, there are currently no established universal treatment guidelines. Treatment has primarily been empirically based, typically involving surgical intervention, radiation therapy when necessary, and adjuvant chemotherapy, although definitive protocols have yet to be established [3-16]. A comprehensive summary of the treatment approaches for all reported cases of axillary SRCHC is provided in Table 2.

In conclusion, our comprehensive analysis confirms the diagnosis of SRCHC in this case. Accurate diagnosis of SRCHC requires a meticulous and comprehensive evaluation encompassing clinical examination, imaging studies, and immunohistopathology. Additionally, establishing a genetic link to SRCHC remains challenging. Our report contributes valuable insights to the understanding of this rare cancer, facilitating further investigations.

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