Histol Histopathol (2025) 40: 911-917

Histology and Histopathology
From Cell Biology to Tissue Engineering

ORIGINAL ARTICLE Open Access

Clinicopathological diagnosis of axillary signet-ring cell-like/histiocytoid carcinoma: A case report and literature review

Ling Zhang, Li Li, Yun Wang and Xiao ling Wang

Department of Pathology, Guang'an Men Hospital, China Academy of Chinese Medical Sciences, Beijing, PR China

Summary. Objective. To explore the clinicopathological and morphological characteristics, diagnosis, differential diagnosis, treatment, and prognosis of primary signet-ring cell/histiocytoid carcinoma (SRCHC) of the axilla.

Methods. The clinical manifestations, pathomorphological characteristics, and immunohistochemical staining results of a case of primary SRCHC in the axilla were retrospectively analyzed, and the relevant literature was reviewed.

Results. The patient was a 69-year-old male. Subcutaneous gray-white nodules with unclear boundaries were visible. Microscopic examination: The tumor was located in the dermis and subcutaneous tissue. The tumor cells were arranged in a cord-like, soldier-like, or nest-like shape, with mild to moderate atypia. Some cells had obvious nucleoli. The tumor cytoplasm was eosinophilic, and mucoid material inside and outside the cells could be seen, showing a signet-ring-like or histiocytoid appearance. Immunohistochemical staining was positive for GCDFP-15, CK7, E-cadherin, AR, P120, GATA3 and negative for Villin, S-100, CK20, SMA, P63, CD68, TTF-1, NapsinA, ER, PR, and Ki-67 proliferation index (8%), HER2(2+) and FISH(-). The special staining AB-PAS (AB+,PAS-).

Conclusion. Cutaneous axillary primary SRCHC is extremely rare and highly invasive and needs to be differentiated from a variety of metastatic tumors (breast, digestive system, lung, etc.).

Key words: Axilla, Signet ring cell-like/histiocytoid, Primary

Introduction

Cutaneous primary signet-ring cell/histiocytoid carcinoma (SRCHC) is an extremely rare adnexal tumor that mostly occurs in the eyelids; there are also a few reports of it occurring in the axilla (Cameselle et al., 1997; Kuno et al., 1999a,b; Swinson et al., 2006; Mortensen et al., 2008). The tumor develops mostly in elderly men, and the typical clinical manifestation is progressive painless swelling. The tumor cells show a signet-ring cell-like or histiocytoid appearance and diffuse infiltration into the dermis and subcutis, without epidermal involvement. Because its histopathological morphology is similar to signet ring cell cancer derived from the breast or stomach, it is often misdiagnosed as metastatic cancer (Requena et al., 2011). This article reports a case of primary axillary SRCHC combined with the relevant literature; its clinical pathological characteristics, diagnosis, and differential diagnosis are analyzed.

Corresponding Author: Li Li, Department of Pathology, Guang'an Men Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, PR China. e-mail: fliml@163.com

www.hh.um.es. DOI: 10.14670/HH-18-828

Materials and methods

Clinical data

The patient was a 69-year-old male. Two years ago, he noticed a painless mass in his left armpit but did not pay much attention to it. Two years later, he realized that the mass was larger than before, so he came to the hospital to have it removed.

Methods

The specimens were fixed with 10% buffered formalin and embedded in conventional paraffin. Sections of 3 μm thickness were cut and stained with hematoxylin-eosin (HE) and observed under a light microscope.

Immunohistochemical staining (IHC) used the EnVision method, with antibodies AE1/AE3, CD68, CK20, S-100, CK7, Villin, P63, SMA, GCDFP-15, NapsinA, TTF-1, E-cadherin, AR, and GATA3 and the kit was purchased from Beijing Zhongshan Jinqiao Biotechnology Co., Ltd. The operation was performed with the BOND-MAX fully automatic immunohistochemistry machine of the LEICA Company. ER, PR, and

HER-2 were used as an automated stainer for immunostaining (Ventana Medical Systems, Bench Mark ULTRA). Each antibody was equipped with positive and negative controls. Alcian blue (PH2.5)-periodic acid-Schiff (Di AB-PAS) reagent was purchased from Zhuhai Beso Biotechnology Co., Ltd.

Results

Gross examination: one piece of skin tissue, size 1.8x0.9x0.7 cm, skin area 1.8x0.9 cm, contained a nodule under the skin on the cut surface, size 1.3x0.7x0.7 cm, which was gray-white, moderate texture, and with an invasive boundary.

Microscopic examination: The tumor tissue was mainly located in the dermis and subcutaneous tissue, with small to medium-sized cells growing infiltratively. The cells were arranged in cords and small nests, with mild to moderate atypia, and some cells had obvious nucleoli (Fig. 1A-C); the cytoplasm of the tumor cells was eosinophilic, and mucoid material inside and outside the cells could be seen, and some were signet-ring-like or histiocytoid in appearance (Fig. 1D-F). Immunohistochemical staining: tumor cells GCDFP-15 (+), CK7 (+), E-cadherin (+), ER (-), PR (-), AR (+), GATA3 (+), S-100 (-), P120 (+), HER2 (2+) and FISH(-), P63 (-), and the rest (CK20, SMA, CD68, NapsinA, and TTF-1) were negative, with a Ki-67 proliferation index of 8%. The special staining AB-PAS (PAS-, AB+) indicates that the cytoplasm of the tumor cells contains acidic mucoid material (Fig. 2A-L).

No tumors were found in the patient's breast, digestive system, lungs, or other parts. Because the surgeon thought the tumor was benign before the first operation, the simple mass was removed. Due to positive margins on the final permanent sections, the patient attended another hospital for further treatment. Further wide resection and axillary lymph node dissection were performed a month later. Postoperative pathology showed axillary lymph node metastasis (12/21). Chemotherapy and radiotherapy were performed a month later. The patient was followed up for two years, and no recurrence or metastasis was found.

Discussion

Primary cutaneous SRCHC literature is scarce, consisting mostly of case reports. Rosen et al. reported the first case of SRCHC originating in the eyelids in 1975 (Rosen et al., 1975). Cameselle-Teijeiro et al. (1997) reported the first case of SRCHC occurring in the axilla1. SRCHC was recently proposed in the 2018 version of the World Health Organization classification of skin tumors (Kazakov et al., 2018). It often occurs in the eyelids of elderly men. Some studies believe that it originates from the Moll glands of the eyelids (Iwaya et al., 2012). Axillary SRCHC is rare and may originate from the apocrine glands.

We searched the foreign literature and found a total of 48 reports of 80 cases, including 55 cases on the eyelids and 25 in the axilla. The clinical and pathological characteristics of 25 cases of axillary SRCHC are

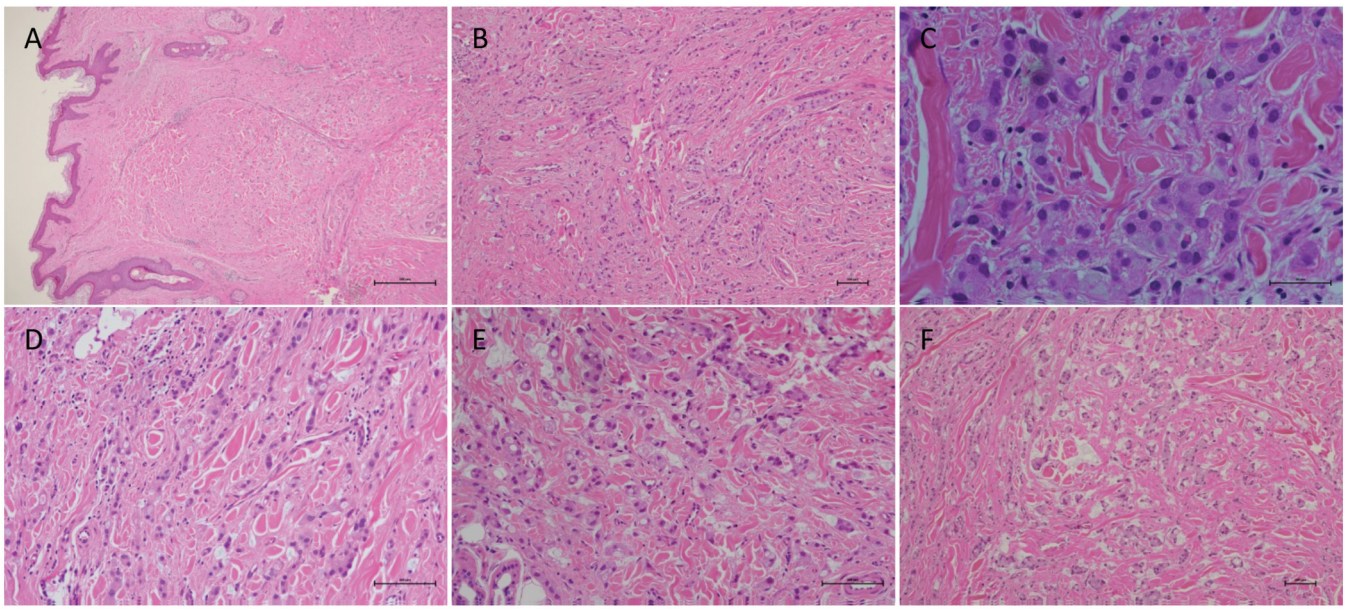

Fig. 1. Histopathological findings of signet-ring cell/histiocytoid carcinoma (SRCHC). **A.** Tumor is located in the dermis and subcutaneous tissue. **B.** Tumor cells grow invasively and are arranged in the form of nests or cords. **C.** The nuclei of tumor cells are obvious. **D.** Tumor cells are eosinophilic and the nucleus is round or oval. **E.** Tumor cells are signet-ring-like or histiocytoid in appearance, and intracellular mucoid material can be seen. **F.** Extracellular mucoid material can be seen. (HE). A, x 40; B, F, x 100; C, x 400; D, E, x 200.

summarized as follows (Table 1).

Clinical characteristics

Cutaneous axillary primary SRCHC is more likely to occur in older men, with a male-to-female ratio of 24:1, and the onset age is 55-88 years; only one patient was 42 years old, which is relatively young. The clinical manifestations are mostly painless, slow-growing subcutaneous nodules or plaques in the axilla, which can sometimes grow to more than 10 cm.

Pathological characteristics

Cutaneous SRCHC cancer tissue diffusely infiltrates into the dermis and subcutaneous tissue, and some are arranged like soldiers. These cancer cells are histiocyte-like, foamy, or granular with eosinophilic cytoplasm, not involving the epidermis, and have no surrounding fibrous connective tissue reaction. Under high magnification, intracytoplasmic vacuoles, a few signet-ring-like cells, and crescent-shaped nuclei can be seen; mitotic figures are rare (Palakkamanil et al., 2020). This

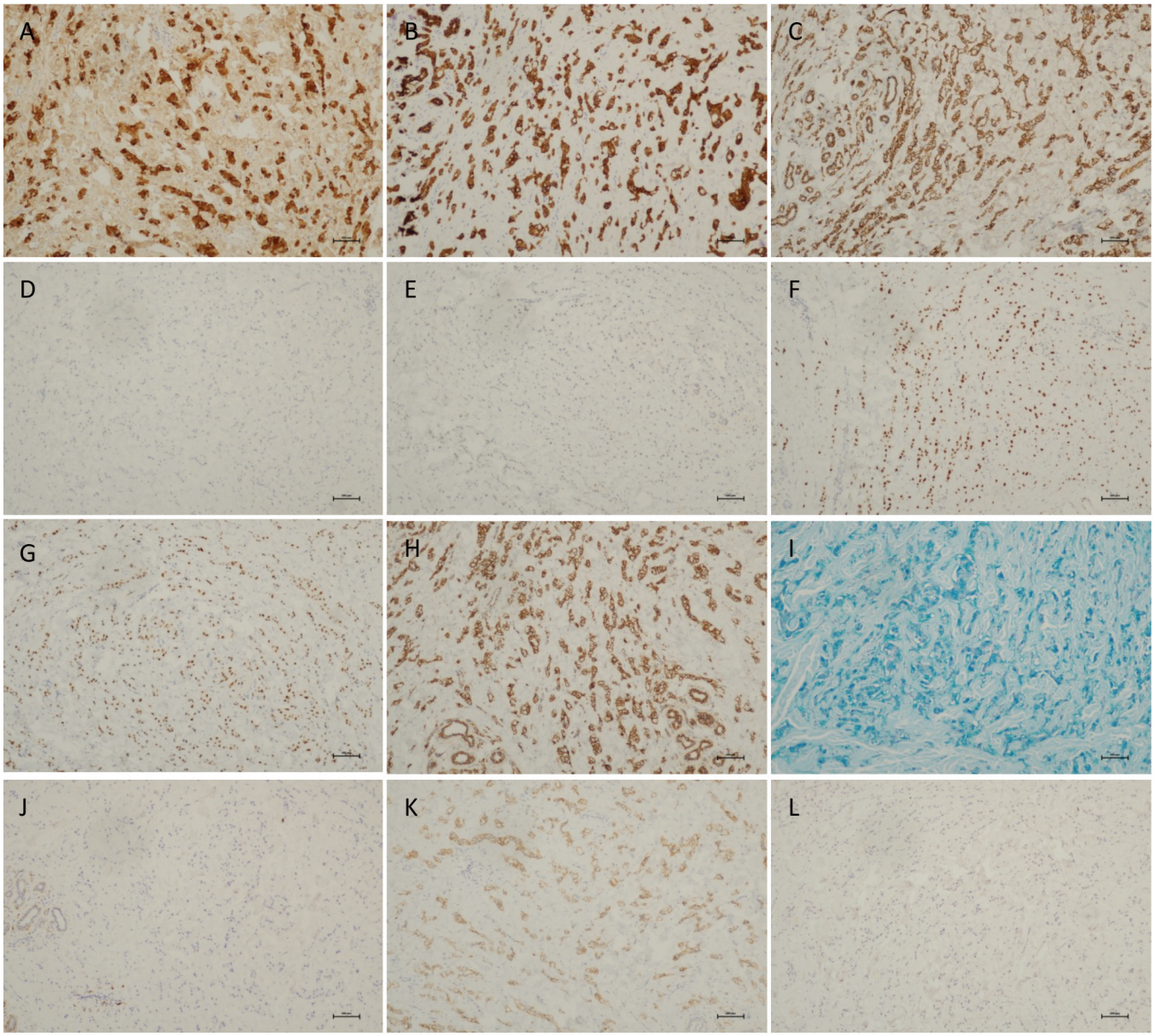

Fig. 2. A. IHC with GCDFP-15 (+). **B.** IHC with CK7 (+). **C.** IHC with E-cadherin (+). **D.** IHC with ER (-). **E.** IHC with PR (-). **F.** IHC with AR (+). **G.** IHC with GATA3(+). **H.** IHC with P120 (+). **I.** Special dyeing AB-PAS (AB+, PAS-) indicates that the cytoplasm of the tumor cells contains acidic mucoid material. **J.** IHC with S-100 (-). **K.** IHC with HER2 (2+). **L.** IHC with P63(-). A-G, I, J, L, x 100; H, K, x 200.

article reports a case of SRCHC whose pathological morphology is consistent with the literature reports.

The immune phenotype is diverse, it is positive for AE1/AE3, CK7, GCDFP-15, AR, E-cadherin, and GATA3, and negative for CK20, TTF-1, P63, CDX2, S-100, and PAX-8 (Goto et al., 2021). AR was first used by Sakamoto et al. (2017). who reported SRCHC of the eyelids, and the results were positive. GATA3 first tested positive when Palakkamanil et al. (2020) reported it. This article reports a case of axillary SRCHC, where AR and GATA3 were positive, which is consistent with the above literature reports.

Differential diagnosis

The diagnosis of primary SRCHC of the skin is difficult and needs to be differentiated from other metastatic adenocarcinomas. The most important differentiation is from invasive lobular carcinoma (ILC) of the breast because the tissue morphology of the two is very similar, such as histiocytoid cells arranged like soldiers. There are also similarities in immune pheno-

Table 1. Clinical and pathological characteristics.

Case No	Gender	Age	Histopathological features	Immunohistochemical features and specialdyeing	Treatment	Metastasis	Outcome	Reference
1	male	42	Signet-ring cell-like or histiocytoid appearance cells were arranged isolated or small clusters or striped or single rows and infiltrated in th dermis and subcutaneous tissue.	EMA (+), CEA (+), GCDFP-15 (+)	Surgery and radiation	Axillary lymph nodes	AWD, 5 Years	Cameselle-Teijeiro et al., 1997
2	male	59	Signet-ring cell-like or large eosinophilic cells were arranged isolated or small clusters or striped or single rows.Intracellular mucus was seen.	CK (+), GCDFP-15 (+), lysozyme (+), CK20 (-), S-100 (-)	Surgery	None	AWD, 8 months	Kuno et al., 1999a,b
3	Female	68	Numerous signet-ring cell-like cells were occasionally arranged in a file.	CK (+), GCDFP-15 (+), lysozyme (+)	Surgery	None	None	Kuno et al., 1999a,b
4	male	74	Tumor cells were polygonally shaped and had eosinophilic vacuolated cytoplasm with round or oval nuvlei and often arranged in a single.file.There were occasional siget ring cells.	CK(+), GCDFP-15 (+), lysozyme (+), S-100 (-), PSA (-)	Surgery and radiation and chemotherapy	Axillary lymph nodes	Died of unrelated cause, 2 years	Kuno et al., 1999a,b
5	male	62	The tumor cells were composed of atypical cells with abundanteosinophilic,vacuolated cytoplasms.Occasional signet ring cells were also seen.The tumor cells were scattered singly,in groups of several cells,or arranged in single file among collagen fibers,presenting a trabecular pattern.	GCDFP-15 (+),CEA (weak+), CK34βE12 (weak+), CEA (weak+), CA125 (weak+), CK20 (weak+), S-100 (-)	Surgery and chemotherapy	Axillary lymph nodes	Died of unrelated cause, 9 months	Kiyohara et al., 2006
6	male	71	The growth pattern focally showed small roud to oval nests.And some tuomr cells were arranged in columns.	EMA (+),CEA (+), CK7 (+), CK20 (+), ER (+), PR (+), PAS (+), p63 (-), CK5/6 (-),SMA (-), Ecadherin (-)	Surgery	None	AWD, 3 years	Zelger et al., 2008
7	male	55	Cytology demonstrated a highly cellular neoplasm made up of malingnant cells arranged in small clusters and singly dispersed.Cells had intracytoplasmic mucin vacuole with targetoid mucin blobs in some.	PAS (+)	Surgery	None	AWD with Recurrence and Axillary lymph nodes metastasis, 1 months	Pai et al., 2006
8	male	55	Tumor cells were characteristic of histiocytoid cells.Tumor cells were arranged in cords and small islands or formed a single-file pattein,sometimes forming an intracellular lumen.	CK7 (+), GCDFP-15 (+), HER-2 (2+), p63 (-), CK20 (-), Ecadherin (-), MART-1 (-), CD68 (-), ER (-), PR (-)	Surgery and chemotherapy and Targeted to HER-2	Axillary lymph nodes	AWD, 1 years	Misago et al., 2011
9	male	59	Histiocytoid-like cells cells. Trabecular. occasionally signet-ring like cells	AB-PAS (+), AE1/AE3 (+), CK7 (+), GCDFP-15 (+), S-100 (-), ER (-), PR (-), CK20 (-), p63 (-), HER-2 (3+)	Surgery and radiation and Targeted to HER-2	Axillary lymph nodes	AWD, 14 months	Miyake et al, 2012

type. For example, CK7, GCDFFP-15, and HER-2 can all be expressed, but ILC is often positive for ER and PR, while skin SRCHC is negative for ER and PR (Misago et al., 2011). E-cadherin is positive in this article, but reviewing 25 cases of axillary SRCHC in the literature, we found seven negative cases and only nine were positive. Past literature studies have also shown that ILC lacks E-cadherin expression and frequently shows diffuse expression of ER and PR (Skotnicki et al., 2012; Shin et al., 2019). Thus, immunohistochemistry for ER, PR, and E-cadherin would be useful to distinguish SRCHC of the skin from ILC. There are reports in the literature that skin SRCHC P63 positivity can be distinguished from breast cancer (Philips et al., 2017). The case reported in this article was P63-negative, which was different from the above literature but consistent with the cases reported by (Ishida and Okabe, 2013).

Metastatic tumors, including those originating from the lung, gastrointestinal tract, prostate, and urinary system, also need to be differentiated from primary SRCHC of the skin. 1: Metastatic lung adenocarcinoma is mostly moderately differentiated, with mucoid material in the cytoplasm, and glandular differentiation at least focally, and is generally positive for CK7, TTF-1, and NapsinA. The tumor reported in this article was signet-ring-like or histiocytoid, glandular differentiation was not found and TTF-1 and NapsinA were negative.

Table 1. (Continued).

10	male	61	Histiocytoid-like cells cells. large oval to round cells, single nucleols, eosinophilic cytoplasm. isolated, private-like, occasional mucus in the cytoplasm	CK7 (+), GCDFP-15 (+), HER-2 (3+), CK20 (-), p63 (-), Ecadherin (-), CD68 (-), ER (-), PR (-), CD56 (-), Syn (-), CgA (70% cell+)	Surgery	Axillary lymph nodes	AWD, 43 months	Ishida et al., 2013
11	male	63	Signet ring or Histological cell-like cells.Mild atypical cells, rich in cytoplasm, round to oval nucleus.isolated or small clustered.	CK (+), GCDFP-15 (+), CK7 (+), AR (+), HER-2 (2+) FISH (-), ER (-), PR (-), p63 (-), CK5/6 (-), TTF1 (-), CD68 (-), S-100 (-), CK20 (-), PSA (-)	Surgery and radiation	Axillary lymph nodes	Recurrence twice in 3 months, and there is no follow-up record after that.	Droubi et al., 2013
12	male	71	Tumor cells had an abundant granular and eosinophilic cytoplasm and nuclear atypia was mild.Many foci of signet ring and histiocytoid.These cells were arranged cords,sheets and single files.	CK7 (+), GATA3 (+), GCDFP-15 (+), AR (+), E-cadherin (+), ER (-), PR (-), HER2 (-), CK20 (-), TTF1 (-), PSA (-)	Surgery	lymph nodes, Bone	Died, 15 months	Berdugo et al., 2017
13	male	58	Tumor cells showed single filing or diffuse sheets.Tumor cells were characterized by a histiocytoid appearance with mild pleiomorphism,Signet ring cells were also seen.	CK7 (+), CK5/6 (+), P63 (+), GATA3 (+), GCDFP-15 (+), HER2 (3+), TTF1 (-), CDX2 (-), E-cadherin (-), ER (-), PR (-), mammaglobin (-)	radiation and chemotherapy	lymph nodes, Bone, liver	None	Philips et al. 2017
14	male	85	Tumor cells were organized in the form of single cells and/or cords.Tumor cells were characteristic histopathological features of the histiocytoid appearance.And signet-ring cells also could be seen.	CK7 (+), GCDFP-15 (few cells+), GATA3 (+), AR (+), CK20 (-), ER (-), PR (-)	chemotherapy	the left subclavicular lymph nodes	AWD, 1 years	Ito et al., 2021
15	male	53-88	Signet-ring/histiocytoid-like cells were seen.Mild nuclear atypical (4/11). Moderate nuclear atypical (7/11). Small tubular structure were seen (2/11). Intraductal tumor or intraglandular tumor components were seen (4/11). Apocrine gland hyperplasia was seen. (1/11)	CK7 (+), CK19 (+), AR (+), GCDFP-15 (+), GATA3 (+), P63 (-), ER (-), PR (-), TTF-1 (-), CDX2 (-) in 11 case. E-cadherin (-) in 3 case. HER2 (3+) in 1 case.	Surgery and radiation and chemotherapy (2/11), Surgery and radiation (4/11), Surgery (3/11), radiation and chemotherapy (1/11), chemotherapy (1/11)	Lymph node metastasis (8/11). Distance transfer (5/11)	2 case died. 9 case alive. 3 months-13 years and 5 months.	Goto et al., 2021

AWD, Alive without disease; CK, Cytokeratin;ER,Estrogen receptor; GCDFP-15, Gross cystic disease fluid protein-15; HER2, Human epidermal growth factor receptor 2; PR, Progesterone receptor; AR, Androgen receptor.

The most important point was that there was no tumor in the lungs. 2: Metastatic colorectal cancer poorly differentiated from adenocarcinoma (including signet-ring cell carcinoma), with obvious nuclear atypia, neutrophil infiltration, and focal tumor necrosis in the cancer nest, may be positive for CK7 but negative for GCDFP-15 and P63. 3: Prostate cancer rarely metastasizes to the skin and is PSA positive. 4: Urothelial carcinoma expresses CK7 and p63, but is often negative for GCDFP-15 and HER-2 (Saeed et al., 2004).

Molecular profiling

Genotyping of axillary SRCHC was performed for the first time by Ito et al. in 2020 and found that there is a *PIK3CA* mutation (c1633G>A) but no *CDH1* gene mutation was detected, which overlaps and is different from breast ILC (Ciriello et al., 2015). Ciriello et al. (2015) reported that breast ILC cases were significantly enriched for *CDH1* mutations (63%), and *PIK3CA* mutations were found (48%) in 127 ILC cases. Goto et al. (2017) reported 11 cases of SRCHC and molecular testing of three cases found *PIK3CA* and *P53* mutations but no *CDH1* mutations. The first documented genetic analysis of eyelid SRCHC by Raghavan et al. (2020) detected mutations in *NTRK3*, *CDKN1B*, and *PIK3CA*. Six cases of palpebral SRCHC and three of axillary SRCHC were screened for genomic alterations. *PIK3AC* (3q26.32) mutations were detected in all cases (Michalek et al., 2023).

Clinical treatment

The treatment of SRCHC mainly involves extensive local excision and lymph node dissection, supplemented by chemotherapy. If there is metastasis of axillary lymph nodes, radiotherapy can be added. Because some tumors express ER, PR, and HER2, endocrine therapy and HER2-targeted therapy have been reported in the literature (Miyake et al., 2012). Androgen receptor-targeted hormonal therapy could also be a promising marker for both diagnostic and eventually therapeutic purposes (Piris et al., 2014). An *NTRK3* mutation may have therapeutic relevance (Raghavan et al., 2020). PIK3CA mutations constitute possible therapeutic targets (Michalek et al., 2023). However, due to the small number of reported cases, there is a lack of data to prove the effectiveness of these treatments (Berdugo et al., 2017); thus, more work will need to be conducted to determine whether such therapies would influence patient survival.

Prognosis

The literature reports suggest that SRCHC occurring on the eyelids is more invasive than in the axilla (Cameselle et al., 1997; Kuno et al., 1999; Requena et al., 2011). However, Goto et al. (2021) found that axillary SRCHC had a higher lymph node metastasis rate than that in the eyelid [8/11 (73%) vs. 1/4 (25%)], even if the tumors in the eyelid cases were larger. The distant metastasis rates were similar [5/11 (45%) vs. 2/4 (50%)]. Ito et al. (2021) reviewed 11 cases of axillary SRCHC reported in the literature and found that seven cases had lymph node metastasis. No deaths were seen in any of the cases after 8 months to 5 years of follow-up, suggesting that the prognosis of this tumor is not poor. However, Berdugo et al. (2017) reported a case of cutaneous apocrine carcinoma with *in situ* components and histiocytic/signet-ring cell-like cells, where bone metastasis occurred and the patient died after 15 months of follow-up, suggesting that occasionally this tumor has a poor prognosis. A patient with SRCHC reported in this article was followed up for two years, and no recurrence or metastasis was found.

Summary

There are few reports of cutaneous primary SRCHC at home and abroad. It is more likely to occur in older men. Pathological diagnosis needs to be differentiated from a variety of metastatic tumors. At present, immunohistochemical staining is mainly relied on to assist in diagnosis. Individual cases underwent molecular testing. Treatment experience for such patients was insufficient, thus more cases need to be collected for further study of molecular genetics, tumor prognosis, and selection of the treatment plan.

References

Berdugo J., Dumont-Mackay V., Brissy-Lachery S., Leclerc Y.E., Doyon J., Mitchell A., Petrella T. and Désy D. (2017). Cutaneous apocrine carcinoma with an *in situ* component and histiocytoid and signet-ring cells. Am. J. Dermatopathol. 39, e76-e78.

Cameselle-Teijeiro.J., Alfonsín B.N., Allegue F. and Caeiro M. (1997). Apocrine carcinoma with signet ring cells and histio-cytoid features. A potentially confusing axillary tumor. Pathol. Res. Pract. 193, 721-722.

Ciriello G., Gatza M.L., Beck A.H., Wilkerson M.D., Rhie S.K., Pastore A., Zhang H., McLellan M., Yau C., Kandoth C., Bowlby R., Shen H., Hayat S., Fieldhouse R., Lester S.C., Tse G.M.K., Factor R.E., Collins L.C., Allison K.H., Chen Y.-Y., Jensen K., Johnson N.B., Oesterreich S., Mills G.B., Cherniack A.D., Robertson G., Benz C., Sander C., Laird P.W., Hoadley K.A., King T.A., TCGA Research Network and Perou C.M. (2015). Comprehensive molecular portraits of invasive lobular breast cancer. Cell 163, 506-519.

Droubi D., Zeitouni N.C., Skitzki J. and Bogner P.N. (2013). Primary signet-ring cell carcinoma of the axilla. J. Cutan. Pathol. 40, 269-273.

Goto K., Kukita Y., Honma K., Ogawa K., Nishida H., Takai T., Oishi T., Hishima T., Tanaka M. and Isei T. (2021). Signet-ring cell/histiocytoid carcinoma of the axilla: a clinicopathological and genetic analysis of 11 cases, review of the literature, and comparison with potentially related tumours. Histopathology 79, 926-939.

Ishida M. and Okabe H. (2013). Primary signet-ring cell/histiocytoid

carcinoma ofthe axilla. Pathol. Int. 63, 374-376.

Ito Y., Ishida M., Ohe C., Miyasaka C. and Tsuta K. (2021). Signet-ring cell/histiocytoid carcinoma in the axilla: A case report with genetic analysis using next-generation sequencing. J. Cutan. Pathol. 48, 102-105.

Iwaya M., Uehara T., Yoshizawa A., Kobayashi Y., Momose M., Honda T. and Ota H. (2012). A case of primary signet-ring cell/histiocytoid carcinoma of the eyelid: immunohistochemical comparison with the normal sweat gland and review of the literature. Am. J. Dermatopathol. 34, e139-e145.

Kazakov D.V., Brenn T., Kutzner H., Requena L. and Sangueza O.P. (2018). Signet-ring cell/histiocytoid carcinoma. World Health Organization classification of skin tumours. Lyon. IARC Press. p 182.

Kiyohara T., Kumakiri M., Kouraba S., Tokuriki A. and Ansai S. (2006). Primary cutaneous signet ring cell carcinoma expressing cytokeratin 20 immunoreactivity. J. Am. Acad. Dermatol. 2006 54, 532-536.

Kuno Y., Numata T. and Kanzaki T. (1999a). Adenocarcinoma with signet ring cells of the axilla showing apocrine features:a case report. Am. J. Dermatopathol. 21, 37-41.

Kuno Y., Tsuji T. and Yamamoto K. (1999b). Adenocarcinoma with signet ring cells of the axilla: two case reports and review of the literature. J. Dermatol. 26, 390-395.

Michalek I.M., Dos Santos F.L.C., Zwolinski J. Olszewski W., Gałazka A., Prochorec-Sobieszek M. and Durzynska M. (2023). Signet-Ring Cell/Histiocytoid carcinoma: report of two cases and systematic review of the literature on the epidemiology, clinical characteristics, and pathological and molecular findings. Am. J. Dermatopathol. 45, 626-630.

Misago N., Shinoda Y., Okawa T., Aoki S., Toda S., Koike K. and Narisawa Y. (2011). Histiocytoid and signet-ring cell carcinoma of theaxilla: a type of cutaneous apocrine carcinoma equivalent to histiocytoid lobular carcinoma ofthe breast?. Clin. Exp. Dermatol. 36, 874-877.

Miyake T., Yamasaki O., Sugiu M., Hamada T., Otsuka M., Yanai H., Morishita Y. and Iwatsuki K. (2012). Primary signet-ring cell/histiocytoid carcinoma of the axilla expressing human epidermal growth factor receptor 2. J. Dermatol. 39, 1038-1040.

Mortensen A.L., Heegaard S., Clemmensen O. and Prause J.U. (2008). Signet ring cell carcinoma of the eyelid - the monocle tumour. APMIS 116, 326-332.

Pai R.R., Kini R.J., Achar C., Rau A. and Kini H. (2008). Apocrine (cutaneous) sweat gland carcinoma of axilla with signet ring cells: a diagnostic dilemma on fine-needle aspiration cytology. Diagn. Cytopathol. 36, 739-741.

Palakkamanil M.M., Mahmood M.N. and Chan A. (2020). Diagnostic and treatment challenges of a case of primary cutaneous signet-ring cell/histiocytoid carcinoma of the eyelid. BMC Ophthalmol. 20, 410.

Philips R., Langston L., Hwang H., Vandergriff T., Trynosky T. and Berlingeri-Ramos A.C. (2017). Primary cutaneous histiocytoid carcinoma with distant metastasis. J. Cutan. Pathol. 44, 376-380.

Piris A., Peng Y., Boussahmain C., Essary L.R., Gudewicz T.M. and Hoang M.P. (2014). Cutaneous and mammary apocrine carcinomas have different immunoprofiles. Hum. Pathol. 45, 320-326.

Raghavan S.S., Clark M., Louie C.Y., Jensen K.C., Dietrich B., Beadle B.M., El-Sawy T., Baik F., Kunder C.A. and Brown R.A. (2020). Molecular profiling of a primary cutaneous signet-ring cell/ histiocytoid carcinoma of the eyelid. J. Cutan. Pathol. 47, 860-864.

Requena L., Prieto V.G., Requena C., Sarasa J.L., Manzano R., Seco M., Rütten A., Kazakov D.V., Cerroni L. and Kutzner H. (2011). Primary signet-ringcell/histiocytoid carcinoma of the eyelid: a clinicopathologicstudy of 5 cases and review of the literature. Am. J. Surg. Pathol. 35, 378-391.

Rosen Y., Kim B. and Yermakov V.A. (1975). Eccrine sweat gland tumor ofclear cell origin involving the eyelids. Cancer 36, 1034-1041.

Saeed S., Keehn C.A. and Morgan M.B. (2004). Cutaneous metastasis: a clinical, pathological and immunohistochemical appraisal. J. Cutan. Pathol. 31, 419-430.

Sakamoto K., Ito T., Tanioka F., Fukamizu H. and Tokura Y. (2017). Primary signet-ring cell/histiocytoid carcinoma of the eyelid expressing androgen receptors andtreated with bicalutamide. J. Dermatol. 44, e230-e231.

Shin S.J., Desmedt C., Kristiansen G., Reis-Filho J.S and Sasano H. (2019). Invasive lobular carcinoma. In WHO Classification of Tumours. Breast tumours. 5th edn. IARC Press. Lyon. pp 114-118.

Skotnicki P., Ryś J., Blecharz P., Reinfuss M., Jakubowicz J., Ambicka A., Kruczak A. and Lackowska B. (2012). Invasive lobular carcinoma of the breast: cytometric and immunohistochemical characteristics of 96 cases. Pol. J. Pathol. 63, 112-120.

Swinson B., Ryan F., Barrett A.W., Jerjes W., Landon G., Calonje E. and Kalavrezos N. (2006). Histiocytoid eccrine sweat gland carcinoma of the eyelid: report of a case. Clin. Exp. Dermatol. 31, 786-789.

Zelger B.G., Stelzmueller I., Dunst K.M. and Zelger B. (2008). Solid apocrine carcinoma of the skin:report of a rare adnexal neoplasm mimicking lobular breast carcinoma. J. Cutan. Pathol. 35, 332-336.

Accepted October 4, 2024