Cutaneous metastasis of signet ring cell carcinoma from unknown origin.

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ABSTRACT:

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Cutaneous metastasis from signet ring cell carcinoma is uncommon. A 54-year-old Cambodian woman presented with a 4-month history of multiple painless nodules on her back. The biopsy revealed aggregations of signet ring cell in the dermis. Immunohistochemical staining can help differentiate the origin of signet ring cell carcinoma. Further investigations should be performed to identify the hidden tumor.

Key words: Cutaneous metastasis, Signet ring cell carcinoma

บทคัดย่อ:

จันทณัชธน์ วิทวัสชัยกุล วรพล เวชชาภินันท์ การแพร่กระจายของเซลล์มะเร็งชนิดคล้ายแหวน (SIGNET RING CELL CARCINOMA) มาที่ผิวหนัง (CUTANEOUS METASTASIS) โดยยังไม่ทราบอวัยวะต้นกำเนิด วารสารโรคผิวหนัง 2559; 32: 154-160.

สถาบันโรคผิวหนัง กระทรวงสาธารณสุข

การแพร่กระจายของเซลล์มะเร็งชนิดคล้ายแหวน (Signet ring cell carcinoma*)* มาที่ผิวหนัง (Cutaneous metastasis*)* พบได้ไม่บ่อย รายงานนี้เป็นการนำเสนอผู้ป่วยหญิงชาวกัมพูชาอายุ 54 ปี มาพบแพทย์ด้วยเรื่อง มีก้อนนูน ไม่เจ็บ หลายก้อน ที่บริเวณหลัง เป็นระยะเวลา 4 เดือน การตัดชิ้นเนื้อส่งตรวจทางพยาธิวิทยาพบ การรวมตัวกันของเซลล์มะเร็งชนิดคล้ายแหวนที่บริเวณชั้นหนังแท้ ซึ่งการส่งย้อมพิเศษชิ้นเนื้อทางอิมมูโนพยาธิวิทยา และการส่งตรวจทางห้องปฏิบัติการเพิ่มเติมจะสามารถนำไปสู่การวินิจฉัยมะเร็งต้นกำเนิดได้

คำสำคัญ: การแพร่กระจายของเซลล์มะเร็งมาที่ผิวหนัง, เซลล์มะเร็งชนิดคล้ายแหวน

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Introduction

About 10% of all visceral malignant tumors develop cutaneous metastases, which represent 2% of all skin tumors. Cutaneous metastases most frequently derive from carcinomas of breast, lung, colon, rectum, ovary, head, neck, kidney, and the gastrointestinal tract.

These skin metastases may be the first sign of an unknown malignancy. They usually present as asymptomatic nodules or plaques. Metastatic dissemination is largely via lymphatic vessels and less frequently via the blood stream (to liver, peritoneal cavity, lung, adrenal gland, and skin).

We describe a patient diagnosed with cutaneous metastasis of signet ring cell carcinoma from unknown origin.

Case report

A 54-year-old Cambodian woman presented with a 4-month history of multiple painless, erythematous lumps on her back. She denied any constitutional symptoms and weight loss. She could eat regularly and had no difficulty of swallowing. She had no fever, no chronic cough and never had any lumps like this before. No one in her family had cancer. The patient had a history of gastrectomy for three years with unknown reason due to the communication barrier.

On physical examination, there were multiple, painless, confluent, shiny, smooth-surfaced, erythematous, firm-to-rubbery consistency nodules on the left side of the back. Some similar lesions were scattered on the right side of the back, right cheek and left upper chest (Figure 1). Liver and spleen were not palpable. There was solitary, painless, smooth-surfaced, hard-consistency lymphadenopathy 0.5 cm in diameter on the left supraclavicular area. Complete blood count, renal function test, liver function test and urinalysis were within normal limit.

Figure 1. **1A** Multiple, painless, confluent, shiny, smooth-surfaced, erythematous nodules on the left side of the back (left) **1B** Close up view (right)

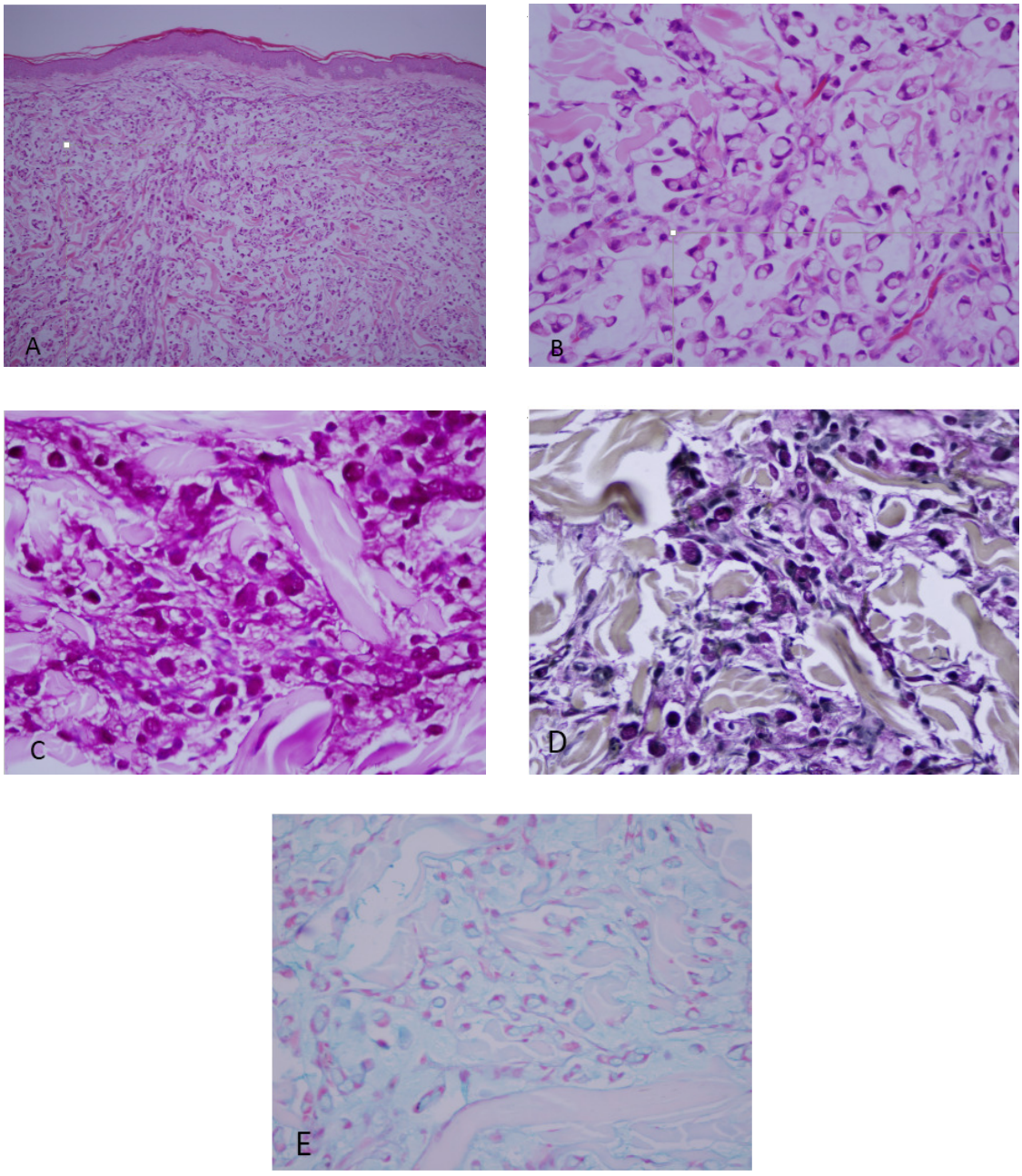

Figure 2 Skin biopsy from the back. **A** H&E stain (X100 เท่า). **B** H&E stain (X400 เท่า). **C,D,E** PAS, Mucicarmine and Alcian blue pH 2.5stains, respectively showed positive stain in the tumor cells.

Histopathological study reported multiple aggregations of atypical signet ring cells in the dermis without epidermal connection. Some of those arranged in cords and strands. Immunohistochemical studies showed positivity for PAS, Mucicarmine and Alcian blue pH 2.5 and negativity for PAS-Diastase (Figure 2).

According to the left supraclavicular lymphadenopathy, the most likely diagnosis was *Cutaneous metastasis of signet ring cell carcinoma* which the differential diagnosis was primary cutaneous signet ring cell carcinoma. She was lost to follow up during the referral to National Cancer Institute for further investigation.

Table 1 Shows different types of cancers with signet ring cells[4,5,6,7,8,11,12]

Primary skin tumor	● Primary cutaneous signet ring cell carcinoma ● Squamous cell carcinoma ● Basal cell carcinoma ● Melanocytic nevus ● Malignant melanoma ● Liposarcoma ● Trichilemmal carcinoma ● Hidradenoma ● Cylindroma ● Epitheloid sarcoma ● Dermatofibroma ● Cutaneous T-cell lymphoma ● Non-Hodgkin's lymphoma ● Infundibular cyst
Metastatic skin tumor	● Lung ● Breast ● Gallbladder ● Esophagus ● Stomach ● Pancreas ● Colon ● Appendix ● Rectum ● Prostate ● Ovary ● Endometrium ● Urinary bladder

Discussion

Cutaneous metastasis from internal malignancies is rarely observed. The incidence is ranging from 0.7% to 10%, and it could be the first sign of an unknown malignancy.[1,2,3] The cell type of signet ring cell cutaneous metastasis is belonged to a type of epithelial cell called glandular cells in origin. Its cancer is a rare form of mucinous adenocarcinoma. Cutaneous metastasis usually presents as painless nodules, plaques with or without ulceration or necrosis. Pain can be observed in some cases. Herpetiform lesions may occur.[4,8,11] Since the abnormal of cellular secretion or excretion mechanisms, excess mucin presents in a cytoplasm. It compresses the nucleus of the cell and makes the cell looks like a ring. However, other types of primary skin neoplasms have been reported to contain signet ring-like cells. Thus, skin tumors of signet ring cell morphology may be primary or metastatic.

The histopathology of cutaneous metastasis typically shows a diffuse dermal infiltrate sometimes with extension into the subcutis. The overlying epidermis is usually intact and there is an underlying spared zone of uninvolved dermis (grenz zone). The tumor cells are often found in narrow strands between bundles of collagen.[5]

The cytoplasmic mucin-staining vacuoles are only seen in primary cutaneous signet ring cell carcinoma, which is apocrine in nature, and metastatic adenocarcinoma.[6]

The mucinous content looks clear with routine stains, while it stains positive with Periodic acid-Schiff without diastase and positive with mucicarmine.

Distinction of primary cutaneous signet ring cell carcinoma from a metastatic lesion is challenging. The former is apocrine origin which positively stained with lysozyme, GCDFP-15 (Gross cystic disease fluid protein 15), CK7 and CK 20.[6,7]

Immunohistochemical stains could assist to differentiate the origin of signet ring cell metastasis, as shown in Table 2.

Table 2 Shows immunohistochemical staining in primary and secondary adenocarcinomas.[4,5,6,7,8,10,11]

Type of carcinoma	Major localization	CK 7	CK 20	TTF-1	Anti-TG Ab	PSA	RCC-MA	CA19-9
Primary adenocarcinoma								
Primary cutaneous signet ring cell carcinoma	Eyelids, axilla	+	+	-	-	-	-	-
Secondary adenocarcinoma								
Breast	Thorax, back, face (eyelid, nose), umbilicus	+	-	-	-	-	-	-
Lung	Trunk, scalp, neck, face	+	-	+	+	-	-	-
Gastrointestinal	Abdomen, scalp, neck, face	-	+	-	-	-	-	+
Renal cell	Upper trunk, torso, scalp	-/+	-	-	-	-	+	-
Thyroid	Abdomen, head	-	-	+	-	-	-	-
Ovary	Umbilicus	+	-/+	-	-	-	-	+/-
Prostate	Suprapubic	-/+	-/+	-	-	+	-	-
Urinary bladder	Trunk, pre-auricular	+	+	-	-	-	-	-
Pancreas	Umbilicus	+	-	-	-	-	-	+

+, almost all are positive; -, almost all are negative; +/-, most are positive; -/+, most are negative

TTF-1,Thyroid transcription factor-1; Anti-TG Ab, Antithyroglobulin antibody; PSA, Prostate specific antigen; RCC-MA, Renal cell carcinoma marker; CA19-9, Carbohydrate Antigen 19-9

When a diagnosis of cutaneous metastasis from signet-ring cell carcinoma is made, a search for primary tumor is needed. Complete physical examination and the immunohistochemical staining of the biopsied tissue can be helpful. The blood testing for complete blood cell count, liver function tests, biochemical serum profile, serological tumor markers (AFP, B-HCG, CA.125, CEA, CA.19-9), urinalysis, including chest X-

ray, stool occult blood testing, esophagogastroduodenoscopy, colonoscopy, whole abdominal computed tomographic scan should be done.

Although the thorough physical examination and investigations are performed, the origin of occult malignancy can not be identified. Of all cutaneous metastasis, the incidence of unknown primary site is 4.8-7.8%.[3,8] Once the diagnosis of skin metastasis is established, the prognosis is grim. The average survival time following the initial diagnosis of cutaneous metastasis is 7.5 months. Approximately, Thirty percent of the patients die within the first month and half of the patients expire within the first 6 months.[8,9]

Treatment of skin metastases of visceral tumors almost exclusively pursues palliative goals. Surgical excision, radiation, focal chemotherapeutics or immunotherapies can be performed on a case-by-case basis. Systemic therapies are indicated for immuno- or chemotherapy-responsive tumors.[10]

Our case was a 54-year-old woman, from Cambodia with the past history of gastric surgery. Multiple, painless, disseminated nodules with left supraclavicular lymphadenopaty and the histopathological finding of aggregations of atypical signet ring cells in the dermis without epidermal connection suggested the malignancy in nature. The identification of the primary malignancy can lead to the appropriate care for our patient. As a result, the patient was referred to National Cancer Institute for further investigation. Unfortunately, the patient was lost to follow up before performing any work-up.

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