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Keratin 19-positive cutaneous squamous cell carcinoma with elevated serum cytokeratin 19 fragment 21-1 level: A case report

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Abstract. Cytokeratin 19 fragment 21-1 (CYFRA21-1) is a marker of lung cancer useful for evaluating clinical diagnosis and prognosis. To the best of our knowledge, there have been no reports of cutaneous squamous cell carcinoma (SCC) with high levels of CYFRA21-1 to date. We herein report a case of a 79-year-old man with a large subcutaneous tumor of the left shoulder, which was diagnosed as primary cutaneous poorly differentiated SCC. The tumor nests were composed of poorly differentiated atypical squamous cells exhibiting high-grade malignancy and mitotic figures; multinuclear cells were also identified inside lymph vessels. Keratin 19 (K19) was intensely expressed in tumor cells. A significantly elevated level of CYFRA21-1 (33 ng/ml) was observed preoperatively. After surgery, the level of CYFRA21-1 was significantly decreased (from 33 to 5.0 ng/ml). Our case demonstrated that K19-positive primary cutaneous undifferentiated SCC induced high levels of CYFRA21-1 in the serum. Thus, CYFRA 21-1 may be a marker indicative of poorly differentiated cutaneous SCC exhibiting K19 expression.

Introduction

Cytokeratin 19 fragment 21-1 (CYFRA21-1) is a circulating soluble fragment of keratin 19 (K19) (1). CYFRA21-1 is a marker of lung cancer useful for evaluating clinical diagnosis and prognosis (2). However, to the best of our knowledge, no previous cases of cutaneous squamous cell carcinoma (SCC) with high levels of CYFRA21-1 have been reported to date.

We herein report a case of K19-positive cutaneous SCC with elevated CYFRA 21-1 levels.

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Key words: cytokeratin 19 fragment 21-1, keratin 19, primary cutaneous squamous cell carcinoma

Case report

A 79-year-old man presented to our hospital (Meiwa Hospital, Nishinomiya, Japan) with a large subcutaneous tumor on the left shoulder. The patient's past medical history included duodenal ulcer, appendicitis, liver cirrhosis and hepatitis C. One month prior to the first visit, the patient noticed a tumor on the left shoulder exhibiting rapid growth. On clinical examination at the first visit, the tumor was solid, sized 16x10x5 cm, with a cauliflower-like appearance and accompanying hemorrhage, necrosis and ulcerations (Fig. 1).

The laboratory findings included elevated white blood cell count (13,100/μl) with a left shift, with 86% neutrophils, and anemia (hemoglobin 5.7 g/dl). Three months prior to the first visit, the hemoglobin concentration was 10.0 g/dl.

An elevated C-reactive protein level was also found (6.90 mg/dl). The levels of carcinoembryonic antigen (3.4 ng/ml) and SCC antigen (1.7 ng/ml) were within normal limits. However, the level of CYFRA21-1 was significantly elevated (33 ng/ml).

Enhanced magnetic resonance imaging examination revealed a pedunculated tumor on the deltoid muscle on T2-weighted images. The normal range of CYFRA21-1 is >3.5 ng/ml. Computed tomography revealed metastasis to the neck, subclavicular and mediastinal lymph nodes.

On histopathological examination, tumor nests were identified in the entire thickness of the dermis. The tumor nests were continuous with the epidermis and were composed of poorly differentiated atypical squamous cells exhibiting high-grade malignancy, with mitotic figures and multinuclear cells (Fig. 2). Lymph vessels invaded by poorly differentiated cutaneous SCC cells were also identified (Fig. 3).

Based on the abovementioned clinical and histopathological findings, the diagnosis was cT3N2M1 (stage IV) poorly differentiated primary cutaneous SCC, metastatic to the regional lymph nodes (left axilla, neck and mediastinum).

The tumor was widely excised, with partial excision of the deltoid and trapezius muscles. Grafting with a latissimus dorsi flap was performed with axillary lymph node dissection. Three cycles of postoperative chemotherapy with pepleomycin sulfate (a total of 85 mg) were administered. Following surgery, the level of CYFRA21-1 was significantly reduced. Further treatment was not performed, and the patient's current condition is not known as there were no follow-up hospital visits.

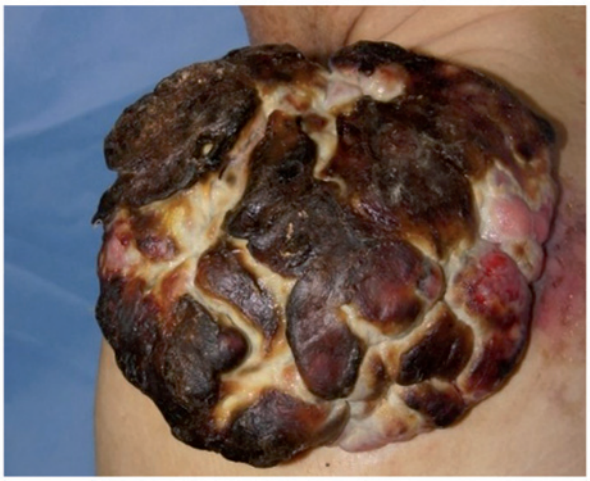

Figure 1. Clinical examination at the first visit revealed a large cauliflower-like solid tumor on the left shoulder, sized 16x10x5 cm, exhibiting hemorrhage, necrosis and ulcerations.

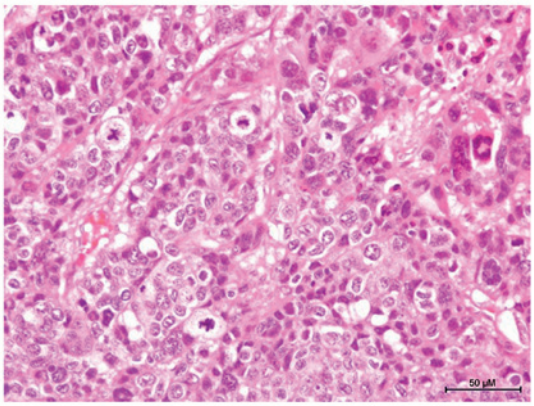

Figure 2. The tumor nests were composed of poorly differentiated atypical squamous cells, exhibiting high-grade malignancy, mitotic figures and multinuclear cells.

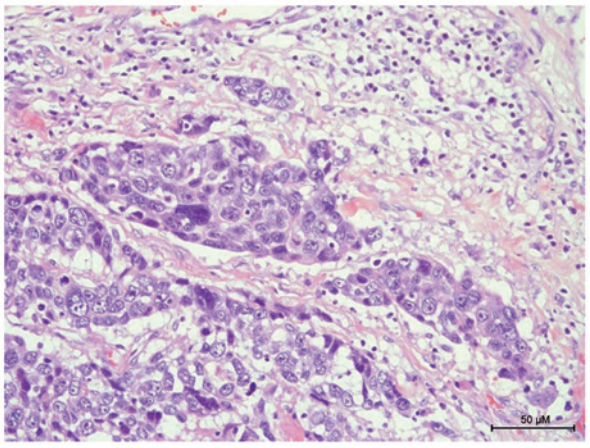

Figure 3. Poorly differentiated cutaneous squamous cell carcinoma cells were observed in lymph vessels.

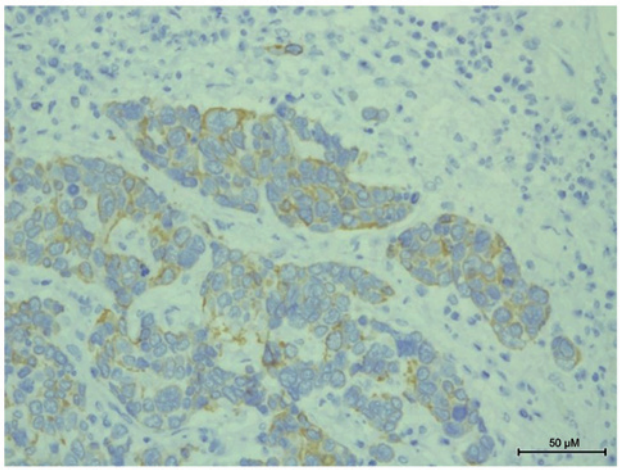

Figure 4. Keratin 19 was strongly expressed in tumor cells.

On immunohistochemical examination for keratin expression, the labeled streptavidin-biotin (LSAB) method was used (Dako, Carpinteria, CA, USA). The mouse anti-human keratin antibodies used in this study were as previously described (3): 34βB4 (K1; dilution 1:50), LP5K (K7; dilution 1:10), LP3K (K8; dilution 1:50), HP1 (K10; dilution 1:50), LL002 (K14; dilution 1:200), LHK15 (K15; dilution 1:40), LL025 (K16; dilution 1:20), E3 (K17; dilution 1:25), 5D3 (K18; dilution 1:20) and b170 (K19; dilution 1:100), all from Novocastra Laboratories Ltd., Newcastle upon Tyne, UK. The LSAB method was applied according to the manufacturer's instructions, as previously reported (3). K19 was significantly expressed in tumor cells (Fig. 4). K7 was weakly expressed in tumor nests. K8, K18 and the other keratins were not expressed in tumor cells.

Patient's written informed consent was obtained for publication of this case study and the accompanying images.

Discussion

Keratins are the most diverse intermediate filaments, and may be used as markers of epithelial tumors, stage of differentiation and origin of epithelial tumors. There are a total of 54 human functional keratin genes (4).

K19 is the smallest keratin, with a molecular weight of 40 kD. The CYFRA21-1 circulating fragment is a marker of K19. In normal skin, K19 is present in the outermost cells of the hair follicle and in simple ductal epithelia (4); it is also found in lung adenocarcinoma and SCC (5).

As regards keratin expression in cutaneous SCC, stratified differentiated keratins (K1 and K10) are commonly detected in well-differentiated SCC, whereas simple epithelial keratins (K7, K8, K18 and K19) are detected in poorly differentiated SCC. These keratins are involved in tumor invasion and epithelial-mesenchymal interactions (6).

As regards elevated CYFRA21-1 levels in primary cutaneous carcinoma, two cases of eccrine porocarcinoma were previously reported (7).

K19 is present in the ductal cells of eccrine sweat glands. Therefore, the presence of K19 in eccrine sweat glands may be reflected in elevated CYFRA21-1 in eccrine porocarcinoma. To the best of our knowledge, no previous cases of cutaneous SCC with elevated CYFRA21-1 have been reported. K19 is not present in the normal epidermis. Although K19 expression was not detected in blood vessels, we hypothesized that

K19 in tumors is lysed by protease, resulting in spreading in the tissue, lymph vessels and lymph nodes. Subsequently, K19 enters blood vessels and is identified as elevated CYFRA21-1, a soluble cytokeratin fragment. In our case, CYFRA21-1 level was decreased following surgery. This result may reflect the clinical prognosis of the tumor. However, further similar cases should be accumulated in the future.

In summary, we reported a case of K19-positive cutaneous SCC with elevated serum CYFRA21-1 level. CYFRA21-1 level may reflect the clinical course of cutaneous SCC and it may be a marker of primary poorly differentiated cutaneous SCC, useful in the diagnosis and as an indicator of the clinical course.

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