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Abstract

Primary cutaneous signet ring cell carcinoma (PCSRCC) is a very unusual but distinctive clinicopathologic entity that can simulate metastatic adenocarcinomas. It is defined as a diffuse malignant epithelial neoplasia localized in the dermis and subcutis without epidermal involvement, showing variable amounts of signet ring cells, without evidence of visceral adenocarcinoma. We present 2 cases of PCSRCC, which involved eyelids and axilla respectively. Despite thorough systemic workup, primary sources could not be demonstrated in either case. The tumor cells are positive for gross cystic disease fluid protein 15 in addition to a variety of glandular markers. Furthermore, both cases were immunostained with cytokeratin 20 (CK20).

In conclusion, we report 2 cases of PCSRCC expressing CK20 immunoreactivity. CK20-positive primary cutaneous tumors should include PCSRCC in addition to Merkel cell carcinoma.

Key words: Signet ring cell carcinoma, Cytokeratin 20, Metastatic adenocarcinoma, Mucin

Cytokeratin (CK20) is a low-molecular-weight cytokeratin, that was originally identified by Moll et al.[1-3] as protein IT in 2-dimensional gel electrophoresis of cytoskeletal extracts of intestinal epithelia. In normal tissues, CK20 is expressed only in the gastrointestinal epithelium, urothelium, and Merkel cell.[2-5] There has been recent interest in the application of CK20 antibody for determining the primary site of carcinomas.[2,5,6]

Among skin tumors, Merkel cell carcinoma and metastatic adenocarcinomas may be positive for CK20, but CK20-positive primary cutaneous adenocarcinomas have not previously been reported. We describe herein two cases of CK20-positive Primary cutaneous signet ring cell carcinoma (PCSRCC), a rare variant of primary cutaneous adenocarcinomas.

MATERIALS AND METHODS

CASE REPORTS

Case 1

We encountered a 73-year-old man with a 7-year history of multiple nodules and swelling around the right orbit. Physical examination demonstrated diffuse swelling and erythema with a dozen of papules and nodules in the upper and lower eyelids (Fig 1). Each papule and nodule was 5 to 6 mm in diameter. A few subcutaneous nodules were present. The patient could not open his right eye. There was no superficial lymphadenopathy. The results of routine laboratory examinations were normal except for slight anemia. Tumor markers, including squamous cell carcinoma, carcinoembryonic antigen (CEA), CA19-9, and alfa-fetoprotein were within the normal range in serum. Magnetic resonance imaging (MRI) of the head demonstrated a well-defined lesion from the right orbit to the periorbital skin, which corresponded to the papules, nodules, and swelling. Computed tomographic scans, MRI, various scintigrams, and gastrointestinal examinations did not demonstrate any evidence of other primary or metastatic lesions. Radical surgery including exenteration plus the removal of any involved contiguous facial skin was performed, followed by ^{60}Co irradiation (total 65Gy). However, the tumor recurred in the left perioribital area 5 years after resection.

Case 2

A 62-year-old man presented with a brown tumor in the right axilla, which had progressively enlarged over about 14 years. Physical examination demonstrated a 5.7x3.7-cm, elastic hard tumor located in the right axilla. The rough surface of the tumor was accompanied by red nodules (Fig 2). The right axillary lymph node was swollen. Laboratory examinations demonstrated several abnormal results caused by chronic NK-cell lymphocytosis: anemia, leukocytosis, thrombopenia, and liver dysfunction. Various natural killer cell markers including CD2, 7, 16, 56, and 57, were elevated in the peripheral blood. Clonal rearrangement of T-cell receptor genes was not detected by Southern blot analysis. Among the tumor markers, serum CEA was slightly elevated. Computed tomographic scans, MRI, various scintigrams, and gastrointestinal examinations did not demonstrate any evidence of other primary sources. Despite the administration of combination chemotherapy, the patient died 9 months after the initial consultation because of leukemia subsequent to chronic NK-cell

lymphocytosis.

HISTOPATHOLOGY

Skin lesions from both cases and the swollen axillary lymph node from patient 2 were excised. Both skin lesions had almost identical microscopic findings. Histological examinations demonstrated a solid tumor extending from the upper dermis to the subcutaneous tissue without connection to the epidermis or appendages. The tumor cells were scattered singly, in groups of several cells, or arranged in a single file among collagen fibers, presenting a trabecular pattern (Fig 3). Intercellular lumina were partly formed by several cells. The tumors were composed of atypical cells with abundant eosinophilic, vacuolated cytoplasms. Occasional signet ring cells were also seen (Fig 4). Histological findings of the lymph node from patient 2 showed poorly differentiated adenocarcinoma.

HISTOCHEMISTRY

Both cases showed identical histochemical results. The tumor cells, including the signet ring cells, were positive for diastase-resistant PAS and alcian blue.

IMMUNOHISTOCHEMISTRY

Sections cut from formalin-fixed, paraffin-embedded tissues were mounted on silanized glass slides. Immunohistochemical staining was performed using the labeled streptavidin-biotin method as described previously.[7] The antibodies included CK20 (Dako Corporation, Carpinteria, CA; cytokeratin 20, clone Ks20.8, Code M7019; dilution: 1:100), MNF-116 (Dako Corporation; low-molecular-weight cytokeratin, clone MNF116; dilution: 1:50), 34 β E12 (Dako Corporation; high-molecular-weight cytokeratin, clone 34 β E12; dilution: 1:50), BCA225 (Cambridge Laboratories; clone CU18; dilution: 1:10), GCDFP15 (Cambridge Laboratories; clone D6; dilution: 1:100), CEA (Dako Corporation; clone II-7; dilution: 1:25), CA125 (Immunotech; clone OC125; prediluted preparation), CA15-3 (Dako Corporation; clone DF3; dilution: 1:50), CA19-9 (Dako Corporation; clone 116-NS-19-9; prediluted preparation), S-100 protein (Dako Corporation; polyclonal; prediluted preparation), and CD15 (Becton-Dickinson, Franklin Lakes, NJ; clone LeuM1;dilution: 1:5). Briefly, the sections were incubated with primary antibodies at room temperature for 60 minutes followed by biotinylated rabbit antimouse immunoglobulin for 60 minutes and then avidin-biotin-peroxidase complex for 60 minutes. The color reaction was developed with 0.1% diaminobenzidine. Appropriate positive and negative controls were used.

Both cases showed identical immunohistochemical results. The tumor cells, including signet ring cells, were strongly positive for MNF116, CA15-3, BCA225, GCDFP15, and weakly for 34 β E12, CEA, CA125. They were negative for CA19-9, S-100 protein, and CD15. Both cases demonstrated weak positivity for CK20 (Fig 5).

ELECTRON MICROSCOPY

Fresh tissue obtained from patient 1 was processed for electron microscopy by routine procedures. The tumor cells showed cytoplasmic pseudolumens with microvilli and flocculent mucus material. In addition, electron-dense granules were membrane-bound.

RESULTS

Histologically, the tumors were localized in dermis and subcutis without epithelial involvement, showing variable amounts of signet ring cells. The tumor cells were positive for GCDFP15 in addition to a variety of ductal and glandular markers, such as MNF116, BCA225, CEA, CA15-3, and CA125. These cells were also positive for CK20.

DISCUSSION

CK20 is consistently present in colonic adenocarcinoma and their metastases to lymph nodes, liver, lung, and ovaries.[5] Adenocarcinomas of the upper gastrointestinal tract, pancreas, and cholangiocarcinomas show variable reactivity.[5] Hepatocellular carcinomas and carcinoid tumors often showed focal reactivity limited to scattered tumor cells.[5] In contrast, CK20 is virtually absent in primary adenocarcinomas of lung, ovaries, and endometrium.[2,5,6] Notable exceptions among ovarian tumors were mucinous neoplasms that showed variable, sometimes significant CK20 reactivity.[5] Transitional cell carcinoma is usually positive, while prostatic and renal adenocarcinomas are negative. Typically, squamous cell carcinomas of all organs and carcinomas of the breast are also negative. Merkel cell carcinomas of the skin show consistent reactivity, while small cell carcinomas of the lung are negative. CK20 is a suitable adjunct marker especially to separate adenocarcinomas of gastrointestinal versus nongastrointestinal origin.

GCDFP15 was initially thought to be specific for apocrine glands and tumors with apocrine differentiation.[8] However, the antigen is demonstrated in normal eccrine glands.[9,10] Whether GCDFP15 is specific for apocrine tumors is currently under discussion.[11] Although this antigen is found also in mammary and salivary glands, it is not found in gastrointestinal mucosa.[12-14] Regardless, GCDFP15 is very useful for distinguishing between primary and metastatic adenocarcinomas of the skin.

The distinction between primary and metastatic adenocarcinomas has crucial therapeutic and prognostic implications. CK20 and GCDFP15 are considered useful adjuncts in determining origin. For example, it is possible to distinguish between primary and secondary perianal Paget's disease.[15]

PCSRCC was first described by Rosen et al. in 1975.[16] Thereafter, similar cases of PCSRCC have been reported, exclusively involving the eyelids.[17-19] Recently, a few cases involving the axilla have been reported.[20,21] None of the reported cases had any detectable primary internal malignancies. Previous investigators have agreed that PCSRCC is of eccrine origin,[14,16,18] while recent investigators have insisted on an apocrine origin.[18,20] Either way, PCSRCC is a primary cutaneous, poorly differentiated, mucin-producing adenocarcinoma.[18]

The lesions of these two patients demonstrated the range of clinical and histologic features of signet ring cell carcinoma. Thorough systemic workup could not detect primary sources in either case. Furthermore, tumor cells were positive for GCDFP15, suggesting a cutaneous origin. Therefore, both cases were regarded as PCSRCC. Although CK20 is considered a marker of metastatic carcinomas of the skin, rare PCSRCC demonstrated immunoreactivity for CK20 in the present study. Histochemical and electron microscopic findings demonstrated mucin deposits. Interestingly, mucinous adenocarcinoma of the ovary could produce mucin and show variable, sometimes significant CK20 reactivity.[5]

In conclusion, we report 2 cases of PCSRCC expressing CK20 immunoreactivity. CK20-positive primary cutaneous tumors should include PCSRCC in addition to Merkel cell carcinoma.

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Legends

Fig 1. A dozen of papules and nodules were accompanied by diffuse swelling and erythema. (right eyelids of patient 1)
Fig 2. A 5.7x3.7-cm, elastic hard tumor was accompanied by red nodules. (right axilla of patient 2)
Fig 3. The scanning view shows a solid tumor from the upper dermis to the subcutaneous tissue without connection to the epithelia. (Hematoxylin-eosin stain of patient 1; original magnification x10)
Fig 4. The tumor cells were scattered singly, in clusters of several cells, or arranged in a trabecular pattern. Occasional signet ring cells were seen. (Hematoxylin-eosin stain of patient 1; original magnification x50)
Fig 5. Positive reaction was seen in the cytoplasm of tumor cells. (Cytokeratin 20 immunostain of patient 2; original magnification x100)

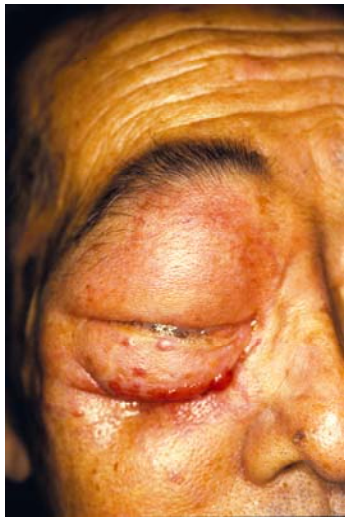

Fig 1.

Fig 2.

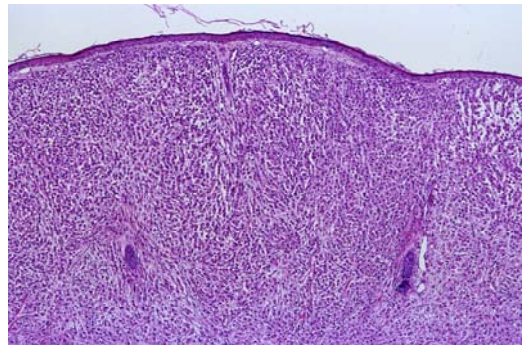

Fig 3.

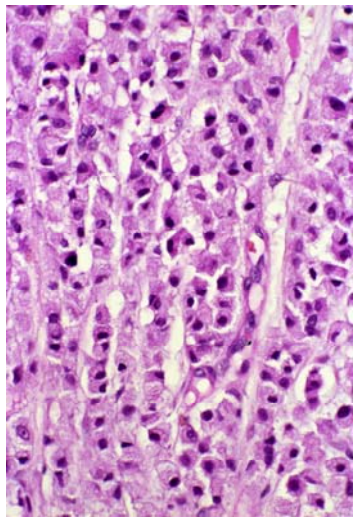

Fig 4.

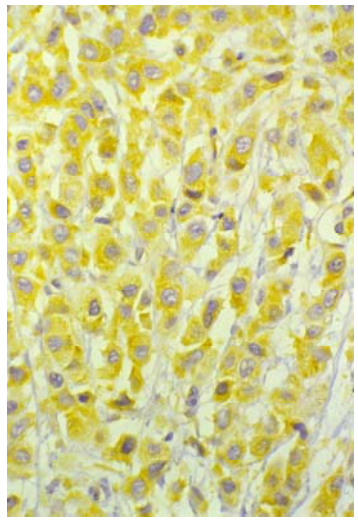

Fig 5.