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Metastatic Carcinoma to Subcutaneous Tissue and Skeletal Muscle: Clinicopathological Features in 11 Cases

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Objective: Metastatic carcinoma to subcutaneous tissue or skeletal muscle is relatively rare. The present study aimed to clarify the clinicopathological features for confirming the diagnosis as soft tissue metastasis and determining the primary site.
Methods: We reviewed records of 11 patients with soft tissue metastasis who were in our institution from 1996 to 2009.
Results: In 9 of 10 patients who underwent magnetic resonance imaging, findings consisted of poorly circumscribed high-intensity lesions around the tumor on T2-weighted images, irregular peritumoral enhancement and poorly enhanced lesions at the center of the tumor on T1-weighted images. Systematic immunohistochemical examination was more valuable for diagnosing as soft tissue metastasis and confirming the primary site. The expression patterns of cytokeratins 7 and 20 and tissue-specific antibodies such as thyroid transcription factor-1, MUC5AC and CDX2 were useful diagnostic markers. The primary site could be determined in five patients with cytokeratin 7/20 immunophenotype and positivity for tissue-specific antibodies. In four cases, determination of the primary site finally became possible by comparison with the histological findings of operative specimens in past carcinoma and/or in consideration of radiological findings and the results of cytokeratin 7/20 phenotyping.
Conclusions: Systematic immunohistochemical examination is helpful for confirmation of the primary origin in soft tissue metastasis of carcinoma in addition to clinical information such as the history and condition of past carcinoma, radiological findings and comparison between the histology of biopsy specimens and past carcinoma.

Key words: soft tissue – neoplasms – metastasis – immunohistochemistry

INTRODUCTION

Metastatic carcinoma to subcutaneous tissue or skeletal muscle is relatively rare (1), and only five case series were previously reported (2–6). Differentiation between primary soft tissue sarcoma and metastatic carcinoma is often difficult at presentation (7). Proper determination of the primary site is important for therapeutic decision-making in particular tumor types. Although a painful soft mass with a known history of carcinoma and the magnetic resonance (MR) imaging feature of peritumoral enhancement show higher possibility of soft tissue metastasis (6), these findings are not specific, and pathological examination is extremely important for the diagnosis of metastatic carcinoma and determination of the primary site. The expression patterns of cytokeratin (CK) 7 and CK20 are particularly valuable diagnostic markers in determination of the primary site of origin. The usefulness of the CK7/CK20 immunophenotype for determination of the primary site in metastatic adenocarcinoma has been described (8,9). Moreover, tissue-specific antibodies such as thyroid transcription factor-1 (TTF-1) and PE-10 for lung carcinoma (10,11), CDX2 for colorectal carcinoma (12), MUC5AC and HIK1083 for gastrointestinal carcinoma (13,14), gross cystic disease fluid protein-15 (GCDFP-15) for breast carcinoma (15) and Hep-Par1 for

hepatocellular carcinoma (16) are valuable for determining the primary origin. However, studies utilizing these immunohistochemical markers for diagnosing soft tissue metastasis and confirming the primary site are sparse. The purpose of the present study was to clarify the clinical and pathologic features for confirming the diagnosis as soft tissue metastasis and determining the primary site. For this purpose, we reviewed test methods for diagnosis of soft tissue metastasis and determination of the primary site by retrospective clinicopathological analysis.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of 11 patients with soft tissue tumors that were subsequently proven to have metastasized from distant primary carcinoma at our institution from 1996 to 2009. All of the patients presented with soft tissue lesions. Criteria for selection included location of the tumor within skeletal muscle or subcutaneous tissue. Excluded from this series were the following: metastases of melanoma, metastases to lymph nodes, needle tract metastases after biopsy, metastases to reactive area around wounds exposed at the time of primary tumor excision and direct extension from adjacent tumors.

Medical records of all patients were reviewed to assess clinical history, anatomical location of metastasis, finally diagnosed primary organ, and biochemical, radiological and histological examinations. Biochemical examination and MR imaging were performed in 8 and 10 cases, respectively. Needle or open biopsy of the mass lesion was performed in all cases.

To confirm the histological diagnosis of metastatic soft tissue tumors and identification of the primary lesions, immunohistochemical studies were performed in all cases in addition to hematoxylin and eosin (H & E) staining. The antibodies used in this study included CK7 (1:70 dilution; DAKO), CK20 (1:70; DAKO) and AE1/AE3 (1:100; DAKO) for epithelial origins, TTF-1 (1:100; DAKO) and PE-10 (1:200; DAKO) for lung carcinoma; MUC5AC (1:100; Novocastra) and HIK1083 (1:20; Kanto Chemical) for gastric carcinoma, Hep-Par1 (1:50; DAKO) for hepatocellular carcinoma, CDX2 (1:100; BioGenex) for colorectal carcinoma, GCDFP-15 (1:50; Covance) for breast carcinoma and CD10 (1:100; Novocastra) for renal cell carcinoma. Before immunostaining, antigen retrieval was carried out by microwave treatment of the tissue sections for 30 min in a 50 mM citrate buffer (pH 6.0) for PE-10, Hep-Par1 and GCDFP-15 antibodies, or in a 10 mM Tris-HCl buffer containing 1 mM EDTA (pH 8.0) for CK7, CD20, AE1/AE3, TTF-1, MUC5AC, CDX2 and CD10 antibodies. Horseradish peroxidase-conjugated goat anti-mouse IgG (Fab') (MAX-PO(M)) (Nichirei) was used as secondary antibody, and peroxidase activity was visualized with a diaminobenzidine/hydrogen peroxide solution. Counterstaining was carried out with hematoxylin.

Table 1. Predictable primary origin by the patterns of CK 7/20 immunophenotype and valuable tissue-specific antibodies for determination of primary carcinoma

CK7/20 immunophenotype	Predictable primary origin	Tissue-specific antibody
CK7+/CK20+	Bladder	
	Pancreas	
	Ovary (non-mucinous)	
CK7+/CK20−	Lung	PE-10, TTF-1
	Breast	GCDFP-15
	Bile duct	MUC5AC, HIK1083
	Ovary (mucinous)	
CK7−/CK20+	Colon	CDX2
CK7−/CK20−	Liver	Hep-Par1
	Kidney	CD10
	Prostate	PSA

CK, cytokeratin; TTF-1, thyroid transcription factor-1; GCDFP-15, gross cystic disease fluid protein-15.

In the process of histological evaluation, immunohistochemical examination of CK7 and 20 was performed if an epithelial tumor was suspected in the HE specimen, and some differential diagnoses were focused on following previous reports (Table 1) (8,9). Afterward, immunohistochemical staining with tissue-specific antibodies for the predictable carcinoma was evaluated. Comparison was also made between the biopsy specimen and the primary histology at the same time in cases with a history of surgery for carcinoma.

RESULTS

The clinical and histological data for the 11 patients are summarized in Table 2. Five patients were male and six were female and ages ranged from 61 to 79 years, with a mean of 70 years. Localization of soft tissue metastases included upper extremity (four cases), trunk (three cases) and lower extremity (four cases). Four patients had metastasis of subcutaneous tissue and seven patients had metastasis of skeletal muscle. Seven patients had a history of carcinoma at presentation. Four patients had no recurrence after resection of the primary lesion, but one patient had recurrence at presentation. Seven patients already had multiple metastases at diagnosis of soft tissue metastasis (Table 2). In 9 cases of 10, MR findings consisted of (i) poorly circumscribed high-intensity lesions around the tumor on T2-weighted images, (ii) irregular peritumoral enhancement on T1-weighted images with intravenous gadolinium enhancement and (iii) poorly enhanced lesions at the center of the tumor on T1-weighted images (Fig. 1). Tumor markers such as CEA, CA 19−9 and CA 15-3 were examined in eight patients, but

Table 2. Clinical and histological data of the patients

Patient no.	Age (years) and gender	Soft tissue metastasis		History of carcinoma	Primary organ	Condition of primary lesion	Other metastases	Immunohistochemical phenotype	
		Site	Depth					CK 7/ CK 20	Others
1	79F	Groin	Muscle	Uterus	Unknown	—	None	−/+	CDX2(−), MUC2(−)
2	71M	Thigh	Muscle	None	Lung	Not resected	Lung	+/−	PE-10(−), TTF-1(−), HIK1083(−)
3	61M	Chest wall	Muscle	None	Stomach	Not resected	LN	+/−	MUC5AC(+)
4	73F	Arm	Subcutaneous	Liver	Unknown	—	None	+/+	Hep-Par1(−)
5	76M	Hand	Subcutaneous	Colon	Colon	Resected	Lung, Brain	−/+	CDX2(+)
6	56F	Forearm	Muscle	Breast	Breast	Recurrence	LN, Lung, Liver	+/−	GCDFP-15(−), ER(−)
7	68F	Calf	Muscle	Lung	Lung	Resected	None	+/−	TTF-1(−), PE-10(−)
8	72M	Calf	Muscle	Lung, bile duct	Bile duct	Resected	LN	+/−	MUC5AC(+), TTF-1(−)
9	62F	Back	Muscle	None	Lung	Not resected	None	+/−	TTF-1(−), PE-10(−)
10	77M	Shoulder	Subcutaneous	Kidney	Kidney	Resected	Lung	−/−	AE1/AE3(+), CD-10(+)
11	76F	Thigh	Subcutaneous	None	Lung	Not resected	Brain	+/−	TTF-1(+)

LN, lymph node; ER, estrogen receptor.

these data were not helpful to detect the primary tumor. Histological tests with hematoxylin and eosin staining showed poorly differentiated adenocarcinoma in nine cases. In immunohistochemical findings, the expression patterns of CK7 and CK20, which are epithelial markers, indicated the CK7+/CK20− immunophenotype in seven cases, CK7−/CK20+ in two cases, CK7+/CK20+ in one case and CK7−/CK20− in one case. In Case 3, gastrointestinal or bile duct carcinoma was strongly suspected because of the CK7+/CK20− immunophenotype with MUC5AC positivity (Fig. 2), and stomach carcinoma was finally identified at endoscopy. In Case 5, the CK7−/CK20+ immunophenotype with CDX2 positivity was diagnosed as rectal carcinoma. In Case 8, a patient with a prior history of bile duct and lung carcinoma, bile duct carcinoma was suspected because of the CK7+/CK20− immunophenotype with MUC5AC positivity (Fig. 3). In Case 10, a patient with a mass on her back, metastasis of renal cell carcinoma was diagnosed because tumor tissue obtained by needle biopsy showed the CK7−/CK20− immunophenotype with AE1/AE3 and CD10 positivity. In Case 11, a patient without a prior history of carcinoma, immunohistochemical findings showed CK7+/CK20− with TTF-1 positivity and the patient was finally diagnosed with lung carcinoma after the addition of the appearance of a mass lesion in the lung. As four cases were negative for tissue-specific antibody, the primary sites were identified by investigation of a prior history of carcinoma, histological findings of primary carcinoma, the CK7/CK20 immunophenotype and radiographic findings. However, the CK7/CK20 immunophenotype was not consistent with the common CK7/CK20 immunophenotype for prior carcinoma in two cases (Cases 1 and 4). Although it was also thought that the soft tissue tumor in Case 4 might be metastasis of hepatocellular carcinoma, the primary origin could not be determined because the patient had recurrent tumor in the primary site with the possibility of elevation of alpha-fetoprotein, and this could not be confirmed as the same tumor by comparison between the histology of a primary and metastatic lesion. In Case 1, the primary origin could not be determined because treatment of uterine carcinoma was performed 20 years earlier and comparison between the histology of uterine carcinoma and soft tissue tumor could not be made. The primary tumor was finally diagnosed in the lung (four cases), bile duct (one case), stomach (one case), colon (one case), breast (one case), kidney (one case) and of unknown primary origin (two cases).

DISCUSSION

Distant metastases to soft tissue are rare conditions, and very few studies on case series have been reported (2–6). Herring found a very low incidence of 0.03% (15 cases among 54 000 cases) in his institution over 16 years (4). Glockner reported that 11 patients with soft tissue metastases were culled from a group of 1421 patients with a solitary mass over a 14-year period (3). In our institution, only 11 cases were diagnosed as

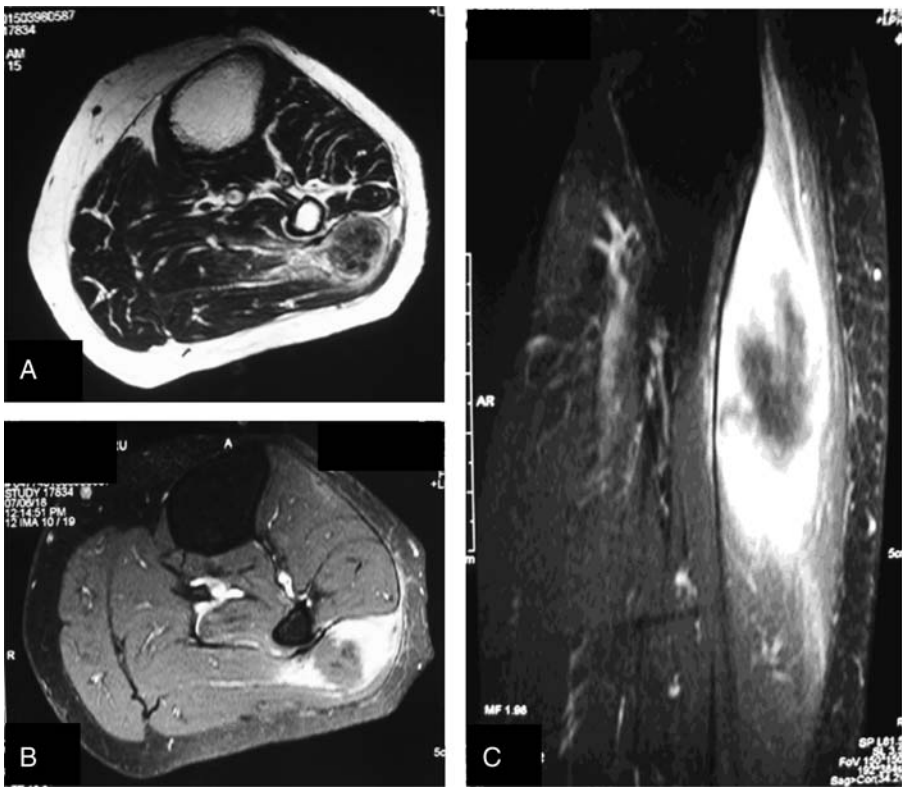

Figure 1. Magnetic resonance findings of a 72-year-old man (Patient No. 8) with metastasis to calf muscle. (A) The axial T2-weighted image revealed poorly circumscribed high-intensity lesion around the tumor. (B) The axial T1-weighted image with intravenous gadolinium enhancement showed irregular peritumoral enhancement. (C) The sagittal enhanced T1-weighted image demonstrated poorly enhanced lesion at the center of the tumor.

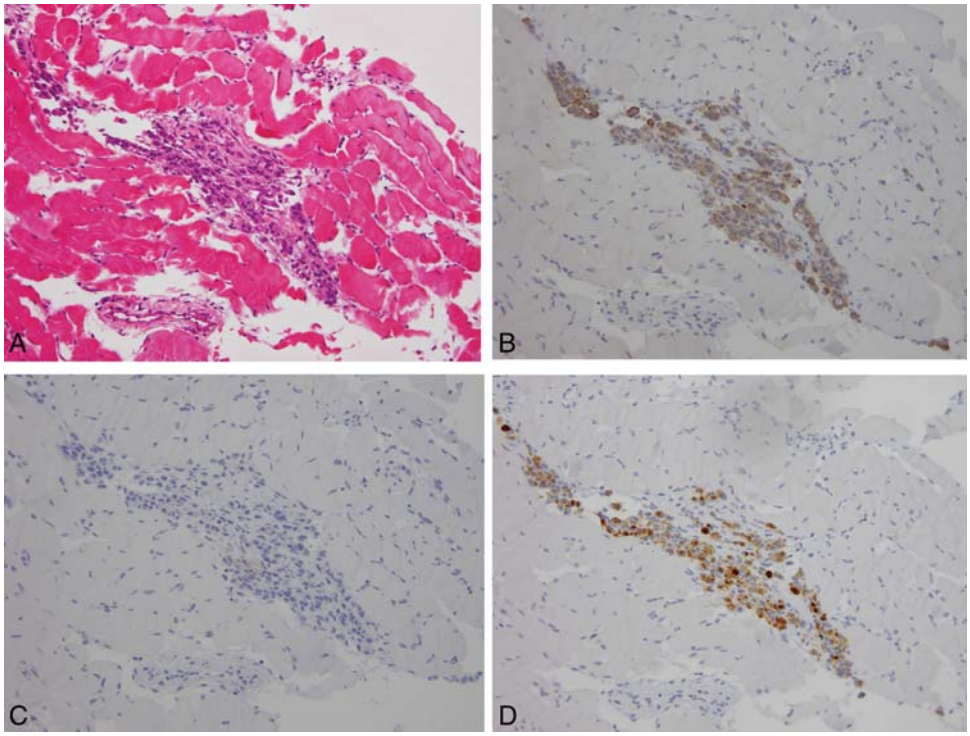

Figure 2. Histological findings of Patient No. 3. (A) Hematoxylin and eosin staining. A biopsy sample shows positive staining with cytokeratin (CK) 7 (B), but no staining for CK 20 (C). Carcinoma cells show cytoplasmic staining with MUC5AC (D) (original magnification, ×100 in (A–D)).

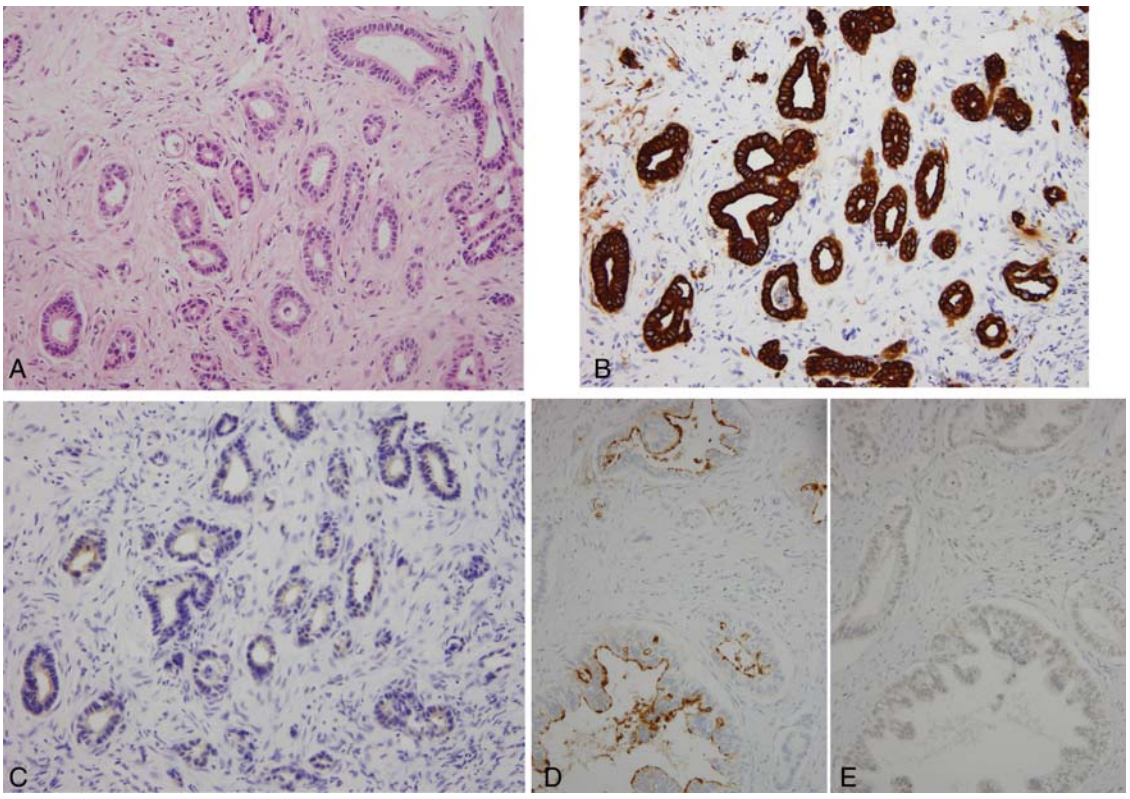

Figure 3. Histological findings of Patient No. 8. (A) Hematoxylin and eosin staining. A biopsy sample shows positive staining with CK 7 (B) but no staining for CK 20 (C). Carcinoma cells show cytoplasmic staining with MUC5AC (D), but no staining for thyroid transcription factor 1 (E) (original magnification, ×100 in (A–C), ×200 in (D) and (E)).

soft tissue metastasis over 14 years. Several factors have been implicated in the rarity of soft tissue metastases, such as (i) lactic acid production by skeletal muscle may inhibit the growth of tumor cells (17,18), (ii) varying tissue pressure in skeletal muscle may affect tumor implantation under the influence of β adrenergic receptors (1,17) or (iii) protease inhibitors in the muscle extracellular matrix may resist invasion by tumor cells (19). Under these unfavorable conditions, particular circumstances may be needed for soft tissue metastases to occur. An autopsy series suggested a higher incidence of metastases to skeletal muscle (7,20,21), and this may suggest that metastases to soft tissue cannot be formed without extensive existence of tumor cells in the blood. In fact, 7 patients of the 11 cases of the current study already had multiple metastases at presentation.

The differentiation between primary soft tissue sarcoma and metastatic carcinoma to soft tissue is important at presentation because the treatments and prognoses are markedly different. Early diagnosis and treatment are important for better prognosis to soft tissue metastases of carcinoma. Soft tissue sarcoma is initially suspected in cases of a solitary mass caused by a subcutaneous and muscle lesion with rapid growth. Though there are great similarities between primary soft tissue sarcoma and metastatic carcinoma to soft tissue, Tuoheti suggested that the extensive peritumoral enhancement associated with central necrosis, which was detected on 92% of MR images, is a characteristic feature of skeletal muscle metastasis (6). This radiological feature was also noted in 9 of 10 patients in our series, together with the findings of poorly circumscribed high-intensity lesions around the tumor on T2-weighted images and irregular peritumoral enhancement on T1-weighted images with intravenous gadolinium enhancement. Although these findings are not specific for soft tissue metastasis of carcinoma, MR imaging should be performed at presentation to decide the biopsy site and to obtain valuable information with regard to the differentiation between primary soft tissue sarcoma and metastatic carcinoma to soft tissue. In biochemical examination, serum CEA and CA19-9 levels were elevated in several cases, but these findings were not useful for identifying the primary site because the elevation of CEA and CA19-9 levels is often seen in many carcinomas.

Pathological examination of biopsy specimens provided the most useful findings to differentiate the soft tissue metastasis of carcinoma from soft tissue sarcoma and, furthermore, to determine the primary tumor site correctly. Immunohistochemical demonstration of the expression of CK in the tumor cells was also important for differentiating from soft tissue sarcoma. The expression patterns of CK7 and CK20 were particularly valuable diagnostic markers in determination of the primary site of origin. The usefulness of the CK7/CK20 immunophenotype for determination of the primary site in metastatic adenocarcinoma has been described (8,9). Tot indicated that in the reviewed literature

lung adenocarcinoma showed the CK7+/20− phenotype in 84%, ovarian non-mucinous adenocarcinoma in 93%, breast carcinoma in 88%, biliary carcinoma in 76% and colorectal adenocarcinoma showed the CK7−/20+ phenotype in 78% of biopsied samples. Moreover, ovarian mucinous adenocarcinoma showed the CK7+/20+ phenotype in 76% and renal cell carcinoma, prostate carcinoma and hepatocellular carcinoma showed the CK7−/20− phenotype in 71, 76 and 75%, respectively (8,9). The primary origin of soft tissue metastasis can also be discriminated efficiently by immunohistochemical examination with the tissue-specific antibodies, such as TTF-1 and PE-10 for lung carcinoma, CDX2 for colorectal carcinoma, MUC5AC and HIK1083 for gastrointestinal carcinoma, GCDFP-15 for breast carcinoma and Hep-Par1 for hepatocellular carcinoma, after evaluation of the CK7/CK20 immunophenotype (13,22–24). In five cases of our series, we could obtain definite findings for diagnosing the primary origin using tissue-specific antibodies in conjunction with CK7/CK20 (Cases 3, 5, 8, 10 and 11). Although immunohistochemical examination with the tissue-specific antibodies were negative, determination of the primary site of origin finally became possible by comparison with the histological findings of operative specimens in past carcinoma and/or in consideration of radiological findings and the results of the CK7/CK20 phenotype in four cases (Cases 2, 6, 7 and 9). In Cases 2 and 9, patients without a history of carcinoma, some differential diagnoses by the CK7/CK20 immunophenotype could be focused on. However, in the patient of Case 4 with a history of recurrent hepatocellular carcinoma, the primary origin could not be discriminated because comparison between the histology of the primary and metastatic lesion could not confirm the diagnosis as the same tumor, and the expression pattern of CK showed CK7+/CK20+ (a less common pattern in metastasis from hepatocellular carcinoma (25)). The reason for negative tissue-specific antibodies might be that 9 out of 11 soft tissue metastases in our series were poorly differentiated (5). These results might show a limitation of primary origin determination by pathological examination alone. Therefore, it is also important for the diagnosis of soft tissue metastasis of carcinoma and determination of the primary tumor site to combine clinical information such as the past history of carcinoma, the condition of past carcinoma, radiological findings and comparison between the histology of biopsy specimens and past carcinoma.

Though the usefulness of immunohistochemical examination in the diagnosis of soft tissue metastasis of carcinoma had been described previously (5), there has been no report on the use of an antibody panel combining CK7, CK20 and tissue-specific antibodies in differentiating the primary origin of metastatic carcinoma to subcutaneous tissue and skeletal muscle. In our hospital, patients generally bring radiological data such as CT or MR images at presentation, so we can perform a core needle biopsy as the first examination after confirmation of localization and properties of the tumor. In this study, it was shown that when CK7/CK20 and tissue-specific antibodies were used, the primary origin of soft tissue metastasis of carcinoma could be only roughly determined. However, definitive determination of the primary origin could be achieved in a short time by combination with clinical information such as the past history of carcinoma, the condition of past carcinoma, radiological findings and comparison between the histology of biopsy specimens and past carcinoma, in addition to systematic immunohistochemical evaluation of biopsy specimens.

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Conflict of interest statement

None declared.

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