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

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Running Head: Metastatic Carcinoma to Soft Tissue

ABSTRACT

Objective: Metastatic carcinoma to subcutaneous tissue or skeletal muscle is relatively rare. The purpose of the present study is to clarify the clinicopathological features for confirming diagnosis as soft tissue metastasis and determining the primary site.

Method: We reviewed records of 11 patients with soft tissue metastasis in our institution from 1996 to 2009.

Result: In 9 of 10 patients who underwent magnetic resonance imaging, findings consisted of (ⅰ) poorly circumscribed high intensity lesions around tumor on T2-weighted images, and (ⅱ) irregular peritumoral enhancement and (ⅲ) poorly enhanced lesions on the center of 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 particularly useful diagnostic markers. Although 9 of 11 patients had poorly differentiated carcinoma, the primary site could be determined in 4 patients with cytokeratin 7 / 20 immunophenotype and positivity for tissue-specific antibodies. In 5 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.

Conclusion: Magnetic resonance imaging and biopsy are essential for differential diagnosis between soft tissue metastasis of carcinoma and soft tissue sarcoma. Moreover, systematic immunohistochemical examination enables confirmation of the primary origin in soft tissue metastasis of carcinoma.

Mini-abstract

Magnetic resonance imaging and biopsy are essential in differential diagnosis between soft

tissue metastasis of carcinoma and soft tissue sarcoma. Systematic immunohistochemical examination enables confirmation of the primary origin.

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 known history of carcinoma and 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 primary site of origin. The usefulness of 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 primary origin. However, studies utilizing these immunohistochemical markers for diagnosing as soft tissue metastasis and confirming the primary site are sparse. The purpose of the present study is to clarify the clinical and pathologic features for confirming diagnosis as soft tissue metastasis and determining the primary site. For this purpose, we reviewed test methods for diagnosis of soft

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tissue metastasis and determination of 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 metastasize from distant primary carcinoma at our institution from 1996 to 2009. All of the patients presented with soft tissue lesions, and seven patients had a history of carcinoma. 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, direct extension from adjacent tumors.

  Medical records of all patients were reviewed to assess anatomical location of metastasis, finally diagnosed primary organ, and biochemical, radiological, and histological examinations. In particular, biochemical data, MR imaging features, and histological findings were closely evaluated, and valuable findings for diagnosis of metastatic carcinoma and identification of the primary site were reviewed. Biochemical examination and MR imaging were performed in eight and ten 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) and CK20 (1:70 dilution; DAKO) for epithelial origins, TTF-1 (1:100 dilution; DAKO) and PE-10 (1:200 dilution; DAKO) for lung carcinoma, MUC5AC (1:100 dilution; Novocastra) and HIK1083 (1:20 dilution; Kanto Chemical) for gastric carcinoma, Hep-Par1 (1:50 dilution; DAKO) for hepatocellular carcinoma, CDX2 (1:100 dilution;

BioGenex) for colorectal carcinoma, and GCDFP-15 (1:50 dilution; Covance) for breast

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, TTF-1, MUC5AC, and CDX2 antibodies. HRP-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 by hematoxylin.

RESULTS

The clinical data for the 11 patients are summarized in Table 1. Five patients were male, 6

were female, and ages ranged from 61 to 79 years, with a mean of 70 years. Localization of

soft tissue metastases included upper extremity (4 cases), trunk (3 cases), and lower extremity

(4 cases). Four patients had metastasis of subcutaneous tissue and 7 patients had metastasis of

skeletal muscle. Seven patients had a history of carcinoma at presentation. In 9 cases of 10,

MR findings consisted of (ⅰ) poorly circumscribed high intensity lesions around tumor on

T2-weighted images, (ⅱ) irregular peritumoral enhancement on T1-weighted images with

intravenous gadolinium enhancement, and (ⅲ) poorly enhanced lesions on the center of

tumor on T1-weighted images (Fig. 1). Tumor markers such as CEA, CA 19-9, and CA 15-3

were examined in 8 patients, but these data were not helpful to detect the primary tumor

(Table 2). Histological tests with hematoxylin and eosin staining showed poorly differentiated

adenocarcinoma in 9 cases (Table 3). In immunohistochemical findings, the expression

patterns of CK7 and CK20, which are epithelial markers, indicated the CK7+/CK20-

immunophenotype in 7 cases, CK7-/CK20+ in 2 cases, CK7+/CK20+ in 1 case, and

CK7-/CK20- in 1 case (Table 3). In case 3, gastrointestinal or bile duct carcinoma was

strongly suspected because of CK7+/CK20- immunophenotype with MUC5AC positivity

(Fig. 2), and stomach carcinoma was finally identified at endoscopy. In case 5, CK7-/CK20+ immunophenotype with CDX2 positivity was diagnosed as rectal carcinoma. In case 8, a patient with prior history of bile duct and lung carcinoma, bile duct carcinoma was suspected because of 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 CK7-/CK20- immunophenotype with AE1/AE3 and CD10 positivity. In case 11, a patient without prior history of carcinoma, immunohistochemical findings showed CK7+/CK20- with TTF-1 positivity and the patient was finally diagnosed as lung carcinoma after addition of the appearance of mass lesion in lung. As 4 cases were negative for tissue-specific antibody, the primary sites were identified by investigation of prior history of carcinoma, histological findings of primary carcinoma, CK7/CK20 immunophenotype, and radiographic findings. However, CK7/CK20 immunophenotype was not consistent with common CK7/CK20 immunophenotype for prior carcinoma in 2 cases, and they were diagnosed with unknown primary site. The primary tumor was diagnosed finally in the lung (4 cases), bile duct (1 case), stomach (1 case), colon (1 case), breast (1 case), kidney (1 case), and of unknown primary origin (2 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 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 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 solitary mass caused by 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 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 cytokeratin (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 primary site of origin. The usefulness of 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). 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 CK7/CK20 immunophenotype (13,22-24). In 4 cases of our series, we could obtain definite findings for diagnosing primary origin using tissue-specific antibodies in conjunction with CK7/CK20 (cases 3, 5, 8, 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 CK7/CK20 phenotype in 5 cases (cases 2, 6, 7, 9, and 10). However, in the patient of case 4 with history of recurrent hepatocellular carcinoma, the primary origin could not be discriminated because the expression pattern of CK showed CK7+/CK20+ (a less common pattern in metastasis from hepatocellular carcinoma (25)), and

Hep-Par1 and other tissue-specific antibodies were negative. 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 limitation of primary origin determination by pathological examination alone.

Though the usefulness of immunohistochemical examination in 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 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 core needle biopsy as the first examination after confirmation of localization and properties of the tumor. In this study, it was shown that when tissue-specific antibodies were used in conjunction with CK7/CK20, the primary origin of soft tissue metastasis of carcinoma could be roughly determined. Definitive determination of primary origin could then be achieved in a short time by additional examinations after pathological evaluation of biopsy specimens.

Conflict of interest statement

None declared.

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Table 1. Clinical data of the patients

Patient No.	Age (years) and gender	Soft tissue metastasis		History of carcinoma	Primary organ
		Site	Depth		
1	79F	Inguinal	Muscle	Uterus	Unknown
2	71M	Thigh	Muscle	None	Lung
3	61M	Chest wall	Muscle	None	Stomach
4	73F	Arm	Subcutaneous	Liver	Unknown
5	76M	Hand	Subcutaneous	Colon	Colon
6	56F	Forearm	Muscle	Breast	Breast
7	68F	Calf	Muscle	Lung	Lung
8	72M	Calf	Muscle	Lung, Bile duct	Bile duct
9	62F	Back	Muscle	None	Lung
10	77M	Shoulder	Subcutaneous	Kidney	Kidney
11	76F	Thigh	Subcutaneous	None	Lung

Table 2. Hematological data of the patients

Patient No.	CEA (ng/ml)	CA19-9 (U/ml)	CA15-3 (U/ml)	AFP (U/μl)
1	0.9	56.5	-	<40
2	9.2	4603.0	-	-
3	31.3	0.0	-	<40
4	4.2	80.8	-	1910
5	15.0	2896.0	-	-
6	1.6	-	13.1	-
7	-	-	-	-
8	1.8	296.3	-	-
9	4.1	-	-	-
10	-	-	-	-
11	-	-	-	-

Normal range of CEA: <3.4 ng/ml, CA19-9: <37 U/ml, CA15-3: <25 U/ml, AFP: <40 U/μl.

Table 3. Histological data of the patients

| Patient No.	Histologic type	CK 7 / CK 20	others
1	Poorly differentiated adenocarcinoma	- / +	CDX2(-), MUC2(-)
2	Poorly differentiated adenocarcinoma	+ / -	PE-10(-),TTF-1(-), HIK1083(-)
3	Poorly differentiated adenocarcinoma	+ / -	MUC5AC(+)
4	Poorly differentiated adenocarcinoma	+ / +	Anti-hepatocyte antibody(-)
5	Poorly differentiated adenocarcinoma	- / +	CDX2(+)
6	Poorly differentiated adenocarcinoma	+ / -	GCDFP-15(-), ER(-)
7	Poorly differentiated adenocarcinoma	+ / -	TTF-1(-), PE-10(-)
8	Well-differentiated adenocarcinoma	+ / -	MUC5AC(+), TTF-1(-)
9	Poorly differentiated adenocarcinoma	+ / -	TTF-1(-), PE-10(-)
10	Adenocarcinoma, clear cell type	- / -	AE1/AE3(+), CD-10(+)
11	Poorly differentiated adenocarcinoma	+ / -	TTF-1(+)

CK = Cytokeratin; TTF = Thyroid transcription factor;
GCDFP = Gross cystic disease fluid protein; ER = Estrogen receptor.
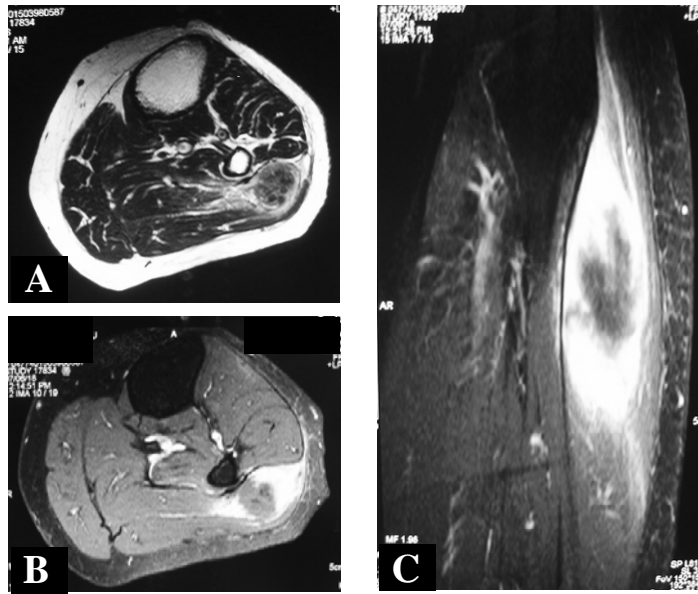
Figs. 1A-C MR findings of a 72-year-old man (patient No. 8) with metastasis to calf muscle.
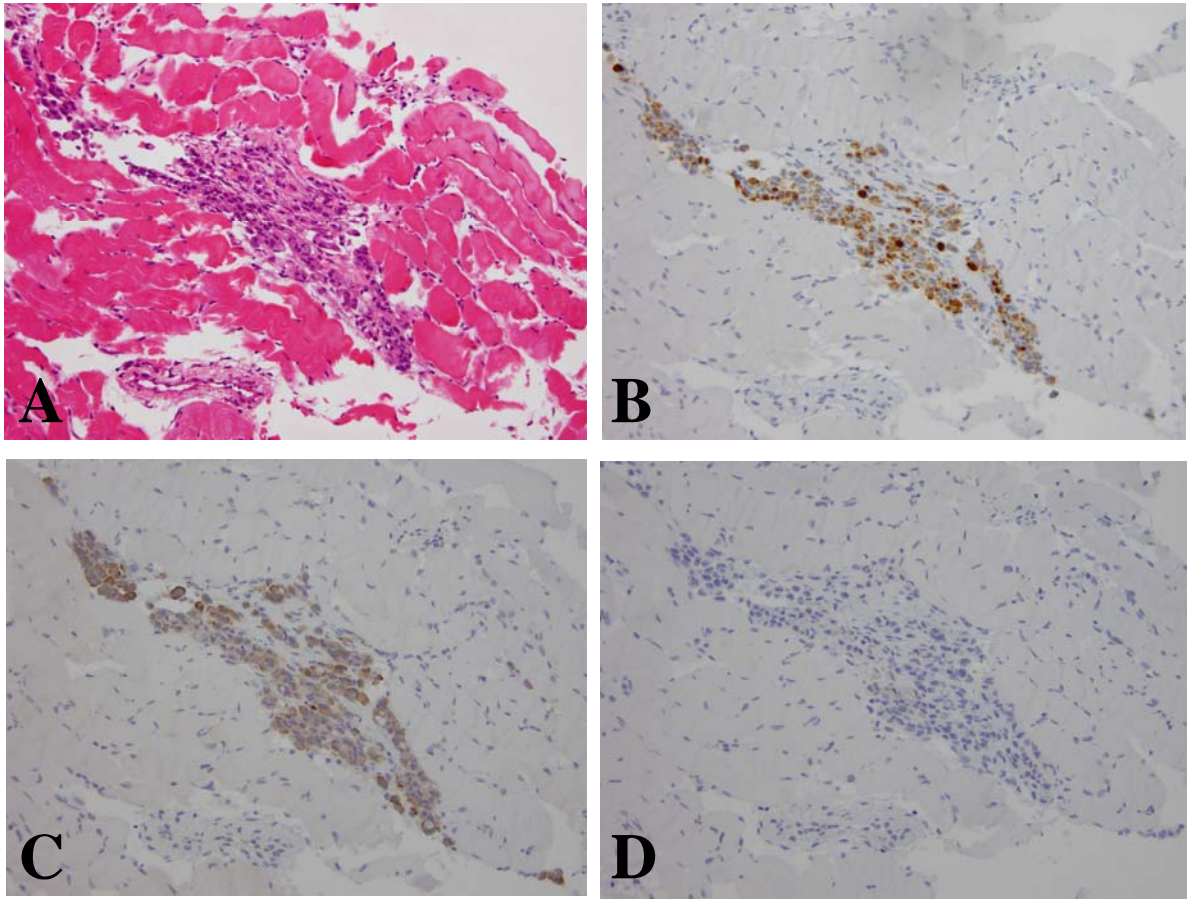
Figs. 2A-D Histological findings of patient No. 3.
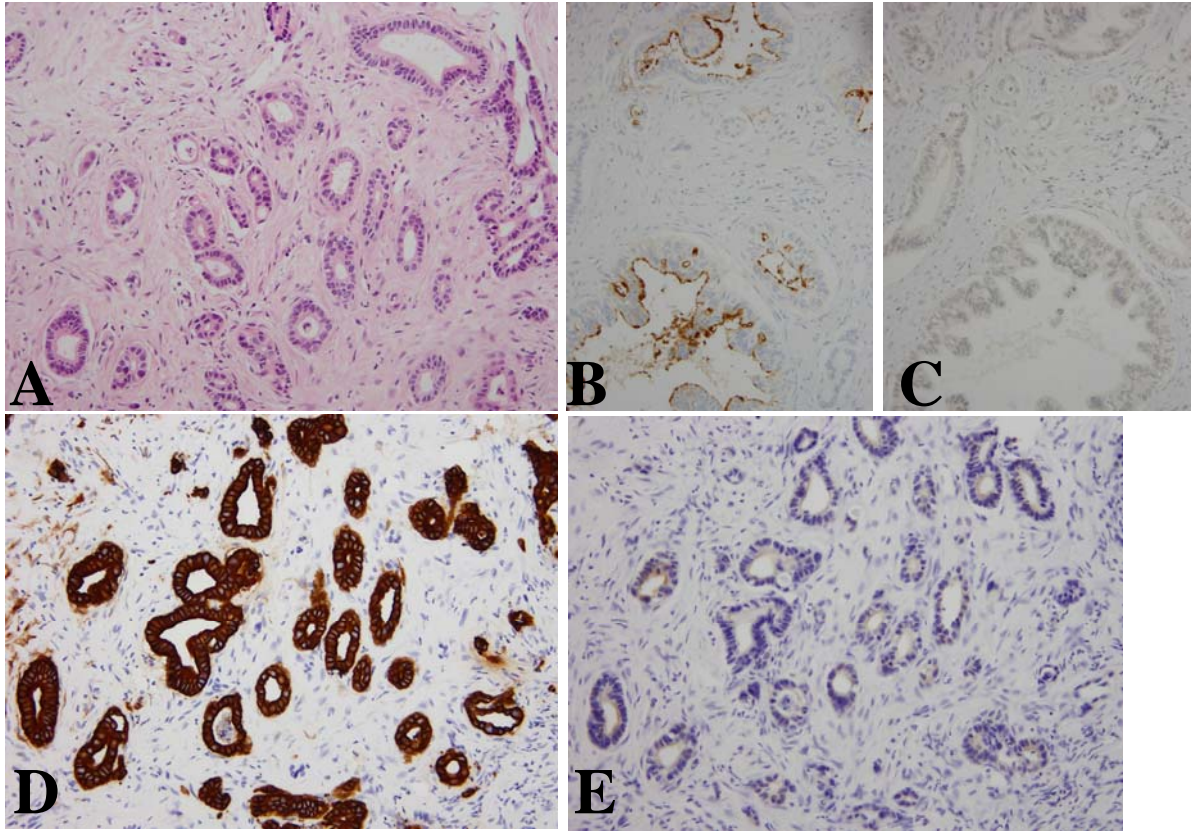
Figs. 3A-E Histological findings of patient No. 8.