An Autopsy Case of Carcinosarcoma of the Esophagus

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ABSTRACT :   A case of carcinosarcoma, a rare polypoid tumor of the esophagus is presented. The characteristic gross and microscopic features as well as a discussion of the histogenesis of the sarcomatous elements are presented by microscopic, immunohistochemical and electron micronscopic examinations. Immunohistochemically, keratin and EMA (epithelial membrane antigen) were demonstrated in the islands of squamous cell carcinoma within the sarcomatous elements and in the carcinoma in situ at the border of normal mucosa. Vimentin, desmin, actin, myoglobin, factor VIII, S-100 protein, NSE, neuraminidase were not demonstrated in both the carcinomatous and the sarcomatous elements except for a positive reactivity to α-1-antichymotrypsin in the sarcomatous elements at part. It is suggested that the sarcomatous elements are of epithelial origin based on the facts as follows : ① transition from overlying epithelium or carcinomatous islands to sarcomatous elements existent ; ② some small tubules were formed within the sarcomatous elements, which showed transition into the sarcomatous elements ; and ③ a part of the sarcomatous elements revealed either positive or weak reactivity to keratin and EMA. Further, weak reactivity to keratin and EMA in the more anaplastic lesion may reflect the lack of tonofilaments and desmosomes in the ultrastructural findings.

INTRODUCTION

Carcinosarcoma of the esophagus, a polypoid malignant tumor composed of both epithelial and sarcomatous elements, has been sporadically reported (5, 6, 10, 11, 12, 15, 17-19, 22, 23). Carcinosarcoma is generally divided into two categories, "true" and "so-called" carcinosarcoma. Several possible histogenetic theories of the sarcomatous elements have been proposed up to now. That is, the original nature of the sarcomatous elements is considered either epithelial (2, 7, 9, 16), mesenchymal neoplastic, or mesenchymal reactive such as pseudosarcoma from results of microscopic, immunohistochemical and electron microscopic study. The sarcomatous elements in the "so-called" carcinosarcoma are thought to be of epithelial origin. However, the nature of sarcomatous elements in the "true" carcinosarcoma has not been definitely confirmed and remains debatable.

Pseudosarcoma is noted as quite similar to

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"so-called" carcinosarcoma in regard to their histopathological and biobehavioral features (1, 3, 14). It is generally accepted that their distinctive features are the presence or absence of intermingling between the carcinomatous elements and the sarcomatous elements, or histopathological features in the metastatic lesions. Virtually, it is very difficult to distinguish "so-called" carcinosarcoma from pseudosarcoma. They are easily confused due to the use of uncertain diagnostic criteria and their similar biological behavior. Matsusaka *et al.* (9) and Osamura *et al.* (13) postulated these two tumors as the same entity on the basis of the close resemblance in their histopathological and biobehavioral features, but not on the basis of their histogenesis. Matsusaka *et al.* (9) called them "pseudosarcomatous carcinomas", and Osamura *et al.* (13) proposed the term of "polypoid carcinoma". In this study, we investigated and discussed the original nature of the sarcomatous elements using the immunohistochemical technique and electron microscopy.

CASE REPORT

A 67-years-old white man was admitted to Sasebo General Hospital on November 24, 1987 with 2-month history of progressive dysphagia, weight loss and hoarsness. On admission, malnutrition, generalized emaciation of the body and anemia were marked. Neither jaundice nor superficial lymphonode swelling was evident, except for moist rale on both lower lung fields. He was followed after receiving a blood tranfusion and antibiotics. He was hospitalized on December 12, 1987 with sever dyspnea, orthopnea and cough associated with viscous sputum. Chest roentogenogram revealed a large mass shadow in the superior mediastinum, a small coin lesion in the left lower lung and an infiltration shadow on both lower lung fields. Bronchofiberscopy revealed that the upper trachea was being compressed at posterior part. Endoscopy could not be performed due to his poor condition. Only tracheotomy was performed to relieve his dyspnea, in spite of suspicion of a malignant tumor of the esophagus and its metastasis. He developed sever dyspnea and died of sudden

respiratory arrest on Desember 19, 1987. The postmortem examination was performed immediately.

MATELIALS AND METHODS

LIGHT MICROSCOPY

The entire organs were fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin and eosin stained sections were routinely prepared and reviewed. Additional slides of the primary tumor of the esophagus and metastatic lesion were used for immunohistochemical study including Masson-trichrome stain, Elastica Van Gieson stain, phosphotungstic acid-hematoxylin (PTAH) stain, PAS and silver stain.

IMMUNOHISTOCHEMISTRY

The immunohistochemical study was performed using avidin-biotin-peroxidase (ABC) technique. The antibodies used are tabulated in Table 1. Sections were incubated with the primary antibodies for 1 hour after blocking endogenous peroxidase activity with 0.3% hydrogen peroxide in methanol. Following a wash in phosphate-buffered saline (PBS, pH = 7.6), sections were incubated for 20 minutes in biotinylated goat anti-rabbit (or goat anti-mouse) antibody (Vector Corp., Santa Barbara, CA). Those sections were rinsed and washed in PBS, then incubated 20 minutes in an avidin-biotin-peroxidase complex solution (Vector Corpo.). After washing in PBS, sections were incubated in 0.02% diaminobenzidine (DAB) and 0.006% hydrogen peroxide in Tris-HC 1 buffered solution (pH7.6) for 3 to 10 minutes. Sections were washed in tap water and counterstained with hematoxylin. After dehydrating in graded series of alcohols, sections were cleared in xylene and cover-slipped.

ELECTRON MICROSCOPY

For electron microscopic study, tissues from sarcomatous lesion of the representative tumor were processed according to conventional technique.

Table 1. Immunohistochemical reagent antibodies

Antibody	Source	Dilution
Keratin	DAKOPATSS Co.	1 : 50
EMA	DAKOPATSS Co.	1 : 150
Vimentin	DAKOPATSS Co.	1 : 200
Desmin	DAKOPATSS Co.	1 : 50
Actin	Biomedical Technologies Inc.	1 : 50
Myoglobin	DAKOPATSS Co.	1 : 200
Factor VIII	DAKOPATSS Co.	1 : 200
S-100 protein	DAKOPATSS Co.	1 : 500
NSE	DAKOPATSS Co.	1 : 800
Neuraminidase	DAKOPATSS Co.	1 : 200
α-1-antichymotrypsin	DAKOPATSS Co.	1 : 200
Biotinylated goat antimouse globulin	Vector Laboratories, Burlingame, CA, U. S. A.	Prediluted
Biotinylated goat antirabbit globulin	Vector Laboratories, Burlingame, CA, U. S. A.	Prediluted
Avidin-biotin peroxidase complex	Vector Laboratories, Burlingame, CA, U. S. A.	Prediluted

RESULTS

GROSS FEATURES ON AUTOPSY

A huge pedunculated polypoid tumor measuring 13×7×5cm attached to the anterior wall of upper esophagus by a short, broad stalk, which originated from 1 cm below the esophageal introitus (Fig. 1). The upper esophagus was remarkably dilated because of the tumor occupation. The tumor appeared fleshy and pale brownish to dark brownish with firm consistency. The surface of the tumor was mostly smooth, partly coarse and eroded. Most of the tumor was not covered with mucosa, although a part of the stalk was covered with a white mucosa continuous with normal esophageal mucosa. The cut surface of the tumor was grayish white associated with a large amount of hemorrhage and necrosis. A brownish yellow, right pleural effusion (150ml) and right fibrinous pleuritis were observed. Two small metastatic nodules, 1.5×1.3cm and 1.3×0.8cm respectively, were found in the lower lobe of the left lung (Fig. 2), and two 0.4cm nodules were found in the upper lobe of the right lung.

Both lower lobes of the lung were complicated with the patchy consolidation of bronchopneumonia and organized pneumonia (Fig. 2).

MICRSCOPIC FEATURES

The bulk of the primary tumor of the esophagus was composed of sarcomatous elements, which occupied from just below the squamous epithelium to the tunica adventitia of the esophagus in an expansive way. Most of the surface of the tumor was eroded. while a part of its edge was covered by intact and atrophic squamous epithelium. Squamous cell carcinoma in situ was observed only at the border of the normal mucosa, which showed abrupt transition from normal squamous epithelium (Fig. 3). The sarcomatous lesion showed a high degree of cellularity with intervention of a small amount of interstitial collagen. Sarcomatous elements were composed of an admixture of interlacing bundles of spindle cells (Fig. 4) and an anaplastic lesion (Fig. 5). Those two lesions were associated with bizarre multinucleated giant cells (Fig. 5). The spindle cells in the sarcomatous lesion had regular blunt-ended nuclei showing nuclear palisading

Fig. 1. Gross finding of the tumor of the esophagus.
A huge pedunculated polypoid tumor attached to the anterior wall of the eshophagus by a short, broad stalk. The surface of the tumor is fleshy and brown, with erosion.
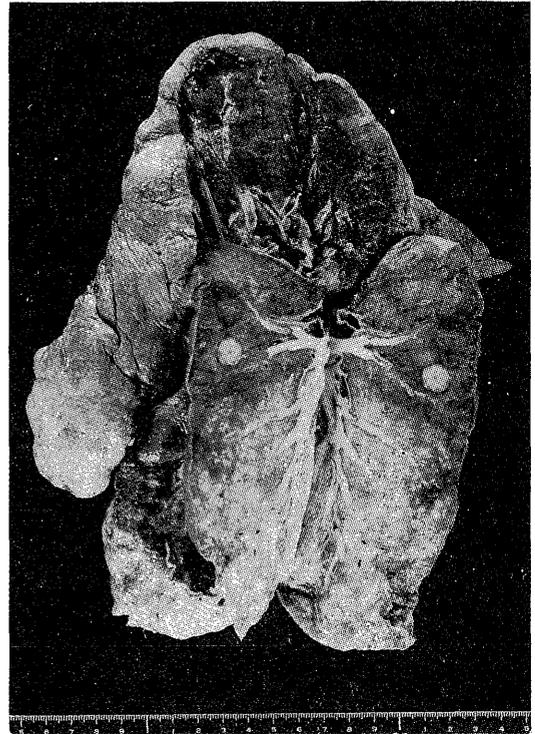
Fig. 2. Cut surface of the left lung.
Lower lobe demonstrates a metastatic nodule and patchy consolidation of bronchopneumoina.

Fig. 3. Microscopic finding showing transition zone between normal squamous epithelium and in situ carcinoma.(H. E stain, ×40)
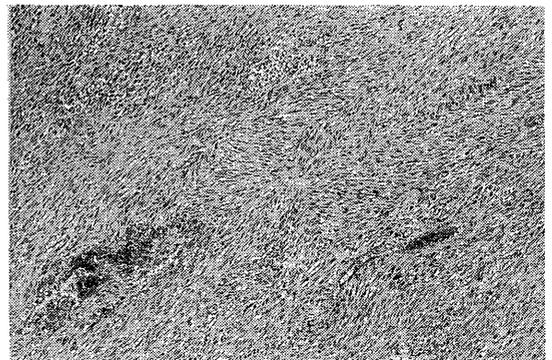
Fig. 4. Spindle cells within the sarcomatous lesion are arranged in a storiform pattern.(H. E stain, ×40)

in part. and occasional cells had perinuclear vacuoles. Anaplastic lesion showed more pleomorphic nuclei. Atypical mitotic figures between 40 and 75 mitoses/1OHPF were observed. Rhabdomyoblastic, chondroblastic or osteoblastic differentiation were not detectable. Reticulin fibers were uniformly
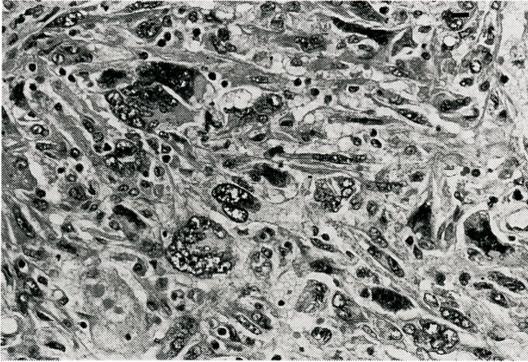
Fig. 5. Anaplastic feature of the sarcomatous lesion.
Multinucleated giant cells, atypical cells with bizarre nuclei and atypcial spindle cells are intermingled in haphazard. Abnormal mitotic figures are scattered. (H. E stain, ×200)

distributed enclosing individual tumor cells, forming a delicate network. Longitudinal striations within the spindle cells were not observed with Masson trichrome, phosphotungsticacid-hematoxylin (PTAH) and PAS stain. PAS positive granules were observed within the cytoplasm of the multinucleated giant cells.

Some islands of well differentiated squamous cell carcinoma were found within the sarcomatous elements (Fig. 6). Some atypical cells were scattered in cords or at random around the carcinomatous islands, which appeared to show transition from the carcinomatous islands. Further, small tubular structure or nests

of atypical cells were embedded within the sarcomatous elements (Fig. 11), a part of which showed gradual transition into anaplastic spindle cells. "Dropping-off" : the transition from the overlying in situ carcinoma to the sarcomatous elements seemed to exist (Fig. 7).
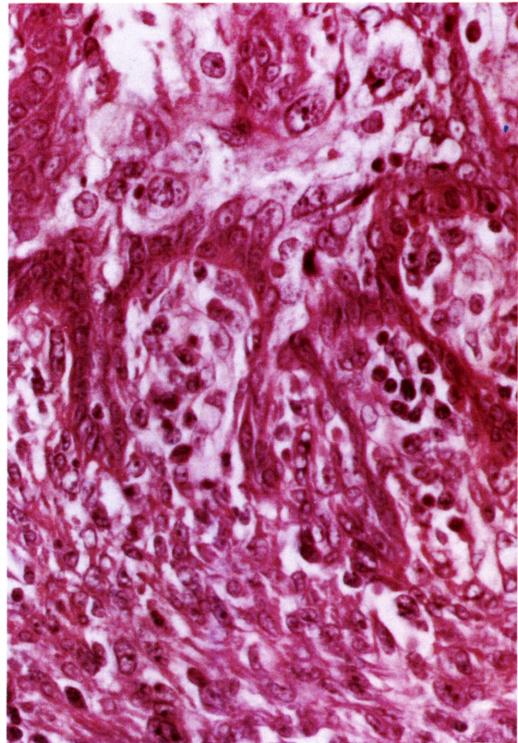

Fig. 7. Transiton zone between in situ carcinoma and spindle cells within sacomatous lesion.(H. E stain, ×100)

IMMUNOHITOCHEMISTRY

The result of immunohistochemical study is presented in Table 2. Keraitn and EMA (epithelial membrane antigen) were demonstrated in the in situ carcinoma and the islands of squamous cell carcinoma within the sarcomatous elements (Fig. 10), as well as in the normal squamous epithelium. All atypical cells within the in situ carcinoma showed moderate reactivity to keratin (Fig. 9) and EMA, while normal horny and squamous layer showed intense reactivity to keratin and EMA instead of their absence in the basal layer (Fig. 8). In the sarcomatous elements, most of the

Fig. 6. The islands of well differentiated squamous cell carcinoma are scattered throughout the sarcomatous lesion. (H. E stain, ×40)

Table 2. Immunohistochemical study in the normal squamous epithelium, carcinomatous and sarcomatous lesion

Antibody \ Site	Normal squamous epithelium	In situ or invasive squamous cell carcinoma	Sarcomatous lesion
Keratin	horny layer : +++ squamous cell layer : ++ basal layer : −	in situ ca. : +~++ invasive ca. : ++	mostly : − a few : +~(+)
EMA	horny layer : ++ squamous layer : + basal layer : −	in situ ca. : ++ invasive ca. : ++	mostly : − a few : +~(+)
Vimentin	−	in situ ca. : − invasive ca. : −	−
Desmin	−	in situ ca. : − invasive ca. : −	−
Actin	−	in situ ca. : − invasive ca. : −	−
Myoglobin	−	in situ ca. : − invasive ca. : −	−
Factor VIII	−	in situ ca. : − invasive ca. : −	−
S-100 protein	horny layer : − squamous layer : − basal layer : −	in situ ca. : − invasive ca. : −	−
NSE	−	in situ ca. : − invasive ca. : −	−
Neuraminidase	−	in situ ca. : − invasive ca. : −	−
α-1-antichymo-trypsin	−	in situ ca. : − invasive ca. : −	+ (partly)

+++ : Intense positive reactivity ++ : Moderate positive reactivity + : Mild positive reactivity
(+) : Faint positive reactivity (−) : Negative reactivity

cells showed little or no reactivity to keratin and EMA, although positive reactivity to them was shown in a few atypical cells around the islands of squamous all carcinoma (Fig. 12), and in the small tubules (Fig. 11).

The positive intensity of Keratin and EMA appeared to decrease in accordance with the progression of anaplasia (Fig. 13). Positive reactivity to α-1-antichymotrypsin was observed in the sarcomatous elements. Vimentin, desmin, actin, myoglobin, Factor VIII, S-100 protein, NSE and neuraminidase were not observed in either carcinomatous or sarcomatous elements.

Ultrastructure finding

In the sarcomatous elements, the nuclei of spindle cells were folded, notched or were deeply cleft with many invaginations. A few mitochondria, sparse elements of endoplasmic reticulum, paucity of pinocytotic vesicles and Golgi complex were observed. Neither tonofilament or desmosome were apparently detected.

DISCUSSION

The histogenesis of carcinosarcoma is still controversial. Matsusaka *et al.* (9) suggested the division of carcinosarcoma into two groups : 1) " true " carcinosarcoma composed of a carcinoma and a genuine sarcoma, and 2) " so-called " carcinosarcoma composed of a primary carcinoma having a sarcoma-like appearance. Meyer (10) hypothesized three possible explanations for " true " carcinosarcoma : ① collison
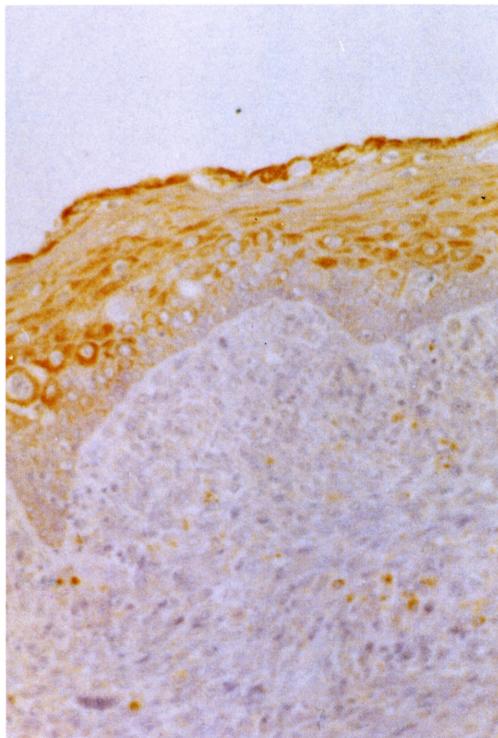
Fig. 8. Keratin stain of the normal squamous epithelium.
Positive reactivity to keratin is demonstrated in the squamous and horny layer but not in the basal layer.(keratin stain, ×40)
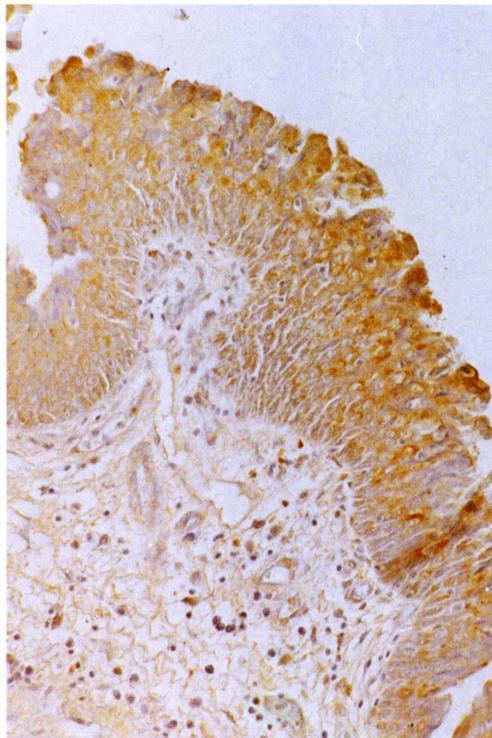
Fig. 9. Keratin stain of the in situ carcinoma. Moderate positive reactivity to keratin is demonstrated in all of the in situ carcinoma, whose reactivity does not have a staining gradient as with normal epithelium (compare with Fig. 9). (keratin stain, ×40)

tumor, in which carcinomatous and sarcomatous elements arise independently, then invade and itermingle within one tumor ; ② combination tumor, wherein both epithelial and mesenchymal elements deriving from the same stem cell undergo malignant conversion, and ③ composition tumor, in which two separate cell lines of epithelial and mesenchymal elements, undergo malignant conversion, respectively. Further, Harvey and Hamilton (5) proposed four possibilites of carcinosarcoma ; ① carcinoma associated with sarcoma, both of which develop independently ; ② carcinoma associated with sarcoma, which develops as a result of reactive change to the carcinoma ; ③ carcinoma with spindle cell metaplastic variants of epithelical cells, and ④ carcinoma with benign and active stromal reactions. The latter two propositions by Harvey and Hamilton are

supposed to be " so-called " carcinosarcoma. In other respects, Saphier and Vass (15) pointed out the case of carcinoma invading a benign tumor such as leiomyoma, and the primary sarcoma invading normal epithlium, in which the remaining epithelium was misunderstood as carcinoma. It seems that a definite diagnostic criteria does not exist to differentiate between "true" or "so-called" carcinosarcoma and pseudosarcoma.

A majority of authors suppose " so-called " carcinosarcoma to be merely an anaplastic carcinoma with spindle-shaped transitional cells by histological, immunohistochemical or ultrastructural examinations (2,6,7,8,9,16). In our case, an epithelial origin of sarcomatous elements was suggested by the occurence of some transitions between overlying epithelium and the sarcomatous elements, or between
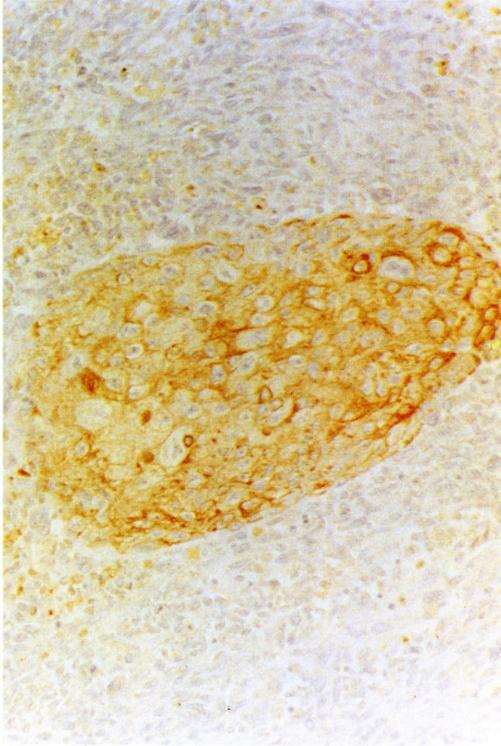
Fig. 10. Keratin stain of squamous cell carcinoma island within sarcomatous lesion (keratin stain, ×100)

Fig. 12. Transition zone between carcinomatous island and sarcomatous lesion. Spindle anaplastic cells demonstrate positive reactivity to keratin. (Kerain, ×200)
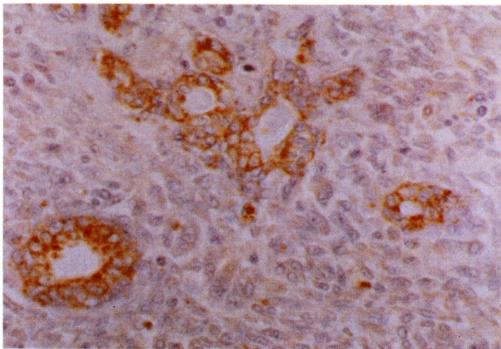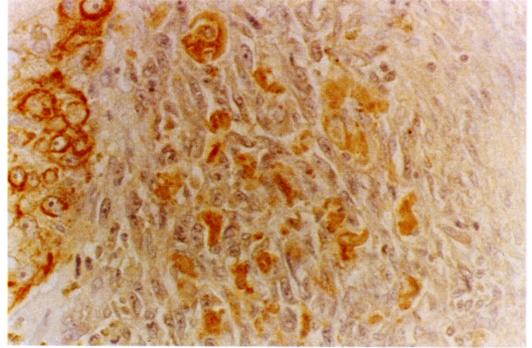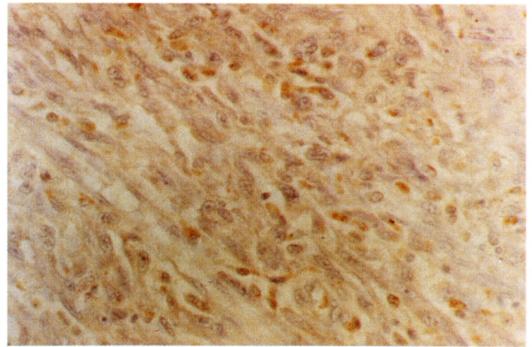

Fig. 11. Some tubules formed within the sarcomatous lesion show positive reactivity to keratin. A part of the tubules transits into spindle cells, which show faint reactivity to keratin.(keratin stain, ×200)

Fig. 13. Anaplastic atypical cells within sarcomatous lesion demonstrate faint reactivity to keratin.(keratin stain, ×200)

carcinomatous islands and the sarcomatous elements, which were supported by evidence of positive reactivity to keraitn and EMA (21) in the sarcomatous elements. As for the stronger evidence of the epithelial origin of the sarcomatous elements, some keratin and EMA positive tubules were formed within the sarcomatous elements, which gradually transformed into anaplastic cells. This finding may also show that the anaplastic cells are originally of epthelial, and slight differentiation in them may lead to the formation of tubules. On the other hand, normal squamous epithelium showed a progressive increase of the reactivity to keratin and EMA from basal layer to horny layer. Furthermore, the more anaplastic or poorly differeniated the sarcomatous elements became, the less weak reactivity to keratin and EMA the lesion showed. These findings may reflect that tonofilaments and desmosomes are less common in poorly differentiated squamous carcinoma, ultrastructurally as suggested by Kuhajda (7). It is suggested that the sarcoma-

tous elements in our case were derived from epbthelial origin. Therefore, this case is concluded not to be " true " carcinosarcoma but rather " so-called " carcinosarcoma, which is supported by the negative reactivity of vimentin, desmin, actin, myoglobin and Factor VⅢ of mesenchymal origin (20).

It is interesting to note that some part of the sarcomatous elements showed positive reactivity to α-1-antichymotrypsin. This finding may suggest the presence of the reactive growth of fibroblast, where collagen fibrils were rich in the stroma.

We considered fibrosarcoma, malignant fibrous histiocytoma (MFH), and rhabdomyosarcoma a possible cause for differential diagnosis of the sarcomatous elements. If, in the case of fibrosarcoma, it is expected that the sarcomatous elements lack the multinucleated giant cells, then prominent neoplastic fibroblasts will be detected ultrastracturally. According to the description by Ghadially (4), detection of the " fibrohistiocyte " is the important clue in distinguishing MFH from fibrosarcoma ultrastructurally. Myoglobin, which is expressed in the striated muscle, would be demonstrated in the rhabdomyosarcoma (20). We denied these three categories as a diagnosis for the sarcomatous elements since our case lacked the necessary findings to permit their confirmation.

On the other hand, sarcomatous lesion in the pseudosarcoma is supposed to be a sharply demarcated mass from the epithelial origin, and to be produced by the non-neoplastic response to the epithelial elements, or granulomatous tissue mass. But the causative factor in production of this sarcomatous lesion is not clear. If in the case of pseudosarcoma, α-1-antichymotrypsin and non-neoplastic fibroblasts will be dominantly demonstrated as a possible corollary from our result. It appears to be virtually impossible to distinguish carcinosarcoma from pseudosarcoma by the presence of an intermingling of both epithelial and sarcomatous elements, and/or the lack of a juxtaposition of them (14). The morphological features in the metastatic lesion may not be helpful to distinguish carcinosarcoma from pseudosarcoma, since they may both have a

potentiality to give rise to either carcinomatous elements, sarcomatous elements, or both, as a metastatic features.

It would be helpful to use parallel applications of immunohistochemical and ultrastructural studies in order to define the nature of the sarcomatous elements.

ACKNOWLEDGEMENT

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