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Clinical pathology analysis of esophageal sarcomatoid carcinoma

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Abstract ***Objective:*** The purpose of this study was to study the clinical, imaging characters and pathological characteristics of esophageal sarcomatoid carcinoma. ***Methods:*** We reviewed 23 cases of esophageal sarcomatoid carcinoma from January 2006 to December 2013 in four hospitals. The data of patients who were esophageal sarcomatoid carcinoma operated were retrospectively analyzed. All cases had completed upper gastrointestinal barium images materials and 14 of these cases had completed CT images materials. Upper gastrointestinal barium images and CT imaging features include tumor location, size, shape, and strengthen, etc. The biological parameters of lesions including the express of cytokeratin AE1/AE3, 34βE12, p63, Vimentin, desmin, Actin, S-100 and Ki-67 detected by immunhistochemical UltraSensitive™ S-P method (n = 23), and the patients' data of contrastographic picture (n = 23), imaging characters of CT scan (n = 14), and their relationship were studied. ***Results:*** Upper gastrointestinal barium images, CT imaging and gastrointestinal fiberscopy revealed lobulated intraluminal filling defect 0.4 cm to 5.7 cm × 3.5 cm × 1.3 cm (mean = 3. 7 cm) in the mid (n = 14), lower (n = 7) and upper (n = 2) intrathoracic esophagus. Among 23 cases of esophageal sarcomatoid carcinoma, 19 patients were of mushroom type, 2 patients was of ulcer type, and 2 patients were of medulla type; 19 patients were pedunculated, and 4 patients were no pedunculated (2 patients was of ulcer type). The tumor surface was relatively smooth and esophageal compliance was maintained. The pathological changes of esophagus such as lightly locked, rigid wall no-manifest partly, esophageal lumens expand partly, major filling sublobe defect could be shown through contrast medium. Normal esophagus was no unpack obviously over pathological changes. Enhanced computed tomography showed tumors in the intrathoracic esophagus and 8 lymph nodes metastases in 3 cases. Histologically, carcinomatous and sarcomatous components coexist. Microscopically, the tumor comprised poorly differentiated squamous cell carcinoma and spindle-shaped cells resembling leiomyosarcoma. Immunohistochemically, spindle-shaped sarcomatous cells displayed weekly positive reaction to cytokeratin AE1/AE3. Transitional zone was seen between sarcomatous and carcinomatous elements in 5 cases. The 17 lymph nodes metastases in 5 cases (53 lymph nodes) among 23 cases esophageal sarcomatoid carcinoma (187 lymph nodes) were observed. ***Conclusion:*** The clinical and radiologic features of esophageal sarcomatoid carcinoma overlap with those of other esophageal neoplasms. There are the radiologic imaging changes such as a large, intraluminal, polypoid mass, major filling sublobe defect and pedicle skin flap tumor in esophageal lumen, esophageal lumen extension partly, dissepiment rigidity wall no obviously, etc. Histologically, carcinomatous and sarcomatous components coexist and the biphasic pattern is the key diagnostic feature. However, esophageal sarcomatoid carcinoma has a more favorable prognosis than other malignant esophageal neoplasms. Immunohistochemical staining seems necessary to distinguish these lesions from other esophageal neoplasms.

Key words esophagus; sarcomatoid carcinoma; barium sulfate; tomography, X-ray computer; pathology; diagnosis

Sarcomatoid carcinoma of the esophagus is a malignant neoplasm involving both carcinomatous and sarcomatous components. Esophagus sarcomatoid carcinoma is a rare malignancy accounting for approximately 1%–2% of all esophageal neoplasms [1–3]. This unusual malignancy is defined as a squamous cell carcinoma with a variable sarcomatoid spindle cell component [1, 4, 5]. It is also known by a variety of other terms, including carcinosarcoma, pseudosarcomatous squamous cell carcinoma, polypoid carcinoma, and squamous cell carcinoma with a spindle cell component [1, 5, 6]. Immunohistochemically, the sarcomatoid cells may also be focally immunoreactive with

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cytokeratin, in addition to the epithelial component. The clinical and radiologic findings resemble other esophageal neoplasms. A few reports of esophageal sarcomatoid carcinomas have been published, sometimes the carcinomatous element may not be obvious, especially in limited biopsies, and the tumor may be mistaken for a pure sarcoma [2, 4].

Materials and methods

Materials

Twenty-three cases of esophageal sarcomatoid carcinoma were collected during excision surgery at Rizhao People's Hospital, China (n = 10), Tai'an Central Hospital, China (n = 6), Rizhao Traditional Chinese Medicine Hospital, China (n = 5), and Rizhao Jufeng Hospital, China (n = 2) from January 2006 to December 2013. Esophageal sarcomatoid carcinoma diagnosis was verified by histological methods, and pathological categorization was determined according to the current World Health Organization classification of the digestive system (WHO 2010). All patients signed informed consents, and this study was approved by Local Ethical Committee.

Among them there were 4 cases of female and 19 cases of male, age ranged from 42 to 77 years, mean 59. 8 years. The esophageal sarcomatoid carcinoma biological parameters including the express of cytokeratin AE1/AE3, 34βE12, p63, Vimentin, desmin, Actin, S-100 and Ki-67 detected by immunohistochemistry UltraSensitive™ S-P method, and the serum levels of carcino-embryonic antigen (CEA), tumor specific growth factor (TSGF), and carbohydrate antigen 125 (CA125) measured in serum (n = 17) with electrochemiluminescence method and their relationship were studied.

Methods

The data of 23 cases of esophageal sarcomatoid carcinoma from January 2006 to December 2013 in four hospitals were retrospectively analyzed. All cases had complete upper gastrointestinal barium images materials and 14 of these cases had complete CT images materials. Upper gastrointestinal barium images and CT imaging features included tumor location, size, shape, and strengthen, etc. The biological parameters of lesions including the express of cytokeratin AE1/AE3, 34βE12, p63, Vimentin, desmin, Actin, S-100 and Ki-67 detected by immunhistochemical UltraSensitive™ S-P method (n = 23), and the patients' data of contrastographic picture (n = 23), imaging characters of CT scan (n = 14), and their relationship were studied.

Immunohistochemistry

Tissue samples were fixed in 10% neutral buffered formalin and embedded in paraffin. Tissue sections were deparaffinized and rehydrated using standard procedures. Immunoreactions were processed using the UltraSensitive™ S-P kit (Maixin-Bio, China) according to the manufacturer's instructions, and signals were visualized using the DAB substrate, which stained the target protein yellow. The pathological specimens were reviewed independently by two pathologists and the pathologists were blinded to the subject's clinical history, and the results of the immunohistochemistry staining assay. In brief, a proportion score was assigned that represented the estimated proportion of positive tumor cells on the entire slide. For each histological section, the percentage of positive cells was scored as 0 (< 5%), 1 (6%–25%), 2 (26%–50%), 3 (51%–75%) and 4 (> 75%), and the staining intensity was scored as 0 (negative), 1 (weak), 2 (moderate) and 3 (strong). The immunoreactive score (IRS) was obtained by multying the percentage of positive cells of esophageal sarcomatoid carcinoma and the staining intensity. Immunohistochemical results with an IRS of 0 were considered negative(–), 1–4 weak positive (+), 5–8 moderate positive (++) and 9–12 strong positive (+++). Tumors expressing of Ki-67 in > 5% of the tumor cells were considered as positive. In addition, for the percentage of cancer cells of Ki-67 expression showing a nuclear reactivity was recorded after inspection of all optical fields at 200× and the mean value was used to score each case. Tumors with expression of > 5% of tumor cells were considered to be positive.

Measure of biomarkers in blood serum samples

We performed biomarkers of blood serum analysis in 17 patients. For squamous cell carcinoma-related antigen, CA153, TSGF, CA125 and CEA analysis, 3 mL heparinized blood was drawn from each individual. The biomarkers were detected with electroc-hemiluminescence method in the Clinical Laboratory in Rizhao People's Hospital, China.

Results

Clinical features

Twenty-three cases of esophageal sarcomatoid carcinoma were diagnosed during excision surgery at the four hospitals. The median age at diagnosis for esophageal sarcomatoid carcinoma was 59. 8 years, age ranged from 42 to 77 years. Among them there were 19 cases of male and 4 cases of female (M : F = 4.75 : l). Twenty-three cases who were dentist by profession from West Bengal presented in with complaints of dysphagia to solids for 12 years aggravated for 1 month. Duration of the disease of 23 cases was six weeks to 11 months (mean = 2.1 months). The 19 patients presented with progressive dysphagia, and three cases had no loss of appetite. Three cases had loss of weight, 3 cases presented with chest discomfort, 5 cases

had burning retrosternal pain, nausea, and vomiting, and 3 cases physical examination were unremarkable. There were no multiple tumors among the 23 cases. They were diagnosed with radiography or upper endoscopy. The 14 cases (60.9%) of tumors arose in the mid esophagus, 7 cases (30.4%) in the distal esophagus, and 2 cases (8.7%) in the proximal esophagus. Partial or total esophagectomy with regional lymph node dissection was performed for 15 cases of esophageal sarcomatoid carcinoma. Tumor markers of carcinoma-related antigen, CA153, TSGF, CA125 and CEA were negative within normal limits. Among 23 carcinosarcoma patients, twenty patients (87.0%) underwent surgical resection, two patients (8.7%) underwent local excision and one patient underwent endoscopic resection. Involvement of regional lymph nodes was seen in 5 of 23 patients (21.7%) with sarcomatoid carcinoma.

Imaging features

Upper gastrointestinal barium images, CT imaging and gastrointestinal fiberscopy revealed lobulated intraluminal filling defect 0.4 cm to 5.7 cm × 3.5 cm × 1.3 cm (mean = 3.7 cm) in the mid (n = 14), lower (n = 7) and upper (n = 2) intrathoracic esophagus. Among 23 cases of esophageal sarcomatoid carcinoma, 19 patients were of mushroom type, 2 patients was of ulcer type, and 2 patients were of medulla type; 19 patients were pedunculated, and 4 patients were no pedunculated (2 patients was of ulcer type). Barium studies showed large intramural mass (n = 17; 73.9%), with ulceration/tracking (n = 4; 17.4%), expansile intraluminal masses (n = 1; 4.3%), or areas of luminal narrowing (n = 1; 4.3%). The tumor surface were relatively smooth and esophageal compliance was maintained. The pathological changes of esophagus such as lightly locked, rigid wall no-manifest partly, esophageal lumens expand partly, major filling sublobe defect could be shown through contrast medium. CT imaging may show inhomogenous enhancing intramural mass. Normal esophagus was no unpack obviously over pathological changes. Enhanced computed tomography showed tumors in the intrathoracic esophagus and 8 lymph nodes metastases in 3 cases.

Pathology

Macroscopically, among 23 cases of esophageal sarcomatoid carcinoma, 19 patients were of mushroom type, 2 patients was of ulcer type, and 2 patients were of medulla type; 19 patients were pedunculated, and 4 patients were no pedunculated (2 patients was of ulcer type). The tumor surface were relatively smooth and esophageal compliance was maintained. Histologically, tumor specimens showed a tumor comprising squamous cell carcinoma with spindle cell components, and carcinomatous and sarcomatous components coexisted. These tumors were biphasic, containing a mixture of carcinoma and malignant sarcomatoid elements, with the latter generally forming the bulk of tumor (Fig. 1a and 1b). Microscopically, the tumor comprised poorly differentiated squamous cell carcinoma and spindle-shaped cells resembling leiomyosarcoma. Immunohistochemically, spindle-shaped sarcomatous cells displayed focally weekly positive reaction to cytokeratin AE1/AE3, 34βE12 (Fig. 1c and 1d), p63, and positive reaction to vimentin, a marker of mesenchymal components. The expression of desmin, Actin, S-100 were negative. Ki-67 labeling index was high (Ki-67 LI ≥ 30%) in both components. Transitional zone was seen between sarcomatous and carcinomatous elements in 5 cases. The

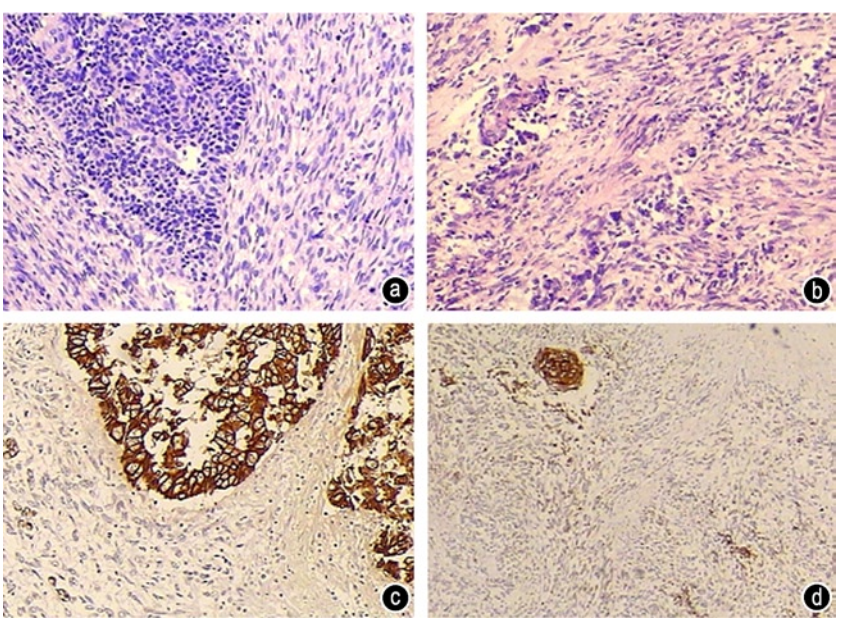

Fig. 1 Histological findings of tumor and immunochemical staining for cytokeratin. (a) It revealed a mixture of epithelial and stromal elements (H&E stain, × 100); (b) The nest of differentiated squamous cell carcinoma was observed areas of well-differentiated squamous cell carcinoma (upper left) admix with malignant spindle cell component, the stromal portion of the tumor contains spindle cells (H&E stain, × 100); (c) Immunochemical staining for cytokeratin AE1/AE3, carcinomatous component showed a positive reaction, sarcomatous component showed focal positive reaction, SP × 200; (d) Immunohistochemical stain for cytokeratin 34βE12, sarcomatous component showed a focal weekly positive reaction, SP × 100

17 lymph nodes metastases in 5 cases (53 lymph nodes) among 23 cases of esophageal sarcomatoid carcinoma (187 lymph nodes) were observed.

Discussion

Esophagus sarcomatoid carcinoma is an uncommon malignancy, representing approximately 2% of esophageal carcinomas [1–3, 5–7]. It has also been referred to as carcinosarcoma, pseudosarcoma, pseudosarcomatous squamous cell carcinoma, spindle cell carcinoma, and polypoid carcinoma, reflecting the uncertainty of its pathogenesis [8–10]. Histologically, carcinomatous and sarcomatous components coexist. The clinical and radiologic findings resemble other esophageal neoplasms. Sarcomatoid carcinoma often presents as a large, intraluminal, polypoid mass on barium esophagram. Despite its size, however, sarcomatoid carcinoma has a more favorable prognosis than other malignant esophageal neoplasms, likely because of its exophytic growth into the lumen, rather than deep invasion [2].

Duration of symptoms varies from days to months but is usually 3 months or less. Esophageal sarcomatoid carcinomas occur more commonly in men, typically, those aged 60 to 70 years [2, 8, 9]. The median age at diagnosis for esophageal sarcomatoid carcinoma is 60 years [2–4]. About 60% of tumors arise in the middle esophagus, nearly 30% in the distal esophagus, and less than 10% in the proximal esophagus. Patients often present at an early stage because of the relatively large size and obstructive symptoms. Patients with esophagus sarcomatoid carcinoma commonly present with progressive dysphagia, weight loss, chest discomfort, and sometimes with burning retrosternal pain, nausea, and vomiting [2, 11].

Like other esophageal neoplasms, they are diagnosed with radiography or upper endoscopy. Barium studies may show large intramural mass with ulceration/tracking, expansile intraluminal masses, or areas of luminal narrowing [2, 4, 5, 11]. The lumen may be dilated, and the wall stretched. The characteristic radiographic finding is a bulky tumor expanding, but not obstructing, the lumen. CT imaging may show inhomogenous enhancing intramural mass [2, 4]. Endoscopically, these are characterized by polypoid and exophytic masses and rarely as ulcerating tumour. The lumen may be dilated, and the wall stretched. The characteristic radiographic finding is a bulky tumor expanding, but not obstructing, the lumen. The surface may be smooth, intact, or ulcerated. The tumors are commonly attached to the wall by a pedicle, but occasionally, there is no pedicle, and the polypoid tumors are attached to the esophageal mucosa by a broad base [2, 4, 9, 11]. The surrounding mucosa is generally found grossly to be normal. The cut surface is typically white-gray, soft, and fleshy. Upper gastrointestinal studies and gastrointestinal fiber gastroscope revealed a lobulated intraluminal filling defect 0.4–5.7 cm long in the lower intrathoracic esophagus. The tumor surface may be smooth, intact, or ulcerated, and esophageal compliance was maintained. Tumor invasion was limited to the esophageal wall. Enhanced computed tomography showed a tumor in the lower intrathoracic esophagus. Metastatic lesions including lymph node metastases were observed [2, 4, 5, 11].

Histologically, carcinosarcomas has both carcinomatous and sarcomatous components. The sarcomatous component of carcinosarcoma is composed of dense interlacing bundles of spindle-shaped cells in the submucosa. Carcinomatous and sarcomatous components coexist. Microscopically, the tumor comprised poorly differentiated squamous cell carcinoma and spindle-shaped cells resembling leiomyosarcoma [1–3, 12]. Test results show the epithelial component of a sarcomatoid carcinoma is cytokeratin positive, whereas the mesenchymal element exhibits strong immunoreactivity with vimentin and may occasionally exhibit immunoreactivity with cytokeratin, but when present, it is almost always focal and less intense. The sarcomatoid cells are occasionally immunoreactive with actin and desmin. The tumor cells in the transitional zone between the carcinomatous and sarcomatous elements may have the same immunoreactivity as the sarcomatous element. Because of the combination of sarcoma and carcinoma, the debate has centered upon whether the two components are independent or the sarcomatous component is derived from metaplasia of the carcinomatous component [2, 4, 5, 11]. Immunochemical staning for cytokeratin AE1/AE3, carcinomatous component shows a positive reaction, sarcomatous component shows focal positive reaction. Transitional zone was often seen between sarcomatous and carcinomatous elements. Several immunohistochemical studies have found the sarcomatoid cells to be immunoreactive with cytokeratin, suggesting epithelial derivation, and earning the label of sarcomatoid carcinoma. However, other studies report the stromal component to exhibit only vimentin immunoreactivity and failed to exhibit cytokeratin immunoreactivity [2, 4–9, 11]. Other studies reveal the sarcomatous component consisted of anaplastic spindle and pleomorphic tumor cells that mimicked malignant fibrous histiocytoma (MFH). Both the sarcomatous and carcinomatous components were positive for p53 immunohistochemically. Further molecular analysis revealed that the two components had the same somatic mutation in the p53 gene. These results suggest a monoclonal origin of this biphasic tumor [12]. Chen *et al* analyzed 31 patients with esophageal sarcomatoid carcinoma who underwent surgery the clinicopathological characteristics and prognosis. In their study, in the carcinomatous components, positive expression of CK and EMA was found in all the 31 cases, and positive expression of vimentin in 5 of the 31 cases. In

the sarcomatous components, positive expression of CK, EMA and vimentin was found in 29, 28 and 23 cases, respectively [13].

The differential diagnosis includes other polypoid esophageal lesions, which include benign lesions, such as squamous papilloma and fibrovascular polyp, or malignant neoplasms, such as squamous cell carcinoma, malignant melanoma and malignant fibrous histiocytoma [2, 4, 7]. Sarcomatoid carcinoma often presents as a large, intraluminal, polypoid mass on barium esophagram. The clinical features of esophageal sarcomatoid carcinoma overlap with those of other esophageal malignancies. It is the radiologic imaging changes such as major filling sublobe defect and pedicle skin flap tumor in esophageal lumen, esophageal lumen extension partly, dissepiment rigidity wall no obviously, etc. It presents as a bulky intraluminal polypoid lesion mainly in the mid to lower esophagus, which harbors both carcinomatous and sarcomatous components histologically, and the biphasic pattern is the key diagnostic feature. It often presents relatively early because of its rapid intraluminal growth. Histologically, a biphasic pattern is the key diagnostic feature. Immunohistochemical staining seems necessary to distinguish these lesions from other esophageal neoplasms. The lack of malignant epithelial elements help in differentiating pure sarcomas from sarcomatoid carcinomas, but the epithelial component might not be sampled in the biopsy specimen.

The prognosis of sarcomatoid carcinoma is much better than that of common squamous cell carcinoma because the sarcomatoid carcinoma tumors tend to grow into the lumen rather than into the wall. Despite its large size and cytologic atypia, a sarcomatoid carcinoma tends to have a good prognosis. These lesions are usually treated surgically with esophagogastrectomy. Early detection and treatment by surgical resection are fundamental to long-term survival. Chemoradiotherapy may be considered before resection for bulky tumors [2, 4, 5, 11, 14]. Esophageal sarcomatoid carcinoma is a particular type of esophageal malignancy with unique clinicopathological features. Esophageal sarcomatoid carcinoma is reported mainly in small case series [1, 2, 4, 9, 12], with the largest series having 31 cases reported by Chen *et al* [13], and 22 cases reported by Yu *et al* [12]. In Chen's study, the 1-, 3-, and 5-year survival rates were 80.6%, 55.9% and 33.4%, respectively, and the median survival time was 40 months [13]. Esophageal sarcomatoid carcinoma is a particular type of esophageal malignancy with unique clinicopathological features. The diversity and complexity of the carcinomatous and sarcomatous components and their potential of transformation and differentiation lead to different prognosis from each other. The metastases may be carcinomatous, sarcomatoid, or mixed. Metastatic sites include the regional lymph nodes, followed by the lung and pleura.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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