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CASE REPORT

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# 식도 암육종 환자에서 이시적으로 발생한 식도 편평상피세포암 1예

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## A Case of Metachronous Development of Esophageal Squamous Cell Carcinoma in the Patient with Esophageal Carcinosarcoma

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Esophageal carcinosarcoma is a rare malignant esophageal neoplasm consisting of both carcinomatous and sarcomatous elements, with an incidence of 0.5%. There have been only a few case reports of carcinosarcoma and squamous cell carcinoma coexisting in the esophagus. However, all of these are cases of synchronous or metachronous development of carcinosarcoma after chemoradiotherapy in patients of esophageal squamous cell carcinoma. A 53-year-old man underwent esophagogastroduodenoscopy because of chest pain for several months. Endoscopic examination revealed a huge pedunculated esophageal polypoid mass. Endoscopic submucosal dissection (ESD) was performed and histopathologic examination confirmed spindle cell carcinoma (carcinosarcoma). He refused additional esophagectomy. After 21 months, third follow-up endoscopy showed poorly-demarcated flat, faint discolored lesions at different location from the previous ESD site and endoscopic biopsies confirmed squamous cell carcinoma. To the best of our knowledge, this is the first case of metachronous development of esophageal squamous cell carcinoma in a patient with esophageal carcinosarcoma. **(Korean J Gastroenterol 2014;64:364-369)**

**Key Words:** Esophageal squamous cell carcinoma; Carcinosarcoma; Spindle cell carcinoma

## INTRODUCTION

Carcinosarcoma of the esophagus is a rare malignant neoplasm consisting of both carcinomatous and sarcomatous elements. Its reported incidence is approximately 0.5% of all esophageal neoplasms.[1] There have been only a few case reports on development of both esophageal carcinosarcoma and squamous cell carcinomas in a patient, all of which were cases of synchronous or metachronous development of carcinosarcoma after chemoradiotherapy in patients of esophageal squamous cell carcinoma. There were no reports on development of esophageal squamous cell carcinoma following carcinosarcoma. In most cases involving development of esophageal carcinosarcoma following squamous cell carcinoma, it has been suggested that the sarcomatous element of esophageal carcinosarcoma generally results from differentiation of carcinoma cells into mesenchymal tumor cells.[2] In contrast, in the histogenesis of squamous cell carcinoma from carcinosarcoma, it is unclear whether both of them have a common clonal origin or not. Here, we present a case of metachronous development of esophageal squamous cell carcinoma in a patient who had undergone endoscopic re-

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section of esophageal carcinosarcoma, 21 months ago.

## CASE REPORT

A 53-year-old man presented to our hospital complaining of epigastric pain for several months. He was diagnosed with hepatitis B associated liver cirrhosis 10 years ago and underwent endoscopic variceal ligation twice three years ago. He had smoked one-third pack of cigarettes a day and drank heavily for 30 years but had stopped binge drinking three years ago.

An endoscopic examination revealed a huge pedunculated esophageal polyp, polyp stalk originating at 25 cm from the upper incisors. The polyp head extended down to 33 cm from the upper incisors and was almost filling the lumen (Fig. 1). The endoscopic biopsies showed some atypical spindle cells, therefore, spindle cell carcinoma or other undifferentiated carcinoma was suspected. A CT scan of the chest and PET-CT were negative for metastasis. Endoscopic submucosal dissection (ESD) was performed. The size of the resected specimen was 4.2×3.0×2.5 cm and the histopathologic examination confirmed spindle cell carcinoma (carcinosarcoma) with more than seven mitoses per high power field (HPF) (Fig. 2). Immunohistochemically, the spindle-shaped sarcomatous cells showed negative reaction to cytokeratin, S-100 protein, smooth muscle actin, c-Kit, DOG-1, and epithelial membrane antigen (EMA), but a positive reaction to vimentin. No transitional zone was seen between sarcomatous and carcinomatous elements (Fig. 3). The patient was finally diagnosed with true esophageal carcinosarcoma. The tumor had involvement of deep resection margin, with no evidence of vascular or lymphatic invasion. We recommended additional esophagectomy because of the possibility of remnant tumor. He refused the esophagectomy, thus, follow-up endoscopy and CT were performed at 2 months, 5 months, and 1 year after ESD.

At 21 months after ESD, the patient complained of dysphagia over one month. An endoscopic examination showed a whitish fibrotic scar by previous ESD at 25 cm from the upper incisors and poorly-demarcated flat, faint discolored lesions, which were unstained by Lugol solution, at 30-34 cm from upper incisors (Fig. 4). The endoscopic biopsy of faint discolored lesions indicated squamous cell carcinoma with well differentiated type (Fig. 5). He wanted and transferred to another hospital. A chest CT showed small paraesophageal lymphadenopathy at subcarina and a PET-CT showed a hypermetabolic nodule of the left retropharynx. He underwent ESD at the esophagus and piecemeal endoscopic mucosal resection (EMR) at the left hypopharynx in another hospital. Histopathologic examination of the esophagus showed squamous cell carcinoma, moderately differentiated with submucosal invasion at a depth of 150 μm. Histopathologic examination of the left hypopharyngeal mass also showed invasive squamous cell carcinoma with moderately differentiated type. Immunohistochemically, the squamous cell

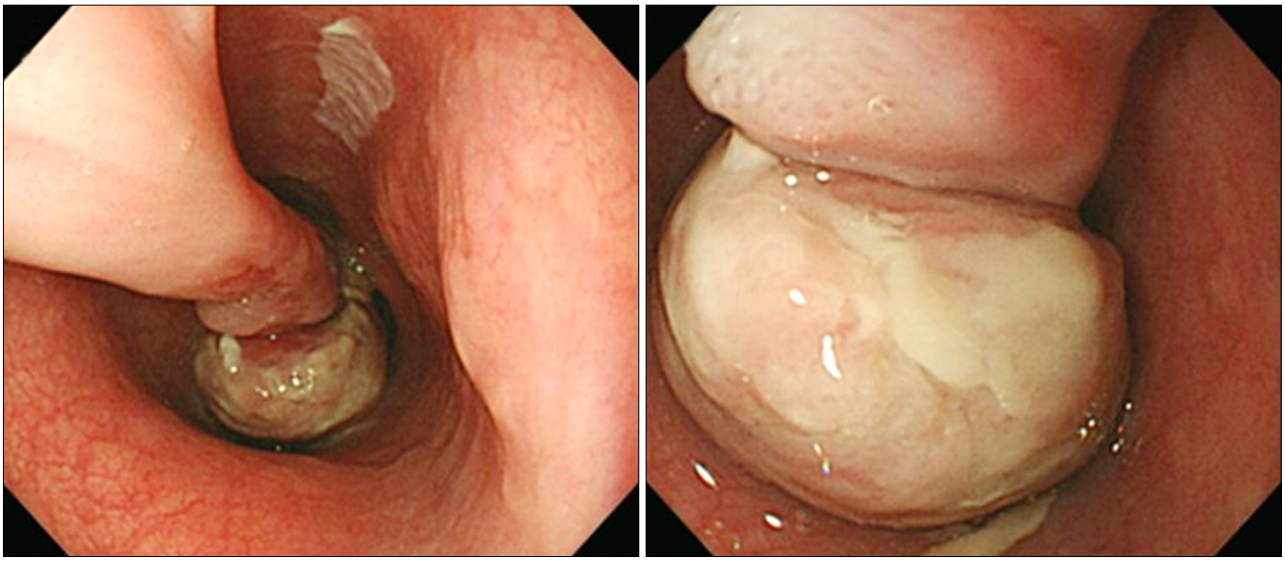

**Fig. 1.** Endoscopic examination reveals a huge pedunculated esophageal polyp. The polyp stalk originates at 25 cm from the upper incisors and the polyp head extends down to 33 cm.

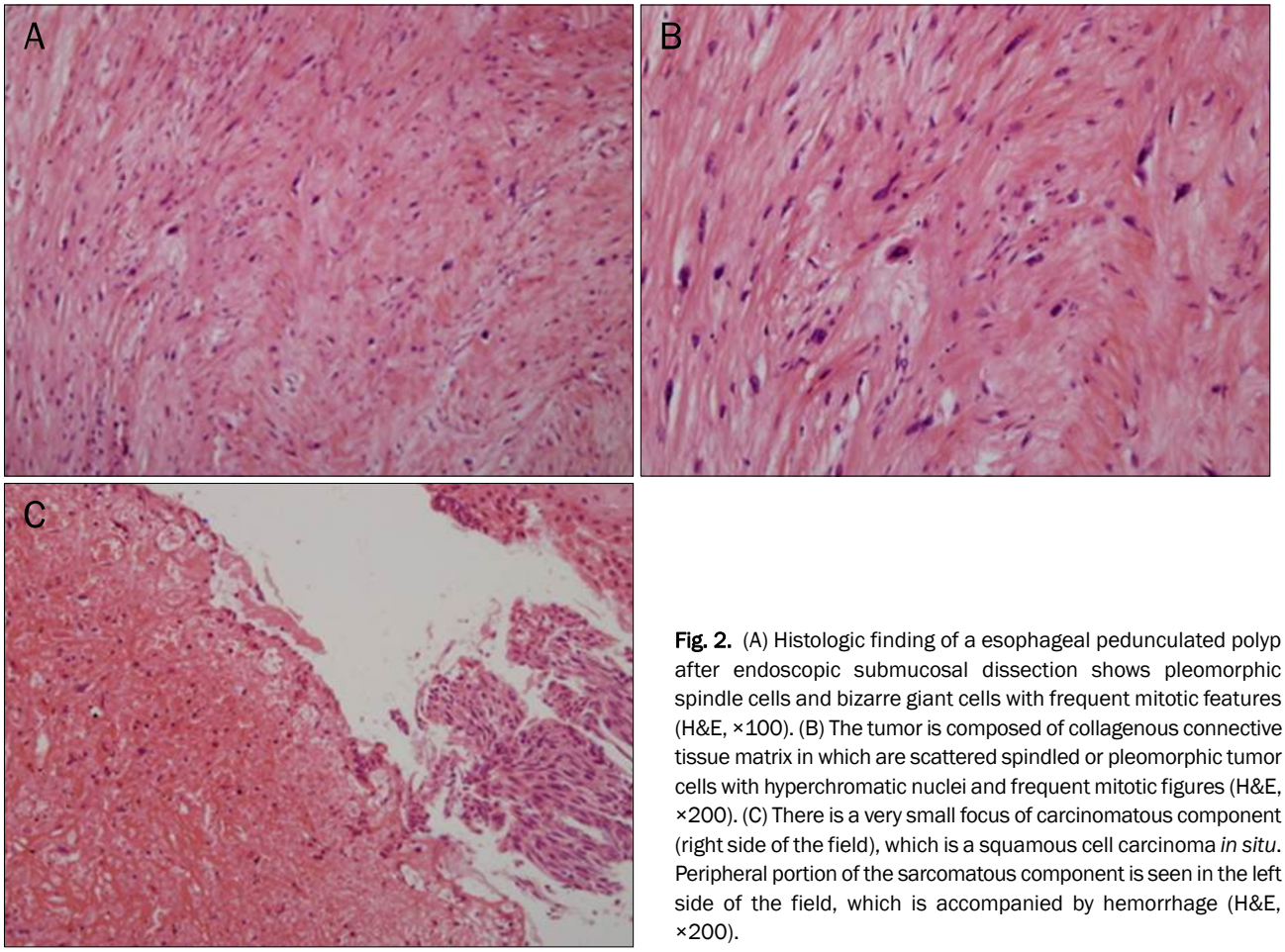


**Fig. 2.** (A) Histologic finding of a esophageal pedunculated polyp after endoscopic submucosal dissection shows pleomorphic spindle cells and bizarre giant cells with frequent mitotic features (H&E, ×100). (B) The tumor is composed of collagenous connective tissue matrix in which are scattered spindled or pleomorphic tumor cells with hyperchromatic nuclei and frequent mitotic figures (H&E, ×200). (C) There is a very small focus of carcinomatous component (right side of the field), which is a squamous cell carcinoma *in situ*. Peripheral portion of the sarcomatous component is seen in the left side of the field, which is accompanied by hemorrhage (H&E, ×200).

carcinoma in the esophagus had shown a diffuse and strong positive reaction to p53 protein. There was no further management of the paraesophageal lymph node. He transferred back to our hospital and underwent two cycles of chemoradiation therapy with 5-fluorouracil and cisplatin. He died from sepsis after one month from last chemotherapy and radiotherapy.

## DISCUSSION

The current case was the metachronous development of squamous cell carcinoma following carcinosarcoma of the esophagus in a patient on the basis of histologic evidence. There have been several case reports on synchronous carcinosarcoma and squamous cell carcinoma in the esophagus,[3-5] and a case report of esophageal carcinosarcoma arising from squamous cell carcinoma after chemoradiation.[6] In a study with Taiwanese patients, Kuo et al.[7] reported that approximately 33% (4/12) of carcinosarcoma had previous head and neck squamous cell carcinoma that occurred metachronously. However, there has been no previous report on metachronous development of esophageal squamous cell carcinoma in a patient with carcinosarcoma.

Like squamous cell carcinoma of the esophagus, esophageal carcinosarcoma occurs most often in middle-aged men with a history of smoking or drinking or both.[8] The current patient has been a heavy drinker and smoker, and did not have previous history of any other malignancy before diagnosis of esophageal carcinosarcoma.

Carcinosarcoma of the esophagus, also termed sarcomatoid carcinoma, pseudosarcoma, spindle cell carcinoma, or polypoid carcinoma, is an unusual malignant tumor of the esophagus, consisting of both carcinomatous and sarcomatous components. The various terms in use reflect the uncertain pathogenesis of this tumor.[9]

Chino et al.[10] reported that the carcinomatous component was differentiated squamous cell carcinoma and the sarcomatous component was spindle cell carcinoma. Histological

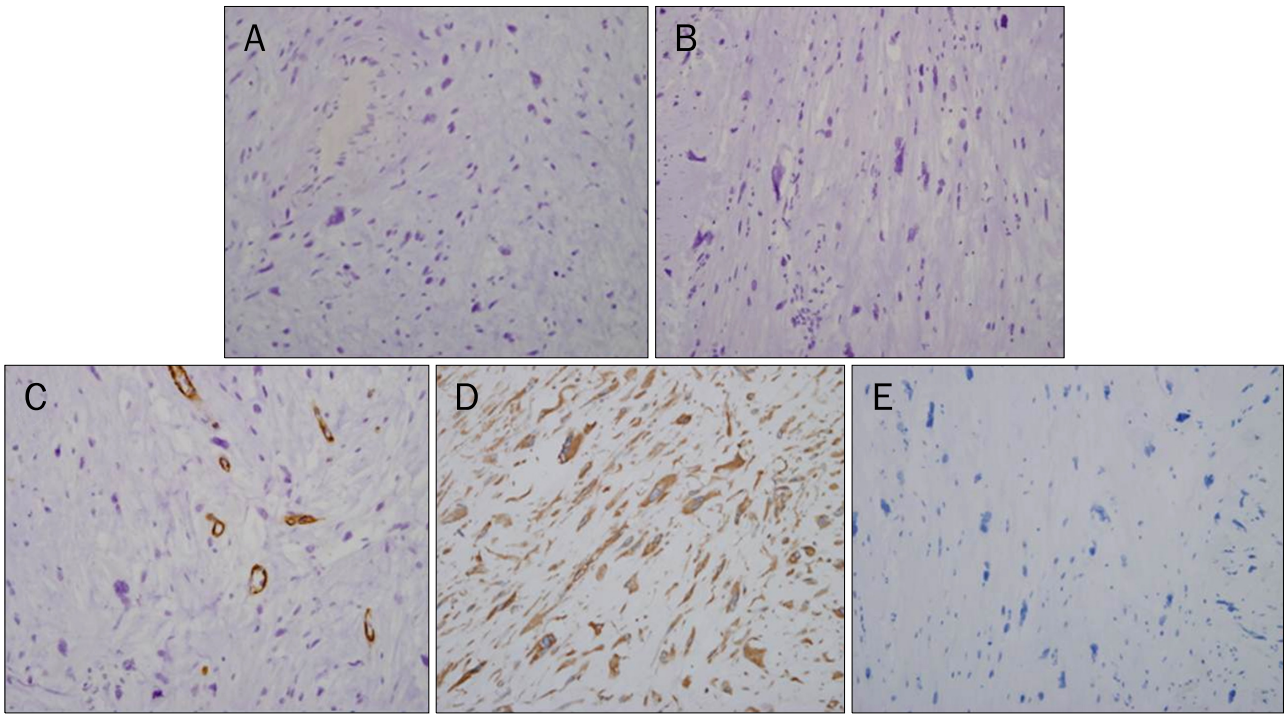


**Fig. 3.** (A) The tumor cells are negative for cytokeratin (×200). (B) The tumor cells are negative for S-100 protein (×200). (C) The tumor cells are negative for smooth muscle actin. In contrast, normal smooth muscle cells around blood vessels are positive for smooth muscle actin (×200). (D) Many tumor cells are positive for vimetin (×200). (E) The tumor cells are negative for epithelial membrane antigen (×200).

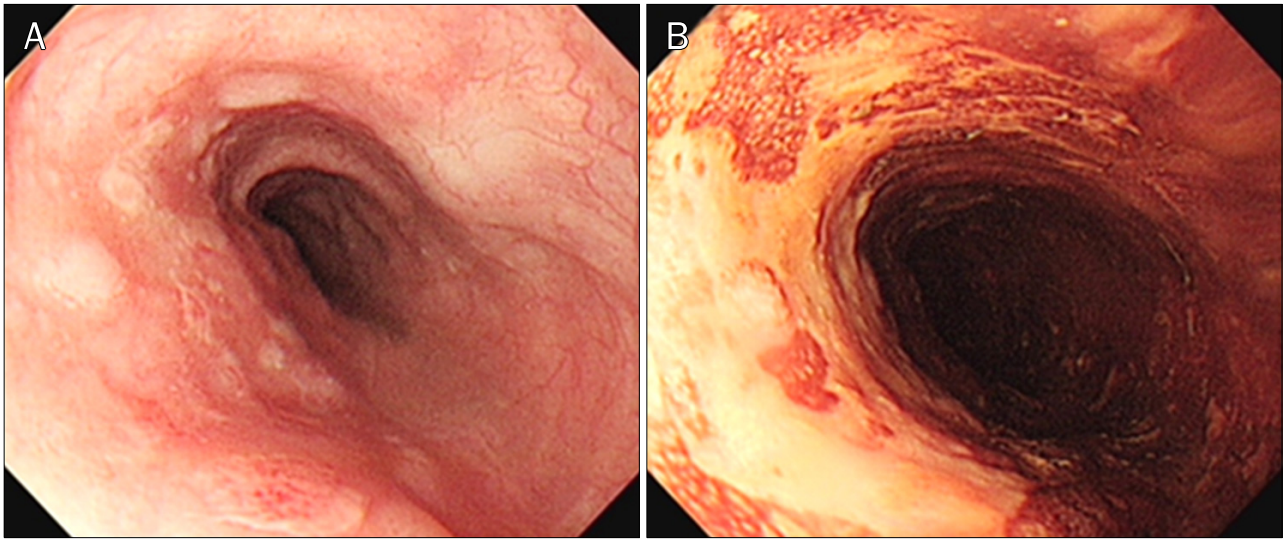


**Fig. 4.** Twenty-one months later, endoscopic examination demonstrated poorly-demarcated flat, faint discolored lesions at 30-34 cm from the upper incisors (A), which are unstained by Lugol solution (B).

analyses showed that the majority of the protruding tumors consisted of the sarcomatous component, while the ulcerating tumor consisted mainly of squamous cell carcinoma. In our case, the tumor was a huge pedunculated protruding mass consisting of an almost sarcomatous component.

According to the Japanese Society for Esophageal Disease, three main hypotheses have been proposed for the pathogenesis of carcinosarcomas. The first is the metaplastic concept, which proposes that the individual components of this malignancy may be derived from a single, common ancestor

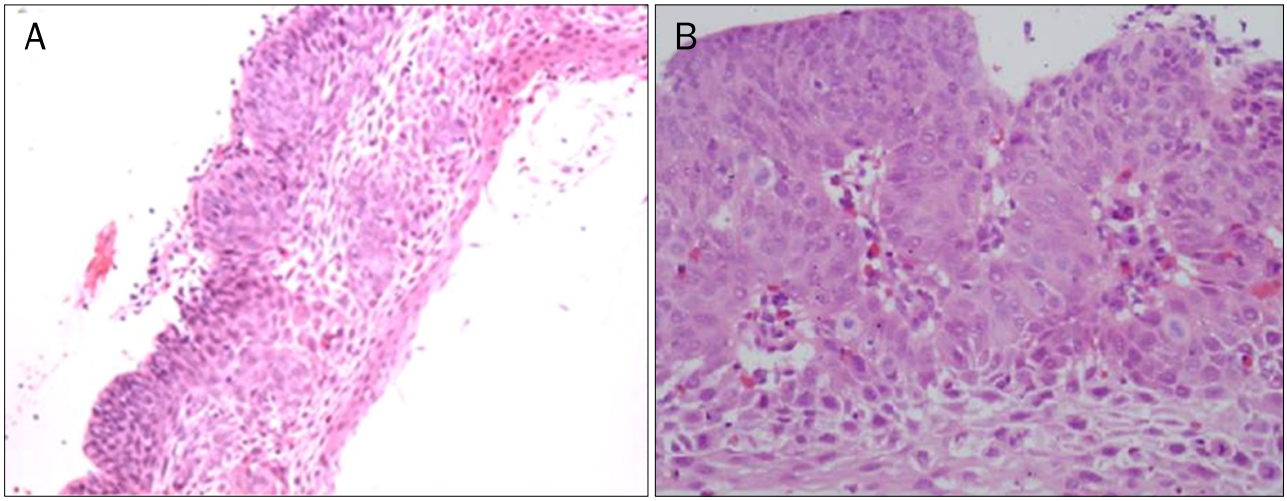


**Fig. 5.** A forcep biopsy specimen from flat discolored lesions in the esophagus shows well-differentiated squamous cell carcinoma (H&E; A, ×100, B, ×400).

cell (so-called carcinosarcoma), in other words, the sarcomatous components are considered to result from metaplasia of carcinoma cells.[9] This theory is supported by the frequent finding of a transition zone between the two cell populations and identical genetic alterations are observed in both components.[11] The second is the collision concept, which hypothesizes that two individual stem cells may undergo malignant transformation (true carcinosarcoma) independently and simultaneously, and are actually separate tumors that have merged.[9] Expression of cytokeratin and vimentin were mutually exclusive in the carcinomatous or sarcomatous elements, which may support the collision concept. The third theory suggests that the spindle cell component is a reaction to the carcinoma.[9] In most cases, the metaplastic concept is generally accepted. In the current case, there was no transition zone between carcinomatous and sarcomatous components and the tumor cells showed an immunochemically negative reaction to cytokeratin and a positive reaction to vimentin. Therefore, the patient was finally diagnosed with true carcinosarcoma.

The clinical presentation of esophageal carcinosarcoma is similar to that of squamous cell carcinoma with dysphagia as the most prominent and frequent symptom.[12] They are typically large (mean, 6-7 cm) and polypoid at presentation.[13] Because of accelerated intraluminal growth, esophageal carcinosarcoma often presents relatively early.[9] Despite the huge size of the tumor, it does not invade as deeply as an esophageal squamous cell carcinoma. In spite of their propensity to cause symptoms earlier because of their large size and the fact that more than 80% of tumors are limited to the submucosa or muscularis propria at presentation,[8,13] these tumors might behave aggressively. Sasajima et al.[14] reported the doubling time of their case to be 2.2 months, whereas that of ordinary esophageal squamous cell carcinoma was 5 months.

The treatment of esophageal carcinosarcoma did not differ from that of other esophageal malignant lesions. Esophagectomy has traditionally been considered as the first option for esophageal carcinosarcoma patients.[13] With the advances in micro-invasive techniques, endoscopic procedures, including endoscopic polypectomy, endoscopic mucosal resection or ESD, may represent an alternative to esophagectomy for superficial esophageal carcinosarcoma.[15] Chemotherapy and concomitant radiation therapy must also be considered for residual microscopic disease and local control.

Esophageal carcinosarcomas do not necessarily have a better prognosis and some authors showed that there is no significant difference in the 5-year survival rates.[1,3] In a study with 20 cases of esophageal carcinosarcoma, Iyomasa et al.[1] reported that recurrence due to hematogenous metastasis was more frequent in esophageal carcinosarcoma than esophageal squamous cell carcinoma. They emphasized that radical resection with lymph node dissection was necessary for treatment of carcinosarcoma regardless of the depth of invasion.

In conclusion, this is a first case report of metachronous

development of esophageal squamous cell carcinoma following carcinosarcoma in a patient. The clinicopathological characteristics and histogenesis of both tumors are not clearly known; therefore, further molecular studies and more cases are needed.

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