

Case Series

Sarcomatoid Carcinoma of the Esophagus

Patricia D Pittman, Cynthia D Guy, Diana M Cardona, Shannon J McCall, and Xuefeng Zhang*

Department of Pathology, Duke University Medical Center, USA

*Corresponding author

Xuefeng Zhang, Department of Pathology, Duke University Medical Center, Box 3712, Durham, NC 27710, USA, Tel: 919-660-0336; Fax: 919-681-8868; Email: xuefeng.zhang@duke.edu

Submitted: 22 June 2016

Accepted: 17 August 2016

Published: 22 August 2016

Copyright

© 2016 Zhang et al.

OPEN ACCESS

Keywords

- Esophagus
- Sarcomatoid carcinoma

Abstract

Background: Sarcomatoid carcinoma of the esophagus is an unusual malignancy with a biphasic histological appearance containing both epithelial and mesenchymal elements. The most common epithelial component is squamous cell carcinoma; the spindle cell component is typically high grade. These tumors usually present as large pedunculated masses with intraluminal growth but show minimal invasion.

Aims: We report three cases of esophageal sarcomatoid carcinoma with relatively uncommon morphologic and clinical features, and further discuss the biological and clinical behaviors of this rare tumor.

Methods: The pathology database was retrospectively searched and three cases of esophageal sarcomatoid carcinoma were retrieved. These cases were thoroughly reviewed and summarized.

Results: All three tumors exhibited a prominent spindle cell component with variable nuclear pleomorphism and cytokeratin/p63 expression. Osteoid formation was present in one case. The epithelial component also varied. Case 1 contained keratinizing squamous cell carcinoma with in situ component, composing of 10% of the tumor volume. In case 2, the bulk of the tumor was non-keratinizing basaloid squamous cell carcinoma without carcinoma in situ. Case 3 was biopsy only and no carcinomatous component was present. These tumors also showed unusual clinical behaviors. In case 1, the patient developed peritoneal metastasis and anastomotic recurrence at 4 months after surgery despite clear margins and exophytic tumor growth with only focal muscularis propria invasion. In contrast, in the other two cases with invasive tumor growth, both patients survived more than 5 years.

Conclusion: Many aspects of sarcomatoid carcinoma remain unclear. Further investigation is necessary to elucidate the etiology, pathogenesis, biological and clinical behaviors of this rare tumor.

INTRODUCTION

Sarcomatoid carcinoma of the esophagus is an unusual malignancy with a biphasic histological appearance containing both epithelial and mesenchymal elements. The most common epithelial component is squamous cell carcinoma, which may be exclusively carcinoma in situ. The spindle cell component is typically high grade [1]. Synonyms include spindle cell carcinoma, metaplastic carcinoma, pseudosarcomatous squamous cell carcinoma, polypoid carcinoma, and squamous cell carcinoma with a spindle component [1,2]. Currently, sarcomatoid carcinoma of the esophagus is classified as a special subtype of esophageal squamous cell carcinoma. The reported incidence of the neoplasm ranges from 0.26% to 2% of all esophageal malignancies [1,3]. This malignant neoplasm is unique in that it can grow to a very large size and still remain minimally invasive [1]. These tumors are commonly attached to the mucosal wall by

a pedicle, therefore giving the tumor a polypoid appearance on endoscopic and gross examination. Due to the large intramural growth, early detection with obstructive symptoms is common. Early detection and the minimally invasive nature of the tumor usually confer a good long term prognosis for these patients [1,2,4,5].

We reviewed our cohort of esophageal sarcomatoid carcinoma and present three illustrative cases which have relatively uncommon morphological and clinical features in contrast to the majority of cases cited in the literature.

MATERIALS AND METHODS

The Duke University Medical Center pathology database was retrospectively searched from 1999 to 2014 and three cases of esophageal sarcomatoid carcinoma were retrieved. These cases were thoroughly reviewed. The clinicopathological features are

described below. Illustrative teaching points are elaborated upon in the discussion.

RESULTS AND DISCUSSION

Case 1

A 58 year old male with end stage renal disease and a 17.5 pack-year history of smoking presented with a chief complaint of progressive dysphagia and a 20-pound weight loss. An upper gastrointestinal endoscopy revealed a distal esophageal mass. A biopsy showed high grade malignant tumor with a spindle cell morphology. An intraesophageal stent was placed. The patient underwent esophagogastrectomy without preoperative chemotherapy or radiation.

The esophagogastrectomy specimen displayed a 10.0 cm white, firm, exophytic mass, which was attached to the mucosal surface by a stalk. The stalk was 3.7 cm proximal to the gastro esophageal junction and occupied 40% of the circumference. Microscopically, the tumor consisted predominantly of a high grade pleomorphic sarcomatoid component. There were areas with variable cellularity and pleomorphism. Myxoid stroma and osteoid formation were identified. Moderately to poorly differentiate keratinizing squamous cell carcinoma was present, accounting for less than 10% of the tumor volume. Squamous cell carcinoma in situ was also identified. The sarcomatoid component was also diffusely positive for vimentin, focally positive for pan-cytokeratin, but completely negative for other epithelial markers (p63, p40, Ber-Ep4, MOC-31). Immunohistochemistry for S-100, melanA, HMB-45, CD117, CD34, and CEA was negative. The tumor focally invaded muscularis propria with lymphovascular invasion, but there was no perineural invasion or lymph node metastasis (pT2, N0, Mx). The surgical margins were free of tumor; the closest margin was the circumferential/adventitial margin at 3 mm. Although the tumor was confined within the muscularis propria, the esophagus showed deep ulceration and small adventitial abscesses.

Following surgery, the patient had multiple readmissions related to post-operative complications including anastomotic leak and fistula formation. At four months after the esophagogastrectomy, bronchoscopy showed a near completely obstructing endobronchial mass protruding into the right mainstem bronchus. The endobronchial tumor was removed endoscopically, and it was morphologically consistent with sarcomatoid carcinoma. Evidence of tumor recurrence was noted at the anastomosis. A PET scan showed extensive metastatic disease including peritoneal carcinomatosis. The patient was discharged to palliative care without further follow-up.

Case 2

A 70 year old woman with an unknown smoking history presented with a one year history of progressively worsening dysphagia which was initially to solids and progressed to liquids. These symptoms were associated with regurgitation and a 6-pound weight loss. A CT scan showed a large distal esophageal lesion causing near total luminal occlusion. The patient underwent an esophagogastrectomy with placement of a jejunostomy feeding tube.

The gross examination revealed a 5.5 cm sessile hemorrhagic mass in the distal esophagus which extended to the inked circumferential margin. Microscopically, the bulk of tumor consisted of nodules and islands of poorly differentiated non-keratinizing squamous cell carcinoma with basaloid features, intermingled with a relatively uniform spindle cell population. The sarcomatoid component accounted for a minor component in this case (approximately 30%). The esophagus showed extensive ulceration and erosion, and squamous cell carcinoma in situ was not identified. Immunohistochemically, the squamous cell carcinoma displayed strong and diffuse immunoreactivity for p63 and patchy positivity for pancytokeratin. The spindle cell component showed focal nuclear positivity for p63 but was negative for pan-cytokeratin. Ki67 proliferative index was up to 90% in the carcinomatous areas, and approximately 30-40% in the sarcomatoid areas. The tumor invaded the periesophageal soft tissue (adventitia) and involved the circumferential margin. Perineural invasion and lymphovascular invasion were identified, but no lymph node metastasis (pT3, N0, Mx).

She had an uneventful post-operative course and appropriate advancement of diet without difficulty. At 32 months after surgery, an upper gastrointestinal endoscopy and biopsy revealed no evidence of recurrence. She expired of unknown cause at 60 months after surgery.

Case 3

A 78 year old male with a 40-pack year smoking history presented with a right neck mass. A radical neck dissection showed metastatic squamous cell carcinoma in four lymph nodes, however, the primary site was unknown. He completed radiotherapy of 24 Gy.

Two years later, he presented with a new left pinna ear lesion that on biopsy was proved to be invasive moderately differentiated squamous cell carcinoma. Following this discovery, a PET scan was conducted which showed hypermetabolism in the right neck and in the thoracic esophagus. An endoscopic ultrasound was conducted and displayed a 3.0 cm ulcerating mass in the mid-esophagus that was partially obstructing and characterized by intraluminal growth. The ultrasound was also suggestive of muscularis propria invasion, but not conclusive for adventitial invasion.

The esophageal biopsy revealed solid areas of spindle cell proliferation with prominent nuclear pleomorphism. There was ulceration and tumor necrosis. Neither an epithelial component nor squamous cell carcinoma in situ was present. Immunohistochemistry was positive for vimentin, pan-cytokeratin and p63.

Over the next five years the patient had multiple biopsies and FNAs from the head and neck, all of which returned as squamous cell carcinoma without any spindle cell component. He completed three additional rounds of radiation to the neck and esophagus, as well as multiple regimens of chemotherapy. However, due to the extensiveness of the disease, surgery was not considered as an option. Despite aggressive treatment, this patient's disease continued to progress. The patient expired of unknown cause at 62 months after the detection of esophageal sarcomatoid carcinoma, and 89 months after the detection of

metastatic squamous cell carcinoma in neck lymph nodes, the origin of which remained unclear.

The clinicopathological features are summarized in (Table 1).

Virchow first defined the entity “carcinosarcoma” in 1865 which he described as a tumor consisting of malignant epithelial and spindle cell components [1,6]. To date, a limited number of cases have been described in the literature, and many aspects of this rare tumor remain unclear.

Sarcomatoid carcinoma usually occur in the mid-esophagus (60%), followed by the distal esophagus (30%), with rare reports (10%) of occurrence in the proximal esophagus [1,2]. Additionally, like classic esophageal squamous cell carcinoma, sarcomatoid carcinoma occurs most often in middle-aged and elderly men with male-to-female ratio of approximately 4:1 [5,6], and associated with a history of smoking and/or drinking [2,7]. In keeping with the literature, the tumors in this study were located in the distal (2 cases) and mid (Figure 1) esophagus. Two of the three patients had a significant smoking history.

Grossly, sarcomatoid carcinoma commonly presents as a large pedunculated mass with minimal invasive growth. This type of growth pattern may contribute to early symptoms and result in early diagnosis. Sessile or broad-based mass lesions are considered unusual. One tumor in this study exhibited pedunculated growth with a wide pedicle (40% circumferential) and focal muscularis propria invasion. The other two tumors were broad based with widely invasive growth. However, such invasive growth and deep invasion may not necessarily be associated with a poor prognosis (see below for further discussion).

The histologic hallmark of sarcomatoid carcinoma is the presence of biphasic morphologic appearance, with a mixture of carcinoma and sarcomatoid elements. The epithelial component is usually squamous in nature, with variable differentiation and keratinization. As many cases in the literature, keratinizing squamous cell carcinoma with carcinoma in situ was present in one of our cases. One case in this study showed exclusively poorly differentiated non-keratinizing squamous cell carcinoma with basaloid features. A similar case of predominant basaloid squamous cell carcinoma with keratinizing squamous cell carcinoma has been reported [8]. Rare cases of sarcomatoid carcinoma with adenocarcinoma component have also been described [9]. The sarcomatoid portion is typically composed of undifferentiated, spindle-shaped cells. The spindle cells may be arranged in a fascicular or storiform pattern. The malignant

nature is usually apparent given the cellularity, pleomorphism, and increased mitotic activity. In tumors with more prominent pleomorphism, such as case 1 and case 3 in this study, the sarcomatoid component may display patternless growth, marked pleomorphic nuclei, and bizarre giant cells. Edematous and myxoid changes can be seen. Although the sarcomatoid element usually does not exhibit evidence of specific lineage, osseous, cartilaginous and rhabdomyoblastic differentiation have been described [1]. Osteoid deposits were also observed in one of our cases.

The proportion of the two elements may vary. The epithelial component can be scarce or limited to squamous cell carcinoma in situ. The diagnosis is usually straightforward when both components are identified, particularly when keratinizing squamous cell carcinoma is present. Therefore, adequate sampling is crucial. The diagnosis may be challenging in the absence of an epithelial component, especially in small endoscopic biopsy specimens. Two cases in this study showed esophageal/tumor ulceration, which made squamous cell carcinoma in situ difficult to identify. When the carcinomatous component is absent, a panel of immunohistochemical markers, including cytokeratin, p63, mesothelioma and melanoma markers is necessary to establish the diagnosis. However, distinction between sarcomatoid carcinoma and true sarcoma may still be challenging. First, immunoreactivity for epithelial markers is typically focal and less intense in the sarcomatoid component, and can even be negative. The three cases in this study showed a wide spectrum in immunoreactivity for cytokeratin and p63: one case with very focal and weak positivity for pan-cytokeratin and negative for p63; one with patchy immunoreactivity for p63 but negative for pan-cytokeratin; one with relatively strong immunoreactivity for both p63 and pan-cytokeratin. Secondly, virtually any type of sarcoma, on occasion, can express cytokeratin. Despite the lack of specificity in immunohistochemical markers, it is reasonable to assume that a pleomorphic or spindle cell malignant neoplasm arising in the esophagus is sarcomatoid carcinoma until proven otherwise. Strong and diffuse expression of epithelial markers, especially when demonstrated with multiple antibodies, supports a diagnosis of sarcomatoid carcinoma.

The pathogenesis of this rare malignant entity is unclear. Most of the uncertainty revolves around the etiology of the spindle cell components [2]. The key question is whether the two components are independent of each other or whether the sarcomatoid component is derived from carcinomatous metaplasia of the epithelial component [1,8]. One theory

Table 1: Summary of the clinicopathological features.

Case	Age	Sex	Growth pattern	CIS	Epithelial component	Sarcomatoid component	Staging	Survival
1	58	M	Exophytic	+	Moderately to poorly differentiated, keratinizing SCC	Pleomorphic sarcoma with osteoid differentiation CK focally +, p63 -	pT2,N0,M1	N/A
2	70	F	Invasive	-	Poorly differentiated, non-keratinizing SCC with basaloid features	Spindle cell sarcoma CK -, p63 focally +	pT3,N0,Mx	60 months
3	78	M	Invasive	-	Absent	pleomorphic sarcoma CK +, p63 +	cT2,N0,Mx	62 months

Abbreviations: CIS: squamous cell carcinoma in situ; SCC: Squamous Cell Carcinoma; CK: pan-cytokeratin

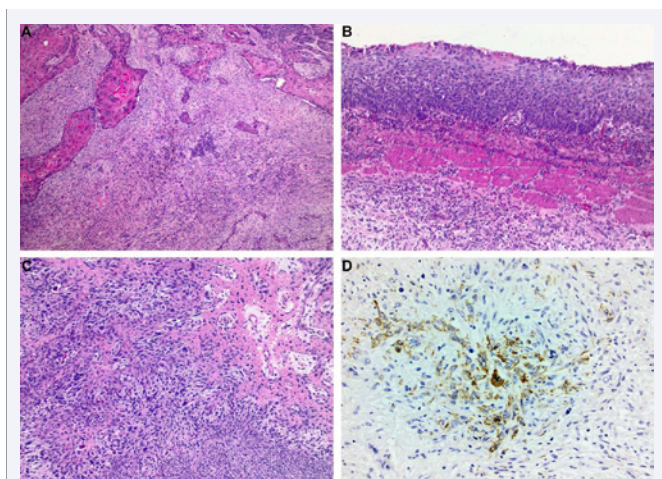


Figure 1 Representative photomicrographs of histological findings in case 1. Keratinizing squamous cell carcinoma (A,H&Estain), and squamous cell carcinoma in situ(B,H&E stain) were present. The sarcomatoid component consisted of pleomorphic spindle cells with osteoid formation (C, H&E stain). There is focal immunoreactivity for pan-cytokeratin in the sarcomatoid area (D, immunohistochemistry).

hypothesizes that sarcomatoid population may be a concomitant sarcoma or collision tumor, i.e. two distinct malignancies coexist and then collide and intermingle [6,10,11]. In contrast, ultrastructural and molecular investigations have supported the hypothesis that these neoplasms are epithelial in nature, and the sarcomatoid component is a variant of poorly differentiated squamous cell carcinoma, stemming from a single epithelial element or undifferentiated “stem cell” [6,8]. A report by Amatya et al [8] describes a case of esophageal sarcomatoid carcinoma that displayed similar TP53 point mutations in the squamous carcinoma and the sarcomatous elements, suggesting a clonality between the two. In some studies, the spindle cells have been shown to exhibit ultrastructural features of epithelial differentiation (desmosomes and tonofibrils) [1]. One study analyzed the Ki-67 proliferative index in sarcomatoid carcinoma and explained the sarcomatoid predominance phenomenon in these tumors. It was found that the average Ki-67 proliferative index in the squamous areas was 0.44, whereas that in the spindle component was 0.68, a statistically significant difference ($p < 0.0001$). The authors thus argue that the sarcomatoid component has a “growth advantage” [5]. The opposite finding was observed in our case with basaloid squamous cell carcinoma: Ki67 proliferative index was up to 90% in the carcinomatous areas, and approximately 30-40% in the sarcomatoid areas. That may explain why the carcinoma component forms the bulk of tumor (70%) in this case.

About 50-60% of sarcomatoid carcinomas have lymph node metastasis, comparable to that of esophageal squamous cell carcinoma [6,7]. This supports the carcinoma nature of this entity, since lymph node metastasis is typically rare in true sarcomas. An important determining factor of metastatic potential is the level of invasion at time of excision. Risk of metastasis may be as low as 25% in cases of lamina propria involvement and as great as 75% in cases where tumor is present at the adventitia at time of resection [1]. Metastasis can be of carcinomatous,

sarcomatous or mixed components and occur most commonly in the regional lymph nodes, followed by the lungs and pleura [1]. Distant metastasis to liver, brain and bone has been described [7]. One study reported that tumor size maybe a factor when evaluating for metastasis, as lesions with a median size of 11 cm were proved to have greater nodal metastasis than those lesions of 6.5 cm or less [5]. In this study, one case showed peritoneal carcinomatosis; the tumor was large (15 cm) but only exhibited focal muscularis propria invasion. The tumor also recurred at four months after surgery despite clear margins.

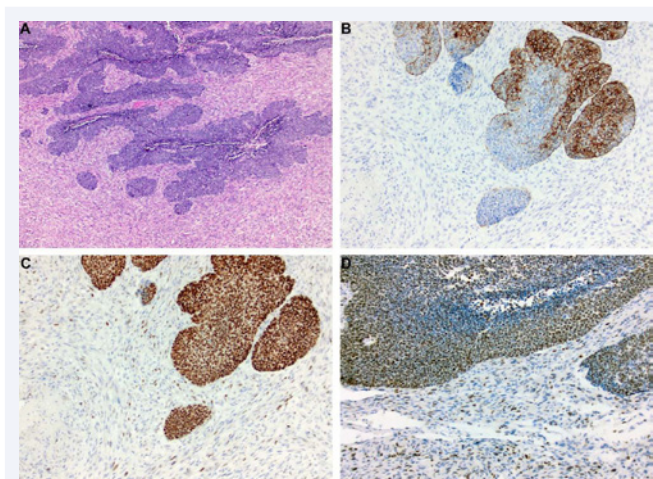


Figure 2 Representative photomicrographs of histological findings in case 2. The tumor consisted of non-keratinizing squamous cell carcinoma with basaloid features and a relatively uniform population of spindle cells (A, H&E stain). The sarcomatoid component is negative for pan-cytokeratin (B,immunohistochemistry) and focally positive for p63 (C,immunohistochemistry). The Ki-67 proliferative index was up to 90% in the carcinoma and around 40% in the sarcomatoid area (D, immunohistochemistry).

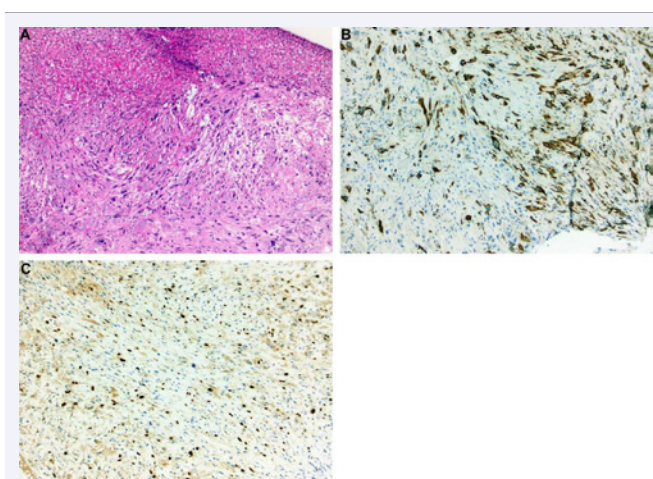


Figure 3 Representative photomicrographs of histological findings in case 3. The biopsy revealed a pleomorphic spindle cell population with ulceration and necrosis (A, H&E stain). An epithelial component or squamous cell carcinoma in situ was not present. The tumor cells exhibited relatively diffuse immunoreactivity for pan-cytokeratin (B, immunohistochemistry) and p63 (C,immunohistochemistry).

The treatment of choice for patients with sarcomatoid carcinoma is surgical resection with adequate lymph node dissection [2,7]. Some patients may also receive neoadjuvant chemotherapy or post-operative radiation depending on the stage at presentation [6]. Prognosis of sarcomatoid carcinoma has been reported to be better than that of classic squamous cell carcinoma [1,2,4] despite the large size at presentation. The favorable prognosis of sarcomatoid carcinoma is usually attributed to early detection and the lack of deep invasion at the time of resection. However, for T1 cases only, sarcomatoid carcinoma patients had statistically poorer prognosis than did squamous cell carcinoma patients [2]. Overall, the limited numbers of reported sarcomatoid carcinoma cases preclude detailed stage-by-stage comparison. Two patients in this study survived for more than 5 years despite advanced disease. In both cases, the tumor displayed broad-base and invasive growth pattern. In one patient (Figure 2), the tumor invaded adventitia (pT3) and involved the circumferential margin. However, an upper gastrointestinal endoscopy and biopsy at 32 months after surgery revealed no evidence of recurrence, and the patient survived for 60 months after surgery. Another patient (Figure 3) had an ulcerating mass with radiographic muscularis propria invasion and possible adventitial invasion. Although the patient was not considered as a surgical candidate because of widespread metastatic squamous cell carcinoma in neck lymph nodes (uncertain primary), and was treated with chemoradiation only, he survived for 62 months after the detection of esophageal sarcomatoid carcinoma. In these two patients, the long-term survival is difficult to be explained with early presentation or minimally invasive disease. The underlying mechanisms for such unique tumor behavior warrant further studies.

CONCLUSION

Sarcomatoid carcinoma of the esophagus is an uncommon malignancy with a distinctive phenotype including both carcinoma and sarcomatoid elements. The diagnosis may be challenging in biopsy specimens when epithelial component is absent. Further investigation is necessary to elucidate the etiology, pathogenesis,

biological and clinical behaviors of this rare tumor.

REFERENCES

1. Raza MA, Mazzara PF. Sarcomatoid Carcinoma of the Esophagus. Arch Pathol Lab Med. 2011; 135: 945-948.
2. Sano A, Sakurai S, Kato H, Sakai M, Tanaka N, Inose T, et al. Clinicopathological and Immunohistochemical Characteristics of Esophageal Carcinosarcoma. Anticancer Res. 2009; 29: 3375-3380.
3. Sun-Kui K, Hong-Bing D, Ying-Jie C, Yun-Peng C, Yuan Z, Chao H. Esophageal Sarcomatoid Carcinoma Presenting as a Fever With Elevated Serum Leukocytes. Ann Thorac Surg. 2014; 98:123-125.
4. Natsugo S, Matsushita Y, Chuman Y, Kijima F, Haraguchi Y, Shimada M, et al. So-called carcinosarcoma of the esophagus: A clinicopathologic, immunohistochemical and DNA flow-cytometric analysis of 6 cases. Oncology. 1999; 57: 29-35.
5. Lauwers G, Lawrence G, Scott G, Carr N, Sobin L. Spindle Cell Squamous Carcinoma of the Esophagus: Analysis of Ploidy and Tumor Proliferative Activity in a Series of 13 cases. Hum Pathol. 1998; 29: 863-868.
6. Iacone C, Barreca M. Carcinosarcoma and Pseudosarcoma of the esophagus: Two Names, One Disease-Comprehensive Review of the Literature. World J Surg. 1999; 23: 153-157.
7. Au J, Sugiyama G, Wang H, Nicasstri A, Lee D, Ko W. Carcinosarcoma of the oesophagus - a rare mixed type of tumor. J Surg Case Rep. 2010; 2010: 7.
8. Amatya V, Takeshima Y, Kaneko M, Inai K. Esophageal carcinosarcoma with basaloid squamous carcinoma and rhabdomyosarcoma components with TP53. Pathology Int. 2004; 54: 803-809.
9. Orsatti G1, Corvalan AH, Sakurai H, Choi HS. Polypoid adenosquamous carcinoma of the esophagus with prominent spindle cells. Report of a case with immunohistochemical and ultrastructural studies. Arch Pathol Lab Med. 1993; 17: 544-547.
10. Tomizawa Y, Taniguchi M, Mori, M. An Unusual Case of Intraluminally Growing Esophageal Tumor. Gastroenterology. 2011; 141: e10-11.
11. Ooi A, Kawahara E, Okada Y, Mizukami Y, Sugawara S, Noto Yand Fujita H. Carcinosarcoma of the esophagus. An immunohistochemical and electron microscopic study. Acta Pathol Jpn. 1986; 36: 151-159.

Cite this article

Pittman PD, Guy CD, Cardona DM, McCall SJ, Zhang X (2016) Sarcomatoid Carcinoma of the Esophagus. JSM Gastroenterol Hepatol 4(4): 1067.