

Adenosquamous Carcinoma of the Stomach and Review of the Literature

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Received: 15 October 2014 / Accepted: 22 December 2014 / Published online: 8 January 2015
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Abstract Adenosquamous carcinoma of the stomach is a very rare disease, consisting of less than 0.4 % of all stomach cancer. From 1991 to 2013, a total of 2800 patients received gastrectomy for gastric cancer at Taipei Veterans General hospital. Among them, seven patients (0.25 %) diagnosed as adenosquamous carcinoma were enrolled. The clinicopathologic characteristics and prognosis were analyzed. The mean age of the seven patients was 62.3 years-old. There were 5 males and 2 females. Six patients were stage III disease and one patient was stage IV disease. Four patients finally died of

gastric cancer. Only one patient had no recurrence until death. Among the seven patients, adenocarcinoma component comprises the majority of the metastatic lymph node in 6 patients (85.7 %). The only one patient with major squamous cell carcinoma component in metastatic lymph node had no tumor recurrence till death. Adenosquamous carcinoma of stomach is a rare disease and is associated with a poor prognosis. The component of adenocarcinoma and squamous cell carcinoma in the metastatic lymph node may influence the prognosis.

Keywords Adenosquamous carcinoma · Adenocarcinoma · Squamous cell carcinoma · Metastatic lymph node

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Introduction

Gastric cancer is one of the most common malignant tumors in Asia. Of all pathologic types, adenocarcinoma is the most prevalent. Whereas adenosquamous carcinoma is very rare, comprising of only <0.5 % of all gastric malignancies [1–3]. Among the reported gastric adenosquamous carcinoma cases, most of them are Asians.

To be defined as adenosquamous carcinoma of the stomach, both adenocarcinoma and squamous cell carcinoma (SCC) components have to be present. The SCC component has to be greater or equal to 25 % of all tumor mass. Adenosquamous carcinoma has aggressive clinicopathological features and a poorer prognosis than typical adenocarcinomas.

Past literature reports of adenosquamous carcinoma of stomach were summarized in Table 1 [4–13]. In the study of Saito et al., only 4 patients with SCC component greater or equal to 25 % were enrolled in Table 1. Sizes of tumor ranged from nearly 1 cm to up to 9 cm. Tumors are mostly advanced

Table 1 The summary of adenosquamous carcinoma of the stomach from previous literature

Author	Patient No.	Tumor Size (cm)	Tumor site	Stage	Chemotherapy	Recurrence site	Prognosis /survival months	% of SCC
Samejima et al. [4]	1	6.7	L	N/M	N/M	N/M	N/M	N/M
Watanabe et al. [5]	1	9	LM	N/M	N/M	N/M	N/M	N/M
Hirai et al. [6]	1	3	L	IV	N/M	N/M	DOD/7	N/M
Horikawa et al. [7]	1	3.5	M	I	N/M	N/M	N/M	N/M
Johzaki et al. [8]	1	1.0	L	IV	N/M	N/M	DOD/8	N/M
Yasuda et al. [9]	1	2.7	M	N/M	N/M	N/M	N/M	N/M
Nishidoi et al. [10]	1	0.8	M	I	N/M	N/M	N/M	N/M
Yoshida e al. [11]	1	2.1	L	IV	N/M	N/M	DOD/17	N/M
Faria et al. [12]	1	8	L	IIIc	+	Liver, LN	DOD/27	80 %
Saito et al. [13]	No. 1	8	M	IV	+	Peritoneum	DOD/17	75 %
	No. 2	6	U	IIIb	–	Peritoneum	DOD/6	40 %
	No. 3	3	U	Ia	–	N/M	Alive/118	25 %
	No. 4	6.7	L	N/M	N/M	N/M	N/M	N/M

L lower third of stomach, *M* middle third of stomach, *U* upper third of stomach, *LN* lymph node, *DOD* died of disease, *N/M* not mentioned

stage (stage III to stage IV) with lymph node metastasis at time of diagnosis. Prognosis was poor with most cases died of disease at less than 30 months. However, the impact of the component of adenocarcinoma and SCC in the metastatic lymph node on patient survival is still unknown. Adenosquamous carcinoma of the stomach is reported to be unresponsive to TS-1 based chemotherapy [13], and there has been no standard chemotherapy established up to now.

The aim of this study is to investigate the clinicopathologic characteristics and the prognosis of adenosquamous carcinoma of the stomach.

Materials and Methods

This study was approved by the institutional review board (IRB) in accord with the ethical standards established by Taipei Veterans General Hospital in which the experiments were performed and are in accord with the Helsinki Declaration of 1975 (see Encyclopedia of Bioethics. 3rd ed. New York, NY: Macmillan; 2003), as revised in 2008 (<http://www.wma.net/en/30publications/10policies/b3/>).

From 1991 to 2013, a total of 2800 patients received gastrectomy for gastric cancer at Taipei Veterans General hospital. Among them, 7 patients were diagnosed as adenosquamous carcinoma. The clinicopathologic characteristics and prognosis of the 7 patients were analyzed. The pathological staging of gastric cancer was determined according to the seventh AJCC/UICC TNM classification [14].

Prior to surgery, all patients underwent chest radiography, abdominal sonography, or abdominal computed tomography

scan for tumor staging. The patients were evaluated on the basis of their gender, age, tumor size, tumor location, operative methods, combined organ resection, pathological tumor and lymph node stage, lymphovascular invasion, stromal reaction type, gross appearance, and recurrence pattern. Regarding the stromal reaction type, a cancer with a small number of stromal cells was classified as medullary, and a cancer with a large number of stromal cells was classified as scirrhous; an intermediate cancer was histologically intermediate (between the medullary and scirrhous types).

A total or distal subtotal gastrectomy was performed depending on the distance between the cardia and the tumor: a margin of 3 cm is needed for superficial and well-defined tumors, and a margin of 5 cm is needed for advanced or poorly defined tumors. A subtotal gastrectomy is the standard procedure for distal gastric cancer, whereas a total gastrectomy is the more common procedure for proximal gastric cancer. For early gastric cancer, at a minimum, a D1 + α dissection was performed. For advanced gastric cancer, a minimum of a D2 lymph node dissection was performed, except in those for whom curative resection was not possible. For D2 resection, combined-organ (i.e., en bloc) resection, including hemipancreaticosplenectomy, splenectomy alone, partial liver resection, and transverse colectomy, might be performed to facilitate curative resection.

Follow-up

Follow-up assessments were performed every 3 months for the first 5 years after surgery and every 6 months thereafter until death. The follow-up procedures included medical

histories, physical examinations, routine blood tests, liver function tests, tumor marker levels (carcinoembryonic antigen and carbohydrate antigen 199), chest radiography, and other imaging studies.

Biopsy sampling confirmed recurrent disease or distant metastases. Biopsies of new, multiple pulmonary lesions, or lesions characteristic of osseous metastases that were noted during CT or whole-body bone scans were not obtained. Tumor recurrence in the hepatoduodenal ligament, celiac axis, or peripancreatic region was considered to be a locoregional recurrence. Remote lymphatic metastasis (para-aortic, Virchow's, and inguinal nodes) and pulmonary lymphangitic spreading were defined as distant lymphatic recurrence. Using metallic staples at both the proximal and distal cut ends, we were able to readily identify the anastomotic sites and therefore could diagnose a recurrence at the anastomotic sites or duodenal stumps. Recurrence was classified as locoregional, hematogenous, distant lymphatic, or peritoneal. Patients who experienced recurrence of gastric cancer after surgery could receive chemotherapy with 20 mg/m² cisplatin, 450 mg/m² fluorouracil, and 90 mg/m² leucovorin (PFL) administered in 0.5 L normal saline and infused intravenously and simultaneously over 96 h every 21 days. This treatment could be delayed or modified according to the protocol if the patient experienced toxic effects.

Results

The summary of the clinicopathological characteristics of the seven patients with adenosquamous carcinoma of the stomach is listed in Table 2.

Among the seven patients, the median age is 62.3 years-old. Five patients are male and two are female. Patient No.1

was stage IV disease; and he died 4 months after surgery. Six patients were stage III disease and time of survival ranged from 2 to 47 months. Three stage IIIc patients (No.2, No.5, and No.7) died of gastric cancer disease itself. One stage IIIc patient (No.7) received chemotherapy with PFL after initial surgery and she had peritoneal seeding and bowel obstruction 12 months after surgery. She received bypass surgery and subsequent chemotherapy with taxol and 5-FU, and she is now still alive 18 months after initial surgery. Two stage IIIa patients (No.3 and No.4) only had one lymph node metastasis (1/34 and 1/27 respectively) and died of other causes. Patient No.3 did not receive adjuvant chemotherapy and he died of pancreatitis 41 months after surgery without tumor recurrence. Patient No.4 had liver metastasis 4 months after surgery and received radiofrequency ablation therapy for four times, and she finally died of aspiration pneumonia 47 months after surgery. In general, the percentage of SCC component is 40–90 %. Adenocarcinoma occupies a major portion of metastatic lymph nodes in six out of seven (85.7 %) patients. SCC occupies a major portion of metastatic lymph node in patient No.3, who is the only one patient without tumor recurrence until death.

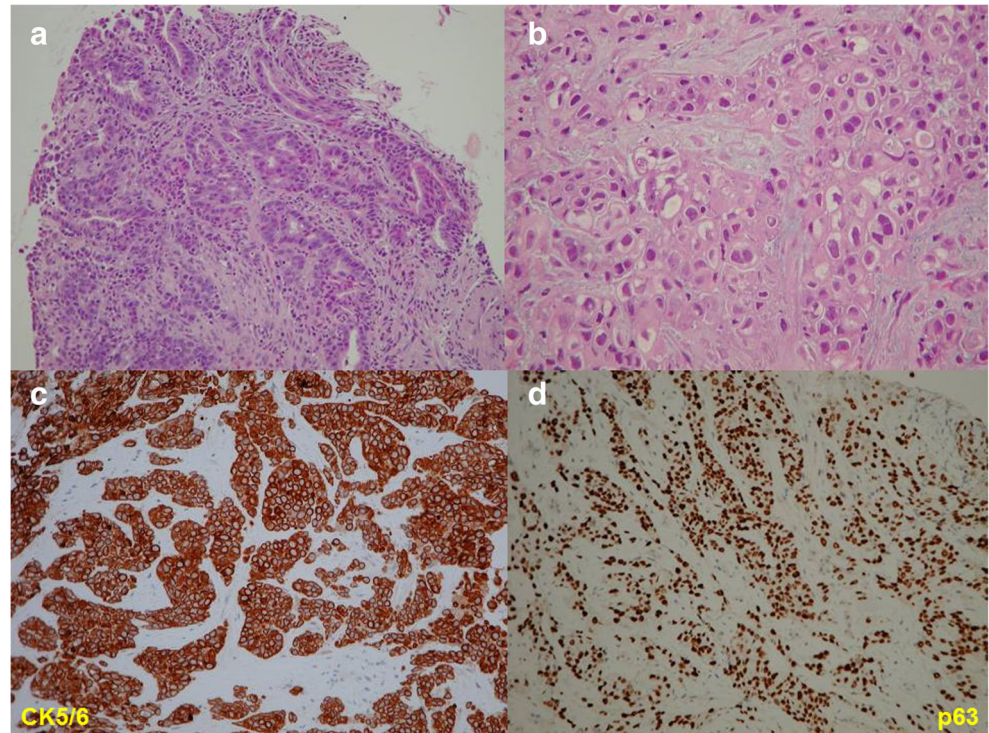
On microscopic examination, there was both adenocarcinoma and SCC component demonstrated in all the cases. The SCC component of the tumor was about 40–90 % and the rest was adenocarcinoma. Mucin secretion and tumor cells in glandular or tubular arrangement were demonstrated in the adenocarcinoma component. SCC component revealed p63 and CK5/6 positivity in immunohistochemical studies. Both components were moderately to poorly differentiated. The histopathology findings of two tumors were demonstrated in Figs. 1 and 2. The lymph nodes with metastatic lesions were analyzed, revealing that adenocarcinoma was the major component in six patients, and SCC was the major component in one patient.

Table 2 Summary of the clinicopathological characteristics of the 7 patients of adenosquamous carcinoma of the stomach

Patient No.	Age/gender	Extent of Gastrectomy	Pathological TNM	Stage	Tumor size (cm)	Location	Chemotherapy	Recur or metastasis site / period (month)	Outcome/ peroid (month)	% of SCC in tumor	Components in metastatic LNs
1	70 M	RTG	T4bN3bM1	IV	9	L	–	Peritoneum	DOD/3	90 %	Adeno major
2	47 M	RTG	T4aN3aM0	IIIc	10.	U	–	Brain/6	DOD/27	80 %	Adeno major
3	66 M	RTG	T4aN1M0	IIIa	4.3	U	–	Nil	DO/41	90 %	SCC major
4	75 F	RTG	T4aN1M0	IIIa	5	M	–	Liver/4	DO/47	50 %	Adeno major
5	73 M	RSG	T4aN3aM0	IIIc	11	M	+	Liver/2	DOD/2	40 %	Adeno major
6	56 F	RTG	T4bN3bM0	IIIc	6.5	U	+	Liver	Alive/18	50 %	Adeno major
7	49 M	RTG	T4bN3bM0	IIIc	11	U	–	Peritoneum	DOD/6	85 %	Adeno major

RSG radical subtotal gastrectomy, RTG radical total gastrectomy, L lower third of stomach, M middle third of stomach, U upper third of stomach, DOD died of disease, DO died of other causes, *adeno* adenocarcinoma, *SCC* squamous cell carcinoma, *LN* lymph node

Fig. 1 Histological findings of the resected stomach of No.6 patient. **a** There is infiltration of moderately differentiated adenocarcinoma component in tubular and glandular arrangement. **b** Squamous cell carcinoma (SCC) component in nests arrangement. (Hematoxylin and Eosin staining, $\times 100$). **c** SCC component was positive staining for CK5/6. (CK5/6, $\times 100$) **d** SCC component was positive staining for p63. (p63, $\times 100$)



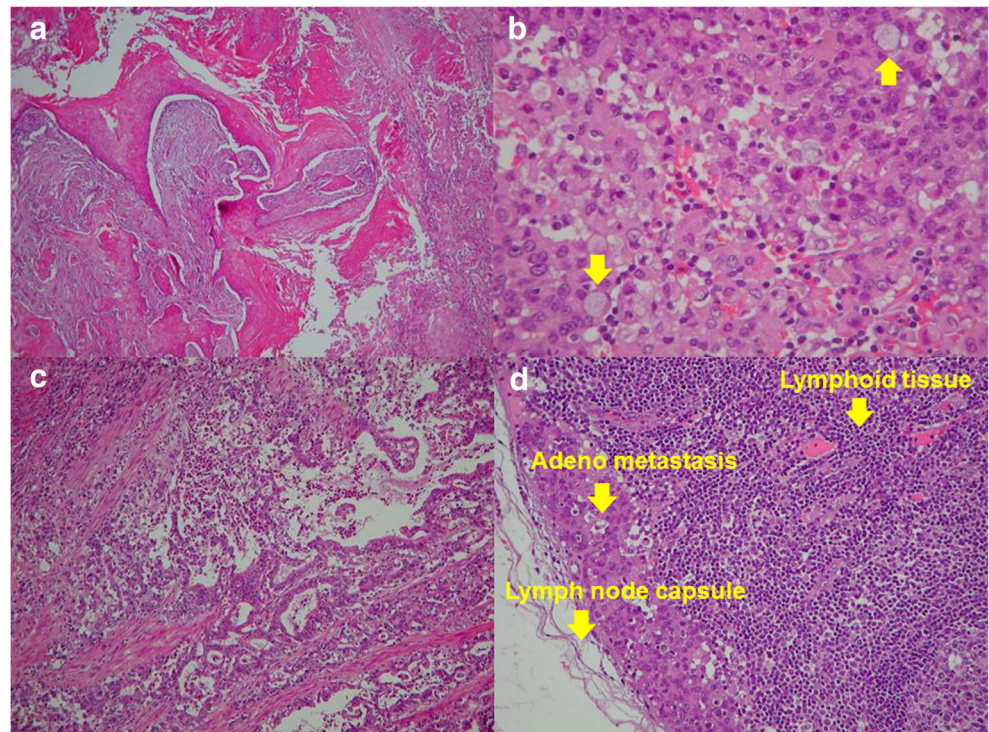
Discussion

Gastric adenosquamous carcinoma is a rare entity of gastric cancer. Frequently, the disease is diagnosed at advanced stage, usually extending to muscular layer, with venous and

lymphatics invasion. The disease nature of adenosquamous carcinoma was reported to be more aggressive than adenocarcinoma entity [12].

Histogenesis of adenosquamous carcinoma has not been clearly defined. There are five possible hypotheses: 1)

Fig. 2 Histological findings of the resected stomach of No.7 patient. **a** Keratin formation was demonstrated in the SCC component. (Hematoxylin and Eosin staining, $\times 100$). **b** Moderately differentiated adenocarcinoma component in fused glandular arrangement. (Hematoxylin and Eosin staining, $\times 200$) **c** Poorly differentiated adenocarcinoma component with signet ring cells were demonstrated. (Hematoxylin and Eosin staining, $\times 400$) **d** The poorly differentiated adenocarcinoma was the major component in the positive lymph nodes (H & E, 400X)



squamous metaplasia of an adenocarcinoma, 2) cancerization of metaplastic non-neoplastic squamous cells, 3) cancerization of ectopic squamous epithelium, 4) differentiation of multipotential undifferentiated cancer cells toward both squamous and glandular cells, and 5) collision of concurrent adenocarcinoma and SCC [11].

In gastric adenosquamous carcinoma, the biological behavior is usually determined by the adenocarcinoma component. Adenocarcinoma components are predominantly found in hematogenous and hepatic metastases. The component of adenocarcinoma or SCC in the metastatic lymph node remain controversial in literature review [13]. The SCC component of primary tumor in our series range from 40 to 90 %. Most of the cases are comprised majorly of SCC part, however, in metastatic lymph nodes, the major component is adenocarcinoma. Adenocarcinoma component appears to be more aggressive in distant spreading. Reports show that adenosquamous carcinoma does not respond to the use of TS-1-based chemotherapy [13], thus further standard chemotherapy still needs to be established.

The fact that the only one patient whose tumor component in metastatic lymph nodes is majorly SCC has had no tumor recurrence till death, is very interesting. In contrast, all the six patients whose tumor component in metastatic lymph nodes is majorly adenocarcinoma have either tumor recurrence or distant metastasis at diagnosis. As we know, lymph node metastasis is one of the strongest prognostic factor after surgery for gastric adenocarcinoma. It is still unknown how the ratio of adenocarcinoma/squamous carcinoma in metastatic lymph node influences the prognosis of adenosquamous carcinoma. The hypothesis is that gastric adenosquamous carcinoma with major component of adenocarcinoma in metastatic lymph node may be more aggressive than those with major component of SCC in metastatic lymph node. However, adenosquamous carcinoma is so rare (0.25 %) in our gastric cancer population, that more patient enrollments are required in the future to testify the above hypothesis.

Conclusion

In conclusion, adenosquamous carcinoma of the stomach is a rare disease. The behavior of adenocarcinoma component of metastatic lymph nodes may determine the prognosis of the disease. Patients with adenosquamous carcinoma of the

stomach are usually diagnosed at a late stage and are associated with a poor prognosis.

Acknowledgment This research was supported by a grant from the Division of Experimental Surgery of the Department of Surgery and Taipei Veterans General Hospital (V103C-135).

Conflict of Interest All authors have no conflicts of interest.

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