

Fever as a first manifestation of advanced gastric adenosquamous carcinoma: A case report

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Core tip: Totally laparoscopic total gastrectomy for advanced primary adenosquamous carcinoma of the stomach with fever as the initial manifestation is an interesting combination of a rare lesion with an atypical presentation and an uncommon complex surgical procedure. Given the aggressive nature and advanced stage at diagnosis, there are no reports of this carcinoma in the English literature. To the best of our knowledge, this is the first case of its kind reported in the English literature.

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Abstract

Gastric adenosquamous carcinoma (ASC) is a rare type of gastric cancer. It is a mixed neoplasm, consisting of glandular cells and squamous cells. It is often diagnosed at an advanced stage, thus carrying a poor prognosis. We describe a case of a 73-year-old male, who presented with refractory fever and an intra-abdominal mass on imaging. He underwent a laparoscopic exploration followed by a successful totally laparoscopic total gastrectomy with D2 lymphadenectomy for gastric cancer. Postoperative pathology revealed primary gastric ASC (T4aN0M0). The patient received adjuvant radiotherapy and chemotherapy with S1 and is alive 20 mo after surgery without recurrence. This is the first case of advanced gastric ASC with fever as the initial presentation treated with totally laparoscopic total gastrectomy reported in the English literature.

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INTRODUCTION

The first case of gastric adenosquamous carcinoma (ASC) was reported by Rolleston and Trevor^[1]. ASC accounts for less than 1% of all gastric cancers worldwide^[2], compared with the predominant adenocarcinoma type which has an incidence of more than 90%^[3]. Since the first reported case, ASC has only been reported in case reports (Table 1), mostly from Asian countries^[4-6] and very few case series (Table 2) have been reported in the English literature. It has a male to female preponderance with a 4:1 ratio, and peaks in the 6th decade of life, occurring on average earlier than sporadic adenocarcinoma^[2]. It is usually aggressive in nature, diagnosed at an advanced stage and carries a poorer prognosis than adenocarcinoma^[2].

The application of laparoscopic approaches for distal gastric lesions, benign or early gastric cancers, has been

Table 1 Reported cases of gastric adenosquamous carcinoma

Author	Year	Country	Gender	Age (yr)	Signs and symptoms	Preop diagnosis	Surgical procedure	Tumor size (cm)	Location	Metastasis	Staging	Adjuvant treatment	Prognosis
Rolleston and Trevor ^[12]	1905	-	M	39	-	-	-	-	P	-	-	-	-
Lubarsch ^[12]	1906	-	-	-	-	-	-	-	P	-	-	-	-
Herxheimer ^[12]	1907	-	-	-	-	-	-	-	P	-	-	-	-
Boedecker ^[12]	1926	-	F	35	-	-	-	-	P	-	-	-	-
			F	65	-	-	-	-	P	-	-	-	-
Oberling and Wolf ^[12]	1927	-	F	67	-	-	-	-	P	-	-	-	-
Pasternack ^[12]	1935	-	M	48	-	-	-	-	P	-	-	-	-
Martin and Pollosson ^[12]	1936	-	F	64	-	-	-	-	B	-	-	-	-
Takagi ^[12]	1937	-	M	33	-	-	-	-	B	-	-	-	-
Scheffler and Falk ^[12]	1940	-	M	74	-	-	-	-	B	-	-	-	-
Wood ^[12]	1943	-	M	51	-	-	-	-	P	-	-	-	-
			M	37	-	-	-	-	P	-	-	-	-
Strassman ^[12]	1946	-	M	85	-	-	-	-	B	-	-	-	-
O'Brien and Meehan ^[12]	1950	-	M	40	-	-	-	-	P	-	-	-	-
Milanes <i>et al</i> ^[12]	1950	-	M	50	-	-	-	-	B	-	-	-	-
Bellagie and Dahlin ^[12]	1951	-	M	42	-	-	-	-	B	-	-	-	-
			M	49	-	-	-	-	B	-	-	-	-
Hirai <i>et al</i> ^[12]	1963	-	M	37	-	-	-	-	B and P	-	-	-	-
Straus, Heschel and Fortmann ^[12]	1968	-	F	70	-	-	-	-	P	-	-	-	-
Lee <i>et al</i> ^[1]	1970	SK	M	43	A ² , EP, HP, TS	-	Sub-G + O	-	A	LN	-	-	-
Taira <i>et al</i> ^[13]	1976	J	F	45	-	-	-	-	-	-	-	-	-
Fujitomi <i>et al</i> ^[14]	1983	J	-	-	-	-	-	-	-	-	Bor IV	-	-
Jalif <i>et al</i> ^[15]	1984	S ¹	F	68	-	-	-	-	-	-	-	-	-
Sato <i>et al</i> ^[16]	1984	J	F	76	-	-	TG + S	-	-	-	Bor III	-	-
Matsumoto <i>et al</i> ^[17]	1984	J	M	56	UAD	-	TG	5.0 × 4.0	A and B	LN	Bor III	-	-
Masuda <i>et al</i> ^[18]	1985	J	-	53	UAP	ASC	Sub-G	-	B	-	Bor III	-	-
³ Horikawa <i>et al</i> ^[19]	1987	J	F	56	-	-	-	-	-	-	EGC	-	-
³ Johzaki <i>et al</i> ^[20]	1988	J	F	78	-	-	Par-G	-	-	-	EGC	-	-
³ Butov <i>et al</i> ^[21]	1989	R	-	-	-	-	-	-	-	-	EGC	-	-
Shigematsu <i>et al</i> ^[22]	1989	J	F	74	EP + AL	-	-	-	-	LN	Bor III	-	-
⁴ Yamamoto <i>et al</i> ^[23]	1989	J	M	61	-	-	Sub-G	-	-	L, L ¹ LN	-	-	-
Honda <i>et al</i> ^[24]	1990	J	M	57	UAP	-	-	-	Angle region	-	Grade II ASC	-	-
Tsukino <i>et al</i> ^[25]	1990	J	M	61	-	-	-	-	-	LN	Bor IV	-	-
Kawabe <i>et al</i> ^[26]	1990	J	-	-	-	-	-	-	Fornix and B	-	-	-	-
Coard <i>et al</i> ^[27]	1991	J and C	-	-	-	-	-	-	-	-	-	-	-
Tenma <i>et al</i> ^[28]	1993	J	M	51	-	-	TG post chemo	-	-	-ve	Bor III	-	-
Ito <i>et al</i> ^[29]	1993	J	-	-	-	-	-	-	-	-	-	-	-
Cabello Rodríguez <i>et al</i> ^[30]	1994	S ¹	F	84	-	-	-	-	A	-	-	-	-
Toyota <i>et al</i> ^[6]	1996	J	F	72	RHE	-	P	-	-	-	Bor 2 + EGC	-	-
³ Yoshida <i>et al</i> ^[5]	1996	J	M	66	EP	SCC	Par-DG	2.1 × 2.0	A	L, LN	-	-	Died 2 yr post op ²
Manna <i>et al</i> ^[31]	1998	P	M	55	-	-	-	-	-	-	-	-	-
Mori <i>et al</i> ^[32]	2000	J	M	59	-	-	TG + H	-	RS	L, LN	-	-	Died 2 mo post H ¹
Blázquez <i>et al</i> ^[33]	2005	S ¹	F	56	CA	-	-	-	A	-	-	-	Died few days post op
Endo <i>et al</i> ^[7]	2005	J	M	55	F and A ¹	ASC	Par-G + D3	7.0 × 8.0	A	LN, L ²	T2N2M0	-	-

Nomura <i>et al</i> ^[34]	2006	J	F	62	A ¹	-	DG	B and A	-	LN	T3N3M0	Neoadjuvant chemo	-
Terada ^[35]	2009	J	F	87	N and V	SCC	TG + C1 + S	10 × 8 × 7	-	SM, LV	Bor IV	-	Died 5 mo post op
			F	77	EP	SCC	G	6 × 5 × 7	-	SM, LV	Bor III	-	Died 8 mo post op
Faria <i>et al</i> ^[2]	2010	P	F	84	EP	-ve	Sub-G	8 × 5 × 1.1	A	LN, L	T3N1M1	-	-
Fukuda <i>et al</i> ^[36]	2012	J	M	70	-	-	TG + D2 + H	-	-	L	-	-	-
Ebi <i>et al</i> ^[8]	2012	J	M	74	AP and M	SCC	Par-G	-	B	LN	Advanced type 3	S1 monotherapy	Alive post op 2 yr 10 mo
Saito <i>et al</i> ^[37]	2013	J	M	60	UBP	ASC	No surgery	-	B-A	LN	-	DC-S1	Pt died 3 mo post chemo
³ Kimura <i>et al</i> ^[41]	2013	J	M	77	-	-	LADG	-	-	LN; Recurrence in liver	ECG	S-1 and cisplatin (CDDP)	Alive 14 mo post op
Harsha Ajoodhea <i>et al</i> (present case)	2013	C	M	73	Fever	ADC	TLTG+D2	8 × 7.5	B-A	-ve	T4a N0 M0	Rand S1	Alive at 20 mo post op

¹Died of lymphangitis carcinomatosa of the lung 2 mo after right hepatectomy; ²Died of liver failure due to multiple metastases 2 yr after operation; ³Early gastric cancer; ⁴Hypesthesia and pain in both legs, and progressive difficulty in walking. A1: Anemia; A2: Anorexia; AL: Appetite loss; CA: Chronic anemia; EP: Epigastric pain; HP: Hunger pain; F: Fatigue; V: Vomiting; N: Nausea; RHE: Routine health examination; TS: Tarry stool; M: Melena; UAP: Upper abdominal pain; UAD: Upper abdominal discomfort; J: Japan; S1: Spain; P: Portugal; M: Maroc; C: China; R: Russia; SK: South Korea; JC: Jamaica and Commonwealth Caribbean; S: Splenectomy; Sub-G: Subtotal gastrectomy; Par-G: Partial gastrectomy; P: Pylorogastrectomy; H: Hepatectomy; DG: Distal gastrectomy; C1: Cholecystectomy; ASC: Adenosquamous carcinoma; Par-DG: Partial distal gastrectomy; SSC: Squamous cell carcinoma; ADC: Adenocarcinoma; A: Antrum; B: Body; F: Fornix; C: Cardia; P: Pylorus; O: Omentectomy; RS: Remnant stomach; Borr: Borrmann type; L: liver; L1: Lung; SM: Systemic metastases; LN: Lymph node metastases; LV: Lymphovascular metastases; L2: Lymphatics; R: Radiotherapy; S1: S1 chemotherapy; DC-S1: Docetaxel, cisplatin and S-1 (DCS); EGC: Early gastric cancer; LADG: Laparoscopic-assisted distal gastrectomy; TLTG: Totally laparoscopic total gastrectomy.

Table 2 Reported case series of gastric adenosquamous carcinoma

Author	Year	Country	No. of cases	Mean age (yr)	Location
Boswell and Helwig ^[12]	1965	-	11 ¹	49.1	P: 9 pts; LC: 1 pt; F: 1 pt
Urban <i>et al</i> ^[12]	1966	-	10 ²	54.7	P and B: 1 pt; C and B: 1 pt P: 6 pts; C: 2 pts
Aoki <i>et al</i> ^[38]	1978	Japan	11 ³	61.2	A: 5 pts; B: 2 pts; F: 4 pts
Mori <i>et al</i> ^[4]	1986	Japan	28	-	-
Namatame <i>et al</i> ^[39]	1986	Japan	5 ⁴	62.8	Lower body along lesser curvature
Rottenberg ^[40]	1987	Russia	5	-	B and P

¹10 males and 1 female; ²6 males and 1 female; ³10 males and 1 female; ⁴2 males and 3 females. Pt: Patient; A: Antrum of stomach; P: Pylorus; LC: Lesser curvature of stomach; F: Fundus of stomach; B: Body of stomach; C: Cardia of stomach.

accepted worldwide. The advantages and long-term benefits in these patients are also very well known and appreciated. Despite the advances in minimally invasive techniques and their advantages, several issues have been raised in the setting of a totally laparoscopic total gastrectomy. Moreover, in patients with advanced cancer, a minimally invasive approach is not commonly used. The case presented here is that of a patient with an advanced primary ASC extending to the serosal layer. This is the first case of ASC treated completely laparoscopically reported in the English literature.

CASE REPORT

We report a case of a 73-year-old male, who was referred to the surgical department after refractory medical treatment for an irregular high fever. The patient was previ-

ously treated for pneumonia 2 mo before admitted to the Infectious Disease Department because of irregular high fever. Except for mild anemia (hemoglobin 8 g/L), white blood cell (WBC) count of $15.8 \times 10^9/L$ and C-reactive protein (CRP) level of 72.4 mg/L, all other laboratory tests, physical examination and past/family history were insignificant. Despite aggressive treatment, his fever (Figure 1A) persisted and the WBC count (Figure 1B) and CRP level (Figure 1C) increased. He was then referred to the surgical department due to the presence of an intra-abdominal mass found on imaging. An abdominal ultrasound revealed a hypoechoic mass in the upper abdomen suggesting gastric cancer with surrounding lymph node involvement. Abdominal computed tomography (CT) showed a mass in the upper abdomen between the stomach and the left lobe of the liver (Figure 2). Gastroscopy showed a raised lesion on the gastric antrum surface,

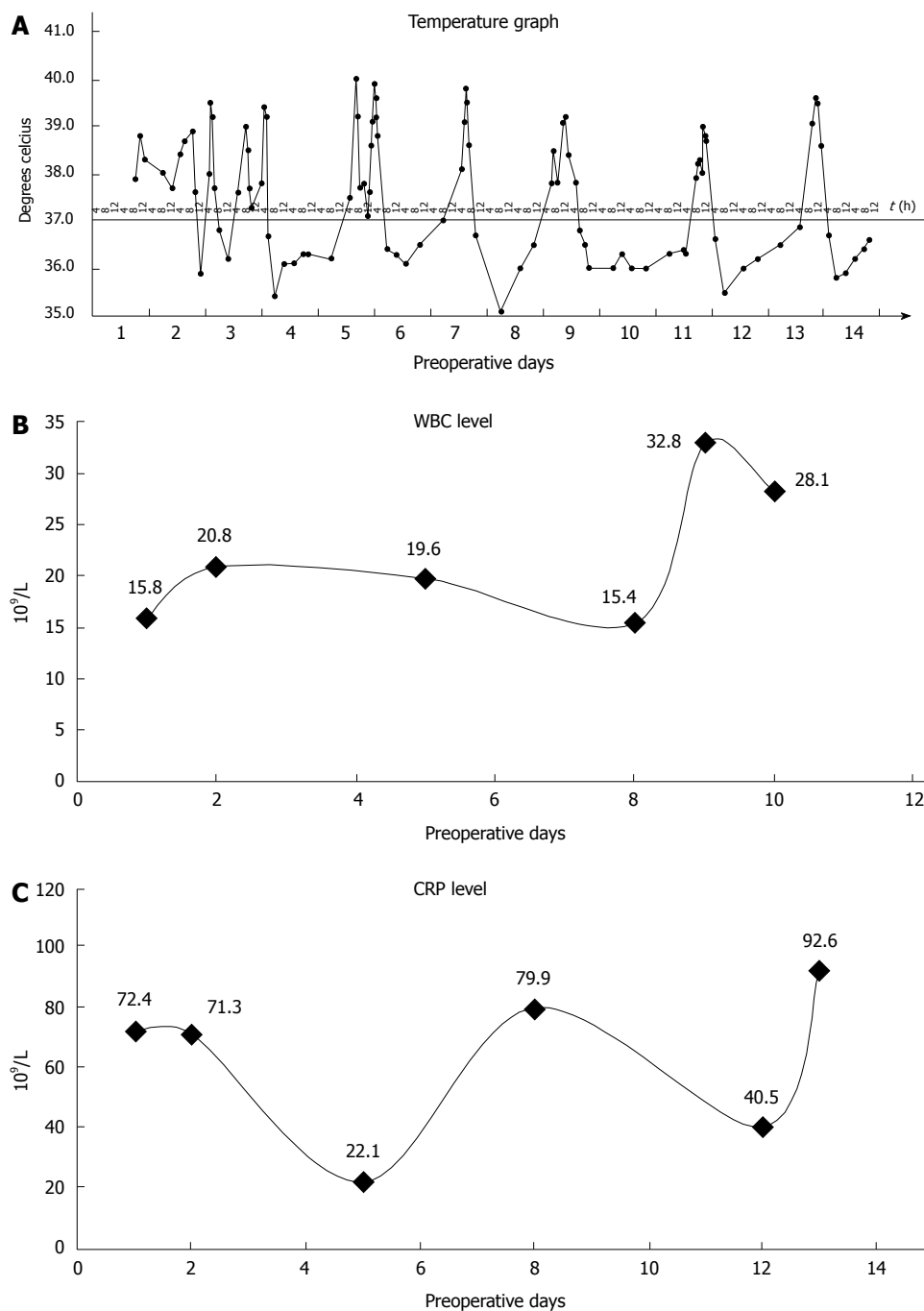


Figure 1 Preoperative graphs. A: Preoperative temperature; B: Preoperative white blood cell (WBC) count; C: C-reactive protein (CRP) level.

with ulceration, and involving the lower part of the body of the stomach (Figure 3). The preoperative biopsy pathology showed an adenocarcinoma, and the patient was found to be *Helicobacter pylori* positive. He underwent a totally laparoscopic total gastrectomy accompanied by D2 lymphadenectomy, and an esophagojejunal Roux-en-Y anastomosis was performed. The patient was placed in the supine position with the head slightly elevated under general anesthesia. The surgeon and the second assistant holding the laparoscope stood on the right side of the patient and the first assistant stood on the left. Carbon dioxide pneumoperitoneum was established (CO₂

at 15 mmHg) using a Veress needle. The first 10-mm trocar was placed at the umbilicus for the laparoscope. A 30-degree telescope was inserted to examine the peritoneal cavity to rule out metastatic disease and assess the feasibility of the procedure. After general examination, an additional four trocars (one of 12 mm, three of 5 mm) were inserted and the five trocars were arranged in a V-shape. The operation was started by retracting the greater omentum superiorly using the grasper and bluntly dissecting along the transverse colon border to enter the lesser sac (Figure 4A). The stomach together with the greater omentum was then retracted superiorly using

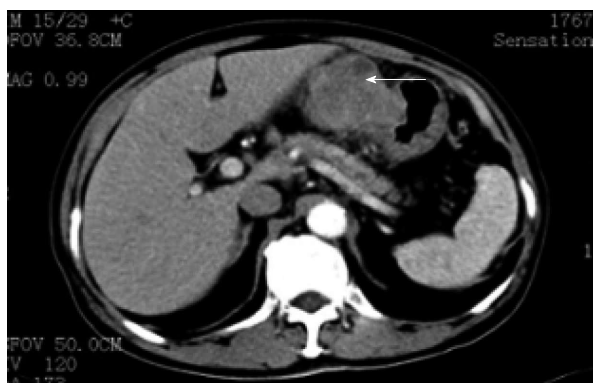


Figure 2 Abdominal computed tomography showing an upper abdominal mass between left lateral hepatic lobe and stomach, as shown by arrow.



Figure 3 Gastroscopy. Gastric antrum raised lesion, with ulceration, easy to bleed and involving the lower part of the body of the stomach.

the grasper to allow better visualization of anatomical landmarks. The right gastroepiploic vessels were identified, clipped using Hem-o-lock and excised (Figure 4B and C). Next, mobilization began at the superior edge of the pancreas, thus revealing the celiac trunk. The common hepatic artery, right gastric artery, left gastric artery and splenic artery and their respective lymph nodes were identified and excised. The right gastric artery, left gastric artery and vein were then clipped using the Hem-o-lock and excised (Figure 4D). The hepatoduodenal and hepatogastric ligaments were then dissected. The esophageal wall was detached from the surrounding tissue and completely mobilized (Figure 4E). The cardia vagus nerve was cut 3 cm above the cardia. Once the structures were completely mobilized, the duodenum was then transected using an endoscopic linear stapler 3 cm from the pylorus (Figure 4F). The jejunum was stapled using an endoscopic linear stapler 20 cm from the ligament of Treitz. A small opening was made 10 cm from the stump on the distal jejunum and the latter was then pulled up to the esophagus, in which a small side opening was also made. A side-to-side antiperistaltic esophagojejunostomy was then performed using linear staplers (Figure 4G) and the entry hole was then closed using staplers (Figure 4H). The esophageal wall was sutured to the diaphragm wall to avoid tension, thus preventing anastomotic failure. The specimen was placed in a retrieval bag and pulled out through an enlarged umbilical incision. Pneumoperitoneum was re-established. A routine Roux-en-Y anastomosis was performed laparoscopically between the distal jejunum (40 cm from the esophagojejunostomy) and the proximal jejunum. Any defects in the mesentery were closed. The postoperative pathology result was an 8 cm × 7.5 cm sized gastric ASC (Figure 5) located in the body and antrum, with a 3 cm × 2 cm central ulcer invading the serosal layer. Pathological findings showed an adenocarcinoma component with glandular formation, and a squamous cell component with keratinization (Figure 6A and B). There was no obvious border between the two components. The adenocarcinoma cells were well to moderately differentiated with a proportion of 40% and were found in the upper one-third, and the squamous cells were well differentiated with a proportion of 60%

and were found in the lower two-thirds of the stomach. Additional immunohistochemical staining for CK Low (Figure 6C) showed strong positive staining for adenocarcinoma, and staining for P63 (Figure 6D) showed nuclear positive staining for squamous cell carcinoma. No lymph node metastasis (0/35), lymphatic or vascular invasion were found and a negative margin was achieved (TNM staging was Stage IV-T4aN0M0 and Bormann type 4).

After surgery, there was an immediate decrease in temperature (Figure 7A), WBC count (Figure 7B) and CRP level (Figure 7C). The patient was started on liquid food 3 d after surgery, followed by semi-liquid food on the 8th day. The length of postoperative hospital stay was 14 d. No postoperative morbidity was noted. After operation, the patient received adjuvant radiotherapy and chemotherapy with S1. He was followed for nearly 20 mo and was in good health without recurrence as confirmed by CT scan at follow-up. His nutritional status was reported to be better compared to preoperative status.

DISCUSSION

ASC is a special type of gastric cancer. It occurs mainly in the distal and the body of the stomach (Table 1). Macroscopically, most tumors are Bormann type 2 or 3 advanced gastric cancer^[7]. Very few reports are available in the English literature on early gastric ASC^[41]. The most common site of metastasis is the liver^[7] and lymphovascular metastases are common^[8]. For the diagnosis of true ASC, collision tumors should be excluded. True ASC is a combination of adenocarcinoma and squamous cell carcinoma, with transitions between the two components^[9]. Although the lesion is a combination of the two different histologic types, the biologic behavior is decided by the adenocarcinoma component.

The highlights of this case report are as follows: (1) atypical presentation in the patient; (2) the presence of ASC at final postoperative diagnosis; and (3) totally laparoscopic total gastrectomy for advanced gastric cancer. The chief complaints of patients with gastric ASC are similar to those of any gastric adenocarcinoma patient, and include epigastric pain, nausea and vomiting^[8]. This is the first case of advanced gastric ASC reported in the

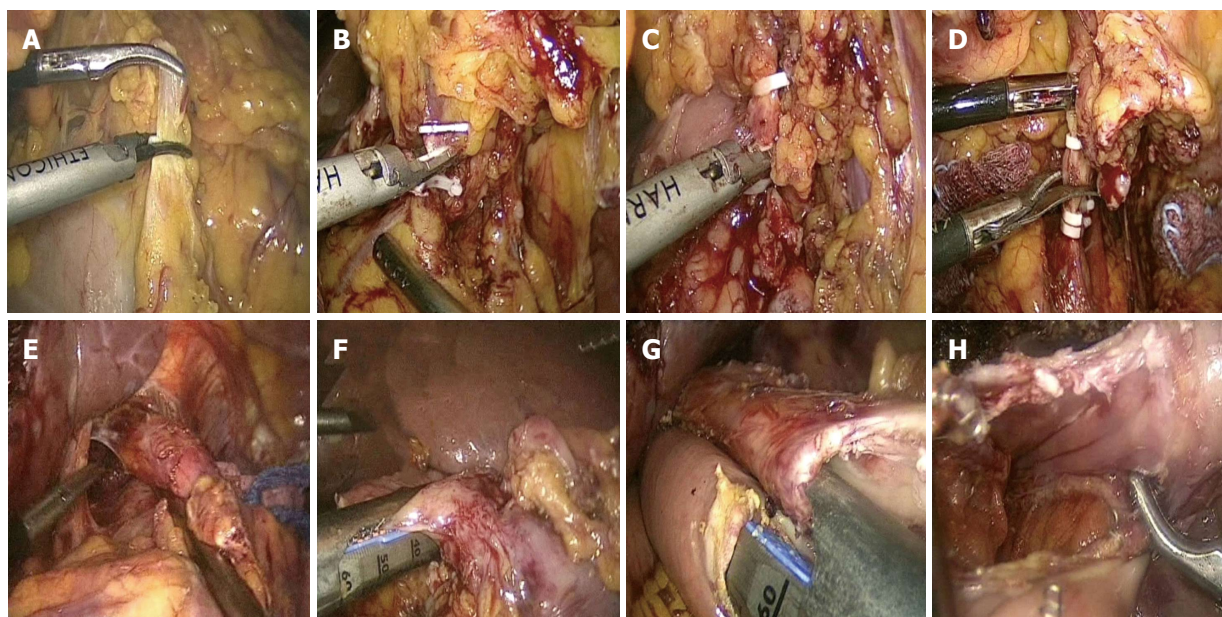


Figure 4 Surgical procedure. A: Dissection of the greater omentum; B, C: Clipping and cutting of right gastroepiploic vein and artery, respectively; D: Clipping and cutting of left gastric artery; E: Mobilization of esophagus; F: Transection of duodenum; G: Antiperistaltic reconstruction of esophagus and jejunum using linear stapler; H: Entry hole as seen after stapling.



Figure 5 Gross Operative specimen. An 8 cm x 7.5cm mass with a 3 cm x 2 cm ulcer, invading the serosal layer (mass cut open), as shown by arrow.

English literature with fever as the initial presentation. Preoperatively, it was difficult to rule out lung infection as the cause of fever, given the patient's previous history of pneumonia. As a result of non-responsiveness to medical treatment, the patient underwent surgery for suspected gastric cancer. The preoperative fever in this patient is believed to be associated with the necrotic tissues found in the lesion. There was a decrease in temperature immediately after the operation, along with a reduction in the WBC count and CRP level, which confirmed that the gastric mass was the cause of the fever.

Of interest was the presence of squamous cells in a glandular cellular area not contiguous with squamous epithelium. The final pathological diagnosis was gastric ASC. Since the first case reported more than one century ago, no confirmed evidence has been available on the pathogenesis of this lesion.

A few hypotheses^[2] have been proposed regarding its

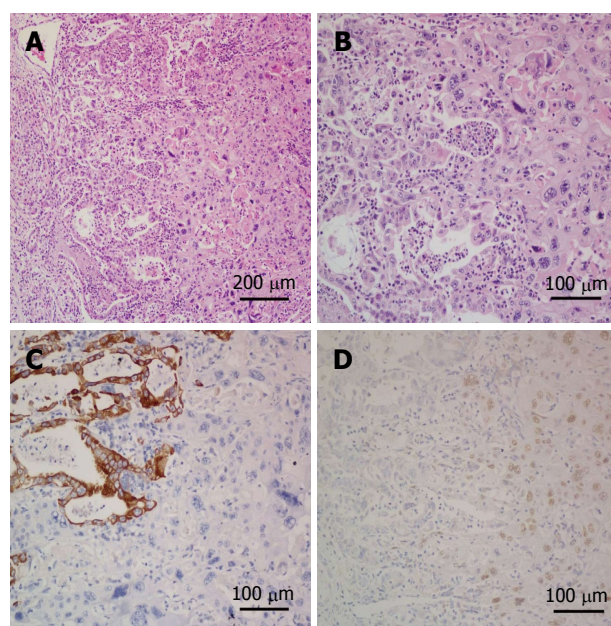


Figure 6 Microscopic specimen. A and B: Both adenocarcinoma and squamous cell carcinoma components. Adenocarcinoma component shows gland formation and squamous carcinoma component shows keratinization (hematoxylin and eosin staining, A: x 10 magnification; B: x 20 magnification); C: Immunohistochemical (IHC) staining for cytokeratin (low), on the left side adenocarcinoma is strongly positive and on the right side squamous cell carcinoma is negative (IHC x 20 magnification); D: IHC staining for P63, on the left side adenocarcinoma is negative and on the right side squamous cell carcinoma is nuclear positive (IHC x 20 magnification).

origin, such as: (1) metaplastic transformation of an adenocarcinoma; (2) cancerization of metaplastic squamous cells; (3) cancerization of ectopic squamous epithelium; (4) collision of an adenocarcinoma and a squamous cell carcinoma; and (5) stem cell differentiation towards both

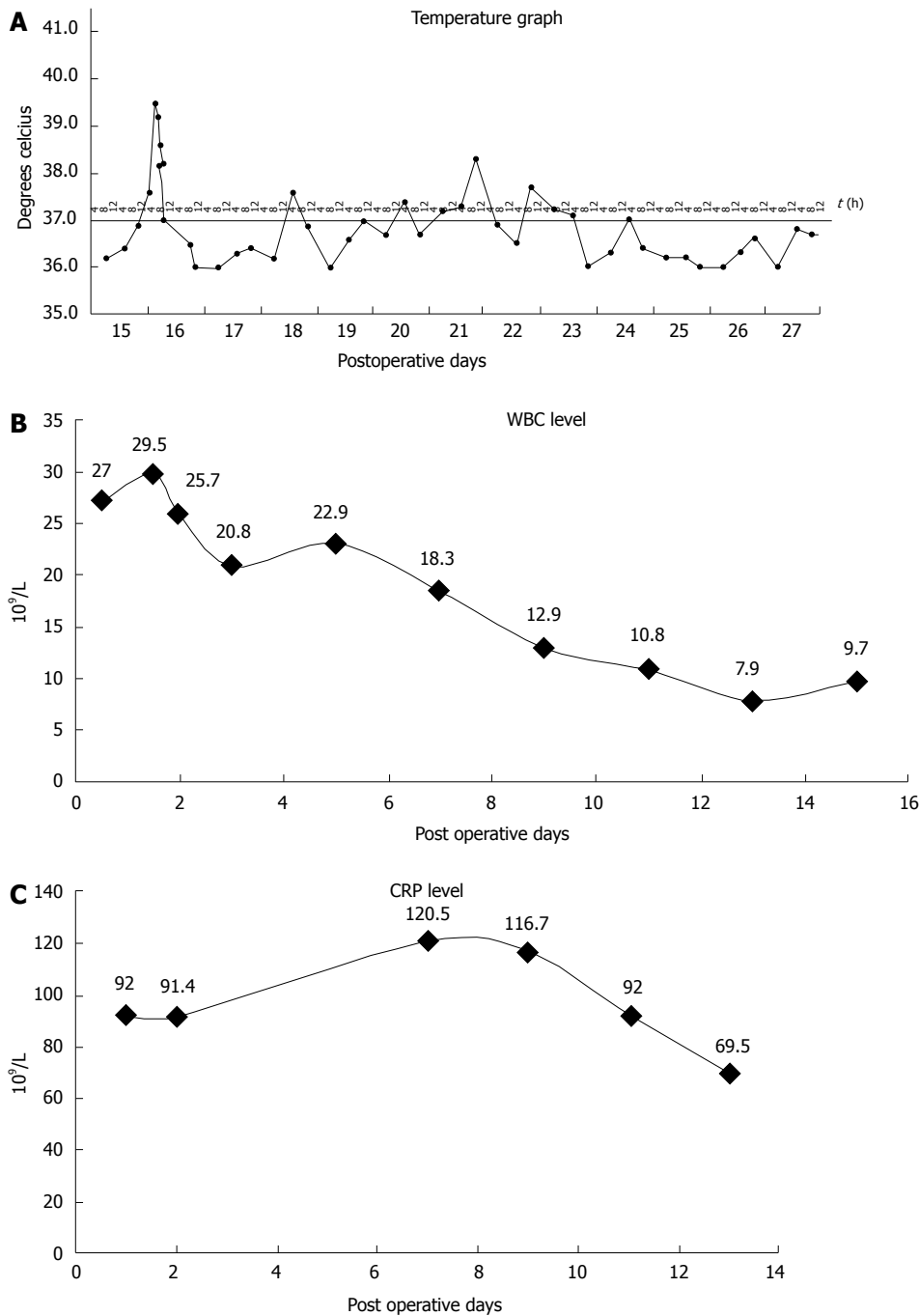


Figure 7 Postoperative graphs. A: Postoperative temperature; B: Postoperative white blood cell (WBC) count; C: Postoperative C-reactive protein (CRP) level.

cellular lines. Furthermore, another noteworthy point in the present report is the mismatch of preoperative and postoperative pathological results. This may be explained by the fact that despite gastroscopy, which is the gold standard for gastric cancer, the tissue sample taken during the biopsy showed that differentiation into adenosquamous cells had not occurred or had not yet occurred. Therefore, our preoperative biopsy result showed only gastric adenocarcinoma. Hence, ASC cannot be ruled out preoperatively and should be considered in the differential diagnosis, especially in patients with atypical presentations.

To the best of our knowledge, this is the first case

of primary advanced gastric ASC with fever as the initial manifestation treated by totally laparoscopic total gastrectomy reported in the English literature. Laparoscopic surgery has been adopted since 1991 in the treatment of gastric cancer. In 1994, laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection was first performed by Kitano *et al*^[10]. As the safety and surgical quality of LADG have been proved to be equivalent to open gastrectomy, LADG has been accepted as a less invasive treatment for early gastric cancer^[11]. Advances in laparoscopic surgical techniques have now made it possible to perform all necessary surgical procedures, including intra-abdominal reconstruction^[11]. This has led to the

introduction of totally laparoscopic distal gastrectomy. Unfortunately, totally laparoscopic total gastrectomy with D2 lymphadenectomy is not yet popular due to the complexity of the procedure. Our case underwent a totally laparoscopic total gastrectomy with D2 lymphadenectomy and esophagojejunostomy Roux-en-Y anastomosis (antiperistaltic side-to-side anastomosis). The patient had an uneventful and quick recovery after operation without morbidity. He received adjuvant radiotherapy and S1 chemotherapy and is still alive 20 mo after operation, without recurrence. Therefore, laparoscopic surgery should be considered for advanced gastric cancer patients in selected high volume centers and by highly specialized laparoscopic surgeons.

In conclusion, primary advanced gastric ASC can present with atypical manifestations and should be considered in the differential diagnosis in atypical gastric cancer patients. Surgery should be attempted in such patients.

COMMENTS

Case characteristics

A case of advanced gastric adenosquamous carcinoma (ASC) in a 73-year-old male who presented with an irregular high fever refractory to medical treatment.

Clinical diagnosis

He was diagnosed initially with a lung infection due to the presence of an irregular high fever at presentation.

Differential diagnosis

In the differential diagnosis, lung infection, fever of unknown origin, and cancer-related fever were considered and therefore, blood and sputum cultures, sputum acid fast staining, PPD test, TSPOT test, bone marrow aspiration, abdominal ultrasound, computed tomography and bone scintigraphy were ordered.

Imaging diagnosis

Abdominal ultrasound revealed a hypoechoic mass in the upper abdomen suggesting gastric cancer with surrounding lymph node involvement. Abdominal computed tomography showed a mass in the upper abdomen between the stomach and the left lobe of the liver.

Pathological diagnosis

The preoperative pathological diagnosis was adenocarcinoma, and the patient was found to be *Helicobacter pylori* positive.

Treatment

A totally laparoscopic total gastrectomy was performed and the patient received postoperative radiotherapy and chemotherapy with S1.

Experiences and lessons

Primary gastric ASC can present with atypical manifestations and should be considered in the differential diagnosis in atypical gastric cancer patients, even if the preoperative pathological results state otherwise. Surgery should be attempted in such patients.

Peer review

Adenosquamous carcinoma of the stomach is very rare, and fever is an unusual presentation of gastric cancer. Furthermore, totally laparoscopic surgery is not usually performed for advanced gastric cancer. Thus, the present case is interesting and worth reporting.

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