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CASE REPORT

Hepatoid adenocarcinoma of the stomach with neuroendocrine differentiation: A case report and review of literature

He Fei, Ze-Feng Li, Ying-Tai Chen, Dong-Bing Zhao

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Abstract

BACKGROUND

Both hepatoid adenocarcinoma of the stomach (HAS) and neuroendocrine differentiation (NED) are rare histological subtypes of gastric cancer with unique clinicopathological features and unfavorable outcomes. HAS with NED is even rarer.

CASE SUMMARY

Here, we report a 61-year-old man with HAS with NED, as detected by gastric wall thickening by positron emission tomography/computed tomography for a pulmonary nodule. Distal gastrectomy was performed, and pathological examination led to the diagnosis of HAS with NED. However, liver metastases occurred 6 mo later despite adjuvant chemotherapy, and the patient died 27 mo postoperatively.

CONCLUSION

We treated a patient with HAS with NED who underwent adjuvant chemotherapy after radical surgery and still developed liver metastases. We first report the detailed processes of the treatment and development of HAS with NED, providing an important reference for the clinical diagnosis and treatment of this condition.

Key Words: Gastric cancer; Hepatoid adenocarcinoma; Neuroendocrine differentiation; Liver metastasis; Case report

Core Tip: Hepatoid adenocarcinoma of the stomach (HAS) with neuroendocrine differentiation (NED) is rare histological subtype. We first reported the detailed processes of surgery and chemotherapy of HAS with NED and the survival time was 27 mo combined with postoperative chemotherapy, which provided an important reference for clinical diagnosis and treatment of this condition.

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INTRODUCTION

Hepatoid adenocarcinoma of the stomach (HAS) accounts for approximately 0.3% to 1.0% of all gastric cancers and is an extremely rare subtype with tissue morphology similar to hepatocellular carcinoma (HCC)[1]. Most, but not all, HAS cases produce alpha-fetoprotein (AFP)[2], and increased serum AFP is mainly due to hepatoid cells[3-5]. Neuroendocrine neoplasms (NENs) can be divided into neuroendocrine tumors and neuroendocrine carcinomas (NECs). NEC is characterized by neuroendocrine differentiation (NED) and divided into small-cell NEC (SCNEC) and large-cell NEC (LCNEC); the latter has better survival prognosis than the former[6]. Ninety percent of SCNECs originate from the lung. The incidence of LCNEC is 1.8/100000, with only 3% occurring in the stomach[7]. Nonneuroendocrine components (adenocarcinoma and squamous carcinoma) are frequently observed in high-grade NECs[8], and adenocarcinoma with NED is also found in other organs. However, HAS with NED is extremely rare. Herein, we report a case of a 61-year-old male who underwent radical surgery, and we also summarize the relevant literature.

CASE PRESENTATION

Chief complaints

Positron emission tomography/computed tomography (PET/CT) revealed thickening of the gastric lesser curvature at 1 wk.

History of present illness

A 61-year-old man underwent PET/CT for pulmonary nodules. PET/CT revealed thickening of the gastric lesser curvature with metabolic hyperplasia.

History of past illness

In addition, he was diagnosed with hypertension 5 years prior and took nifedipine daily. He had been drinking alcohol at approximately 250 g/day and smoking 20 cigarettes/day for over 40 years.

Personal and family history

The patient denied any family history of malignant tumors.

Physical examination

Physical assessment revealed no abnormalities.

Laboratory examinations

Laboratory examinations, including tumor marker levels, revealed no abnormalities.

Imaging examinations

PET/CT (Figure 1) revealed thickening of the gastric lesser curvature with metabolic hyperplasia. Gastroscopy (Figure 2) showed a localized ulcerative lesion extending from the angle to the antrum of the stomach that was mainly located in the mucosal layer and submucosal layer. The lesion was diagnosed as poorly differentiated carcinoma based on biopsy pathology.

Postoperative pathological results

The surgically resected specimen showed an ulcer-type tumor with a size of 2 cm × 1.5 cm × 0.5 cm in the lesser curvature of the gastric antrum. Postoperative pathology revealed HAS with NED. Histological examination showed that the tumor invaded the submucosal layer and subserous fat with multifocal growth. There was angiolymphatic invasion, but no nerve invasion was noted. The surrounding gastric mucosa showed chronic active inflammation with massive *Helicobacter Pylori* infection (Figure 3). Some lymph nodes were found to have metastatic carcinoma (4/29). One lymph node on the

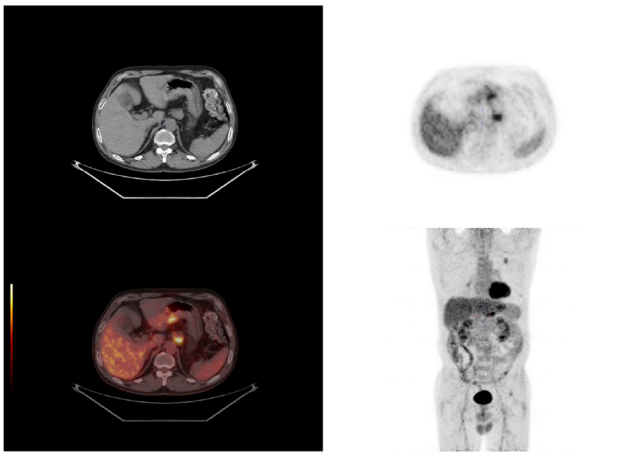

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Figure 1 Positron emission tomography/computed tomography images: Thickening of the gastric lesser curvature with metabolic hyperplasia.

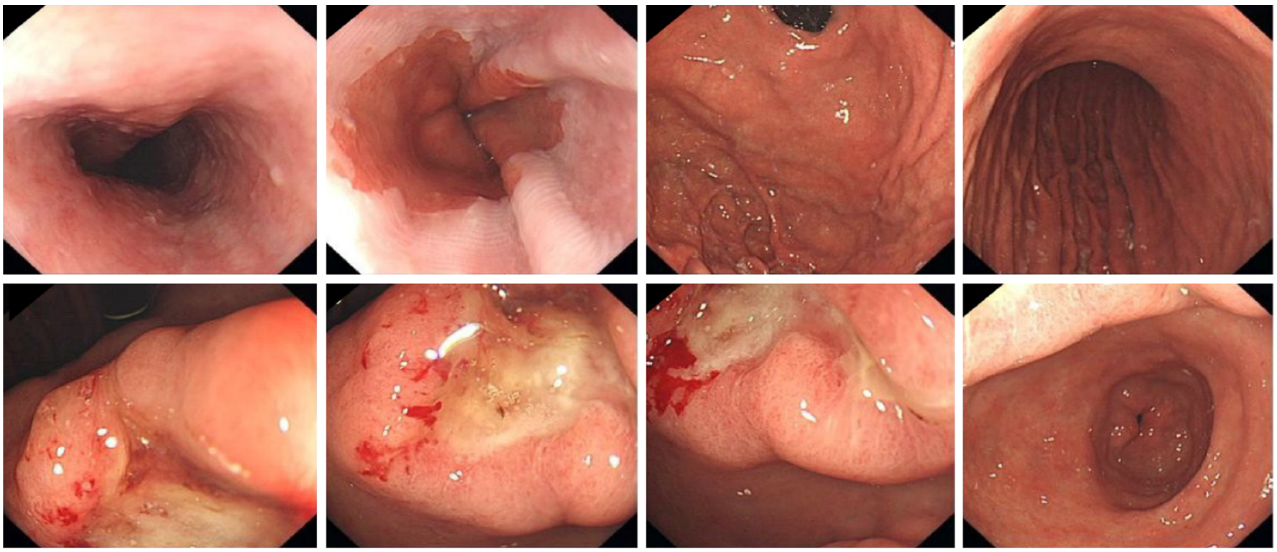

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Figure 2 Endoscopic images: Localized ulcerative lesion extending from the angle to the antrum of the stomach.

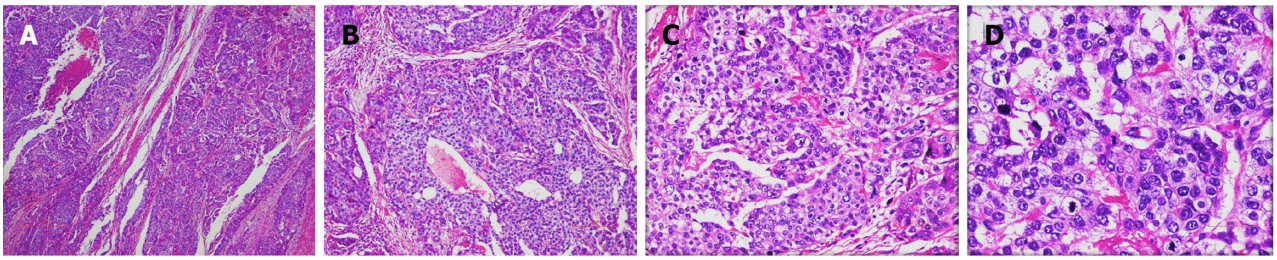

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Figure 3 Histological findings of the primary lesion. A: A low-power histological view, hepatoid adenocarcinoma of the stomach [hematoxylin-eosin (HE), × 40]; B-D: High-power view shows that the characteristics and arrangement of the cancer cells are similar to those of liver cancer cells, with abundant and eosinophilic cytoplasm. Some of the tumor cells have clear cytoplasm with large and prominent nucleoli located in the center of the cell (B: HE, × 100); (C: HE, × 200); (D: HE, × 400).

greater curvature (1/8) was positive, and two lymph nodes on the lesser curvature (2/16) were positive. The tumor node metastasis classification was T3N2M0 (stage III) (Figure 4). Immunohistochemical staining showed SALL4 (+), AFP (+), Glypican-3 (GPC-3) (+), Synaptophysin (Syn) (+), and Chromogranin A (CgA) (+) (Figure 5). Hepatoid components

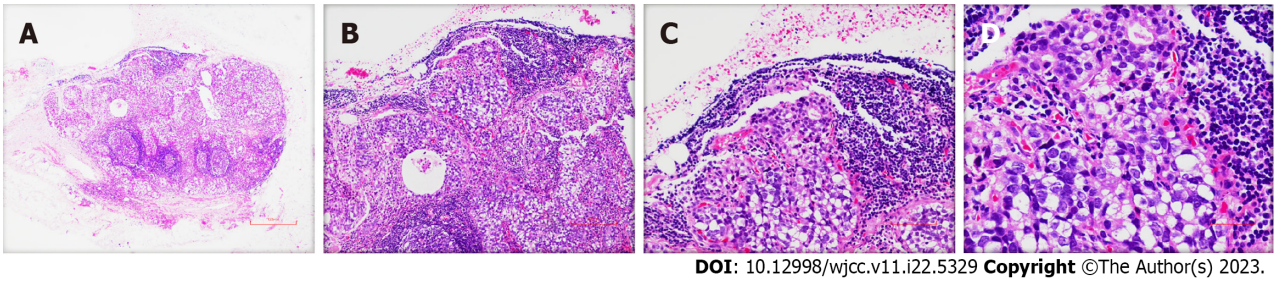

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Figure 4 Histological findings of metastatic lymph nodes. A: A low-power histological view and metastatic lymph nodes show hepatoid adenocarcinoma cells [hematoxylin-eosin (HE), × 40]; B-D: A high-power view shows that the tumor cells are similar to those of the primary lesion; (B: HE, × 100); (C: HE, × 200); (D: HE, × 400).

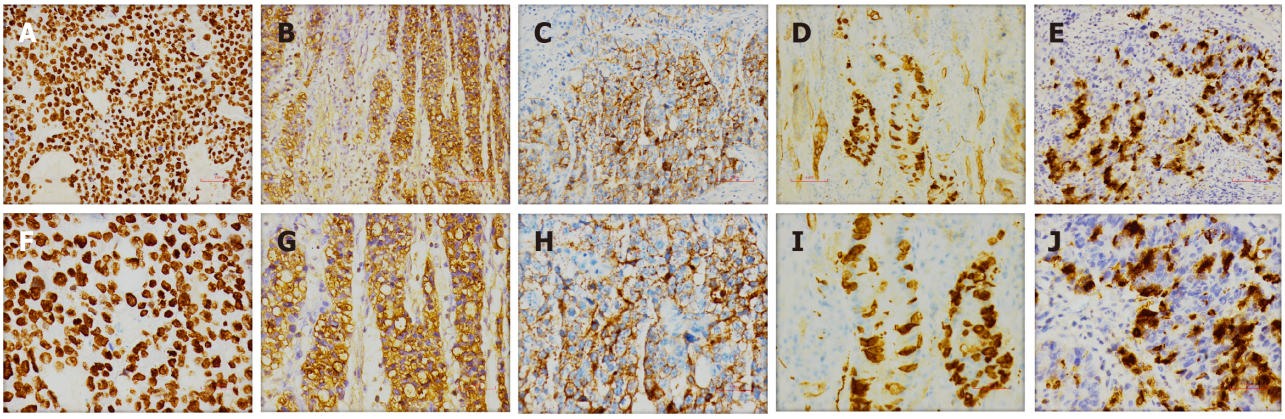

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Figure 5 Presentations of immunohistochemical stains. A: SALL4 (+, × 200); B: Alpha-fetoprotein (AFP) (+, × 200); C: Glypican-3 (GPC-3) (+, × 200); D: Synaptophysin (Syn) (+, × 200); E: Chromogranin A (CgA) (+, × 200); F: SALL4 (+, × 400); G: AFP (+, × 400); H: GPC-3 (+, × 400); I: Syn (+, × 400); J: CgA (+, × 400).

produced SALL4, AFP and GPC-3, and the neuroendocrine markers Syn and CgA revealed the presence of NED.

FINAL DIAGNOSIS

The patient was diagnosed with HAS with NED pT3N2M0 (stage III), accompanied by hypertension.

TREATMENT

The patient underwent distal gastrectomy with D2 lymphadenectomy at our hospital. He was discharged from the hospital with satisfactory recovery. The patient then received ten cycles of systemic chemotherapy (regimen: 60 mg docetaxel on day 1, 140 mg oxaliplatin on day 2, and 1.5 g capecitabine twice a day on days 1-8, half a month on each course). CT scanning revealed lymph node metastasis in the cardia and peritoneum at 4 mo postsurgery and multiple liver metastases at 6 mo postsurgery. In addition, he underwent thoracentesis and intrapleural injection chemotherapy (regimen: 40 mg cisplatin four times, 60 mg Endostar twice, and 2.3 million units interleukin-2 twice) for malignant pleural effusion. He then received three cycles of second-line chemotherapy treatment (280 mg irinotecan on day 1, 60 mg S-1 twice a day on days 1-10, and 500 mg apatinib once a day, two weeks on each course). S-1 is a combination product of tegafur, gimeracil, and oteracil potassium. Unfortunately, the liver metastases continued to progress, and he experienced grade 3 neutropenia, causing him to refuse further treatment.

OUTCOME AND FOLLOW-UP

He died at 27 mo after the operation due to the tumor multiple metastases. We think that aggressive surgical resection with postoperative chemotherapy to control tumor progression may improve patients' outcome.

DISCUSSION

We retrieved 6 patients with stomach cancer including hepatoid adenocarcinoma and neuroendocrine Components. The clinicopathologic features of these cases are summarized in Table 1. The average age of the patients was 65 years (range: 48–83 years). Four of 6 patients were men. All of them developed lymph node metastases, which indicated the aggressive nature of these components. AFP and CgA expression was detected in the carcinomatous elements. Six patients underwent surgery, and 2 patients received chemotherapy. For the 4 patients with survival data, survival was 6 to 53 mo after gastrectomy; 2 patients developed liver recurrence.

Although hepatoid adenocarcinoma can occur in various organs, the stomach is the most common site. HAS mixed with common adenocarcinoma components is frequently observed[9], but the origin remains obscure. Previous studies have indicated that adenocarcinoma cells can switch from the intestinal type to the hepatoid phenotype[10], with the two components possibly arising from pluripotent precursor cells[11]. Pathological diagnosis is still the gold standard for HAS. In our case, gastric lesions were detected by PET, which can diagnose and stage HAS accurately. Immunohistochemistry staining for AFP, SALL4, and GCP3 indicated hepatoid differentiation[12,13]. All three markers were detected in this case. HAS is highly aggressive, and patients with high serum AFP levels are more likely to have lymph nodes and liver metastases[14]. LIN28 combined with SALL4 shows 98% specificity in discriminating HAS from HCC[15]. In summary, the availability of various auxiliary tests assists in accurate diagnosis.

The clinical manifestations of HAS lack specificity, and are were no significant differences from gastric cancer with regard to symptoms. In most cases, the tumor is at an advanced stage when diagnosed. In general, HAS is aggressive and has a high recurrence rate[15]. Current research on HAS is controversial. The median OS was reported to be 11 mo (range 0.1-102), with a one-year survival rate of 55%[16]. The five-year disease-free survival was only 20.7%[17-19]. However, Zhou *et al*[18] found that the prognosis of HAS is not as poor as previously believed[18], and the 5-year survival reached 41.1% after radical surgery[5]. One recent study showed that the independent prognostic factors of OS include the serum AFP level[20,21] in gastric cancer; another study showed that preoperative carcinoembryonic antigen levels of 5 ng/mL or more can be used to predict worse prognosis[9].

Radical surgery combined with adjuvant chemotherapy is considered the primary choice for these patients, but no consensus has been reached regarding therapy[22]. Adjuvant chemotherapy is an independent favorable prognostic factor of HAS[23,24]. Retrospectively, more than half of cases are at advanced stages at diagnosis, and the recurrence rate is quite high (47%)[25,26]. Metastatic HAS lacks standard therapy; therefore, determining a suitable treatment regimen is a clinically urgent issue to be solved. Cisplatin-based chemotherapy is considered the mainstay of therapy[27]. Two patients who received cisplatin and etoposide regimens achieved complete responses[28,29]. FOLFOX might be a therapeutic option for HAS[30]. The antiangiogenic agent ramucirumab led to a clinical response in a chemotherapy-resistant patient[31], offering a novel perspective on treatment. Immune checkpoint inhibitors are a promising class of anticancer drugs. Li *et al*[14] reported that patients benefited from programmed cell death 1 (PD-1) monoclonal antibody plus chemotherapy compared with chemotherapy alone or combined with Herceptin/Apatinib regarding the median progression-free survival time (22.0 mo *vs* 5.0 mo)[14]. For another case of recurrence, the patient achieved complete remission after five cycles of PD-1, and the serum AFP level decreased from more than 1210 mg/L to normal[32]. However, another patient responded poorly[33]. Microsatellite instability has been reported for a minority of patients [34], and the mechanism needs further study.

The stomach is the most common organ of mixed adeno-neuroendocrine carcinoma[35], and NED is usually the dominant component[36]. NED represents a special type of tumor that can express various polypeptide hormones, such as synaptophysin and chromogranin A[37], and the Ki67 index is always more than 20%. Our case was mixed with two distinct components, and the etiopathogenesis of this phenomenon is still controversial. Domori and colleagues found that nearly 70% of gastric NECs presented with an adenocarcinoma component, and a previous report indicated that NECs originate from a preceding adenocarcinoma[38]. Conversely, Fujimoto *et al*[39] considered that the adenocarcinoma component might arise from the NEC component[39]. Sun *et al*[40] found that the NED component in gastric mixed adeno-neuroendocrine carcinoma (MANEC) showed marked genetic heterogenicity because the NED components of different cases were not clustered in hierarchical clustering analysis[40]. Similar to gastric adenocarcinoma, TP53 is the most commonly mutated gene in gastric MANEC[41]. Scardoni *et al*[42] considered a monoclonal origin of gastric MANECs with the same TP53 mutation and level of p53 protein expression in two cases, as detected by next-generation sequencing[42].

G-NEC is a highly aggressive neoplasm with a large proportion of metastasis at diagnosis, and NED is the principal component of the metastatic foci in MANECs[43]. Moreover, the presence of liver metastases correlates with poor prognosis in G-NEC patients[44,45]. Because of its rare occurrence, systemic treatment options are limited, and currently, chemotherapy is still the main therapeutic approach. Cisplatin or carboplatin combined with etoposide is the standard chemotherapeutic regimen for the treatment of G-NEC according to the standard systemic therapy of pulmonary small-cell lung cancer (SCLC)[46,47]. A multicenter retrospective analysis reported a median overall survival (OS) of 13.3 mo for GNEC[48]. No evident difference was apparent between platinum-based chemotherapy regimens[49]. The choice of treatment options should be selected based on the toxicity profile[50]. Nevertheless, the prognosis of gastric NEC remains dismal[46]. There are limited data on the efficacy of second-line therapy. The FOLFIRI regimen has the potential to improve outcomes of patients for whom first-line therapy fails[51]. Peptide receptor radionuclide therapy should be considered an alternative to existing treatment options, and more research is needed[52,53]. Immune checkpoint inhibitors offer new hope for treatment of NECs. Gastric tumor tissues express higher levels of PD-L1 mRNA than respective controls[54]. Kim *et al*[55] found significantly increased expression of PD-L1 in high-grade tumors, and PD-L1-positive tumors were associated with decreased OS[55]. Yang and colleagues confirmed that high expression of PD-L1 in G-NECs correlates with poor prognosis, providing a basis for immunotherapy targeting the PD-1/PD-L1 pathway in G-

Table 1 Reported cases of gastric cancer including hepatoid adenocarcinoma and neuroendocrine components

Ref.	Rassidakis *et al*[60]	Okamoto *et al*[61]	Suzuki *et al*[62]	Lipi *et al*[63]	Wincewicz *et al*[64]	Li *et al*[65]	Current case
Age	48	78	83	50	73	60	61
Sex	Man	Woman	Man	Man	Woman	Man	Man
TNM stage	N3	T3N2M0	T4N2M1	N3	T3N3M1	T2N1Mx	T3N2M0
Tumor location	Anterior wall of the gastric body	Pyloric antrum	Upper-third of the stomach	Cardia		Gastric antrum	Gastric antrum
Tumor size	70 mm × 55 mm	90 mm × 60 mm × 30 mm	75 mm × 110 mm	85 mm × 65 mm × 45 mm	60 mm × 40 mm	16 mm	20 mm × 15 mm × 5 mm
Histologic patterns	HAC, NED	HAC, NEC, TAC	HAC, NEC, TAC	HAC, LCNEC, TAC	HAC, NED, OGCs	HAC, NED	HAC, NED
Immunohistochemistry	CGA, AFP	CK8, AE1/AE3, AFP, CGA	CGA, AFP, SP	AFP, Syn, CGA, CK	CGA, AFP, AE1/AE3, CK	AFP, Syn, CGA	SALL4, AFP, GPC-3, Syn, CgA
Surgery	Total gastrectomy	Subtotal gastrectomy with lymphaden-ectomy	Gastrectomy	Total gastrectomy		R2 radical gastrectomy	Distal gastrectomy with D2 lymphadenectomy
Treatment	Doxorubicin, mitomycin-C, 5-fluorouracil, octreotide (4 cycles)			Cisplatin + VP 16 (2 cycles)			Docetaxel + oxaliplatin + capecitabine (10 cycles), irinotecan + S-1 + apatinib (3 cycles)
AFP, ng/mL	800 (post-op)	168 (pre-op)				1683 (pre-op)	
Outcome	Alive, 12 mo	Died, 53 mo, liver recurrence	Died, 6 mo		Liver recurrence	Alive, 6 mo	Died, 27 mo, liver recurrence

GC: Gastric cancer; HAC: Hepatoid adenocarcinoma; NEC: Neuroendocrine carcinoma; NED: Neuroendocrine differentiation; TAC: Tubular adenocarcinoma; OGCs: Osteoclast-like giant cells; AFP: Alpha-fetoprotein; CGA: Chromogranin A; Syn: Synaptophysin; CK: Cytokeratin; pre-op: Preoperatively; post-op: Postoperatively; LCNEC: Large-cell NEC.

NECs[56,57]. After combination immunotherapy with ipilimumab and nivolumab, 43% of patients with pancreatic NENs [58] and 19% of SCLC patients[59] achieve an objective response. Further research is necessary to investigate the therapeutic efficacy of immune checkpoint inhibitors.

CONCLUSION

Mixed carcinomas usually raise a clinical dilemma with respect to diagnosis and treatment decisions. Only a few cases of HAS with NED have been reported, and we first report the detailed processes of treatment and development, we thought that aggressive surgical resection with postoperative chemotherapy to control tumor progression may improve patients' outcome, providing an important reference for clinical diagnosis and treatment of this condition. We hope that our report provides valuable experience to other clinicians.

FOOTNOTES

Author contributions: Chen YT and Zhao DB designed the research study; Fei H contributed to manuscript writing and editing; Li ZF reviewed the pathological sections; All authors wrote the manuscript; All authors have read and approved the final manuscript.

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