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Hepatoid adenocarcinoma of the stomach with neuroendocrine differentiation: A Case Report and Literature Review

HAS with NED

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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 (PET/CT) for a pulmonary nodule. Distal gastrectomy was performed, and pathological examination led to 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

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Core Tip: Core Tip: Hepatoid adenocarcinoma of the stomach (HAS) with neuroendocrine differentiation (NED) is rare histological subtypes. 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.

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[1]. Most, but not all, HAS cases produce AFP[2], and increased serum AFP is mainly due to hepatoid cells[3-5][Ed1]. Neuroendocrine neoplasms can be divided into neuroendocrine tumors and neuroendocrine carcinomas (NECs). Neuroendocrine carcinoma (NEC) is characterized by neuroendocrine differentiation 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 1.8/100,000, with only 3% occurring in the stomach[7][Ed2]. Nonneuroendocrine components (adenocarcinoma and squamous carcinoma) are frequently observed in high-grade neuroendocrine carcinomas[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

PET/CT revealed thickening of the gastric lesser curvature at 1 wk.

History of present illness

A 61-year-old man underwent positron emission tomography/computed tomography (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 greater curvature (1/8) was positive, and two lymph nodes on the lesser curvature (2/16)

were positive. The TNM (tumor node metastasis) classification was T3N2M0 (stage III) (**Figure 4**). Immunohistochemical staining showed SALL4(+), AFP(+), GPC-3(+), Syn(+), and CgA(+) (**Figure 5**). Hepatoid components 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

+ADw-html+AD4APA-p+AD4-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.+ADw-/p+AD4APA-/html+AD4-

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 of 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[15], but the origin remains obscure. Previous studies have indicated that adenocarcinoma cells can switch from the intestinal type to the hepatoid phenotype[16], with the two components possibly arising from pluripotent precursor cells[17]. 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 ifferentiation[18, 19]. 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 node and liver metastases[20]. LIN28 combined with SALL4 shows 98% specificity in discriminating HAS from hepatocellular carcinoma (HCC) [21]. 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[Ed1] . In most cases, the tumor is at an advanced stage when diagnosed. In general, HAS is aggressive and has a high recurrence rate[21]. 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%[22]. The five-year disease-free survival was only 20.7%[23-25]. However, Zhou, K. *et al* found that the prognosis of HAS is

not as poor as previously believed [24], 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[26, 27] in gastric cancer; another study showed that preoperative carcinoembryonic antigen levels of 5 ng/mL or more can be used to predict worse prognosis[15].

Radical surgery combined with adjuvant chemotherapy is considered the primary choice for these patients, but no consensus has been reached regarding therapy[28]. Adjuvant chemotherapy is an independent favorable prognostic factor of HAS[29, 30]. Retrospectively, more than half of cases are at advanced stages at diagnosis, and the recurrence rate is quite high (47%)[31, 32]. 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[33]. Two patients who received cisplatin and etoposide regimens achieved complete responses[34, 35]. FOLFOX might be a therapeutic option for HAS[36]. The antiangiogenic agent ramucirumab led to a clinical response in a chemotherapy-resistant patient[37], offering a novel perspective on treatment. Immune checkpoint inhibitors are a promising class of anticancer drugs. Li, W. *et al* reported that patients benefited from 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)[20]. 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[38]. However, another patient responded poorly[39]. Microsatellite instability has been reported for a minority of patients[40], and the mechanism needs further study.

The stomach is the most common organ of mixed adeno-neuroendocrine carcinoma[41], and NED is usually the dominant component[42]. NED represents a special type of tumor that can express various polypeptide hormones, such as synaptophysin and chromogranin A [43], 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[44]. Conversely, Murata *et al* considered that the adenocarcinoma component might arise from the NEC component[45]. Sun *et al* 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[46]. Similar to gastric adenocarcinoma, TP53 is the most commonly mutated gene in gastric MANEC[47]. Scardoni *et al* 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[48][Ed2] .

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[49]. Moreover, the presence of liver metastases correlates with poor prognosis in G-NEC patients [50, 51]. 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)[52, 53]. A multicenter retrospective analysis reported a median overall survival (OS) of 13.3 mo for GNEC[54]. No evident difference was apparent between platinum-based chemotherapy regimens[55]. The choice of treatment options should be selected based on the toxicity profile[56]. Nevertheless, the prognosis of gastric NEC remains dismal[52]. 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[57]. Peptide receptor radionuclide therapy (PRRT) should be considered an alternative to existing treatment options, and more research is needed[58, 59]. Immune checkpoint inhibitors offer new hope for treatment of NECs. Gastric tumor tissues express higher levels of PD-L1

mRNA than respective controls[60]. Seung *et al* found significantly increased expression of PD-L1 in high-grade tumors, and PD-L1-positive tumors were associated with decreased OS[61]. 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-NECs[62, 63]. After combination immunotherapy with ipilimumab and nivolumab, 43% of patients with pancreatic neuroendocrine neoplasms (NENs) [64] and 19% of SCLC patients[65] 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.

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