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REVIEW ARTICLE

Hepatoid adenocarcinoma of the stomach – proper identification and treatment remain a challenge

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ABSTRACT

Objective The term hepatoid adenocarcinoma (HAC) of the stomach was introduced three decades ago with the observation of high serum α-fetoprotein (AFP) levels in some gastric adenocarcinoma patients. This very rare gastric cancer patient subgroup is likely frequently misdiagnosed. **Material** Two patients who were recently diagnosed with HAC of the stomach at our institution are presented. We also performed a structured literature search and reviewed pertinent articles to provide knowledge to improve the proper identification, diagnosis and management of patients with gastric HAC. **Results** HAC is a rare subgroup of gastric carcinoma with poor prognosis. Clinical management of this population may be challenging. The scientific literature is largely based on very small patient series or case reports, and the evidence for proper decision making and management is considered weak. **Conclusion** All physicians involved in the diagnosis and treatment of patients with gastric cancer should pay attention to this rare subgroup to improve identification.

Introduction

Although the term hepatoid adenocarcinoma (HAC) of the stomach was introduced in 1985 by Ishikura et al., with the observation of high serum α-fetoprotein (AFP) levels in seven patients with gastric adenocarcinoma,[1,2] an AFP-producing gastric tumour was first reported by Bourreille et al.[3] in 1970. HAC may also originate from other gastrointestinal localisations,[4,5] including the pancreas.[6,7] Moreover, this extrahepatic hepatoid cancer type has also been diagnosed in the ovary,[8] uterus,[9] lungs,[10,11] and several other organs.[4,12] The scientific literature, however, is mostly based on case reports or very small patient series.[1,13–17]

Although previous reports have suggested that the incidence of gastric HAC is between 0.38% and 0.78%, [15,18] recent reports from Korea [14] and China [19] have provided figures of 0.17% and 0.36%, respectively. HAC is considered an aggressive type of gastric adenocarcinoma with a detrimental prognosis.[14,19–22] Thus, challenges remain both with regard to the appropriate identification and diagnosis of this rare entity and concerning effective treatments to improve this unfavourable prognosis.

Based on a review of the available literature and the presentation of two patients who were recently treated at our institution, some relevant clinical aspects are addressed to bring to the attention of both involved clinicians (i.e. gastroenterologists, gastroenterologic surgeons, and oncologists) and pathologists and radiologists: the importance of the correct subclassification of gastric cancer and a better understanding of the characteristics of each subtype to improve early diagnosis and enable appropriate treatment.[23,24]

Material and methods
Literature search

We searched the PubMed and Ovid Medline databases for articles published between January 2005 and June 2015 using combinations of the terms 'hepatoid adenocarcinoma', 'stomach', 'gastric', 'gastric cancer', 'adenocarcinoma', 'alpha-fetoprotein', 'treatment', 'prognosis', and 'surgery'. Earlier seminal and highly regarded publications were considered. References were selected based on the information provided, with an emphasis on patient series and reports that expanded diagnostic
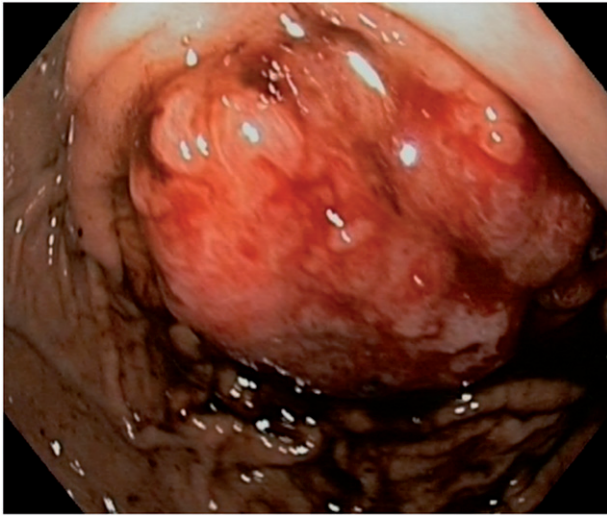
Figure 1. Pt #1: Male 48 years of age. Endoscopic view of the gastric tumour located in the fundus.

Figure 2. Time trends of the AFP levels in Pt #1 during the trajectory of his disease.

Patients

Case report #1

An otherwise healthy male (49 years of age), with a two-year history of increasing fatigue, epigastric discomfort, nausea, anaemia, and slightly increasing serum α-fetoprotein (AFP) levels for the last 12 months, was extensively examined over the past year at other hospitals by gastroscopy, coloscopy, liver imaging, including magnetic resonance (MR) imaging, and positron emission tomography–computer tomography (PET-CT) without any significant findings.

Due to anaemia and vague epigastric pains, he was then referred to our hospital where a repeat gastroscopy revealed a large and soft tumour in the proximal part of the stomach (Figure 1). Serum AFP levels were extremely elevated at 21,045 kU/L (normal, <60 kU/L) (Figure 2). Except for a slightly elevated serum chromogranin A (CgA) value of 8.8 nmol/L (normal <6.0 nmol/L), other tumour markers, including carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA 19-9), were completely normal. Abdominal computer tomography (CT) revealed a large gastric tumour (size: $63 \times 77 \times 86$ mm) with a suspicious tumour infiltration of the diaphragm, left liver, and spleen (Figure 3), but without distant metastases. Histology of the endoscopic biopsy revealed a pattern consistent with gastric adenocarcinoma of the hepatoid subtype (Figure 4). Upon extended immunohistochemical examination (IHC), strong AFP staining was observed (Figure 4), but there
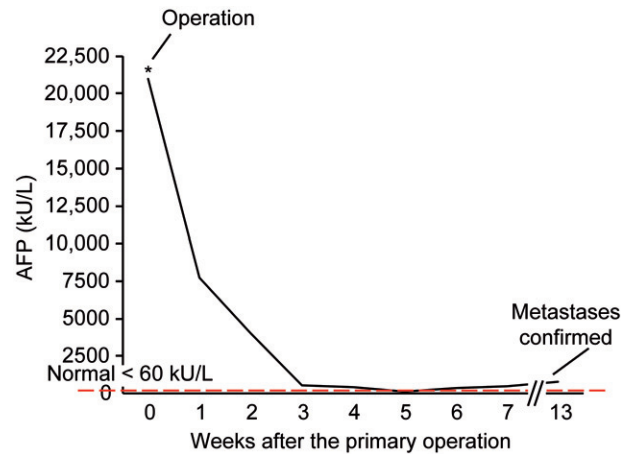

Figure 3. Pt #1: Coronal multi detector computer tomography(MDCT) shows the gastric tumour (T) in the left hypochondrium with infiltration of the left hemidiaphragma (stapled arrow) and the greater curvature (arrow) of the stomach.

was no staining of synaptophysin, chromogranin A (CgA), CD 56, or HER2.

The patient consented to surgical treatment, which included a total gastrectomy with a wedge resection of the liver and a distal pancreas resection including a splenectomy. In addition, a partial resection of the left diaphragm and a limited resection of the inferior lobe of the lung were performed. The tumour diameter was
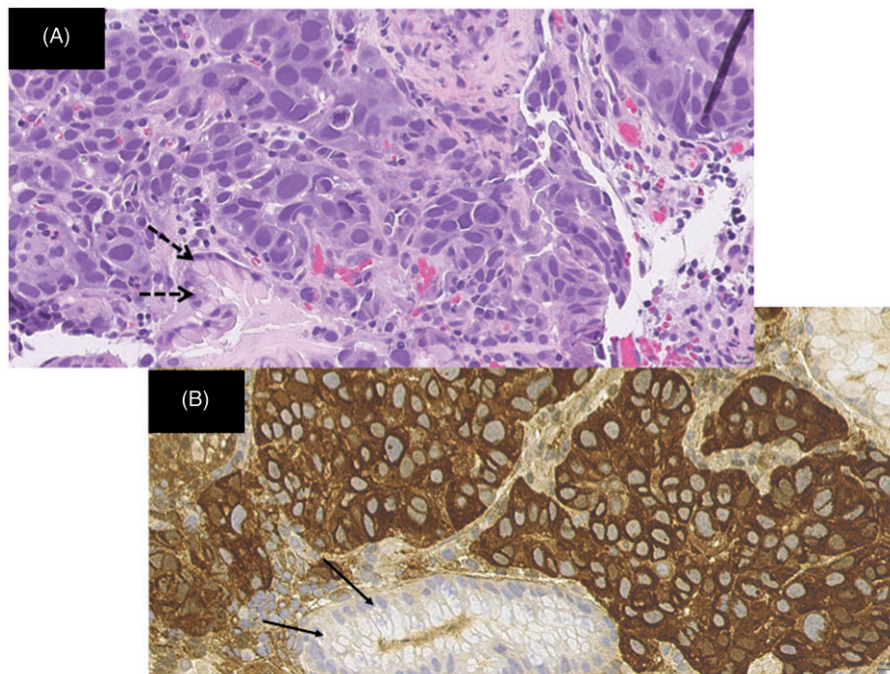
Figure 4. (A) Histopathology of hepatoid carcinoma in the gastric mucosal primary lesion The tumour comprised a mixture of pseudoglandular and hepatoid components. Note the normal glandular structure *(arrows)* (haematoxylin and eosin staining; original magnification, ×400). (B) Immunohistochemical staining showing intracytoplasmic positivity for AFP (dark brown). Note the non-staining normal glandular structure (arrows) (original magnification, x400).

80 mm, with minimal microscopic infiltration into the liver, diaphragm, and lung, but without evidence of infiltration into the spleen or pancreas. Specimen margins were microscopically tumour free (R0 resection). The tumour was classified (WHO 2010) as pT4bN1M0. Additional IHC of the resected tumour did not show any staining for CD117 (c-kit), and no epidermal growth factor receptor (EGFR) mutation was found with a molecular genetic test.

The post-operative course was complicated by small bowel obstruction that prompted a re-laparotomy on the eighth post-operative day, with a re-suture (additionally enforced by biological mesh) of the partly disrupted left diaphragm suture line, which had caused an obstruction of a short wedged-in segment of the small bowel. Thereafter, no other specific post-operative surgical complications were encountered, but the patient recovered very slowly after being discharged from the hospital, suffering subjectively from extensive fatigue, which he had also experienced over the last 6 to 9 months pre-operatively, and regaining a normal diet was a challenge. Adjuvant chemotherapy was considered, but due to the patient's impaired clinical condition (ECOG 3) and his own preference, adjuvant treatment was not offered.

At follow-up 3 months after surgery, lung CT revealed small nodules in the upper left lobe, and abdominal CT demonstrated a metastatic liver lesion of 23 mm in diameter, located in the right hemiliver far away from the wedge resection line. Although his general physical status had improved slightly, he was hardly fit for any palliative chemotherapy, which he also refused. The patient died 9 months after surgery for a confirmed hepatoid adenocarcinoma of the stomach.

Case report #2

An 81-year-old female with weight loss for two months, was admitted with haematemesis. Gastroscopy revealed a large suspicious tumour of the distal stomach. Further work-up including a CT confirmed a large and diffuse gastric tumour, with tumour growth into the surrounding tissues and enlarged mesenteric lymph nodes (LN) in addition to enlarged LN of the lesser curve (Figure 5). No liver or lung metastases were observed. Tumour markers, including CEA and CA-125, were normal. A significantly elevated serum AFP value of 14,414 kU/L (normal, < 60 kU/L) was encountered. Histology concluded primarily with an adenocarcinoma of the stomach. Based on the increased AFP levels, additional IHC examination of the gastric biopsy was done. A strong staining for AFP was shown, but in addition a few scattered cells (<5%) stained positive both for synaptophysin and for chromogranin A(CgA). This pattern,
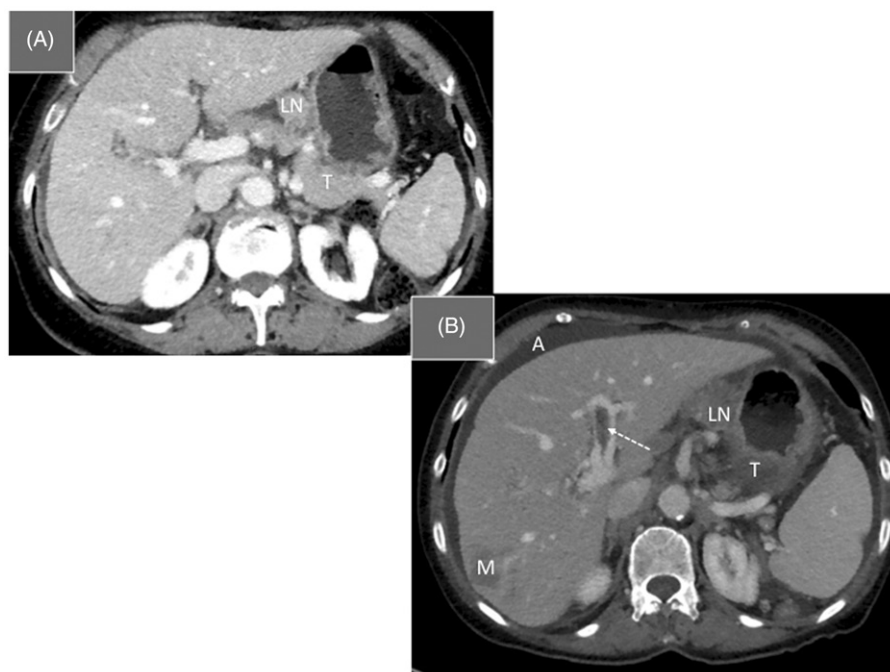
Figure 5. Pt # 2: Female 81 years of age. (A) Axial MDCT at the time of diagnosis showing the gastric tumour (T) located in the antrum, with lymph nodes (LN) at the lesser curvature. (B) Five months after primary diagnosis: disease progression with liver metastasis (M), tumour and lymph node growth (T) along the lesser curvature, ascites (A) and thrombus in portal veins (white arrow).

however, did not allow for the diagnosis of a neuroendocrine tumour. Thus, morphologically the diagnosis of a gastric HAC was made.

Due to the locally advanced tumour and the general health condition of the patient (ECOG 3; ASA 4) as well as her own strong preferences, tumour-directed therapy (i.e. surgery or systemic chemotherapy) was not employed. During the course of the disease, moderate signs of delayed gastric emptying were encountered, and a follow-up CT with findings of a significant tumour growth was performed 6 months after the primary diagnoses. In addition, serum AFP levels of 166,000 kU/L were found, which was a 10-fold increase over the 6 months since the time of diagnosis. After a few short hospital admissions for transfusions and supportive care, the patient eventually died 7 months after the diagnosis of a gastric HAC was made.

Results

The frequency of HAC is extremely low, and the scientific literature comprises mostly case reports or very small patient series. Su et al. reviewed the literature on hepatoid adenocarcinoma between 2001 and 2011 and recently presented a summary on 217 patients, including 182 (83.9%) patients with hepatoid adenocarcinoma located in the stomach.[4] To add data obtained in more recent years, we have collected pertinent information from recent publications that included a minimum of

10 patients,[14,19,20,23,25] and relevant information is presented in Table 1. In their review of 26 patients, Baek et al.[14] observed the predominance of males, the presence of local advanced or metastatic disease in half of the patients at the time of diagnosis, and a Bormann type-III cancer [26] most frequently found with gastroscopy. A tumour located at the distal area of the stomach (i.e. antrum) was commonly encountered. Similar clinical patterns were in essence reported by two studies from China, one earlier [15] and one more recent,[26] with 31 and 20 patients, respectively. Of note is the detrimental prognosis, with an overall survival of less than a year in a large proportion of the patients. Based on the available heterogeneous and limited literature comprising case reports, reliable figures for the true incidence, clinical characteristics, and treatment outcomes are not easily provided.

Discussion

A proper identification of patients with gastric HAC remains a challenge. Reliable clinical patterns and clues are lacking.

Imaging does not provide features specific for gastric HAC. Ren et al.[13] reported six cases with extensively thickened gastric walls by heterogeneous contrast enhancement and a polypoid mass identified at CT. These observations are generally supported by others, who also emphasise the common findings of

Table 1. Patient characteristics and outcomes presented in five recent series.

Author	Study type Time period Country	No. of patients Gender Age, range (years)	Stage	Elevated Serum AFP	Endoscopy	Therapy	Survival, Median (range) Months
Lin et al. (2015)	Institution series 2001–2010 Taiwan	10 Male 60% Median 65.5	Lymph node metastasis 70% Distant (liver) metastasis 50%	In 7 of 8 pts (88%) Median 359.2 ng/mL range, 4.3–6,335.6 ng/mL)	Borrmann Type III 60%	Surgery in 5 patients (50%) without metastasis – adjuvant chemo therapy in 4 of these	OS 7.2 (0.7–131.8) 20% 5-year survival
Xie et al. (2015)	Institution series 1999–2014 China	19 Male 85% Median 61 (41–80)	≥ pT3 84.2% pN+ 70.6% Stage IV 15.8%	In 10/12 patients with information (range 2.0–4375 ng/mL)	Localisation: Cardia 42.1% Body 36.8% Antrum 21.1%	Surgery for cure in 85%. Adjuvant chemotherapy offered in 12/16 (75%) resected patients.	OS 12.0 DFS 7.0
Yang et al. (2014)	Institution series 2005–2012 China	31 Male 68% Mean 51.2 (32–87)	Stage I 22.6% Stage II 19.4% Stage III 32.3% Stage IV 25.7%	87.1% of patients 37–6400 ng/mL	Borrmann Type I 48% Type II 26% Type III 23% Type IV 3%	Details not available	OS 6 31.6% 3-year survival
Baek et al. (2011)	Institution series 1996–2008 Korea	26 Male 85% Median 63	Stage IB 12% Stage II 23% Stage III 27% Stage IV 39%	In 7 of 11 patients (64%) Median 208 ng/mL (range 5–4,750,000 ng/mL)	Borrmann Type I 9% Type II 22% Type III 48% Type IV 4% EGC* 17%	Gastrectomy with curative intent in 18 patients (69%). Adjuvant chemotherapy offered in 9 of these patients.	17 months RFS after gastrectomy. OS 28 months in Stages I–III and 8 months in Stage IV. OS was 8 months in patients who received palliative chemotherapy.
Zhang et al. (2011)	Institution series 1998–2009 China	20 Males 80% Median 60 (40–81)	Stage II 20% Stage III 40% Stage IV 40%	Reliable information not available	Borrmann Type II 35% Type III 35% Protrudet Type 15% Unspecified 15%	One gastrectomy, 13 subtotal resections, and 5 palliative resections. 8 patients (40%) received post-op adjuvant chemotherapy. No surgery in one patient	Median OS 12 months, with a 3-year survival rate of 20%, and 27.5% for those surgically treated.

*EGC: early gastric cancer; OS: overall survival; RFS/DFS: relapse-free survival/disease-free survival.

lymphadenopathy and distant metastases in these groups of patients.[16,27] Magnetic resonance imaging (MRI) may help provide a more specific diagnosis, as suggested recently.[28] In contrast to our male patient without any uptake on PET-CT, others have reported positive findings in patients with HAC.[5,29]

Morphologically, hepatoid adenocarcinoma of the stomach is a type of extrahepatic carcinoma with a complex histological picture, including enteroblastic and hepatic differentiation.[30] However, its similarity to hepatocellular carcinoma (HCC) of the liver is evident. As originally described by Ishikura et al.,[1] these gastric carcinomas comprise both adenocarcinomatous and hepatocellular differentiations. The adenocarcinomatous and hepatoid areas were often intermingled with each other, and an extensive venous involvement by tumour cells was noted.[1] Moreover, the tumour cells contain various serum proteins, including AFP, alpha-1 antitrypsin (AAT), alpha-1 antichymotrypsin (ACT), albumin, and prealbumin, in their cytoplasm, which can be shown by positive immunohistochemical staining. Because HAC and HCC cannot be differentiated on the basis of morphology alone, differences in immunehistochemical reaction patterns may enable the correct diagnosis. As shown in several reports, immune staining for CK7, CK8, CK18, CK19, CK20, alpha-fetoprotein (AFP), p-CEA, and HepPar1 revealed that hepatoid areas of both primary and metastatic HAC have a specific immune profile that is distinct to this entity.[31–34] This should help the pathologist once a diagnosis of HAC has been considered.

AFP is a foetal serum protein produced by foetal and yolk sac cells and by some foetal gastrointestinal cells. After birth, the level of the protein in the serum rapidly decreases. AFP as a tumour marker is not by itself diagnostic, only suggestive. Whereas elevated levels of AFP are mainly associated with the occurrence of a hepatocellular carcinoma (HCC), a number of other tumours including non-seminomatous germ cell tumours and endodermal sinus tumours (i.e. york sac carcinoma) can give rise to increased AFP levels.[5,6,35–38] If AFP is measured, the interpretation of a raised AFP level may not be straightforward, which is particularly important in endemic areas with a high incidence of chronic hepatitis B and C and HCC. Although most patients (at least 80%) with gastric HAC will have elevated serum AFP levels, this is not the case in all patients with gastric HAC. [4] As observed in our male patient and as observed by others, a resection of the tumour causes a decrease in AFP levels, which eventually increases again when distant metastases are evident.

Thus, hepatoid adenocarcinoma (HAC) is a rare but important specific type of extrahepatic adenocarcinoma that should be distinguished from HCC.[4] Although the stomach is by far the most prevalent location, other gastrointestinal locations [39–41] and the genitals have been reported.[4,8,37]

The so-called composite or mixed tumour with hepatoid and neuroendocrine differentiation in the same gastric tumour has been reported,[42–44] which has also been encountered in HAC tumours of other locations (i.e. pancreas).[7,38] Still, the clinicopathologically importance and understanding of the composition of a gastric HAC and a neuroendocrine cancer remains uncertain.[43] As also shown in the tumour of our patient #2, a very weak IHC staining (<5% of the cells) for CgA was encountered, although fare too weak to support a diagnosis of a mixture with a HAC and a neuroendocrine tumour in this case.

We have not been able to find any evidence for a relationship between gastric HAC and known risk factors for developing a common gastric adenocarcinoma, such as *H. pylori* infection or chronic atrophic gastritis. Of note is a reported substantial male predominance,[4,14] but it remains to be shown if any specific factors can explain this gender difference.

Recently, Vivekanandarajah et al.[21] claimed that they were the first to report on a patient with AFP-producing gastric adenocarcinoma without hepatic metastases. Neither of our two patients had liver metastases as demonstrated by imaging at the time of diagnosis, and although advanced disease is common in this particular subgroup of patients with gastric cancer, recent reports have already shown that a proportion of these patients are diagnosed with local disease.[4,20]

Although prognosis appears detrimental despite the treatments employed, a number of patients have been surgically treated. Our male patient had a locally advanced disease, and radical surgery with free margins was achieved. Nevertheless, an early recurrence and a short survival were observed, which has also been reported by others.[4,19,20] Adjuvant chemotherapy treatments have been employed, but it remains to be shown which drugs or combinations of drugs should be used, and the evidence is weak based on the limited clinical experience.[14,19,45] The same applies for neoadjuvant chemotherapy [46,47] and palliative systemic treatments,[48,49] which have been offered to a small number of patients.

As already stated by Ishikura et al.[1] when they first described this entity in 1986, the observed poor prognosis may be attributed to the observed mixture of adenocarcinomatous foci and hepatoid areas and to the production of AFP and the presence of alpha-1 antitrypsin (AAT) and alpha-1 antichymotrypsin (ACT), which have immunosuppressive and protease-inhibitory

properties. The detrimental prognosis and the aggressive biological behaviour of this gastric cancer subtype may also be partly explained by the finding of a high malignant potential (high proliferative activity, weak apoptosis, and rich neovascularisation) in AFP-positive gastric cancers compared with AFP-negative gastric cancers.[50]

Likely, a number of gastric cancer patients with the HAC subtype, whether it is AFP-producing or not, are misdiagnosed.[23] The correct diagnosis of malignancy, a precise classification of the tumour type and an appropriate staging of the disease are all important factors to provide suitable and individualised surgical or oncologic treatment to improve prognosis and patient care. This pathology was first described almost three decades ago,[1,2] and since then, a number of reports have been published, mostly in the context of case reports and small patient series. Nevertheless, the community of gastroenterologists, hepatologists, endoscopists, gastrointestinal surgeons, pathologist, radiologists, and oncologists should all bring this disease to their attention to arrive at a correct diagnosis that may enable appropriate treatment to improve patient care and the dismal prognosis of this pathology.

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Disclosure statement

The authors report no conflict of interest.

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