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A Rare Case of Synchronous Intraductal Papillary Mucinous Neoplasm-Associated Pancreatic Adenocarcinoma and Signet Ring Cell Gastric Adenocarcinoma

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Data Interpretation D
Manuscript Preparation E
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Patient: Female, 76-year-old
Final Diagnosis: Synchronous intraductal papillary mucinous neoplasm associated pancreatic adenocarcinoma and signet ring cell gastric adenocarcinoma
Symptoms: Abdominal pain
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Rare coexistence of disease or pathology

Background: Synchronous malignancies are primary cancers that are diagnosed in a single individual within a 2-month period. Synchronous malignancies are uncommon, involving only 2.4-8% of all cancer cases, with a very low number of cases of simultaneous gastric and pancreatic cancer. Although cases of synchronous malignancies do exist, synchronous pancreatic adenocarcinoma and signet ring cell (SRC) gastric adenocarcinoma have not been documented.

Case Report: A 76-year-old woman with a previously diagnosed intraductal papillary mucinous neoplasm (IPMN) presented with left-sided abdominal pain. Initial workup, including computed tomography imaging and endoscopic ultrasound with biopsy, led to the diagnosis of pancreatic adenocarcinoma. Within 1 month of diagnosis, the patient underwent an extended Whipple procedure and was also found to have a primary SRC gastric adenocarcinoma on evaluation of the gastric tissue margins that were removed during the procedure. The patient was initiated on chemoradiation therapy with 5-fluorouracil. However, following a subsequent decline in performance status and multiple hospitalizations, she could not tolerate further cancer treatment and died soon afterwards.

Conclusions: Few cases of synchronous malignancies involving the stomach and pancreas have been reported. Because gastric cancer could easily be missed on screening endoscopy; physicians must have a high index of suspicion. In those patients with a prior history of cancer, biopsies should be performed to aid in early diagnosis. To our knowledge, only metachronous cases of SRC gastric and pancreatic adenocarcinoma have been documented. Therefore, this report represents the first case of synchronous SRC gastric adenocarcinoma and IPMN-associated pancreatic adenocarcinoma in the literature.

Keywords: Neoplasms, Multiple Primary • Pancreatic Cancer, Adult • Stomach Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935242

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Background

Synchronous malignancy is a term used to refer to multiple primary cancers that are diagnosed in a single individual at the same time or within a 2-month period [1]. Per Vogt et al, it is estimated to be diagnosed in only 2.4-8% of all cancer cases, making it an uncommon finding with a poor prognosis [2]. Currently, synchronous malignancies most commonly occur in cases of gastric carcinoma; however, reports of coexisting gastric and pancreatic cancer are limited and account for only 3.8% of all synchronous carcinoma cases per Muroni et al [3]. Even more uncommon are synchronous cases of signet ring cell (SRC) gastric cancer and pancreatic adenocarcinoma, of which there are no prior documented reports. Therefore, we present a case of a patient who underwent resection for pancreatic adenocarcinoma and then was found to have a distinctly separate primary SRC gastric adenocarcinoma.

Case Report

A 76-year-old Caucasian woman presented with left-sided abdominal pain, nausea, and poor appetite accompanied by a 10-pound unintentional weight loss. Significant past medical history included gastric ulcer disease status post-antrectomy with a Billroth I reconstruction, with previously unremarkable biopsies and known intraductal papillary mucinous neoplasm (IPMN) for which the patient had continued followup with gastroenterology and surgical oncology. The patient denied alcohol, tobacco, or drug abuse and family history was insignificant.

On physical examination, her temperature was 97.7°F, blood pressure 132/70 mmHg, and heart rate 87 beats per minute. Her abdomen was soft and nondistended with normoactive bowel sounds but left upper and lower quadrant tenderness with guarding was present. Computed tomography (CT) scan of the abdomen and pelvis was completed and showed a 4.7-cm multiloculated cystic lesion in the pancreatic head along with the development of pancreatic ductal dilatation measuring 10 mm (**Figure 1A**). Thickening of the gastric antrum was also present. Given the patient's history of known pancreatic cysts, a previous study completed 2 years prior was available for comparison and showed findings consistent with an IPMN that measured 2.5 cm and communicated with the main pancreatic duct, which measured 3 mm. Additional review of previous endoscopic ultrasounds (EUS) displayed no concerning features. Followup assessment of cancer antigen 19-9 (CA 19-9) level was 223 ng/mL. Repeat EUS and fine needle aspiration (FNA) was recommended for further evaluation given the increasing size of the cysts. The patient did undergo EUS, which showed an irregular solid-cystic mass with grape-like cystic regions measuring 4.8 cm, in the head of the pancreas. FNA of the lesion using a transduodenal approach with a 25-gauge needle revealed adenocarcinoma (**Figure 1B, 1C**). Further imaging showed no metastasis and preoperative esophagogastroduodenoscopy showed no mucosal findings concerning for malignancy.

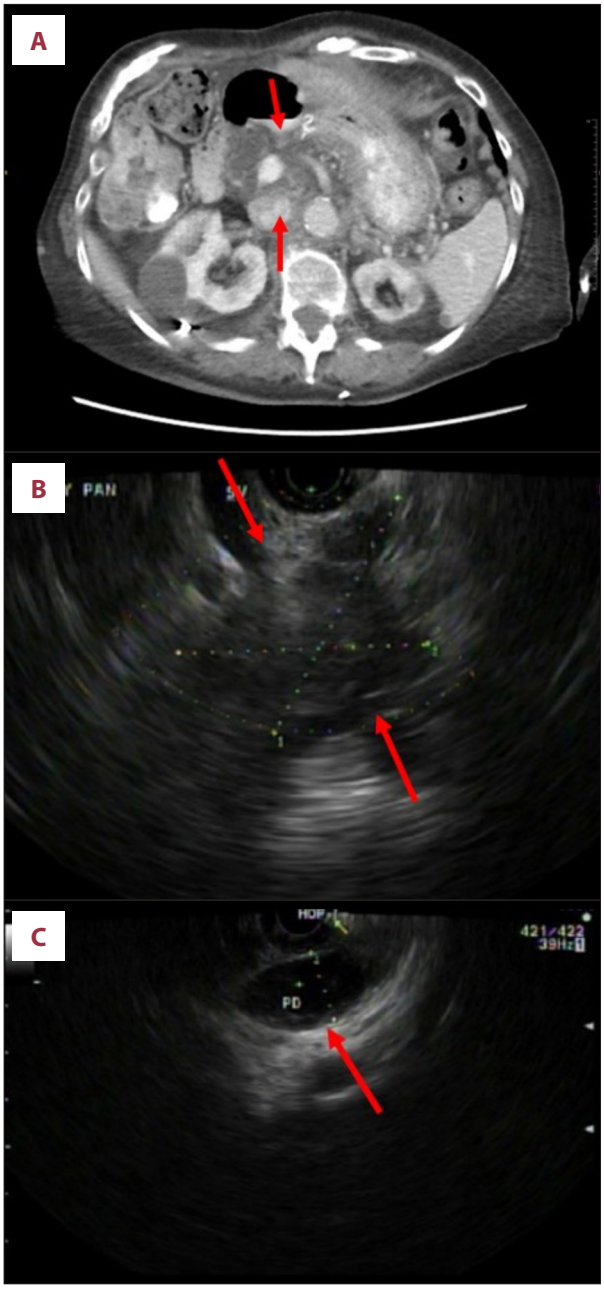

Figure 1. (**A**) Abdominal CT showed 4.7-cm multiloculated cystic lesions in the pancreas head/body (arrow). (**B**) Endoscopic ultrasound showed a heterogenous solid and cystic mass, similar in size to that visualized by the CT scan, in the pancreatic body (arrows). (**C**) The pancreatic duct was dilated to 15 mm (arrow).

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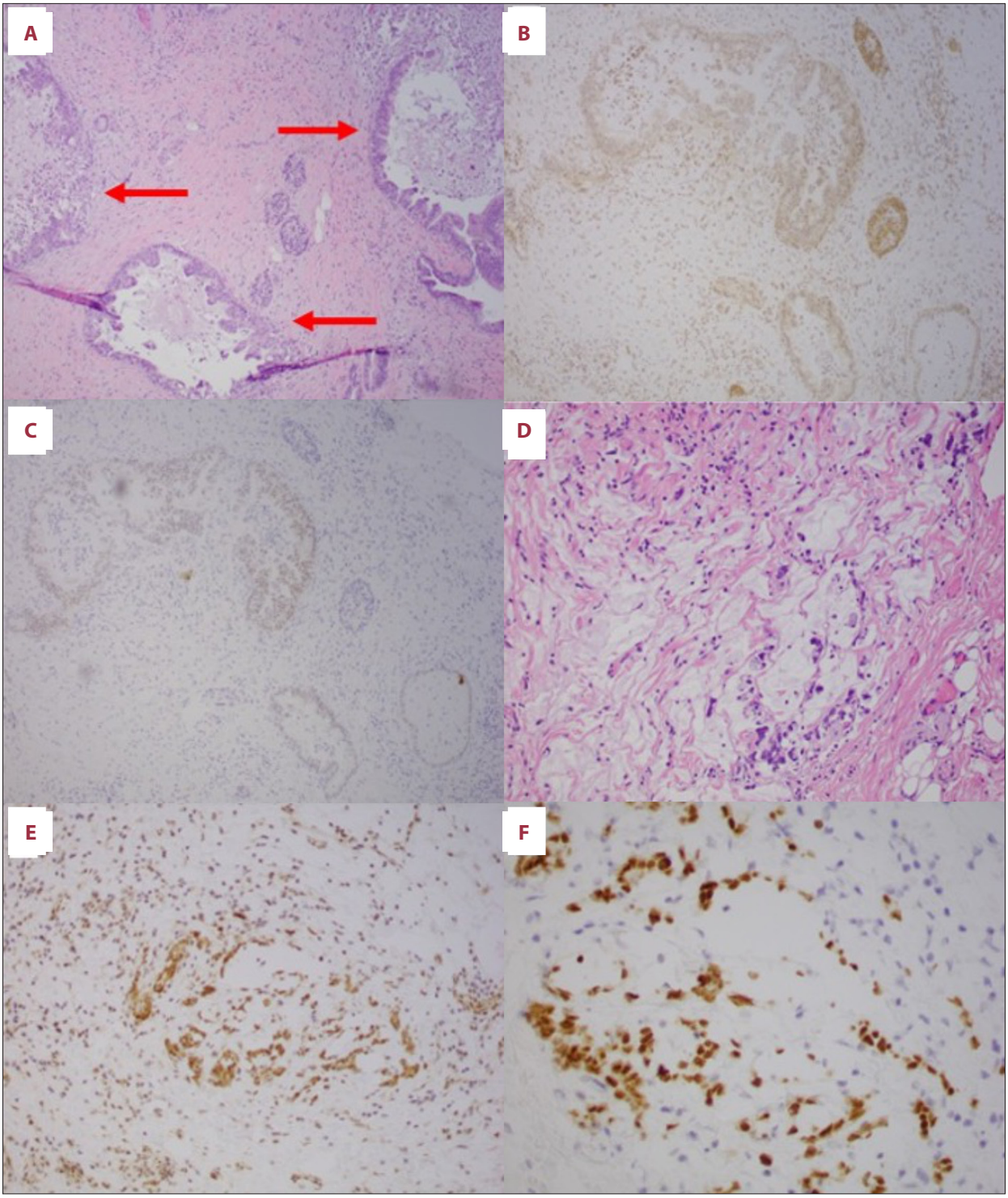

Figure 2. (**A-C**): H&E stain (10×) of pancreatic tissue (**A**) showing well-defined malignant glands (arrows). A loss of expression of DPC4 revealed by immunohistochemistry stain (10×) in (**B**) and weak to absent nuclear expression on CDX1 immunohistochemistry (10×) in (**C**) confirmed a diagnosis of pancreatic adenocarcinoma. (**D-F**): (**D**) H&E stain (20×) of gastric antral tissue showing poorly differentiated adenocarcinoma with signet ring features. (**E**) DPC4 immunohistochemistry stain (20×) and (**F**) CDX2 immunohistochemistry stain (20×) showing intact nuclear expression within the gastric carcinoma.

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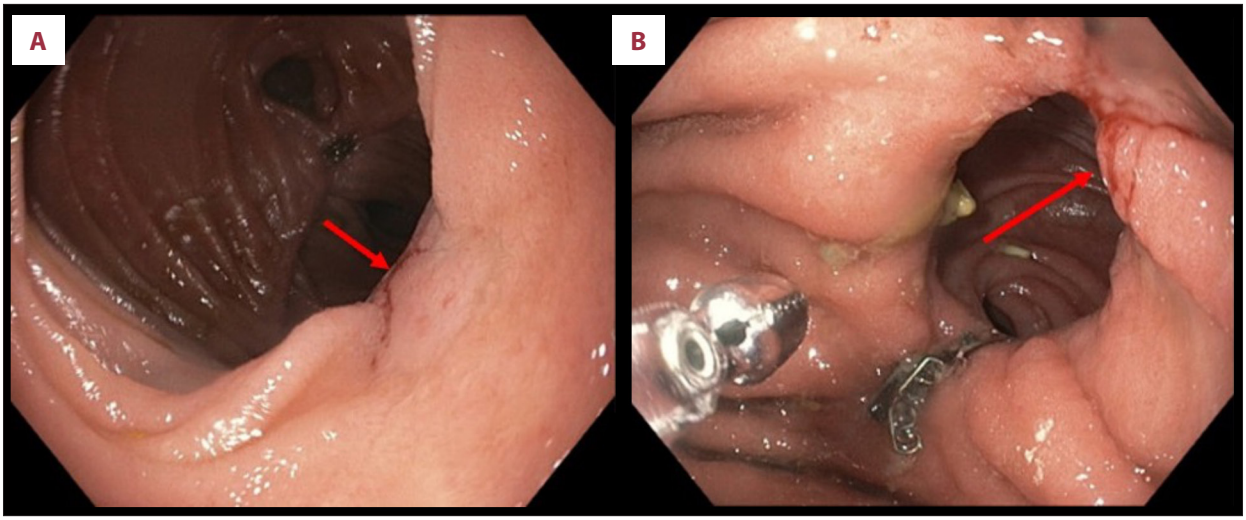

Figure 3. (**A**) Area of erosion (arrow) seen proximal to the gastrojejunostomy junction. (**B**) Biopsy taken from the area resulting in minor bleeding (arrow).

One month later, the patient underwent an extended Whipple procedure. Histological evaluation of the pancreatic tissue showed IPMN of the gastric type which was contiguous with the multifocal invasive tubular-type adenocarcinoma that extended into the pancreatic duct (**Figure 2A-2C**). Unfortunately, evaluation of the gastric tissue at the margins demonstrated poorly differentiated adenocarcinoma that was morphologically different from the pancreatic adenocarcinoma. Given the new gastric findings, the patient underwent repeat esophagogastroduodenoscopy with gastric mapping to further evaluate the extent of the synchronous gastric cancer. The esophagogastroduodenoscopy revealed a residual area of erosion at the gastrojejunostomy junction (**Figure 3**), and the biopsy taken from this area reidentified the presence of poorly differentiated gastric adenocarcinoma with focal SRC morphology involving both the gastric mucosa and submucosa. This was further confirmed through immunohistochemistry evaluation. The malignant pancreatic tissue showed weak to absent DPC4 and CDX2 expression while the gastric tissue showed strong expression of both (**Figure 2D-2F**).

Following the Whipple procedure and incidental diagnosis of synchronous gastric adenocarcinoma, the patient was referred to both medical and radiation oncology. The decision was made to initiate her on preoperative concurrent chemoradiation therapy with 5-fluorouracil for the pancreatic and gastric cancer along with radiation to the affected pancreatic area. The plan was for her to then eventually undergo complete pancreatectomy and possible gastrectomy. Unfortunately, the patient's baseline health status continued to decline, leading to multiple hospitalizations and failure to thrive with inability to tolerate chemoradiation. The patient rapidly deteriorated, and she and her family agreed to transition to palliative care. The patient subsequently died shortly after. Prior to her death, she had been set up to undergo genetic and genomic testing but died prior to this being completed.

Discussion

Cases of multiple primary tumors can be separated into 2 categories: synchronous and metachronous. Synchronous cancers are those in which multiple independent, primary cancers are diagnosed within a 2-month time period, while metachronous cancers are cases of successive primary cancers diagnosed more than 2 months apart [1]. Our patient was diagnosed with a synchronous malignancy composed of a primary tubular-type pancreatic adenocarcinoma and primary SRC gastric adenocarcinoma.

Primary pancreatic carcinomas infrequently coexist alongside a second primary malignancy. Smaller cohort studies such as Su-Jin Shin et al report an incidence of 8.4% for pancreatic cancers being associated with double cancers while larger cohort studies such as Makino et al report an incidence of 5.6% [4,5]. This is likely attributable to the fact that pancreatic malignancies have a high mortality rate that mirrors their incidence [6]. Diagnosis is challenging as pancreatic cancer often remains asymptomatic until advanced disease develops, with 90% of cases being complicated by distant metastasis. In the 20% of cases for which initial resection was offered as a potential treatment option, the 5-year survival rate was 25%, and many patients unfortunately experience disease recurrence [6,7]. Therefore, pancreatic cancer patients typically have a short life expectancy, and this theoretically limits their likelihood of developing a second malignancy. However, as advancements in medicine are made, the prognosis of pancreatic cancer is improving. Consequently, improving survival and life

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expectancy places individuals at a hypothetically increased risk of developing double cancers, leading to increasing incidence.

IPMN is a major risk factor and a precursor of pancreatic adenocarcinoma. There are different types of IPMN that are differentiated on the basis of their epithelial lining and each is associated with a different likelihood of invasion and risk of malignant progression [8,9]. Our patient had a gastric-type IPMN, which has a very favorable prognosis and a lower likelihood of malignant progression in comparison with the higher-grade intestinal and pancreatobiliary types [8]. For this reason and despite the classified type, patients with identified IPMN must undergo routine examination and surveillance to ensure early detection of progression to pancreatic adenocarcinoma. Additionally, studies have shown that IPMN has been seen to accompany other forms of independent malignancies; specifically, different forms of gastric and ductal carcinoma of the pancreas. IPMN should therefore serve as a diagnostic clue to prompt more thorough examination and workup [10].

Endoscopy with gastric biopsies is the gold standard for diagnosing various forms of gastric cancer. Although endoscopy has proven to be a very successful method for detecting gastric cancer, frequent discussions have been had regarding the magnitude of missed lesions [11]. A systemic review and meta-analysis completed by Pimenta-Melo et al revealed that 1 out of 10 gastric cancers could potentially be missed by endoscopic screening [12]. Poor endoscopic techniques, location and size of the cancer, and lack of mucosal invasion resulting in failure to obtain biopsies can all result in missed or delayed diagnosis of cancer [13]. In addition to pancreatic adenocarcinoma in the setting of IPMN, our patient was also found to have a synchronous SRC gastric adenocarcinoma. The SRC gastric adenocarcinoma was diagnosed through histological analysis of the gastric margins from the Whipple procedure. Preoperative endoscopy was completed a month prior to the operation but no biopsies were taken as no mucosal findings suggesting gastric cancer had been seen at that time. It can therefore be speculated that the gastric cancer may have been present at that time, but missed due to the cancer originating in the submucosa. In retrospect, it is important to have a high index of suspicion in patients with IPMNs, especially those with known pancreatic cancer, as these patients would benefit from more aggressive endoscopic surveillance and routine biopsies.

To our knowledge, no synchronous cases of SRC gastric adenocarcinoma and pancreatic adenocarcinoma have been documented; only metachronous occurrence has been reported in the literature. In such cases, the gastric cancer was diagnosed 5-19 years following the diagnosis of pancreatic malignancy [14]. The patients were between 38-68 years of age, predominantly males, and from diverse ethnicities [14-17]. Some patients survived for years after undergoing successful gastrectomy [15] while others died shortly after palliative surgery [16]. This highlights the importance of early diagnosis and prompt treatment, along with continuous aggressive surveillance for secondary malignancies. The exact cause behind the development of SRC gastric carcinoma following surgical resection for pancreatic adenocarcinoma is unknown, but the most widely recognized hypothesis attributes this to morphological mucosal changes that result from prolonged biliary reflux following pancreatoduodenectomy [15,16].

In previous cases of synchronous occurrence of pancreatic and gastric cancers, pancreatic adenocarcinoma has been found to coexist with Lauren intestinal-type gastric adenocarcinoma [3], gastric tubular adenocarcinoma [18], gastric mucinous adenocarcinoma [19], and gastrointestinal stromal tumors [20]. The present case is unique in that it documents the only synchronous case of SRC gastric cancer and primary pancreatic adenocarcinoma in the literature to date. In the present case and all cases of synchronous and metachronous double cancer, genetic and genomic testing should be completed, given their rarity, high morbidity and mortality, and history of a hereditary basis. Although our patient was unable to undergo testing, testing for mutations in the *STK11* (Peutz-Jeghers Syndrome), *ABO,* and *BRCA1/2* genes, as well as the Lynch-syndrome-associated genes *MLH1, MSH2,* and *MSH6*, should be completed to identify a hereditary component in each case of disease [6,21,22].

Conclusions

While there are documented cases of various synchronous malignancies, this is the first documented case in the literature of SRC gastric adenocarcinoma and IPMN-associated pancreatic adenocarcinoma. It is important to recognize that gastric carcinoma can often be missed during perioperative screening endoscopy and therefore proceduralists should have a high index of suspicion and low threshold to perform biopsies in patients who have already been diagnosed with a single primary malignancy. Pancreatic and gastric malignancies independently carry poor prognoses, making early diagnosis imperative as a synchronous malignancy of this type is a very grim diagnosis.

Site of Research Project

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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