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【 CASE REPORT 】

Late Onset of Non-islet Cell Tumor Hypoglycemia Managed via Multidisciplinary Treatment in a Patient with a Solitary Fibrous Tumor

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Abstract:
Solitary fibrous tumor (SFT) is a rare subtype of soft tissue sarcoma (STS). We herein describe a case of late onset of non-islet cell tumor hypoglycemia (NICTH) that was managed via multidisciplinary treatment in a patient with SFT. A 67-year-old man previously diagnosed with SFT 4 years prior to this presentation and treated with several rounds of surgery, presented with massive tumors. Eighteen months following his prescribed chemotherapy, the patient developed hypoglycemia. He was diagnosed with NICTH, after confirming the presence of high molecular weight insulin-like growth factor-2. This case suggests that paraneoplastic syndrome can occur even in cases of rare cancers, such as STS.

Key words: non-islet cell tumor hypoglycemia, solitary fibrous tumor, high molecular weight IGF-2, paraneoplastic syndrome, multidisciplinary treatment

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Introduction

Soft tissue sarcoma (STS), which accounts for approximately 1% of all malignancies, constitutes a heterogenous group of rare solid tumors of mesenchymal cell origin with distinct clinical and pathologic features (1). The pathological diagnosis is established based on the guidelines of the fourth edition of the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone published in 2013. More than 50 different histologic subtypes are included under STS. Among them, the age-standardized incidence of solitary fibrous tumor (SFT) is estimated to be 1.4 cases per million (2). Although SFT has been thought to occur exclusively in the thoracic cavity, rare cases of SFT originating from extrapleural sites have also been reported (3). Non-islet cell tumor hypoglycemia (NICTH) is one of the major causes of fasting hypoglycemia and it can occur with SFT in rare cases. In most patients with NICTH, high molecular weight insulin-like growth factor (IGF)-2 derived from the tumor causes hypoglycemia.

Surgical resection with negative margins is the most suitable approach for treating STS. In some instances, radiotherapy is used to shrink a bulky tumor prior to surgical resection or improve the survival of postsurgical patients. Chemotherapy with single agents is used for patients with unresectable or metastatic disease. Over the past several decades, doxorubicin has been the most commonly used agent to treat histologically non-specific STS. However, doxorubicin-based combination regimens do not improve the overall survival and yield only a marginal therapeutic response at the expense of increased toxic adverse events (4). In recent years, new chemotherapeutic agents, including pazopanib (5), trabectedin (6), and eribulin (7), have been

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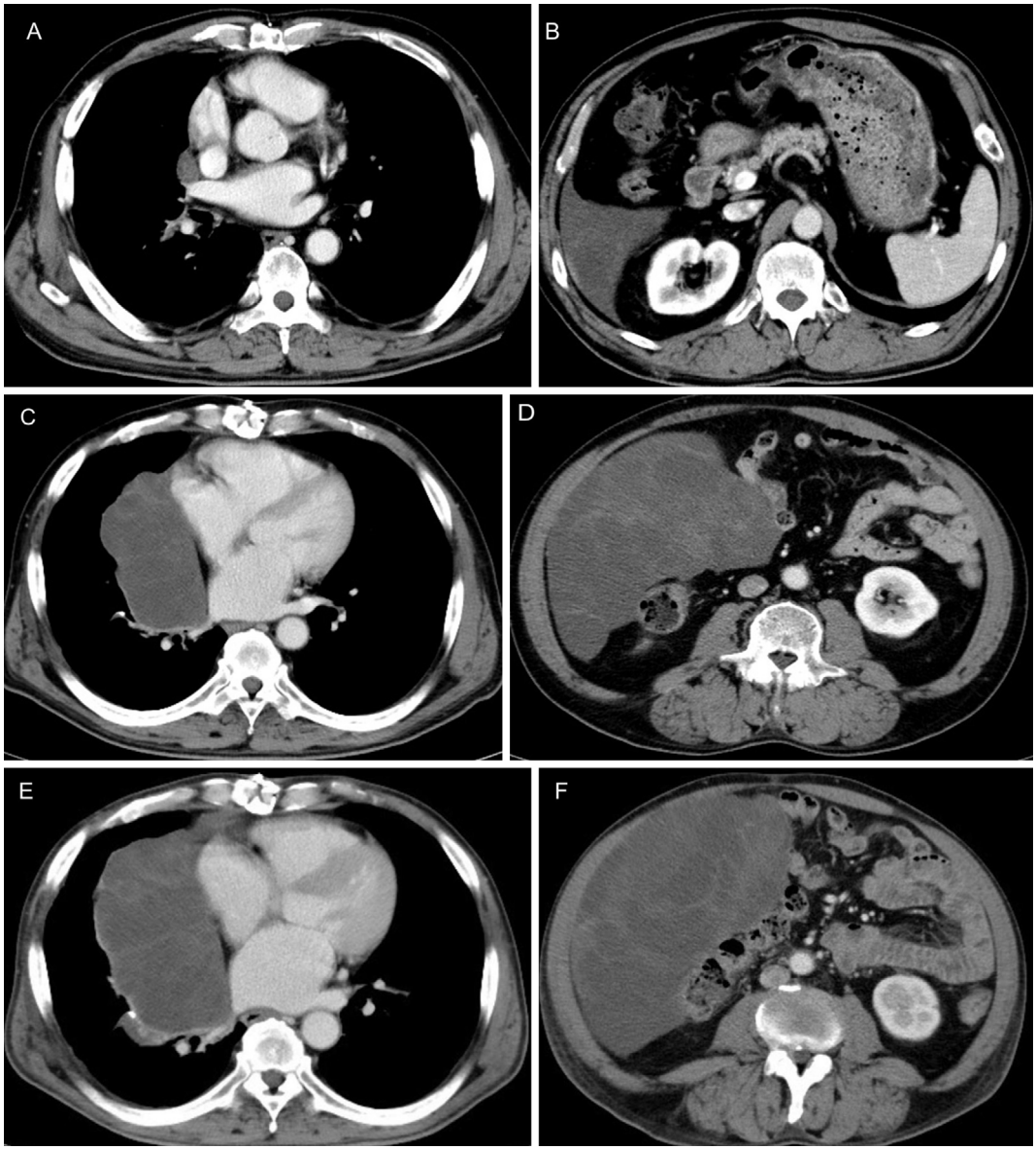

Figure 1. Contrast enhanced computed tomography scan. A CT scan prior to initiating first-line doxorubicin monotherapy (A and B), prior to initiating third-line trabectedin (C and D), and after 5 cycles of trabectedin (E and F). The tumors showed remarkable growth during chemotherapy; however, the patient demonstrated no symptoms until the hypoglycemia episode.

emerging since the application of standard doxorubicin-based chemotherapy. We herein present a case of late onset NICTH that was managed via multidisciplinary treatment in a patient with a solitary fibrous tumor.

Case Report

In 2014, a 67-year-old man with pleural and peritoneal tumors was referred to our institute for systemic chemotherapy. In 2010, the patient had been pathologically diagnosed with SFT originating from the pleura. At the discretion of his physician, he underwent surgery as the initial treatment; following which the patient underwent three additional rounds of surgeries to treat recurrences in his chest. As multiple pleural and peritoneal tumors were detected on the follow-up examination, the patient was referred to our institute for additional treatment consultation.

The patient was in good health prior to his first visit to our institute and was able to conduct all pre-disease performance without any restrictions [i.e., Eastern Cooperative Oncology Group (ECOG) performance status 0]. No abnormalities were detected upon physical examination except for post-operative scars in the chest. Contrast enhanced computed tomography revealed pleural and peritoneal tumors (Fig. 1A and B). There was no other metastasis to any other organs.

Doxorubicin monotherapy was chosen as the first-line chemotherapy and it was administered for up to a maximum of 6 cycles. The best tumor response was stable disease. Subsequently, he attended follow-up visits for 6 months without chemotherapy until disease progression occurred. Pazopanib, an oral multi-targeted angiogenesis inhibitor, was

Table. Hypoglycemic Values Relative to the Reference Range.

	Clinical values (normal range)
WBC (cells/μL)	3,500 (3,500-9,300)
Hb (g/dL)	10.6 (13.4-18.6)
Platelets×10⁴(cells/μL)	12.6 (12.0-40.0)
Total protein (g/dL)	6.1 (6.7-8.3)
Albumin (g/dL)	3.0 (4.0-5.0)
Total bilirubin (mg/dL)	0.8 (0.3-1.2)
Direct bilirubin (mg/dL)	0.2 (0-0.3)
AST (U/L)	24 (13-33)
ALT (U/L)	18 (8-42)
LDH (U/L)	270 (119-229)
ALP (U/L)	325 (115-359)
Blood urea nitrogen (mg/dL)	6 (8-22)
Creatinine (mg/dL)	0.47 (0.60-1.10)
Na (mEq/L)	147 (138-146)
K (mEq/L)	2.8 (3.6-4.9)
Cl (mEq/L)	110 (99-109)
Total cholesterol (mg/dL)	116 (128-220)
Triglyceride (mg/dL)	80 (80-112)
Blood glucose (mg/dL)	54 (80-112)
Hemoglobin A1c (%)	4.1 (4.6-6.2)
Serum C-peptide (ng/mL)	0.04 (0.69-2.45)
Immunoreactive insulin (μU/mL)	<0.5 (1.1-17.0)
Urine C-peptide creatinine ratio (ng/mgCr)	1.2 (36.9-73.3)
Free T3 (pg/mL)	2.28 (2.1-3.8)
Free T4 (ng/dL)	1.07 (0.82-1.63)
Adrenocorticotropic hormone (pg/mL)	42.99 (7.2-63.3)
Cortisol (μg/dL),	4.4 (4.0-23.3)
24-hour urinary cortisol (μg/day)	84.8 (26.0-180.7)
Human growth hormone (ng/mL)	<0.10 (<2.1 ng/mL)
IGF-1 (ng/mL)	164.0 (68.0-216.0)

administered as a second-line chemotherapy. However, the drug was discontinued only 2 weeks later because of liver dysfunction. Although his pleural and peritoneal tumors showed remarkable growth at this time (Fig. 1C and D), he maintained an adequate visceral function and a good performance status. Trabectedin, a cytotoxic alkaloid that demonstrates antitumor activity in a variety of human malignancies including STS, was chosen as a third-line therapy and it was administered over 5 cycles without any significant adverse events.

Before the sixth round of treatment consisting of trabectedin, the patient was suddenly admitted to our institute because of a loss of consciousness. The tumors had grown slightly larger in spite of the trabectedin administration (Fig. 1E and F). Laboratory tests upon admission revealed hypoglycemia and hypokalemia; however, markers of endogenous insulin secretion, including C-peptide, immunoreactive insulin (IRI), and urine C-peptide creatinine ratio were suppressed (Table). Considering these results, insulinoma was not deemed to be the cause of hypoglycemia. The serum levels of thyroid hormone, adrenocorticotropic hormone, cortisol, and human growth hormone were within the normal limits. The serum level of insulin-like growth factor (IGF)-1, secreted by the liver as a result of stimulation by human growth hormone, was also within the normal range. Considering these diagnostic imaging and laboratory data, hypoglycemia due to NICTH was suspected.

As the next step in the diagnostic process, a biopsy of the abdominal tumor was performed. The tumor tissue was immediately fixed with 10% formalin and embedded in paraffin. Then, 4-μm-thick paraffin sections were subjected to routine Hematoxylin and Eosin (H & E) and immunohistochemical staining (Fig. 2A-C). A strong expression of both STAT6 and IGF-2, markers for SFT, was observed (Fig. 2B and C). Before his initial surgery, the patient's blood glucose level was relatively low according to his previous doctor [blood glucose 55 mg/dL and glycated hemoglobin (HbA1c) 5.5%] and he had never experienced a loss of consciousness due to hypoglycemia. Hence, we conducted H & E and immunohistochemical staining of the surgical specimen obtained during the first surgery performed 4 years prior to the initiation of his chemotherapeutic regimen (Fig. 2D). Positive staining for both STAT6 and IGF-2 were retrospectively confirmed at the time of initial diagnosis (Fig. 2E and F, respectively). Although the patient's serum level of IGF-2 could not be tested, the diagnosis of NICTH was made based on the results of a Western blot analysis, which revealed the presence of high molecular weight IGF-2 (Fig. 3).

The clinical course of the patient is shown in Fig. 4. He underwent several rounds of surgery over a period of 4 years before referral. Since he was referred to our institute, the HbA1c level had been generally stable. However, the HbA1c level immediately plunged when the patient was administered trabectedin. Since he had never experienced an episode of hypoglycemia for 18 months since the referral, we presumed that multidisciplinary treatment consisting of surgery and chemotherapy might be able to effectively suppress NICTH. As the blood glucose level could be maintained via glucose infusion and the administration of dexamethasone, the patient was in good condition and demonstrated no concerning symptoms. However, he was subsequently transferred to the intensive care unit owing to sudden cardio-pulmonary arrest (CPA). He was able to successfully recover from the first bout of CPA without any sequela, however, he passed away because of a second occurrence of CPA. Although an autopsy was not conducted in accordance with the family's will, sinus node dysfunction due to tumor invasion was considered to be the cause of the CPA.

Discussion

We herein described a case of late onset of NICTH that was managed via multidisciplinary treatment in a patient with SFT. According to the WHO classification, SFTs are categorized as having an intermediate malignant potential with a low risk of metastasis and a relatively indolent dis-

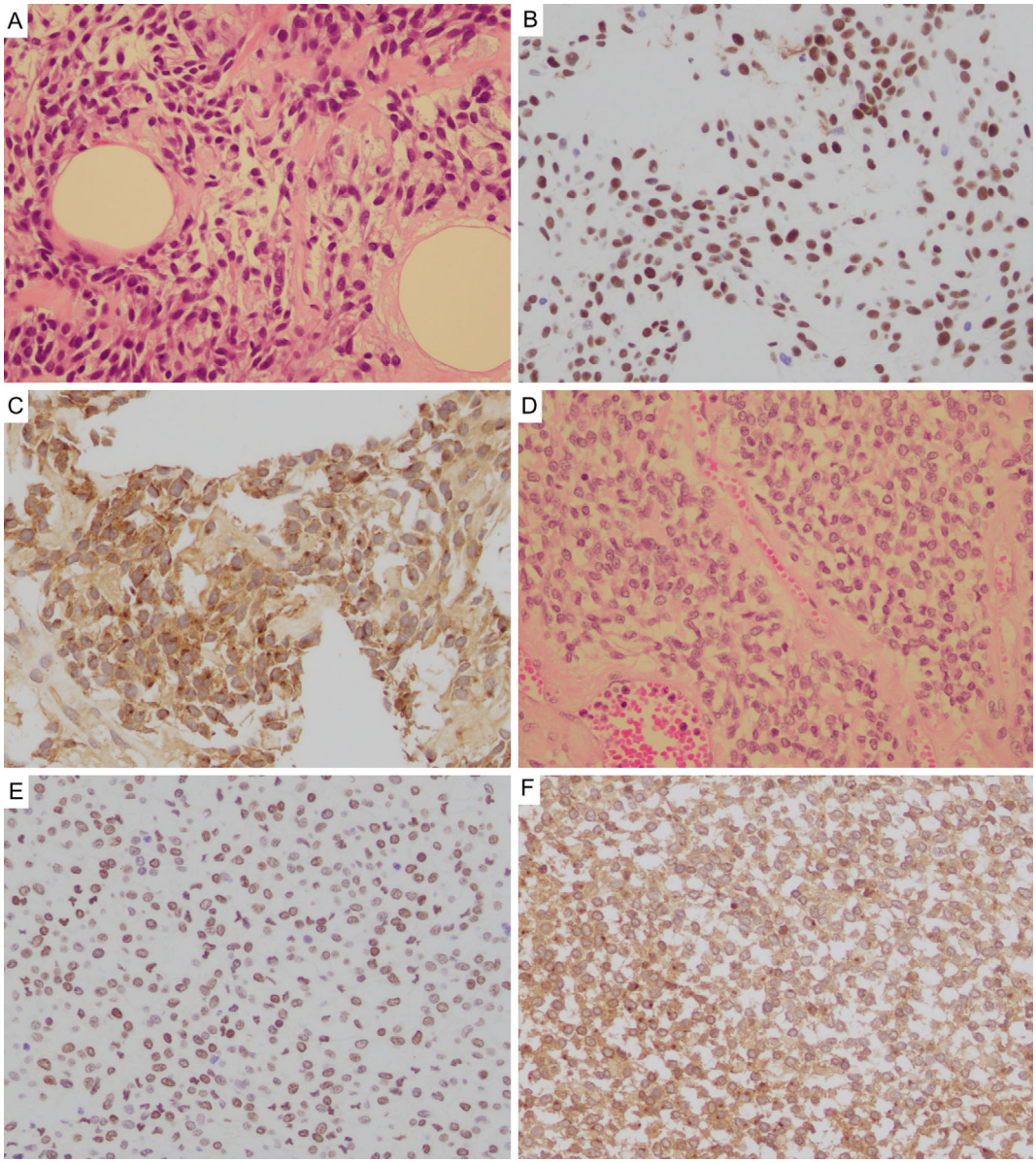

Figure 2. **Examination of biopsy specimens. Hematoxylin and Eosin (H&E) staining (A) and immunohistochemical staining for (B) STAT6 and (C) IGF-2 showing positive results of SFT in the biopsied specimen of the abdominal tumor obtained at the time of loss of consciousness. Positive SFT staining was also confirmed using the initial surgical specimen. (D) H&E staining. Immunohistochemical staining for (E) STAT6 and (F) IGF-2 (original magnification×40).**

ease course. Demicco et al. reported that large tumors, old age, and mitotic figures are high-risk factors of both metastasis and death in SFT (8). Furthermore, the clinical behavior of individual tumors is difficult to predict (9). In the present case, the patient had SFT for five and a half years; however, hypoglycemia was not apparent until 1 month before his death. By the time that hypoglycemia became apparent, the tumors had already grown remarkably, and the patient had been treated with third-line chemotherapy with trabectedin. Thus, multidisciplinary treatment consisting of surgery and chemotherapy might have suppressed NICTH, which occurred as a part of paraneoplastic syndrome accompanied with SFT.

NICTH is characterized by recurrent fasting hypoglycemia and it is caused by the production of unprocessed forms of precursors of IGF-2 (i.e. high molecular weight IGF-2) (10). IGF-2 is biologically active and present in high amounts in the serum of NICTH patients. As the serum level of total IGF-2 is not elevated in most cases, high molecular weight IGF-2 seems to have specific properties. It provides a continuous increased insulin-like effect that may lead to sustained hypoglycemia (11).

The exact incidence and prevalence of NICTH in SFT are unknown. It is reported that NICTH is four times less common than insulinoma, but the true incidence may be higher because many cases remain unrecognized (12). Previous studies have reported that malignant SFT can accompany NICTH, owing to the secretion of high molecular weight

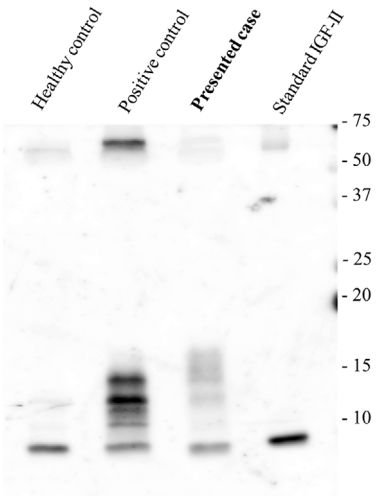

Figure 3. **Western blot of IGF-2 in serum. The presence of high molecular weight IGF-2 (7.5 kDA) can be confirmed in our case (right lane) in comparison with a healthy control (left lane). Primary antibody and secondary antibody were clone S1F2 (Merck Millipore) and #7,076 (Cell Signaling Technology), respectively.**

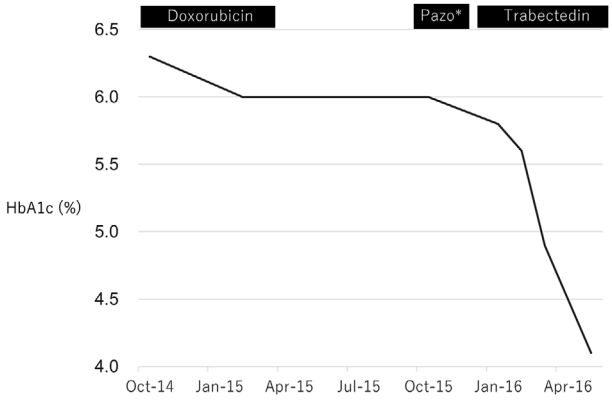

Figure 4. **Clinical course of the patient. The HbA1c level had been generally stable during treatment. However, it plunged suddenly during treatment with third-line trabectedin monotherapy. The lowest HbA1c level (4.1%) was observed when the patient was admitted to our institute because of hypoglycemia. Pazo*: pazopanib**

IGF-2 by the tumor (10, 13-15). The detection of high molecular weight IGF-2 in the tumor is considered to be the gold standard for making an NICTH diagnosis. Additionally, there are several complementary methods for making a diagnosis. As NICTH suppresses insulin secretion by beta-cells, low C-peptide, growth hormone, and beta-hydroxybutyrate levels was observed (16, 17). Other factors including cachexia, renal dysfunction, and liver dysfunction can also contribute to hypoglycemia (18). However, the patient in this report had no organ dysfunction associated with tumor invasion.

The correlation between the tumor size and the onset of symptom is unknown. Tsuro et al. reported the mean tumor size was 11.8±8.6 cm in 20 Japanese patients with IGF-2 producing tumors (19). However, their report included histologies other than SFT. Additionally, it was unknown whether the presence of high molecular weight IGF-2 was confirmed for all patients. Considering the present case, the progression of a large tumor may have caused the symptoms observed in this case because the patient had demonstrated no symptoms until near the end of his clinical course. A decreased liver glucose output caused by tumor invasion may also be a factor for the onset of hypoglycemia, but this was not assessed in the present case.

NAB2-STAT6 gene fusion is the defining driver mutation of SFT. NAB2-STAT6 fusion products harbor the early growth response-binding domain of NAB2 fused to the activation domain of STAT6 (20). Although the presence of *NAB2-STAT6* gene fusion could not be confirmed by reverse transcription polymerase chain reaction or sequencing in this present case, immunostaining for STAT6 yielded clearly positive results.

There is no standard treatment for NICTH other than the surgical removal of the tumor. When radical resection is not possible, various treatments have been attempted to alleviate the hypoglycemia. Holt et al. reported that growth hormone could successfully treat NICTH, as the administration of growth hormone leads to an increase in both IGF-binding protein-3 and acid labile subunit production from the liver (21). Glucocorticoid therapy may also be effective, owing to its suppressive effects on high molecular forms of IGF-2 (16). In the present case, dexamethasone was administered to maintain the blood glucose level. However, a change in high molecular weight IGF-2 levels could not be confirmed because of the sudden onset of CPA. New chemotherapeutic agents including pazopanib, trabectedin, and eribulin continue to emerge for the treatment of STS; however, no patients with SFT were included in the phase 3 studies (5-7). Moreover, although these agents demonstrated an improvement in disease-free survival despite a response rate of ≤10%, they are not frequently administered in clinical practice. Therefore, the number of patients with paraneoplastic syndrome including NICTH may increase in the future, even in cases of rare cancers such as STS because of a prolonged treatment period.

In conclusion, we herein described a case of late onset NICTH managed via multidisciplinary treatment in a patient with SFT. The diagnosis of NICTH was established by confirming the presence of high molecular weight IGF-2. However, hypoglycemia was not apparent during most of the disease course. As new chemotherapeutic agents are emerging for the treatment of STS, we should be aware of patients with rare paraneoplastic syndromes, even in STS.

The authors state that they have no Conflict of Interest (COI).

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