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CASE REPORT

Recurrent undifferentiated embryonal sarcoma of the liver in adult patient treated by pembrolizumab: A case report

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Author contributions: Yu XH and Huang J were the patient's interventional radiologists, reviewed the literature and contributed to manuscript drafting; Ge NJ reviewed the literature and contributed to manuscript drafting; Zhao JY performed next generation sequencing and immuno-histological analyses and interpretation and contributed to manuscript drafting; Yang YF made the treatment plan and contributed to manuscript drafting; Zhao JY and Yang YF were responsible for the revision of the manuscript for important intellectual content; All authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

Undifferentiated embryonal sarcoma of the liver (UESL) is a neoplasm that rarely develops in adults. The main treatments for UESL are upfront gross total surgical resection and adjuvant multiagent chemotherapy. Here, we report a case of recurrent UESL in an adult treated with pembrolizumab and discuss a method to identify proper candidates for antibody of programmed cell death protein 1 (anti-PD-1) treatment.

CASE SUMMARY

A 69-year-old woman was admitted for abdominal pain that developed for 1 wk. Computed tomography showed a 16 cm mass in the right lobe of the liver. Right hemihepatectomy and lymphadenectomy were performed, and histological diagnosis was UESL. Six months later, the patient suffered from painless obstructive jaundice, and positron emission tomography-computed tomography revealed multiple metastases. Then, percutaneous transhepatic cholangial drainage was applied to reduce jaundice, and radiofrequency ablation was used to control the lesion near the hepatic hilum. However, the patient suffered from a serious fever caused by the tumor. The patient received treatment with pembrolizumab, and the prescribed dosage was 2 mg/kg every 3 wk. After the seventh dose, positron emission tomography-computed tomography revealed that the multiple metastases had nearly disappeared. Radiologic exam was used to evaluate the disease state, and no new lesions were found. Next-generation sequencing and immunohistology were applied to determine the reason why the patient had such a favorable response to pembrolizumab. Tumor mutation burden, microsatellite instability, and programmed death ligand 1 expression can

be combined to predict the effect of PD-1 antibodies. When every one of these biomarkers are detected in a tumor patient, the patient may be a proper candidate for PD-1 antibodies.

CONCLUSION
Anti-PD-1 treatment for tumors needs further research to identify indications and proper biomarkers.

Key Words: Undifferentiated embryonal sarcoma of the liver; Pembrolizumab; Programmed cell death protein 1; Tumor mutation burden; Immunohistology; Case report

Core Tip: Undifferentiated embryonal sarcoma of the liver is a neoplasm rarely diagnosed in adults, which was mainly treated by resection and adjuvant multiagent chemotherapy. Immunotherapy, such as antibody of programmed cell death protein 1, has not been reported to be used to treat this disease. Here we reported a recurrent undifferentiated embryonal sarcoma of the liver case in an adult that was treated by pembrolizumab and discussed the way to find the proper candidates for antibody of programmed cell death protein 1 treatment.

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INTRODUCTION

Undifferentiated embryonal sarcoma of the liver (UESL) is a mesenchymal tumor that was first described in 1978[1]. UESL is an aggressive pediatric tumor that is classically diagnosed in adolescents and rarely diagnosed in adults[2]. The main treatments for UESL are upfront gross total surgical resection and adjuvant multiagent chemotherapy, which have led to improved long-term survival[3]. However, immunotherapy, such programmed cell death protein 1 (anti-PD-1) antibodies, has not been reported to be used to treat this disease. Here, we report a case of recurrent UESL in an adult treated with pembrolizumab (Keytruda, Merck Sharp & Dohme Ltd) and discuss a method to identify proper candidates for anti-PD-1 treatment.

CASE PRESENTATION

Chief complaints

A 69-year-old woman was admitted for abdominal pain that developed for 1 wk (Figure 1).

History of present illness

Right hemihepatectomy and lymphadenectomy were performed in Oct 2016.

History of past illness

She had no history of a previously diagnosed malignancy.

Physical examination

No abnormalities.

Laboratory examinations

Serum levels of tumor markers (carcinoembryonic antigen, CA-19-9, alpha-fetoprotein and prostate-specific antigen) were all within normal limits, and she was negative for

work.

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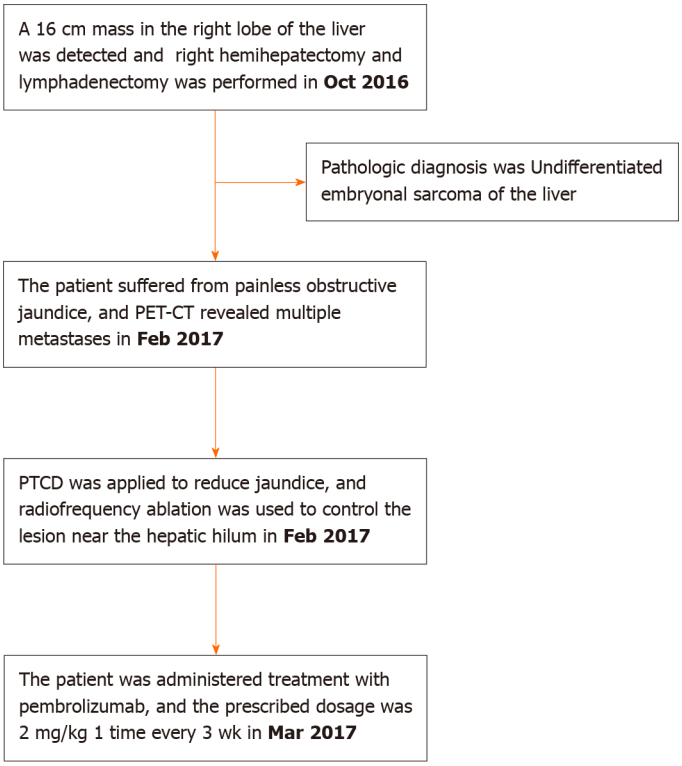

Figure 1 Timeline of the case. PET-CT: Positron emission tomography-computed tomography; PTCD: Percutaneous transhepatic cholangial drainage.

hepatic viral markers (hepatitis B surface antigen and anti-hepatitis C virus).

Imaging examinations

Abdominal contrast-enhanced computed tomography (CT) showed a 16 cm mass in the right lobe of the liver, and positron emission tomography-CT showed radioactive concentration of 18F-fluorodeoxyglucose on the tumor rim with no radioactive concentration in other areas of the body (Figure 2).

FINAL DIAGNOSIS

The histological report showed a solitary 16.0 cm × 12.5 cm × 10.5 cm well-defined and encapsulated tumor. Tumor cells were found in some dilated lymph vessels. The immunohistological stain was positive for vimentin, S-100 protein, A1AT, LCA, CD68 and Ki67. The staining for CD20, CD45R0, CK, CAM5.2, smooth muscle actin, CK8/18, CK20, CK19, villin, AFP, HSA, HMB45, A103, TTF-1, CA125, caldesmon, MyoD1, CD34, CD21 and CD57 demonstrated negative findings. The diagnosis of UESL was made using the examinations mentioned above.

TREATMENT

Six months after surgery, the patient suffered from painless obstructive jaundice. Liver ultrasonography revealed a new lesion near the hepatic hilum and intrahepatic bile duct dilation. Then, positron emission tomography-CT revealed multiple metastases located in the liver, mediastinum and peritoneum (Figure 3). Next, percutaneous transhepatic cholangial drainage and stenting were applied to reduce jaundice. After that, radiofrequency ablation with intraductal chilled saline perfusion to prevent bile duct injury through percutaneous transhepatic cholangial drainage was used to control the lesion near the hepatic hilum[4]. However, the patient suffered from a serious fever caused by the tumor. Due to the fever, the patient became asthenic and was afraid to undergo chemotherapy or targeted therapy. Therefore, the patient was received pembrolizumab for treatment, and the prescribed dosage was 2 mg/kg once every 3 wk.

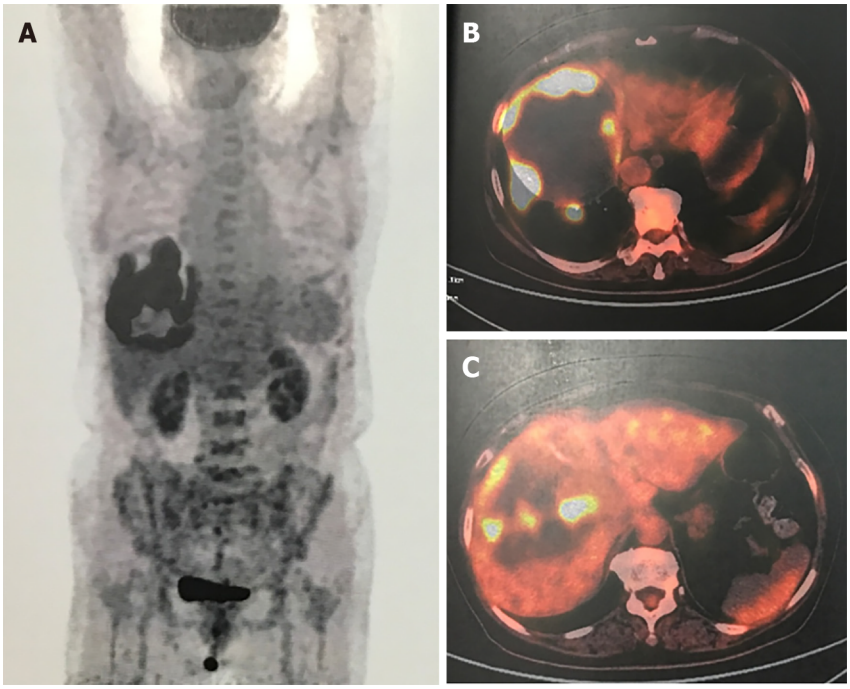

Figure 2 Positron emission tomography-computed tomography. A-C: Radioactive concentration of 18F-fluorodeoxyglucose on the tumor rim, and no radioactive concentration was observed in other areas of the body.

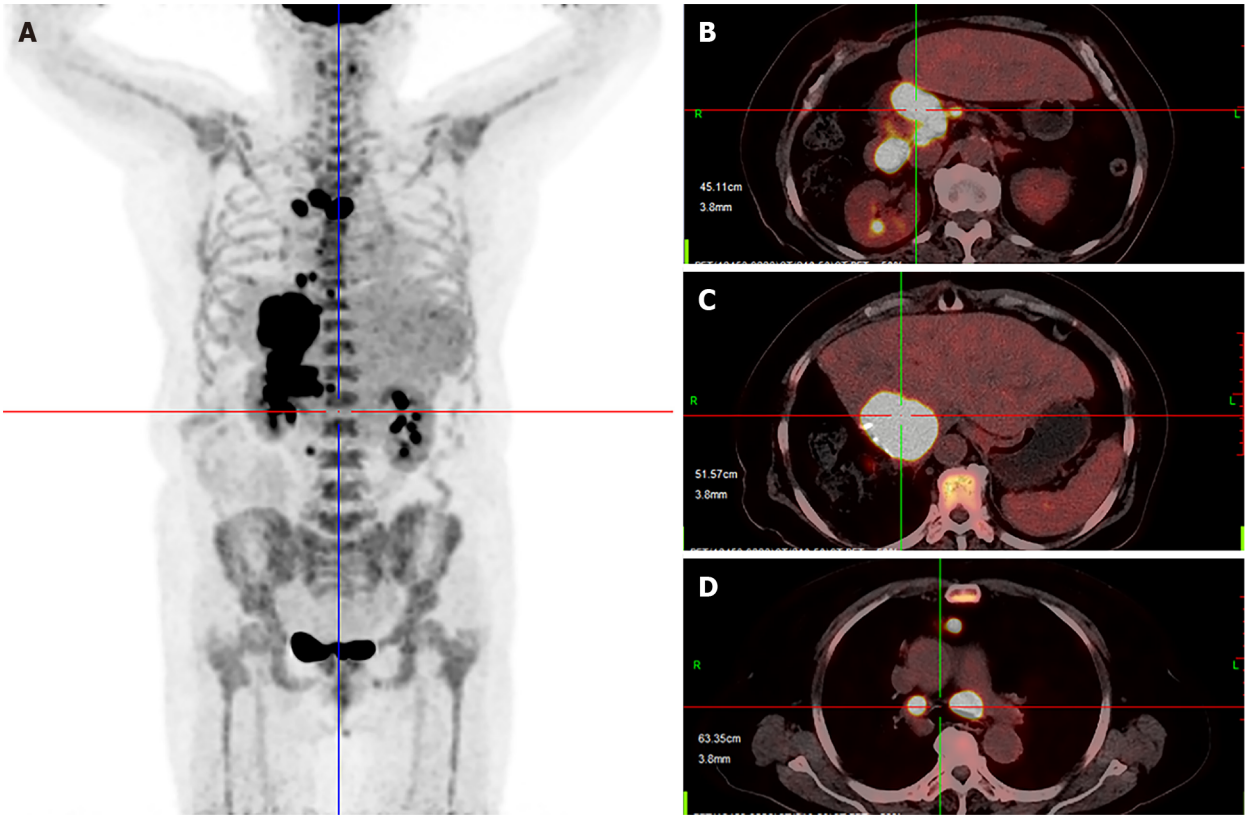

Figure 3 Positron emission tomography-computed tomography. A-D: Multiple metastases located in the liver, mediastinum and peritoneum.

OUTCOME AND FOLLOW-UP

Two days after the first dose, the fever was relieved. After the seventh dose, new positron emission tomography-CT was conducted revealing that the multiple metastases had nearly disappeared (Figure 4). The patient received six more doses of pembrolizumab. Every 6 mo, chest CT and abdominal contrast-enhanced CT were

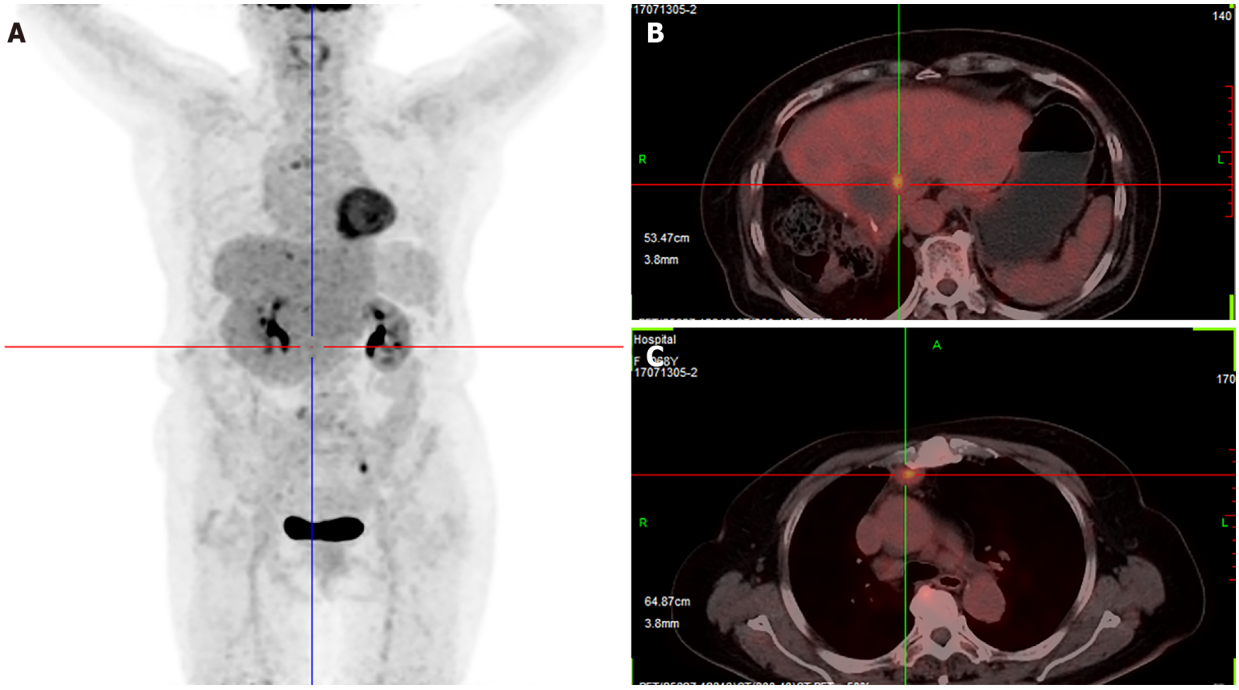

Figure 4 Positron emission tomography-computed tomography. A-C: Multiple metastases had nearly disappeared.

used to evaluate the disease state, and no new lesions were found. To determine the reason why the patient had such a favorable response to pembrolizumab, biopsy and peripheral blood were used for next-generation sequencing (NGS). NGS revealed *PTK2* gene amplification, *FGF10* gene amplification and *USP34/XPO1* gene rearrangement. The tumor mutation burden (TMB) was 3.2 muts/Mb (< 75%), and the tumor showed microsatellite stability. There was no strong association between the favorable response and NGS result, as previously reported[5]. Then, further immunohistological staining of CD68, CD8 and CD4 were used to detect macrophage and T cell distribution in the tumor, and immunohistological staining of programmed death ligand 1 (PD-L1) was used to detect the expression of PD-L1 in the tumor cell. Immunohistological staining showed that there was high expression of CD8, low expression of CD4 and little expression of CD68 in the tumor, and up to 90% of tumor cells expressed PD-L1 (Figure 5).

DISCUSSION

Anti-PD-1 treatment, as a new immunotherapy, has the advantages of few side effects, limited pain and long-lasting effects[6]. Therefore, an increasing number of researchers have attempted to use anti-PD-1 to treat multiple types of tumors[7,8]. For the first time in this case, pembrolizumab was used to treat UESL, and the result was encouraging. Pembrolizumab may be a new method to treat UESL.

In our case, radiofrequency ablation was applied to control the lesion near the hepatic hilum. Although ablation does not provide a cure, it may assist pembrolizumab in destroying tumor cells. Local ablation can destroy tumor cells, and then tumor antigens are released into the microenvironment and blood. Recent research has revealed that immunotherapy combined with local treatment can prolong the survival time of liver cancer[9]. Other research has revealed that local treatment, such as radiotherapy, can release antigenic peptides from tumors, cause the activation and migration of dendritic cells and enhance antigen presentation by dendritic cells leading to enhanced antitumor T-cell recognition and activity[10].

We were curious why the patient had a good response to pembrolizumab and wanted to determine how other appropriate candidates for anti-PD-1 treatment could be identified. In our case, biopsy and peripheral blood were used to perform NGS. However, the gene mutations found in this patient were not associated with a favorable response to pembrolizumab. High TMB and microsatellite instability in tumors are associated with a favorable response to pembrolizumab, and the Food and Drug Administration has authorized pembrolizumab to be used to treat multiple types

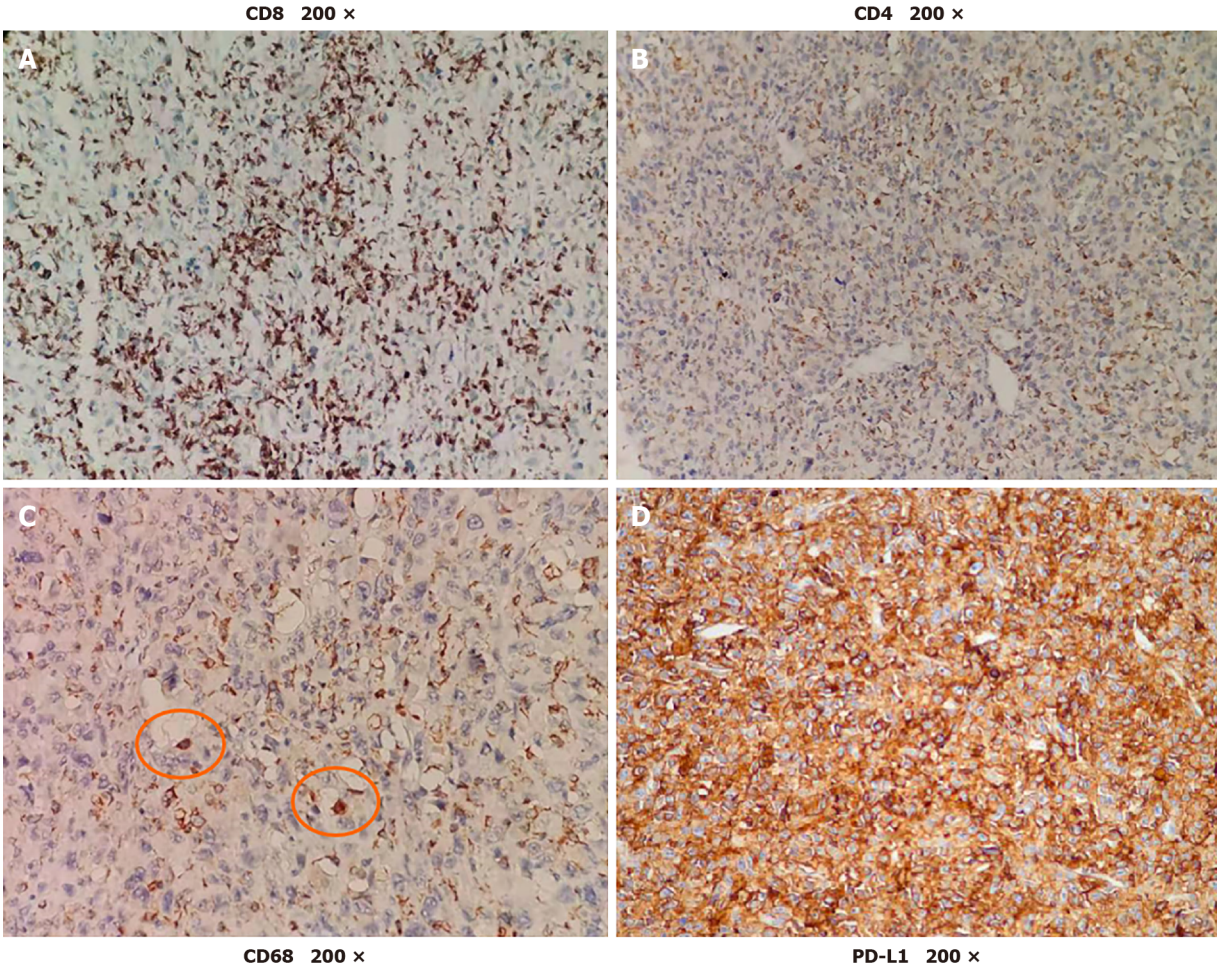

Figure 5 Immunohistological staining. A-D: There was high expression of CD8, low expression of CD4 and little expression of CD68 in the tumor. Up to 90% of tumor cells expressed programmed death ligand 1 (PD-L1).

of tumors with high TMB and microsatellite instability[11]. However, in this case, NGS showed that the tumor had low TMB and microsatellite stability, which was contradictory to other responsive tumors[5]. Therefore, low TMB and microsatellite stability were not contraindications for anti-PD-1 treatment.

Then, immunohistological staining showed that up to 90% of the tumor cells expressed PD-L1. This may be the reason why the patient had a favorable response to pembrolizumab. Many researchers have found that PD-L1 is expressed in many types of tumors, and high-level expression of PD-L1 is always associated with poor tumor prognosis[12]. In some types of tumors, such as lung cancer, high-level expression of PD-L1 is associated with a good response to anti-PD-1 treatment[13]. However, in other types of tumors, the expression of PD-L1 is not associated with responses to anti-PD-1 treatment[14]. Defining the high-level expression of PD-L1 is also controversial[15]. Moreover, the location of PD-L1 expression also needs further research[16]. Therefore, PD-L1 expression, as a biomarker for predicting the effect of PD-1 antibodies, also needs further research.

In our opinion, TMB, microsatellite instability and PD-L1 expression can be combined to predict the effect of PD-1 antibodies. When every one of these biomarkers is detected in a tumor patient, the patient may be a proper candidate for PD-1 antibodies. However, anti-PD-1, as a new treatment for tumors, needs further research to identify the indications and proper biomarkers.

CONCLUSION

We reported a case of recurrent UESL in an adult patient treated with pembrolizumab, and UESL had a nearly complete response to pembrolizumab. Immunohistological staining of PD-L1 was highlighted and corresponded to the effect of pembrolizumab.

Therefore, PD-L1 expression may be combined with TMB and microsatellite instability to predict the effect of PD-1 antibody treatment.

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