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Neoadjuvant Therapy with Everolimus for Subependymal Giant Cell Astrocytoma: A Case Report

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Abstract

Direct surgical resection remains to be the standard treatment for tuberous sclerosis complex (TSC) with subependymal giant cell astrocytoma (SEGA). Medical therapy with everolimus (mammalian target of rapamycin inhibitor or mTOR) serves as a second-line treatment for patients with SEGA who are determined to be ineligible for surgical resection. Some recent studies have reported that neoadjuvant therapy for SEGA may be a useful, novel treatment.

In this study, we herein present a case of SEGA and demonstrate the efficacy of preoperative everolimus therapy. We have also examined the utility and safety of neoadjuvant therapy for SEGA and investigated four previously reported cases of preoperative administration of mTOR inhibitors. In these cases, everolimus was administered preoperatively to shrink the tumor although the duration of treatment varied. Afterward, gross total tumor removal was conducted in all the cases. No postoperative complications were reported during the follow-up period. These findings indicate that neoadjuvant therapy with an mTOR inhibitor can be a potential treatment for SEGA. The findings of this present study also suggested that a short administration period of about 2 months may be sufficient to achieve preoperative tumor reduction.

Keywords: tuberous sclerosis complex, SEGA, SEN, mTOR inhibitor

Introduction

Tuberous sclerosis complex (TSC) is known to be an autosomal dominant disorder affecting approximately 1 in 5,800 to 13,520 individuals.[1-4] Subependymal giant cell astrocytoma (SEGA) is a World Health Organization (WHO) grade I central nervous system disease classified as an intraventricular tumor belonging to the astrocytoma group; it has been determined to occur in 5-20% of patients with TSC.[5,6] Medical therapy with everolimus (mammalian target of rapamycin inhibitor or mTOR) is considered a second-line treatment for patients with SEGA who are ineligible for surgical resection,[7] but there are only a few reports of preoperative medical therapy for this condition.[8,9] Thus, we herein report a case of SEGA that was successfully treated with neoadjuvant therapy with everolimus before surgical tumor resection. The utility of preoperative medical therapy based on the present and previous reports is also discussed.

Case Report

A 15-year-old male patient with no remarkable medical or family history presented with a slight headache and transient, right lower limb paralysis. His head computed tomography (CT) scan revealed a tumor consisting of substantial and cystic components in the left frontal horn of the lateral ventricle near the foramen of Monro and associated hydrocephalus. A subependymal nodule was also detected (Fig. 1a). Contrast-enhanced brain magnetic resonance imaging (MRI) demonstrated marked enhancement of the substantial component (Fig. 1b, c).

The patient underwent a semi-urgent, endoscopic tumor biopsy for diagnosis and a simultaneous cystostomy for

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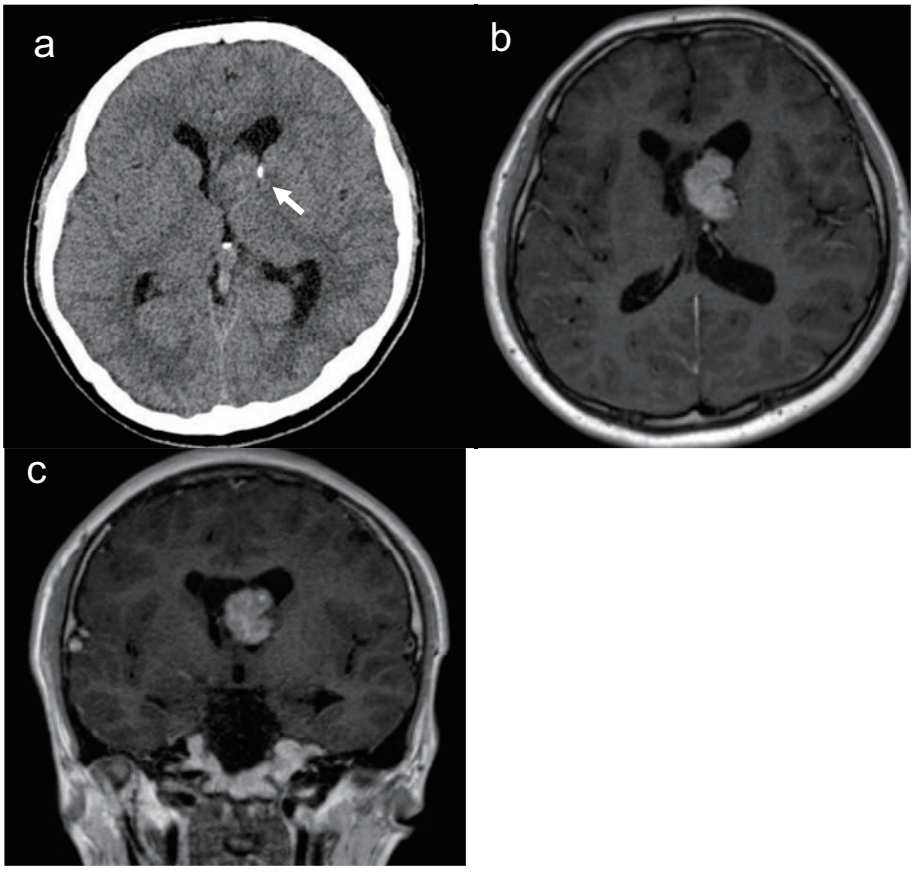

Fig. 1 (a) (b) (c) Axial computed tomography (CT) and enhanced axial and coronal T1-weighted magnetic resonance imaging (MRI) of the intracranial tumor. (a) Preoperative head CT demonstrates a left ventricular mass (30 mm × 37 mm × 29 mm) with hydrocephalus. Slight calcification (subependymal nodule) can be seen in the left ventricle wall (white arrow). (b) (c) The tumor shows contrast in a mosaic pattern. Hydrocephalus can also be seen.

the hydrocephalus. Fenestration of the cyst was able to reduce the tumor size, improving cerebrospinal fluid (CSF) circulation. The diagnosis of SEGA was confirmed through pathological tissue analysis.

There were no other physical findings that met the diagnostic clinical criteria for TSC. As the patient's postoperative course was deemed uneventful and the headache improved, he was discharged and continued to receive follow-up on an outpatient basis. However, 8 months later, the patient experienced headache and vomiting and was readmitted for hydrocephalus recurrence. Because the foramen of Monro was obstructed by a tumor, fenestration of the septum pellucidum and CSF reservoir (Ommaya reservoir) implantation were performed. At the time, since the patient and his family declined tumor resection, everolimus 5 mg (3.0 mg/m^2) was administered to shrink the tumor. Meanwhile, the hydrocephalus was controlled using a CSF reservoir. The symptoms of hydrocephalus improved 16 days after the start of everolimus therapy. The dosage was adjusted to achieve a blood concentration of 5-15 ng/mL. Stomatitis, possibly a side effect of everolimus, was observed. His CT on day 50 demonstrated that the tumor has gotten smaller (Fig. 2a, b, c, d): from measuring 16.1 cm^3 on day 2, the tumor volume has shrunk to 7.2 cm^3 on day 50 after the start of everolimus therapy; this indicates a 55% reduction in size (ellipsoid volume method). On day 49, contrast-enhanced MRI was performed (Fig. 3a, b, c, d), and craniotomy with tumor removal was conducted; explanations during medical treatment were provided, and consent was also obtained.

Surgical findings

Surgery was performed via the interhemispheric approach. The border between the tumor and brain parenchyma was easily discernible, and total tumor removal was achieved. The amount of blood loss was 62 mL, and no blood transfusion was required.

Postoperative course

No postoperative complications were noted. On postoperative day 2, contrast-enhanced brain MRI demonstrated an absence of residual lesions. The hydrocephalus had also

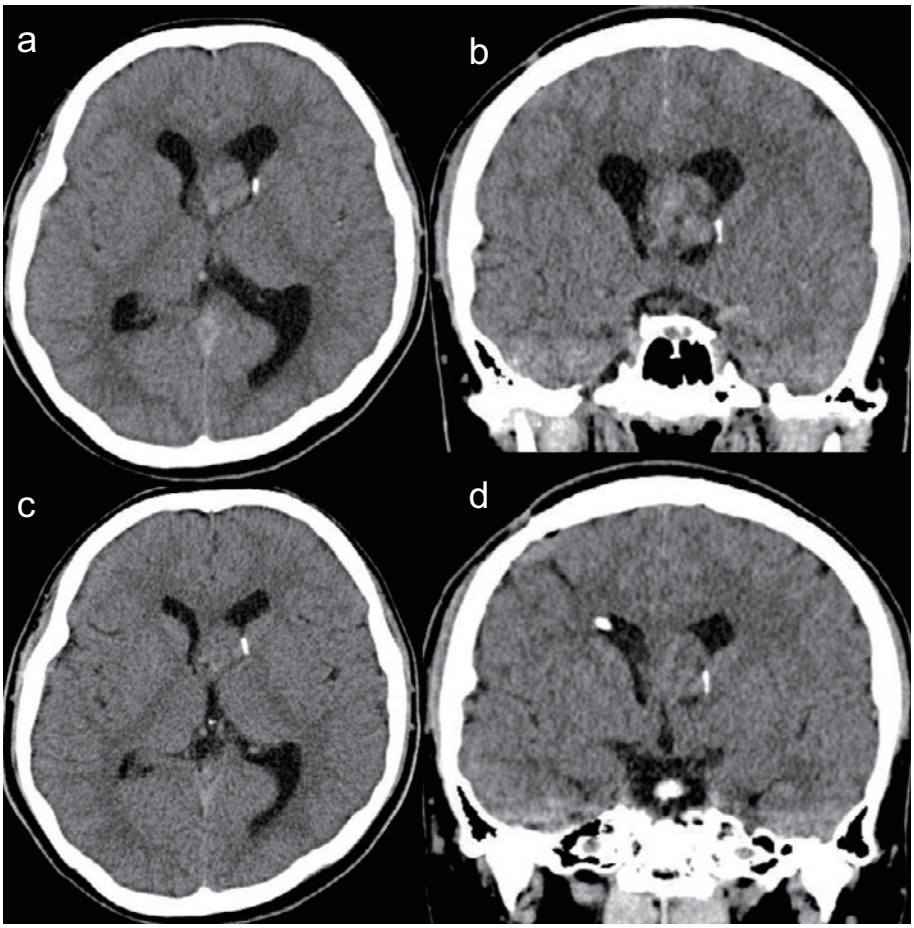

Fig. 2 (a) (b) Axial and coronal computed tomography (CT) after 2 days of oral everolimus administration. Image shows a 30 mm × 37 mm × 29 mm mass with high- to low-density areas in the left lateral ventricle accompanied by hydrocephalus. A subependymal nodule was detected in the lateral ventricular wall. (c) (d) Axial and coronal CT after 50 days of oral mTOR inhibitor administration. Image shows a 25 mm × 24 mm × 24 mm mass with relatively low-density areas.

improved. Everolimus was thereafter discontinued, and the patient was followed up postoperatively. MRI at postoperative month 12 demonstrated no recurrence (Fig. 3e, f).

Pathological findings

The biopsy findings revealed large cells with coarse chromatin in the nucleus and abundant eosinophilic cytoplasm, which lead to the diagnosis of SEGA. All the tumor cells observed were large (Fig. 4a, b). A histological analysis following mTOR inhibitor treatment demonstrated that the previously identified, large tumor cells were still present, but that most of the tumor cells had become smaller (Fig. 4c, d). Thus, although the cellular density appeared high at first glance, the proliferative activity, as indicated by Ki-67, was less than 1% and seemed to have slightly decreased as compared to the Ki-67 observed during the biopsy.

Discussion

TSC is an autosomal dominant genetic disease emerging from mutations in the *TSC-1* or *TSC-2* gene.[10] SEGA is a benign, non-infiltrative brain lesion associated with TSC although it too, albeit rarely, occurs in the absence of TSC.[6,11] *TSC-1* and *TSC-2* are identified to be tumor suppressor genes involved in the same signaling pathway. *TSC-1* is located on chromosome 9, q34, and encodes hamartin, while *TSC-2* is located on chromosome 16, q13, and encodes tuberin. Hamartin and tuberin interact directly and produce the hamartin-tuberin complex, which, in turn, inhibits mTOR activity downstream of the *PI3K-Akt* system. In tuberous sclerosis, the hamartin-tuberin complex fails to function, owing to abnormalities in *TSC-1* or *TSC-2*; this results in increased mTOR activity.[12,13] The mechanism of the development of proliferative lesions in tuberous sclerosis, including SEGA, can be explained by mTOR activation. This fact has led to the development of mTOR inhibitors as therapeutic agents.[14]

Patients with SEGA can achieve dramatic alleviation of their symptoms via gross total resection of the tumor,[15] which is of the highest priority in acute, symptomatic

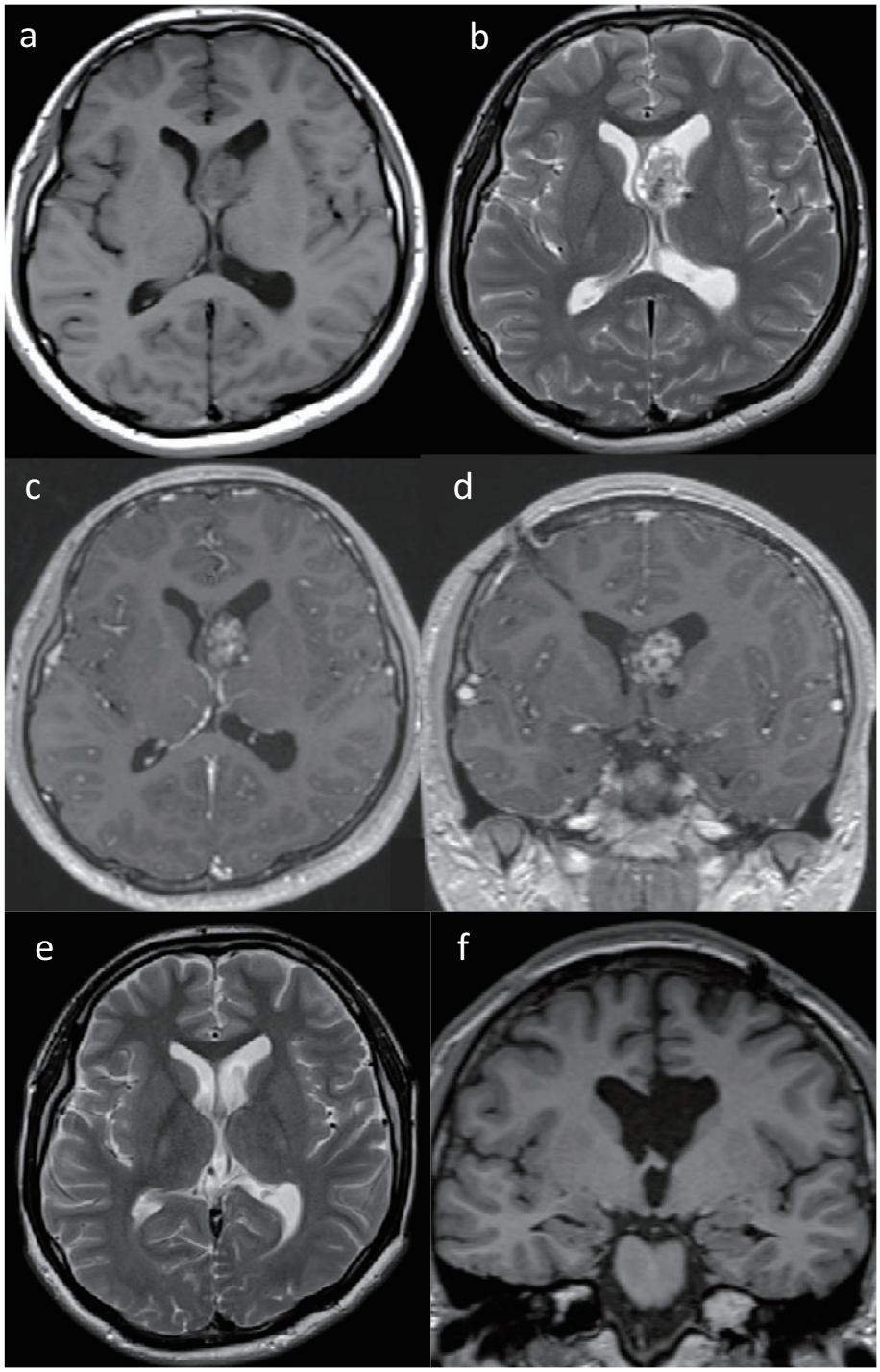

Fig. 3 (a) (b) (c) (d) This is an enhanced magnetic resonance imaging (MRI) at 49 days after everolimus administration. (a) (b) Preoperative MRI of the intracranial tumor. (a) Non-contrast T1-weighted image. (b) Non-contrast T2-weighted image. (c) (d) Contrast-enhanced axial and coronal T1-weighted images. SEGA can be seen near the left anterior horn of the foramen of Monro. The intraventricular tumor consists of enhancing and cystic components with mosaic enhancement. The indicates the ventricular wall at the site of tumor occurrence. (e) (f) Postoperative 12-month follow-up MRI images. (e) Axial T2-weighted sequence. (f) Coronal image on FLAIR (fluid attenuated inversion recovery) sequence. No residual tumor was observed.

cases.[3] If the patient is asymptomatic and without tumor growth, follow-up is acceptable. The treatment of non-acute, symptomatic, or asymptomatic SEGA with tumor growth remains to be controversial. Some reports have suggested that the rate of postoperative complications and the size of SEGA may be correlated.[16,17] The best indication

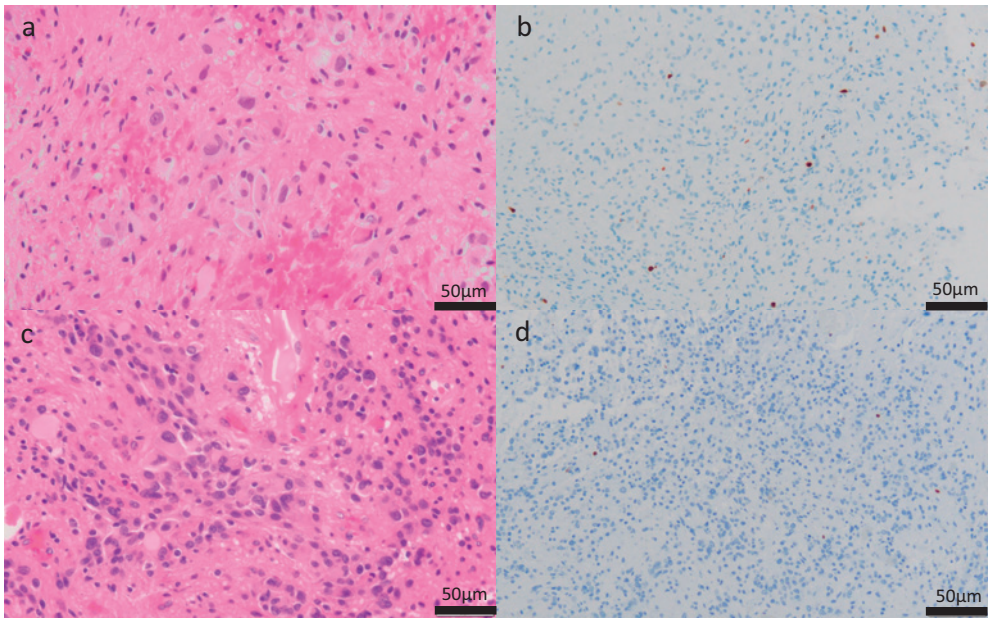

Fig. 4 (a) Pathological specimens of the lesion (H&E staining). Specimens from endoscopic tumor biopsy (H&E staining, ×20). (b) Immunostaining for anti-Ki-67 antibody in the endoscopic tumor biopsy specimen. (c) Pathological specimens of the lesion (H&E staining). Tumor resection specimens. (d) Immunostaining for anti-Ki-67 antibody in a tumor resection specimen. The MIB-1 index was less than 1% in both specimens.

Table 1 Data summary of the five patients with SEGA who received an mTOR inhibitor as neoadjuvant chemotherapy

Author	Age	Sex	Lesion	Other lesions	Treatment period	Tumor size at diagnosis (mm)	Tumor size after mTOR inhibitor (mm)	Extent of tumor resection	Postoperative complications
Jiang [8]	12	M	Left lateral ventricle	Kidney	15 months	38 × 28 × 47	26 × 27 × 25	GTR	None
Jiang [8]	5	M	Right lateral ventricle	Multiple renal cysts	6 months	35 × 30 × 42	30 × 21 × 40	GTR	None
Jiang [8]	5	F	Right lateral ventricle	Multiple renal cysts	1 year	56 × 37 × 65	41 × 27 × 46	GTR	None
Cheng [9]	15	F	Left lateral ventricle	N.D.	3 months	37 × 30 × 35	30 × 20 × 23	GTR	N.D.
Present case	16	M	Left lateral ventricle	None	50 days	30 × 37 × 29	25 × 24 × 24	GTR	None

mTOR, mammalian target of rapamycin; GTR, gross total resection; N.D., not described

for surgery is a tumor size of <2-3 cm and tumor location in a single ventricle. Larger tumors are associated with a higher complication rate.[15,18,19] Therefore, a treatment method in which everolimus is administered preoperatively to shrink the tumor before resecting it has been considered. In fact, the histopathological findings in our case suggested that the mTOR inhibitor inhibited cellular proliferation, which is activated via the mTOR/AKT pathway. The changes shown in the images were consistent with the mild tumor shrinkage observed before and after mTOR inhibitor administration. Therefore, it can be inferred that the effect of mTOR inhibition in SEGA, which is characterized by low cell proliferation, is achieved by reducing the size of the tumor cells themselves and thereby gradually shrinking the tumor.

There have been a few studies examining the efficacy of preoperative medical therapy with everolimus or rapamycin.[8,9] Table 1 summarizes the findings of these reports and those of the current case. Thus far, five cases of preoperative medical therapy with an mTOR inhibitor (everolimus or rapamycin) have been reported, including this present case. The patients' age ranged from 5 years to 15 years. Although the duration of treatment varied, everolimus was administered as medical therapy in all the cases to shrink the tumor before gross total removal. There were no postoperative complications during the follow-up period. The most notable feature of our case was that it had the shortest duration of everolimus treatment (less than 2 months)

of all the reported cases, which nonetheless reduced the tumor size sufficiently. The concern regarding the administration of mTOR inhibitors is its potential adverse effects. However, according to previous reports, most of these adverse effects are relatively easy to manage.[19] However, the risks of long-term administration are yet to be elucidated, and the administration of mTOR inhibitors for SEGA requires careful weighing of the risks and benefits. A previous, open-label study of oral everolimus therapy[20] reported that the most significant tumor reduction occurred within the first 3 months of treatment, with 62% of cases achieving a reduction rate of at least 30%; meanwhile, 35% of cases achieved a reduction rate of 50% or more at 3 months after administration. However, one case of tumor enlargement was observed for the first time at 24 months after administration. Based on these findings, it can be concluded that everolimus has a higher likelihood of achieving tumor reduction during the early stages of treatment. Moreover, no cases of increased intracranial pressure or exacerbation of hydrocephalus were observed during its administration. Therefore, considering the potential to reduce SEGA during short-term treatment spanning several months followed by surgical resection, it may be a viable treatment option.

If SEGA demonstrates a tendency toward rapid enlargement or consent for surgery cannot be obtained, everolimus may be considered as an alternative treatment. It is desirable to keep the treatment period as brief as possible; in this present case, tumor shrinkage was confirmed within 50 days of the start of therapy.

Conclusion

Treatment is indicated for symptomatic SEGA with a large tumor size, but the high rate of surgical complications should be taken into consideration. mTOR inhibitors are found to be effective to some extent, but the disadvantages of its long-term administration cannot be ignored.

Neoadjuvant therapy with everolimus for SEGA may be effective in increasing the safety of gross tumor removal. As per the findings of this present study, treatment of less than 2 months' duration may be sufficient to achieve tumor mass reduction.

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Declaration of Patient Consent

The authors certify that the patient provided consent to the publication of his case.

Conflicts of Interest Disclosure

None of the authors have any conflict of interest to declare.

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