Clinical Features, Radiological Profiles, Pathological Features and Surgical Outcomes of Pituicytomas: A Report of 16 Cases and a Pooled Analysis of Individual Patient Data

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Abstract

Background: Pituicytomas are rare neurogenic tumors of the sellar region. The diagnosis and treatment of pituicytoma needs to be further elucidated.

Patients and Methods: This research included 16 patients with pituicytomas that were pathologically diagnosed in Tiantan Hospital from 2012 to 2019. And 68 other previously published cases of pituicytoma to analyze the predictive factors of the results.

Results: Our cohort included 7 males (43.75%) and 9 females (56.25%), with a mean age of 49 years. The tumor was located in the suprasellar in 7 cases (43.75%), intrasellar in 6 cases (37.5%), and intrasellar-suprasellar mixed in 3 cases (18.75%). All patients were misdiagnosed with other common tumors in the sellar region before the operation. During the operation, gross total resection (GTR) of the tumor was achieved in 9 cases (56.25%) and subtotal resection (STR) in 7 cases (43.75%). The mean progression-free survival time (PFS) was 34.63 months. Tumor progression after surgical resection occurred in 5 patients (31.25%). Among them, 57.14% of the patients with STR had progression, while 11.11% of the patients with GTR had progression. Combined with 68 cases in the literature, it was found that GTR was an independent risk factor for PFS ($P < 0.05$).

Conclusions: Pituicytomas are more common in middle-aged people and the suprasellar region. The clinical manifestations of pituicytomas are different, there are no diagnostic clinical features, and its blood supply is abnormally abundant. Currently, GTR is the best approach for the treatment of pituicytomas.

Background

Pituicytoma is a benign fusiform astrocytoma, which originates from the neurohypophysis or pituitary stalk [1–3]. It is a localized, generally solid, low-grade glial tumor that consists of bipolar fusiform cells arranged in bundles or striations [4]. Pituicytomas are exceedingly rare. At present, about 119 cases of pituicytoma have been reported [5, 6].

Pituicytoma can be easily confused with other tumors in the sellar region. However, it can be differentiated from other tumors in the sellar region by microscopic cell morphology and immunohistochemistry [7]. The treatment of pituicytoma generally involves surgical resection [6]. Through reviewing the information of all patients in our hospital from 2012 to 2019, we report 16 patients with pathologically proven pituicytoma and their long-term follow-up results. To the best of our knowledge, this study involves the largest number of pituicytoma cases from a single center. We believe that the clinical, radiological, and pathological features of pituicytomas studied will enable the better diagnosis and treatment of pituicytomas in the future.

Patients And Methods

Clinical data from our center

This research retrospectively analyzed the clinical features and surgical results of patients with histologically diagnosed pituicytoma at Beijing Tiantan Hospital from 2012 to 2019. This research was approved by the Ethics Committee of Beijing Tiantan Hospital. All patients underwent cranial contrast magnetic resonance imaging (MRI) and testing of their hormone levels before the operation. The clinical data were collected by reviewing clinical case information and telephone follow-up and included clinical symptoms, radiographic examination, surgical results, immunohistochemical results, and follow-up results.

Surgical Treatment

The preoperative examination was completed, and contraindications were excluded. All patients underwent endoscopic transsphenoidal surgery or craniotomy under general anesthesia. The extent of tumor resection was divided into gross total resection (GTR) and subtotal resection (STR), obtained from analyzing the postoperative cranial contrast MRI and surgical records. Mucosal flap repair was performed in all patients with definite or suspected cerebrospinal fluid leakage during endoscopic transsphenoidal surgery.

Pathological examination

The tumor specimens of all patients were sent for pathological evaluation, including hematoxylin and eosin (HE) staining and immunohistochemical examination.

Postoperative immunohistochemical staining included GFAP, S100, Vimentin, TTF-1, EMA, CD34, MIB-1, and SYN. Pituicytomas were diffusely positive for S100 protein and vimentin protein, weakly to moderately positive for GFAP, and displayed nuclear immunoreactivity for TTF-1, and flaky positive distribution of EMA in the cytoplasm [8].

Literature research

This study searched the literature about pituicytoma published from January 1958 to January 2020 with the keywords of "pituicytoma". The selection criteria were as follows: (1) patients with pituicytoma confirmed by operation and pathology; (2) patients who had been followed up for more than half a year; (3) cases reported in English literature. The exclusion criteria were as follows: (1) pituicytoma with other intracranial tumors; (2) patients with other space-occupying lesions in the sellar region; (3) cases without follow-up information. The information of each case was carefully reviewed by two authors (J.H.C and D.N) and any repeated cases were excluded. The information collected includes the general condition of the patient (sex, age at the time of diagnosis, location of the tumor) and the treatment (surgical approach, extent of tumor resection, radiotherapy and chemotherapy) and outcome (tumor recurrence or progression). 68 cases of pituicytoma reported in the literature are listed in Supplementary material 1.

Follow-up and statistical analysis

The clinical data of the research included clinical symptoms, radiographic examination, surgical results, immunohistochemical results, and follow-up results were collected by reviewing clinical case information and telephone follow-up. Among them, the clinical history of the patients was collected by the method of retrospective chart review. Potential risk factors assessed included age, sex, tumor size and location, surgical resection extent, and other adverse predictors, such as progression-free survival (PFS). The Cox regression model was used for univariate and multivariate analysis. Use the IBM SPSS statistics software package (version 22.0 IBM Corp). For analysis, the significance was $p < 0.05$.

Results

Clinical Features

Table 1 records the clinical features and treatment of 16 patients with pituicytoma. Pituicytoma occurred in 7 males (43.75%) and 9 females (56.25%), aged from 24 to 65 years, with an average of 49 years. Preoperative symptoms included vision loss (43.75%), dizziness (18.75%), headache (25%), endocrine disorders (6.25%), and asymptomatic patients (18.75%). Of the total, 68.75% were undergoing their first operation for pituicytoma, while 31.25% were due to a recurrence. Notably, case 8 was diagnosed as pituitary adenoma by pathology in the first operation, while the pathological diagnosis of the second operation was pituicytoma.

Imaging characteristics

The lesions were suprasellar in 7 cases (43.75%), intrasellar-suprasellar in 3 cases (18.75%), and intrasellar in 6 cases (37.5%) (A-C, Fig. 1). MRI showed that the boundary of the tumor was clear in 15 cases (93.75%) and unclear in 1 case (6.25%). Contrast-enhanced MRI showed homogeneous enhancement in 8 cases (50%), inhomogeneous enhancement in 8 cases (50%), and cystic degeneration in 3 cases (18.75%). Obvious vascular flow emptiness could be seen in 1 patient (Fig. 1C). The parenchyma of the tumor showed isointense T1 and T2 signal in 10 cases (62.5%), hyperintense T1 and hyperintense T2 signal in 3 cases (18.75%), isointense T1 and hyperintense T2 signal in 3 cases (18.75%). The maximum tumor diameter ranged from 15 to 32 mm, with a mean size of 24.2 mm. The tumor size was 10–30 mm in 14 cases (87.5%) and larger than 30 mm in 2 cases (12.5%). The tumor compressed the optic chiasma in 12 cases (75%) (Fig. 1D) and invaded the cavernous sinus or internal carotid artery in 5 cases (31.25%) (Fig. 1E). The tumor both oppressed the optic chiasma and invaded the cavernous sinus or internal carotid artery in 3 cases (18.75%) (Fig. 1F).

In our study, all patients were misdiagnosed before surgery. Among them, 5 patients (31.25%) were misdiagnosed as craniopharyngioma and 11 patients (68.75%) were misdiagnosed as pituitary adenoma.

Surgical treatments and outcomes

All patients underwent surgical resection, including 11 cases (68.75%) of craniotomy and 5 cases (31.25%) of endoscopic transsphenoidal surgery, standard transsphenoidal approach in 4 cases (80%) and extended transsphenoidal approach in 1 case (20%) (Supplementary material 2). GTR was performed in 9 cases (56.25%) and STR in 7 cases (43.75%). During the operation, the tumor was found to be hard in 11 cases (68.75%), soft in 2 cases (12.5%), and uneven in 3 cases (18.75%). All tumors were red or grayish red, and the blood supply was extremely abundant, of which 2 cases (12.5%) received an intraoperative blood transfusion because of excessive bleeding. In the craniotomy, the postoperative complications included hypopituitarism in 5 cases (31.25%) and intracranial infection in 2 cases (12.5%). In our case, there were 5 patients (31.25%) with diabetes insipidus due to hypophysis after operation. The average postoperative hospital stay of patients undergoing craniotomy was 18.36 days (range: 8–48 days). No hypophysis and intracranial infection occurred after endoscopic transsphenoidal surgery. The average postoperative recovery time was 8.2 days (range: 6–10 days). Figure 2A-C shows the resection of tumors during endoscopic transsphenoidal surgery.

After long-term follow-up, it was found that no patient received radiotherapy or chemotherapy after operation. Recurrence occurred in 5 patients (31.25%) after the operation, with an average recurrence time of 48.6 months. The patients with postoperative recurrence received surgical treatment again in our hospital.

We further analyzed the factors affecting tumor progression. The average follow-up time for the whole group was 34.63 months. Five cases (31.25%) had tumor progression or recurrence, and the average PFS was 48.6 months. Tumor progression accounted for 80% of STR and 20% of GTR. On the whole, 57.14% of the patients with STR had progression, while 11.11% of the patients with GTR had progression.

Pathological examination

After HE staining, the tumor cells were seen to be spindle-shaped, and the nucleus was deeply stained under the light microscope (Fig. 2D-F). The immunohistochemical results showed that all patients were S100 positive, 11 were TTF positive (68.75%), 8 were GFAP positive (50%), 1 was Vimentin positive, 12 were EMA positive (75%), 5 were CD34 positive (31.25%), and 2 were SYN positive (12.5%). The Ki-67 proliferation index was between 1% and 3% in 10 cases (62.5%), and more than 3% in 6 cases (37.5%).

Statistical analysis of prognostic factors of PFS in summary cases

After literature search, we collected the information of another 68 patients with complete data and follow-up data who were diagnosed as pituicytoma, plus our 16 patients, a total of 84 patients were analyzed for prognosis. Overall, the average age of the patients was 47.65 years old, and the median age was 40.0 years old, of which 40 (47.62%) were males, 44 (52.38%) were females, 45 cases (53.57%) were suprasellar tumors, 22 cases (26.19%) were intrasellar-suprasellar tumors, and 17 cases (20.24%) were tumors in the intrasellar. We further analyzed the factors affecting tumor progression. The average follow-up time for the whole group was 29.32 months (median follow-up time: 24 months). Nineteen cases (22.62%) had tumor progression or recurrence, and the average PFS was 35.73 months. The multivariate analysis showed that total tumor resection was an independent risk factor for PFS (HR = 4.13, 95% CI = 0.902 to 18.417, $P = 0.048$) (Table 2). The Kaplan–Meier analysis showed that the extent of tumor resection affected the PFS of patients (Fig. 2G).

Further analysis of the impact of the surgical approach on gross total resection of the tumor, it was found that craniotomy approach to achieve GTR accounted for 40%, transsphenoidal approach to achieve GTR accounted for 46%. The total resection rate of tumors in intrasellar, intrasellar-suprasellar, and suprasellar was 64.28%, 29.17%, and 47.82%, respectively.

Discussion

Pituitary tumor is extremely rare and has a high misdiagnosis rate. Compared with pituitary adenoma and craniopharyngioma, pituitary tumor is an anecdote. Therefore, it is delusional to think that pituitary tumor can be diagnosed before operation in the diagnosis and treatment of sellar region diseases. However, the statistical analysis of large sample can provide help for the preoperative diagnosis of pituitary tumor, in order to choose a more suitable surgical approach, but also provide better preparation for difficult intraoperative bleeding.

Epidemiology and clinical characteristics

Pituitary tumor, which is a low-grade neurogenic tumor (WHO I), is a very rare spindle-shaped astrocytic tumor that originates from the posterior lobe or stalk of the pituitary [9, 10]. Until now, only 4 articles have reported more than 6 cases of pituitary tumor [11–14]. This makes it challenging to obtain useful, detailed, and accurate information regarding the diagnosis and treatment of pituitary tumors. The number of cases reported in this study is currently the largest number reported by a single center. From the case data we reported, there was no significant gender difference, which was slightly different from the larger number of male patients reported in the previous literature [15]. Pituitary tumors can occur at any age but are more common in the middle-aged and elderly [16]. In our study, the average age of onset of patients was 49 years (range: 24 to 65 years). The clinical symptoms of pituitary tumors vary due to the different sizes and locations of compression. Some of the adenohypophyseal insufficiency found in the patients in this study without diabetes insipidus is due to the gradual, dorsal and non-destructive extension of the tumor at the lowest part of the pituitary stalk, which can cause vasopressin to leak into the systemic circulation before reaching the affected segment of the pituitary stalk, while the hypothalamic release factor through the pituitary portal system is interrupted and the tumor growth oppresses the optic nerve, resulting in visual field damage and pituitary compression. Causes pituitary dysfunction and headaches, and oppresses the hypothalamus to cause mental health symptoms [4, 17, 18]. Some patients also have hyperprolactinemia due to secondary hyperprolactinemia caused by hypothalamic dopamine transport disorders caused by funnel compression [19], as in case 5, who had slightly increased prolactin before the operation. Most of the reported pituitary tumors have clear boundaries, and a few have been reported to invade the cavernous sinus [20, 21].

Radiological features

Pituitary tumors are easily confused with other tumors in the sellar region, such as pituitary adenomas and craniopharyngiomas. Pituitary tumors are mostly located in the suprasellar region. However, some are located in the sellar or the sellar-suprasellar. Most of the pituitary tumors are uniformly enhanced, some are inhomogeneous, and some cystic degeneration can be seen [22]. MRI showed that the tumors were solid masses, and most of them had clear boundaries. It has been reported in the literature that pituitary tumors are isointense on T1-weighted images and slightly hyperintense or iso-intense on T2-weighted images [23]. In our cases, most pituitary tumors showed iso-signal on T1-weighted images, slightly hyperintense or iso-signal on T2-weighted images. Some cases showed hyperintensity on T1-weighted T2-weighted images. Some authors suggest that the early contrast enhancement of dynamic MRI or angiography should be used as a differential feature, which reflects the high vascularity of pituitary tumor [24, 25]. The empty shadow of vascular flow can be seen on T1-weighted images in case 1, indicating that the blood supply of the tumor was abundant. Although pituitary tumor has no special imaging features, they display no calcification on CT and can be distinguished from craniopharyngioma. Pituitary adenomas are homogeneously enhanced and easily invade the surrounding tissues, which can be distinguished from pituitary tumors. Pituitary tumors can be distinguished from other tumors in the sellar region by these radiological characteristics. It is worth noting that pituitary tumor lacks calcification and rarely has cystic changes, which help to distinguish them from ameloblastic craniopharyngiomas in the sellar region or suprasellar region.

Pathogenesis findings

The final diagnosis of pituitary tumor depends on the pathological findings. During the operation, the boundary of pituitary tumor is clear, and most are tough and smooth. There have been a few reports of soft texture or cystic degeneration [7, 26]. Most of the tumors are red or grayish red, with abundant blood supply and no invasion of the surrounding tissue. It can be challenging to distinguish the adhesion between the tumor originating from the pituitary stalk and the posterior pituitary lobe [27]. Immunohistochemical staining showed that S-100 was strongly positive [28], GFAP could be invisible or weakly positive [7, 29], EMA was rarely positive, and positive TTF-1 was helpful for the diagnosis of pituitary tumor [8]. In our 16 cases, S-100 immunoreactivity was strongly positive, which was consistent with the diagnosis of pituitary tumor.

Treatments and outcomes

At present, the pathogenesis of pituitary tumor is still unknown. They are theoretically benign biological behaviors with neither malignant histological features nor tumor-derived metastasis. Currently, the GTR of tumors is the primary treatment. The surgical approach includes transfrontotemporal craniotomy and a transnasal transsphenoidal approach. Compared with craniotomy, transsphenoidal surgery is minimally invasive and can reduce the risk of postoperative complications. The transsphenoidal approach includes standard transsphenoidal approach and extended transsphenoidal approach. For giant pituitary tumors invading cavernous sinus, the extended transsphenoidal approach is adopted to achieve the purpose of total resection. Most of the patients with poor preoperative vision have varying degrees of clinical improvement after operation, and most of the patients with deteriorated vision are patients undergoing craniotomy. However, the effect of the surgical approach on the GTR rate of pituitary tumors needs to be further evaluated. Due to the rich blood supply of the tumor, uncontrollable bleeding is often encountered in the process of tumor resection, which leads to subtotal resection of the tumor [30–32]. However, angiographic studies become inevitable before reoperation, and another goal is to rule out the existence of vascular iatrogenic lesions [33]. In most of the reported literature, pituitary tumors show inert growth, have a long recurrence cycle, and patients with subtotal resection are more likely to relapse [7, 28, 34]. However, there are still cases of recurrence after GTR [18, 34]. In our research, we also confirmed the effect of tumor resection extent on tumor progression. A

retrospective analysis of previous cases found that gender is also one of the potential factors that affect tumor progression, but further verification is needed. Some authors suggest that stereotactic segmentation or conventional radiotherapy should be used systematically to control tumor residue during subtotal resection of tumors[35], while others suggest that these treatments are limited to smaller tumors that do not affect visual acuity[36], but further data are needed to prove the effect. Recently, Mende et al has proved strong immunostaining of vascular endothelial growth factor receptor (VEGF-R) in a small series of pituitaryoma [14]. Based on these results, anti-VEGF-R therapy (bevacizumab) and somatostatin analogues may be a promising treatment option, although its use has not yet been approved.

Conclusions

In summary, pituitaryoma is exceedingly rare and is easily misdiagnosed as another type of tumor in the sellar region, such as pituitary adenoma, and craniopharyngioma. Currently, GTR of the tumor is the most effective treatment. Pituitaryoma has no specific radiological features, and the diagnosis needs to be pathologically confirmed. The blood supply of the tumor is very abundant. Reducing intraoperative bleeding so as to increase the total resection rate of pituitaryoma should be studied in the future. Although, as we emphasized above, making an accurate suspicious diagnosis is an extremely difficult task.

Abbreviations

GTR:Gross total resection, STR:subtotal resection, ETS:Endoscopic transsphenoidal surgery,PFS:Progression-free survival

Declarations

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Author contributions

PZ and JC conceived and designed the study. JC, BL, and DN conducted the data analysis. CL, SG, ZZ performed the sample collection and analysis. JC and PZ wrote the manuscript. Luigi Maria Cavallo revised the paper and gave some recommendation. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University (Beijing, China).

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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Tables

Table 1 Clinical, radiologic, and pathological characteristics of 16 pituicytomas

No	Sex/age, years	Signs and symptoms	Tumor location	Surgical approach	Extent of resection	Radiology	Postoperative complications	Immuno-histochemistry	PFS/ month
1	M/46	dizzy	Suprasellar	Craniotomy	GTR	solid	hypophysis, intracranial infection	S100(+), EMA(+), TTF-1(+),ki67(2%)	12/0
2	F/46	None	Suprasellar	Craniotomy	GTR	solid	hypophysis	S100(+),GFAP+/-, TTF-1(+),EMA(+),CD34+/-,ki67(1%)	34/1
3	F/47	headache	Intrasellar	ETS	GTR	solid	hypophysis, intracranial infection	GFAP(+),TTF-1(+),CD34(+),S100+/-PR(+),EMA+/-, ki67(1%)	34/0
4	M/63	Vision loss	Intrasellar and suprasellar	ETS	STR	Uneven softness and toughness	None	S100(+),GFAP+/-, TTF-1(+),EMA(+),ki67(1%)	36/1
5	F/60	Decreased vision with headache and dizziness	Suprasellar	Craniotomy	GTR	solid	None	CD68(+),S-100(+),SYN(+),GFAP(+),ki67(5%)	50/0
6	F/50	Vision loss	Intrasellar and right parasellar	ETS	GTR	solid	None	GFAP(+), S100+/-, EMA+/-, ki67(5%-15%)	36/0
7	M/54	Vision loss	Suprasellar	ETS	STR	solid	None	GFAP(+), S100+/-, SYN(+),Vimentin(+),SMA(+),ki67(1%-3%)	64/0
8	M/53	Vision loss	Intrasellar	Craniotomy	STR	solid	None	S100(+),GFAP+/-, TTF-1(+),EMA(+),Vimentin(+),ki67(1%)	88/1
9	M/32	Headache with decreased vision	Suprasellar	Craniotomy	GTR	solid	hypophysis	GFAP(+), S100+/-, EMA+/-, TTF-1(+), ki67(1%-3%)	24/0
10	F/51	Vision loss	Intrasellar	Craniotomy	STR	Uneven softness and toughness	hypophysis	GFAP(+), S100+/-, EMA+/-, TTF-1(+), ki67(1%-5%)	22/1
11	M/55	None	Suprasellar	Craniotomy	GTR	Uneven softness and toughness	None	GFAP(+), S100+/-, SMA(+),CD34(+),ki67(1%)	13/0
12	F/24	Visual field defect	Intrasellar	Craniotomy	STR	solid	intracranial infection	GFAP(+), S100+/-, SMA(+),CD34(+),ki67(1%)	63/1
13	F/65	None	Intrasellar and Suprasellar	Craniotomy	STR	soft	None	S100(+),GFAP+/-, TTF-1(+),EMA(+),ki67(1%)	12/0
14	F/38	Menstrual disorder	Suprasellar	Craniotomy	STR	solid	None	GFAP(+), S100+/-, EMA+/-, TTF-1(+),CD34(+),ki67(4%)	28/0
15	F/54	headache	Intrasellar	ETS	GTR	soft	None	S100(+), EMA+/-, TTF-1(+),CD34(+),SMA(+),ki67(1%-3%)	22/0
16	M/47	dizzy	Suprasellar	Craniotomy	GTR	solid	Hypophysis and anemia	S100(+), EMA+/-, TTF-1(+),ki67(2%)	16/0
GTR = Gross total resection, STR = subtotal resection, ETS = Endoscopic transsphenoidal surgery									

Table 2 Univariate and multivariate analysis prognostic factors in the pooled 84 cases

Variable	Univariate analysis	P-value	Multivariate analysis	P-value
	PFS		PFS	
	HR(95%CI)		HR(95%CI)	
Age > 40yrs	0.838(0.275–2.559)	0.753		
Male	0.267(0.095–0.750)	0.007*	3.169(0.819–12.259)	0.095
Extent of resection(STR)	0.282(0.081–0.991)	0.027*	4.13(0.902–18.417)	0.048*
Tumor location	1.645(0.644–4.204)	0.311		
Surgical approach	1.088(0.411–2.879)	0.866		

PFS=Progression-free survival

Figures

Figure 1

Radiological features of pituitaryomas. (A) The tumor is completely located in the intracellar region. (B) The tumor is located in the intracellar-suprasellar region. (C) The tumor is completely in the suprasellar region. (D) Pituitaryoma has invaded the right cavernous sinus. The lesion has surrounded the internal carotid artery, and the optic chiasma was not compressed. (E) The optic chiasma was oppressed and elevated by the tumor, and the cavernous sinus was not involved. (F) Pituitaryoma can be seen to have invaded the right cavernous sinus, the optic chiasma is compressed, and the tumor is accompanied by cystic degeneration.

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Figure 2

Endoscopic transsphenoidal surgery to remove pituitaryoma. (A) Successfully exposed the saddle bottom and smoothed the bone structure of the saddle bottom. (B) Opening the bottom of the saddle to expose the tumor. It can be seen that the tumor is red, the blood supply is rich, and it is adjacent to the optic nerve. (C) The tumor was successfully removed, and the optic nerve was well protected. (a) Optic nerve; (b) Tumor; (c) Posterior pituitary lobe; (d) Tumor cavity

(D-F) Histopathological examination of the pituicytoma specimen. (G) Kaplan–Meier survival curve showing the effect of tumor gross total resection (GTR) and subtotal resection (STR) with patient’s progression-free survival (PFS). (Chi square= 5.621, p=0.05)

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