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Clinical features of 18 perivascular epithelioid cell tumor cases

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Abstract

To investigate the biological behavior and clinical characteristics of perivascular epithelioid cell tumor (PEComa).

Eighteen PEComa patients admitted to Zhongshan Hospital and the Central Hospital of Xuhui District in China from January 2006 to October 2018 were included. All patients were diagnosed based on pathological findings and treated with surgical resection or medication.

Among the 18 patients, 1 underwent lymph node biopsy for multiple enlarged lymph nodes and 17 underwent mass resection. The median disease-free survival was 22 months after the first resection and over 12 months following a second resection. Treatment with mechanistic target of rapamycin (mTOR) inhibitors was effective for patients with unresectable or metastatic lesions. The median progression-free survival was approximately 13 months.

Surgery is the predominant treatment approach for PEComa and patients can benefit from multiple operations. mTOR inhibitors are considered for patients with multiple lesions or intolerance to surgery. Anti-angiogenetic drugs can be selected when mTOR inhibitors fail to control the illness.

Abbreviations: AML = angiomyolipoma, ASPS = alveolar soft part sarcoma, CCST = clear-cell "sugar" tumor of the lung, DFS = disease-free survival, FISH = fluorescence in-situ hybridization, HMB = human melanoma black, IHC = immunohistochemistry, LAM = lymphangioleiomyomatosis, MITF = melanocyte-inducing transcription factor, MRI = magnetic resonance imaging, mTOR = mechanistic target of rapamycin, NCCN = National Comprehensive Cancer Network, NCI-CTC = National Cancer Institute Common Toxicity Criteria, OS = overall survival, PEComa = perivascular epithelioid cell tumor, PFS = progression-free survival, PR = partial response, SMA = smooth muscle actin, TFE3 = Transcription factor E3, TSC = tuberous sclerosis complex.

Keywords: mechanistic target of rapamycin, perivascular epithelioid cell tumor, transcription factor E3, tuberous sclerosis complex

1. Introduction

Perivascular epithelioid cell tumor (PEComa) belongs to a rare mesenchymal tumor family with unknown origins and exhibits the characteristics of perivascular epithelioid cells, melanocytes, and smooth muscle cells.[1] Angiomyolipoma (AML), lymphangioleiomyomatosis (LAM) and clear-cell "sugar" tumor of the lung (CCST) are typical PEComas. These tumors appear at various sites of the body, with the uterus, retroperitoneum, urogenital system, and gastrointestinal tract most involved.[1] There are several subclasses of PEComa based on markers shown in the tumor including melanocytic markers as human melanoma black (HMB)-45, Melan-A and microphthalmia transcription factor (MiTF), as well as typical smooth muscle markers as smooth muscle actin (SMA) and desmin.[2] Among them, the transcription factor E3 (TFE3) gene fusion subclass shows more expression of melanocytic markers. LAM and AML carry biomarkers of SMA and desmin. Due to their inert behavior, most PEComas respond poorly to chemical therapy or cytotoxic agents; therefore, surgical resection has become the first-line therapeutic approach.[1] However, the potential benefits of biological therapy became apparent following the discovery of the aberrance of certain genes in PEComa patients. Tuberous sclerosis complex (TSC), a type of autosomal dominant genetic disorder, involves the mutation of the TSC1 or TSC2 gene as well as subsequent activation of the mechanistic target of rapamycin (mTOR) pathway, which has been demonstrated to be present in PEComa.[1] TSC2 alterations and TFE3 translocations are mutually exclusive genetic alterations present in PEComas. TFE3 gene fusion is indicative of a tendency of the tumor to young population and the morphologic features of purely epithelioid without spindle cell or fat components.[3] Moreover, TFE3 fusion enhances mesenchymal-epithelial transition factor (MET) promoter activity and imparts an invasive feature to

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Written informed consent was obtained from all the patients for publication of this study.

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

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PEComa.[2,4] Although not being used to figure prognosis, the inhibitors of mTOR or MET are now being expected in the treatment of the disease. Nevertheless, comprehensive investigations on PEComa remain insufficient due to the relatively low incidence. The present study collected and analyzed the clinical data of 18 PEComa cases to elucidate the potency of different therapeutic approaches and the prognosis of patients.

2. Patients and methods

2.1. Basic clinical data

Eighteen PEComa patients admitted to Zhongshan Hospital and the Central Hospital of Xuhui District of Shanghai in China from January 2006 to October 2018 were recruited, including 3 men and 15 women. Age, sex, primary sites of tumor, therapeutic options, immunohistochemistry (IHC) outcome, and follow-up data were recorded (Table 1). The research ethics committee of Zhongshan Hospital reviewed and approved the study protocol before the enrollment of patients. All participants were informed of the details of the study and signed the corresponding consent forms.

2.2. Diagnosis

Pre-operational differential diagnosis of PEComa from other tumors, such as leiomyosarcomas, ectopic pheochromocytoma, lymphoma, neurogenic tumors, and teratoma renal hamartoma, depended on age, tumor sites, size, symptoms, signs, lab tests, and imaging features. A low density (<-20 HU) on computed tomography (CT) scans indicated mature adipose tissue, which supported the diagnosis of angiomyolipoma. The magnetic resonance imaging (MRI) plain scan featured a clear boundary, round edges, and lower signal at the in-out phase, suggesting the presence of little fat. An inhomogeneous high signal on fat-selective suppression T2-weighted imaging indicated hemangioma features in the lesion, which might be related to the composition of the vessels involved. Equal or slightly elevated signal on diffusion weighted imaging as well as a relatively high signal on the corresponding apparent diffusion coefficient images compared to adjacent liver parenchyma indicated more water in tumor or abundant cytoplasm in tumor cells. Unlimited water diffusion and intricate constitution indicated vessel-dominated lesions, which showed a prominent intensified signal in the arterial phase and lower signal in the delayed phase. Tiny, tortuous vessels as well as abnormal supplying arteries or draining veins inside lesions on enhanced MRI scans contributed to the diagnosis of PEComa.

IHC tests were carried out to confirm the diagnosis further. Specimens were collected from all 18 patients through biopsy or surgery and were reviewed by 2 experienced pathologists independently. IHC was conducted by a professional laboratory staff. The differential diagnosis of PEComa from renal cell carcinoma, leiomyosarcoma, and pheochromocytoma was based on the pathological features of the tumor.

The diagnostic criteria recommended by Folpe in 2005 suggest identifying the malignant PEComa on at least 2 of the following items: tumor size >5 cm, aggressive growth, significant nuclear atypia, cell necrosis, mitotic cells ≥ 1/50 high power field (HP) and venous invasion. PEComa with undetermined malignantpotential (PECoMa-UMP) characterizes tumors with only polymorphic or multinuclear giant cells or tumor sizes larger than 5 cm without other histological disorders.

2.3. Therapy and follow-up

The individual therapeutic approach for each patient was determined by multiple departments engaged in the treatment of soft tissue tumors and was conducted by experienced physicians. The follow-up parameters included overall survival (OS) from the confirmation of diagnosis, disease-free survival 1 (DFS1) from the first complete resection, DFS2 from the second complete resection, progression-free survival (PFS) during the medical therapy as well as grade III or IV toxicity. Evaluation of the therapeutic effect was based on the effect evaluation criterion for solid tumors described by WHO (RECIST 1.1), while evaluation of the side effects or toxicity was based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC 2.0).

2.4. Statistical analysis

SPSS Statistics 19.0 software was employed for all survival analysis.

3. Results

The primary onset age of the 18 PEComa patients was from 23 to 53 years, with a median age of 38 years. The manifestations involved abdominal distension and pain, backache, hematuria, and slight fever. The tumor was found during physical examination or accidentally in 4 cases. The maximal size of the mass was from 2 to 25 cm, with an average of 11.1 cm. Eight patients (8/18, 44%) had a tumor in the retroperitoneum, among which 62% (5/8) was in the kidney.

IHC detected SMA in 13 of 16 cases (81.2%), melan-A in 10 of 17 (94%), S-100 in 8 of 15 (53.3%), ≥30% of Ki67 in 3 of 14 (21.4%) and ≤5% of Ki67 in 8 of 14 (57.1%). Two patients underwent a fluorescence in-situ hybridization (FISH) assay, which showed no rearrangement of the TFE3 gene. Four patients received gene sequencing and no TSC1/TSC2 mutation was found.

Among the 18 patients, 1 underwent lymph node biopsy for multiple enlarged lymph nodes with the diagnosis of LAM and 17 were subject to mass resections. The median OS (mOS) was from 18 to 151 months. Fourteen in 18 patients underwent complete tumor resection after the primary diagnosis and the post-operational median DFS1 (mDFS1) was 22.0 months with a 95% confidence interval (CI) ranging from 17.6 to 26.4 months (Fig. 1).

The 18 patients were divided into malignant and UMP subgroups, which showed significantly deviated DFS1 curves. The malignant subgroup had an mDFS1 of 20 months with a 95%CI from 15.8 to 24.2 months, whereas the UMP group had no mDFS1 due to the few case number and a short follow-up time, which was inadequate for statistical analysis (Fig. 2).

Eight patients relapsed during the study. Five of them underwent a second complete resection and had a DFS2 from 12 to 89 months. One patient underwent resection 5 times. Six patients received mTOR inhibitor treatment and the median PFS was 13 months with a 95%CI from 4.4 to 21.6 months (Fig. 3). Grade II oral mucositis occurred in 2 patients, who recovered after reducing the sirolimus dosage and gargling a kangfuxin solution. Nine patients remained in a DFS state till the end of the study.

4. Discussion

The present study aimed to offer more insight on the manifestation of PEComas. Among the 18 patients evaluated, one underwent lymph node biopsy for multiple enlarged lymph

Table 1

Clinical information for 18 PEComa cases in the study.

				Immunohistochemistry								Follow-up	
cases	Age/Sex	Primary site (Size cm)	Therapy	SMA	Desmin	Melan-A	HMB45	TFE3	S-100	Vimentin	Others	Effect	Current state
1	30–40/F	Retroperitoneum 7 × 5 (Possibility of left kidney invasion)	Ivermos, Sotan and Tumor Resection operation	focal+	–	–	part+	part+	–	+	ki67: 40%	Ivermos PFS: 9 m; OS: 18 m	DOD
2	20–30/F	Retroperitoneum 10 × 6 (left kidney invasion)	Operation	+	few+	–	+	+	–		ki67: 10%		NED (15 m)
3	40–50/F	Retroperitoneum 8 × 7 × 4 (right kidney invasion)	Operation	+	–	+	scattered +	+/-	focal+	–	ki67: 2%		NED (16 m)
4	40–50/F	Retroperitoneum 3.5 × 2 (left)	Operation	+	part +	–	few +		–		ki67: 5%		NED (20 m)
5	20–30/F	Retroperitoneum 25 × 22 × 8 (left kidney invasion)	First operation, second operation after relapse	+	part +	+	+		+		ki67: 1%		NED (20 m)
6	30–40/F	Left pelvis 8 × 8	Palliation, chemotherapy, radiotherapy, Apatinib, ivermus and sirolimus								P70S++, PTEN (+/–), 4EBP1++, mTOR100%+ +~+++ pmTOR- TSC2+ +	Ivermos PFS: 4 m, sirolimus: 5 m, OS: 33 m	DOD
7	50–60/F	Retroperitoneum 11×11×9.5 (right kidney invasion)	Operation	+	+	part +	scattered +		focal+		ki67 <2%		NED (26 m)
8	30–40/F	Left kidney 8 × 6 × 5	Two partial nephrectomies, 1 partial lobectomy	+		+	–		–			OS: 128m	DOD
9	40–50/M	Left kidney 14 × 7	Left nephrectomy, Second operation after relapse	+	–	+	+		part+		Ki67: 30%, mitotic nuclear: 2 /50 HPF		NED (29 m)
10	40–50/F	Left retroperitoneum 17 × 11 × 8	Operation	–	few+	+	+	+ FISH-	–		ki67: 30%		NED (28 m)
11	20–30/M	Left kidney; 16.7 × 11.4	Partial left nephrectomy, Left lower lobectomy, radical left nephrectomy	part +	–	+	+		part+	++	ki67 <2%	OS: 45 m+	lost
12	30–40/F	Right liver lobe; 14 × 6	Five tumor mass resections, Sirolimus, intervention	few+	–	–	+		+	–	ki67: 10% mTOR50%+ PMTOR-; TSC1, TSC2 no mutation	sirolimus PFS: 13 m; OS: 151 m+	AWD
13	40–50/M	Multiple enlarged lymph nodes, maximum diameter 4 × 3	Sirolimus			+	few +			+	TSC1, TSC2 no mutation	sirolimus PFS: 83 m+	AWD
14	30–40/F	Right pelvic wall; 13 × 4 × 3	Operation, Sirolimus	++++	+	–	+				TSC1, TSC2 no mutation	sirolimus PFS: 64 m+	AWD
15	40–50/F	Left liver lobe; 15 × 13 × 12	Operation, local treatment, Sirolimus	–		focal+	part +		-		ki67: 5%, mTOR-, PMTOR (part+), mitotic nuclear >5/HPF, TSC1, TSC2 no mutation	OS: 33 m+	lost
16	30–40/F	Pelvic Sacral region; 8 × 7.5	Post-palliatio	–	–	–	++		–	–	ki67<1%		lost
17	20–30/F	Left lower abdomen 2 × 1 × 1	Operation	Vascular wall+		–	++		++	vessel+	ki67: 15%, mTOR+, PMTOR (part+), TSC2++		NED (38 m)
18	50–60/F	Retroperitoneum 16 × 12 × 7	Operation	+	+	part +	+	FISH-	+	–	ki67: 2%		NED (14 m)

AWD = alive with disease, DFS = disease-free survival, DOD = died of disease, NED = no evidence of disease, OS = over-all survival, PFS = progression-free survival.
Follow-up data was updated on October 31, 2018.

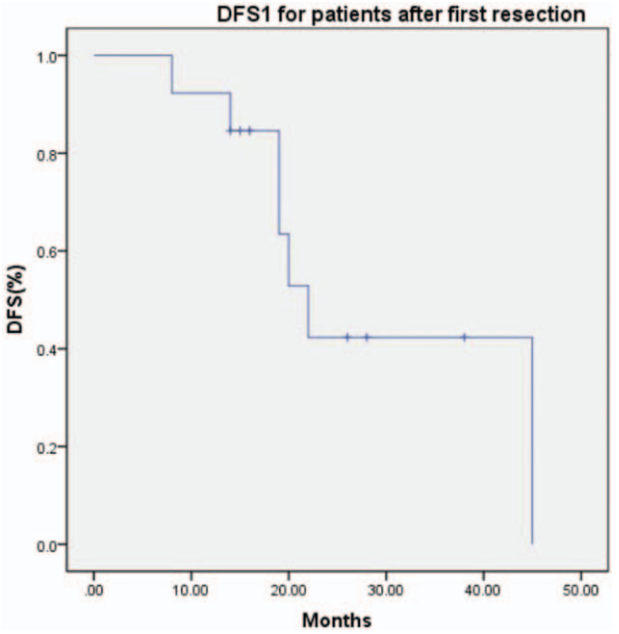

Figure 1. Disease-free survival 1 (DFS1) of PEComa patients after the first complete tumor resection.

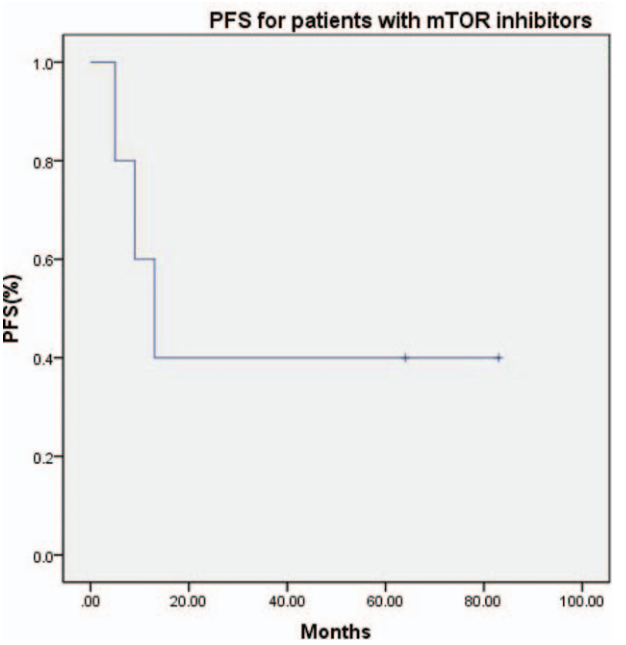

Figure 3. Progression-free survival (PFS) of PEComa patients with mTOR administration.

nodes and 17 received mass resections. The mOS ranged from 18 to 151 months and the survival time was closely related to malignancy. Eight patients relapsed during the study, 5 of whom underwent a second complete resection, with DFS2 ranging from 12 to 89 months. Six patients received mTOR inhibitor treatment with a median PFS of 13 months.

The proportion of female to male patients in this study was 5:1, consistent with the notion that PEComas are more likely to occur in women. Retroperitoneum was the most common site for PEComa. Due to the dormant nature, the tumor is usually found with a large mass and a tendency to invade surrounding tissues such as the kidneys, which might elicit compression symptoms. Most of the PEComas showed inertial behavior and were resistant to radiotherapy and traditional cytotoxic drugs; hence, surgical resection has become the predominant treatment. In the present study, the mDFS was 22 months after the first complete resection. For local relapse after the first resection, a second surgery was performed for 5 patients who had a DFS2 of over 12 months. Repeated recurrence resulted in 1 patient receiving surgery 5 times.

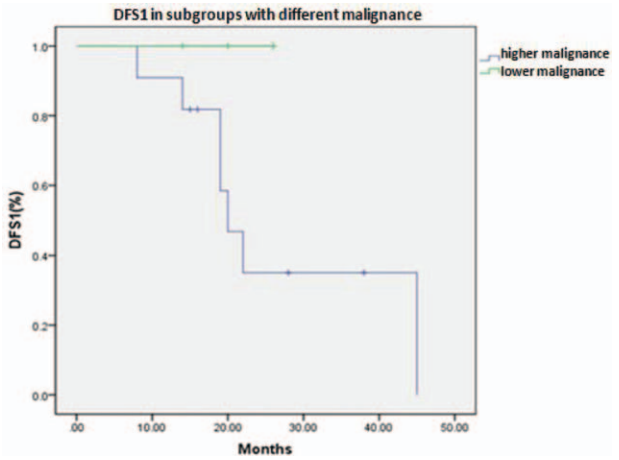

Figure 2. DFS1 for PEComa patients in subgroups with different levels of malignance after the first complete tumor resection. DFS = disease-free survival.

Some PEComas are related to TSC, an autosomal dominant disease, which involves the mutation of TSC1 in 9q34 (27%) or TSC2 in 16p13.3 (73%). TSC1 and TSC2 encode hamartin and tuberin, respectively, and their heterodimer suppresses the Rheb/mTOR/p70S6K signal pathway, inhibiting mTORC1 kinase. The mutation of TSC1 or TSC2 activates the mTOR pathway abnormally, promoting cell proliferation and angiogenesis. This process has also been reported in TSC-irrelevant PEComa, where the IHC staining of p70S6K was positive and treatment with mTOR inhibitors was effective.[1]

The studies on PEComa patients are quite less, most of them being case report containing 1 to 5 cases.[3,5,6] In a retrospective analysis on 53 cases, mTOR inhibitors created a 41% of objective response rate (ORR) and a 9 months of mPFSin patients with locally advanced or metastatic PEComa.[5] However, due to the lack of prospective data, the evidence level for mTOR inhibitors for PEComa therapy is 2 A in the National Comprehensive Cancer Network (NCCN) guidelines.[7–9] In the present study, the mPFS for patients who received mTOR administration was 13.0 months, with a 95% CI from 4.4 to 21.6. Among them, 1 patient was primarily given everolimus, but the condition could not be controlled. Sirolimus was subsequently prescribed and showed a clear curative effect. Four patients chose sirolimus as the first approach, and the maximum oral administration time was 83 months. These patients obtained satisfactory results and reached the partial response (PR). Side effects and toxicity were also present, including skin erythema nodosum in 1 case and oral mucositis in 2 cases. These symptoms were restrained by

adjusting the mTOR inhibitor dosage according to the rapamycin concentration in the blood, which was then held at the dose of 5 to 15 ng/mL. IHC showed strong positive staining of mTORC1 in these 4 patients, but gene sequencing identified no TSC1 or TSC2 mutation. Thus, even though the common viewpoint supports that TSC1 and TSC2 gene mutations account for the activation of the mTOR pathway and the sensitivity of tumor to mTOR inhibitor, our study demonstrated that PEComa without TSC1/2 gene disorders can also benefit from mTOR inhibitor treatment.

TFE3 lies on the short arm of the X chromosome and is 1 of the 4 members of the helix-loop-helix MiT transcription factor family.[10,11] Argani et al identified the TFE3 fusion gene using the FISH technique in 29 PEComas patients, revealing 5 with an aberrant TFE3 gene and 4 with strong overexpression of the TFE3 protein. Folpe and Dickson[12,13] reported that 30% to 100% of PEComa cases showed different levels of TFE3 protein expression. PEComa with TFE3 fusion behaves more invasive, with local recurrence and distant metastasis rates of 8.7% and 20.3%, respectively.[14] However, this is just a possible finding instead of a confirmative viewpoint. Researches on large number of cases with or without TFE3-rearranged feature should be conducted to compare the pathological manifestation, clinical information and survival time before a conclusion being drawn. Additionally, 72% of PEComa cases without TFE3 fusion are accompanied by TSC2 mutation.[15] The mechanism behind the role of TFE3 gene rearrangement in PEComa might be same as that of other TFE3-related tumors such as alveolar soft part sarcoma (ASPS) and renal cell carcinoma with Xp11.2 translocation, in which TFE3 gene fusion elicits binding of it with MET promoter and activation of MET pathway.[16] Therefore, for PEComa with TFE3 gene fusion, MET inhibitors should be a reasonable treatment choice. Four patients in the present study underwent IHC assays to detect TFE3 protein. However, the results showed different levels of expression, but not strong positive staining. Even in 1 case, FISH confirmed no expression of TFE3. Based on the above findings, strict criteria need to be established for the detection of TFE3 gene fusion and the subsequent diagnosis of PEComa.

Anti-angiogenesis drugs can also be applied when the standard therapeutic approach is unavailable or no specific target gene is found. From the pathomorphological view, tumors located around the blood vessels radially are sensitive to the antiangiogenic therapy. A case report had shown the therapeutic benefits of antiangiogenic agents such as pazopanib, sorafenib and sunitinib in treating PEComa which achieved a 8.3% of ORR and 5.4 months of mPFS.[5] If possible, VEGFR2 and PDGFR assays are also suggested. Two patients in the present study were tentatively given Sotan and Apatinib, but the treatment was stopped due to hypertension and drug-induced liver injury. Beyond that, pazopanib, a tyrosine kinase inhibitor, has been used to treat PEComa, and exhibits certain effects with PFS from 0.9 to 9.6 months.[1,17,18] In terms of the anti-tumor outcomes of nano-rapamycin, a multicenter phase II clinical trial on the use of ABI-009 (Nab-rapamycin) for PEComa (NO. NCT02494570) is ongoing and the results are highly anticipated.

5. Conclusions

In summary, we analyzed the clinical and pathologic data of 18 PEComa patients. The results demonstrated that surgery was most frequently adopted to treat the disease and the prognosis was satisfactory. mTOR inhibitors appear to be effective that can even benefit patients without TSC1 or TSC2 mutation. Anti-angiogenetic drugs may be another choice when mTOR inhibitors fail to control the situation.

5.1. Ethics approval and consent to participate

This study was approved by the ethics committee of Zhongshan Hospital and the Central Hospital of Xuhui District. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The written informed consent was obtained from all the patients.

Author contributions

RJ analyzed and interpreted the patient data regarding the PEComa, and was a major contributor in writing the manuscript. XY made the main idea of the paper. YZ gave the modification of the paper. LJ, YW and XG gather the data of cases. YJ and XN performed the histological examination of the cases. All authors read and approved the final manuscript.

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