A single-center analysis of clinical features of 145 tuberous sclerosis complex—associated renal angiomyolipoma cases in China

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Research

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Abstract

Background: Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disease with multiple organ system involvement. Renal angiomyolipoma (RAML) is a leading cause of death in TSC-adult patients. The aim of the study was to investigate the clinical features of tuberous sclerosis-associated renal angiomyolipoma among Chinese population so that clinicians can make better clinical diagnosis.

Methods: Retrospective review of clinical data of 145 patients with tuberous sclerosis-associated renal angiomyolipoma treated in the Department of Urology, Peking Union Medical College Hospital from January 2014 to January 2019. Analysis of age and gender distribution, tumor stage, and combined clinical manifestations. All analyses used a significance level of 0.05 and were presented in SPSS23.0 software.

Results: A total of 145 patients were enrolled. There were 51 males and 94 females. The male to female ratio was 1:1.84, with mean age of 30.50 ± 9.79 years (range 7-58 years). 92 cases were mainly distributed in 21-40 age group, accounting for 63.45%. Among all 6 age groups, 21-30 age group contained the largest number of patients (48 cases, 33.10%). 86 (59.31%) renal angiomyolipoma cases were classified stage 6; 19 cases had a history of tumor rupture and hemorrhage, including 7 selective arterial embolization, 8 partial nephrectomy and 4 nephrectomy. Subependymal nodules (104/122 cases, 85.24%), angiofibromas /fibrous cephalic plaque (121 cases, 83.44%), hypomelanotic macules (89 cases, 61.39%), shagreen patch (65 cases, 44.83%) and ungual fibromas (62 cases, 42.07%) were the main combined clinical manifestation. 91.30% (42/46) lymphangioleiomyomatosis cases were female.

Conclusion: Patients with TSC-RAML were mainly young and middle-aged females with giant Angiomyolipoma. Most tumor were ranged in stage 5 and 6. Nervous system characteristics (subependymal nodules), dermatological lesions (angiofibromas or fibrous cephalic plaque, hypomelanotic macules, shagreen patch and ungual fibromas) were common combined clinical manifestations. Lymphangioleiomyomatosis showed an obvious difference in gender distribution

Background

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disease^[1]. The pathogenesis is the mutation of TSC1 or TSC2 gene, resulting in excessive activation of the mammalian target of rapamycin (mTOR) pathway, which causes disorders of cell

growth, proliferation, and angiogenesis. The target organ of TSC includes the nervous system^[2], skin^[3], kidney^[4], heart^[5], lung^[6], liver^[7] and almost every organ. As a rare disease with an incidence of 1/5800^[8], few major cases report the clinical characteristics of TSC at home and abroad. In order to improve the understanding of this disease, this article reviews and analyzes retrospectively clinical characteristics of 145 patients with tuberous sclerosis complex-associated renal angiomyolipoma (TSC-RAML) diagnosed in Peking Union Medical College Hospital from January 2014 to January 2019.

Methods

Patient

From January 2014 to January 2019, 145 patients with TSC-RAML diagnosed in Department of Urology of Peking Union Medical College Hospital were enrolled. The clinical featuresimaging of CT scan of head, chest and abdomen, ophthalmoscope and ultrasound results were retrospectively analyzed.

Diagnostic criteria

Clinical diagnosis according to criteria of 2012 International Tuberous Sclerosis Complex Consensus Conference^[9]Table 1. 11 major features and 6 minor features were adopted.

RAML Imaging Clinical Classification Standard

The size, number, and kidney morphology of RAML were evaluated by MRI or CT, as shown in Table 2^[10].

Statistical Analysis

Data were expressed as the mean ± standard deviation (M ± SD) or n (%). All statistical analyses were performed with IBM SPSS Statistics 23. Statistical significance was determined by Chi-square test or unpaired Student’s t-test in cases of standardized expression data. P < 0.05 was considered statistically significant.

Table 1 Clinical diagnostic criteria

Major features

1. Hypomelanotic macules (≥3, at least 5-mm diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasias*
7. Subependymal nodules (SEN)
8. Subependymal giant cell astrocytoma (SEGA)
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)^Δ
11. Angiomyolipomas (≥2) ^Δ

Minor features

1. “Confetti” skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibromas (>2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Definite diagnosis: Two major features or one major feature with ≥2 minor features

Possible diagnosis: Either one major feature or ≥2 minor features

* Includes tubers and cerebral white matter radial migration lines.

^ΔA combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.

Table 2 Renal angiomyolipoma staging criteria

Stage	Number of angiomyolipomata	size	Kidney anatomy
0	None	None	Normal
1	≤5	1–3.5 cm	Normal
2	≤5	1–3.5 cm	Normal
3	≤5	At least 1 ≥3.5 cm	Kidney intact
4	≤5	1–4 ≥3.5 cm	Kidney intact
5	≤5	5 or more ≥3.5 cm	Kidney recognizable
6	≤5	At least 1 ≥5.0 cm	Kidney not recognizable

Results

Gender and age distribution

Our study included 51 men and 94 women (male to female ratio 1:1.84), with mean age of 30.50±9.79 years old (range 7–58 years). *p* value 0.153<0.05. The two largest number of patients are in 21–30y group (48 cases, 33.10%) and 31–40y group (41 cases, 28.28%), followed by 41–50y group (24 cases, 16.55%) and 11–20y group (21 cases, 14.48%). Only 5.52% were under 10 years old (4 cases, 2.76%) and over 50 years old (4 cases, 2.76%), **Figure 1**.

RAML clinical stage

The clinical stage of TSC-RAML is shown in **Table 3**. Among the 145 patients, 108 cases, 71.96% were at or above stage 5 with unrecognizable kidneys, of which 86 cases were at stage 6 (**Figure 2**). 19 cases had a history of tumor rupture and hemorrhage, including 3 cases in stage 2, 2 cases in stage 4, 2 cases in stage 5 and 12 cases in stage 6, respectively.

Table 3. TSC-RAML clinical stage

Stage	Number	hemorrhage
1	2	0
2	13	3
3	6	0
4	16	2
5	22	2
6	86	12
	145	19

TSC-RAML clinical characteristics

Characteristics of 145 TSC-RAML cases were shown in **Table 4** . Subependymal nodules was the most common features with a total of 104 in 122 cases (85.24%); facial angiofibromas or fibrous cephalic plaque (121 cases, 83.44%) and hypomelanotic macules (89 cases, 61.39%) were the most common skin lesions; Ungual fibromas, Shagreen patch, and cortical dysplasia were roughly equal in distribution (**Figure 3**); only 2 cases suffered from cardiac rhabdomyomas. Among minor criteria—the majority manifestation was dental enamel pits (112 cases, 77.24%). In terms of gender distribution, 91.30% (42/46) LAM patients were female, and the proportion was significantly higher than that in other groups, p value ≤ 0.05 .

Table 4. Clinical characteristics of patients with TSC-RAML

	Number 145	Male 51	Female 94	<i>P</i> Value
epilepsy	24/145	10/51	14/94	0.466
Major criteria				
Hypomelanotic macules (≥ 3)	89/145 61.39%	33	56	0.545
Angiofibromas (≥ 3) or fibrous cephalic plaque	121/145 83.44%	42	79	0.794
Ungual fibromas (≥ 2)	62/145 42.07%	17	45	0.091
Shagreen patch	65/145 44.83%	19	46	0.177
Multiple retinal hamartomas	5/53 9.43%	2	3	0.765
Cortical dysplasias	47/122 38.52%	12	35	0.446
Subependymal nodules	104/122 85.24%	28	76	0.132
SEGA	13/122 10.65%	5	8	0.454
Cardiac rhabdomyoma	2/25 8.00%	1	1	0.667
LAM	46/115 38.98%	4	42	0.05
Renal AML	145 100%	51	94	-
Minor criteria				
Dental enamel pits	112/145 77.24%	28	83	
Intraoral fibromas	26/145 24.30%	19	7	
Nonrenal hamartomas	26/145 17.93%	9	17	
Retinal achromatic patch	8/53 15.09%	4	4	
Confetti skin lesions	9/145 6.54%	4	5	
Multiple renal cysts	17/145 11.72%	5	12	

Discussion

Tuberous sclerosis complex was first reported by Bourneville in 1880, so it is also known as Bourneville disease, a clinically rare autosomal dominant genetic disease, often involving multiple organ systems^[1]. In the 1990s, Fryer^[11] and Kandt^[12] respectively found two disease-causing genes and named them TSC1 and TSC2. It has been shown that TSC1 or TSC2 mutations can abnormally activate the mammalian target of rapamycin (mTOR) and cause tuberous sclerosis complex^[13].

Epidemiology

An epidemiological survey in the UK showed a frequency of 1 / 12000 to 1 / 14000 under the age of ten^[14]. Osborne et al. claimed a birth incidence was about 1/5800 by improving methods of ascertainment^[8]. The age-dependent expression of clinical manifestations was disclosed by Curatolo^[15].

Clinical characteristics

Of the 145 patients with TSC-RAML in this study based on the clinical diagnostic criteria proposed by 2012 International Tuberous Sclerosis Complex Consensus Conference, male to female ratio 1:1.84, p value 0.153 (Student's t -test), showing no statistical significance in gender and age distribution. As the most two common features, 121 cases (83.44%) had angiofibromas or fibrous cephalic plaque and 89 cases (61.39%) had hypomelanotic macules. In addition, 130 patients had at least one skin criteria including hypomelanotic macules, angiofibromas or fibrous cephalic plaque, shagreen patch, ungual fibromas or confetti skin lesions, accounting for 89.66%. Another clinical data of 112 cases of TSC-RAML showed that 95.5% (107/112) had at least one of the above-mentioned skin lesions, which is basically consistent with our study results^[16]. Subependymal nodules were the most common neurological features (104 out of 122, 85.24%), followed by cortical dysplasias (47 cases, 38.52%). Among 24 patients with a history of epilepsy, subependymal nodules or (and) cortical dysplasias were detected at least. Only 2 cases were diagnosed with cardiac rhabdomyomas, which may be associated with development and outcome of the disease. In a multicenter and prospective studies enrolled 130 infants with definite TSC, cardiac rhabdomyomas was the most common initial feature, accounting for about 59%. Moreover, up to 82% were detected with cardiac rhabdomyomas and prevalence increased with months before 1 year old^[5], then the prevalence decreased significantly after the age of five. Generally, lesions regress spontaneously over time and complete during childhood^[15]. In our study, 38.98% (46 in 115 cases) were TSC-LAM patients, of which women accounted for 91.30% (42/46), p value 0.05 (Chi-square test), showing significant differences in gender distribution, which was also the only statistically significant difference among all the major criteria. Lymphangiomyomatosis (LAM) is a rare, neoplastic disease that occurs mainly in women^[17]. Most patients have clinically progressive dyspnea and repeated pneumothorax. The chest high-resolution CT mainly manifests diffused thin-wall cystic changes in the lungs^[9]. There are two types of LAM, sporadic and TSC-LAM, which are caused by mutation in TSC gene. TSC mutation defects tuberin-hamartin protein complex, activates the mTOR pathway and promotes the abnormal proliferation of LAM cells^[18]. In women with TSC, the prevalence of LAM ranges from 26% to 38%^[6]. A single-center, 12-year retrospective clinical study showed that LAM was an age-dependent disease with an increasing risk by about 8%. The prevalence of LAM was about 27% among female TSC patients ≤ 21 y, and 80% in those ≥ 40 y^[19]. This phenomenon may be related to the expression of estrogen and progesterone receptors in LAM cells. Clinical observations show that LAM seems to progress when estrogen levels are elevated (such as during pregnant period or taking exogenous estrogen). Ovariectomy and aromatase inhibitor decreased MMP-2 activity and expression of related markers in LAM-like tumors of uterine-specific Tsc2-null mice. Further research indicates that estrogen is likely to promote the survival and metastasis of Tsc2-null Cells through ERK and AKT pathway^[20, 21].

As an international disease registry aimed to address knowledge of TSC, TOSCA (Tuberous sclerosis registry to increase disease Awareness) enrolled 2,093 patients with TSC, involving 171 research centers in 31 countries, 1009 males, 1084 females, male to female ratio 1 : 1.07, age distribution 0-70 years, average age 13 years^[22]. According to the renal manifestation in TOSCA, 47.2% (987 cases) were diagnosed renal angiomyolipomas with male to female ratio 1:1.35, of which 34.8% had lesions > 3 cm

and 22.8% was reported multiple renal cysts. The proportion (89.66% , 130 cases) of TSC-RAML in our study ranged stage 3 or above was significantly higher, while only 17% multiple renal cysts cases. In addition, the proportion of epilepsy and cardiac rhabdomyoma in TOSCA was obviously higher than those in our study (83.5% vs 16.56%; 34.3% vs 8.00%). Noticeably, compared with the adults as main subjects of this study (the average age 30.50y, the main age distribution 21-40y, 63.45%), 63.3% TOSCA patients were < 18y, and the proportion of children was as high as 57%, which may account for these differences. And this study mainly analyzed the clinical characteristics of TSC-RAML, which may be another reasons for the difference in statistics. Similar to the results in TOSCA, facial angiofibromas and hypomelanotic macules were the two most common dermatological manifestations. Subependymal nodules were still one of the most common neurological manifestations.

Treatment

Compared with sporadic AML, TSC-RAML is more onset in infancy and more common in female patients. It often presents as a bilateral, multiple, large tumor that grows faster and increases the risk of spontaneous rupture and hemorrhage^[23]. Studies have further shown that patients with TSC2 gene mutations have more severe kidney destruction and a higher risk of ruptured bleeding^[24]. Renal complications have also become an important cause of death in patients with TSC^[25]. Therefore, reasonable and correct treatment is particularly important. Selective arterial embolization and partial nephrectomy as important treatment methods for TSC-RAML have achieved satisfactory clinical results^[26]. A clinical study involving 7 cases of TSC-RAML selective renal artery embolization showed that embolization was safe and effective, and had a small effect on renal function^[27]. In addition, partial nephrectomy can maximize the retention of nephrons for complicated RAML^[28]. In addition to surgery, Novartis's Afinitor (everolimus, an mTOR inhibitor) is currently the only FDA-approved drug for TSC-RAML that do not require immediate surgery. In a multicenter, randomized, double-blind, placebo-controlled phase III clinical trial conducted by Bissler et al, a total of 118 patients were enrolled, of which 79 were in everolimus group (10 mg / day, with an average treatment time of 38 weeks), 39 patients were in placebo control group (mean 34 weeks). The response rate (50% reduction in tumor volume) was 42% (33/79) vs 0% in the placebo group^[16]. During the extension of the trial, the response rate increased to 54% with everolimus median treatment for 28.9 months^[29]. A single-center, non-randomized, open-label phase II clinical trial conducted 15 cases of TSC-RAML in China demonstrated that everolimus was well tolerated and effective in Chinese patients with TSC-RAML^[30].

Limitation

Our study was a retrospective observational study of TSC-RAML based on a single center statistics. We provided the largest cases in China, however, some patients were unable to complete all TSC diagnostic criteria examinations due to economic factors or regional medical conditions. In addition, no follow-up data were available in this study because patients were lost to follow-up or the follow-up period was short. Therefore, the above content needs to be improved in the future. Furthermore, subjects of this study

were mainly adults with fewer children. Children cases should be collected as much as possible to obtain more complete clinical characteristics of TSC patients in future studies.

Conclusion

This study retrospectively analyzed the clinical manifestations of 145 cases of TSC-RAML. As the first and largest sample report of TSC in China, it is served as reference for summarizing the characteristics of TSC-RAML in China.

Abbreviations

TSC: Tuberous sclerosis complex; mTOR: mammalian target of rapamycin; CT: Computed tomography; MRI: Magnetic resonance imaging; RAML: Renal angiomyolipoma; SEN: Subependymal nodules; SEGA: Subependymal giant cell astrocytomas.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable as no private information was disclosed.

Availability of data and materials

Data generated in this study are not publicly available. Only summary have been provided in the manuscript.

Competing interests

The authors declared that they had no competing interests.

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Authors' contributions

YSZ designed the study. XW and WDW acquired the data. XW, YZ and ZW analyzed the data. XW prepared the first draft. YSZ, YZ and ZW reviewed critically and contributed to the final revision. All authors read and approved the final manuscript.

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Figures

Figure 1

Gender and age distribution of TSC

Figure 2

TSC-RAML Common combined clinical major features

Figure 3

Subependymal nodules was the most common features with a total of 104 in 122 cases (85.24%); facial angiofibromas or fibrous cephalic plaque (121 cases, 83.44%) and hypomelanotic macules (89 cases, 61.39%) were the most common skin lesions; Ungual fibromas, Shagreen patch, and cortical dysplasia were roughly equal in distribution