

## Original Article

# Clinical features and prognosis of Kaposi's sarcoma in Urumchi, China

Xuefeng Wan<sup>1\*</sup>, Xiaobo Lu<sup>2\*</sup>, Maimaitiali Wubuli<sup>2</sup>, Palida Abuliz<sup>1</sup>

<sup>1</sup>Department of Dermatology, First Affiliated Hospital of Xinjiang Medical University, Urumchi 830054, Xinjiang, P.R. China; <sup>2</sup>Department of Infectious Diseases, First Affiliated Hospital of Xinjiang Medical University, Urumchi 830054, Xinjiang, P.R. China. \*Co-first authors.

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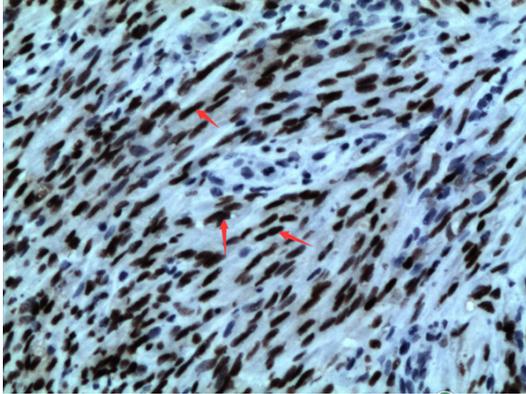
**Abstract:** Aims: This study is to describe the major clinical features and to evaluate the prognosis of classic and Acquired Immune Deficiency Syndrome (AIDS) related Kaposi's sarcoma (KS) in Urumchi, China. Methods: The clinical data of 59 KS patients from the First Affiliated Hospital of Xinjiang Medical University were retrospectively reviewed and analyzed. Results: There were 36 patients of classic KS, 22 patients of AIDS-KS, and 1 patient of iatrogenic KS. Classic KS patients were diagnosed at an average age of 59.47 years (male/female, 17:1), including 29 Uygur, 6 Kazak and 1 Mongolian. Most of the lesions (97.22%) were confined to the skin, and the lesion of 1 patient involved inguinal lymph nodes. No mucosa and visceral organs were involved. Cutaneous lesions mainly involved bilateral distal limbs, such as the hands and feet. The AIDS-KS patients were diagnosed at an average age of 43.00 years (male/female, 9:2) including 21 Uygur and 1 Han. Lesions were widely distributed, including limbs, trunk, mucous membranes and visceral. The iatrogenic KS patient only had lesions on trunk without involvement in the mucosa, lymphnodes or visceral organs. Of 36 classic KS patients, the efficacy of local radiotherapy was 71.43% (10/14) and the efficacy of local radiation therapy combining with interferon was 83.33% (10/12). Ten patients did not receive any therapy due to financial constraint or other reasons. Of 22 AIDS-KS patients, 10 patients were treated with high-level antiretroviral therapy. The treatment effectiveness was 80.00% (8/10). Two patients died of hemoptysis. Twelve patients refused the treatment suggestion, and 10 of them died after 6 months of follow-up and 2 patients had increased skin lesions. There were no significant differences in treatment efficacy between classic KS patients and AIDS-KS patients. The lesion of iatrogenic KS patient improved after decrease of cyclosporine dosage. Conclusions: The lesions in classic KS and iatrogenic KS are confined to skin and seldom involve lymph nodes and visceral, on the contrary, the lesions in AIDS-KS are not confined, and may invade the lymph nodes and visceral organs. The classic KS is more common in male Uygur patients and treatment is more effective, while AIDS-KS involves more visceral organs and have much worse prognosis.

**Keywords:** Kaposi sarcoma, acquired immunodeficiency, clinical features, prognosis

## Introduction

Kaposi's sarcoma (KS) is a tumor caused by infection with human herpesvirus 8 (HHV8) and is firstly described by the Hungarian Dermatologist Moritz Kapo in 1872 [1]. KS is a rare tumor that involves the skin and mucous membrane and can be categorized into 4 types based on etiology and epidemiological characteristics, including classic KS, local KS, iatrogenic KS and Acquired Immune Deficiency Syndrome related Kaposi's sarcoma (AIDS-KS). The classic KS is found in the elderly over the age of 60 years without Human Immunode-

fiency Virus (HIV) infection in the Eastern European and Mediterranean regions (90%). The initial presentations are violet or reddish brown macules and papules in hand and foot, which can spread to arms and legs (the most common attack sites) after years [2]. A total of 10% of patients have visceral and mucosal involvement [3]. Local KS is divided into two subtypes. The first type is found in middle-aged adults (25-50 years) living in sub-Saharan Africa with only focal involvement and the second type is mainly found in children under the age of 10 years, characterized as systemic lymphadenopathy, with aggressive clinical



**Figure 1.** Positive HHV-8 immunohistochemical staining of fusiform cells. Red arrows indicate positive HHV-8 expression. Magnification: 100 ×.

behaviors that lead to death two years after diagnosis [4].

AIDS was first reported in 1981 and KS is one of the main manifestations occurred in 30-40% of AIDS patients [5]. AIDS-KS is mainly found in homosexuals, bisexuals and intravenous drug users [5]. The lesions first appear on face, trunk, and limbs, and the main manifestations are oral mucosal purple patches with mild pain, followed by plaques and nodules [5]. Visceral lesions are common, especially in the gastrointestinal tract and the lung [6]. Iatrogenic KS is mainly found in solid organ transplant recipients, and in patients with use of immunosuppressive agents for treatment of neoplastic diseases and autoimmune diseases [7]. The clinical and morphological features of iatrogenic KS are similar with those classic KS. Cessation of immunosuppressive therapy usually leads to the lesion regression and may increase the risk of graft failure [8].

Chang et al found that HHV-8 was a KS-associated herpes virus that may cause all types of KS [1]. The occurrence of KS is not only associated with herpes virus infection, but also with angiogenic factors, inflammatory cytokines and HIV *tat* gene [9, 10]. However, whether KS is a true malignant tumor or just a reactive hyperplasia is controversial [11].

KS is a systemic disease associated with the occurrence of vascular tumors, therefore the treatment is essentially different from that of other tumors [12]. There is currently no standard treatment guideline for KS. The KS treat-

ment depends on the subtypes, staging and the patient's immune status [13]. The current KS treatments include topical treatments such as surgery, radiotherapy, local chemotherapy (injection of vincristine) or topical immunotherapy (interferon, all-trans retinoic acid, or imiquimod) [4, 14-17] and topical  $\beta$ -receptor blocking agent [18]. Patients with dispersed lesions may receive systemic chemotherapy or immunotherapy, such as polyethylene glycol doxorubicin liposomes, paclitaxel, and interferon alpha-2b [19, 20]. Treatment for classic KS includes local radiation therapy and a-2b interferon treatment and dispersed lesions requires systemic chemotherapy [21]. The treatment of AIDS-KS is mainly based on highly active anti-retroviral therapy (HAART), and combined with systemic chemotherapy (adriamycin, bleomycin and vincristine) if necessary.

Xinjiang is located in the northwest of China, where classic KS is of high incidence. This study focused on the clinical features, treatment outcomes and prognosis of patients with KS and AIDS-KS.

### Materials and methods

#### Subjects

This is a retrospective study. Totally, 59 patients with KS who were hospitalized in Department of Dermatology and Department of Infectious Diseases, First Affiliated Hospital of Xinjiang Medical University from 2002 to 2013 were enrolled. Clinical data was collected. KS was diagnosed by pathology or immunohistochemical staining of HHV-8 (**Figure 1**). Enzyme immunoassay was used for screening anti-HIV antibodies. Patients received ultrasound examination for superficial lymph nodes and abdominal lesions, and, chest X-ray and thoracic or abdominal Computed Tomography (CT) for tumor staging. All data were anonymously analyzed using the patient hospital number. Prior written and informed consent were obtained from every patient and the study was approved by the ethics review board of The First Teaching Hospital of Xinjiang Medical University

#### Tumor staging

Brambilla staging was used for determining the four stages [22]. Stage I was patch stage that lesions were confined to the distal limbs; stage

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**Table 1.** Clinical feature and tumor staging of three subtypes of KS patients

	Classic KS	AIDS-KS	Iatrogenic KS	P value
Cases	36	22	1	
Demographic				
Male (Female)	34 (2)	18 (4)	1	0.277
Uygur (Other nationalities)	29 (7)	21 (1)	1	0.228
Mean onset-age (Year)	59.47 ± 13.52	43.00 ± 15.61	32	0.001
Mean duration (Month)	32.92 ± 12.11	10.05 ± 16.93	8	0.006
Lesion distribute				
Hand	23	2	0	0.001
Foot	30	7	0	0.001
Upper limbs (except hand)	14	15	0	0.030
Lower limbs (except foot)	15	15	0	0.050
Trunk	0	16	1	0.001
Head and face	0	8	0	0.001
Oral mucosa	0	7	0	0.001
Superficial lymphadenopathy	1	22	0	0.001
Visceral involvement	0	15	0	0.001
Tumor staging				
Stage I	15	0	0	0.001
Stage II	17	0	0	0.001
Stage III	3	12	0	0.001
Stage IV	1	10	1	0.001

Note: There was only 1 iatrogenic KS case. Thus, the comparison was performed between classic KS and AIDS-KS.

II was infiltration stage that lesions were widely distributed in the distal extremities; stage III was vigorous growth stage that lesions were usually ulcerated involving one or more limbs; stage IV was dissemination stage that the scope of the tumor expanded to trunk and other organs. The progression of the disease was classified as slow or rapid according to the increase in the number of lesions or total area over 3 months.

### *Analysis of clinical data and prognosis*

Demographic information was evaluated, including gender, ethnicity, age at onset, and clinical characteristics such as KS clinical subtype and lesion location (**Table 1**). In addition, the treatment methods, outcome and tumor recurrence were observed (**Table 2**). The treatment outcome was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST Guidelines) [23]: "complete remission" refers to that the KS lesions are improved substantially during follow-up compared with that at first admission; "partial remission" refers to lesion reduction by at least 30%; "stable" refers to lesion reduction by less than 30%. And all

above indicate no new lesions or lesions progress.

### *Statistical analysis*

Statistical package of social sciences 17.0 software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Quantitative data (including mean onset-age and duration) are expressed as mean and standard deviation (SD) and were analyzed by a two-sample independent measures Z test. Categorical data (including gender, nationality, lesion distribute, superficial lymphadenopathy and visceral involvement) are expressed as frequency and percentage. Chi-square test was used to compare the difference of categorical data. P<0.05 was considered to indicate a statistically significant difference.

## **Results**

### *Baseline characteristics of patients*

The demographic characteristics of KS patients including age, gender, ethnicity and duration of symptoms before diagnosis were summarized.

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**Table 2.** The treatment and prognosis of the three subtypes of KS patients

	Treatment method		
	Radiation therapy	Radiation therapy + interferon	Without therapy
Classic KS patients (n = 36)			
Treated cases	14	12	10
Effective cases	10	10	N/A
Total death		3*	
Loss follow-up		3	
AIDS-KS patients (n = 22)	HAART	HAART + ABV	Without therapy
Treated cases	7	3	12
Effective cases		8	N/A
Total death		10	
Loss follow-up		0	
Iatrogenic KS (n = 1)		Lower dose of Cyclosporine	
Treated cases		1	
Effective cases		1	
Total death		0	
Loss follow-up		0	

Note: HAART, highly active antiretroviral therapy; ABV, Adriamycin + bleomycin + vincristine. \*These 3 patients were died of Parkinson, diabetic nephropathy and pulmonary heart disease, respectively.



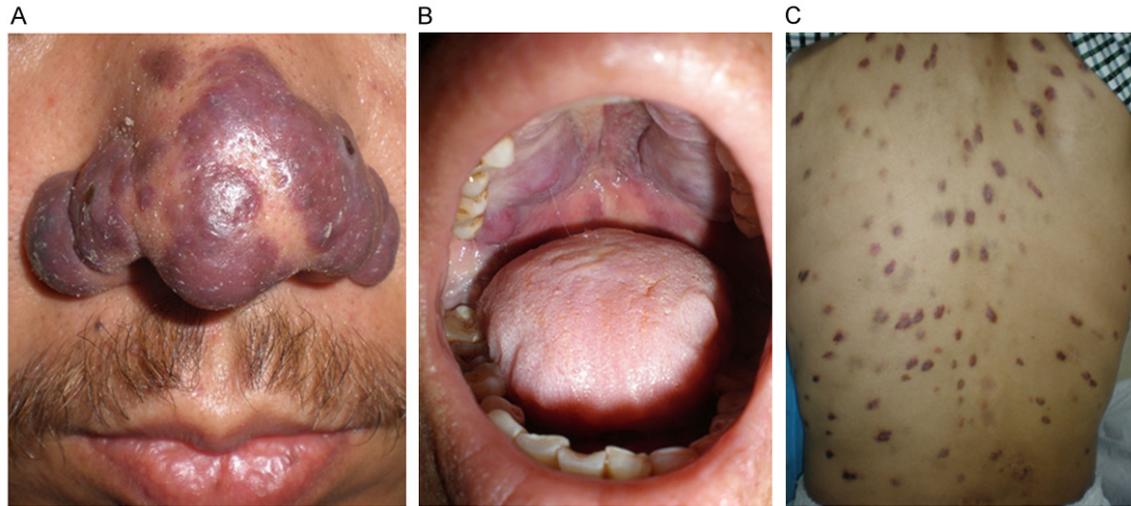
**Figure 2.** Classic Kaposi's Sarcoma. Violaceous plaques and nodules on foot and leg.

For the 36 classic KS patients, 94.44% (n = 34) were male patients and 5.56% (n = 2) were female patients with the ratio of male to female of 17:1. There were 29 patients of Uyghur, 6 patients of Kazak and 1 patient of Mongolian. No patient of Han was included. The mean age at diagnosis was 59.47 years (SD = 13.52), ranging from 17 to 83 years. The duration of symptoms before diagnosis was 32.92 months (SD = 12.11).

For the 22 patients with AIDS-KS, 81.82% (n = 18) were male patients and 18.18% (n = 4) were female patients, male to female ratio of 9:2. There were 21 patients of Uyghur and 1 patient of Han. The mean age at diagnosis was

43.00 years (SD = 15.61), ranging from 24 to 69 years. The onset age of classic KS (59.47 ± 13.52 years) was elder than that of AIDS-KS patients (43.00 ± 15.61 years) (Z = -3.808; P = 0.001). The duration of symptoms before diagnosis was 10.05 ± 16.93 months in AIDS-KS patients, which was significantly shorter than that of classic KS patients (32.92 ± 12.11 months) (Z = -2.742; P = 0.006). The iatrogenic KS patient was a 32-year-old Uyghur male patient.

Of the 36 classic KS patients, 20 patients were without underlying diseases and 16 patients had hypertension, diabetes, chronic bronchitis, bronchial asthma, pulmonary heart disease,



**Figure 3.** AIDS Kaposi's Sarcoma. Violaceous plaques and nodules on the nose (A), tumor-like lesion on the hard palate (B), and multiple violaceous plaques on the trunk (C).



**Figure 4.** Iatrogenic Kaposi's Sarcoma. Violaceous plaques on the trunk.

pulmonary tuberculosis, hypopituitarism, cerebral infarction, or Parkinson's disease.

*The classification and staging of patients*

As shown in **Table 1**, of the 59 KS patients, 36 were classic KS, 22 were AIDS-KS and 1 was iatrogenic KS. For classic KS patients, 15 patients were in stage I, 17 were in stage II, 3 were in stage III, and 1 was in stage IV. Among patients with AIDS-KS, 12 patients were in stage III and 10 were in stage IV. The iatrogenic KS patient was in stage IV.

*Clinical features of patients*

The lesion locations and presentations of KS patients were summarized. The 97.22% (35) of

classic KS patients involved only skin, without mucosa, lymph nodes or visceral involvement and one (n = 1) patient had inguinal lymph node involvement. Skin lesions of classic KS distributed symmetrically on limbs, most commonly on feet (n = 30), hands (n = 23), legs (n = 15), and arms (n = 14). The involvement of head and face, neck, trunk, or oral mucosa involvement was not found (**Figure 2**).

All patients with AIDS-KS had mucosa or other organ involvement, including 7 patients of oral mucosa involvement, and 8 patients of visceral involvement (commonly liver and lung). Skin lesions of AIDS-KS patients were most commonly on trunk (n = 16), followed by the lower limbs (except feet) (n = 15) and arms (except hands) (n = 15), face (n = 8), feet (n = 7), oral mucosa (n = 7), neck (n = 4) and hands (n = 2) (**Figure 3**). The one patient with iatrogenic KS developed a number of purple nodules on the chest and abdomen after use of methylprednisolone and cyclosporine for 8 months (**Figure 4**) because of nephrotic syndrome. Compared with AIDS-KS patients, classic KS lesions were more common in the hands and feet, rarely seen in the head, trunk and oral mucosa, and less affected by superficial lymphadenopathy and visceral involvement ( $\chi^2 = 16.720, 15.689, 12.281, 36.156, 10.201, 53.937, \text{ and } 33.108$ , respectively; all  $P < 0.05$ ) (**Table 1**). However, AIDS/KS patients usually had generalized lesions that involved mucosa, lymph nodes and visceral organs (**Table 1**).

### *Results of laboratory examinations*

Patient medical charts were reviewed for the laboratory examination results. Among the 36 classic KS patients, there was 1 patient of anemia (Hb of 44 g/l, RBC of  $1.48 \times 10^{12}/l$ ) with pulmonary tuberculosis; no KS-related abnormalities were detected by abdominal ultrasound; 1 patient showed inguinal lymphadenopathy; no KS-related abnormalities were detected among the 6 patients who underwent pulmonary or abdominal CT examination; no KS-related abnormalities were detected in the patient who underwent Emission CT scan.

Among the 22 AIDS-KS patients, 6 had anemia with normal liver and kidney function; 22 had enlarged neck, axillary or inguinal lymph nodes detected by ultrasound; 6 had retroperitoneal lymphadenopathy detected by ultrasound; 8 had liver, lung involvement or lymphadenopathy detected by chest X-ray/CT or abdominal CT; and 1 had colon involvement detected by colonoscopy.

The iatrogenic KS patient had renal dysfunction (blood urea nitrogen of 11.1 mmol/l) due to nephrotic syndrome; other laboratory and imaging examinations showed no abnormalities. It indicates that iatrogenic KS usually present on trunk without involvement of mucosa, lymph nodes or visceral organs, different from that of classic KS.

### *Treatment and prognosis of patients*

To determine treatment outcome, their treatment strategies and prognosis were described. The treatment for classic KS included local treatment such as radiation therapy alone or combination with interferon- $\alpha$ -2b immunotherapy (subcutaneous injection 3 million international units, 3 times/week) for 5 weeks to 6 months. As shown in **Table 2**, there were 14 patients received local radiotherapy alone and the efficacy was 71.43% (10/14); 12 patients were treated with local radiation therapy combined with interferon, and the efficacy was 83.33% (10/12); 10 patients were not treated due to financial constraint or other reasons. A total of 33 patients completed the follow-up with a mean follow-up time of 47.64 months (SD = 28.15). Three patients died of Parkinson's disease, diabetic nephropathy or pulmonary heart disease. No patient died of KS.

The AIDS-KS were treated based on the patient's condition. Ten patients were treated with high-level antiretroviral therapy [zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV)]. Three of them received combined treatment of systemic chemotherapy with ABV plan [intravenous injection of Adriamycin (40 mg/m<sup>2</sup>) + bleomycin (15 mg/m<sup>2</sup>) + vincristine (2 mg/m<sup>2</sup>), once/2 weeks for 6 times]. The treatment effectiveness was 80.00% (8/10). Two patients died of hemoptysis after 1 month of treatment. There were twelve patients refused the treatment suggestion. And, ten of them died after 6 months of follow-up and 2 patients had increased skin lesions. There were no significant differences in treatment efficacy between classic KS patients (71.43% in radiation group, 83.33% in local radiation + interferon) and AIDS/KS patients (80.00% in HAART group). The patients with hemoptysis received HAART treatment and the symptoms of 2 patients aggravated during a 6-month's follow-up.

The skin lesion of iatrogenic KS patient improved after decrease of cyclosporine dosage. It indicates that the development of iatrogenic KS may be associated with organ transplantation or use of immune suppressant.

### **Discussion**

Classic KS is a rare disease with a specific geographic incidence, and its incidence is associated with the ethnicity, gender, age and immune status of patients [1]. Xinjiang Uygur Autonomous Region is located in the northwest of China with minority ethnic groups accounting for 59.43% of the total population, including Uygur, Kazak, Mongolian, Hui, Kirgiz and Xibo. The Uighur and Kazak are the two main minority ethnic groups. The HLA-B gene analysis suggests that Uighur and Kazak are both Caucasians who originated in Europe 3000 years ago, migrated to Central Asia and Xinjiang, then merged with the local ethnic groups and evolved into the current race [24, 25]. In addition, Xinjiang is geographically adjacent to Europe. Therefore, it is likely that certain ethnic groups migrated to Xinjiang in ancient times [26, 27]. The incidence of classic KS is high among minority ethnic groups, especially in Uygur. No Han people with classic KS has been reported in Xinjiang yet. Similarly, in this study, the classic KS included 29 Uygur patients, 6

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Kazak patients, 1 Mongolian patient, and no Han patients. Positivity rate of serum HHV-8 is reported to be different among racial groups, with 30.4-46.6% in Uighur and 12.5% in Kazakhstan [28].

The onset age of classic KS in this study was elder than that of AIDS-KS patients. Classic KS usually attacks the elderly, while AIDS-KS is more common in young people who are sexually active. Gender also plays a role in classic KS. The male/female ratio was 17:1 in the current study, which is slightly higher than the previous reported ratio of 10:1 to 15:1 [29]. Iscovich et al showed the similar ratio of male/female in the population and male dominance in classic KS [30], indicating the protective effect of luteinizing hormone in female on the development of KS [4].

Clinically, non-AIDS-KS usually manifests as multiple symmetrical lesions on lower limbs [30]. Consistently, multiple lesions in all classic KS patients of the current study were symmetrically distributed. The most common sites were foot, hand, thigh and calf, upper arm and forearm, trunk; while head, neck and oral mucous membrane were not involved. One patient had inguinal lymph node involvement. One patient had anemia that was considered to be associated with its tuberculosis. The remaining patients did not have visceral involvement. The classic KS lesions mainly present on limbs and extremities, seldom on face, trunk, mucosa, lymph nodes or visceral organs.

The most common skin lesions in AIDS-KS patients were on trunk, lower limb (except foot) and upper limb (except hand), head, feet, mucosa, neck and hand. Some AIDS/KS patients had systemic involvement: 6 patients had anemia, 22 had superficial lymphadenopathy, 6 had retroperitoneal lymphadenopathy, 8 had liver and lung involvement, and 1 had gastrointestinal involvement. The above showed that the distribution, superficial lymph node and visceral involvement of classic KS and AIDS-KS was different, consistent with Hong's study [31].

In this study, 36 classic KS received local radiation therapy or local radiation therapy combined with interferon treatment, with treatment efficacy of about 80%, and for AIDS-KS patients

who received HAART treatment, the treatment efficacy was comparable to that of classic KS. No untreated KS patient died because of KS during follow-up. In comparison, 12 untreated AIDS-KS patients died of AIDS and comorbidities during 6 months' follow-up. The results suggest that classic KS has little visceral involvement and has great prognosis. The prognosis of AIDS-KS patients is significantly worse than that of classic KS.

In conclusion, this study has analyzed the clinical manifestation, treatment and prognosis of KS patients in a tertiary dermatology center from 2002 to 2013. In addition to HHV-8 infection, individual factors such as race origin, age, gender and immune status shows no impact on the development of KS. Compared with AIDS-KS, classic KS and iatrogenic KS patients have similar skin presentations, mostly on extremities and less involvement of trunk, mucosa, lymph nodes and visceral organs, with good prognosis and response to local or systemic treatment.

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### Disclosure of conflict of interest

None.

**Address correspondence to:** Palida Abuliz, Department of Dermatology, First Affiliated Hospital of Xinjiang Medical University, No. 137 South Liyushan Road, Urumchi 830054, Xinjiang, P.R. China. Tel: 13079945443; Fax: 0991-4362701; E-mail: xjwanyanan@163.com

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