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Clinical Characteristics, Risk Factors, Diagnostic Methods and Therapeutic Response of Cutaneous Sporotrichosis Infection In An Endemic Region

(Ciri-ciri Klinikal, Faktor Risiko, Kaedah Diagnostik dan Tindak Balas Terapeutik Jangkitan Sporotrikosis Kulit di Kawasan Endemik)

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Abstract

Cutaneous sporotrichosis is a fungal infection caused by traumatic inoculation of Sporothrix. We aimed to study the clinical characteristics of human sporotrichosis, risk factors for infection, the yield of diagnostic methods and therapeutic response to standard clinical therapy. A cohort study of was performed. A total of 29 patients with clinical features suggestive of sporotrichosis were recruited within a one-year period from all public hospitals in Kedah, Malaysia. Majority were females (86%) who were housewives (69%). The most common comorbidities were diabetes mellitus (38%), hypertension (31%) and dyslipidaemia (21%), none was a significant risk factor for severity of infection. Mean duration of disease was 2±2 months. More than 2/3 of the patients (79%) had pet cats, 14(48%) recalled minor cat-inflicted trauma. Lymphocutaneous sporotrichosis (62%) was more common than fixed cutaneous type, affecting the upper limbs in 94%. Ulcerations and nodules were the main lesion morphology. Histopathology showed granulomatous inflammation in 72%, culture grew Sprorothrix in 55% and polymerase chain reaction (PCR) detected Sporothrix schenkii sensu stricto in 65%. Itraconazole was effective with 93% of patients achieving complete resolution with 4 months of therapy. Sporotrichosis in Malaysia remains endemic. Feline contact is the most important risk factor for infection. Diagnosis is best confirmed with tissue PCR while culture and histopathology are also useful. Sporothrix schenkii sensu stricto was the only species identified and itraconazole is an effective first line therapeutic agent.

Keywords: Sporothrix schenchkii sensu stricto, sporotrichosis, mycosis, zoonosis.

Abstrak

Sporotrikosis kulit ialah jangkitan yang berpunca dari inokulasi traumatik kulat Sporotrix. Kajian ini bertujuan untuk menyelidik ciri-ciri klinikal sporotrikosis di kalangan manusia, risiko jangkitan, hasil kaedah diagnostik dan tindak balas terapeutik terhadap terapi klinikal standard. Kajian kohort telah dijalankan. Seramai 29 pesakit yang disyaki mengalami sporotrikosis dalam tempoh setahun dari semua hospital awam di Kedah, Malaysia diambil menyertai kajian. Majoriti adalah wanita (86%) yang merupakan suri rumah (69%). Komorbiditi yang paling biasa adalah kencing manis (38%), darah tinggi (31%) dan dislipidemia (21%) yang bukan merupakan risiko yang signifikan untuk tahap keterukan jangkitan. Tempoh purata penyakit ialah 2±2 bulan. Lebih daripada 2/3 daripada pesakit (79%) mempunyai kucing peliharaan, 14 (48%) mengingati trauma kecil akibat kucing. Sporotrikosis limfokutis (62%) adalah lebih kerap daripada jenis fixed, menjejaskan anggota atas dalam 94%. Ulser dan nodul adalah morfologi morfologi utama lesi yang dijumpai. Histopatologi menunjukkan keradangan granulomatus dalam 72%, kultur positif Sprorothrix dalam 55% dan tindak balas rantai polimerase (PCR) mengesan Sporothrix schenkii sensu stricto dalam 65%. Itraconazole berkesan dengan 93% pesakit sembuh selepas rawatan selama 4 bulan. Sporotrikosis di Malaysia kekal endemik. Kecederaan berpunca dari kucing adalah risiko terpenting jangkitan. Diagnosis paling baik disahkan dengan PCR tisu manakala kultur dan histopatologi juga berguna. Sporothrix schenckii sensu stricto adalah satu-satunya spesies yang dikenal pasti dan itraconazole ialah agen rawatan barisan pertama yang berkesan.

Kata kunci: Sporothrix schenchkii sensu stricto, sporotrichosis, mycosis, zoonosis.

INTRODUCTION

Sporotrichosis was first described as a fungal cutaneous infection in 1898 by Benjamin Schenck (Schenck 1898). Subsequently the pathogenic fungus was named *Sporothrix schenkii* by Hektoen and Perkins in 1900 (Hektoen & Perkins 1900). The lymphocutaneous form of the disease was observed in humans and rats in 1907 (Lutz & Splendore 1907). Sporothrix species are dimorphic, with saprophytic mycelium phase at 25-28 ^{0}C and yeast-like pathogenic phase at 36-37 ^{0}C. There are 6 sibling species of *Sporothrix schenkii*: S. *brasilensis*, *S. globose*, *S. mexicana*, *S. luriei*, *S. pallida*, and *S. schenkii sensu stricto* (formerly known as *S. schenkii*). *S. mexicana* and *S. pallida* belongs to the less pathogenic *S. pallida complex* (Orofino-Costa et al. 2017). These species vary in terms of geographical distribution, virulence and antifungal susceptibility. Identification of species in *S. schenkii* complex is important for accurate diagnosis which will guide choice of treatment. Conventional mycological procedures for phenotypic identification is the gold standard for diagnosis. Advances in genetic and molecular tools improved diagnostic accuracy and differentiate species with their pathogenic potential.

Sporotrichosis is often caused by traumatic inoculation of the skin from contaminated soil, plants, wood and decaying matter. Infection is associated with occupations such as gardening, farming, and mining. This mycosis was initially commonly observed in rats. In the last century, Sporothrix's host shifted from rats to cats, as cats are major predator of rats and an oral route of transmission is postulated. Cat scratch and bite are the most common preceding trauma to infection in our country (Tang et al. 2012).

This study aimed to describe the clinical characteristics of human sporotrichosis, risk factors for severity of infection, yield of diagnostic methods and therapeutic response to standard clinical therapy in the state of Kedah in Malaysia, an endemic region in Southeast Asia.

MATERIALS AND METHODS

This was a cohort study involving all nine public hospitals in Kedah. Kedah is an agricultural state known as the 'rice bowl' of the country, located in the north of Peninsular Malaysia, covering 9492km^2 with a population of 2.2 million in 2024 (Department of Statistics Malaysia. 2024).

Using universal sampling, patients aged 18 and above who presented with clinical features suggestive of sporotrichosis from May 2020 to April 2021 were included in the study. Informed consent was obtained. Data collected included age, sex, ethnicity, occupation, place of residence, history of trauma at the affected area, pets, duration of symptoms and comorbidities. Cutaneous sporotrichosis infection was clinically classified into: (1) lymphocutaneous - papulonodular appearance along regional lymphangitic channels. Nodules may ulcerate, develop fistula, and heal forming gummatous lesions, (2) fixed - a single lesion, similar to inoculation chancre, (3) disseminated - multiple subcutaneous nodules, gummatous lesions, or abscesses affecting at least two anatomic sites and (4) extracutaneous - disseminated extracutaneous involvement of osteoarticular skeletal system, lungs, nervous system, or mucous membranes (ocular, oral, nasal).

Skin biopsy for fungal culture, fungal polymerase chain reaction (PCR) and histopathology examination were performed for all patients. Skin specimens were processed by aqueous extraction and direct plating techniques. Several dilutions of extracted samples were plated on Sabouraud dextrose agar (SDA) separately and incubated at 30°C. A minimum of two plates were cultured for undiluted supernatant and each dilution. Colonies suspected to be *S. schenckii* were again subjected to culture on SDA after 7–10 days of incubation. Macroscopic morphology of these colonies and microscopic features of growth isolates on lactophenol cotton blue(LCB) mounts were examined. These isolates were then processed further to determine the gene sequences to the internal transcribed spacer region and also the calmodulin gene of *S. schenckii*. The isolates were genetically characterized based on calmodulin gene sequencing using the primers CL1 (5′-GAR TWC AAG GAG GCC TTC TC) and CL2A (5′-TTT TTG CAT CAT GAG TTG GAC), as well as sequencing part of the rRNA operon using the primers ITS1 (5′-TCC GTA GGT GAA CCT TGC GG) and ITS4 (5′-TCC TCC GCT TAT TGA TAT GC). These loci have been extensively used for phylogeny and taxonomy of this complex of cryptic species.

All subjects received standard treatment for sporotrichosis, itraconazole 200mg twice daily. Terbinafine 250mg twice daily is the second line agent in patients who developed adverse reaction or had contraindications to itraconazole. The patients were followed up at 2 months, 4 months and 6 months to assess clinical resolution, and treatment adverse effects including drug induced hepatitis, gastrointestinal symptoms such as nausea, diarrhoea, abdominal pain; peripheral neuropathy and hypersensitivity reactions.

The data collected were analyzed using the IBM SPSS Statistics for Windows Version 21.0. Chi-square test and independent t-tests were used with $p<0.05$ as the significant point. Clinical data are reported as means with standard deviation and percentages.

This study was approved by the Medical Research and Ethic Committee, National Institute of Health, Malaysia (NMRR 20-247-53160).

RESULTS

A total of 29 patients with mean age of 49±17 years were enrolled in this study. Most were females 25(86%). The most frequently observed comorbidities were diabetes mellitus 11(37.9%), hypertension 9(31.0%) and dyslipidaemia 6(20.7%). Other diseases were asthma, trigeminal neuralgia and chronic cutaneous lupus erythematosus. Half of the patients had no other past medical history. More than two-third were housewives 20(69.0%), there were one gardener, two clerks, two lorry drivers, two petrol station workers, two students and three were unemployed (Table 1).

Table 1: Demographic and clinical characteristics of study population

Characteristic		**N=29**
		Mean±SD or median (IQR) or n(%)
Age (year)		49± 17
Gender	Female	25(86)
	Male	4(14.0)
Comorbidities	Diabetes mellitus	11(37.9)
	Dyslipidaemia	6(20.7)
	Hypertension	9(31.0)
	Others	3(10.3)
	None	14(48.3)
Occupation	Housewife	20(69.0)
	Gardener	1(3.0)
	Others	8(28.0)
Duration of disease, months		2(2.0)
Risk factors	Pet cat	23(79.0)
	Gardening	1(3.0)
Preceding skin trauma	Cat bite	3(10.0)
	Cat scratch	11(38.0)
	None	15(52.0)
Type of sporotrichosis	Lymphocutaneous	18 (62)
	Fixed cutaneous	11(38)
Anatomical site affected	Upper limb	17(94.4)
in lymphocutaneous disease	Lower limb	1(5.6)
Anatomical site affected	Upper limb	4(36.3)
in fixed cutaneous disease	Lower limb	4(36.3)
	Face	3(27.3)
Lesion morphology	Ulcerated	13(44.8)
	Nodule	14(48.3)
	Verrucous plaque	2(6.9)

Most patients, 23(79%) kept pet cats. Two-thirds 14(61%) of them recollected a history of skin trauma due to cat scratch or bite. Eight of the cats had ulcers on the face, four died before the patients' presentation to our clinic. About 52% could not recall trauma prior to the onset of the cutaneous eruption, while the gardener denied cuts or thorn pricks. More than 90% of patients presented to our clinic within 6 months of the lesion appearance, with median duration of 2 months (Table 1). Two patients were undiagnosed for 12 and 18 months respectively. Eighteen (62%) had lymphocutaneous disease, 11(38%) patients had fixed cutaneous lesion. Location of fixed cutaneous lesions were upper limbs 4(36.3%), lower limbs 4(36.3%) and face 3(27.3%). Clinical characteristics of the study population is summarized in Table 1. Figure 1 showed a patient with lymphocutaneous disease.

Figure 1. The ulcerated nodule on the dorsum of the hand was the first lesion that appeared. Multiple nodules later developed in a linear pattern along the forearm and arm.

Skin specimen for fungal culture grew *Sporothrix schenkii* in 16(55.2%), there was no growth in 13(44.8%). PCR detected *Sporothrix schenkii* in 69% of the negative cultures. Histopathological examination of skin biopsies demonstrated granulomatous reactions with mixed inflammatory infiltrate comprising of lymphocytes, neutrophils, plasma cells, histiocytes, and multinucleated giant cells in 21(72.4%) cases. There were acute and chronic inflammatory infiltrates without granuloma formation in the remaining seven cases. All samples were stained with either periodic acid-Schiff or Gomori–Grocott methenamine silver, and four cases demonstrated spores in the dermis. Results of the various diagnostic investigations are presented in Table 2.

Table 2: Results of various diagnostic investigations

Investigation		N=29 n(%)
Culture		
	Sporothrix schenckii	16 (55.2)
	No growth	13 (44.8)
PCR		
	Sporothrix schenckii	19(65.5)
	Negative	10(34.5)
Histology		
	Granulomatous inflammation	21(72.4)
	Fungal bodies	4(13.8)
	Non-specific	8(27.5)

PCR: polymerase chain reaction

History of skin trauma and inoculum method were the only factors significantly associated with sporotrichosis type. Cat bite or scratch was observed more in lymphocutaneous type, while most of fixed cutaneous type was not associated with skin trauma. Cat scratch rather than bite was associated with lymphocutaneous type, while cat bite was associated with fixed cutaneous type, with $p<0.01$. Fixed cutaneous type was associated with longer duration of disease (5 months), in contrast lymphocutaneous type generally presented earlier (1-2 months). Age, gender and comorbidities did not show statistically significant association with the type or severity of the disease.

Table 3. Factors associated with sporotrichosis type/ severity

Parameter		**Lymphocutaneous type N= 18 n(%) or mean±SD**	**Fixed typeN=11 n(%) or mean±SD**	**p value**
Age		50 ± 15	46 ± 19	0.298
Gender	Male	2(50)	2(50)	0.592
	Female	16 (64)	9 (36)	
Comorbidities	Hypertension	5(56)	4(44)	0.628
	Diabetes mellitus	5(45)	6(55)	0.149
	Dyslipidaemia	4(67)	2(33)	0.794
History of trauma	Cat bite/scratch	12 (86 %)	2 (86 %)	0.004
	None	6 (40 %)	9 (40 %)	
Inoculum method	Cat bite	1	2	0.004
	Cat scratch	11	0	

All patients were treated with oral itraconazole 200mg twice daily according to standard clinical practice except for one patient who received oral terbinafine 250mg twice daily. Terbinafine was chosen to avoid itraconazole- carbamazepine interaction in a patient with trigeminal neuralgia. Treatment duration was guided by clinical response, and treatment was extended one month after complete resolution of lesions. There were no adverse events recorded. Only one patient was lost to follow up after one month of treatment. Mean duration of treatment was 4±1.9 months and all patients had complete clinical resolution. Two patients developed recurrence of lesions 4 and 5 months after completion of treatment with itraconazole. The first patient was treated with terbinafine 500mg twice daily as she was pregnant. Her lesions resolved after 6 months of treatment. The second patient was most likely re-infected due to continued exposure to her untreated cat. She was re-treated with itraconazole for 5 months with complete resolution of the nodules.

DISCUSSION

Prevalence of sporotrichosis in Malaysia is unknown as sporotrichosis is not a notifiable disease. A 6-year review in an urban tertiary centre from 2004 to 2010 recorded 19 cases (Tang et al. 2015). One hundred and forty-three cases were reported in northern peninsular Malaysia between 2013 to 2018 (Teh et al. 2018). The incidence of sporotrichosis in Kedah is estimated to be 1.33 per 100,000 population based on this study cohort. Incidence in hyperendemic area such as Peru ranged from 48 to 98 cases per 100 000 (Pappas et al. 2000). In Asia, sporotrichosis occurs mainly in China, Japan, Korea and India (Chakrabarti et al. 2014).

Risk factors for infection

The main risk factor for infection is feline contact and exposure to soil and decaying matter related with occupation or leisure activities. The main mode of transmission in our cohort was zoonotic i.e. from cats. Sporotrichosis due to sapronotic transmission associated with occupation is not common in our population (Tang et al. 2012; Teh et al. 2018). *Sporothrix* has been isolated from 100% of skin lesions, 66.2% of nasal cavities, 41.8% of oral cavities, and 39.5% of the nails of cats with sporotrichosis (Schubach et al. 2002). There was a marked female preponderance in our study population as women were more frequently engaged in domestic activities including caring for pets. In northeast India, there was a higher prevalence of infection in females as more females than males were engaged in agricultural activities (Bhutia et al. 2011). In Brazil and South Africa, the incidence rate in males was higher than females with a 3:1 ratio as males were more frequently involved in outdoor activities and mining-related occupations (deRosa et al. 2004; Govender et al. 2015). The largest epidemic of zoonotic sporotrichosis due to *Sporothrix brasilliensis* occurred in Rio de Janeiro, Brazil with 178 cases diagnosed between 1998 to 2001 (Barros et al. 2004). More than 90% of the patients reported domestic or professional contact with cats. Other mammals have been proposed as carriers of *Sporothrix*, including armadillos, bats, dogs, and squirrels as well as invertebrates such as mosquitoes, ants, and spiders (Zhang et al. 2015).

Risk factor for severe infection

Sporotrichosis affects both immunocompetent and immunocompromised hosts. Severe infection in disseminated or extracutaneous forms affect the lungs, bone, eyes and the central nervous system (do Monte et al. 2020; Aung et al. 2012; Ramos et al. 2021; Ahmad-Fauzi et al. 2021). Risk factors for severe infection includes human immunodeficiency virus (HIV) infection, organ transplant and diabetes mellitus (Tshisevhe et al. 2021; Poester et al. 2020; Moreira et al. 2015; Ferreira et al. 2019; Fichman et al. 2021; do Monte et al. 2020). Immunocompromised patients usually have a more severe disease course, unusual clinical manifestations, higher burden of infection and require longer duration of therapy (Moreira et al. 2015; Toriello et al. 2021; Queiroz-Telles et al. 2019). A systematic review of HIV patients with sporotrichosis found most patients had cutaneous disease with involvement of other organs with median CD4 T-lymphocyte count 97cells/uL (Moreira et al. 2015). No disseminated or extracutaneous sporotrichosis were detected in our cohort. We did not observe significant differences between lymphocutaneous type and fixed cutaneous type in terms of age, gender, hypertension, diabetes and dyslipidaemia. History of skin trauma and method of fungal inoculation into the skin may influence burden of infection and therefore type and severity of disease in our patients. However further investigation is required to clarify this observation.

Clinical features

Lymphocutaenous type generally presented earlier than fixed cutaneous type among our patients. Diagnosis is delayed in patients with fixed cutaneous disease in our cohort either due to misdiagnosis by non-dermatologists or late presentation as the lesions appear less severe. Lymphocutaneous disease is the most common type of clinical manifestation reported in the literature as well as in our patients

(Vismer et al. 1997; Yao et al. 2020; Ghosh et al. 1999; Chakrabarti et al. 2014; Verma et al. 2012). However, there were no significant differences between fixed sporotrichosis compared with lymphocutaneous disease in other reports (Govender et al. 2015; Tshisevhe et al. 2021; Conias et al. 1998). Extracutaneous and disseminated sporotrichosis are uncommon, with the prevalence ranging from 0.5% to 9% (Pappas et al. 2000; Conias et al. 1998). Most of the studies found a significant higher proportion of upper extremity involvement in sporotrichosis as in our cohort (Tang et al. 2012; Govender et al. 2015; Verma et al. 2012; Conias et al 1998). Upper extremity lesions are much more common in lymphocutaneous presentation compared with fixed cutaneous nodules (Tang et al. 2012; Govender et al. 2015; Verma et al. 2012; Conias et al 1998). Three of our patients with fixed cutaneous lesions on face had pet cats but no history of trauma, bite or scratch. *Sporothrix* maybe have been transmitted from saliva of infected cats to minor injury on the face during cat-kissing.

Yield of diagnostic methods

Mycological culture is the gold standard for definitive diagnosis. Culture was positive in half of our patients. *Sporothrix* was detected by PCR in more than 2/3 of those with negative cultures. Sensitivity of combining both methods was higher. Both culture and PCR test failed to detect *Sporotrix* despite granulomatous dermatitis with spores demonstrated in the histopathological examination of four patients. Culture and PCR results in our study may have been affected by specimen handling during transportation as district hospitals are located far from the laboratory. An increasing trend of *S. globosa* infection has been observed in Jilin China, Japan and India (Rodrigues et al. 2014; Moussa et al. 2017). *S.globosa* transmission is almost exclusively saprotic (Kauffman et al. 2007; Moussa et al. 2017). All of our PCR results revealed *S. schenkii senso stricto* species. This is the only species identified thus far in both cats and humans in Malaysia (Kamal Azam et al. 2020).

Therapeutic response

Therapeutic options for cutaneous sporotrichosis include local measures, oral saturated solution of potassium iodide (SSKI), azoles, polyenes and allylamines (Kauffman et al. 2007). Complete resolution of lesions was observed in all our patients treated with an average of 4 months of itraconazole or terbinafine with no adverse effects. This is in keeping with success rates of 90%–100% with low rates of adverse events in previous reports (de Lima Barros et al. 2011; Song et al. 2011; Sharkey-Mathis et al. 1993; Conti Diaz et al 1992). Drug resistance is unlikely as re-treatment with itraconazole in one of our patients who developed re-infection was successful.

CONCLUSION

Zoonotic transmission via cats is the main mode of sporotricosis transmission in our population. Lymphocutaneous subtype with primary lesions in the upper limbs is the most common clinical presentation. Culture with PCR optimizes laboratory confirmation of the diagnosis. *Sporothrix schenkii sensu stricto* is the only species identified. Itraconazole remains the most effective first line treatment in cutaneous sporotrichosis.

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