Chronic Recurrent Dermatophytosis in the Tropics: Studies on Tinea Imbricata in Indonesia

Kusmarinah Bramono

Department of Dermato-Venereology, Faculty of Medicine, University of Indonesia, Jakarta

= Abstract =

Dermatophytosis is one of the major public health problems in tropical countries, especially the chronic recurrent type. Tinea imbricata (TI), a dermatophytosis caused by *Trichophyton concentricum* (TC), is endemic in several remote and isolated areas in Indonesia. This dermatophytosis is unique due to its predominant genetic predisposition, which leads to chronic recurrent conditions among the affected. Moreover, hot and humid climate, low socio-economic conditions, lack of hygiene, inadequate treatment due to difficult access to health care facilities, and persistent source of re-infections, are among other factors that maintain the chronic-recurrent state. Studies on TI in Indonesia have been done since the 1960s, encompassing the epidemiology, clinical features, and efficacy of antifungal treatment. Griseofulvin is still the mainstay treatment, but relapse rates are high. The latest effort in reducing relapse includes the training of healthcare providers and provision of fungal disinfectant for clothing and bedding to patients in West Papua in addition to standard treatment. Higher cure rate was achieved at the end of treatment and the four-month follow-up in comparison to previous studies. Parallel studies on the same patient populations showed that: 1. clothing and bedding were fomites and potential sources of re-infections; 2. sodium hypochlorite worked well as a fungal disinfectant, followed by anionic detergent and pine oil containing cleaner; 3. terbinafine was the most effective antifungal agent for TC *in vitro*, followed by griseofulvin; itraconazole, and fluconazole were less effective. In conclusion, to eradicate TI in endemic areas, appropriate and affordable antifungal treatment, concurrent with health education and efforts to identify and eradicate the source of re-infections are very important.

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Key Words: Tinea imbricata, Indonesia

INTRODUCTION

Dermatophytosis is still an important public health problem in the world, especially in tropical countries where yearlong warm temperature and high humidity are ideal environment for fungal growth. This disorder is not fatal, but the intractable pruritus and cosmetic disfigurement that affect the patients can decrease their quality of life and productivity. The chronic recurrence condition will create an economic burden, and the repeated

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†Corresponding author: Kusmarinah Bramono, jl. Bambu Kuning # 15 Jakarta, 12560 Indonesia.
Tel: +62-21-7812677, Fax: +62-816-808336, e-mail: kbramono@yahoo.com

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and long-term treatment will increase the risk of antifungal resistance. Recurrences could be related to inadequate treatment, difficulties in eliminating the predisposing factors, and unnoticed source of re-infection.

One type of chronic recurrent dermatophytosis is tinea imbricata (TI), which has many local synonyms such as kaskado in Papua, kihis in Central Kalimantan, chimbere in Bolivia, and le pita in Tokelau island. TI is endemic in several remote and isolated tropical areas in South Pacific, South-East Asia, Central and South America, and Mexico[1,2]. In Indonesia, the endemic foci are located in Sulawesi, Papua, Kalimantan, and some of the islands in the middle part of Eastern Indonesia[3].

This dermatophytosis is caused by *Trichophyton concentricum* (TC), a slow growing anthropophilic dermatophyte, that appears to be population-group specific, as it is found in particular races, but not easily transmitted to other races. It affects the skin and scalp, but never on the hair. The nail is sometimes affected. Clinically, it is characterized by multiple scaly papulosquamous plaques arranged in concentric rings, with the free edges of the scales facing the center. There is slight or no erythema. Early lesions are usually very pruritic, but it may be absent in the chronic stage. In some cases, clinical pattern variations can be found due to scratching or coexistence of other skin diseases. The diagnosis of TI is mostly based on clinical examination and direct mycological examination. Fungal culture is needed when the characteristic concentric rings are not present[2,4].

During the last three decades, several studies on TI had been done in Indonesia. Several aspects of TI that can be obtained from those studies, e.g. epidemiology, clinical patterns, and responses to treatment with antifungal agents will be discussed in this manuscript with brief remarks on the related studies outside of Indonesia. The recent study on TI treatment that was conducted in West Papua with simultaneous studies on the detection of fomites, effort to eliminate viable TC with disinfectants, and sensitivity of TC against antifungal agents will also be described.

Epidemiology

Indonesia is a vast equatorial archipelago of around 17,000 islands, with 5 largest islands of Sumatra, Java, Kalimantan (Indonesian Borneo), Sulawesi, and the Indonesian part of New Guinea (known as Papua or Irian Jaya). Based on data from the 1970s cited by Widyanto[5], TI was still endemic in all the 5 big islands, including the most developed island Java. The prevalence in Mauk village, West Java, was very low 7.3/10,000 population (0.07%). The prevalence in remote areas outside Java was believed to be much higher, but the accurate number was not available. However, based on the prevalence number of 18% in remote area in New Guinea[6] and 9.1% in remote area in Malaya[7], the prevalence in the other islands in Indonesia must be more or less the same. In Java, TI was mostly found in the coastal area[5,8].

A follow-up study in the 1980s at the same village of Mauk[5] showed a bit lower prevalence of 0.04% (4.3/10,000), with a male to female ratio of 1:1. The youngest was 9-years old and the oldest was 70 years old, with peak incidence between 40~49 years old. The average duration of the disease was 17.3 years, ranging from 7.2~27.5 years. In this study, a trichophytin intradermal test revealed that 97% patients showed no response of delayed hypersensitivity, indicating decreased cellular immunity. A similar result was also reported by Hay in his survey in Papua New Guinea[9].

In the 1990s, a survey on TI was conducted by Budimulya in 23 villages located at Central Kalimantan[10]. The results revealed average prevalence of 2.83%, ranging from 0.06~20.14%. Vil-

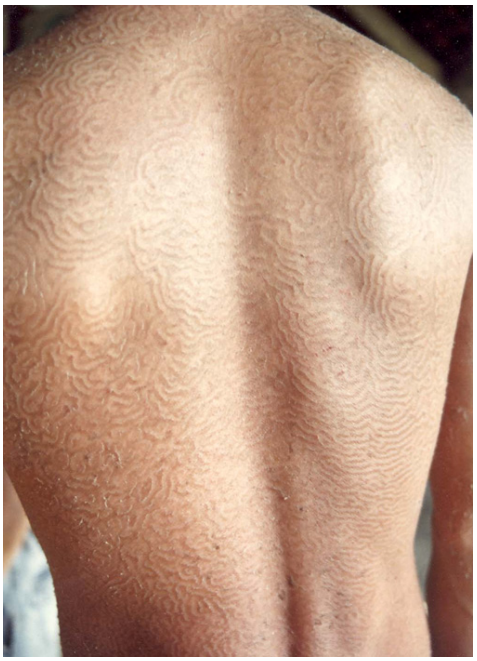

Fig. 1. The classic concentric imbricated rings.

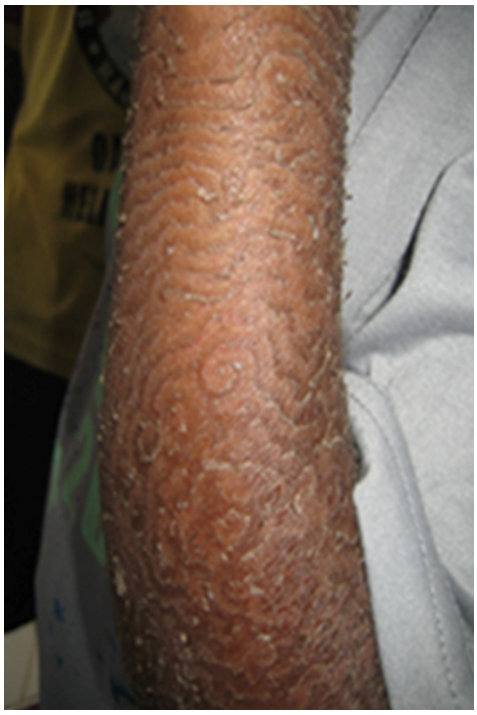

Fig. 2. The lamellar pattern with large coarse scales.

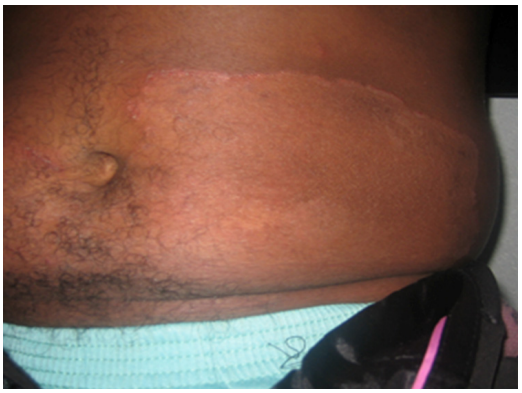

Fig. 3. The hypochromic pattern which still show active border.

lages with low prevalence were located close to the big cities. The youngest age affected was 6 months old, and the oldest was 70 years old, with peak incidence between 25~44 years old. This survey also showed that male and female were equally affected. They were from low socioeconomic status with low education level and poor personal and environmental hygiene. A genetic study in concomitant with the survey confirmed that susceptibility to TI was inherited through the autosomal recessive trait, which was already shown in previous studies[11,12].

All of these studies indicated that TI occurs in all age group in a chronic manner, which can begin at a very young age, with no gender predominance.

Despite the persistent high prevalence number in the endemic foci in Kalimantan and Papua since the 1990s, the endemic foci in Java is no longer existent[10]. Java is currently the most populous island with mixed ethnicity, and compared to the other islands it is the most developed in terms of socioeconomic condition, healthcare facilities, and transportation. It is possible that those conditions that are found in Java attributed to the decline of TI incidence.

Clinical patterns

Widyanto[5] reported only 20% of his cases suffered from pruritus in Mauk, West Java. He also revealed that more than 50% of the cases had widespread lesions on the whole body, with some involving the scalp and nail. Among the cases with localized lesions, 80% had characteristic concentric features; but in cases with widespread lesions, all of them were ichthyosiformis with no concentric rings.

Budimulya[10] reported that 67% of his cases in Central Kalimantan had more than 50% skin involvement, while about 17.5% was universally affected. Unlike the findings by Widyanto, all of the cases had specific concentric lesion configurations.

Based on the clinical features variation, Hay et al.[13] distinguished 7 different patterns from a study in Goodenough island, Papua New Guinea in 1984: concentric, lamellar, lichenified, plaque-like, annular, palmar/plantar, and onychomycosis. They also found that hypopigmentation was the prominent feature. In 2004, Bonifaz et al.[1] added 2 more patterns to the list: seborrheic-like and hypochromic/hyperchromic. It is speculated that the skin clinical variations are related to chronic scratching.

The study in Raja Ampat found that out of 47 cases, 6 (12.8%) had lesions on the whole body and 3 (6.4%) with onychomycosis. Pruritus was present in 89% of the cases. The clinical features varied, comprising of all proposed by Bonifaz, with a trend that each village had a particular predominant feature. It is yet to be investigated whether the clinical feature variant is only due to chronic scratching, or also due to different strain of TC or other patient's habit.

The diagnostic confirmation of TI with direct fungal examination and culture are necessary since several reports indicated that concentric rings mimicking TI could be present in other skin diseases[14~17]. Furthermore, the characteristic feature is not always present in TI. However, the remote location of the endemic area makes culture impractical. The delayed culture examination and the slow-growing nature of TC, which is easily contaminated, resulted in low success rate of isolation as reported by Pihet et al. (33%)[18] and Wingfield et al. (61%)[19]. Specimen pre-treatment with 70% alcohol as suggested by Budimulja et al.[5] produced better success rate, as was also shown by our Raja Ampat Study with 93.6% success rate.

Responses to antifungal treatment

Almost all the TI studies in Indonesia were associated with antifungal treatment assessment. In 1965, Halde and Ong[8] used various dosage schedules of griseofulvin on hospitalized cases in West Java. Eighty eight percent of the cases responded well to the treatment, but relapse occurred in 59% of the cases within 3-4-month follow-up.

In 1988, a study in Sulawesi evaluated ketoconazole at 200 mg/day on 23 cases[20]. Only 3 out of the 23 cases showed clinical clearance, but all of them still showed positive KOH examination.

An open study on griseofulvin 250~500 mg/day versus terbinafine 250 mg/day for four weeks was conducted in Central Kalimantan in 1992[21]. The result was 47.8% and 90% clinical cure and 86.7% and 43.5% mycological cure, respectively for griseofulvin and terbinafine. Drop-out in the griseofulvin group was 38%, but none in the terbinafine group. Relapse rate two weeks later was 22% in griseofulvin, none in terbinafine. In 1993 the same investigators[22] evaluated terbinafine at 250 mg/day versus itraconazole at 100 mg/day for four weeks, and showed 100% clinicomycological cure rate in the terbinafine group versus 88.6% in the itraconazole group. Relapse rates three months later were 16.2 and 75% for

terbinafine and itraconazole groups respectively. Drop-out rate was as high as 22.5%.

In 2004, Wingfield et al. compared[19] four weeks terbinafine at 250 mg/day, or griseofulvin 2 × 500 mg/day, or fluconazole 200 mg/week, and one week itraconazole 2 × 200 mg/day for TI patients in Southern Papua. Drop-outs of 31.4% were observed. The clinical cure rates were 98%, 80%, 33%, and 8% respectively for the treatments regiments above among the returned cases. Itraconazole showed the highest relapse rate at follow-up.

Our last study in Raja Ampat islands used a different approach. To empower the locals to assist TI treatment program, health education and training on the detection and management of TI were conducted for the local healthcare providers (local doctors, midwives, and nurses) and volunteers. They were then involved in TI surveillance and treatment program and case follow-up in their community. Among a total of 47 cases eligible for systemic antifungal treatment, griseofulvin 2 × 500 mg/day for six weeks was given for 28 cases with an adjusted dose for children. For 11 cases with a history of unresponsiveness to griseofulvin or with onychomycosis, terbinafine 250 mg/day for four weeks (for skin involvement) and three months (for onychomycosis) were provided. All patients were given sodium hypochlorite solution and pine oil containing cleaner to clean their clothing and bedding in addition to their own daily used detergents. The healthcare volunteers were assigned to monitor the treatment and hygiene compliance. The results which were recorded with the help of the local healthcare providers showed 89.3% clinical cure rate in griseofulvin group at the end of treatment and 78.5% at four-month follow-ups. In the terbinafine group, 100% clinical cure rate was seen on both observations. There were 14.6% drop-outs with known reasons, such as allergic reaction or incompliance. These results indicated that the involvement of the local healthcare providers and healthcare volunteers in the TI controls helped to reduce the drop-out's number. The higher total dose of griseofulvin might have contributed to the higher cure rates and lower relapses.

Fomites and disinfectants in *Trichophyton concentricum*

Relapses in dermatophytosis can be due to an inadequate treatment or inadequate cellular immune response resulting in a remaining hidden source of viable fungus on the skin or nail. However, it also could be due to re-infection from other patients, fomites, or infective arthrospores found in the environment[23~25].

In concomitant with the treatment study in Raja Ampat, a study to identify the presence of viable fungus in the clothing and bedding of the patients was conducted. The result showed that viable TC was recovered in 15 out of 40 (37.5%) patients' clothing samples and 9 out of 40 (22.5%) bedding samples[26]. Those results proved that clothing and bedding are potential fomites for disease transmission and source of re-infection in TI.

The study was followed by an investigation on the disinfectant activities of several household cleaners commonly used in Raja Ampat: anionic detergent 0.2% w/v, sodium hypochlorite solution 5.25% w/v, and a pine oil containing cleaner. Chlamydospores-rich isolates was subjected to the cleaner solutions for 15, 30, 60, 120 minutes. It showed that sodium hypochlorite killed all isolates within 15 minutes, anionic detergent killed 68% after 120 minutes, and pine oil containing cleaner killed 50% after 120 minutes[27].

Susceptibility of *Trichophyton concentricum* to antifungal agents

Griseofulvin has been the mainstay treatment

for dermatophytoses in the developing world. It is relatively cheap and safe for the treatment of dermatophytoses[28]. Long term use of antifungal agent will lead to the emergence of resistant fungus. In order to elucidate the presence of resistant TC to antifungal agents, an antifungal susceptibility study was conducted. Using the disk diffusion method, 40 TC isolates from Raja Ampat population was subjected to terbinafine, griseofulvin, itraconazole, and fluconazole. The results showed that the sensitivity was 100% to terbinafine, 65% to griseofulvin, 27.5% to itraconazole, and 2.5% to fluconazole[29]. This *in vitro* result reflected the clinical efficacy of these antifungals.

Conclusions

Based on the many factors that influence the chronic-recurrence of TI, a multi-approach program is needed in TI eradication. Griseofulvin is still effective, but resistant strains should be given terbinafine. Since the genetic predisposition is difficult to eliminate, aside from affordable and adequate treatment, a susceptible person should be kept away from infectious source. It is necessary to identify and to manage the source of re-infection such as unnoticed nail infection, infected contact person, fomites, and other potential source of infection in the surrounding environment. Since most endemic areas are located in remote locations, the role of local healthcare providers, either professionals or volunteers are very important to maintain close monitoring of the patients.

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