Am. J. Trop. Med. Hyg., 107(6), 2022, pp. 1196–1202
doi:10.4269/ajtmh.22-0108

Case Report: Autochthonous Disseminated Cutaneous, Mucocutaneous, and Visceral Leishmaniasis Caused by *Leishmania martiniquensis* in a Patient with HIV/AIDS from Northern Thailand and Literature Review

Saranya Srivarasat,[1] Narisa Brownell,[2] Padet Siriyasatien,[2] Nopadon Noppakun,[1] Pravit Asawanonda,[1] Krittaya Rattanakorn,[3] Kanok Preativatanyou,[2]* and Chanat Kumtornrut[1]*

[1]*Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;* [2]*Center of Excellence in Vector Biology and Vector-Borne Disease, Department of Parasitology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;* [3]*Division of Dermatology, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand*

Abstract. Autochthonous leishmaniasis cases have been increasing continuously in Thailand over the years. We report multiple presentations of leishmaniasis in a 47-year-old patient with HIV/AIDS from Chiang Rai Province, northern Thailand. Physical examination showed multiple ulcerated papules, nodules, and plaques in a sporotrichoid distribution. Firm mucosal nodules on the hard palate and nasal opening, hepatosplenomegaly, and bilateral inguinal lymphadenopathy were found. Histopathological examination of the biopsies revealed an inflammatory infiltrate containing intramacrophage amastigotes compatible with *Leishmania* infection. In addition, *Leishmania* promastigotes were isolated successfully from the palatal biopsy and assigned the code MHOM/TH/2022/CULE6. Using internal transcribed spacer 1 polymerase chain reaction and sequence analysis, the causative parasite was identified as *Leishmania martiniquensis*. A definitive diagnosis of multiform leishmaniasis with disseminated cutaneous, mucocutaneous, and visceral involvement was established. The patient was administered intravenous amphotericin B 1 mg/kg/d for 2 weeks, followed by oral itraconazole 400 mg daily. At the 2-month follow-up, the cutaneous and mucosal lesions had improved significantly. To our knowledge, this is the first report of mucocutaneous involvement caused by *L. martiniquensis* in an immunocompromised patient with HIV/AIDS. In addition, we provide a literature review of leishmaniasis cases, reported formally in Thailand, resulting from this autochthonous parasite.

INTRODUCTION

Leishmaniasis is a neglected infectious disease with a varied clinical spectrum that can be categorized into cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (MCL), and visceral leishmaniasis (VL).[1,2] The variation of clinical presentation depends primarily on the infecting species and host immune status.[3] *Leishmania martiniquensis* is an obligatory intramacrophage trypanosomatid that belongs to the newly identified subgenus *Mundinia*.[4] This parasite has been reported previously in horses with CL in the United States and Central Europe, and in bovines in Switzerland.[5–7] Since 1996, leishmaniasis cases in Thailand have been increasing continuously, mostly in northern and southern provinces, and most of these autochthonous cases were identified as *L. martiniquensis*.[8] Autochthonous leishmaniasis caused by *L. martiniquensis* can exhibit various clinical manifestations, including localized cutaneous leishmaniasis, disseminated or diffuse cutaneous leishmaniasis (DCL), and VL.[8–17] However, MCL has not yet been reported in leishmaniasis cases diagnosed with *L. martiniquensis*. We present the first confirmed case of a patient with HIV with multiform presentations of DCL, MCL, and VL caused by *L. martiniquensis* from northern Thailand. More importantly, we compile all clinical literature data on indigenous leishmaniasis resulting from this parasite in patients reported formally, which will help clinicians to diagnose accurately and provide more effective treatment of this emerging parasitic disease, especially in patients with HIV/AIDS.

CASE DESCRIPTION

A 47-year-old woman with HIV from Chiang Rai Province presented with multiple ulcerated plaques surrounded by a roll-edged border on both shins for 3 months. The lesions first appeared on her groins 5 years earlier and then spread progressively to her torso, extremities, and face. She denied a history of traveling abroad. Her current antiretroviral medications included tenofovir, nevirapine, and lamivudine.

Physical examination showed multiple ulcerated papules, nodules, and plaques all over the face and body. The lesions on both the upper and lower extremities were arranged in a sporotrichoid pattern. Multiple firm nodules on the hard palate mucosa and nasal opening, hepatosplenomegaly, and bilateral lymphadenopathy on both sides of her groins were noted (Figure 1). Biopsies from the papulonodular lesion on her left leg, palatal nodule, and right inguinal lymph node revealed an inflammatory infiltrate consisting of lymphocytes and macrophages with numerous intracellular amastigotes, suggestive of leishmaniasis (Figure 2). Laboratory investigations revealed a CD4 count of 185 cells/mm^3, a hemoglobin level of 10.9 g/dL, a white blood cell count of 2,700 cells/mm^3 (neutrophils, 68.6%; lymphocytes, 22%; monocytes, 7.5%; eosinophils, 1.3%; and basophils, 0.6%), a platelet count of 100,000 platelets/mm^3, and normal liver function test. Computed tomography of the whole abdomen also showed hepatosplenomegaly without focal lesions, and multiple subcutaneous nodules along the posterior back and bilateral groin nodes. *Leishmania martiniquensis* DNA was detected molecularly in her saliva, cutaneous nodular biopsy, and whole blood specimens using *Leishmania*-specific polymerase chain reaction (PCR) targeting the internal transcribed spacer 1 (*ITS1*)

*Address correspondence to Kanok Preativatanyou, Center of Excellence in Vector Biology and Vector-Borne Disease, Department of Parasitology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, E-mail: kanok.pr@chula.ac.th **or** Chanat Kumtornrut, Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, E-mail: chanat_1@yahoo.com

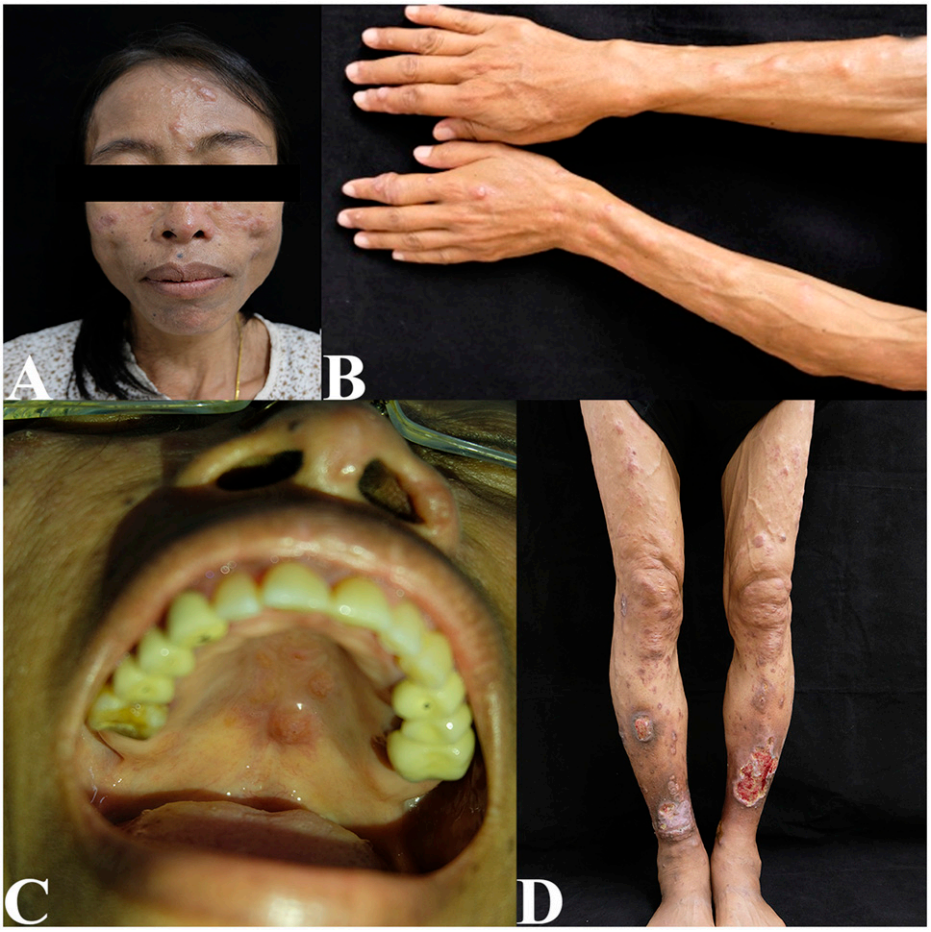

FIGURE 1. (**A**) Multiple cutaneous nodules on the face. (**B** and **D**) Disseminated papules, nodules, and plaques were arranged on the extremities in a sporotrichoid manner. (**C**) Mucocutaneous nodules were also observed on the hard palate.

region, as described previously[18] (Figure 3). Furthermore, *Leishmania* promastigotes were cultivated successfully from the palatal nodule specimens. Our culture isolate was given the WHO code MHOM/TH/2022/CULE6. Sanger sequencing and a nucleotide BLAST (BLASTn) search indicated that the retrieved *ITS1* sequence was 100% identical to the *L. martiniquensis* reference in the GenBank. Phylogenetic analysis also reaffirmed that the obtained sequence clustered closely with other *L. martiniquensis* sequences available in the database (Figure 4). The identified sequence was submitted to GenBank under accession no. OM688240.

Therefore, we established a definitive diagnosis of autochthonous multiform leishmaniasis, including DCL, MCL, and VL, resulting from *L. martiniquensis* in our patient. She was treated with amphotericin B deoxycholate 1 mg/kg/d for the first 2 weeks, followed by 400 mg daily of oral itraconazole. The mucosal nodules resolved during the 2-month follow-up, and cutaneous patches and papulonodules improved significantly.

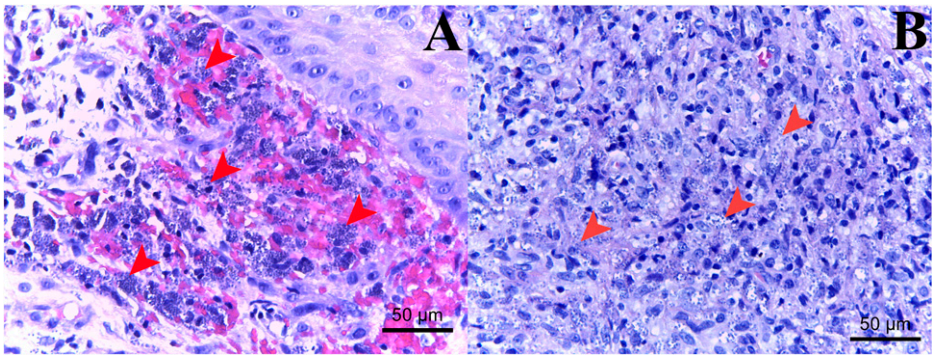

FIGURE 2. Histopathological examination of the tissue biopsies from the cutaneous papulonodule (**A**) and the hard palate nodule (**B**) demonstrates a chronic lymphohistiocytic infiltrate of lymphocytes and heavily parasitized macrophages containing numerous *Leishmania* amastigotes (arrowheads).

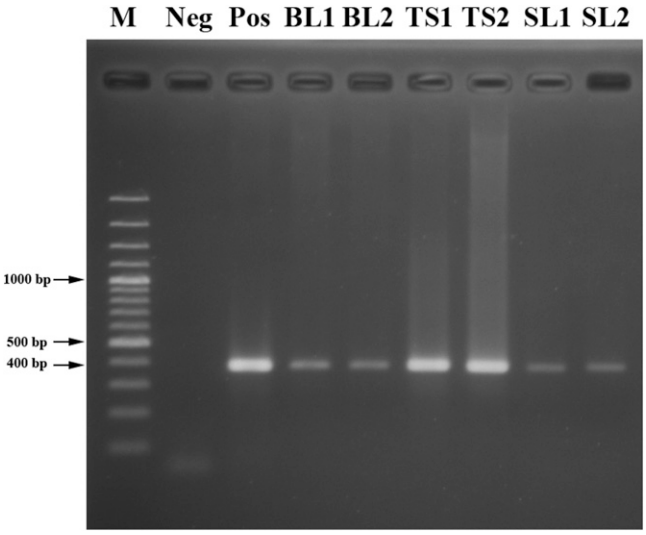

FIGURE 3. Agarose gel (1.5%) electrophoresis shows internal transcribed spacer 1 polymerase chain reaction products with a size of 379 bp, amplified from the clinical specimens (whole blood, nodule biopsy, and saliva) of this patient. BL1/2 = whole blood samples 1 and 2, respectively; M = 100-bp ladder marker; Neg = negative control; Pos = *Leishmania martiniquensis* positive control; (Pos); SL1/2 = saliva samples 1 and 2, respectively; TS1/2 = tissue biopsies 1 and 2 respectively.

DISCUSSION

Leishmaniasis is a multispectral disease that can manifest clinical polymorphisms including CL, MCL, and VL, depending on the infecting species and host immune responses.[1–3] In general, clinical manifestations of CL can vary from localized to disseminated or diffuse cutaneous papules, plaques, and nodules with central ulceration, typically surrounded by roll-edged borders. In addition, severe CL in the head region may progress into the so-called leonine face.[1,2] Our patient presented with disseminated papulonodular lesions distributed linearly along the lymphatic system of the extremities, exhibiting a sporotrichoid pattern. This pathognomonic manifestation suggests lymphocutaneous involvement, most likely a result of various infectious diseases (e.g., atypical mycobacteria infection, sporotrichosis, nocardiosis, and leishmaniasis) and noninfectious causes (e.g., lymphoma and lymphocutaneous metastasis).[19] Microscopic examination of the cutaneous lesion and groin node biopsies also revealed a chronic inflammatory infiltrate containing lymphocytes and heavily parasitized macrophages. In addition, pancytopenia, hepatosplenomegaly, and lymphadenopathy were found, consistent with VL.

More interestingly, this patient also presented with nodules on the hard palate mucosa and nasal opening (Figure 1C), prompting a clinical suspicion of MCL. MCL, or so-called espundia, is typically caused by members of the *Viannia* and *Leishmania* subgenera, including *Leishmania* (*Viannia*) *braziliensis*, *Leishmania* (*Viannia*) *guyanensis*, *Leishmania* (*Viannia*) *panamensis*, and *Leishmania* (*Leishmania*) *amazonensis*.[20] The progression of mucocutaneous involvement usually depends on the host immune status and the infecting *Leishmania* species.[20,21] This manifestation could result from either a direct extension or hematological spreading to the upper respiratory tract. If left untreated, the nasal septum can be perforated, resulting in tissue ulceration and deformation of the nasal bridge, also known as tapir nose.[21] However, MCL in patients with HIV needs to be diagnosed differentially with other opportunistic infections, such as tuberculosis, syphilis, and paracoccidioidomycosis as well as HIV-associated cancers such as Kaposi sarcoma.[20–22] In our patient, a palatal nodule was also sampled for histopathological examination and showed a lymphohistiocytic infiltrate with intramacrophage amastigotes. In addition, *Leishmania* promastigotes could be isolated successfully from the palatal biopsy, confirming MCL. Therefore, our patient is the first case of leishmaniasis with mucocutaneous involvement that has ever been reported in Thailand.

In our patient, histopathological examination, promastigote isolation, *Leishmania ITS1*-specific PCR, and DNA sequencing helped ensure the accurate diagnosis of autochthonous multiform leishmaniasis. Positive *ITS1* amplification was shown in all clinical samples, including whole blood, tissue biopsy, and saliva. Based on the BLASTn result, *L. martiniquensis* was diagnosed. Consistently, our retrieved sequence was clustered phylogenetically with other *L. martiniquensis ITS1* sequences derived from the cutaneous lesion of a patient with HIV and DCL from Lamphun Province, northern Thailand (accession no. MG731229); the bone marrow of a patient with HIV and VL (accession no. JQ001751); and *Sergentomyia khawi* sandfly (accession no. MK603826) from Songkhla Province, southern Thailand with very high bootstrap support.[12,16,23] Also, the *ITS1* phylogenetic analysis revealed the identification of *L. martiniquensis*, including our isolate, as a member of the same *Mundinia* clade as *L. enriettii*, *L. orientalis*, and *Leishmania* sp. *Ghana*.

As reviewed in Table 1, most of the autochthonous leishmaniasis cases infected by *L. martiniquensis* in the country are people with HIV who have a CD4 count of < 200 cells/mm^3, indicative of WHO clinical stage 4 of HIV infection or AIDS.[24] It was noted that VL was common in all reported patients, whereas combined DCL and VL were diagnosed exclusively in most HIV-infected cases. In addition, DCL has been reported in an HIV-seronegative Burmese male who was treated with prednisolone.[14] Thus, this indicates that a severe form of CL caused by *L. martiniquensis* is mainly associated with immunosuppression, especially resulting from HIV infection and steroid therapy. Previous studies[24,25] claimed that *Leishmania* can induce HIV replication, consequently accelerating the AIDS status. In addition, stimulation of the T-helper type 1 (Th1) immune response, which is the main protective mechanism against leishmaniasis, was found to decrease significantly in patients with coinfection of HIV and VL.[26] HIV infection also induces the T-helper type 2 (Th2) response that provokes the disease progression of leishmaniasis.[27] Therefore, suppressed Th1 and activated Th2 immune responses in patients coinfected with HIV and *Leishmania* can affect the progression of disease severity and cause a high relapse rate.[24–28] In our patient, we also speculated that atypical disease progression to MCL was most likely a result of her severely immunodeficient status. Furthermore, nephritis & nephrotic syndrome has been reported[10] previously as a complication in a male patient with VL coinfected with HIV and *L. martiniquensis* from Chanthaburi Province, eastern Thailand.

Amphotericin B has been considered the drug of choice for the treatment of VL in Thailand. This antileishmanial drug is highly effective, with a high cure rate in immunocompetent patients.[29] However, a high incidence of relapses of VL and DCL after treatment with amphotericin B has been

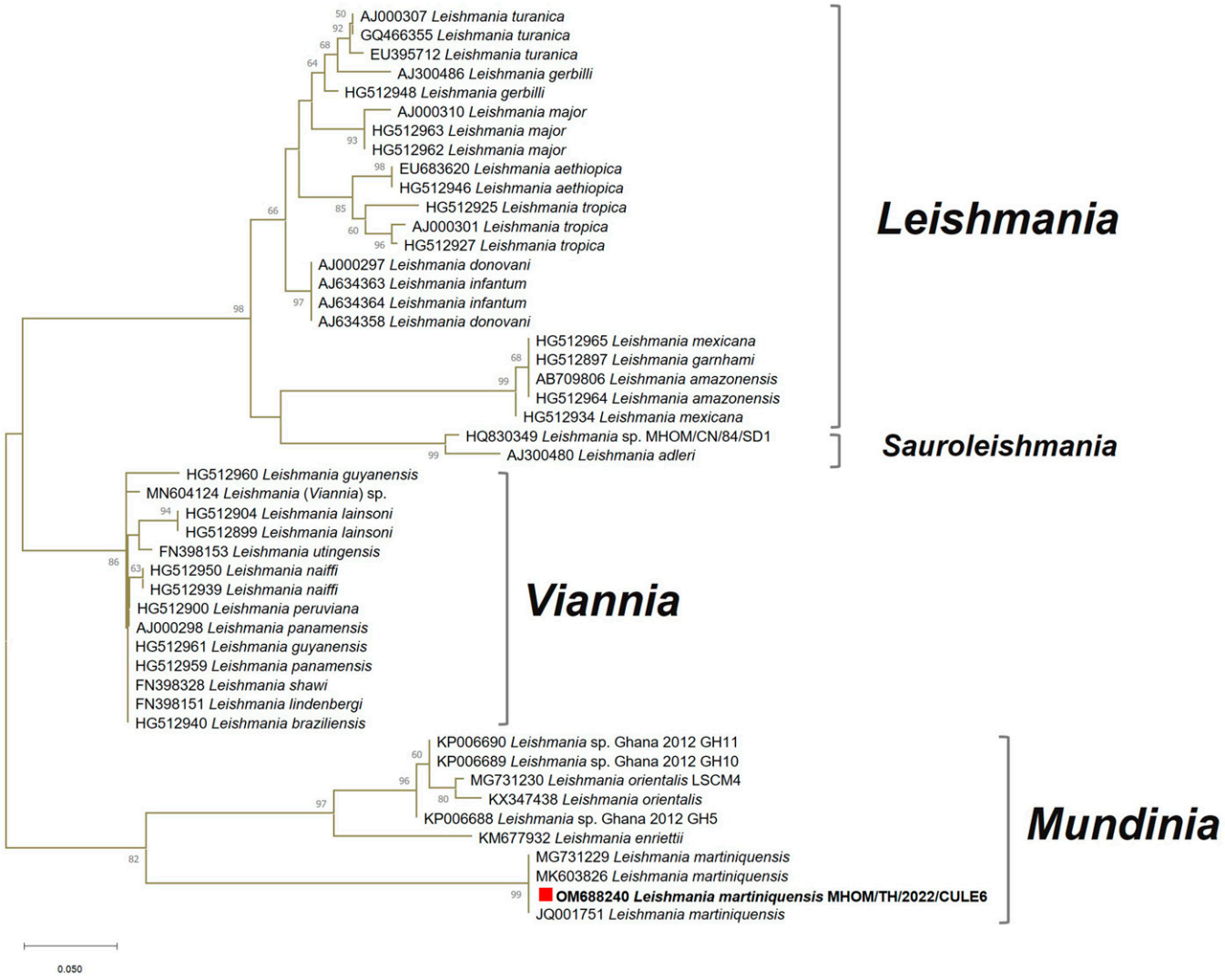

FIGURE 4. Phylogenetic analysis of enrolled *Leishmania* internal transcribed spacer 1 sequences from four *Leishmania* subgenera identified our clinical isolate as *Leishmania martiniquensis* in the *Mundinia* clade.

documented, especially in patients with HIV/AIDS.[30] According to our literature review (Table 1), some indigenous cases in Thailand had an early relapse shortly within the first 6 months after first-line antileishmanial therapy, and the occurrence of relapse could last up to 3 years.[9,11–13,16,17] As recorded, an extended course of amphotericin B with 6 consecutive months of prophylaxis was administered to a 7-year-old girl who was seronegative, with two episodes of relapse before a definitive cure was obtained.[11] In addition, reduced efficacy of amphotericin B against *L. martiniquensis* CU1R1 isolated from a patient who experienced a relapse from Songkhla Province was reported,[31] suggesting that clinicians might need to increase the dosage of chemotherapy, extend the duration of treatment, and monitor closely those patients who relapse. Hence, a combination of parasite virulence, host immune status, and drug resistance could affect treatment outcomes.[31]

Because of the continuous increase of autochthonous cases in Thailand, this situation has raised the question of which insects are the primary vectors responsible for disease transmission in the country. Phlebotomine sandflies have been widely accepted as the natural vectors of *Leishmania* parasites in the subgenera *Viannia*, *Leishmania*, and *Sauroleishmania*.[32,33] However, the principal vectors and reservoirs of *Leishmania* species in the subgenus *Mundinia* remain unclear.[34,35] In Thailand, *S. khawi*, *Sergentomyia barraudi*, *Sergentomyia iyengari*, and *Phlebotomus stantoni* have been previously proposed as possible vectors of *L. martiniquensis*.[23,34,36,37] Furthermore, *Culicoides mahasarakhamense* biting midges collected from the CL transmission area in Lamphun Province recently showed positive for *L. martiniquensis* DNA, supporting a possible role of a leishmaniasis vector in northern Thailand.[38] In addition, *L. martiniquensis* DNA was detected in the liver tissues of the black rat (*Rattus rattus*) from Songkhla Province, and the buffy coat of the black rat from Chiang Rai, implicating it as a natural reservoir in Thailand.[34,37] Ultimately, molecular characterization of virulence in *L. martiniquensis* clinical isolates needs to be elucidated further to help us better understand this emerging parasite for developing effective treatment, prevention, and control of this parasitic transmission.

TABLE 1

Review of clinical data on indigenous leishmaniasis resulting from *Leishmania martiniquensis* formally recorded in Thailand from 2006 to date

Year, province, part of the country	Age, gender	HIV status, CD4 count	Form of leishmaniasis	Clinical manifestations (duration)	First-line treatment	Relapse and retreatment
2006, Phang Nga, South[9]	55, male	Negative	VL	Intermittent fever, anemia, weight loss, epistaxis, gum bleeding, hepatosplenomegaly, and pancytopenia (3 years)	Intravenous amphotericin B (100 mg daily) for 2 weeks	Relapse of VL after 2 months (retreatment information not available)
2009, Chanthaburi, East[10]	37, male	Positive, 129 cells/mm^3	VL	Prolonged fever, hepatomegaly, anemia, thrombocytopenia, and nephritis & nephrotic syndrome (8 weeks)	Intravenous amphotericin B (2 mg/kg/d on alternate days) for 2 weeks followed by oral itraconazole (400 mg daily)	No relapse at 3-month follow-up
2010, Stun, South[11]	7, female	Negative	VL	Hepatosplenomegaly, anemia, and thrombocytopenia (2 years)	Intravenous amphotericin B (1 mg/kg/d) for 3 weeks	Relapse of VL twice at 3 and 6 months; cured by amphotericin B (1 mg/kg/d) for 5 weeks with monthly prophylaxis 5 consecutive days for 6 months
2011, Songkhla, South[12,13,17]	46, male	Positive, 175 cells/mm^3 (2011); positive, 207 cells/mm^3 (2014)	LCL, VL	A single, punched-out 3 × 3 cm ulcer on the left knee; left groin lymphadenopathy; and anemia (a few months before first admission) Hepatosplenomegaly and thrombocytopenia (4 weeks after receiving a high dose of steroids during the first admission)	Intravenous amphotericin B (1 mg/kg/d) for 2 weeks followed by oral itraconazole (400 mg daily)	First relapse after 2 months of itraconazole and retreated with intravenous amphotericin B (3 mg/kg/d) for 3 weeks followed by oral itraconazole (400 mg daily) Second relapse of multiple cutaneous nodules in 2014 and retreated with intravenous amphotericin B (1 mg/kg/d) for 4 weeks followed by oral itraconazole (300 mg daily) twice a day for 5 months
2011, Trang, South[12,17]	30, male	Positive, 111 cells/mm^3 (2011); positive, 110 cells/mm^3 (2013)	DCL, VL	Multiple papules and plaques with ulcers at the trunk and lower extremities (4 years) Anemia, thrombocytopenia, and hepatosplenomegaly (1 month before admission)	Intravenous amphotericin B (1 mg/kg/d) for 2 weeks followed by oral itraconazole (400 mg daily)	No relapse at 3-month follow-up, but relapse of DCL with multiple papules and ulcers 2 years later (retreatment information not available)
2012, Lamphun, North[15]	52, male	Negative	VL	Subacute fever, weight loss, splenomegaly, and pancytopenia (2 weeks)	Intravenous amphotericin B (1 mg/kg/d) for 3 weeks	Resolved
2013, Chiang Mai, North[16]	48, male	Positive, 121 cells/mm^3	DCL, VL	Multiple, firm cutaneous nodules; hepatosplenomegaly; and pancytopenia (4 years)	Intravenous amphotericin B (1 mg/kg/d) for 20 days followed by oral itraconazole (400 mg daily)	Suspected relapse with multiple papules in December 2014 and continued long-term oral itraconazole
2013, Lamphun, North[16]	38, male	Positive, 543 cells/mm^3	DCL, VL	Multiple hypopigmented papules and nodules, and pancytopenia (4 years)	Intravenous amphotericin B (1 mg/kg/d) for 2 weeks followed by oral itraconazole (200 mg daily)	Resolved
2021, Chiang Rai, North (our patient)	47, female	Positive, 185 cells/mm^3	DCL, MCL, VL	Multiple ulcerated papules, nodules, and plaques; firm mucosal nodules; lymphadenopathy; hepatosplenomegaly; and pancytopenia (5 years)	Intravenous amphotericin B (1 mg/kg/d) for 2 weeks followed by oral itraconazole (400 mg daily)	Improved significantly at 2-month follow-up

DCL = disseminated or diffuse cutaneous leishmaniasis; LCL = localized cutaneous leishmaniasis; MCL = mucocutaneous leishmaniasis; VL = visceral leishmaniasis.

Received February 9, 2022. Accepted for publication August 23, 2022.

Published online November 14, 2022.

Acknowledgments: We acknowledge the staff members of the Division of Dermatology, Department of Medicine, and Center of Excellence in Vector Biology and Vector-Borne Disease, Department of Parasitology, Faculty of Medicine, Chulalongkorn University for their assistance in histopathological, parasitological, and molecular investigations. We also gratefully give thanks to our patient for her contribution to this study.

Authors' addresses: Saranya Srivarasat, Nopadon Noppakun, Pravit Asawanonda, and Chanat Kumtornrut, Division of Dermatology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, E-mails: bellsaranya1992@gmail.com, drnopadon@yahoo.com, fibrosis@gmail.com, and chanat_1@yahoo.com. Narisa Brownell, Padet Siriyasatien, and Kanok Preativatanyou, Center of Excellence in Vector Biology and Vector-Borne Disease, Department of Parasitology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, E-mails: narisa.br@chula.ac.th, padet.s@chula.ac.th and kanok.pr@chula.ac.th. Krittaya Rattanakorn, Division of Dermatology, Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand, E-mail: krittaya.ra005@gmail.com.

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