Case Report: Post-Kala-Azar Dermal Leishmaniasis without Previous History of Visceral Leishmaniasis

Md Golam Hasnain,^{1,2} Mohammad Sohel Shomik,² Prakash Ghosh,² Mamun Or Rashid,² Md Shakhawat Hossain,² Shinjiro Hamano,³ and Dinesh Mondal^{2*}

¹Centre for Clinical Epidemiology and Biostatistics (CCEB), School of Medicine and Public Health, Faculty of Health and Medicine, The University of Newcastle (UoN), New South Wales, Australia; ²Nutrition and Clinical Services Division (NCSD), International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh; ³Department of Parasitology, Institute of Tropical Medicine (NEKKEN), Nagasaki University, Nagasaki, Japan

Abstract. Post-kala-azar dermal leishmaniasis (PKDL) without previous visceral leishmaniasis (VL) is a rare dermatological manifestation of *Leishmania* infection. To date, most of the reported cases neither showed parasitological confirmation nor explained the outcome of treatment. Herein, we report three confirmed cases that were successfully cured after miltefosine treatment.

INTRODUCTION

Post-kala-azar dermal leishmaniasis (PKDL) is a dermal manifestation which usually occurs after treatment of visceral leishmaniasis (VL), and is being studied as a possible source of transmission. It is more prominent in Bangladesh than in India and Nepal.¹ To eradicate kala-azar in southeast Asia, all routes of transmission must be eliminated.^{2,3} The proper diagnosis and management of PKDL cases are key. Although PKDL mainly occurs after VL treatment, some exclusive cases have been reported to occur in patients without a previous history of VL.^{4–7} The identification, confirmation and treatment of such cases were insufficiently described in these reports. Herein, we discuss three parasitologically confirmed cases which were successfully cured after miltefosine treatment. This report also describes how to identify these suspected cases, confirm their diagnosis, and provide a successful treatment option.

CASE 1

A 14-year-old boy had been suffering from the macular type of hypopigmented skin lesions on the face and upper limbs for 12 months (Figure 1). He was referred to the study clinic of International Center for Diarrheal Disease Research, Bangladesh (icddr,b) located in Mymensingh District, Bangladesh. The patient first noticed the lesion on his chin, which then spread to other parts of the face and upper limbs. Three months after the appearance of the skin lesions, he visited a nearby traditional healer but his lesions remained unresolved. Only during a household visit by a team of health workers from another study, was he suspected to be a case of PKDL and referred to the study clinic for further evaluation. The study physician took the patient's history and performed a physical examination. The patient stated he had no history of VL and treatment, but his father had suffered from VL 5 years ago. On physical examination, no abnormalities other than skin lesions were observed, especially no hepatospleno-

megaly. The lesions were nonitching and found to exhibit intact sensitivity. The patient was positive for rk39 strip test. After pictures of the affected skin areas were taken, skin samples were collected and sent to the laboratory of icddr,b, Dhaka, where real-time polymerase chain reaction (PCR) was performed.⁸ The patient was indeed found to be positive for *Leishmania donovani* (LD) DNA. Consequently, he was referred to the subdistrict hospital and treated with oral miltefosine tablet for 12 weeks at a dose of 2.5 mg/kg body weight. He experienced anorexia, nausea, and vomiting. As a result, he was prescribed multivitamin supplements throughout the treatment period, and advised to take antiemetic medication for nausea and vomiting, and oral rehydration saline (ORS) after each episode of vomiting. Twelve months after completion of treatment, he was followed up: His skin lesion completely disappeared (Figure 2) and PCR analysis of a skin sample was negative.

CASE 2

The second case was a 17-year-old female who came to the icddr,b study clinic with a similar macular skin rash on her face for 10 months. According to her statement, the skin lesion first appeared on her chin before spreading to another part of her face. After 6 months, she visited the nearby subdistrict hospital where the physician took her medical history, performed a physical examination and rk39 strip test. The rk39 strip test was positive, and the patient was referred to the icddr,b for parasitological confirmation. At the study clinic, the physician again took her disease history: three of her family members suffered from VL, whereas the patient herself had no previous history of VL or the treatment of it. On physical examination, the patient showed the nonitching macular type of rashes with intact sensitivity. She had no hepatic or splenic enlargement. The skin samples were sent to the icddr,b laboratory for PCR testing, and were positive for LD. The patient was treated with miltefosine for 12 weeks at a dose of 2.5 mg/kg body weight. She experienced weakness, nausea, and vomiting during the first 6 weeks of treatment, which were managed through multivitamin, antiemetic, and ORS. In the 5th week of treatment, she experienced diarrhea; it persisted for 3 days and then resolved spontaneously. Only ORS was taken during the episode. At 12 months after completion of treatment, her facial rash had completely

*Address correspondence to Dinesh Mondal, Nutrition and Clinical Services Division (NCSD), International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), 68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212, Bangladesh. E-mail: din63d@icddr.org

FIGURE 1. Rash before treatment.

disappeared and skin samples tested negative for LD DNA (PCR).

CASE 3

This was a self-reported case of a 36-year-old male who came to the icddr,b study clinic with complaints of skin rashes on the upper part of both thighs for 18 months. At first, he went to the village doctor and then to a skin specialist, but his rash persisted. He mentioned that his skin lesion first appeared on the left thigh, then the right. The study physician took his history; he had no history of VL, but one of his family members had VL treatment. On examination, the physician noted the absence of hepatosplenomegaly and the presence of a nonitching macular type of skin rash with intact sensitivity.

The patient was positive for rk39 strip test. At the icddr,b, skin samples were PCR positive for LD. He received treatment with oral tablets of miltefosine (2.5 mg/kg body weight) for 12 weeks at a nearby subdistrict hospital. Nausea and vomiting experienced by the patient were also managed through antiemetic drugs and ORS. In a follow-up at 12 months after treatment, PCR test results were negative, and the rashes had completely disappeared.

FIGURE 2. Rash after treatment.

Real-time PCR for *Leishmania* diagnosis. Each 3-mm skin punch biopsy sample was stored at -20°C in a microcentrifuge tube containing sodium EDTA Tris (NET) buffer until further processing. DNA was extracted from skin punch biopsies of suspected PKDL patients according to the manufacturer's instructions (DNeasy Blood and Tissue Kit; QIAGEN, Hilden, Germany). Then, quantitative analyses of LD DNA was performed on a Biorad CFX96 icycler system using Taqman primer and probe: 5'-GCGACGTCCGTGGAAAGAA-3', 5'-GGCGGGTACACATTAGCAGAA-3', and reporter (FAM): 5'-CAACGCGTATTCCC-3' (Applied Biosystems Inc., Foster City, CA), as described previously.⁸ In brief, each PCR reaction was performed using 11.0 μL of PCR mix (Applied Biosystems Inc., Foster City, CA) plus 9.0 μL of extracted DNA. Each sample was run in duplicate; however, those samples which showed very late amplification (≥ 40 cycles) were repeated in triplicate.

DISCUSSION

PKDL without a history of VL is a rare dermatological condition, which now poses an advent of quandary in the efforts to eliminate this disease in the Indian subcontinent. Only two such cases have been reported from India but none from Nepal.^{4,5} On the basis of earlier observations in Bangladesh, the proportion of such cases clinically diagnosed among all PKDL was $\sim 9\%$. The incidence of PKDL among cured VL patients is postulated to be 10–17% within 5 years.^{6,9,10} These figures cannot be neglected. Accurate early identification and management of these cases are crucial to eliminating a potential source of outbreak in the future.

The minimum period to be diagnosed as PKDL was 10 months and the maximum was 18 months in three patients. The majority of the patients consulted first with traditional healers or private practitioners before finally being diagnosed with PKDL by the study clinic. Since the median duration for diagnosis after rash appearance is 7 months in Bangladesh and 30 months in India,^{11,12} these patients were diagnosed relatively late by Bangladesh standards. This was probably due to healer shopping by the patient and the absence of specific guidelines to identify such cases.

The patients had a rash like PKDL which was macular—the most common form of PKDL rash in Bangladesh⁶ (nonitching and rk39 strip test positive), which assisted the physician to suspect such PKDL cases. Although none of the cases had a history of VL, they all had family member(s) with a previous history of VL. Therefore, to diagnose such cases, we must consider the aforementioned points, and through field validation, we can standardize case detection of PKDL without VL using set these criteria.

Moreover, these three cases were confirmed to be positive for LD through PCR, whereas previous studies reported from Bangladesh identified cases based simply on clinical diagnosis.^{6,7} Since PCR facilities are available in almost every medical college hospital in Bangladesh, and as the number of cases is very low, we should be able to confirm the potential PKDL cases by PCR at the central level immediately after clinical examination.

Although miltefosine has already been established as the drug of choice for PKDL treatment through several clinical trials in India,^{13–15} the outcome of PKDL cases without VL

after treatment with miltefosine had not been established. This report indicates the success of treatment with miltefosine in treating PKDL cases without previous VL. The adverse events described in this report are all known^{13–15} and manageable with very minimum treatment facilities at the community level.

Moving forward, this report will be useful to the physicians as well as the policy makers on how to suspect, confirm, and treat PKDL cases without a previous history of VL.

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Authors' addresses: Md Golam Hasnain, Faculty of Health and Medicine, University of Newcastle, New South Wales, Australia, and Nutrition and Clinical Service Division (NCSD), International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh, E-mail: mdgolam.hasnain@uon.edu.au. Mohammad Sohel Shomik, Prakash Ghosh, Mamun Or Rashid, Md Shakhawat Hossain, and Dinesh Mondal, Nutrition and Clinical Services Division (NCSD), International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh, E-mails: mshomik@icddr.org, dreamix888@gmail.com, mamorrashid78@gmail.com, realengewe@yahoo.com, and din63d@icddr.org. Shinjiro Hamano, Department of Parasitology, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan, E-mail: shinjiro@nagasaki-u.ac.jp.

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