Corticosteroid Pulse Therapy for Leprosy Complicated by a Severe Type 1 Reaction

Pei-Hsuan Lu, MD; Jing-Yi Lin, MD; Yi-Lun Tsai, MD; Yu-Zon Kuan, MD

A 24-year-old Vietnamese woman presented with a 3-month history of non-itchy erythematous plaques on the face, trunk and limbs. Borderline lepromatous leprosy was confirmed by clinical findings, acid-fast bacilli on skin biopsy specimen and skin smear and a history of exposure. Around the twentieth day of World Health Organization (WHO) multibacillary standard treatment (rifampin 600 mg per month, dapsone 100 mg per day, clofazimine 300 mg per month and 50 mg per day for 1 year), she developed fever, general malaise, blurred vision, cough, nausea, epigastric pain, and arthralgia. The skin lesions also became swollen. During hospitalization, her illness was complicated by retrobulbar optic neuritis, secondary bacterial pneumonia, pleuritis, ascites, hepatitis, antral gastritis, progressive normocytic anemia, and peripheral sensory loss. The patient recovered after receiving systemic steroid pulse therapy (prednisolone equivalent dose 1250 mg) with systemic antibiotics (cefuroxime), adjustment of her anti-lepromatous therapy, and supportive care. She resumed the WHO multibacillary regimen uneventfully. This patient presented with a diverse type 1 reaction, which is a complex immune response in leprosy. We found that the judicious use of high dose steroids followed by a slow tapering course is beneficial in managing patients with a severe type 1 reaction. At the 1-year follow up, the patient had generalized skin hyperpigmentation resulted from long-term clofazamine use and numbness on feet without other systemic sequelae. *(Chang Gung Med J 2008;31:201-6)*

Key words: leprosy, type 1 reaction, optic neuritis, delayed type hypersensitivity, corticosteroid pulse therapy

Leprosy is a chronic granulomatous infection of the skin and peripheral nerves caused by the intracellular bacterium *Mycobacterium leprae*.[1] It is a spectrum of disease presenting with polar tuberculoid (TT), borderline tuberculoid (BT), borderline (BB), borderline lepromatous (BL), or polar lepromatous (LL) forms,[2] based on the immunologic response of the host to *M. leprae*. Several complications may occur during the natural course of this disease. A type 1 reaction, also called a reversal reaction, is a manifestation of a delayed -type hypersensitivity reaction.[3] The clinical presentation includes swollen skin lesions, acral edema, and neuritis. Neuritis classically presents with tender enlargement of the peripheral nerve trunks which are located in fibro-osseous tunnels near the surface of the skin. The sites of predilection include the posterior tibial, ulnar, median, lateral popliteal, and facial nerves. A severe reaction may lead to systemic illness, characterized by a low grade fever, malaise, and anorexia.

CASE REPORT

A 24-year-old Vietnamese woman who had

From the Department of Dermatology, Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine, Taoyuan, Taiwan.
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Correspondence to: Dr. Yu-Zon Kuan, Department of Dermatology, Chang Gung Memorial Hospital. 199, Dunhua N. Rd., Songshan District, Taipei City 105, Taiwan (R.O.C.) Tel.: 886-2-27135211 ext. 3397; Fax: 886-2-27191623;
E-mail: blacksophie@adm.cgmh.org.tw

lived in Taiwan for 5 years presented with a 3-month history of generalized progressive non-itchy erythematous plaques (Figures 1 A and B). The outer margins of these plaques were ill-defined, but the inner margins were well-demarcated. She recalled having an erythematous symptomless plaque on the left side of her inner thigh few years ago, but the rash did not progress until 3 months prior to admission. She had occasional numbness in her hands and feet. She remembered exposure to a person with leprosy in Vietnam during her childhood. On physical examination, she had loss of sensation to light touch and temperature in the center of the skin lesions, and on the palms and soles. There were no palpable enlarged peripheral nerves. We did a skin biopsy on her trunk. A hematoxylin-eosin stain showed slightly foamy histiocytes within the granulomas in the upper dermis (Fig. 2A). Acid-fast bacilli were found on a Fite stain (Fig. 2B) and acid fast stain. The patient was referred to Lo-Sheng Sanatorium. Skin smears performed there showed a bacterial index of 2+. According to the clinical, pathologic, and skin smear features, she was diagnosed with borderline lepromatous leprosy, multibacillary type.

The patient was treated with World Health Organization (WHO) multi-drug therapy (MDT) for multibacillary leprosy with oral rifampin 600 mg, dapsone 100 mg, clofazimine 300 mg on day 1 then 50 mg through day 2 to 28 of a month for 1 year. Around the twentieth day of therapy, she developed a fever, malaise, productive cough, and epigastralgia. In addition, the previous erythematous plaques became swollen (Fig. 1D). Facial (Fig. 1C) and acral edema were observed. After admission, she was given oral prednisolone 30 mg per day (equivalent to 0.6 mg per kilogram per day). Significant laboratory

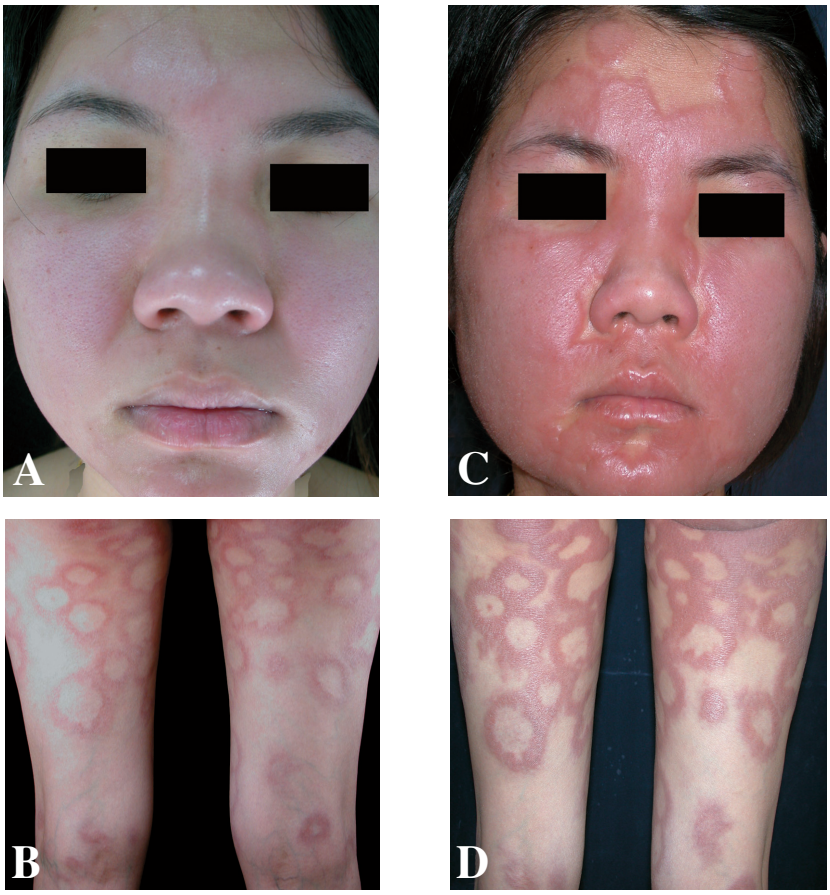

Fig. 1 On initial presentation, multiple erythematous annular plaques on the (A) face and (B) thighs; during the type 1 reaction, edematous erythematous plaques on the (C) face and (D) thighs.

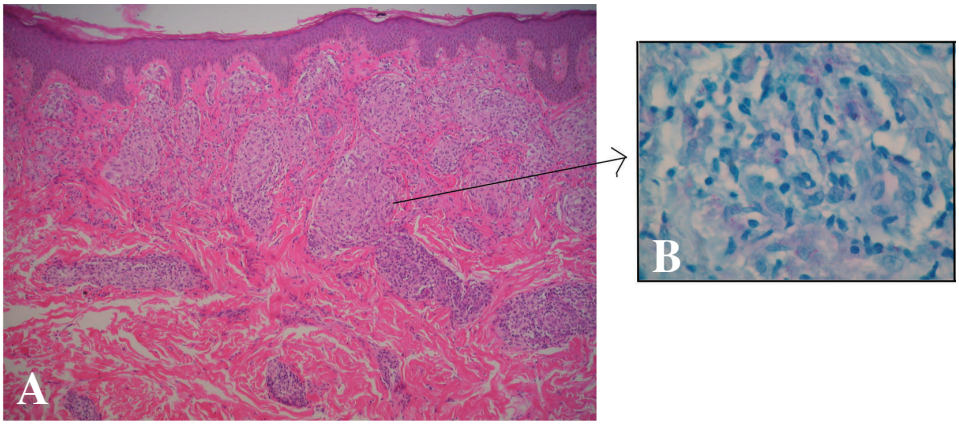

Fig. 2 Multiple granuloma formation in the upper dermis (hematoxylin-eosin, x100) (A) Many acid-fast bacilli shown on a Fite stain (Fite, x 400).

findings included elevated serum levels of alanine aminotransferase (ALT: 592 U/L, normal 0-36 U/L) and aspartate aminotransferase (AST: 437 U/L, normal 0-34 U/L), and normocytic anemia. Moreover, the patient had pneumonia caused by *Hemophilus parainfluenzae*, a right side pleural effusion, antral gastritis, ascites and splenomegaly. Acute painful vision loss in both eyes occurred on the fourth day of hospitalization. Retrobulbar optic neuritis was diagnosed by the clinical presentation and enhanced segments of the retrobulbar optic nerves seen on magnetic resonance imaging (MRI) of the brain. The clinical course is summarized in Fig. 3. The patient was given intravenous methylprednisolone pulse therapy (prednisolone equivalent dose 1250 mg) for 3 days to treat her optic neuritis. One week after the pulse steroid therapy, her body temperature returned to normal and visual acuity completely recovered. Peripheral sensation, hemogram and liver function tests returned to normal two weeks after the pulse steroid therapy. The steroid dose was tapered gradually and discontinued three months after the initiation of treatment without relapse of the systemic signs. During the severe reaction, the patient continued to receive dapsone at half of its original dose due to the concomitant occurrence of anemia and hepatitis. Clofazimine and rifampin were added into the treatment regimen when the reaction subsided. After discharge, the patient took the conventional anti-leprosy MDT. At the 1-year follow up, the patient had only generalized hyperpigmentation resulting from clofazimine use and numbness on feet. She had no other systemic sequelae or optic neuritis from the acute reaction.

DISCUSSION

In Taiwan, the number of cases of leprosy in immigrants from endemic Southeast Asian countries has been increasing in recent years.[4] Difficulty in the diagnosis of leprosy makes it a challenge for medical personnel. The incubation period of leprosy is generally prolonged and varies widely, which causes trouble in obtaining a precise history of exposure. The mean incubation period of leprosy is estimated to be 4 years for tuberculoid and 10 years for lepromatous leprosy.[5]

The onset of leprosy is insidious. In addition, it can mimic many other cutaneous diseases.[6] The diagnosis is made by more than one of the following cardinal signs: hypopigmented or reddish skin lesions with loss of sensation, involvement of the peripheral nerves as demonstrated by their thickening and associated loss of sensation, and acid-fast bacilli on skin smears or biopsy material.[7]

A type 1 reaction is caused by a delayed- type hypersensitivity reaction to the bacilli in dermal macrophages and Schwann cells, leading to inflammation of the skin and nerve trunks.[8] It may occur in patients throughout the whole leprosy spectrum, but is most commonly seen in borderline patients. In a type 1 reaction, the influx of mainly $CD4^+$ T cells and monocytes results in raised serum levels of tumor necrosis factor, soluble interleukin-2 receptors

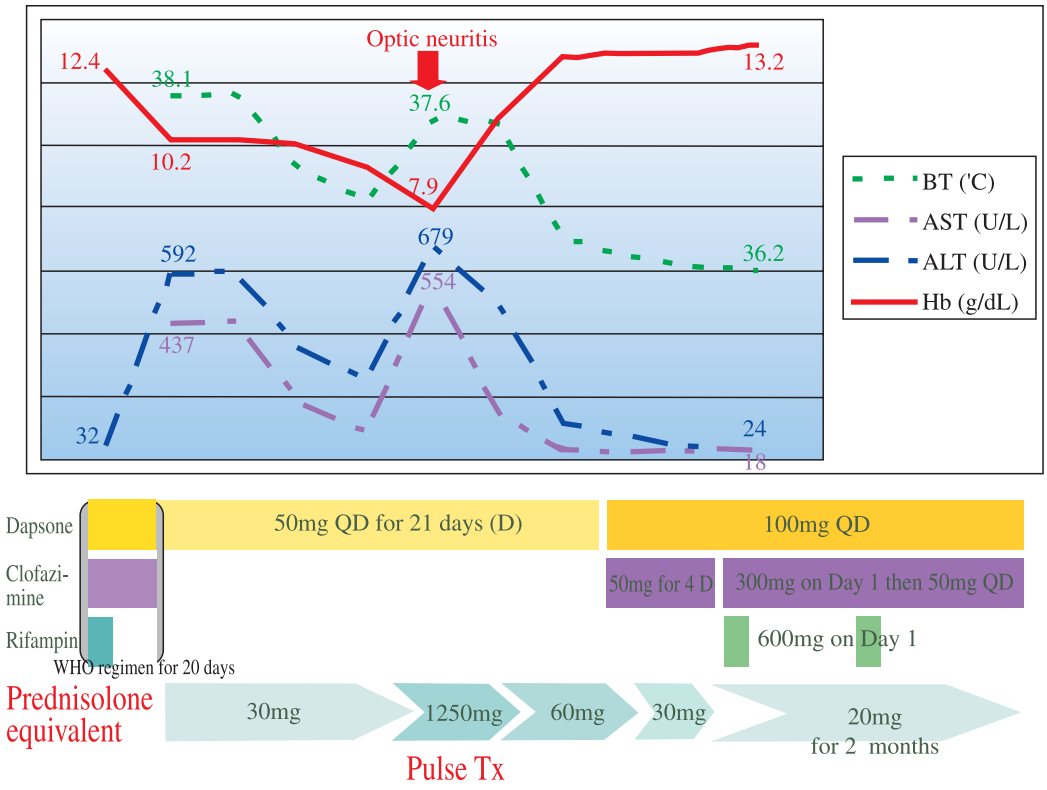

Fig. 3 Summary of the clinical course.

and adhesion molecules.[8] Systemic anti-inflammatory therapies are effective in reversing these abnormalities. Corticosteroids remain the gold standard of therapy. A course of prednisolone, starting from the maximal dose of 1 mg per kilogram per day and decreasing 5 mg every 2-4 weeks after evidence of improvement for total 12 weeks is recommended by WHO.[9] A recent multicenter, double-blind, randomized, controlled study in India suggested a longer duration (20 weeks vs. 12 weeks) ensures a better outcome.[10] Other established immunosuppresants used in a type 1 reaction include cyclosporine[11,12] and azathioprine.[8] The anti-leprosy treatment must be continued during the reaction in order to eliminate antigens present in the skin and nerves.[9] In our patient, the initial dose of prednisolone was 30 mg per day (equivalent to 0.6 mg per kilogram per day), which resulted in gradual improvement of the systemic reaction. The patient then received methylprednisolone pulse therapy due to sudden development of optic neuritis. She had a good response within weeks and had no sequelae at the 1-year follow up.

This patient had various systemic inflammations and a documented pulmonary infection. An association of these systemic inflammations, including optic neuritis, ascites, acute hepatitis, and normocytic anemia, with leprosy has not been recorded in the literature.

The differential diagnosis of hepatitis includes viral hepatitis A, B and C, but they were excluded by serology tests in our patient. Drug-induced hepatitis from the multi-drug therapy regimen in leprosy is less likely because only one dose of rifampin had been used and the hepatitis was alleviated despite continuous use of dapsone. Her laboratory test results showed no evidence of hemolysis or iron deficiency anemia. We did not characterize her pleural effusion and ascites, however, due to their dramatic response to systemic steroids.

After excluding other diagnoses, and because the onset of the reaction occurred after anti-leproma-

tous therapy was started, and she had a quick response to steroids, we speculate that these systemic inflammations, mainly her optic neuritis, acute hepatitis, and anemia, were likely caused by a severe type 1 reaction.

One way to manage this reaction is to prevent its occurrence. The precipitating factors of a type 1 reaction include physical and mental stress, use of MDT, pregnancy, surgical procedures, intercurrent infections, and other antibacterial treatments.[13] A cohort analysis of 534 borderline leprosy patients reported the risk factors which predict the development of a type 1 reaction at any stage during therapy, are the presence of facial lesions (odds ratio = 4.6), involvement of three or more body areas (odds ratio = 2.2), and positive IgM anti-phenolic glycolipid antibodies.[14] A randomized controlled trial in multibacillary patients who received prophylactic prednisolone or a placebo showed significantly fewer reactions in the prednisolone-treated group. However, the protective effect was lost at the end of 12 months.[1] Routine use of prophylactic prednisolone for prevention of a reaction is not currently recommended since a type1 reaction is difficult to be avoided in this manner. For early recognition of a reaction and thus early treatment, education of patients and medical staff about the typical clinical presentation is essential.

In conclusion, we report a case of borderline lepromatous leprosy complicated by a severe type 1 reaction. We suspect the optic neuritis, acute hepatitis, and anemia were part of a type 1 reaction in this patient. We speculate that a systemic delayed- type hypersensitivity reaction may cause multi-system dysfunction. Systemic prednisolone use for a long duration with a slow tapering course is effective in treating this reaction. In addition, prednisolone pulse therapy is indicated in severe neuritis, such as the optic neuritis in this case.

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痲瘋合併嚴重第一型反應──使用脈衝性類固醇治療

呂佩璇 林靜怡 蔡依倫 官裕宗

一位二十四歲越南女性病人，因三個月來臉上、身上及四肢出現無癢性紅色斑塊而至本院求診。由臨床表現、皮膚切片和皮膚抹片呈現抗酸性桿菌，以及接觸史診斷爲邊界結節型痲瘋。在大約第二十天的世界衛生組織痲瘋多菌型標準治療 (rifampin 每月 600 毫克，dapsone 每日 100 毫克，clofazimine 每月 300 毫克及之後每日 50 毫克，使用一年)，病人出現發燒、全身倦怠、視力模糊、咳嗽、噁心、上腹痛和關節痛，皮膚病灶亦呈現腫脹。住院後，完整的評估顯示眼球後視神經炎、續發性細菌性肺炎、肋膜炎、腹水、肝炎、胃竇胃炎、進行性正球性貧血和周邊感覺缺失。在全身脈衝性類固醇治療 (相當於 prednisolone 1250 毫克)、抗生素使用 (cefuroxime)、調整抗痲瘋藥物，以及支持性療法後，病人復原，出院後繼續接受世界衛生組織痲瘋多菌型標準治療。這位病人有多樣性第一型反應，表現出痲瘋複雜的免疫反應。在這類病人的治療，高劑量類固醇和緩慢的減量是非常重要的。在一年後的追蹤，病人除了雙腳發麻和長期使用 clofazimine 造成全身皮膚色素沈著外，無其他後遺症。(長庚醫誌 2008;31:201-6)

關鍵詞：痲瘋，第一型反應，視神經炎，延遲性過敏反應，脈衝性類固醇治療

長庚紀念醫院 台北院區 皮膚科；長庚大學 醫學院
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通訊作者：官裕宗醫師，長庚紀念醫院 皮膚科。台北市105敦化北路199號。Tel.: (02)27135211轉3397; Fax: (02)27191623; E-mail: blacksophie@adm.cgmh.org.tw