Case Report: Therapeutic Dilemma of Refractory Erythema Nodosum Leprosum

Jianyu Zhu,^{1†} Degang Yang,^{2†} Chao Shi,¹ and Zhichun Jing^{1*}

¹Department of Leprosy, Shanghai Dermatology Hospital, Shanghai, People's Republic of China; ²Department of Therapy, Shanghai Dermatology Hospital, Shanghai, People's Republic of China

Abstract. Erythema nodosum leprosum (ENL), also known as type II leprosy reaction, is a severe immune-mediated complication of multibacillary leprosy. For ENL, corticosteroids and thalidomide are the mainstays of treatment. Other immunosuppressants, such as clofazimine, cyclosporine, and azathioprine have also been used. Although most patients with ENL respond well to conventional treatments, a small number are refractory to these therapies and have severe morbidity or mortality. We report the case of a 24-year-old man with refractory ENL treated with high-dose corticosteroids for 15 months. The patient developed steroid-dependence and serious adverse effects, and died of an intracranial infection.

INTRODUCTION

Leprosy, a chronic infection caused by *Mycobacterium leprae*, affects skin, peripheral nerves, and certain other tissues. Leprosy has a wide clinical spectrum, with tuberculoid leprosy occurring in patients with strong immunity and lepromatous leprosy (LL) occurring in patients with weak immunity. Based on the host's immunity and clinical features, many intermediate forms may be seen, such as borderline tuberculoid leprosy, mid-borderline leprosy, and borderline lepromatous leprosy (BL). Leprosy is still endemic in some regions of the world. According to the World Health Organization record, 215,656 new cases of leprosy were reported from 103 countries in 2013.¹

Erythema nodosum leprosum (ENL), also known as type II leprosy reaction, is an immune-mediated reaction occurring in LL and BL patients. The incidence of ENL in patients with multibacillary leprosy is up to 24%.² ENL can occur before, during, or after antileprosy treatment, but it is most common in the first 7–12 months of treatment.^{2,3} ENL has a sudden onset and presents with multiple tender erythematous nodules or ulcers on the face and limbs, accompanied by fever, fatigue, neuritis, lymphadenitis, iridocyclitis, and arthritis. These symptoms may present intermittently for months or even years.

ENL is associated with mental and physical suffering of patients, may even be fatal. Corticosteroids are the mainstay of the treatment of ENL.⁴ Thalidomide and clofazimine are also very effective in treatment of ENL.^{5,6} Patients with an inadequate response to or adverse effects with these drugs, then pentoxifylline, cyclophosphamide, tumor necrosis factor (TNF)- α inhibitors, or other immunosuppressants can be used as treatment options.^{7,8} Although most patients with ENL respond well to these treatments, those refractory to conventional therapies may suffer severe morbidity or mortality.

CASE REPORT

A 24-year-old man presented to our hospital in 2013 with a 3-month history of recurrent multiple painful erythematous

nodules over his limbs (Figure 1), pain in the left elbow and wrist, high fever (39°C), and malaise. In addition, the patient had paresthesia, facial erythema, bilateral inguinal lymphadenopathy, and pronounced bilateral nontender ulnar nerve thickening. Slit-skin smear examinations were positive for acid fast bacilli (bacterial index 4). Histologic examination of the skin showed a clear grenz zone beneath the epidermis separating macrophage granulomata in the dermis from the epidermis (Figure 2), in accordance with the histopathologic characteristics of BL. Laboratory examinations showed white cell count of 16,400/mm³, neutrophils 91.1%, C-reactive protein of 40.0 mg/L, and erythrocyte sedimentation rate of 49.0 mm/hour. Liver and renal function tests were normal. He received the diagnosis of BL with accompanying ENL.

Treatment was initiated for leprosy with multidrug therapy (MDT) (600 mg of rifampin and 300 mg of clofazimine monthly, 100 mg of dapsone and 50 mg of clofazimine daily) and for ENL with methylprednisolone 60 mg/day given orally. After the first decrease in ENL, the methylprednisolone dose was tapered down with the addition of a 3-month course of thalidomide (300 mg/day). The ENL relapsed once the dose of methylprednisolone was reduced to 30 mg/day. Increasing the dose of methylprednisolone to 60–80 mg/day alleviated the ENL symptoms. Upon the second decrease in ENL, the dose of methylprednisolone was tapered down again with the addition of a 3-month course of clofazimine (200 mg/day). However the ENL relapsed when the dose of methylprednisolone was decreased to 25 mg/day. This cycle occurred repeatedly. After 12 months of treatment, the patient started experiencing frequent ENL relapses. At different times, combination therapy with cyclophosphamide, hydroxychloroquine, and leflunomide were also ineffective. Fifteen months after the ENL treatment, the patient had persistent high-grade fever, headache, projectile vomiting, and neck stiffness, followed by coma. The cerebrospinal fluid examination showed white cell count of 3,600/mm³, with a majority of polymorphonuclear cells, glucose 2.19 mmol/L, chloride 116.9 mmol/L, and protein 1.15 g/L. The bacterial culture was positive for *Pseudomonas aeruginosa*, and susceptibility testings were all negative. During this period, the ENL symptoms continued, and the dose of methylprednisolone decreased to 20 mg/day. MDT was stopped at this time. Although the patient was given meropenem (6 g/day), ceftriaxone (4 g/day), and levofloxacin (400 mg/day) for 14 days, the response was poor and the patient eventually

*Address correspondence to Zhichun Jing, Department of Leprosy, Shanghai Dermatology Hospital, No. 1278 Bao De Road, Shanghai 200443, People's Republic of China. E-mail: 35476451@qq.com

†These authors contributed equally to this work.

FIGURE 1. Patient's left arm showing numerous erythematous nodules.

died. Postmortem results indicate that he died of intracranial infection.

DISCUSSION

In this report, the patient suffered from ENL for many months, with a good response to corticosteroids. With prolonged treatment, however, the patient developed steroid dependence and poor response to other immunosuppressants. Steroid dependence signified that tapering off the dose of systemic corticosteroids, caused the patient to either get new ENL or had a worsening of their preexisting ENL. The patient eventually died of an intracranial infection, which may be related to the long-term use of corticosteroids. Corticosteroids have immunosuppressive properties that may predispose to and aggravate fungal, bacterial, viral, or parasitic infections.⁹ Coinfections may be involved in the development and maintenance of leprosy reactions. Intercurrent bacterial or viral infections have been proposed as risk factors for ENL.^{7,10} Studies have suggested that multibacillary patients who present with coinfections might be at a higher risk for ENL.¹⁰

Previous studies have shown that long-term corticosteroids therapy in ENL patients increases the incidence of adverse effects, even severe complications such as diabetic ketoacidosis, septic shock, and pneumonia secondary to immunosuppression.^{11,12} It has been reported that

FIGURE 2. Histopathological image showing (face): a clear grenz zone beneath the epidermis separating macrophage granulomata in the dermis from the epidermis (hematoxylin and eosin [H and E] staining x40).

a patient with ENL died of septicemia, secondary to skin ulcers and urinary tract infection, precipitated by corticosteroids.¹³ Other reports have stated that patients with ENL treated with prolonged oral corticosteroids and thalidomide can cause severe infections, such as *Nocardia farcinica* pleuritis or *Strongyloides* hyperinfection syndrome.^{14,15} Some researchers believe that a significant proportion of ENL deaths occur due to the adverse effects of prolonged corticosteroids therapy, but this remains to be confirmed with epidemiological data.^{12,16}

Pseudomonas aeruginosa is a common nosocomial opportunistic pathogen, resistant to many types of antibiotics. Patients who are immunocompromised, undergoing long-term hospitalization, or recovering from operations are readily susceptible to *P. aeruginosa* infection.¹⁷ The patient received long-term treatment of corticosteroids and immunosuppressants for ENL, which can cause an immunocompromised condition. This could be the main cause of *P. aeruginosa* infection. Disinfection and isolation measures should be more strict, and timely administration of sensitive antibiotics may protect him from *P. aeruginosa* infection.^{17,18}

Corticosteroids have strong anti-inflammatory effects, and are highly effective for ENL. Many patients require high doses of corticosteroids for prolonged periods of time to control their disease which leads to serious adverse effects.^{7,11,12} Thalidomide is another effective treatment of ENL that can be used alone or combined with other immunosuppressants; however, the use of thalidomide is restricted by the risk of teratogenicity and cost.⁵ Clofazimine was used in combination with glucocorticoids;

it has both antileprosy and anti-inflammatory effects that make it suitable for patients with steroid dependency or sustained relapse of ENL.⁶ Other immunosuppressants such as cyclosporine, azathioprine, methotrexate, and TNF- α inhibitors have also been used for ENL, but further clinical studies are needed to support their use.^{7,8}

The mechanism of ENL is poorly understood; treatment is empirical and is often suboptimal. Therefore, further studies on the pathogenesis of ENL may help to provide more effective treatment to reduce mortality.

Received February 16, 2016. Accepted for publication February 15, 2017.

Published online March 27, 2017.

Authors' addresses: Jianyu Zhu, Chao Shi, and Zhichun Jing, Department of Leprosy, Shanghai Dermatology Hospital, Shanghai, China, E-mails: 155284144@qq.com, sc_mac@163.com, and 35476451@qq.com. Degang Yang, Department of Therapy, Shanghai Dermatology Hospital, Shanghai, China, E-mail: ydg007@aliyun.com.

REFERENCES

1. World Health Organization (WHO), 2014. Global leprosy update, 2013; reducing disease burden. *Wkly Epidemiol Rec* 89: 389–400.
2. Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, Lockwood DN, 2006. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg* 74: 868–879.
3. Manandhar R, LeMaster JW, Roche PW, 1999. Risk factors for erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis* 67: 270–278.
4. World Health Organization (WHO), 1998. *Expert Committee on Leprosy*. Technical Report series 874. Geneva, Switzerland: WHO.
5. Walker SL, Waters MF, Lockwood DN, 2007. The role of thalidomide in the management of erythema nodosum leprosum. *Lepr Rev* 78: 197–215.
6. Van Veen NH, Lockwood DN, van Brakel WH, Ramirez J Jr, Richardus JH, 2009. Interventions for erythema nodosum leprosum. *Cochrane Database Syst Rev* 3: CD006949.
7. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL, 2006. The continuing challenges of leprosy. *Clin Microbiol Rev* 19: 338–381.
8. Ramien ML, Wong A, Keystone JS, 2011. Severe refractory erythema nodosum leprosum successfully treated with the tumor necrosis factor inhibitor Etanercept. *Clin Infect Dis* 52: e133–e135.
9. Moghadam-Kia S, Werth VP, 2010. Prevention and treatment of systemic glucocorticoid side effects. *Int J Dermatol* 49: 239–248.
10. Motta ACF, Pereira KJ, Tarquínio DC, Vieira MB, Miyake K, Foss NT, 2012. Leprosy reactions: coinfections as a possible risk factor. *Clinics* 67: 1145–1148.
11. Sugumaran DS, 1998. Leprosy reactions: complications of steroid therapy. *Int J Lepr Other Mycobact Dis* 66: 10–15.
12. Walker SL, Lebas E, Doni SN, Lockwood DN, Lambert SM, 2014. The mortality associated with erythema nodosum leprosum in Ethiopia: a retrospective hospital-based study. *PLoS Negl Trop Dis* 8: e2690.
13. Davis SV, Shenoit SD, Balachandran C, Pai SB, 2002. A fatal case of erythema necroticans. *Indian J Lepr* 74: 145–149.
14. De Souza JN, Machado PR, Teixeira MC, Soares NM, 2014. Recurrence of *Strongyloides stercoralis* infection in a patient with Hansen's disease: a case report. *Lepr Rev* 85: 58–62.
15. Arunthathi S, Ebenezer G, Daniel E, Sugumaran ST, 2001. *Nocardia farcinica* pleuritis in a lepromatous patient with severe necrotizing reaction: an unusual presentation. *Int J Lepr Other Mycobact Dis* 69: 104–107.
16. Walker SL, Balagon M, Darlong J, Doni SN, Hagge DA, Halwai V, John A, Lambert SM, Maghanoy A, Nery JA, Neupane KD, Nicholls PG, Pai VV, Parajuli P, Sales AM, Sarno E, Shah M, Tsegaye D, Lockwood DN, 2015. ENLIST 1: an international multi-centre cross-sectional study of the clinical features of erythema nodosum leprosum. *PLoS Negl Trop Dis* 9: e0004065.
17. Mesaros N, Nordmann P, Plésiat P, Roussel-Delvallez M, Van Eldere J, Glupczynski Y, Van Laethem Y, Jacobs F, Lebecque P, Malfroot A, Tulkens PM, Van Bambeke F, 2007. *Pseudomonas aeruginosa*: resistance and therapeutic options at the turn of the new millennium. *Clin Microbiol Infect* 13: 560–578.
18. Driscoll JA, Brody SL, Kollef MH, 2007. The epidemiology, pathogenesis and treatment of *Pseudomonas aeruginosa* infections. *Drugs* 67: 351–368.