DOI: https://doi.org/10.53555/nnmhs.v9i5.1665 Publication URL: https://nnpub.org/index.php/MHS/article/view/1665

AN UPDATE TREATMENT OF ERITEMA NODOSUM LEPROSUM

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Abstract

Leprosy, also called Morbus Hansen, is a contagious skin disease caused by the bacterium Mycobacterium Leprae. It takes 2–5 years for the disease to show up, and it takes 2–3 weeks for the cells to divide. Leprosy reaction is a sudden event that happens during the long-term course of the disease. It causes skin sores to become very red and swollen. This disease can show up before, during, or after treatment for leprosy, and it can happen to 30–50% of people with leprosy. Reactions to leprosy happen when both cellular and humoral immune responses go wrong. Type 2 or Eritema Nodosum Leprosum (ENL) reactions have a clinical picture of the appearance of nodules in the skin. This reaction occurs in leprosy patients with very large numbers of bacteria, namely the multibacillary type. In contrast to the reversal reaction, the humoral immune response plays an important role in the pathogenesis of ENL. Large amounts of bacterial antigen concentrations in tissues will increase IgM and IgG titers in multibacillary leprosy patients. Th2 cell activation will stimulate the production of IL-4 and IL-10, thereby increasing the humoral immune response and increasing the production of B lymphocytes. The goals of the treatment are to control the inflammation, ease the pain, and stop new cases from happening. In weak cases of ENL, the best way to treat it is to rest and take anti-inflammatory drugs. Most of the time, people take aspirin, which is an anti-inflammatory drug. Other drugs have also been tried, including nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, oral zinc, pentoxifylline, and chloroquine. But each of the current treatment options has its own downsides and limitations, and the best one must be carefully chosen for each case.

Keyword: *Eritema Nodosum Leprosum; Leprody; Morbus Hansen; Mycobacterium Leprae*

INTRODUCTION

Leprosy or Morbus Hansen is an infectious skin disease caused by the bacterium Mycobacterium Leprae which has a long incubation period of between 2 – 5 years and undergoes a long process of cell division between 2 – 3 weeks.[1] Gram-positive, acid-fast Mycobacterium leprae complex bacilli include *M. leprae* and *M. lepromatosis*. The former multiply slowly, taking 12–13 days. This obligate intracellular organism cannot be cultivated in artificial medium and contains fewer than half of functioning TB genes. M. leprae grows best around 27–33 C in labs. This supports the idea that M. leprae spreads faster in cooler body regions.[2,3]

This comprises skin, nerves near the skin, and upper respiratory tract membranes. Nine-banded armadillos, which live in south-central US and have a core temperature of 34 C, also grow this strain. Armadillos, chimpanzees, mangabey monkeys, and cynomolgus macaques have carried M. leprae. Both M. leprae and M. lepromatosis genomes contain several pseudogenes. Several metabolic pathway enzyme genes are missing. Mycobacteria's surplus pseudogenes have helped it become an obligate intracellular creature. M. lepromatosis de novo sequencing revealed nucleotide polymorphisms.[3–5]

Based on WHO data from 138 countries, the prevalence of leprosy recorded globally at the end of 2015 was 176,176 cases (0.2 cases per 10,000 people). The number of new cases reported globally in 2015 was 211,973 (2.9 cases per 10,000 people). The number of new cases in 2014 was 213,899, and in 2013 there were 215,656 cases. Statistics show that 199,992 (94% of cases) were reported from 14 countries where each country reported more than 1,000 new cases. The remaining 6% is obtained from other parts of the world.[6,7]

Around 8.9% of newly discovered cases of leprosy are found in children across the world. The finding rate of new instances worldwide that are accompanied by a disability is approximately 6.7%, which implies that many cases were detected much too late. In 2015, Indonesia reported 17,202 new cases, which meant that the country contributed for 8% of the most new cases worldwide. This percentage was lower than Brazil (13%), which accounted for, and India (60%), which accounted for. There are approximately 84.6% of patients who are affected by the MB kind of leprosy.[6,7]

The WHO classification of leprosy is divided into paucibasiles (PB) and multibacillary (MB). Morbus Hansen PB type with little or no bacteria found, while the MB type with a large number of bacteria.[8] The leprosy eradication program is carried out by breaking the chain of transmission to reduce the incidence of the disease, treat and cure sufferers and prevent disability. The World Health Organization (WHO) Chemotherapy Study Group established a multidrug therapy (MDT) treatment regimen in 1981. The current multidrug therapy (MDT) is a therapy consisting of rifampicin, dapsone and clofazimine.[9]

The prognosis for leprosy is quite good if adequate management is carried out and it rarely causes mortality. Nervous disorders and disabilities generally do not return to normal even after taking the drug, but skin lesions generally disappear within 1 year of therapy. The sooner the patient takes the drug, the less likely the deformity will occur.[10] Patients with leprosy may experience leprosy reactions. We created this article to discuss the update on the management of patients with Erythema Nodosum Leprosum (ENL).

LEPROSY PATHOPHYSIOLOGY

The pathophysiology of leprosy, also known as leprosy or Morbus Hansen, is through infection with Mycobacterium leprae, which is an acid-fast bacilli. Leprosy can manifest differently depending on the immune response of each patient. Patients with a profuse cellular immune response will have the tuberculoid form manifest.[11] Meanwhile, patients with minimal cellular immune response will have lepromatous manifestations. Mycobacterium leprae bacteria are transmitted by close and prolonged contact between susceptible individuals and infected patients through nasal secretions or droplets.[12]

The main route of transmission is nasal secretions. In addition, transmission can also occur through skin erosion. Other routes of transmission such as blood, vertical transmission, breast milk and insect bites, are also possible although rare. Individuals living in endemic areas can be infected with Mycobacterium leprae even if they do not have leprosy. It is characterized by the presence of Mycobacterium leprae DNA in nasal biopsies and seropositivity to bacterial antigens in healthy individuals living in endemic areas.[12]

Genetic factors are thought to influence the development of leprosy. Genetic studies identified mutations in chromosome regions 6p21, 17q22, 20p13 and 10p13 associated with leprosy. Therefore, only about 5 – 10% of the population is estimated to be susceptible to infection.[13] The clinical manifestations of leprosy are influenced by the patient's cellular immune system against Mycobacterium leprae. The first line of defense during Mycobacterium leprae infection is natural immunity represented by epithelial integrity, IgA secretion, NK (natural killer) cells, and activated macrophages.[14]

Inflammatory cytokines and chemokines can direct proliferation into Th1 or Th2 lymphocytes. This response will determine the course of the disease to be tuberculoid or lepromatous. In tuberculoid lesions, a predominance of CD4+ T lymphocytes was found, whereas in lepromatous lesions, a predominance of CD8+ T lymphocytes was found. TNF-α

levels were found to be higher in the serum of tuberculoid patients, indicating Mycobacterium leprae destruction and granuloma formation. TNF-α contributes to tissue damage and symptoms of erythema nodosum leprosum (ENL).[14]

In the lepromatous type there is an increase in TGF-β cytokines, these cytokines can inhibit macrophage activation. Clinical manifestations depend more on the patient's cellular immune system than the penetration and replication ability of bacteria. Clinical manifestations may occur after a long incubation period of 6 months to 20 years. Seropositivity to Mycobacterium leprae antigen can be found 9 years before clinical symptoms appear. The long incubation period of Mycobacterium leprae is caused by slow proliferation, low antigenicity and metabolic limitations.[14]

LEPROSY REACTION

Leprosy reaction is an acute condition in the chronic course of the disease which gives symptoms and signs of acute inflammation in the skin lesions of leprosy patients. This condition can appear before, during and after leprosy treatment which can occur in 30-50% of leprosy patients. Leprosy reactions occur as a result of adverse reactions from cellular and humoral immune responses.[15,16] In general, leprosy reactions are divided into two, namely the reversal reaction (RR) or type 1 reaction and Erythema Nodosum Leprosum (ENL) or type 2 reaction.[17–19]

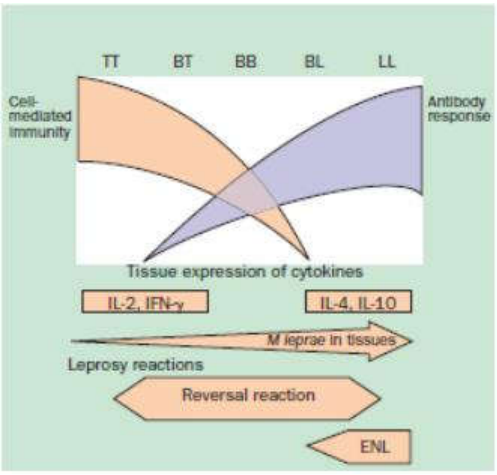

Figure 1. The relationship between the type of reaction and the type of immunity in patients with morbus hansen according to Ridley - Jopling[11]

Type 1 reactions are more commonly referred to as reversal reactions which can only occur in patients who are in the borderline spectrum. The cellular immune response plays an important role, namely there is a sudden increase in SIS. This causes the clinical picture of leprosy to shift towards the tuberculoid type. Reactions usually occur during the first 6 months of MDT treatment.[19] Clinical symptoms that arise in a reversal reaction are the increasing activity of some or all of the existing lesions, accompanied by the appearance of new lesions in a short time. The change in the lesion to be active can be described as a change in the color of the lesion which becomes increasingly erythematous, edematous, or the lesion becomes more infiltrative and more extensive. It is necessary to monitor the incidence of neuritis in this reaction, because it is important to determine the next choice of therapy.[20–22]

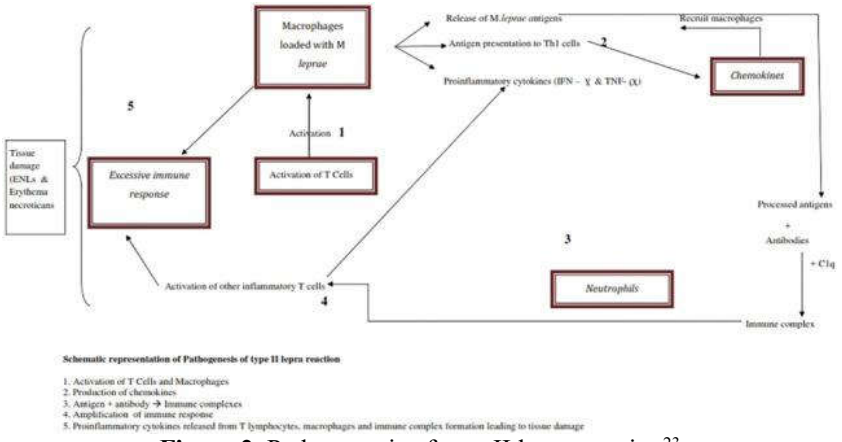

Figure 2. Pathogenesis of type II lepra reaction[23]

Type 2 or ENL reactions have a clinical picture of the appearance of nodules in the skin. This reaction occurs in leprosy patients with very large numbers of bacteria, namely the multibacillary type. In contrast to the reversal reaction, the humoral immune response plays an important role in the pathogenesis of ENL. Large amounts of bacterial antigen concentrations in tissues will increase IgM and IgG titers in multibacillary leprosy patients. Th2 cell activation will

stimulate the production of IL-4 and IL-10, thereby increasing the humoral immune response and increasing the production of B lymphocytes.[20,24]

ENL reactions can occur before treatment, during treatment or after completion, but most occur in the second year of MDT treatment. This happened because during treatment, many M. leprae germs died, so many antigens reacted with antibodies and formed immune complexes. The immune complexes that are formed then enter the blood circulation, then will settle in various organs of the body. Symptoms of a type 2 reaction include painful, erythematous nodules that mainly appear on the skin of the arms and legs. These symptoms generally disappear within a few days or a few weeks, and can also be followed by the formation of new nodes, while old nodes become purplish.[20,24]

Lepromatous leprosy (LL) type and high-bacillary index increase ENL risk. ENL risk is 3.6 for an LL spectrum and 8.6 for a bacillary index (BI) of 6. ENL predominated in BI >3 individuals. Study found that LL patients have more ENL episodes than single episodes. Clofazimine's ENL suppressive and preventative effects are thought to have reduced the probability of ENL after MDT. Several studies have shown that age and gender do not risk ENL. Pregnancy and lactation increase the risk of ENL. Psychological stress, puberty, intercurrent infection, immunization, HIV, malaria, and tuberculosis may be triggers, however the data is insufficient.[25,26]

According 39%–77% had multiple ENL episodes.15.1% of ENL cases have four or more episodes. Approximately a third of Ethiopian ENL patients suffer for more than two years.It lasted 18.5 months in India. Episodes can last anywhere from 14 days to 26 weeks, according to research. Study found five ENL recurrence risk variables. LL subtype, smear >4+, more than five nerves swollen, cutaneous nodules or infiltrate. According 30%–50% of ENL cases were moderate-to-severe.Moderate and severe ENL increased with a 12-month MDT. Most studies identified the highest prevalence of ENL in the first year of MDT, although some detected it in the second and third years.[27,28]

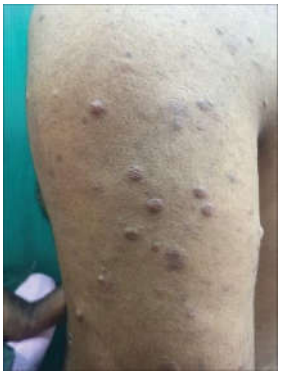

Figure 3. Classical ENL lesions, with crops of erythematous, tender nodules all over the body[23]

Typically, a Type II lepra reaction occurs at the lepromatous extremity of the spectrum. It manifests in various ways, including the classic erythema nodosum leprosum, the erythema polymorphous-like reaction, and the Lucio phenomenon. Multiple harvests of evanescent, erythematous, tender nodules and plaques are characteristic of classic ENL. Lesions such as bullous, pustular, ulcerated, hemorrhagic, and erythema multiforme are uncommon varieties. Lesions are frequently observed on the extensor surface of the extremities or the face. As lesions fade, they may manifest on the forearms and quadriceps as robust induration.[23]

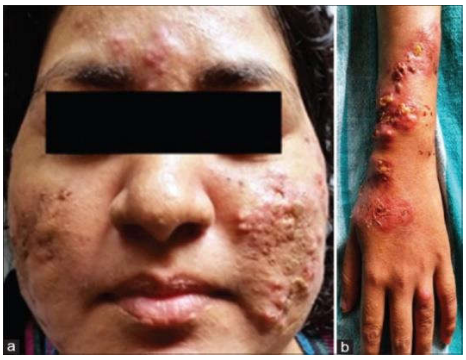

Figure 4. (a) Vasculonecrotic ENL lesions over the face. (b) Vasculonecrotic ENL lesions with ulceration seen over the forearm[23]

UPDATE MANAGEMENT OF ENL

The treatment's objectives are to bring the inflammation under control, provide pain relief, and stop new attacks from occurring. In cases of mild ENL, the recommended treatment consists of rest as well as anti-inflammatory medication. Aspirin is the anti-inflammatory medication that is taken the most frequently. Other medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, oral zinc, pentoxifylline, and chloroquine, have also been tried.

However, each of the current treatment choices has its own set of limits and drawbacks, and the most appropriate one must be carefully chosen for each specific instance.[23]

ENL is frequently treated first with corticosteroids like prednisone since they work immediately. They stop pain and inflammation fast. They are usually administered at the lowest dose necessary to control ENL. The dose slowly decreases as the disease advances. excessive prednisolone doses can cause excessive blood sugar, high blood pressure, and steroid dependency. Stopping a fresh reaction with steroids could cause dependence. Low-dose steroids and thalidomide don't mix. The combination increases deep vein thrombosis risk by 10%.[23]

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Clofazimine is an effective and low-cost anti-inflammatory medication used in ENL. When administered at 300 mg per day, the serum concentration doubles. It inhibits prostaglandins and has an anti-neutrophilic effect. It is especially useful in the management of recurrent and chronic type II reactions, where its steroid-sparing effect is of considerable value. It takes 4–6 weeks to manifest its effects, which is a significant disadvantage. In addition, it causes significant gastrointestinal adverse effects and skin discoloration. Azathioprine and methotrexate are steroid-sparing medicines used with prednisolone to treat ENL.[23]

In 1982, Mshana successfully employed cyclosporine A in chronic steroid-dependent ENL that had failed thalidomide. Cyclosporine A boosts T suppressor cells in ENL lesions. Tenidap is a newer nonsteroidal anti-inflammatory medication that treats rheumatoid arthritis like hydroxychloroquine. Its anti-TNF-α and neutrophil-mediated damage inhibition may help fight ENL. Supidimide, a non-teratogenic thalidomide analog, has successfully treated ENL. Celgene Corporation, USA identified two thalidomide analog groups.[23]

Like thalidomide, the first group reduced TNF-α and PDE-IV and stimulated IL-8 and IL-10. TNF-α, IL-6, and IL-8 were suppressed, however PDE-IV was not. PDE-IV inhibition stimulated T cells. Thus, non-PDE-IV-inhibiting thalidomide analogs do not activate T cells. T-cell activation prevents reversal responses with thalidomide. Thus, its PDE-IV-inactive analogs can be used in reversal reactions. Revlimid and Actimid, two thalidomide analogs from Celgene Corporation, treat myeloma and ENL.[29,30]

TNF-α plays a key role in the pathogenesis of ENL, as has been previously explained which provides the rationale for use of TNF-α inhibitors in ENL. Infliximab is a human-murine chimeric monoclonal antibody against TNF-α, and etanercept is a dimeric fusion protein of the extracellular portion of the p75 TNF receptor coupled to IgG1. Both of these effectively reduce TNF-α levels and have been found to have impressive clinical responses in ENL. The disadvantage with their use, however, is an increased risk of reactivation of latent tuberculosis infection (more so with infliximab as compared to etanercept).[31]

Minocycline treats ENL in one trial. Narang et al. treated 10 cases of chronic or recurrent ENL with oral minocycline at 100 mg daily for 3 months and tapered prednisolone until cessation. 80% responded well. Minocycline is effective in ENL due to its antibacterial, anti-inflammatory, and antiapoptotic characteristics. It inhibits microglial activation, making it neuroprotective.[32] Leprosy neuritis may benefit. Apremilast, an oral phosphodiesterase-IV inhibitor, treats psoriasis, psoriatic arthritis, atopic dermatitis, alopecia areata, and more. Apremilast improved two poorly managed chronic ENL cases in a 2019 case report with no adverse events.[23,33]

Plasma exchange removes ENL-pathogenic immune complexes. Four ENL patients who failed conventional treatment responded to it. Plasma exchange is costly and not viable in most leprosy-endemic countries. Intravenous immunoglobulins (IVIG) reduces cellular and humoral reactions, making it a promising ENL treatment. Mycobacterium w vaccine immunotherapy reduces type 2 reactions in multibacillary leprosy patients. The quick drop in the bacteriological index with this vaccine may explain the lower incidence of type 2 reactions and their earlier appearance than in the control group. Study found an increase in type 2 reactions after using the ICRC vaccine, possibly due to large amounts of M. leprae antigens being broken down and released.[23]

CONCLUSION

The treatment reduces inflammation, relieves pain, and prevents subsequent attacks. Rest and anti-inflammatories treat mild ENL. Aspirin is the most common anti-inflammatory. NSAIDs, colchicine, oral zinc, pentoxifylline, and chloroquine are also used. Each of the existing treatment options has pros and cons, therefore the best one must be picked for each case.

REFERENCES

[1]. White C, Franco-Paredes C. Leprosy in the 21st century. Clin Microbiol Rev. 2015;28(1):80-94.

[2]. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin Microbiol Rev. 2006;19(2):338-381. doi:10.1128/CMR.19.2.338-381.2006
[3]. Han XY, Sizer KC, Thompson EJ, et al. Comparative sequence analysis of Mycobacterium leprae and the new leprosy-causing Mycobacterium lepromatosis. J Bacteriol. 2009;191(19):6067-6074. doi:10.1128/JB.00762-09
[4]. Cole ST, Eiglmeier K, Parkhill J, et al. Massive gene decay in the leprosy bacillus. Nature. 2001;409(6823):1007-1011. doi:10.1038/35059006
[5]. Eiglmeier K, Parkhill J, Honoré N, et al. The decaying genome of Mycobacterium leprae. Lepr Rev. 2001;72(4):387-398.
[6]. mondiale de la Santé O, Organization WH. Global leprosy update, 2015: time for action, accountability and inclusion. Wkly Epidemiol Rec Relev épidémiologique Hebd. 2016;91(35):405-416.
[7]. Chen K-H, Lin C-Y, Su S-B, Chen K-T. Leprosy: A review of epidemiology, clinical diagnosis, and management. J Trop Med. 2022;2022.
[8]. James W, Berger T, Elston D. Andrews' Disease of the Skin, Clinical Dermatology. Elsevier Health Sciences; 2015.
[9]. Worobec SM. Treatment of leprosy/Hansen's disease in the early 21st century. Dermatol Ther. 2009;22(6). doi:10.1111/j.1529-8019.2009.01274.x
[10]. Veit O. Manson's tropical diseases 23rd edition. Travel Med Infect Dis. 2015;13(1). doi:10.1016/j.tmaid.2014.12.012
[11]. Lastória JC, Abreu MAMM de. Leprosy: review of the epidemiological, clinical, and etiopathogenic aspects - part 1. An Bras Dermatol. 2014;89(2):205-218. doi:10.1590/abd1806-4841.20142450
[12]. Mungroo MR, Khan NA, Siddiqui R. Mycobacterium leprae: Pathogenesis, diagnosis, and treatment options. Microb Pathog. 2020;149:104475.
[13]. Fava VM, Dallmann-Sauer M, Schurr E. Genetics of leprosy: today and beyond. Hum Genet. 2020;139:835-846.
[14]. Mi Z, Liu H, Zhang F. Advances in the immunology and genetics of leprosy. Front Immunol. 2020;11:567.
[15]. Handoko R, Djuanda A, Hamzah M, Handoko RP; Djuanda A; Hamzah M; et al. Ilmu Penyakit Kulit Dan Kelamin. 7th ed. Balai Penerbit FKUI; 2017.
[16]. Kahawita IP, Walker SL, Lockwood DNJ. Leprosy type 1 reactions and erythema nodosum leprosum. An Bras Dermatol. 2008;83(1). doi:10.1590/S0365-05962008000100010
[17]. Sanghi S. IAL Textbook of Leprosy. Med J Armed Forces India. 2010;66(3). doi:10.1016/s0377-1237(10)80066-8
[18]. Motta ACF, Pereira KJ, Tarquínio DC, Vieira MB, Miyake K, Foss NT. Leprosy reactions: Coinfections as a possible risk factor. Clinics. 2012;67(10). doi:10.6061/clinics/2012(10)05
[19]. Lor KW, Kransdorf EP, Patel JK, Chang DH, Kobashigawa JA, Kittleson MM. Dapsone-Associated Anemia in Heart Transplant Recipients with Normal Glucose-6-Phosphate Dehydrogenase Activity. J Clin Med. 2022;11(21):6378.
[20]. Kamath S, Vaccaro SA, Rea TH, Ochoa MT. Recognizing and managing the immunologic reactions in leprosy. J Am Acad Dermatol. 2014;71(4). doi:10.1016/j.jaad.2014.03.034
[21]. Fitzpatrick TB, Wolff K, Goldsmith LA, et al. Fitzpatrick's Dermatology in General Medicine [Electronic Resource].; 2008.
[22]. James WD, Elston DM, Treat JR, Rosenbach MA, Neuhaus IM, Wu Q. Andrews' Diseases of the Skin, 13th Edition.; 2019.
[23]. Bhat RM, Vaidya TP. What is New in the Pathogenesis and Management of Erythema Nodosum Leprosum. Indian Dermatol Online J. 2020;11(4):482-492. doi:10.4103/idoj.IDOJ_561_19
[24]. Burns DA, Breathnach SM, Cox NH, Griffiths CEM. Rook's Textbook of Dermatology: Eighth Edition. Vol 1.; 2010. doi:10.1002/9781444317633
[25]. Arora M, Katoch K, Natrajan M, Kamal R, Yadav VS. Changing profile of disease in leprosy patients diagnosed in a tertiary care centre during years 1995-2000. Indian J Lepr. 2008;80(3):257-265.
[26]. Balagon MVF, Gelber RH, Abalos RM, Cellona R V. Reactions following completion of 1 and 2 year multidrug therapy (MDT). Am J Trop Med Hyg. 2010;83(3):637-644. doi:10.4269/ajtmh.2010.09-0586
[27]. Wankhade VH, Debnath P, Singh RP, Sawatkar G, Bhat DM. A retrospective study of the severe and uncommon variants of erythema nodosum leprosum at a tertiary health center in central India. Int J mycobacteriology. 2019;8(1):29-34. doi:10.4103/ijmy.ijmy_174_18
[28]. Kumar B, Dogra S, Kaur I. Epidemiological characteristics of leprosy reactions: 15 years experience from north India. Int J Lepr other Mycobact Dis Off organ Int Lepr Assoc. 2004;72(2):125-133. doi:10.1489/1544-581X(2004)072<0125:ECOLRY>2.0.CO;2
[29]. Kaplan G. Potential of thalidomide and thalidomide analogues as immunomodulatory drugs in leprosy and leprosy reactions. Lepr Rev. 2000;71 Suppl:S117-20. doi:10.5935/0305-7518.20000082
[30]. Van Veen NHJ, Lockwood DNJ, Van Brakel WH, Ramirez JJ, Richardus JH. Interventions for erythema nodosum leprosum. A Cochrane review. Lepr Rev. 2009;80(4):355-372.
[31]. Ramien ML, Wong A, Keystone JS. Severe refractory erythema nodosum leprosum successfully treated with the tumor necrosis factor inhibitor etanercept. Clin Infect Dis an Off Publ Infect Dis Soc Am. 2011;52(5):e133-5. doi:10.1093/cid/ciq213
[32]. Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. Br J Pharmacol. 2013;169(2):337-352. doi:10.1111/bph.12139
[33]. Narang T, Kaushik A, Dogra S. Apremilast in chronic recalcitrant erythema nodosum leprosum: a report of two cases. Br J Dermatol. 2020;182(4):1034-1037. doi:10.1111/bjd.18233