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## Case Report

# Severe type 2 leprosy reaction with COVID-19 with a favourable outcome despite continued use of corticosteroids and methotrexate and a hypothesis on the possible immunological consequences

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## ABSTRACT

Type 2 leprosy reaction (T2LR), or Erythema Nodosum Leprosum (ENL), often poses a therapeutic challenge to clinicians and commonly requires long courses of steroids for control. While immunosuppressants are known to achieve control and lower steroid dependence in T2LR, the prospect of managing a severe T2LR in conjunction with COVID-19, with the concern of worsening COVID-19 with long-term immunosuppression has not previously been encountered. We report a case of severe T2LR treated with oral steroids and methotrexate, with COVID-19 infection acquired during hospital stay, and a favourable outcome achieved despite the continued use of immunosuppressants. We discuss the possible reasons for this both in terms of the drug pharmacodynamics and the immunological profile of T2LR. © 2020 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Type 2 leprosy reaction (T2LR) occurs in 15.4% of lepromatous leprosy patients and in approximately 4.1% of borderline lepromatous leprosy cases (Voorend and Post, 2013); infections have been identified as common trigger factor for T2LR. Prolonged immunosuppression to maintain remission predisposes patients with leprosy to aggravation of infections (Sugumaran, 1998).

Here we report on a patient with lepromatous leprosy with T2LR who was being treated with oral steroids and methotrexate when he tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We highlight the favourable outcome in spite of the use of immunosuppressive agents (ISAs) and propose a hypothesis to explain this outcome. We emphasise the lack of an adverse COVID-19 outcome with continued use of methotrexate and oral corticosteroids and no worsening of T2LR during the infection course.

## Case description

A 26-year-old male diagnosed with lepromatous leprosy with T2LR, on irregular treatment with World Health Organisation multibacillary multidrug therapy (MB-MDT) over the course of one year, presented to the Dermatology Out Patient Department with a recurrence of severe T2LR for one week. The patient had extensive skin lesions of Erythema Nodosum Leprosum (ENL), some of which were ulcerating (Figure 1), along with high grade fever (101–103 ° F), arthralgias and bilateral ulnar neuritis. He had symmetrical glove and stocking anaesthesia, but no nerve function impairment (NFI) related to ulnar neuritis. The clinical severity of T2LR was graded as Erythema Nodosum Leprosum International Study (ENLIST) score 10. A biopsy from a new lesion was suggestive of ENL (Figure 2) and a slit skin smear from the ENL lesions showed fragmented bacilli with a Bacteriological Index (BI) of 4+.

Investigations revealed low haemoglobin of 11.2 mg/dl with the peripheral smear showing microcytic hypochromic anaemia. Blood biochemistry profile and urine routine microscopy were within normal limits and viral markers (Hepatitis B, Hepatitis C, HIV) were negative. Chest X-ray and ultrasound of the abdomen and pelvis were within normal limits.

The patient was started on MB-MDT 1st kit and prednisolone 40 mg (1 mg/kg) daily was added in view of severe T2LR. Tablet Methotrexate

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Figure 1. Multiple ENL lesions on extensor surfaces of both upper and lower limbs.

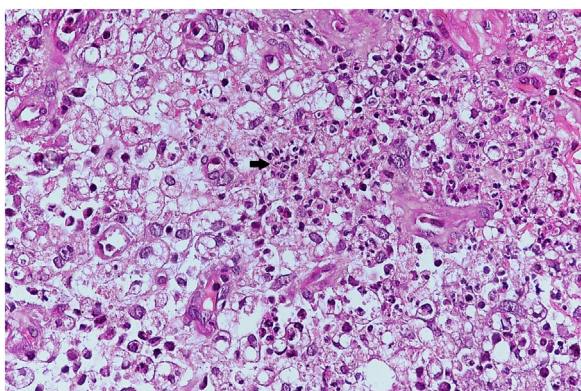


Figure 2. Diffuse infiltrate of foamy histiocytes admixed with many neutrophils singly and in clusters (arrow) (H&E x 40).

10 mg/week was added after a few days as new ulcerating ENL lesions continued to appear. Following this, new ENL lesions stopped appearing and there was significant improvement in systemic complaints. Ulnar nerve neuritis also subsided over 2 weeks.

Two weeks later a nursing staff assigned to the patient tested positive for SARS-CoV-2, and therefore the patient was tested for

SARS-CoV-2 by real time reverse transcriptase–polymerase chain reaction (RT-PCR) from nasal and throat swabs. He tested positive and was moved to an isolation ward. It was decided to continue oral steroids and methotrexate in view of his severe initial presentation. He was additionally prescribed tablet paracetamol 500 mg SOS along with vitamin C 500 mg BD and Zinc 50 mg BD as per the hospital protocols. The patient developed a low-grade fever (99–99.6 °F) which persisted for 3–4 days; there were no respiratory symptoms and oxygen saturation remained above 97% on room air at all times. On testing negative for COVID-19 2 weeks later he was discharged and asked to follow up at the leprosy outpatient clinic. The patient remains controlled on steroids and weekly methotrexate and has no residual symptoms related to COVID-19, up to 4 months post discharge. The course of events in the patient’s illness, treatment and follow-up is illustrated as a timeline in Figure 3.

Discussion

In the ongoing COVID-19 pandemic, there is no authoritative evidence regarding initiation/continuation of ISA and immunomodulatory (IMD) drugs in immune-mediated dermatologic disorders, due to concerns of increased morbidity and mortality. In an endemic area leprosy and T2LR can occur simultaneously and in this case, weighing the severity of the reaction, we decided to persist with the use of the ISAs. We would like to highlight that this was clearly a case of incidental development of COVID-19 in a patient already suffering from ENL and not of ENL following, or triggered by SARS-CoV-2 infection.

A recent paper suggests that the risk of COVID-19 and its adverse outcomes may be minimally affected by IMDs used in dermatological conditions (Holcomb et al., 2020). This paper however did not report on cases of leprosy or on patients on systemic steroids. A previous paper on use of methotrexate in rheumatologic indications did not report adverse COVID-19 outcomes (Monti et al., 2020).

Corticosteroids have broad immunosuppressant effects and are likely to induce SARS-CoV-2 receptor Angiotensin-Converting-Enzyme-2 (ACE2) (Safavi and Nath, 2020). They can precipitate a broad spectrum of bacterial, fungal and viral infections in patients on long-term treatment, and even in those on short-term use of low

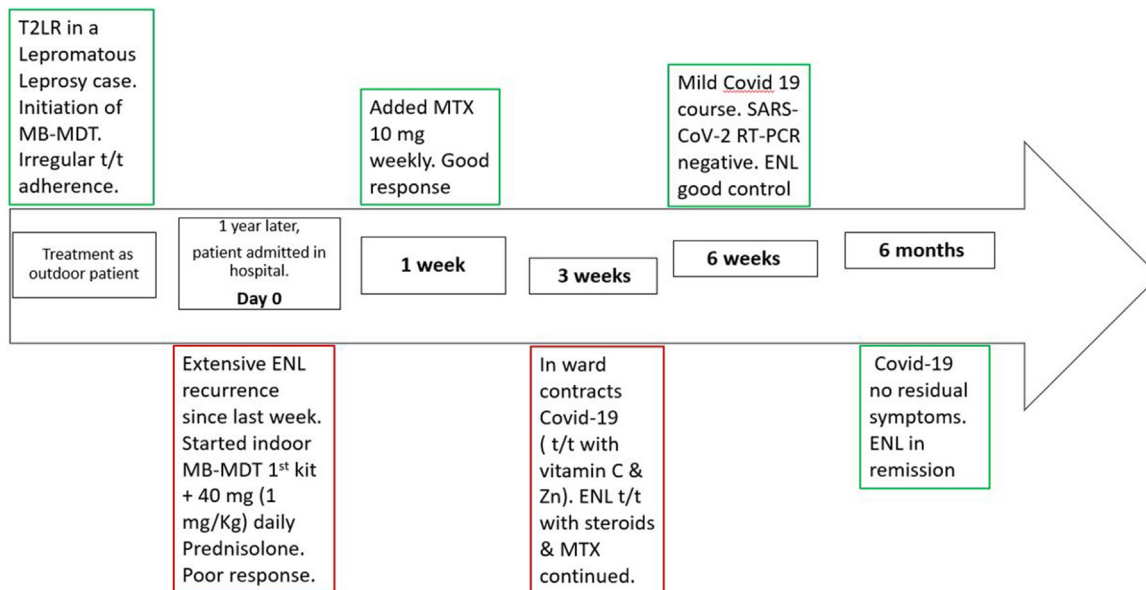


Figure 3. Timeline of course of events in patient's illness and treatment.

doses (Khurana and Saxena, 2020). The preliminary results of the RECOVERY trial support use of dexamethasone for up to 10 days in patients who were receiving invasive mechanical ventilation, but report no benefit and possible harm in the subgroup of hospitalised patients who were not on respiratory support (Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report, 2020). Oral steroids are critical to managing severe T2LRs and need to be started early and in moderate to high doses to control its severe skin and systemic manifestations and prevent permanent neurological damage (Narang and Kamat, 2020). Methotrexate has been shown to be an effective steroid sparing agent (7.5–20 mg/week) and has been used in ENL in conjunction with steroids (Narang and Kamat, 2020; Perez-Molina et al., 2020).

In COVID-19 the tissue damaging hyperinflammatory syndrome is strongly linked to pro-inflammatory effector cytokines, such as tumour necrosis factor (TNF), interleukin (IL)-1 $\beta$ , IL-6, IL-8, granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), chemokines such as monocyte chemoattractant protein-1 (MCP1), interferon gamma inducible protein 10 (IP-10) and macrophage inflammatory protein 1 alpha (MIP1- $\alpha$ ), complement activation and macrophage activation. Notably methotrexate does not affect the innate cells and mediators of anti-viral immune response, while inhibiting production of TNF- $\alpha$ , IL-6 and IL-8 and increasing the secretion of anti-inflammatory cytokine IL-10 and anti-inflammatory Treg cells (Cribbs et al., 2015; Khurana and Saxena, 2020; Sekhri et al., 2016). Methotrexate is possibly the safest conventional ISA in respect of infection complications as reported by most recent meta-analyses and reviews (Khurana and Saxena, 2020; Lacaille et al., 2008; van der Veen et al., 1994). Moreover, high-dose methotrexate with leucovorin rescue has been postulated as an immune stabilization strategy for SARS-CoV-2 induced 'PANIC' attack for severe COVID-19 (Frohman et al., 2020). In our case, with the combined use of methotrexate and oral prednisolone, the patient suffered from only mild symptoms of COVID-19. It is worthwhile mentioning here that T2LRs are associated with a heightened INF- $\gamma$  mediated inflammatory response; considering the important role of this cytokine in clearance of SARS-CoV-2, it is possible that T2LR patients may have a natural protection against severe COVID-19 infection (Khurana and Sardana, 2020; Montalvo Villalba et al., 2020). A gradual decrease in INF- $\gamma$  production with prednisolone (40 mg) has been reported to occur over first 2–3 weeks of treatment in leprosy reactions and thus it is plausible that the levels of INF- $\gamma$  may still have been sufficiently high to effect viral clearance (Manandhar et al., 2002).

## Conclusion

Our case illustrates the unique co-occurrence of severe ENL and COVID-19 infection and may help clinicians managing such cases. A favourable outcome was observed with continued use of methotrexate and steroids. This case raises the possibility that elevated INF- $\gamma$  levels in T2LR may have a favourable effect on COVID-19 co-infection, which may be a promising prospective to explore for therapeutic use.

## Conflict of interest

Nil.

## Funding sources

Nil.

## Ethical approval

Patient consent taken.

## References

- Cribbs AP, Kennedy A, Penn H, Amjadi P, Green P, Read JE, et al. Methotrexate Restores Regulatory T Cell Function Through Demethylation of the FoxP3 Upstream Enhancer in Patients With Rheumatoid Arthritis. *Arthritis Rheumatol* (Hoboken, NJ) 2015;67:1182–92, doi:<http://dx.doi.org/10.1002/art.39031>.
- Dexamethasone in Hospitalized Patients with Covid-19 – Preliminary Report. *N Engl J Med* 2020;., doi:<http://dx.doi.org/10.1056/NEJMoa2021436>.
- Frohman EM, Villemarette-Pittman NR, Cruz RA, Longmuir R, Rowe V, Rowe ES, et al. Part II. high-dose methotrexate with leucovorin rescue for severe COVID-19: An immune stabilization strategy for SARS-CoV-2 induced 'PANIC' 11Prolific Activation of a Network Immune-Inflammatory Crisis [PANIC]. *attack. J Neurol Sci* 2020;415:116935, doi:<http://dx.doi.org/10.1016/j.jns.2020.116935>.
- Holcomb ZE, Santillan MR, Morss-Walton PC, Salian P, Her MJ, Giannotti NM, et al. Risk of COVID-19 in Dermatologic Patients on Long-term Immunomodulatory Therapy. *J Am Acad Dermatol* 2020;., doi:<http://dx.doi.org/10.1016/j.jaad.2020.06.999>.
- Khurana A, Saxena S. Immunosuppressive agents for dermatological indications in the ongoing COVID-19 pandemic: Rationalizing use and clinical applicability. *Dermatol Ther* 2020;e13639, doi:<http://dx.doi.org/10.1111/dth.13639>.
- Khurana A, Sardana K. Immunopathology of reactions. In: Sardana K, Khurana A, editors. *Jopling's Handbook of Leprosy*. 6th ed. New Delhi, India: CBS; 2020. p. 182–91.
- Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. *Arthritis Rheum* 2008;59:1074–81, doi:<http://dx.doi.org/10.1002/art.23913>.
- Manandhar R, Shrestha N, Butlin CR, Roche PW. High levels of inflammatory cytokines are associated with poor clinical response to steroid treatment and recurrent episodes of type 1 reactions in leprosy. *Clin Exp Immunol* 2002;128:333–8.
- Montalvo Villalba MC, Valdés Ramírez O, Muné Jiménez M, Arencibia García A, Martínez Alfonso J, González Baéz G, et al. Interferon gamma, TGF- $\beta$ 1 and RANTES expression in upper airway samples from SARS-CoV-2 infected patients. *Clin Immunol* 2020;220:108576, doi:<http://dx.doi.org/10.1016/j.clim.2020.108576>.
- Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. *Ann Rheum Dis* 2020;79;., doi:<http://dx.doi.org/10.1136/annrheumdis-2020-217424> 667 LP – 668.
- Narang T, Kamat D. Type 2 Leprosy Reaction. In: Sardana K, Khurana A, editors. *Jopling's Handbook of Leprosy*. 6th ed. New Delhi, India: CBS; 2020. p. 211–24.
- Perez-Molina JA, Arce-García O, Chamorro-Tojeiro S, Norman F, Monge-Maillou B, Comeche B, et al. Use of methotrexate for leprosy reactions. Experience of a referral center and systematic review of the literature. *Travel Med Infect Dis* 2020;101670, doi:<http://dx.doi.org/10.1016/j.tmaid.2020.101670>.
- Safavi F, Nath A. Silencing of immune activation with methotrexate in patients with COVID-19. *J Neurol Sci* 2020;415:116942, doi:<http://dx.doi.org/10.1016/j.jns.2020.116942>.
- Sekhri R, Sekhri V, Sardana K. Immunosuppressive drugs. In: Sardana K, editor. *Systemic Drugs in Dermatology*. New Delhi, India: Jaypee; 2016. p. 304–85.
- Sugumar DS. Leprosy reactions—complications of steroid therapy. *Int J Lepr Other Mycobact Dis Off Organ Int Lepr Assoc* 1998;66:10–5.
- van der Veen MJ, van der Heide A, Kruijze AA, Bijlsma JW. Infection rate and use of antibiotics in patients with rheumatoid arthritis treated with methotrexate. *Ann Rheum Dis* 1994;53:224–8, doi:<http://dx.doi.org/10.1136/ard.53.4.224>.
- Voorend CGN, Post EB. A systematic review on the epidemiological data of erythema nodosum leprosum, a type 2 leprosy reaction. *PLoS Negl Trop Dis* 2013;7:e2440, doi:<http://dx.doi.org/10.1371/journal.pntd.0002440>.