



# Successful Remission of Necrobiosis Lipoidica Manifested by Subcutaneous Nodules with Tofacitinib: A Case Report

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## Article Info

### Article Notes

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## Introduction

Granulomatous dermatoses are inflammatory skin diseases primarily composed of macrophages. Necrobiosis lipoidica (NL) is an idiopathic granulomatous disease that leads to the formation of plaques on the lower legs, which often ulcerate. The histological characteristics of NL include palisading granulomatous inflammation horizontally layered within degenerated collagen and moderate infiltration of lymphocytic infiltrate<sup>1</sup>. Due to limited understanding of the molecular pathogenesis of NL, there is currently no reliable and effective treatment available. However, it has been found that the intracellular signaling pathway Janus kinase signal transducer and activator of transcription (JAK-STAT) plays a role in the pathogenesis of many inflammatory skin diseases. Disrupting this cytokine signaling by blocking the downstream JAK-STAT signaling pathway shows promise as a new approach for treating diseases with macrophage overactivation<sup>2</sup>. Recent reports have demonstrated the effectiveness of JAK inhibitors in treating granulomatous dermatoses<sup>3,4</sup>. Data reported by William Damsky indicates that JAK-STAT signaling is activated at low levels in NL<sup>4</sup>, suggesting that JAK inhibitors may become an effective treatment option. Our case report documents a case of NL manifested by subcutaneous nodules treated with tofacitinib alone.

## Case Report

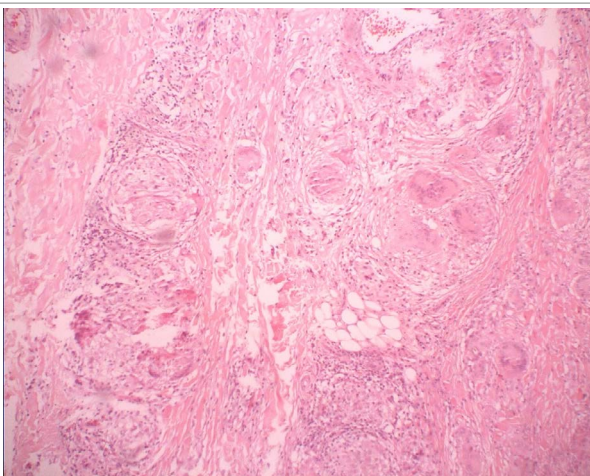
A 43-year-old woman presented to the dermatology department with bilateral subcutaneous nodules in the pretibial area. Upon skin examination, multiple subcutaneous nodules of varying sizes were observed, with the largest being approximately the size of a quail egg. These nodules exhibited a firm texture, poor mobility, normal skin temperature, and no tenderness. They were palpable in the pretibial area below both knees (figure 1). The right knee area was selected for puncture biopsy to obtain samples from the subcutaneous nodules. Histopathological analysis revealed mixed infiltration of histiocytes, lymphocytes, and multinucleated giant cells in the middle and lower dermis as well as fat septum (figure 2). Immunohistochemical testing showed positive results for CD68 (histiocytes), Cluster, LCA (lymphocytes), and TNT-1. Acid-fast, Periodic-acid silver methenamine and PAS staining did not reveal any clear abnormal findings. Molecular pathology indicated that TB-DNA (PCR) was negative. Additionally, blood routine tests, CRP levels, parathyroid hormone levels, cortisol rhythm tests, and Mycobacterium tuberculosis T cell tests all returned normal

results. ANA was found to be at a level of 1:100 while ENA was within normal limits. TSH levels were slightly elevated at 4.37uIU/ml (reference range: 0.27-4.2u IU/ml), but FT3 and FT4 levels were normal. Blood glucose and glycosylated hemoglobin were normal. Color Doppler ultrasound demonstrated localized edema of subcutaneous fat in both lower limbs consistent with necrobiosis lipoidica. During the formulation of the treatment plan, it was discovered that the patient refused systemic use and topical application of glucocorticoids. After excluding pregnancy status, infection, tumor, and abnormalities in blood routine, she was prescribed tofacitinib with an oral dose of 5mg twice daily.

After a month of treatment, the original subcutaneous



**Figure 1.** The clinical presentation of the patient with necrobiosis lipoidica revealed the presence of multiple subcutaneous nodules (indicated by black arrows) beneath both knees. A puncture biopsy was performed on the subcutaneous nodule below the right knee joint in order to conduct a pathological examination of the skin tissue.



**Figure 2.** Medium power microscopy reveals the presence of epithelioid granulomas in the deep dermis, along with a concentration of lymphocytes at the dermal-subcutaneous junction. These findings are indicative of necrobiosis lipoidica.

nodules showed significant softening. Following two months of oral tofacitinib administration, ultrasound examination revealed that the single small subcutaneous nodule had subsided, and the larger nodules were smaller in size compared to before treatment. During follow-up, it was observed that, although there was no complete regression, the remaining subcutaneous nodules continued to soften and shrink based on ultrasound measurements taken before and after treatment.

## Discussion

The histopathological findings indicated granulomatous inflammation, with giant cells observed in the lower middle dermis, but no denatured collagen fibers were present. The possibility of annular granuloma was eliminated, and necrobiosis lipoidica was considered.

Necrobiosis lipoidica (NL) is a type of granulomatous dermatitis that is primarily associated with diabetes. However, an increasing number of NL cases are now being linked to other systemic diseases. While NL typically presents as plaques on the lower legs, often accompanied by ulcers. Although NL in the form of subcutaneous nodules is extremely rare, one case<sup>5</sup> was reported in a 55-year-old woman with a 5-year history of subcutaneous nodules on both thighs where a skin biopsy showed typical NL alterations. This case bears a striking resemblance to the one we are currently dealing with. In addition to the typical skin pathologic support, immunohistochemistry showed predominantly positive CD68 and LCA, which also confirmed that histiocytic and lymphocyte infiltration was predominant. Antacids, periodic-acid silver methenamine and PAS staining, and TB-DNA (PCR) tests did not support the possibility of skin infection causing subcutaneous nodules. In contrast to most cases in NL, this particular patient exhibited normal blood sugar and HBA1c levels, which are not indicative of diabetes. Furthermore, a comprehensive systematic examination failed to reveal any underlying systemic disease. It is suspected that her condition may be attributed to the physical demands of her profession, which necessitate prolonged periods of standing; however, the exact mechanism remains unclear.

In granulomatous inflammation, cytokines are produced by macrophages and lymphocytes, leading to enhanced inflammation. CD4+ helper T cells are the primary lymphocyte population associated with both infectious and non-infectious granulomatous inflammation, secreting high levels of interferon- $\gamma$  (IFN- $\gamma$ ). In mouse models, IFN- $\gamma$  appears to play a crucial functional role in inflammatory polarization of macrophages and in vivo granuloma formation<sup>6</sup>. Many cytokines, including IFN- $\gamma$ , depend on the JAK-STAT pathway<sup>7</sup>. Based on evidence indicating activation of the JAK-STAT signal in NL<sup>4</sup>, drugs that inhibit JAK protein can simultaneously block the activity of these cytokines.

NL is a rare granulomatous condition predominantly affecting middle-aged women. Due to its infrequency in the general population, no standardized treatment guidelines have been established thus far. Recently, numerous efforts have been made to explore new therapeutic options for this condition. Notably, there have been reports of successful treatment outcomes for ulcerative necrobiosis lipoidica using oral tofacitinib (a JAK1/3 inhibitor)<sup>8,9</sup>, as well as improvements in necrobiosis lipoidica with the application of topical ruxolitinib cream (a JAK1/2 inhibitor)<sup>10</sup>. In light of the observation that the subcutaneous nodules in this patient were gradually and effectively reduced solely through oral administration of tofacitinib, it can be concluded that the pan-JAK inhibitor tofacitinib demonstrates efficacy in treating NL as manifested by subcutaneous nodules.

It is widely acknowledged that NL is a condition that typically does not respond well to conventional treatments. First-line therapies generally consist of topical corticosteroids; however, patients exhibit varying degrees of efficacy and experience a range of side effects associated with prolonged use. A review<sup>11</sup> has indicated that Janus kinase inhibitors and biologics, such as ustekinumab and secukinumab, demonstrate effectiveness in patients with refractory NL. Nevertheless, further studies involving larger patient populations are necessary to evaluate the efficacy of different treatment regimens and to establish a consistent therapeutic approach for NL.

## Conclusion

JAK inhibitors have emerged as the most recent approved and effective therapies for various skin diseases. Further multi-center studies are necessary to determine whether JAK inhibitors can be established as the new optimal treatment pathway for NL. These studies will help elucidate the pathogenesis of NL and explore newer, more effective treatment approaches in order to establish uniform treatment recommendations.

**Patient Consent Statement:** The authors obtained written consent from patients for their photographs and medical information to be published in print and online

and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors.

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