

Infliximab therapy in an infant with Netherton Syndrome

Abstract

We present a patient with Netherton syndrome and severe skin manifestations treated with infliximab. By 6 months of age, the child had intractable pruritus, scaling, dry skin, and generalized eczematous lesions resistant to conventional therapies for atopic dermatitis. Clinical improvement was observed following the third infusion of infliximab, and by 12 months of age, the skin lesions completely resolved. Infliximab is a promising option for the management of skin inflammation in Netherton syndrome, even in infants.

2 | CASE REPORT

A 40-day-old male infant presented with recurrent sepsis and generalized itchy eczematous dermatitis with scaling that had been present from birth. His parents were first cousins. Physical examination revealed xerosis and erythroderma with focal scaly plaques typical for ichthyosis linearis circumflexa (Figure 1). He had short, brittle and sparse scalp hair, eyelashes and eyebrows. Light microscopy of scalp hair demonstrated trichorrhexis invaginata. Weight, length, and head circumference were all below the 3rd percentile. The eosinophil count, total serum IgE, and cow's milk protein-specific IgE were elevated. Serum immunoglobulin G (IgG) level was low; IgM and IgA levels were normal (Table 1). Histological findings showed subepidermal neutrophil-rich inflammation. A homozygous mutation in the serine protease inhibitor of the Kazal-type 5 (*SPINK5*) gene (c.410 +1G>A) was detected. Despite emollients, antihistamines, antibiotics, topical corticosteroids, and intravenous immunoglobulin (IVIg), no improvement was found on the skin lesions. At 6 months of age, infliximab infusions (5 mg/kg) were initiated on weeks 0, 2, and 6 and continued every 4 weeks. Laboratory monitoring, including complete blood counts and kidney and liver function tests, was obtained monthly without evidence of abnormality. Clinical improvement of both skin and scalp findings was appreciated following the

1 | INTRODUCTION

Netherton syndrome (NS) is a rare genodermatosis, characterized by ichthyosiform erythroderma, hair shaft abnormalities, and atopic manifestations.

Limited data are available regarding the use of anti-tumor necrosis factor alpha (TNF- α) agents in the treatment of NS in childhood. We present a child with severe skin manifestations of NS who was successfully treated with infliximab.

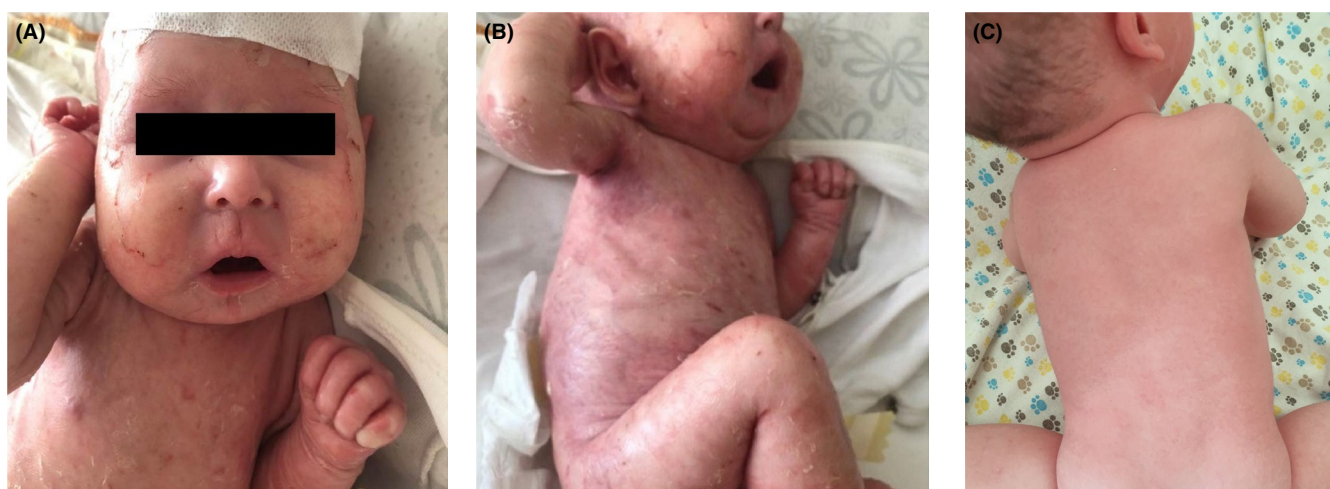


FIGURE 1 Clinical response to infliximab: (A) before infliximab therapy (ichthyosis linearis circumflexa), (B) before infliximab therapy (erythematous scaly patches), and (C) after the 11th infusion (no cutaneous lesions)

TABLE 1 Summary of the clinical features of 3 patients with NS treated with infliximab

	Fontao et al ⁴	Roda et al ⁵	Our patient
Age	25 years	19 years	6 months
Gender	Female	Female	Male
Clinical symptoms	Extensive pruritic dermatitis	Skin eruption	Recurrent infectious diseases, scaling and generalized eczematous skin lesions
Genetic test	<i>SPINK5</i> homozygous mutation in exon 12	<i>SPINK5</i> heterozygous mutations in exon 11 and intron 15, c.891C>T and c.1431-12G>A	<i>SPINK5</i> homozygous mutation, c.410 +1G>A
Findings of physical examination	Diffuse xerosis, ichthyosis circumflexa, vesicular and pustular lesions, recurrent, severe inflammatory flares	Disseminated pruritic, migratory cutaneous eruption, polycyclic erythematous plaques, sparse, thin, fragile hair	Dry skin, generalized itchy erythroderma, ichthyosis linearis circumflexa, and short, brittle, and sparse hair, sparse eyebrows and eyelashes
Laboratory investigations	Total serum IgE: 3660 kIU/L (NR: <87 kIU/L)	Total serum IgE: 686 UI/mL (NR: 150-300 IU/mL)	Total serum IgE: 453 kIU/L (NR: <87 kIU/L), Eosinophils: 1946 K/ μ L (NR: 20-500 K/ μ L) Cow's milk protein-specific IgE: 3.02 kUA/L (NR: <0.35 kUA/L)
Immunological findings	NA	NA	IgG: 291 g/L (NR: 376-685 g/L), IgM: 55 g/L (NR: 36-77 g/L), IgA: 13 g/L (NR: 9-30 g/L), Lymphocyte subsets CD3: 65.5%(7.440 K/ μ L) (NR: 2.5-5.5 K/ μ L), CD4: 51.8% (5.884 K/ μ L) (NR: 1.6-4 K/ μ L), CD8: 12.6%(1.431 K/ μ L) (NR: 0.56-1.7 K/ μ L), CD19: 8.5% (0.965 K/ μ L) (NR: 0.3-2 K/ μ L), CD3-CD16+CD56+: 21.6% (2.453/ μ L) (NR: 0.17-1.1 K/ μ L), NBT: 97% (NR: >0)
Skin biopsy	Acanthotic and spongiotic epidermis with subcorneal accumulation of neutrophils	Subcorneal spongiform pustule with a psoriasiform pattern and irregular acanthosis of epidermis with parakeratosis foci	Subepidermal neutrophil-rich inflammation
Light microscopic examination of hair	NA	Trichorrhexis invaginata (bamboo hair)	Trichorrhexis invaginata (bamboo hair)
Infliximab dose	5 mg/kg on weeks 0, 2, and 6 and continued every 4 weeks	5 mg/kg on weeks 0, 2, and 6 and continued every 8 weeks	5 mg/kg on weeks 0, 2, and 6 and continued every 4 weeks.
The duration of infliximab treatment	2 years	NA	1 year
Other treatments	Systemic dapsone, topical steroids, topical tacrolimus, and topical pimecrolimus	Topical tacrolimus, oral isotretinoin	Emollients, antihistamines, antibiotics, topical corticosteroids, topical tacrolimus, and intravenous immunoglobulin
Outcome	Alive	Alive	Alive
The effect of infliximab	The skin was consistently clear of inflammatory lesions, although xerosis, ichthyosis were not improved.	The skin was cleared of inflammatory lesions and the patient mentioned stronger and longer hair.	Skin and scalp lesions completely resolved.
Side effect of infliximab	No	No	No

Abbreviations: NA, Not available; NR, Normal range; NBT, Nitroblue Tetrazolium test.

third infusion. After a year of treatment, the skin and scalp rash had cleared and infliximab was discontinued. The patient continues to be managed with emollient therapy and has not had an exacerbation for the last 15 months.

Fatih Cicek Sukru Cekic Sara Sebnem Kilic 

Division of Pediatric Immunology, Uludag University Faculty of Medicine, Bursa, Turkey

3 | DISCUSSION

Various topical and systemic therapies have been used in NS. Topical corticosteroids and topical immunomodulators (such as calcineurin inhibitors) are moderately effective in NS,¹ but the risk of systemic absorption and side effects limit their use, particularly in infants. Recent studies have shown that IVIg treatment reduces the incidence of infections and improves skin lesions in NS.² Our patient was refractory to these interventions.

It has been shown that thymic stromal lymphopoietin (TSLP) and TNF- α are overexpressed in the epidermis of patients with NS. Therefore, anti-TNF- α treatment may reduce skin inflammation in NS.^{3,4} However, limited data are available on the clinical use of the monoclonal anti-TNF- α antibody infliximab in NS. To date, there are reports describing two adult cases of NS successfully treated with infliximab.^{4,5} Similar to these reports, a significant improvement was observed in the skin findings of our patient after the use of infliximab, further supporting the theory that TNF- α might play an essential role in the pathogenesis of skin inflammation in NS.

Infliximab treatment effectively improved the skin findings of our patient without causing adverse side effects. Infliximab may be a promising option for controlling disease activity, even in infants. Additional studies are warranted to support the efficacy and safety profile of infliximab in patients with NS.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

KEYWORDS

childhood, ichthyosis, infliximab, Netherton Syndrome, tumor necrosis factor- α

Correspondence

Sara Sebnem Kilic, Division of Pediatric Immunology, Uludag University Faculty of Medicine, Görükle- Bursa 16059, Turkey.

Email: sebnemkl@uludag.edu.tr

ORCID

Fatih Cicek  <https://orcid.org/0000-0001-7348-7081>

Sukru Cekic  <https://orcid.org/0000-0002-9574-1842>

Sara Sebnem Kilic  <https://orcid.org/0000-0001-8571-2581>

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