Immunologic Research (2019) 67:450–453
https://doi.org/10.1007/s12026-019-09100-z

BRIEF REPORT

Infliximab therapy for inflammatory colitis in an infant with NEMO deficiency

Hasibe Artac[1] · Ayca Emsen[1] · Hulya Ucaryilmaz[1] · Halil Haldun Emiroglu[2] · Vedat Uygun[3] · Asbjørg Stray-Pedersen[4]

Published online: 12 November 2019

Introduction

X-linked ectodermal dysplasia with immunodeficiency (X-EDA-ID) is a rare disease caused by hypomorphic mutation in the gene encoding nuclear factor-κB (NF-κB) essential modulator (NEMO) [1–3]. Boys affected with X-EDA-ID have severely impaired host defense, are prone to life-threatening infections, and have susceptibility to atypical mycobacteria. They have also increase risk of inflammatory diseases, in particular inflammatory colitis. NEMO colitis usually occurs early in childhood, causes intractable diarrhea that is difficult to control, and is life-threatening.

A hematopoietic stem cell transplantation (HSCT) reconstitutes the immune cells in NEMO deficiency, but it may worsen non-immune constitutional manifestations, in particular the colitis because of the associated mucosal/epithelial defects that remain after HSCT [4, 5]. TNFα blockage therapy was used as an effective treatment for the intractable NEMO colitis in a few cases [6–9]. We report here a 2-year-old boy with severe steroid refractory colitis caused by X-EDA-ID who was well responsive to infliximab, anti-TNFα monoclonal antibody. We observed that this treatment led to improvement in both his severe inflammatory colitis and skin manifestations.

Case presentation

A 4-month-old boy presented with Staphylococcus aureus pneumonia, disseminated BCG vaccination, septicemia, and persistent diarrhea. At admission, physical examination revealed signs of anhidrotic ectodermal dysplasia with fine and sparse hair, absent eyebrows, thin translucent skin with dry eczema, and hyperkeratosis (Fig. 1). He had also growth retardation, the findings of respiratory distress, and hepatosplenomegaly. His initial laboratory examination showed hypogammaglobulinemia with normal T cell and B cell subsets (Table 1). He had chronic diarrhea and chronic dehydration necessitating enteral feeding and ultimately total parenteral nutrition dependence. The albumin replacement therapy about once a week was required for severe hypoalbuminemia because of enteropathy. No significant pathogen was detected by stool culture. All other infectious etiologies were excluded.

✉ Hasibe Artac
hasibeartac@yahoo.com

Ayca Emsen
aycaceylan14@gmail.com

Hulya Ucaryilmaz
hulyaozdemir1@gmail.com

Halil Haldun Emiroglu
haldunemiroglu@gmail.com

Vedat Uygun
veddat@hotmail.com

Asbjørg Stray-Pedersen
strayped@bcm.edu

[1] Department of Pediatric Immunology and Allergy, Selcuk University Medical Faculty, Alaeddin Keykubat Kampusu, 42130 Konya, Turkey

[2] Department of Gastroenterology and Hepatology, Selcuk University Medical Faculty, Konya, Turkey

[3] Department of Pediatric Hematology and Oncology, Medical Park Antalya Hospital, Antalya, Turkey

[4] Center for Human Immunobiology-Immunology-Allergy-Rhematology, Texas Children Hospital-Baylor College of Medicine, Houston, TX, USA

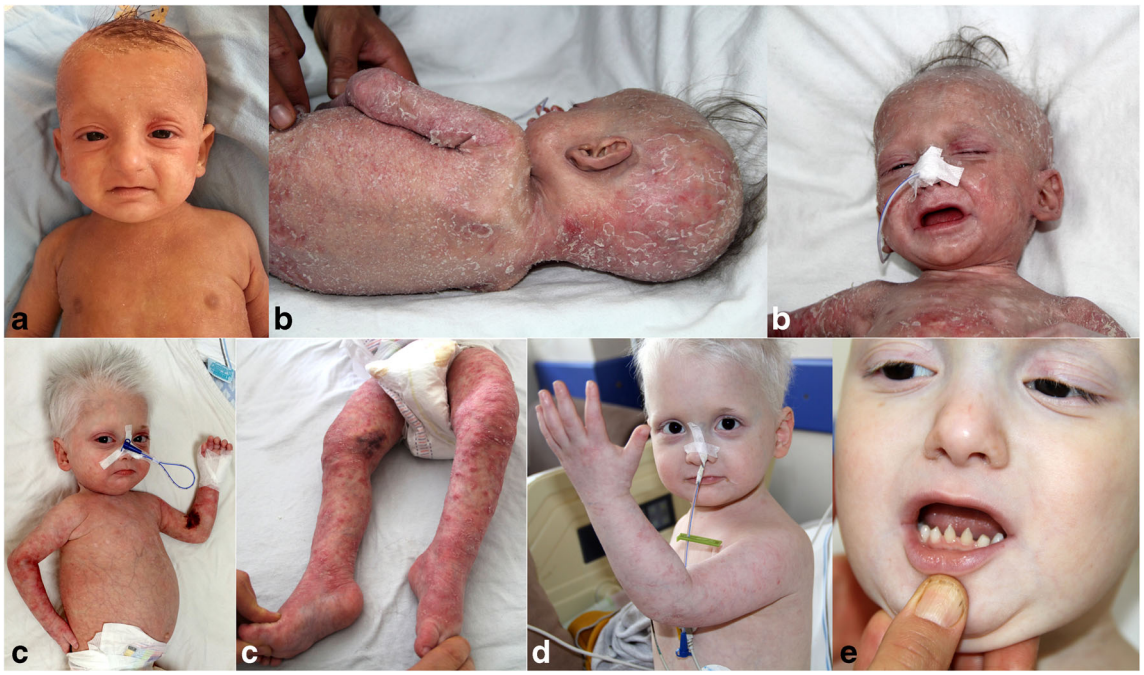

Fig. 1 Clinical appearance of the patient; (**a**) at admission, (**b**) before infliximab treatment, (**c**) and (**d**) are 18 and 36 months after infliximab treatment, respectively, (**e**) dental abnormalities

He was the third child of unrelated Turkish parents. Hyperpigmented lesions were detected in the extremities of his mother, sister, and grandmother (Fig. 2). His genetic analysis showed an X-linked disease-causing IKBKG mutation (c.1167dupC, p.Glu390Argfs*5 [NM_001099857]); his unaffected mother was a heterozygous carrier (69/284 reads by using WES) [10]. Interestingly, the IKBKG mutant allele was observed in only 35% (55/159) of reads in the boy's DNA extracted from blood. This finding was evaluated as revertant mosaicism, which could explain his relatively mild phenotype compared with classic IKBKG-associated immunodeficiency (MIM: 300291) in male subjects.

Table 1 Patient's lymphocyte phenotyping and serum immunoglobulin levels at admission, before HSCT, and during infliximab therapy

	First admission (4 months)	Before HSCT (8 months)	Infliximab therapy			
			First dose (22 months)	12th month	24th month	36th month
Leucocyte count (10^9/L)	46.5	26.8	10.5	9.8	7.5	8.6
Absolute lymphocyte count	10.9	10.5	1	1.5	1.8	4.1
Absolute neutrophil count	27.1	3.55	6.04	6.94	4.41	3.1
Absolute eosinophil count	2.48	10.1	2.33	0.1	0.5	0.2
$CD3^+$ (%)	56.6	71.6	41	56	71.1	77
Absolute count	4.335	8.473	0.44	1.107	1.178	5.261
$CD3^+4^+$ (%)	46.8	58.8	30.1	35.7	43.8	50.9
Absolute count	3.584	6.958	0.323	0.705	0.726	3.478
$CD3^+8^+$ (%)	8.6	11.1	8.1	13.7	22.5	19.9
Absolute count	0.659	1.314	0.087	0.271	0.373	1.36
$CD19^+$ (%)	28.8	18.5	14.2	1.4	6.7	17.6
Absolute count	2.206	2.189	0.152	0.028	0.111	1.203
$CD16^+56^+$ (%)	7.9	4.4	9	17.3	12.2	3.9
IgG (mg/dl)	260	298	580	634	731	984
IgA (mg/dl)	15.3	6.86	110	237	505	330
IgM (mg/dl)	22.1	30.2	64.6	139	71	62
IgE (IU/mL)	24.5	17.1	16.7	5	9.17	-

Hematopoietic stem cell transplantation (HSCT) was performed from HLA-match unrelated donor in the age of 9 months. He achieved maximal donor chimerism of 96% at month + 10, which then declined to 69% at month + 36. At approximately 4 years post-transplant, the chimerism decreased to 40%. Although he had HSCT, his rashes, poor weight gain, and severe intractable diarrhea were continued. In the beginning, endoscopy revealed mucosal redness and edema at his colon. High-dose corticosteroid therapy (methylprednisolone 2 mg/kg, daily) was started for NEMO colitis. Steroid therapy was partially effective in control of colitis and skin lesions, but it did not resolve completely clinical symptoms. In addition to corticosteroid, several alternative therapies (enteral budesonide, oral vancomycin, sirolimus, and tacrolimus) were used for colitis. After the 10-month course of steroid and other treatment, follow-up endoscopy and colonoscopy showed chronic duodenitis, chronic gastric peptic ulcer, and chronic colitis.

The prolonged severe diarrhea that required G-tube feedings and total parenteral nutrition suggested TNF alfa blockage therapy. Informed consent concerning treatment was obtained from the patient's parents. Before initiating infliximab, infections including tuberculosis and cytomegalovirus were rule out. Cardiac function was normal. In 22-month-old, infliximab was given intravenously over 2 h 5 mg/kg 0. 2. 6. week, with follow-up treatments every 8–9 weeks depending on clinical features. On the first day of infliximab treatment, temporary high blood pressure was observed. After infliximab infusion, the frequency of diarrhea dramatically decreased in a week and skin manifestations gradually resolved in years (Fig. 1). Methylprednisolone treatment was reduced gradually and stopped in the sixth month of infliximab treatment. Neither mycobacterial infections nor other infusion reactions were observed. Over the next year of treatment, improvement in stool frequency and a body weight gain of 3 kg were recorded. Colonoscopy after 18 months administration showed colonic aphthous ulcers with mucosal inflammation (Fig. 3). He had hospitalized two times for pneumonia in 4 years. Infliximab was stopped at 40 months of treatment. Now, he is stable with prophylactic antibiotic and regular intravenous immunoglobulin treatment.

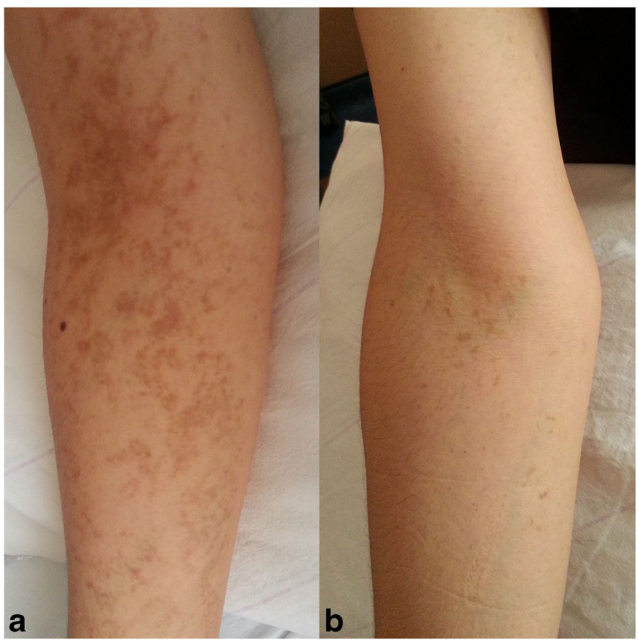

Fig. 2 Hyperpigmented areas were located on the forearm of his mother and grandmother

Discussion

The transcription factor NF-κB, a master regulator of pro-inflammatory responses, functions in gut epithelial cells to control epithelial integrity and the interaction between the mucosal immune system and gut microflora. NEMO deficiency led to increased sensitivity to TNFα-induced apoptosis of intestinal epithelial cells, impaired expression of antimicrobial peptides, and translocation of bacteria into the mucosa [11]. It was reported that TNFα was a key cytokine in the pathogenesis of inflammation and played a major role in the pathogenesis in NEMO colitis. Steroids have always been the mainstay for NEMO-IBD and typically have been quite effective. However, TNF-related intestinal inflammation is responsible for the pathogenesis of NEMO-mediated NF-kappa B signaling defect [11]. Infliximab treatment suppresses the TNFα-mediated inflammatory response by inducing apoptosis of TNFα-producing cells. Herewith, we reported a case with NEMO defect which is treated successfully inflammatory bowel disease with TNFα antagonist in young age.

We observed two prominent problems related to HSCT in this patient: firstly, he had not achieved adequate engraftment; second, he had no improvement in the associated manifestations of his disease. In particular, his skin lesions and colitis

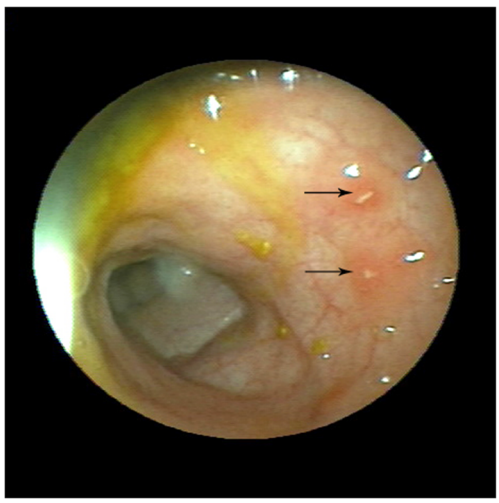

Fig. 3 Colonic aphthous ulcers with mucosal inflammation: small hyperemic nodules with central erosions after 18-month infliximab treatment

was not improved and even worsened. The inflammatory colitis may be expected to potentially worsen with transplantation in this patient. Although HSCT may correct the immune deficiency associated with NEMO, it does not affect the epithelial component [12, 13]. By correcting immune deficit, immune cells can respond to intestinal bacteria and release increased inflammatory cytokines. The risk of life-threatening infections and post-HSCT complications should be evaluated in the HSCT decision.

In addition to the improvement of colitis symptoms, in our patient, infliximab led to resolution his skin findings including eczema and wounds. Nenci et al. showed that an inflammatory response requiring TNF receptor 1 signaling is essential for the pathogenesis of skin lesions in epidermis-specific NEMO-deficient mice [14]. This suggested that infliximab may also benefit in skin manifestations of NEMO deficiency. As a result, anti-TNFα monoclonal antibody therapy should be considered in intractable NEMO colitis and also non-immune findings cause by NEMO.

Acknowledgments We profoundly thank Dr. Jordan Scott Orange for a great support to diagnose NEMO deficiency in the case.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Hanson EP, et al. Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. J Allergy Clin Immunol. 2008;122:1169–1177.e16.
2. Aradhya S, Courtois G, Rajkovic A, Lewis RA, Levy M, Israël A, et al. Atypical forms of incontinentia pigmenti in male individuals result from mutations of a cytosine tract in exon 10 of NEMO (IKK-gamma). Am J Hum Genet. 2001;68:765–71.
3. Pannicke U, Baumann B, Fuchs S, Henneke P, Rensing-Ehl A, Rizzi M, et al. Deficiency of ınnate and acquired ımmunity caused by an IKBKB mutation. N Engl J Med. 2013;369:2504–14.
4. Klemann C, Pannicke U, Morris-Rosendahl DJ, Vlantis K, Rizzi M, Uhlig H, et al. Transplantation from a symptomatic carrier sister restores host defenses but does not prevent colitis in NEMO deficiency. Clin Immunol. 2016;164:52–6.
5. Tegtmeyer D, Seidl M, Gerner P, Baumann U, Klemann C. Inflammatory bowel disease caused by primary immunodeficiencies-clinical presentations, review of literature, and proposal of a rational diagnostic algorithm. Pediatr Allergy Immunol. 2017;28:412–29.
6. Toussi SS, Pan N, Walters HM, Walsh TJ. Infections in children and adolescents with juvenile idiopathic arthritis and inflammatory bowel disease treated with tumor necrosis factor-α inhibitors: systematic review of the literature. Clin Infect Dis. 2013;57:1318–30.
7. Kelsen JR, Grossman AB, Pauly-Hubbard H, Gupta K, Baldassano RN, Mamula P. Infliximab therapy in pediatric patients 7 years of age and younger. J Pediatr Gastroenterol Nutr. 2014;59:758–62.
8. Mizukami T, Obara M, Nishikomori R, Kawai T, Tahara Y, Sameshima N, et al. Nunoi H. Successful treatment with infliximab for inflammatory colitis in a patient with X-linked anhidrotic ectodermal dysplasia with immunodeficiency. J Clin Immunol. 2012;32:39–49.
9. Yang J, Cheuk DK, Ha SY, Chiang AK, Lee TL, Ho MH, et al. Infliximab for steroid refractory or dependent gastrointestinal acute graft-versus-host disease in children after allogeneic hematopoietic stem cell transplantation. Pediatr Transplant. 2012;16:771–8.
10. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, et al. Primary immunodeficiency diseases: genomic approaches delineate heterogeneous Mendelian disorders. J Allergy Clin Immunol. 2017;139:232–45.
11. Nenci A, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, et al. Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature. 2007;446:557–61.
12. Fish JD, Duerst RE, Gelfand EW, Orange JS, Bunin N. Challenges in the use of allogeneic hematopoietic SCT for ectodermal dysplasia with immune deficiency. Bone Marrow Transplant. 2009;43:217–21.
13. Miot C, Imai K, Imai C, Mancini AJ, Kucuk ZY, Kawai T, et al. Hematopoietic stem cell transplantation in 29 patients hemizygous for hypomorphic IKBKG/NEMO mutations. Blood. 2017;130:1456–67.
14. Nenci A, Huth M, Funteh A, Schmidt-Supprian M, Bloch W, Metzger D, et al. Skin lesion development in a mouse model of incontinentia pigmenti is triggered by NEMO deficiency in epidermal keratinocytes and requires TNF signaling. Hum Mol Genet. 2006;15:531–42.