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TCF3 Haploinsufficiency in a Patient with Intractable Psoriasis and Immunodeficiency

Case Report

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Abstract

Transcription factor 3 (*TCF3*) haploinsufficiency has been linked to immunodeficiency. Considering *TCF3's* significant role in epidermal wound repair, its absence may contribute to the development of inflammatory skin cell diseases. The connection between severe inflammatory skin conditions and immunodeficiency in the context of *TCF3* haploinsufficiency has not been previously documented. This study reports a 49-year-old male with a hypogammaglobulinemia since 2009 and a refractory psoriasis since 2013. In 2017 and 2022, genetic panels were performed, each time identifying a heterozygous splice donor variant c.1326+2T>G in *TCF3* gene locus. A cytokine panel showed high levels of IL-6.

In front of this severe exanthem, Upadacitinib was initiated with complete cutaneous resolution in three months. We report the first case *TCF3* haploinsufficiency associated with refractory psoriasis and hypogammaglobulinemia. The aim of this case report is to prove the usefulness of serum panel for cytokines to personalize biotherapy in cases of refractory inflammatory skin diseases, but also to show the mandatory aspect of genetic analysis in patient with severe unresponsive psoriasis. Our report likely demonstrates the role of the *TCF3*-derived proteins in cutaneous homeostasis, giving more insight into psoriasis pathophysiology in line with the immune system.

Keywords: *TCF3*, Interleukin-6, Psoriasis, Common Variable Immunodeficiency, Immune Dysregulation

Introduction

Transcription factor 3 (*TCF3*) haploinsufficiency has been linked to immunodeficiency. Considering *TCF3's* significant role in epidermal wound repair, its absence may contribute to the development of inflammatory skin cell diseases. The connection between severe inflammatory skin conditions and immunodeficiency in the context of *TCF3* haploinsufficiency has not been previously documented.

Case Presentation

In this report, we describe a 49-year-old individual presenting with heterozygous loss-of-function (LOF) *TCF3* variant, exhibiting clinical features characterized by refractory psoriasis and hypogammaglobulinemia. Examination of his serum cytokine profile and genetic sequencing for primary immunodeficiency led to adjusted and successful treatment with a JAK inhibitor agent. The usefulness of these evaluations in cases of atypical and refractory cutaneous exanthem is discussed.

The patient was initially diagnosed with a common variable immunodeficiency (CVID) in 2009 and treated with intravenous immunoglobulin (IVIG). He presented with recurrent sinopulmonary infections, warts and condyloma acuminata and low levels of immunoglobulin (Ig) G, IgA, and IgM. The lymphocyte phenotyping panel showed normal results. Memory B cells (CD19+, CD27+) remained at normal level throughout the years (Table 1).

The patient's past medical history was remarkable for atopic dermatitis in childhood, non-allergic chronic rhinosinusitis, and splenomegaly. In 2013, he presented a severe inflammatory skin disease diagnosed as psoriasis with progression to generalized erythroderma. Numerous medications were attempted without long term success, including: ustekinumab, guselkumab, ixekizumab, brodalumab,

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risankizumab and apremilast. In two separated episodes, skin biopsies showed dermal inflammation with psoriasiform and spongiotic changes. In 2017 and 2022, genetic panels were performed, each time identifying a heterozygous splice donor variant c.1326+2T>G in TCF3 gene locus. Also, in 2022, an extended cytokine panel showed high levels of IL-6 at 18.3ng/ml (Table 2).

Table 1: Immunological Investigations May 2023.

Analysis	Result	Reference Value
Lymphocyte Counts (cells/µL)		
Lymphocyte Count	**1,100,000**	**1,200,000 - 4,000,000**
CD3	847	700-2,100
CD4	646	300- 1,400
CD8	183	200- 900
CD45RO/CD4	400	66- 914
CD45RA/CD4	530	231- 668
CD19	132	100- 500
CD27/CD19	590	18- 120
CD16+CD56+	53	90- 600
Immunoglobulin Levels (g/L)		
IgG	13.40	7.00- 16.00
IgA	0.24	0.60- 4.00
IgM	0.28	0.40- 2.80

Table 2: Main Cytokines, Chemokines and Growth Factors Comparison.

	Before Upadacitinib (October 2022)		After 4 Months of Upadacitinib (May 2023)	
	Results (ng/mL)	**Reference Interval**	**Results (ng/mL)**	**Reference Interval**
IL-6	18.3	0.2-14.4	6.4	0.2-14.4
IL-17A	1.2	0-14.5	3.1	0- 14.5
IL-17E/IL-25	165	54-1,315	64.4	54-1,315
IL-17F	9.9	0-48.1	30.6	0-48.1
IL-22	< 16	0-133	136	0-133
IL-23	< 24.4	0- 55.1	1763	0- 55.1

In front of severe persistent skin eruption unresponsive to multiple psoriasis treatment and immune dysregulation, upadacitinib was started in January of 2023, jointly with the dermatology team. A complete resolution of cutaneous lesions was noticed three months later. The cytokine panel was controlled at that time and showed a decrease level of IL-6. The IL-6 measurement was at 5.4 ng/ml while on upadacitinib (Table 2).

Discussion

TCF3 contributes to T and B lymphocyte differentiation as well as skin stem cell function. In mature activated B cells, *TCF3*-derived proteins also play a role in generating antibody diversity mainly through Activation-Induced Cytidine Deaminase (AID) expression. Originally, mutations in *TCF3* had been described in cases of severe immunodeficiency with either germline monoallelic dominant or biallelic loss-of function (LOF) mutations. *TCF3* haploinsufficiency was first suggested by Ameratunga et al. in a study including 2 family members with heterozygous variant in the *TCF3* gene. More recently, eight cases have been described with heterozygous mutations leading to a dominant negative LOF and haploinsufficiency mechanisms [1]. In the group of patients published by Boast et al., no inflammatory skin disease was described in connection with *TCF3* haploinsufficiency. Interestingly enough, the case we present here manifested with a *TCF3* haploinsufficiency and intractable psoriasis.

Psoriasis is a complex inflammatory skin disease with T helper (Th) 1 and Th17 differentiation abnormalities which promote keratinocyte proliferation. Multiple mutations have been linked to different forms of psoriasis. In atypical cases, diagnosis and treatment may be difficult and genetic testing may therefore be useful [2]. *TCF3* is expressed on different types of stem cells, including skin stem cells and has been described as a key feature of keratinocyte differentiation. In skin wounds, an upregulation of *TCF3* has been observed, and the overexpression of *TCF3* can quicken keratinocyte migration and wound repair. In psoriasis and in condyloma acuminata, *TCF3* was found to be highly expressed, like its keratinocyte regulator lipocalin 2 [3,4].

The patient we hereby discuss presented with a heterozygous *TCF3* variant in the same position as the family E (c.1326) described by Boast et al [1]. In a similar manner, he had low immunoglobulin levels and sinopulmonary infections. However, his CD19 and CD19/CD27 numbers were normal and no dysmorphism was identified. Those findings were compatible, in our patient, with an haploinsufficiency LOF mutation in *TCF3* comparable with the reported cases in the literature showing variable penetrance [1].

IL-6 is a type 1 cytokine which promotes tumor necrosis factor (TNF) -α production, IL-1b production, and Th17 differentiation. When IL-6 binds the Janus kinase (JAK) receptor (specifically tyrosine kinase (TYK) 2, JAK1 and JAK2) it activates the JAK/STAT pathway (particularly STAT3) and has been described to cause autoimmunity, lymphocyte differentiation and effector function, T cell proliferation, and malignancy [5]. The cytokines described to be involved in psoriasis are usually those linked to Th1 and Th17 cells, which play an important role in the psoriasis pathogenesis. Specifically, IL-6 has been described in the psoriasis inflammatory cascade to promote Th17 differentiation and keratinocyte proliferation via JAK1/TYK2 or JAK1/JAK2, as mentioned above [2,3,4].

The JAK inhibitor upadacitinib was chosen in this case because of the cutaneous presentation showing features of both psoriasis and atopic dermatitis with severe pruritus, as well as failure of numerous psoriasis treatments. This JAK inhibitor was also selected because of specific inhibition of JAK1, a tyrosine kinase activated by IL-6 [2]. Since IL-6 has been described to promote keratinocyte proliferation, its inhibition by upadacitinib could also have played a role in the improvement of the patient's skin condition.

STAT3 also plays a role in the regulation of cell growth and differentiation.

When inhibited by JAK inhibitors it is known to induce cell apoptosis. In the pathophysiology of psoriasis, dysfunction in the apoptosis mechanisms is known to play an important role by creating a keratinocyte proliferation disorder [3,4]. In the patient's case, the induction of cell apoptosis by inhibiting STAT3 with upadactinib might have had a positive effect on his severe cutaneous disease by increasing cell apoptosis and therefore decreasing keratinocyte proliferation. It is to be noted that, in our study, the expression and the functionality of the *TCF3*-derived proteins were not evaluated. However, the genetic analysis seemed to guide us towards a functional damage of the gene product. The splice-donor variant found in our patient is predicted to be deleterious.

In conclusion, we report the first case of *TCF3* haploinsufficiency associated with a refractory psoriasis. Treatment with a JAK inhibitor allowed a great clinical and paraclinical response. We proved the usefulness of serum panel for cytokines to personalize biotherapy in cases of refractory inflammatory skin diseases. These measures seem to be an efficient way of guiding the patients' treatment and increasing their quality of life. In this case report, we also show the mandatory aspect of genetic analysis in a patient with severe unresponsive psoriasis, especially in presence of immune abnormalities. In addition to the impact of *TCF3* gene mutations in relation with immunity, our report likely demonstrates the role of the *TCF3*-derived proteins in cutaneous homeostasis, giving more insight into psoriasis pathophysiology in line with the immune system. Further studies will be necessary to better explore the relationship of *TCF3* mutations and other autoimmune or inflammatory diseases.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Authors Contribution

All authors contributed to the study conception and design. The first draft of the manuscript was written by Louis Deschênes and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to Participate and to Publish

Written consent was obtained from the patient in this case report.

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