Case Report

Immune Dysregulation and Chronic Mucocutaneous Candidiasis in a Child With *STAT1* Gain-of-function Mutation: A Case Report and Literature Review

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ABSTRACT

Background: Chronic mucocutaneous candidiasis (CMC) is most commonly associated with gain-of-function (GOF) mutations in *STAT1*, which impair immune regulation and predispose to recurrent fungal infections, autoimmunity, and lymphoproliferative disorders. The clinical spectrum of *STAT1* GOF is broad, ranging from severe multisystem involvement to milder phenotypes. Here, we present a case of a child carrying the *STAT1* GOF mutation A267V, who exhibited an attenuated phenotype limited to mucocutaneous candidiasis.

Case Presentation: A 10-year-old girl presented with recurrent episodes of oral thrush and chronic onychomycosis, consistent with isolated mucocutaneous candidiasis. She had no history of systemic infections, autoimmune disease, or lymphoproliferative manifestations. Family history was notable for early-onset esophageal cancer in her father. Immunological evaluation revealed a preserved CD4/CD8 ratio (2.05), normal immunoglobulin levels, and absence of autoantibodies. Despite normal B-cell counts, her vaccine response was impaired, with non-protective diphtheria-specific IgG levels, suggesting a defect in STAT1-mediated follicular helper T cell function. Genetic analysis confirmed a heterozygous *STAT1* GOF mutation (A267V), consistent with autosomal dominant inheritance of CMC. The patient was treated with fluconazole for fungal infection control and the Janus kinase (JAK) inhibitor baricitinib to modulate hyperactive JAK-signal transducer and activator of transcription (JAK–STAT) signaling. This therapeutic approach resulted in resolution of infections and improvement in inflammatory activity. This case illustrates an attenuated phenotype of *STAT1* GOF disease, in which the A267V variant was associated with susceptibility to candidiasis but preservation of broader immune homeostasis. Unlike the typical presentation of *STAT1* GOF, the patient demonstrated normal immune parameters, including immunoglobulin levels and CD4/CD8 ratio, and no autoimmunity or systemic fungal disease. The clinical response to baricitinib highlights the therapeutic potential of JAK–STAT pathway inhibition in *STAT1* GOF syndromes.

Conclusions: This case expands the clinical spectrum of *STAT1* GOF mutations by demonstrating that the A267V variant can present as an isolated mucocutaneous phenotype without systemic immune dysregulation. It also emphasizes the potential of JAK inhibition as a targeted therapeutic strategy and the importance of long-term cancer surveillance in these patients.

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Introduction

Fungal infections pose a significant clinical concern, particularly in vulnerable populations, such as patients with COVID-19, where they contribute substantially to morbidity and mortality [1]. Opportunistic pathogens, such as *Candida* spp., normally commensal members of the human microbiota, can cause localized disease in immunocompetent individuals but may lead to invasive candidiasis in immunocompromised hosts. This life-threatening manifestation is most frequently observed in patients with human immunodeficiency viruses (HIV) infection, primary immunoregulatory disorders, or those receiving immunosuppressive therapies, including corticosteroids and chemotherapy [2, 3].

Candida species are the primary causative agents of chronic mucocutaneous candidiasis (CMC), an immunological disorder characterized by recurrent or persistent fungal infections of the skin, mucous membranes, and nails [4, 5]. These chronic infections predominantly occur in individuals with underlying immunodeficiencies. Among the genetic etiologies, gain-of-function (GOF) mutations in *STAT1* constitute the principal cause of CMC, although several other genetic defects have also been implicated [6, 7].

The Janus kinase-signal transducer and activator of transcription (JAK–STAT) pathway, which governs cell growth, proliferation, metabolism, differentiation, and apoptosis, relies on *STAT1* as a central transcription factor [8]. Upon stimulation of cellsurface receptors, activated JAK induces STAT1 phosphorylation (p-STAT1), initiating downstream signaling cascades [9]. Over the past 15 years, three classes of monogenic *STAT1*-related disorders have been identified: autosomal dominant GOF mutations, dominant negative loss-of-function (LOF) variants causing Mendelian susceptibility to mycobacterial disease [10, 11], and biallelic LOF mutations leading to severe combined immunodeficiency (SCID) [6, 7].

A defining feature of GOF mutations, beyond classical cytokine signaling pathways, is the prolonged activation of STAT1 proteins [11]. This aberrant activation disrupts immune homeostasis through two principal mechanisms. First, sustained p-STAT1 drives excessive production of STAT1-dependent cytokines (including interferonγ [IFN-γ], IFN-α/β, and interleukin [IL]-27), establishing a positive feedback loop that perpetuates STAT1 hyperactivation [7, 12-14]. Second, these cytokines suppress Th17 cell differentiation, leading to impaired secretion of IL-17A, IL-17F, and IL-22 [15, 16]. The consequent Th17 deficiency represents a key immunological mechanism underlying the heightened susceptibility to CMC observed in affected patients [17].

CMC occurs in most patients with *STAT1* GOF mutations, although the clinical spectrum is highly variable. In addition to recurrent infections, affected individuals frequently present with non-infectious complications such as aneurysms, autoimmune or inflammatory disorders, and malignancies [10, 17]. Management of *STAT1* GOF disease typically involves a combination of long-term antifungal therapy, immune modulation, and treatment of associated autoimmune manifestations. Topical and systemic triazoles are commonly employed for antifungal prophylaxis and treatment [10]. Despite these therapeutic strategies, comprehensive characterization of the clinical features, natural history, and prognosis of *STAT1* GOF patients remains limited. Here, we describe a 10-year-old girl with a confirmed *STAT1* GOF mutation who presented with recurrent mucocutaneous infections, including oral thrush and fungal nail involvement, highlighting the clinical challenges associated with this condition.

Case Presentation

A 10-year-old girl born to consanguineous parents presented to BaAli Hospital in Sari City, Iran, with a history of recurrent oral thrush and chronic fungal nail lesions. Her mucocutaneous symptoms first appeared at 3 years of age and recurred approximately monthly. While episodes of oral thrush typically resolved spontaneously within 7-10 days, the onychomycosis lesions persisted without complete remission (Figure 1 shows the patient's fungal nail involvement).

The clinical picture was marked by typical pseudomembranous oral candidiasis occurring about 12 times per year, chronic onychodystrophy involving multiple fingernails, absence of invasive or systemic fungal infection, no concurrent bacterial or viral pathogen susceptibility, and normal growth rate with normal developmental progression.

The patient's family history was notable for her father, who required long-term antifungal therapy for recurrent oral thrush and died from esophageal carcinoma at the age of 36. This pattern of familial occurrence strongly suggested an autosomal dominant immunodeficiency. The patient's favorable response to antifungal therapy was particularly remarkable, as treatment resistance is frequently observed in individuals with *STAT1*

GOF disorders [17]. This atypical phenotypic presentation prompted a comprehensive immunological evaluation to investigate the underlying cause of immune dysregulation.

Immunological and laboratory results

Flow cytometry demonstrated T-cell predominance, with CD3+ cells at 66% (normal: 60–80%), CD4+ at 43%, and CD8+ at 21%, resulting in a CD4/CD8 ratio within normal limits (2.05). B-cell counts (CD19+/CD20+) were within the normal range (20%; normal: 5–20%), and NK-cell counts were low normal (CD56+ 3%) (Table 1). Autoantibody screening was negative for anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin, and fluorescent antinuclear antibody (FANA). Serum immunoglobulin levels were normal (immunoglobulin [Ig]A 130 mg/dL, IgM 153 mg/dL, IgE 117 IU/mL), but the vaccine response was inadequate, with non-protective diphtheria IgG (0.01 IU/mL). Hematologic evaluation revealed a normal white blood cell count (WBC) (7.5×10^3/µL), and a normal result on the nitroblue tetrazolium (NBT) test (100%) excluded chronic granulomatous disease. Table 2 summarizes the patient's hematological parameters.

Genetic analysis

Targeted sequencing identified a heterozygous pathogenic *STAT1* mutation (c.C800T, p.A267V; American College of Medical Genetics and Genomics [ACMG] classification: pathogenic), associated with autosomal dominant immunodeficiency 31C (chronic mucocutaneous candidiasis) and immunodeficiency 31A (mycobacterial susceptibility).

Treatment and outcome

The patient was treated with fluconazole prophylaxis (150 mg, every other day) which led to complete resolution of mucocutaneous candidiasis and was combined with baricitinib (2 mg daily), a JAK inhibitor targeting the underlying *STAT1* GOF pathology. Supportive therapy included daily sunscreen for prevention of photosensitivity and valacyclovir (500 mg, daily) as antiviral prophylaxis.

Clinical correlations

This case represents an attenuated *STAT1* GOF phenotype, characterized by isolated mucocutaneous candidiasis without the typical severe infections or autoimmune manifestations. Remarkably, the patient maintained a normal CD4/CD8 ratio (2.05), in contrast to the lymphocytic dysregulation usually observed in classical *STAT1* GOF presentations. Key limitations of the study include the lack of p-STAT1 assays and IL-17/IL-22 profiling, which would provide additional insight into the immune dysregulation underlying this genotype–phenotype association and warrant future investigation.

Discussion

CMC is a rare primary immunodeficiency characterized by recurrent or persistent *Candida albicans* infections of the skin and mucosal surfaces. Although *C. albicans* is a commensal organism in healthy individuals, affected patients, primarily children, develop clinically significant infections indicative of impaired antifungal immunity [6].

Genetic susceptibility to CMC has been associated with mutations in several genes, including *STAT1*, *AIRE*, *CARD9*, and *Dectin-1* [15]. Among these, *STAT1* mutations are the most prevalent and can manifest as either GOF or LOF variants. Over 50% of reported CMC cases are caused by *STAT1* GOF mutations, representing the principal molecular mechanism underlying the disease [16].

STAT1 GOF mutations disrupt Th1 and Th17 cell function, resulting in impaired production of critical antifungal cytokines, such as IFN-γ, IL-17, and IL-22, which are essential for mucosal and cutaneous immunity [7]. Additionally, persistent STAT1 activation via IFN-α/β, IFN-γ, and IL-27 signaling further suppresses IL-17 production through mechanisms that are not yet fully understood [12].

While CMC is the most common infectious manifestation in patients with *STAT1* GOF mutations, many also experience additional fungal infections and increased susceptibility to bacterial and viral pathogens [10]. These patients frequently present with a spectrum of autoimmune phenomena, including rheumatoid arthritis, autoimmune cytopenias, and immune-dysregulation, polyendocrinopathy, enteropathy, Xlinked (IPEX)-like syndromes, which in some cases may progress to SCID. Respiratory complications, particularly bronchiectasis, have also been reported in a minority of cases [14, 17].

Clinical manifestation

Patients with *STAT1* GOF mutations typically present with recurrent mucocutaneous candidiasis involving the oral cavity, genitalia, skin, and nails, with onset usually in early childhood [13]. In the present case, a 10-year-old female exhibited classic CMC manifestations, including oral thrush and onychomycosis, but displayed an un-

Table 1. Flow cytometry immunophenotyping report

Marker	Gated (%)	Total (%)
CD3	66	26
CD4	43	31
CD8	21	8
CD19	20	8
CD20	20	8
CD16	4	43
CD56	3	2

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usually restricted phenotype, lacking the bacterial or viral infections and autoimmune manifestations commonly associated with *STAT1* GOF mutations. Genetic testing confirmed a pathogenic *STAT1* variant (A267V), yet comprehensive serological evaluation—including anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin, and fluorescent antinuclear antibodies (FANA)—revealed no evidence of autoimmunity, in contrast to the typical association of *STAT1* GOF with autoimmune disorders [18]. This attenuated phenotype, characterized by isolated mucocutaneous candidiasis without autoimmunity, suggests that the *A267V* variant may exert hypomorphic effects on STAT1 hyperactivation, partially preserving Th1 and Th17 cell function [19].

A previous report has documented *STAT1* GOF mutations associated with CMC and additional cutaneous manifestations, such as rosacea-like demodicosis, underscoring the phenotypic heterogeneity of *STAT1* GOF disease [20].

B-cell findings

Patients with *STAT1* GOF mutations often exhibit reduced circulating follicular T helper (cTfh) cells, impairing antigen-specific B cell responses [21]. This Tfh deficiency is associated with decreased numbers of memory and naïve B cell, as well as low serum IgG2 (38% of patients) and IgG4 (50%) levels [17]. IL-21 plays a central role in B cell differentiation, antibody synthesis, affinity maturation and isotype switching [22]. However, naïve B cells in *STAT1* GOF patients respond poorly to IL-21, resulting in diminished production of IgM, IgG, and IgA [23].

In this case, the patient demonstrated an impaired response to the tetanus-diphtheria (Td) vaccine despite normal B cell counts and baseline immunoglobulin levels. This likely reflects defective T helper cell function, particularly within Th1 and Th17 subsets, which are critical for effective post-vaccination immune activation [24]. Th17 cells are especially important for the devel-

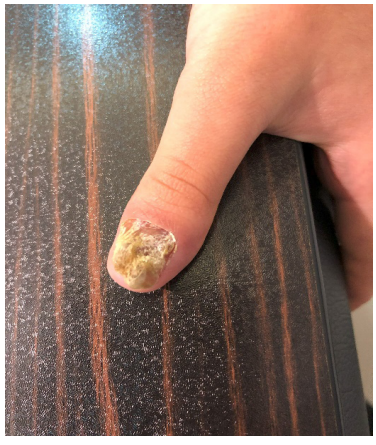

Figure 1. Fungal nail lesion of the patient

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Table 2. The patient's serology, immunology and hematology parameters

Test		Result	Normal Range
Anti TPO (IU/mL)		<10	<35
Anti thyroglobulin (IU/mL)		<20	<40
FANA (titer)		Negative	<1/80
NBT (%)		100	90-100
IgA (mg/dL)		130	27-270
IgE (IU/mL)		117	0-280
IgG (mg/dL)		1020 (mg/dL)	300-1600
IgM (mg/dL)		153 (mg/dL)	10-230
CH50 (U/mL)		78.6 (U/mL)	10.6-95.1
Diphtheria Ab IgG (U/mL)		0.01 (U/mL)	≥0.1
Tetanus Ab IgG (index)		6.8 (index)	>11
Complete blood count	WBC (10^3/uL)	7.5	4-10
	RBC (10^8/uL)	4.82	4.2-5.5
	Hb (g/dL)	13.3	12-16
	HCT (%)	39.5	36-51
	MCV (fL)	81.9 (fL)	80-100
	MCH (pg)	27.7 (pg)	27-34
	MCHC (g/dL)	33.7 (g/dL)	32-36
	PLT (10^3/uL)	289	150-450
	RDW-SD	41.3	35-46
	RDW-CV (%)	13.1	11-16
	PDW	15.5	9-17
	MPV (fL)	8.3	7-12
	P-LCR (%)	13.4	11-45
	Neutrophils (%)	44.1	
	Lymphocytes (%)	46.2	
	Monocytes (%)	7.4	
	Eosinophils (%)	1.9	
	Basophils (%)	0.4	

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Abbreviaions: FANA: Fluorescent antinuclear antibody; Ig: Immunoglobulin; WBC: White blood cell count; NBT: Normal nitroblue tetrazolium; anti-TPO: Anti-thyroid peroxidase; RBC: Red blood cell count; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; PLT: Platelet count; MPV: Mean platelet volume; PDW; Platelet distribution width; PLCR: Plateletlarge cell ratio.

opment of adaptive immune responses, including robust humoral immunity following vaccination. Excessive p-STAT1 in GOF mutations disrupts cytokine signaling, impairing the differentiation and function of T-helper cells necessary for optimal vaccine responses [25]. For the Td vaccine, a strong Th1 response is essential to generate high-affinity antibodies [26]. Thus, despite competent B cells, dysregulated STAT1 signaling can hinder effective T-helper cell-mediated immunity and vaccine responsiveness.

T cells

Patients with CMC often exhibit T lymphocyte dysfunction, typically characterized by normal T cell counts but impaired responsiveness to *Candida* antigens [27]. Although not universal, a reduced proportion of Th17 cells in peripheral blood is frequently observed in individuals with *STAT1* GOF mutations, contributing to their susceptibility to CMC [7].

Cells from these patients display hyperresponsive STAT1-dependent signaling upon stimulation with type I/II interferons (IFNs) and IL-27. These cytokines, which primarily signal through STAT1, are well-established inhibitors of Th17 cell differentiation in both human and murine systems [7].

STAT1 also influences CD4+ and CD8+ T cell responses; however, hyperactive IFN-γ signaling in GOF mutations promotes excessive Th1 expansion, which can further impair CD8+ T cell differentiation and function, exacerbating CD4+ T cell imbalance [28, 29]. In this case, the CD4/CD8 ratio was within normal limits (2.05), in contrast to the CD4+ predominance typically observed in classical *STAT1* GOF presentations [30]. This may reflect compensatory mechanisms specific to the A267V variant or environmental modifiers, such as the microbiome. Alternatively, signaling via other STAT pathways, including STAT3 and STAT5, may help preserve normal T cell subset proportions [31].

Family history implications

Previous studies have demonstrated a strong association between *STAT1* GOF mutations and increased susceptibility to esophageal squamous cell carcinoma (SCC) [32]. Notably, the patient's father died of esophageal cancer at age 36. The proposed mechanism underlying cancer development in *STAT1* GOF patients involves chronic inflammation from persistent candidiasis and candidal enzymatic activity, which generates carcinogenic compounds such as nitrosamines [33].

Given this risk, routine monitoring—including careful assessment of gastrointestinal symptoms—is critical for early detection of malignancy [34]. The JAK–STAT pathway inhibitors, particularly JAK inhibitors, such as ruxolitinib and baricitinib, are emerging as therapeutic options to modulate chronic inflammation in *STAT1* GOF disease and may help reduce the risk of complications, including SCC and autoimmune manifestations [35, 36]. In the present case, baricitinib was administered to prevent chronic inflammation and its potential sequelae. These considerations underscore the importance of long-term cancer surveillance in patients with *STAT1* GOF mutations.

Treatment

The management of *STAT1* GOF mutations in patients with CMC typically involves a combination of antifungal, antibacterial, and antiviral therapies, immunomodulatory treatments, such as JAK inhibitors (e.g. ruxolitinib), and management of associated conditions, including autoimmune or autoinflammatory manifestations, with corticosteroids, immunosuppressants, or biologic agents. Patients with *STAT1* GOF–associated CMC are particularly prone to recurrent fungal infections, predominantly caused by *Candida* species, and azoles remain the mainstay of antifungal therapy [15]. In the present case, treatment included fluconazole, the JAK inhibitor baricitinib, and antiviral prophylaxis. Antiviral agents, such as acyclovir and valacyclovir, are commonly employed to prevent herpes simplex virus (HSV) and Varicellazoster virus (VZV) infections, while ganciclovir or valganciclovir was used for CMV prophylaxis. Because no bacterial infections were observed in this patient, antibacterial therapy was not indicated.

Limitations

This study has several limitations. We were unable to assess IL-17 and IL-22 protein expression, and p-STAT1 assays were not performed. In clinical practice, both evaluations are valuable for stratifying patients with CMC according to the underlying immune defect, thereby facilitating more accurate diagnosis, prognosis, and personalized therapy, particularly in cases with overlapping clinical phenotypes. Additionally, no abnormalities were observed in the patient's total serum IgG level. Although decreased IgG subclass levels (particularly IgG2 and IgG4) have been reported in many patients with CMC and *STAT1* GOF mutations [11], these subclasses were not measured in this case. The absence of recurrent pulmonary infections was a key factor in this decision [37]. Nevertheless, assessment of IgG subclasses

could provide important diagnostic and management insights for patients with CMC.

The family history of early-onset esophageal cancer underscores the importance of long-term malignancy surveillance in patients with *STAT1* GOF, as chronic inflammation and immune dysregulation may increase cancer risk. Although this case expands our understanding of genotype–phenotype correlations in *STAT1* GOF disorders, the absence of IL-17 and IL-22 and p-STAT1 testing represents a diagnostic limitation.

Future studies should investigate how specific *STAT1* variants modulate Th1/Th17 balance and susceptibility to malignancy to optimize monitoring and therapeutic strategies. Overall, this report emphasizes the need for individualized management in *STAT1* GOF syndromes, combining antifungal prophylaxis, targeted immunomodulation, and vigilant cancer screening, while encouraging the development of therapies that restore immune homeostasis without compromising host defense.

Conclusion

This case highlights the broad clinical spectrum of *STAT1* GOF mutations, demonstrating that hypomorphic variants, such as A267V, can present with isolated mucocutaneous candidiasis while sparing patients from the severe infections, autoimmunity, and lymphocytic dysregulation typically seen in typical *STAT1* GOF syndromes. The the patient's CD4/CD8 ratio within the normal range, normal immunoglobulin levels, and absence of autoimmunity suggest that the A267V variant may partially maintain immune homeostasis. Nevertheless, antifungal therapy and JAK inhibition with baricitinib were essential for disease control.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (Code IR.MAZUMS.REC.1404.387). Permission was obtained from the child's parents to publish this case report and any associated photographs. This article adheres to all relevant ethical principles. The patient and her parents have provided written informed consent for publication of this manuscript and collecting images.

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Authors contributions

All authors contributed equally to the preparation of this manuscript.

Conflicts of interest

The authors declared no conflict of interest.

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