Chronic mucocutaneous candidiasis due to signal transducer and activator of transcription 1 mutation in a Saudi patient: a case report

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Abstract

Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency condition caused by a genetic abnormality that increases the risk of recurrent and persistent skin, nail, and mucous membrane infections with Candida species, typically *Candida albicans*. Signal transducer and activator of transcription 1 (STAT1) gene mutation is a genetic trigger that causes CMC, which increases the risk of infections, multisystem disorders, and cancer susceptibility. We describe the first case of a Saudi female patient with clinical features of CMC with an underlying (STAT1) gene mutation.

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Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare primary immunodeficiency condition caused by a genetic abnormality that increases the risk of recurrent and persistent skin, nail, and mucous membrane infections with Candida species, mainly *Candida albicans*.[1] In patients with T-cell deficiencies, CMC is associated with multiple infections and autoimmune diseases.[2] Among those suffering from autosomal dominant (AD) hyper-immunoglobulin E (IgE) syndrome (AD-HIES), CMC is one of the most prevalent infections.[3] Heterozygous Signal transducer and activator of transcription 1 (STAT1) mutations were identified as a cause of CMC in 2011.[4] Since then, about half of CMC patients have been linked to STAT1 gain-of-function (GOF) mutations caused by defective STAT1 dephosphorylation.[5] Autosomal dominant (STAT1) gene mutation is considered the most prevalent genetic cause of CMC.[6] It raises the risk of cutaneous fungal candidiasis, invasive bacterial, viral, and mycobacterial infections, autoimmune diseases, and respiratory and gastrointestinal problems. Additionally, these patients have a higher lifetime chance of acquiring oral, esophageal, and brain squamous cell carcinomas, as well as potentially fatal cerebral and extracerebral aneurysms.[1] It has been demonstrated in recent years that CMC is caused by a number of abnormalities that compromise interleukin-17-mediated immunity.[7] Up to this date, nearly 105 STAT1 GOF mutations have been found in over 400 patients globally, with 65 of them being recurrent.[8] To the best of our knowledge, STAT1 GOF-induced CMC has not been reported previously in the literature on a patient in Saudi Arabia. Herein, we report a case of an eight-year-old Saudi female patient with clinical features of CMC with an underlying (STAT 1 GOF) gene mutation and 31C deficiency.

Case Report

An 8-year-old Saudi female, documented case of hypothyroidism receiving a daily dose of levothyroxine at 62.5 mg, presented to the dermatology outpatient clinic with exacerbation of lesions affecting the fingers, palms, nails, and right toe. The onset of these lesions occurred at the age of

three, progressively worsening over the intervening years. The patient has a history of persistent mucocutaneous fungal infections, notably recurrent oral thrush unresponsive to topical antifungal treatments since 18 months of age. A comprehensive review of her medical history yielded no evidence of recurrent respiratory infections, cough, dysphagia, weight loss, chronic diarrhea, or skin abscess. There is no known family history of autoimmune disorders or similar conditions. Upon cutaneous examination, pronounced thickening and hyperkeratotic plaques with a yellowish configuration over an erythematous background were observed on the thumb and index fingers of both hands, extending to a portion of the right palm. This presentation was further accompanied by fingernail dystrophy, subungual hyperkeratosis, and yellowish distortion on the nails of both thumbs and index fin-

gers (Figure 1 A,B), as well as the right toenail (Figure 2 A,B). Additionally, the patient exhibited an active oral thrush (Figure 3). Fungal culture and histopathological examination of samples obtained from the hard palate confirmed the presence of *Candida albicans*. Nail clip scrapings demonstrated fungal hyphae, with positive staining for fungal pseudohyphae with periodic acid-Schiff (PAS) and Grocott's methenamine silver (GMS), consistent with onychomycosis. Considering the clinical manifestations, a diagnosis of chronic mucocutaneous candidiasis (CMC) syndrome was favored. Subsequent referral to medical genetics for whole exome sequencing (WES) identified an autosomal dominant STAT 1 gene gain-of-function defect (STAT 1 GOF mutation) associated with a 31C immunodeficiency, a variant not previously reported in a CMC patient in Saudi Arabia. Treatment involved a combination of oral systemic itraconazole and topical miconazole, resulting in a substantial clinical remission of the fungal infection (Figure 4 A-D).

Discussion

The diagnosis of chronic mucocutaneous candidiasis (CMC) was made in our patient based on the clinical features of recurrent and persistent oral candida thrush, cutaneous fungal infections, and hypothyroidism. Genes such as STAT 1, STAT 3, IL-17 F, AIRE, IL-17RA, TRAF3IP2, Dectin, CARD 9, IL-12 Rβ1, ROR ηT, and TYK2 have been linked to genetic variants that increase the risk of developing CMC.[8,9] Nearly 50% of CMC patients have been shown to have a STAT 1 mutation, which is followed by an AIRE deficit. However, the prevalence of the genetic mutation in different ethnicities is variable.[10]

Autosomal dominant STAT 1 mutations can be sporadic or familial. It predominantly manifests as mucocutaneous candidiasis, typically as a result of the *Candida albicans* organism.[11] Our patient had mucosal *Candida albicans* infection and associated onychomycosis. According to Toubiana *et al.* and Van FL *et al*., a high proportion of patients with STAT 1 GOF mutations also have

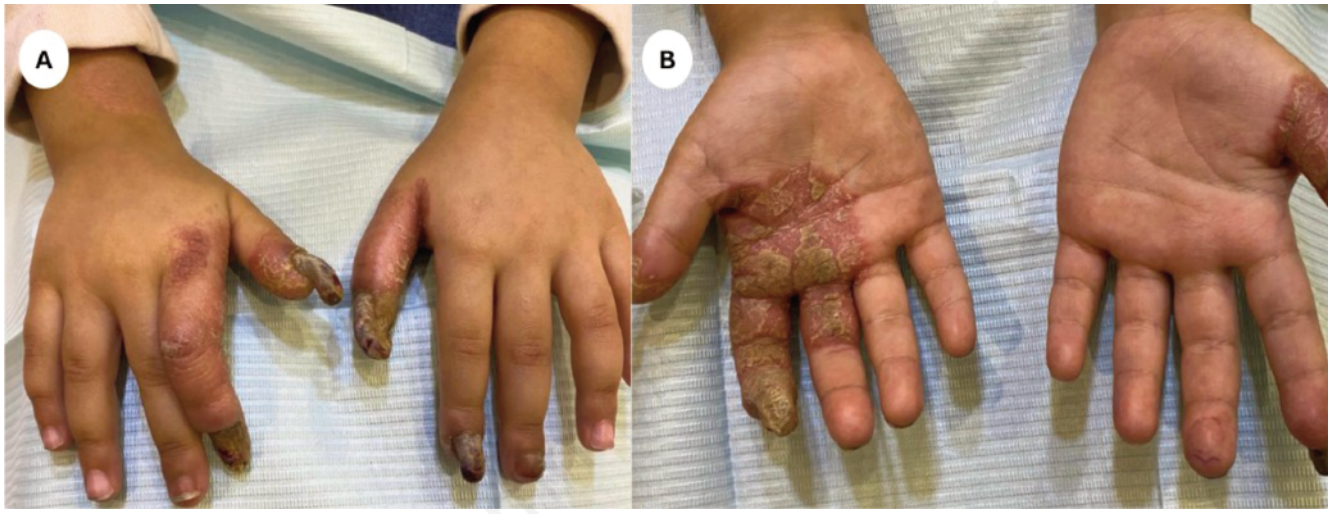

Figure 1. (**A, B**) Severe thickening and plaques of hyperkeratosis with yellowish configuration over an erythematous background located over part of the right palm, index and middle finger, along with subungual hyperkeratosis and yellowish distortion of the nails of both thumbs and index fingers.

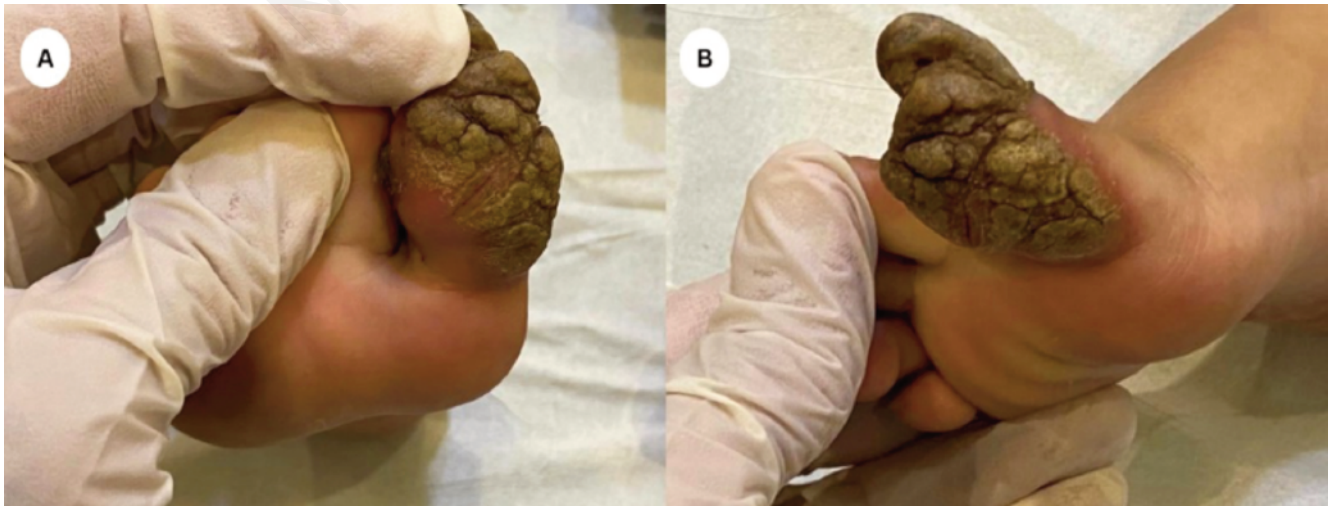

Figure 2. (**A, B**) Subungual hyperkeratosis and yellowish distortion of the right big toe.

autoimmune disorders.[1] Hypothyroidism, type 1 diabetes mellitus, systemic lupus erythematosus illness, vasculitis and skin disorders such as vitiligo and psoriasis are the most commonly reported autoimmune conditions.[1,4] Which explains the coexistence of chronic hypothyroidism and CMC in our patient. A variety of STAT 1 GOF mutations have been reported that result in increased production of IFN- γ, IFN-α/β, and IL-27, which in turn causes an inadequate Th-17 response. These mutations are caused by poor nuclear dephosphorylation, which is confirmed by functional immunological assay.[1,5] Our case, based on the whole exome genetic testing, identified a STAT 1 GOF mutation with heterozygous substitution of c.1154C>T (p.Thr385Met) as DNA variant type. Following the American College of Medical Genetics and Genomics (ACMG) guidelines, the detected variant was classified as "pathogenic" based on the collected evidence. Backed by functional studies, the variant is associated with autoimmune enteropathy and endocrinopathy, susceptibility to chronic infections syndrome, chronic diarrheal disease, combined immunodeficiency and immunodeficiency 31B.[12,13] Vasilev T *et al*. reported a case of autoimmune monogenic diabetes, multiple endocrinopathies and

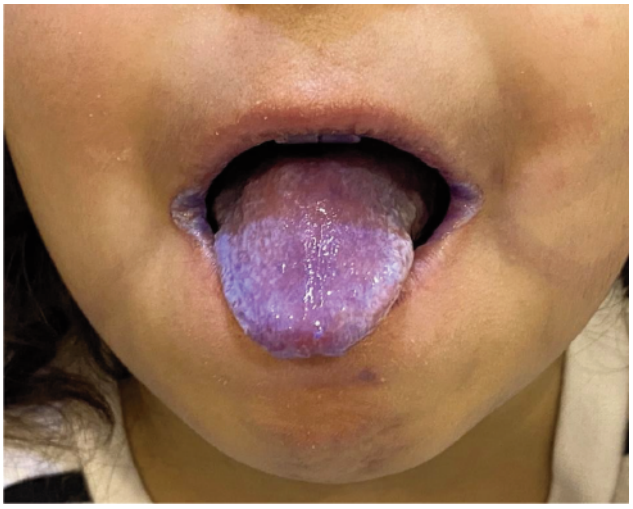

Figure 3. Active oral thrush evident under wood's light with associated angular stomatitis.

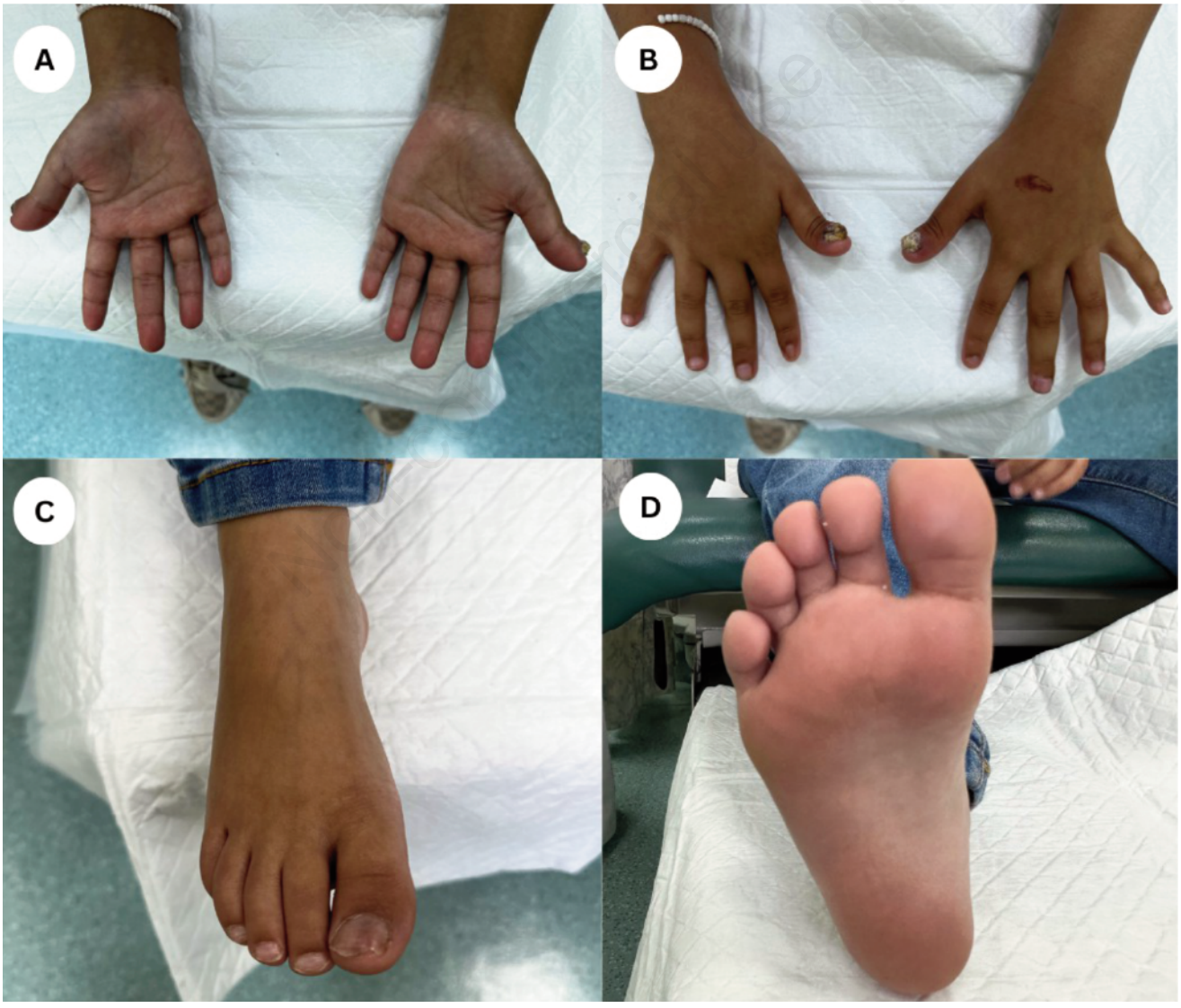

Figure 4. (**A, B, C, D**) Marked improvement noticed after starting combined treatment with topical and systemic antifungal therapy with near-complete clinical remission.

other autoimmune phenomena in combination with immune deficiency, cystic fibrosis-like lung disease and APECED-like syndrome due to STAT1 GOF gene mutation with pathogenic variant of c.1154C>T, (p.Thr385Met).[14] This complex clinical presentation observed in patients with STAT 1 mutation underscores the comprehensive involvement of this gene in autoimmune, hematopoietic, gastrointestinal, and pulmonary systems.

(P.Thr385Met) DNA variant type has been reported previously in cases of CMC-induced STAT 1 GOF mutation, one of which had early esophageal candidiasis that resulted in stricture formations and recurrent HSV infection.[15,16] Fortunately, our patient has not progressed to internal organ compromise.

This case underscores the significance of genetic investigations in elucidating the underlying immunodeficiency contributing to chronic mucocutaneous fungal infections, thereby informing targeted therapeutic interventions. Since there was no family history of overt CMC, it was likely a sporadic event of disease in our patient. Currently, the management of CMC is predominantly symptomatic, commonly employing long-term combined systemic and topical antifungal medications as first-line treatment. Nevertheless, immunoglobulin (IG) infusion, JAK/STAT inhibitors, G-CSF and GM-CSF, hematopoietic stem cell transplantation, and other therapy options are also available.[6]

Conclusions

Chronic mucocutaneous candidiasis (CMC) is an uncommon primary immunodeficiency disorder triggered by multiple gene defects. STAT 1 gene mutations produce a wide range of clinical features, including potentially fatal consequences, including cerebral aneurysm and tumor susceptibility. Early identification of the genetic subset using whole exome sequencing (WES) will aid in early screening, counseling, and treatment of CMC, as well as improving outcomes and minimizing long-term sequelae in such patients.

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