

Chronic Mucocutaneous Candidiasis due to Signal Transducer and Activator of Transcription 1 (STAT 1) Mutation in an Indian Patient – A Case Report

Abstract

Chronic mucocutaneous candidiasis (CMC) is a primary immunodeficiency due to defect in various genes leading to an increase in susceptibility to skin and mucosal infection. Mutation in signal transducer and activator of transcription 1 (*STAT 1*) gene being the most common cause of CMC can lead to increased risk of infections, multisystem abnormalities, and malignancy. We describe a 27 year old Indian woman with clinical features of CMC including esophageal stenosis, gangrene of the finger, endocrinological and immunological abnormalities and *STAT1* mutation (p.Leu407Val). She was treated with antifungals which led to symptomatic improvement.

Keywords: *Candida albicans*, *Candida parapsilosis*, chronic mucocutaneous candidiasis, signal transducer and activator of transcription 1 (*STAT 1*) mutation

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Introduction

Chronic mucocutaneous candidiasis (CMC) is a rare primary immunodeficiency, characterized by persistent or recurrent infections of the skin, nail, or mucosae with candida species.^[1] The autosomal dominant mutation in signal transducer and activator of transcription 1 (*STAT 1*) gene is the most common genetic cause of CMC.^[2] *STAT 1* mutation increases the risk of developing CMC, dermatophytosis, invasive fungal, bacterial, viral, and mycobacterial infections, autoimmune disorders, gastrointestinal symptoms and pulmonary symptoms. There is also an increased lifetime risk of developing life-threatening cerebral, extracerebral aneurysms, oral, and esophageal squamous cell carcinoma in these patients.^[1]

Herein, we describe the clinical features and management of a patient with an underlying *STAT 1* mutation.

Case Report

A 27-year-old lady born at 7 months of gestation to nonconsanguineous parents presented with a history of recurrent oral candidiasis since early childhood. She also noticed discoloration and thickening of finger and toenails associated with recurrent

paronychia from 14 years of age. The left index finger became gangrenous and was amputated. She complained of progressive dysphagia. There was a history suggestive of recurrent herpetic stomatitis (three episodes in the past 1 year), recurrent redness of eyes with blurring of vision, and pustular lesions on the trunk. Her medical history included hypothyroidism diagnosed at 8 years of age and was on levothyroxine 100 mcg since then. None of her family members suffered from CMC.

On examination, she had a diffuse adherent whitish plaque with deep fissures over the tongue [Figure 1]. All toenails and bilateral thumbnails were discolored with distal onycholysis and crumbling. The right index finger showed a hyperkeratotic plaque destroying the nail plate, extending to the proximal nail fold [Figure 2a]. Great toenails are onychogryphotic [Figure 2b].

Laboratory investigations revealed microcytic hypochromic anemia, hypothyroidism, hyperparathyroidism, hypovitaminosis-D, and low ferritin. As per lymphocyte subset analysis, the levels of lymphocytes (CD4, CD19 and CD56) were within the lower range of the normal limit or below the normal range [Table 1].

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Fungal culture from hard palate grew *Candida albicans* (*C.albicans*) and nail plate culture grew *Candida parapsilosis* (*C.parapsilosis*) [Figure 3]. Biopsy from the nail plate with bed of left index finger (amputated specimen) showed evidence of candida infection in the stratum corneum.

Barium swallow revealed cricoid web. Chest X-ray, CT angiogram of major vessels, and CT brain were normal.

Her clinical features favored a CMC syndrome. Molecular analysis on DNA obtained from peripheral blood using next-generation sequencing identified *STAT1* heterozygous mutation c.1219 C>G, p.Leu407Val at DNA-binding domain. This variant has not been reported from India till date to the best of our knowledge.

Fungal infection responded to oral fluconazole. Dysphagia improved with serial dilatations of cricoid web. Calcium correction, iron supplements and thyroxine were continued.

Discussion

The diagnosis of CMC was made in our patient based on clinical features of recurrent mucocutaneous candidiasis, bacterial infections, hypothyroidism, hypovitaminosis D, esophageal stenosis, associated with, CD4, CD19, and CD56 lymphocyte subsets which were either within the lower range of normal limit or low.^[1,3,4] In addition, she also had gangrene of the finger and hyperparathyroidism.

The genetic mutations in various genes, e.g., *STAT 1*, *STAT 3*, *AIRE*, *IL-17RA*, *IL-17 F*, *TRAF3IP2*, *CARD 9*, *Dectin*, *IL-12 Rβ1*, *ROR γT*, *TYK2*, have been associated with susceptibility to CMC.^[5,6] The reported prevalence of mutations is variable in various ethnic groups. *STAT 1* mutation has been reported in around 50% of patients with CMC followed by *AIRE* deficiency.^[2]

Autosomal dominant *STAT 1* mutation can be familial or sporadic, presenting predominantly with mucocutaneous candidiasis typically associated with *C.albicans* infection.^[7] Our patient had mucosal *C.albicans* infection and *C.parapsilosis* associated onychomycosis. Khullar *et al.*,^[8] reported *C.orthosilosis* (species described under *C.parapsilosis*) nail infection in a *STAT 1*-mutated patient.

A range of *STAT 1* GOF mutations secondary to defective nuclear dephosphorylation leading to increased production of IFN-alpha/beta, IFN-gamma, and IL-27 resulting in defective Th-17 response have been described till date.^[1,3] These mutations are confirmed by functional immunological assay. Our patient had a mutation of p.Leu407Val which has been previously reported in 2020, in a 12-year-old Peruvian boy by Platt CD *et al.*,^[9]

Three cases of *STAT 1*-mutated CMC (p.L206H, p.T385M, p.R274Q) have been reported from India.^[1,8] Also, Bhattad *et al.*,^[10] described a case of CMC with a mutation in *TRAF3IP2* in an Indian boy.



Figure 1: Deep fissuring of the tongue



Figure 2: (a) Hyperkeratotic plaque over the right index finger. (b) Onychomycosis of toe nails



Figure 3: Phenotypic appearance of *C.albicans* and *C.parapsilosis* on CHROMAgar. *C.albicans* – green colonies and *C.parapsilosis* – white colonies

Table 1: Results of the laboratory investigations

Hematological assay		
Parameter	Patient	Normal range
Hemoglobin	6.1 g/dL	12-15 g/dL
Total leucocyte count and differential count	5700/mm ³ (neutrophils - 58, eosinophils - 3, lymphocytes -30, monocytes - 9)	4000-1200/mm ³
Platelet count	291,000/mm ³	150,000-450,000/mm ³
Biochemical assay		
TSH	6.987 µIU/mL	0.3-4.5 µIU/mL
T4	12 ug/dL	4.5-12.5 ug/dL
Parathyroid hormone	164.8 pg/mL	8-74 pg/m
Vitamin D	5.8 ng/mL	>30 ng/dL
Ferritin	3.3 ng/mL	10-290 ng/dL
Viral serology		
HIV	Negative	
HBsAg	Negative	
HCV	Negative	
Immunoglobulin assay		
Immunoglobulin (Ig)	Patient result (mg/dL)	Normal range (mg/dL)
Immunoglobulin G (IgG)	1875	800-1700
Immunoglobulin A (IgA)	242	140-420
Immunoglobulin M (IgM)	55	50-190
Lymphocyte subset analysis		
Cluster differentiation molecules (CD)	Absolute count (%)	Absolute count (Normal range)
CD3	1215 (79.4)	1881±407
CD4	358 (23.4)	958±296
CD8	701 (48.8)	707±221
CD19	101 (8)	514±411
CD56	113 (7.4)	358±189

*Abnormal values highlighted in bold

In the absence of overt CMC in the family, the occurrence was probably sporadic in our patient.

At present, management is predominantly symptomatic, with long-term systemic and topical antifungals. However, other treatment options available include immunoglobulin infusion, GM-CSF and G-CSF, JAK/STAT inhibitors, and hematopoietic stem cell transplantation.^[2]

Conclusion

STAT1 gene mutations cause a broad array of clinical features including life-threatening complications like cerebral aneurysm and malignancies, hence identifying the genetic subset will help in early screening, counseling, and treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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