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CASE REPORT

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A Patient Presenting with Chronic Mucocutaneous Candidiasis: A Novel IL12RB1 Mutation

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ABSTRACT

Interleukin 12 receptor beta 1 (IL-12Rβ1) deficiency results in a wide variety of clinical manifestations, ranging from early death in infancy to asymptomatic adulthood. Patients are frequently infected with mycobacteria, with half developing salmonellosis and a quarter developing chronic mucocutaneous candidiasis (CMC). We present a patient with isolated recurrent candidiasis who has a novel IL12RB1 gene mutation (c.903+1G>T).

Keywords: MSMD, mucocutaneous candidiasis, IL12RB1

INTRODUCTION

Mendelian susceptibility to mycobacterial disease (MSMD) is a rare congenital syndrome caused by mutations affecting the interleukin 12(IL-12)- interferon-gamma (IFN-γ) axis among the macrophages and the T cells. IFN- γ secretion mediated by IL-12 is critical for the control of intracellular infections, particularly those caused by mycobacteria. Macrophages and dendritic cells generate IL-12 and IL-23, which bind to their receptors, IL-12R1 and IL-12R2, which in turn are expressed on natural killer cells and T lymphocytes. This induces the synthesis of IFN- γ. IFN- γ interacts with the IFN- γ receptor and phosphorylates a signal transducer and activator of transcription type 1 (STAT1). There are various genes causing MSMD, including IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, IRF8, TYK2, ISG15, NEMO, and CYBB. Among them, IL-12Rβ1 deficiency is the most common (1, 2).

The disease is characterized by a predisposition to infections caused by weakly pathogenic mycobacteria, including the bacille Calmette–Guerin (BCG) vaccine strain and various environmental mycobacteria. Clinical presentation may vary from localized to disseminated infections (3). Apart from mycobacteria, the patients generally suffer from infections caused by other intracellular microorganisms such as *Salmonella spp.*, *Listeria monocytogenes,* and parasites like *Leishmania*. Fungal infections including chronic mucocutaneous candidiasis (CMC) have also been reported in 25% of the patients (1-3). As CMC is related to reduced IL-17 immunity via impaired IL-23 immunity, it is observed in patients with IL-12R1 or IL-12p40 deficiency but not in patients with other genetic etiologies of MSMD (4, 5).

In this case report, we present a patient with isolated recurrent candidiasis with a novel mutation (c.903+1G>T) in the *IL12RB1* gene.

CASE PRESENTATION

A 14-year-old girl from Iraq was referred with resistant mucocutaneous candidiasis. In her medical history, she had been hospitalized for severe diarrhea at 4 years of age and mucocutaneous candidiasis had been detected for the first time during hospitalization. Since then, she had been treated with oral fluconazole intermittently. Although her symptoms had regressed with antifungal therapy, they had never completely resolved. From 10 years of age, she had suffered from a maculopapular rash appearing monthly on her back and legs, pinkish red in

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color. The lesions were itchy. Her family history revealed a first-degree cousin marriage between the parents. Oral moniliasis in the gingivae, buccal mucosa, the root of the tongue, and hard and soft palate, in addition to vaginal candidiasis, and lymphadenopathy in the right anterior cervical area with a diameter of 1x1 cm were present on her physical examination. Laboratory tests showed iron deficiency anemia, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, and elevated immunoglobulin (Ig) A and Ig G. Total IgE levels, lymphocyte subsets, and nitro-blue-tetrazolium (NBT) results were normal (Table I). Oral fluconazole prophylaxis was initiated for CMC.

Whole exome sequencing demonstrated a novel mutation (c.903+1G>T) in the IL12RB1 gene (Figure 1). The patient was followed for possible problems after being diagnosed as MSMD.

DISCUSSION

This article describes a patient who was diagnosed with CMC with an underlying novel mutation in the *IL12RB1* gene. The case is noteworthy since the mutation is unique and the patient has not suffered mycobacterial infections or BCG vaccine-related problems so far.

Chronic mucocutaneous candidiasis is a heterogeneous set of diseases characterized by the presence of chronic noninvasive Candida infections of the skin, nails, and mucous membranes, as well as signs and symptoms of autoimmunity. CMC in its classical form is caused by pathogenic mutations in the autoimmune regulator gene (AIRE) and the signal transducer and activator of the transcription 1 gene (STAT1) (6). T cell immunity is required for protection against both superficial and invasive fungal infections. A lack of IL-17-producing T cells (IL-17RA, IL-17RC, IL-17F, ACT1) is associated with an increasing number of CMC-related conditions (7). Oral candidiasis that is chronic or recurring is abnormal in healthy children and indicates an underlying immunodeficiency.

Deficiency in IL-12Rβ1 leads to a heterogeneous spectrum of clinical presentation ranging from early death in infancy to asymptomatic adulthood. Patients are frequently infected with Mycobacterium bovis - Bacillus Calmette-Guérin (BCG) vaccine strains and nontuberculous environmental mycobacteria, with half having salmo-

Table I. Immunological evaluation of the patient.

	Results	Reference values
Complete blood count		
Hemoglobin(g/dL)	**10.5**	12-16
Leucocytes (/mm^3)	**12150**	4500-11000
Absolute lymphocyte count	2160	1400-3300
Absolute neutrophile count	**9170**	1800-8000
Absolute eosinophile count	120	<500
Thrombocyte (/mm^3)	368.000	150.000-450.000
Sedimentation (mm/hour)	**112**	0-20
CRP(mg/dL)	**21.44**	0-0.5
Immunoglobulins (mg/dL)		
IgA	751	96-465
IgG	4274	907-1958
IgM	237	83-282
Total IgE (UI/mL)	105	
Lymphocyte subpopulations (% and absolute counts)		
CD3	79.9 1727	56-84 1000-2200
CD4	52.2 1120	31-52 530-1300
CD8	20 434	18-35 330-920
CD16+56	5.5 118	3-22 70-480
CD19	8.2 177	6-23 110-570
NBT	100%	
DHR	Normal	

DHR: dihydrorhodamine, **NBT:** nitro-blue-tetrazolium,

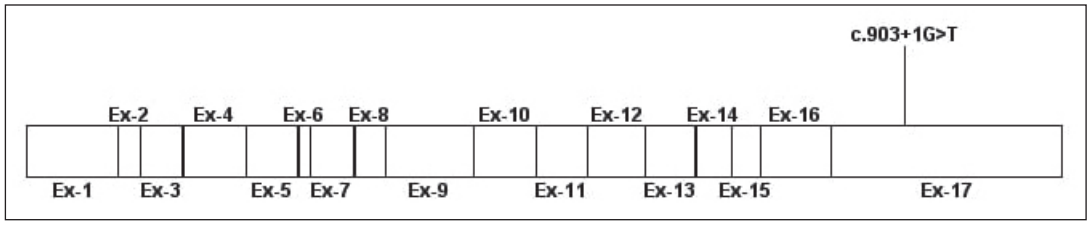

Figure 1. The mutation of the patient in the IL12RB1 gene.

nellosis, and only 50 of 187 (26.7%) having CMC (8). De Beaucoudrey et al. reported mucocutaneous candidiasis in 32 (24%) of 132 symptomatic patients (8). Despite the high prevalence of mucocutaneous candidiasis, disseminated fungal diseases such as histoplasmosis and paracoccidioidomycosis, toxoplasmosis, nocardiosis, and leishmaniasis are uncommon, occurring mostly in endemic areas. Infection patterns in MSMD vary by region. This distinction may be provided by a local endemicity pattern for a specific infection (e.g., Leishmania donovani, Histoplasma capsulatum) (9). Knowing the organism provides a hint to suspecting MSMD.

MSMD should thus be explored in individuals with mycobacterial or salmonella infections, as well as those with CMC alone. Since MSMD is an innate immune system dysfunction, the results of first-line immunological tests are likely to be normal in the majority of patients. When clinical suspicion exists, it appears reasonable to conduct genetic testing early on. In conclusion, individuals who develop recurrent mucocutaneous candidiasis should be tested for IL12Rβ1 deficiency as well.

Conflict of Interest

None declared.

Authorship Contributions

Concept: **Saliha Esenboga, Ilhan Tezcan,** Design: **Saliha Esenboga, Hacer Neslihan Bildik,** Data collection or processing: **Saliha Esenboga, Melike Ocak,** Analysis or Interpretation: **Saliha Esenboga, Deniz Cagdas, Ilhan Tezcan,** Literature search: **Saliha Esenboga,** Writing: **Saliha Esenboga,** Approval: **Saliha Esenboga, Hacer Neslihan Bildik, Melike Ocak, Deniz Cagdas, Ilhan Tezcan.**

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