



Chronic mucocutaneous candidiasis with *STAT1* gain-of-function variant: a case report and review of the literature

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Background: Chronic mucocutaneous candidiasis (CMC) is a rare clinically heterogeneous disease characterized by susceptibility to chronic or recurrent superficial *Candida* infection of the skin, nails and mucous membranes.

Case Description: We report a 14-year-old boy presented with recurrent oral *Candida* infection and oral ulcers complicated by recurrent keratitis, which were first noted shortly after birth. Whole-exome sequencing (WES) revealed a c.821G>A (p.R274Q) heterozygous mutation in the *STAT1* gene. Further analysis by Sanger sequencing of *STAT1* in his parents demonstrated that this variation was a spontaneous mutation.

Conclusions: Dentists should consider primary immune deficiencies when patient presented with persistent, recurrent unresponsive candidiasis.

Keywords: Chronic mucocutaneous candidiasis (CMC); signal transducer activator of transcription 1; point mutation; primary immunodeficiency; case report

Received: 29 May 2019; Accepted: 12 September 2019; Published: 12 October 2019.

doi: 10.21037/fomm.2019.09.03

View this article at: <http://dx.doi.org/10.21037/fomm.2019.09.03>

Introduction

Chronic mucocutaneous candidiasis (CMC) is a clinically heterogeneous disease characterized by susceptibility to chronic or recurrent superficial *Candida* infection of the skin, nails and mucous membranes (1). There are various causes of recurrent oral *Candida* infection, such as human immunodeficiency virus infection and use of glucocorticoids or antibiotics. However, rare primary gene mutations can also cause *Candida* infection. Studies have demonstrated that mutations in gene signal transducer and activator of transcription 1 (*STAT1*), autoimmune regulator (*AIRE*), caspase recruitment domain-containing protein 9 (*CARD9*) and Dectin-1 may be associated with CMC (2). In this study, we present a case of CMC due to a gain-of-function (GOF)-*STAT1* mutation and briefly review the CMC related to mutated GOF-*STAT1* by collecting data from

databases, including Web of Science, Science Direct, PubMed and Google Scholar.

Case presentation

A 14-year-old boy complaining of persistent white membranes in the oral cavity for 14 years was referred to the oral clinic of our hospital for diagnosis and treatment. He had been using sodium bicarbonate mouthwash for many years with a poor response. The patient experienced recurrent oral ulcers in early infancy and repeated keratitis at the age of 2 years. He was physically poor and often required sick leave from his study. There is no family history of illness.

On physical examination, the patient had erythematous patches in the center of his face and nose. There was a white pseudomembrane covering his entire oral cavity, including

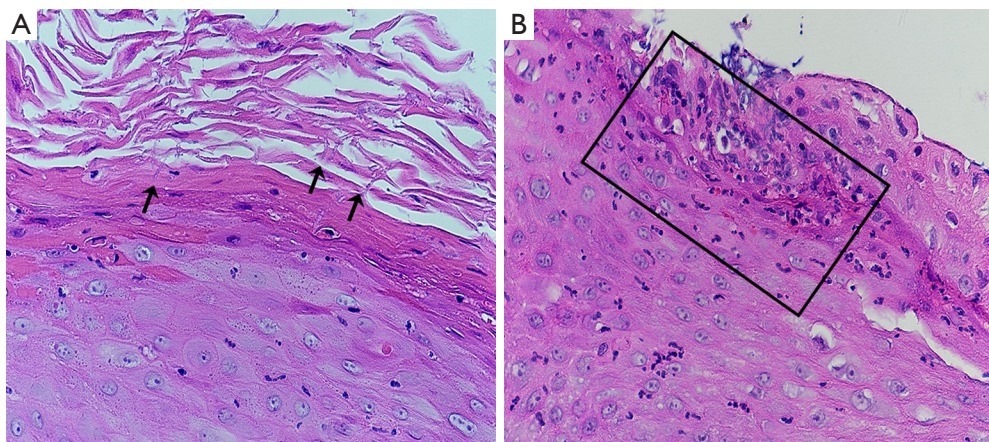


Figure 1 Proliferative candidiasis: hematoxylin and eosin staining of the left tongue tissue. (A) Fungal hyphae (arrows) inserted vertically into the epithelium (original magnification $\times 400$); (B) microabscess (box) formed by neutrophil aggregation in the epithelium ($\times 400$).

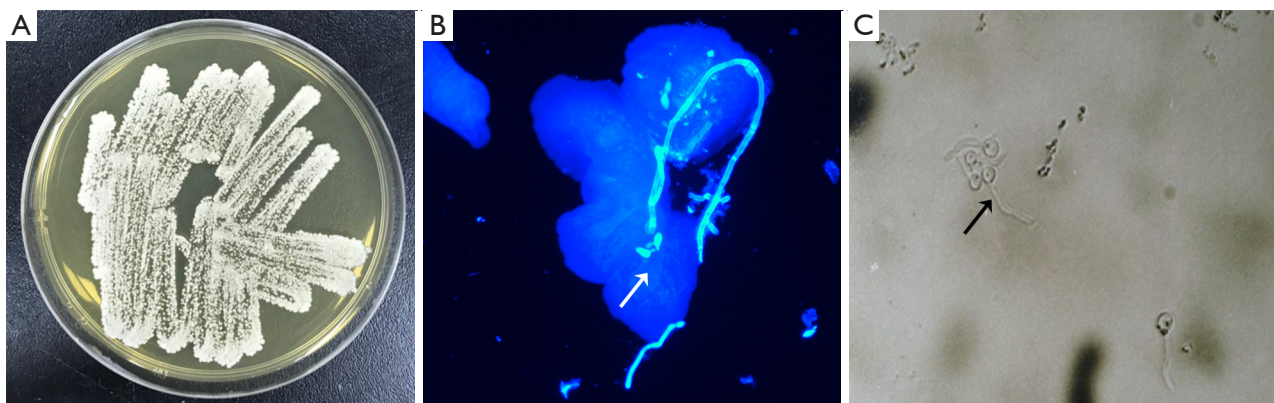


Figure 2 The detection of *Candida albicans*. (A) Fungal culture of the oral cavity: a large number of milky white colonies on the medium; (B) Fungal fluorescent staining of the nail: fungal hyphae surrounded by strong blue fluorescence (arrow, $\times 400$); (C) KOH method used for the skin: bud tube formed by *Candida albicans*: a filamentous cylindrical growth growing from the cell (arrow, $\times 400$).

the palate, tongue and buccal mucosa. The nail on his right forefinger was hyperkeratotic with white discoloration.

Biopsy of the left side of tongue showed proliferative candidiasis with mild epithelial hyperplasia (Figure 1). Fungal culture of the oral white pseudomembrane, fungal fluorescent staining of the right forefinger and KOH microscopic examination of the skin all revealed *Candida* infection (Figure 2). A blood sample was obtained and complete blood counts, and various biochemical and immunological parameters were measured. The complete blood counts were grossly normal apart from a high absolute monocyte count ($0.65 \times 10^9/L$, normal range, $0.1-0.6 \times 10^9/L$) and a low percentage of neutrophil nuclear cells (37.1%, normal range, 40–75%). The absolute

neutrophil counts were $1.9 \times 10^9/L$, which was within the normal range. Immunoglobulin (Ig) levels (IgM/IgA/IgE) were all within normal limits with the exception of high IgG (17.2 g/L, normal range, 7–16 g/L). An examination of lymphocyte subsets showed low CD4 lymphocytes (21.32%, normal range, 31–60%), high CD8 lymphocytes (42.44%, normal range, 13–41%), and thus a low CD4/CD8 lymphocyte ratio (0.51, normal range, 0.9–3.6).

In view of the patient's CMC, autoimmunity and combined immunodeficiency, we performed whole-exome sequencing (WES) with informed consent from his parents to identify genetic causes of the disease. By screening CMC-related genes, we identified a missense variant (NM_007315:c.821G>A, p.R274Q) in exon 10

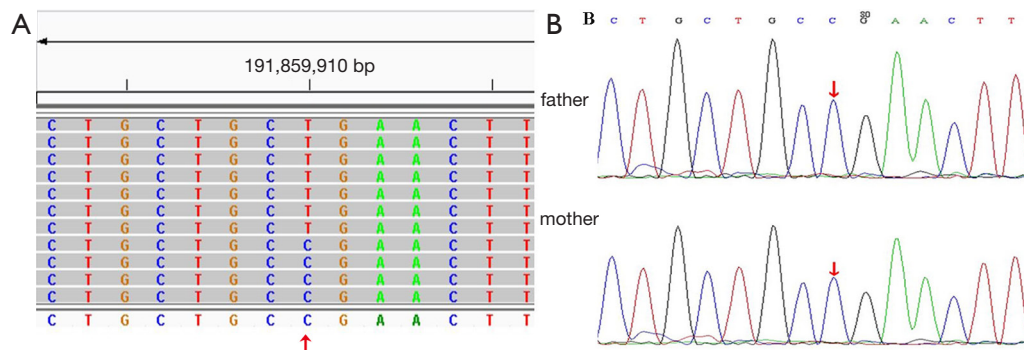


Figure 3 Whole-exome sequencing identified the pathogenic *STAT1* variant in the patient. (A) Integrative Genomics Viewer snapshot of the missense variant (NM_007315:c.821G>A, p.R274Q) in *STAT1* (arrow). (B) Sanger sequencing showed the corresponding normal sequence (arrows) in the patient's parents.

of the *STAT1* gene (Figure 3A). The variant c.821G>A (nucleotide No. 821 from guanine to adenine in the coding region) in *STAT1* resulted in a change of amino acid at p.R274Q (amino acid No. 274 from arginine to glutamine). According to the guidelines of the American College of Medical Genetics and Genomics and the Association of Molecular Pathology (3), this p.R274Q variant can be categorized as pathogenic based on the following factors: PS1, the pathogenicity of this variant for CMC has been reported in the Human Gene Mutation Database. PM2, the frequency of this variant in the normal population database is low. PP3, bioinformatics protein function prediction software SIFT, PolyPhen_2 and REVEL all predicted this variant to be harmful. Sanger sequencing showed the heterozygous *STAT1* variant in the patient, whereas his parents did not have this variant, indicating that the variant was a spontaneous mutation (Figure 3B). The final diagnosis was CMC with *STAT1*-GOF variant.

The patient was treated with oral fluconazole 100 mg/day and ketoconazole ointment was applied to the skin lesions every day. His oral symptoms completely disappeared and the result of fungal culture for the oral swab was negative after 3 weeks of treatment (before treatment: Figure 4A,B,C,D; after treatment: Figure 4E,F,G,H). No recurrence was observed 3 months after discontinuation of fluconazole administration. There was also partial regression of the skin lesions, but this was not as obvious as that of the oral cavity. However, no change in his fingernail was observed after treatment (before treatment: Figure 5A,B; after treatment: Figure 5C,D). The patient was arranged regularly for a follow-up every three months. At each visit, the fungal culture was operated and all the results were negative. During one-year follow-up, the condition was stable.

Discussion

We described a young patient with a GOF-*STAT1* variant. The majority of GOF-*STAT1* mutations affect the coiled-coil domain or DNA-binding domain (4). *STAT1* mutations are phosphorylated, and then increase responses to *STAT1*-dependant cytokines, such as interferon $\alpha/\beta/\gamma$ and interleukin (IL)-27. Finally, these mutations impair the development of IL-17-producing T cells (5). IL-17 has recently been identified as a necessary cytokine in human mucocutaneous defense against *Candida* infection (6).

Major symptoms of CMC include scaling and hyperkeratosis of the skin, erythema of periungual skin, oral thrush, deformation and edema of the fingernails due to persistent *Candida* infections (7). Toubiana *et al.* studied patients with GOF-*STAT1* mutations who had heterozygous GOF-*STAT1* and an unexpected broad clinical phenotype (8). In addition to CMC, these patients were prone to bacterial (74%) infections, mainly due to *Staphylococcus aureus* (36%), and viral (38%) infections, mainly due to *Herpesviridae* (83%). Thirty-seven percent of these patients had autoimmune manifestations, including hypothyroidism (22%), type 1 diabetes (4%), cytopenia (4%) and systemic lupus erythematosus (2%). Alarmingly, patients with CMC had a greater risk of developing both oral and esophageal cancer (8-10), and the patients were often much younger than those without GOF-*STAT1* mutations. Patients with GOF-*STAT1* mutation should pay close attention to the disease and have regular physical examinations and follow-up visits in order to ensure early detection and treatment of complications.

The prognosis of CMC patients is poor. The main treatment for patients with CMC is systemic and topical

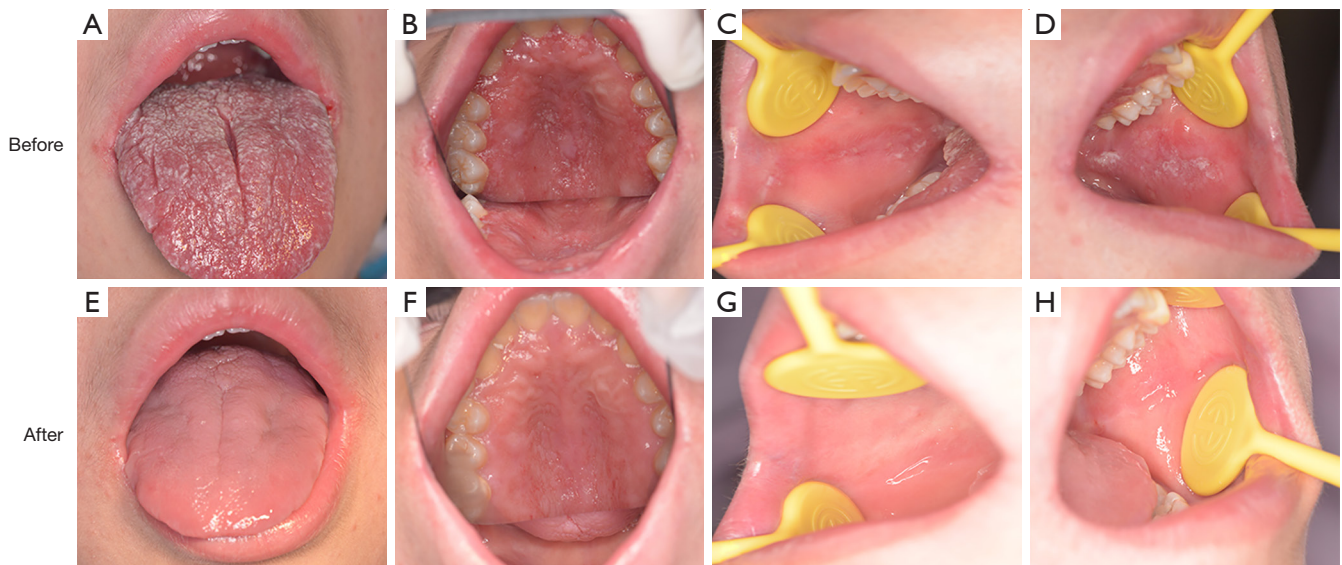


Figure 4 Presentation of the patient's oral cavity before treatment and after fluconazole treatment for 3 weeks. A white pseudomembrane was found covering the entire oral cavity before treatment. However, mucosal lesions due to oral thrush completely disappeared after treatment. (A,E) Tongue; (B,F) palate; (C,G) right buccal mucosa; (D,H) left buccal mucosa.



Figure 5 Photographs show the patient before treatment and after fluconazole treatment for 3 weeks. (A) Facial erythematous patches before treatment; (B) deformation and discoloration of the fingernail before treatment; (C) the facial lesions partially regressed after treatment; (D) no change in the fingernail after treatment.

antifungals. Fluconazole is well tolerated and easy to administer. However, it is harmful to the liver and has the potential for development of drug-resistant strains (11). Drug-resistant *Candida* strains are a common concern. Additional antibiotic prophylaxis and intravenous immunoglobulin can also be considered in patients with recurrent infections (12). In addition to conventional treatments, studies on new immunological therapies have also made progress. Shahar *et al.* reported that a CMC patient with GOF-STAT1 had a beneficial clinical response following treatment with granulocyte macrophage colony stimulating factor (GM-CSF) (13). However, a subsequent study reported failure of this treatment (14). Leiding *et al.* used hematopoietic stem cell transplantation (HSCT) in 15 patients with GOF-STAT1 and made the conclusion that despite having curative potential, only 40% overall post-transplant survival was achieved (15). At present, new insights into hypermorphic STAT1 mutations have identified promising therapeutic targets in the dysregulated STAT1/STAT3/IL-17 pathways (16), such as Janus kinases (JAKs). Bloomfield, Higgins E and Forbes LR all successfully treated CMC patient with STAT1-GOF mutation with the JAK1/JAK2 inhibitor ruxolitinib (17-19). This therapy can be a viable option for treatment for refractory CMC. For diseases caused by gene mutations, the main treatments should target to the symptoms, with the aim to prevent the development of complications and the ultimate goal of cure.

Acknowledgments

Funding: Key Specialty Construction Project {[2013]544}, National Key R&D Program of China (2017YFC0840100, 2017YFC0840110) and Shanghai's top priority clinical medicine center (2017ZZ01011). Clinical Research Project of Multi-Disciplinary Team, Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine [201701006].

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://fomm.amegroups.com/article/view/10.21037/fomm.2019.09.03/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient's parent.

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doi: 10.21037/fomm.2019.09.03

Cite this article as: Yao YL, Shen XM, Shi LJ, Li CX, Wu L. Chronic mucocutaneous candidiasis with *STAT1* gain-of-function variant: a case report and review of the literature. *Front Oral Maxillofac Med* 2019;1:8.