

# Recurrent Oral Aphtha, Diarrhea, Pneumonia, And Respiratory Distress Since Infancy: STAT1 GOF defect

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## Abstract

**Abstract Backgrounds:** Mutations in DNA-binding domains of STAT1 lead to delayed STAT1 dephosphorylation and afterwards gain-of-function. The clinical phenotype is broad and can include chronic mucocutaneous candidiasis and/or combined immunodeficiency. **Objectives:** We report a case of 7-year old female patient. She had recurrent pneumonia since infancy and she was hospitalized several times. She had persistent lymphopenia with normal immunoglobulin levels and lymphocyte subsets. **Findings:** STAT1 mutation was defined by next generation Sequencing PID panel. Despite the antifungal therapy, oxygen requirement continued, methylprednisolone and Janus-associated kinase (JAK) inhibitor (ruxolitinib) was started as therapy. Immunodysregulatory features of disease improved after Janus kinase inhibitor treatment. **Conclusion:** In patients with STAT1 GOF defect, ruxolitinib treatment may be effective for interstitial lung disease if hematopoietic stem cell transplantation can not be performed.

## Introduction

STAT1 [signal transducer and activator of transcription-1] is a critical transcription factor mediating interferon signaling (1). *STAT1* gene defects progress with infection susceptibility, chronic diarrhea, and recurrent skin infections. The genetic dissection of various human infectious diseases has led to the definition of inborn errors of human STAT1 immunity of four types, including autosomal recessive (AR) complete STAT1 deficiency, AR partial STAT1 deficiency, autosomal dominant (AD) STAT1 deficiency, and AD gain of STAT1 activity (1). Heterozygous *STAT1* gain-of-function (GOF) mutations cause autosomal dominant chronic mucocutaneous candidiasis (CMC), but have also been associated with a much broader spectrum of infectious, inflammatory, vascular, and neoplastic manifestations (2). These experiments of nature neatly highlight the clinical and immunological impact of the human genetic dissection of infectious phenotypes (1).

## Case Report

A 7-year old girl was admitted to our center with the complaint of recurrent infections. She had suffered from recurrent oral aphtha, diarrhea, pneumonia, and respiratory distress since infancy. At the age of one she presented with CMC and fluconazol prophylaxis was started. At the age of 5 she received empiric treatment of tuberculosis. Tests for tuberculosis were negative. She was hospitalized with the diagnosis of pneumonia at the age of 6 and treated. Bronchiectasis was detected by chest computed tomography (CT). She had persistent lymphopenia with normal immunoglobulin levels and lymphocyte subsets with low memory and switch memory B cell numbers. At the age of 7, she was admitted to pediatric intensive care unit due to candida pneumoniae. In immunological evaluation, immunoglobulin levels and IgG subgroups were normal,

and low Natural Killer (NK) cell count was detected. She was diagnosed as combined immunodeficiency and antibiotic prophylaxis and monthly intravenous immunoglobulin (IVIG) treatment were started. In the follow-up, infection recurrency reduced. At the age of 9, she admitted with the complaint of respiratory stress. On her physical examination, body weight 13 kg (<3p) (z-score: -4.18), length 110 cm (<3p) (z-score: -2.81), body mass index: 11.2 (z-score: -3.71), weight by age 59% of the standard. On laboratory tests: Hb 7.4 gr/dl, WBC 9800 mm<sup>3</sup>, ANS 9100 mm<sup>3</sup>, thrombocyte 401.000/mm<sup>3</sup>. CT of thorax had bilateral hilar lymphadenopathies and diffuse thickening with esophagitis in the distal end of the esophagus. On physical examination there was red brown, thick scaled plaques on the neck suggesting Candidiasis. Antibacterial and antifungal therapy were started due to respiratory system and skin findings. Next generation sequencing for primary immunodeficiency (PID) was performed and a homozygous *STAT1* mutation was found. (*N397D* gene defect). Despite completing the infection treatment, hypoxia and respiratory stress continued. Interstitial lung disease was considered and methylprednisolone (MPZ) (2mg/kg) was started and respiratory symptoms improved significantly shortly after oxygen requirement decreased from 10 liters per minute to 2 liters per minute and our patient was discharged. *STAT1* phosphorylation was studied and then ruxolitinib was started. Now, the patient takes monthly IVIG treatment and antifungal and antibacterial prophylaxis and ruxolitinib. Oxygen requirement continues at 2 liters per minute. Saturation values increased from 70% to 90%. Bone marrow transplantation is planned as a treatment for our patient. Unrelated donor screening has been continued for the patient who has no HLA matched relative donor.

## Discussion

There are mutations of the *STAT1* gene with function gain and loss of function. Autoimmunity findings predominate in mutations with function acquisition, and immune deficiency findings predominate in those with loss of function. The *N397D* mutation detected in the NGS panel in our patient is the second case in the literature, and similar skin infections with the first detected case were observed with plaque in the mouth and recurrent pneumonia. Bone marrow transplantation was planned as a treatment for our patient. Current therapy for patients with gain of function *STAT1* mutations is based on the use of long-term antifungal and antibacterial drugs (3). *Candida albicans* is a fungus that causes invasive or chronic mucocutaneous disease in immunocompromised patients (1). CMC typically begins in early childhood, although it may first present up to the third decade of life, and signs and symptoms varied within and between families (4). CMC is common in patients with other clinical signs carrying various inborn errors of immunity, including mutations in *STAT3*, *IL12B*, *IL12RB1* and *AIRE*. All these defects are associated with impaired IL-17 immunity. *IL-17A*, *IL-17F* and/or *IL-22* play an important role in mucocutaneous immunity to *C. albicans* (1).

Some patients have been treated with ruxolitinib, G-CSF, GM-CSF, and intravenous immunoglobulin (3). Ruxolitinib is JAK1/JAK2 inhibitor. Treatments targeting the JAK-STAT pathway, such as the JAK1/2 inhibitor ruxolitinib, which has been approved for myelofibrosis treatment, have shown significant clinical efficiency and might become the treatment of choice for severe CMC resistant to antifungals (4). Progression of infections during ruxolitinib treatment in patients despite continued aggressive antifungal therapy is of concern. Indeed, infections are possible complications of ruxolitinib therapy, therefore, it should be followed carefully (2). Using a dephosphorylation assay demonstrate the disease control (5).

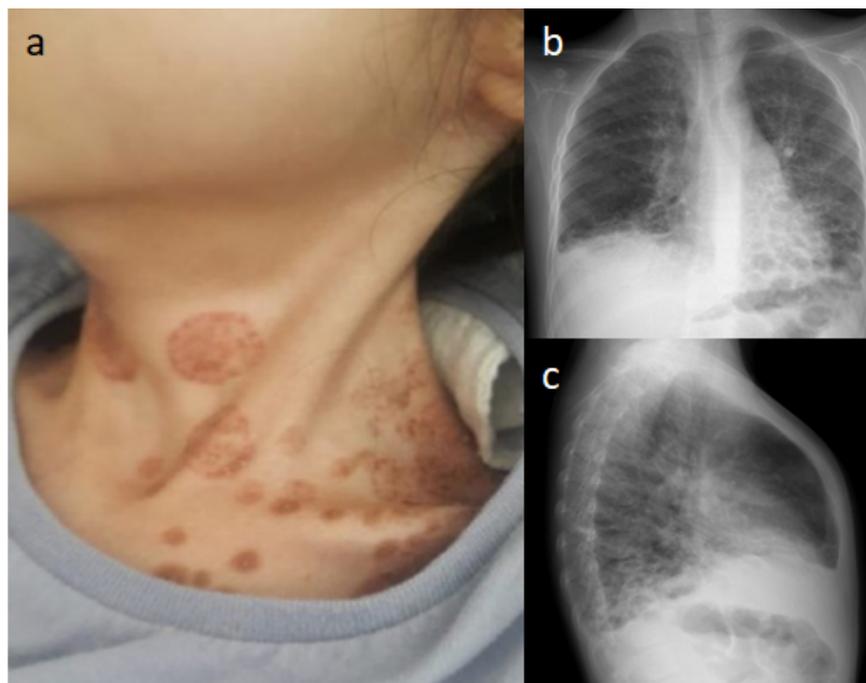
Hematopoietic Stem Cell Transplantation (HSCT) provides an alternative therapeutic option for *STAT1* GOF mutations who have an resistant disease course despite conventional therapy (6). It has been done in many cases and has been successful. Previously a patient with complete functional absence of *STAT1* who underwent HSCT from an unrelated donor, successfully cured (7). Aggressive treatment of complications, close monitoring and early HSCT should be provided for before development of end organ damage (6).

## Conclusion

*STAT1* gene defect should be considered in recurrent fungal infections. After the diagnosis, the phosphorylation study must be done in terms of treatment. HSCT should be considered before complications develop at the time of diagnosis. When HSCT cannot be applied, ruxolitinib can be administered to control autoimmune findings lung findings and candidiasis.

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**Figure 1:** **a.** Red brown, thick scaled plaques on the neck, compatible with fungal skin lesion, **b.** Bilateral infiltration in the lower lung areas, pulmonary conus is prominent, **c.** The anterior posterior diameter of the chest is increased.