CLINICAL CASE OF CYSTIC FIBROSIS-LIKE AND APECED-LIKE SYNDROME DUE TO GAIN-OF-FUNCTION VARIANT IN *STAT1*

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INTRODUCTION

Many gene defects lead to a compromised immune function (dysregulation) with impaired body defense against foreign agents (immune deficiency) and autoimmunuty, including diabetes mellitus (DM). Chronic mucocutaneous candidiasis (CMC) is often presented in the syndromes of immune dysregulation (1).

CLINICAL CASE

We present a patient with immune deficiency, moniliasis and multiple autoimmune phenomena due to STAT1 GOF (Signal Transducer and Activator of Transcription-1 gain-of-function).
Index case. A girl, born to a normal pregnancy with uneventful family history. Since early infancy she suffered with obstructive lung infections and pneumonias, clinically resembling cystic fibrosis, accompanied with mildly elevated sweat chlorides. She developed bronchiectasias very early. At age of 3 years cystic fibrosis was genetically excluded after start of multiple autoimmune phenomena shown on Table 1. APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy) syndrome was excluded by testing for AIRE (autoimmune regulator) gene defects. Through the years chronic lung infection worsened and at the age of 15 the girl was treated for several episodes of syndrome of macrophageal activation. Lung infection progressed to lung abscesses and empyema that needed surgical interventions. She died at the age of 17 years.

Table 1. Chronology of autoimmune phenomena:

Age	Clinical symptoms
Early infancy	Obstructive lung infections Pneumonias, clinical resembling of cystic fibrosis, elevated chloride Moniliasis, Clubbed fingers, Onichomycosiss (Fig. 1)
Since 3 years of age	Autoimmune hepatitis Enteritis Systemic antibiotics and antifungal treatment
Age 10 years (2003)	Diabetes mellitus with severe ketoacidosis Growth retardation Hypothyreosis (TSH 482 mU/L, FT4- 2.94 pmo/L) Positive anti-thyroid and anti ß-cell autoantibodies
Age 13 years (since 2006)	Episodes of autoimmune (Coombs+) hemolytic anemia 1-2 times per year Blood transfusion, Short corticosteroid courses Worsening of moniliasis, Cholelithiasis
Age of 16 (2009)	Lobar lung abscess, pleural empyema Crises of macrophage activation syndrome, EMG (electromyography) data for sensory neuropathy. New short corticosteroid courses Systemic antibiotic and antifungal treatment
Age of 17 (2010)	Died at the regional hospital from acute respiratory insufficiency

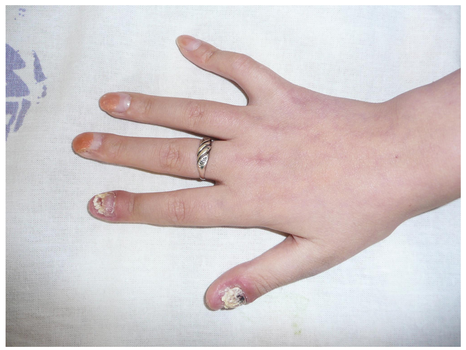
Clinical presentation of the presented clinical case is an example of how the symptoms can lead to overlapping of different diseases that have a similar manifestation.

Overlapping of the main clinical features in a syndromes with Monogenic autoimmune diabetes

	CF	IPEX*	APECED	STAT-1	Index Case
Bacterial/viral infections Bronchiectasies	Yes	Yes Since early infancy	Not typical	Yes Yes	Since early infancy Yes
Eczema Ectodermal dystrophy	Not typical	Since early infancy Hyper-IgE	Yes	Yes	No
Candidiasis	My be secondary	My be secondary	Yes	Yes	Yes
Diarrhea	Yes	Yes	Not typical	Yes	Yes
Endocrine autoimmunuty	No	DM Autoimmune thyroiditis	Hypoparathyroidism M. Addisson DM, Autoimmune thyroiditis	DM Autoimmune thyroiditis	DM Autoimmune thyroiditis
Other immune or autoimmune phenomena	No	Autoimmune pulmonitis, Enteritis, Alopecia, Onychodystrophy, Cytopenia, Renal diseases	Pernicious anaemia, Autoimmune hepatitis Cholelithiasis Vitiligo, Alopecia, Immune-mediated central and peripheral neurological diseases	Cytopenia CD-4 lymphopenia	Autoimmune hepatitis, Cholelithiasis Autoimmune hemolytic anemia Macrophagea l activation syndrome (MAS)
Growth failure Hypergonadotropichypogonadism	Yes	Yes	Yes	Yes	Yes

IPEX*- Immune dysfunction, polyendocrinopathy, enteropathy, X-linked

Fig.1. Clubbed fingers, Onichomycosiss



FINAL GENETIC RESULTS

By using targeted next generation sequencing (Agilent custom capture v5.3/Illumina NextSeq500) at Exeter Molecular Genetic Laboratory we established de novo arisen missense mutation of *STAT1* gene, Exon 14:c.1154C>T, p.(Thr385Met). This variant has been previously reported and is predicted to be pathogenic. This confirms a diagnosis of syndrome of immune dysregulation due to a gain-of-function variant in the *STAT1* gene with CF-like and APECED-like clinical course, rather than IPEX–like one.

DISCUSSION

The overlap of the clinical manifestation of CF (2) and APACED in our patient with *STAT1* GOF can be explained by three putative mechanisms: 1) reduced expression of inducible form of nitric oxide synthase-2; 2) immune intolerance; 3) increased fibrosis.

The inducible form of nitric oxide synthase-2 (NOS2) is reduced in CF airway epithelium from both human subjects and murine models of CF (3–5). Subsequent reduction in NO production has been postulated to play a role in the abnormal regulation of transepithelial sodium absorption observed in CF and in the CF-associated susceptibility to bacterial infection (3, 4). The NOS2 promoter has several regulatory components, including nuclear factor κB (NF-κB), activator protein 1 (AP-1) signal transducer and activator of transcription-1 (Stat1), and IFN regulatory factor-1 (IRF-1) binding sites (6, 7). Stat1 and IRF-1 are components of the IFN-g signaling pathway, and both have been shown to influence NOS2 expression (8, 9).

Immune tolerance that prevents reactions against self-antigens depends on central and peripheral sequestration of autoreactive T-lymphocytes. AIRE (autoimmune regulator) gene controls expression of peripheral self-antigens and central thymic sequestration of autoreactive T-lymphocytes. In APECED, also known as autoimmune polyendocrinopathy syndrome type 1 (APS1), an autosomal recessive disease, mutations in the AIRE gene cause autoimmune destruction of many organ-specific endocrine, but systemic tissues, as well. APECED-related CMC has been associated with the presence of specific autoantibodies against the Th17-related interleukins (IL) 22 and 17F (10).

STAT1 mutations can cause an extensive spectrum of disease, varying from severe bacterial and viral infections to mild disseminated mycobacterial disease, also chronic mucocutaneous candidiasis. Many patients present with autoimmune manifestations as type 1 diabetes, hypothyroidism and systemic lupus erythematosus. There are risks of cancers and cerebral aneurysms.

STAT1 plays protective role in response to injury, and is responsible for activating transcription of key genes involved in cell viability, growth arrest, apoptosis, and differentiation (11, 12).

Mutations in the *STAT1* molecule can cause gain of function (GOF) or loss of function (LOF), both related to different phenotypes of immune defficiencies. STAT 1 GOF was first discovered in patients with Chronic mucocutaneous candidiasis (CMC) (2011) and it is presented among 50 % of them due to impaired generation of TH17 cells. GOF mutations affecting *STAT1* lead to defective TH17 cell development, characterized by reduced production of IL-17 and IL-22; these cytokines are crucial for antifungal and antibacterial defense in skin and mucosa. An increased signaling of interferons and IL-27 through *STAT1* cause an elevated risk of autoimmune phenomena (13).

STAT1 GOF mice exhibit increased fibrosis following exposure to the chemotherapeutic drugs, compared to normally functioning *STAT1* mice, demonstrating that *STAT1* is protective against fibrogenesis (14).

The largest systematic study to investigate the clinical manifestations of patients with STAT1-GOF mutations was reported in March 2021. This study investigated 442 patients proven to have *STAT1* GOF mutations This retrospective review include articles, case reports or case series. (15). Most reports have focused on the molecular and cellular defects of 1 or a small series of patients. This provides useful but incomplete clinical information. The comprehensive clinical features and outcomes of patients with *STAT1* GOF mutations remain undefined.

The clinical case we present is a contribution to the enrichment of the clinical spectrum of *STAT-1* GOF.

CONCLUSIONS

We report our first patient with autoimmune monogenic diabetes, multiple endocrinopathies and other autoimmune phenomena in combination with immune deficiency and CF-like lung disease due to pathogenic variant of the *STAT1* gene. Complex clinical manifestation of reported patient with *STAT1* GOF mutation shows an extensive role of this gene in immune, hematopoietic, gastrointestinal and pulmonary systems.

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