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CASE REPORT

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A child with bronchiectasis, chronic mucocutaneous candidiasis, and hypothyroidism secondary to STAT1 gain-of-function mutation: A case report and review of the literature

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Abstract

STAT 1 GOF mutations are a rare cause of childhood primary immunodeficiency. Recurrent mucocutaneous candidiasis, chest infections, and autoimmune disease are all classic phenotype presentations. Rapid identification and diagnosis of this debilitating disease using whole exon sequencing may improve outcomes and minimize long-term sequelae.

KEYWORDS

immunodeficiency, mucocutaneous candidiasis, STAT 1

1 | BACKGROUND

Signal transducer and activator of transcription 1 (STAT1) are critical STAT family members, which play an essential role in cell differentiation, metabolism, and apoptosis via the Janus family tyrosine kinase–signal transducer and activator of transcription (JAK-STAT) pathway.[1] Moreover, STAT1 is required for signaling type 1 interferon (α, β) and type 2 interferon (γ).[2] Germline heterozygous mutation of the STAT1 leads to primary immunodeficiency, classified as defects in the immune response to pathogens.[3] Mutations to STAT1 impair the host immune system and increase susceptibility to different pathogens, including mycobacteria, fungi, and viruses.[4] Mutations to STAT1 could be either loss-of-function (LOF) or gain-of-function (GOF) mutations, and they exhibit distinct clinical phenotypes.[5] LOF mutations cause the failure of interferon-g- and interferon α/β-mediated immunity leading to susceptibility to mycobacteria and viruses.[6,7] On the contrary, STAT1 GOF defects are caused by mutations in the coiled-coil domain, which impair the nuclear dephosphorylation of activated STAT1.[6,8] STAT1 hyperphosphorylation has been linked to chronic mucocutaneous candidiasis (CMC) due to impaired IL-17 immunity.[9] Patients with IL-17 deficiency are at risk of developing recurrent candida infections, viral infections, and bacterial

infections, including atypical mycobacterium organisms. Herein, we present a child with a scalp abscess, mucocutaneous candidiasis, and bronchiectasis, all of which suggest an underlying immune deficiency.

2 | CASE PRESENTATION

An 8-year-old female patient presents with fever, chronic cough, and scalp swelling. Her past medical history is noteworthy for recurrent tinea capitis infections that failed to respond to prolonged oral antifungal therapy with griseofulvin. Additionally, her parents reported a history of persistent oral thrush despite topical therapy with nystatin, and recurrent chest infections necessitating multiple hospitalizations since she was 2 years old. Neonatal history is remarkable for 2 weeks of neonatal intensive care unit stays for neonatal sepsis. She was immunized up to 1 year of age primarily due to her parents' lack of follow-up. She lives with her parents and two healthy siblings. Family history is unremarkable for recurrent infections or similar conditions.

At admission, she was febrile to 39.2 C, but with normal heart rate (90 beats/minute), respiratory rate (14 breaths/minutes), and blood pressure for age (95/54). Growth parameters indicated a failure to thrive (weight: 16 kg at −3.66 SD, 0.1% percentile) and severe short stature (height: 99.5 cm at −5.50 SD, 0.1% percentile).[10] There were no signs of dysmorphic features. Pertinent physical findings include clubbing in both hands and feet, tender fluctuant scalp abscess, oral thrush, and diffuse bilateral crepitations all over her chest.

Initial laboratory findings included normocytic normochromic anemia (Hb = 9.7 g/dl), an elevated erythrocyte sedimentation rate (ESR = 40 mm/Hr), and elevated c-reactive protein levels (CRP = 7.9 mg/dl). The parameters of liver and kidney function tests were within the normal range. The scalp abscess was drained and cultured, and the patient was empirically started on clindamycin pending culture results.

The patient's history of recurrent chest infections, mucocutaneous candidiasis, and failure to thrive raises concerns about an underlying immunodeficiency. Serology for the human immunodeficiency virus (HIV) was negative. Additional immunological testing was performed and interpreted in accordance with her age. Apart from an elevated IgA level, she had normal results for age for both immunoglobulin levels (IgM = 168 mg/dl, IgG = 1505 mg/dl, IgA = 862 mg/dl, IgE = 4.5 IU/ML) and lymphocytes subset panel (Lymphocytes absolute count = 1.891 $10^{(3)}$/μl, T-lymphocytes (CD3+) = 1.185 cells/ul, T- suppressor cells (CD3+/CD8+) = 309 cells/ul, T-helper cells (CD3+/CD4+) = 812 cells/ul, CD4+/CD8+ ratio = 2.63), NK-cells (CD16+/CD56+) = 122 cells/ul, B-lymphocytes (CD19+) = 562 cells/ul. Whole exon sequencing (WES) revealed a heterozygous missense variant in the *STAT1* gene (NM_007315, 4: C. 1154C>T p. Thr385Met). The GOF STAT1 immunodeficiency was confirmed based on the mutation variant in the STAT 1 gene and the patient's clinical presentation. There was no family history of recurrent infections or similar conditions, suggesting de novo mutation. Nonetheless, her parents' consanguineous marriage may justify testing them for inherited mutations.

Signal transducer and activator of transcription 1 immunodeficiency is associated with CMC, bronchiectasis, recurrent respiratory infections, and endocrinopathy due to underlying autoimmune processes. Indeed, our patient was found to have bilateral diffuse bronchiectasis, bilateral reticular-nodular densities, and multiple small hilar lymph nodes on a chest CT scan. Tuberculosis workup included QuantiFERON-TB Gold and gastric aspirate for acid-fast bacilli stain, and cultures were negative. She was found to have severe hypothyroidism (TSH = 100 uIU/ml normal range is 0.27–4.20, FT4 = 0.9 pmol/L normal range is 9–19), which provides a plausible explanation for her significant short stature. Anti-Tissue Transglutaminase and thyroid antibodies were all negative. Her scalp abscess and oral thrush resolved after 2 weeks of clindamycin and fluconazole, respectively. She responded very well to levothyroxine, showing marked improvement in her growth acceleration on subsequent outpatient visits. She was referred to a tertiary hospital for multidisciplinary service management and consideration of stem cell transplantation vs. Janus kinase 1 inhibitors.

3 | DISCUSSION

Recurrent infections with various microorganisms are a critical indicator of primary immunodeficiency. This report describes an 8-year-old female with multiple complaints, including failure to thrive, MRSA abscesses on the scalp, tinea capitis, recurrent chest infections complicated by bronchiectasis, and persistent oral candida infection. Due to the patient's unusual clinical presentation, we suspected a primary immunodeficiency, including humoral immunity (antibody production) and T-cell defects. Other than elevated IgA, antibody production and lymphocyte subgroups (CD3+, CD4+, and CD8+) were normal in our patient. Yu et al. reported a similar finding of an elevated IgA level in a patient with a STAT 1 GOF mutation.[11] WES was carried out and revealed a heterozygous missense variant in the *STAT1* gene consistent with the clinical phenotype associated with STAT1 GOF mutations.

Signal transducer and activator of transcription 1 GOF mutations cause CMC and autoimmunity mainly because

of augmented T-helper 1 response, deficiency in T-helper 17 development, and antifungal response.[7,9,12] CMC is the most common manifestation of STAT1 GOF mutations owing to the critical role of impaired IL-17 immunity in CMC development.[13] CMC presents primarily as skin, nail, and oropharynx candida species infection.[9,13] Toubiana et al. recruited 274 patients with STAT1 GOF mutations from five continents. CMC is the most common manifestation of STAT1 GOF mutations, accounting for 98% of recruited patients.[4] Approximately 74% of patients in the study had recurrent bacterial infections. The most frequently encountered infections were lower respiratory tract infections (47%), recurrent sinusitis (44%), and skin and soft tissue infections in the form of folliculitis, cellulitis, and abscess (28%). Streptococcus pneumoniae, pseudomonas aeruginosa, and staphylococcus aureus are the most common isolated bacterial organisms in patients with STAT1 GOF mutations. Mycobacterial infections account for a small proportion of all bacterial infections among study participants (6%). In 38% of patients, viral infections were observed, with the most common causative organisms being HSV and VZV.

This case was diagnosed with tinea capitis of the scalp, which has been reported in 16% of the previous studies.[4] Trichophyton and Microsporon species were the causative organisms in 52% of these cases of dermatophyte fungal infections affecting the scalp, skin, and nails.[4] Toubiana et al. and Van FL et al. reported that a significant proportion of patients with STAT 1 GOF mutations also have concurrent autoimmune conditions.[4] The most frequently reported autoimmune conditions were hypothyroidism, type 1 diabetes mellitus, vasculitis, systemic lupus erythematosus disease, or skin conditions such as psoriasis or vitiligo.[4,14] Although our patient did have severe hypothyroidism, thyroid autoantibodies were not detected. The patient's hospitalization was complicated by a mild COVID-19 infection. In literature, three patients with STAT 1 GOF mutations had mild COVID-19 disease,[15–17] suggesting that STAT1 GOF mutations are not associated with severe COVID-19 infection.[15–17] Further research may be conducted to determine the effect of STAT1 GOF on the severity of COVID-19 infection.

Antimicrobial prophylaxis on a long-term basis is critical in patients with STAT 1 GOF mutations to prevent recurrent infections. According to Toubiana et al., approximately 74% of patients required antifungal prophylaxis, with fluconazole being the first-line option, followed by itraconazole and posaconazole. Antibacterial prophylaxis was used in 26% of patients, with trimethoprim-sulfamethoxazole as the primary bacterial prophylaxis to prevent recurrent staphylococcus aureus infections. In a minority of patients, antiviral therapy, immunoglobulin, biological agents, and stem cell transplantation were used.[4] Our patient was discharged home on prophylactic fluconazole 6 mg/kg/day three times per week, and trimethoprim-sulfamethoxazole 2.5 mg/kg/day three times per week, with a referral to a tertiary hospital for consideration of stem cell transplantation or the initiation of rituximab.

4 | CONCLUSION

Although STAT 1 GOF mutations are extremely rare, clinicians should consider them when making a differential diagnosis of patients with chronic cutaneous candidiasis, bronchiectasis, and stunted growth. Additionally, this report emphasizes the value of WES as a rapid and effective method for diagnosing STAT 1 GOF mutations.

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CONFLICTS OF INTEREST
None.

AUTHOR CONTRIBUTION
DA was involved in case diagnosis, study design, literature search, and manuscript editing. LM was involved in data gathering, literature review, and manuscript writing. WA, FM, AA, and WJ contributed to the interpretation of data and manuscript editing. MA assisted with the literature search and critical revision of the manuscript. Final manuscript approved by all authors.

ETHICAL APPROVAL
Obtained.

CONSENT
The patient's parent provided written informed consent to publish this case.

DATA AVAILABILITY STATEMENT
The data supporting the case report findings are available upon request.

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