

Chronic mucocutaneous candidiasis, pancytopenia, and systemic mycosis in a patient with *STAT1* gene mutation ineffectively treated with ruxolitinib

STANISŁAWA BAZAN-SOCHA¹, ADA GRADZIKIEWICZ¹, MAGDALENA CELIŃSKA-LOWENHOFF¹, ALEKSANDRA MATYJA-BEDNARCZYK¹, ANNA MACIOŁEK², KATARZYNA BAŁBOL-POKORA³

¹Department of Internal Medicine, Jagiellonian University Medical College, Cracow, Poland

²Department of Metabolic Diseases and Diabetology, Jagiellonian University Medical College, Cracow, Poland

³Department of Pediatrics, Oncology, Hematology and Diabetology, Medical University of Lodz, Poland

(*Cent Eur J Immunol* 2022; 47 (1): 92-94)

We present a case of a white adult female patient who suffered from chronic mucocutaneous candidiasis (CMC) since infancy. Her parents were not consanguineous, and neither of them nor any other family member, including an older sister, suffered from similar symptoms. The patient often received prolonged courses of antifungal antibiotics, but the regimens were always insufficiently effective. The differential diagnosis included atopic dermatitis or acrodermatitis enteropathica, a rare, usually genetic disorder of zinc metabolism characterized by pustular dermatitis, diarrhea, and nail dystrophy. At the age of 18, the patient was diagnosed with type 1 diabetes mellitus. Five years later, human immunoglobulin substitution was started due to immunoglobulin (Ig) G2 and IgG4 mild deficiency.

At the age of 35, during voriconazole therapy, the patient's clinical state became complicated with severe pancytopenia and invasive candidiasis. She was feverish; laboratory tests revealed neutropenia (1,560/ μ l), lymphopenia (300/ μ l), thrombocytopenia (22,000/ μ l), and mild anemia (hemoglobin 10.1 g/dl). Microbiological swabs of mucosal and skin lesions (Fig. 1) demonstrated massive growth of *Candida albicans* and *Staphylococcus aureus*. Abdominal computed tomography depicted spleen changes, radiologically corresponding to invasive candidiasis (Fig. 1). The patient was treated with liposomal amphotericin and broad-spectrum antibiotics, followed by posaconazole and filgrastim. However, the clinical condition did not improve. Bone marrow biopsy revealed hypocellular smear with severe granulocytic and red blood cell line hypoplasia, atypical megakaryoblast with disturbed platelet formation, single, small CD20⁺ B cells, and numerous CD3⁺ T cells in disseminated and clumping form, without evidence of any neoplastic disorder. The immunosuppressive regimen with intravenous methylprednisolone and immunoglobulins was applied due to suspicion of

autoimmune T cell dysregulation or drug-induced (azoles) pancytopenia, with tremendous clinical and laboratory improvement.

Immunological investigations demonstrated lymphopenia predominantly with absence of circulating B cells and a low number of natural killer cells. Serum immunoglobulins, including IgG subclasses, were in the normal range, mitogen stimulation of lymphocyte culture was normal, while antigen stimulation was ineffective. Chronic granulomatous disease and interferon γ /interleukin 12 axis disturbance were excluded. Next generation sequencing using the NextSeq 550 Sequencing System (Illumina, San Diego CA, USA) with a custom-designed Sure Select QXT Panel (Agilent, Santa Clara CA, USA), comprising 652 genes related to hematological diseases and bioinformatics tools, such as Mutation Taster [1] and PolyPhen [2], documented a de novo heterogeneous pathogenic variant in the DNA-binding domain of the signal transducer and activator of transcription 1 (*STAT1*) gene, which was confirmed by Sanger sequencing. Both parents were also tested, but they were negative for the mutation. That missense c.1170 G>A change refers to the methionine to isoleucine substitution in the 390 position of the *STAT1* protein chain (p.Met390Ile) and according to the predictive software is related to the dominant mode of the primary immunodeficiency with CMC (IMD31C), Online Mendelian Inheritance in Man (OMIM), number sign 614162. The revealed gain of function (GOF) mutation was previously described in a 4-year-old Algerian boy and a 10-year-old boy from Hong Kong with a classical CMC phenotype [3, 4]. Furthermore, a genetic test revealed a homozygous variant of unknown significance in the *NCF1* gene, referred to as the substitution of arginine to histidine in position 90 of the protein chain. Mutation in that gene might be associated with the chronic granuloma-

Correspondence: Stanisława Bazan-Socha, Department of Internal Medicine, Jagiellonian University Medical College, 8 Skawinska St., 31-066 Krakow, Poland, e-mail: stanislawa.bazan-socha@uj.edu.pl
Submitted: 24.02.2022, Accepted: 28.02.2022



Fig. 1. Mucous, skin, and nail candidiasis. Abdominal computed tomography with invasive splenic mycosis

tous disease; however, Phagoburst and nitroblue tetrazolium tests were normal in our patient; thus, we considered the described variant as clinically irrelevant.

Based on the literature data, the patient was administered ruxolitinib, a Janus kinase (JAK) 1 and JAK2 inhibitor, recently shown as effective in patients with *STAT1* GOF mutation [5-10]. However, six months of therapy with that medication in a dose of 10 mg twice a day was not related to a clinically significant improvement, i.e., skin and mucosal changes were still severe, and pancytopenia persisted.

In addition, the patient required regular filgrastim application and frequent red blood cell and platelet transfusion. Therefore, ruxolitinib was discontinued. The follow-up bone marrow biopsy again showed a hypocellular smear with pathological changes corresponding to bone marrow aplasia. Consequently, the diagnosis of aplastic anemia was made, likely related to T-cell dysregulation. The presence of chronic fungal and bacterial skin and mucosal lesions disqualified the patient from bone marrow transplantation, and three months later, she died from sepsis.

In 2016 Toubiana *et al.* [4] described a large cohort of 274 patients from 40 countries with various autosomal dominant heterozygous *STAT1* GOF mutations. Almost all those individuals presented CMC, with a median age at onset of 1 year. Bacterial infections, mainly by *Staphylococcus aureus*, as well as viral and mycobacterial, were also frequent. Furthermore, many patients had autoimmune manifestations, including type 1 diabetes, autoimmune cytopenias, and aplastic anemia, as observed in our patient. Invasive candidiasis, intracranial aneurysms, and cancers were predictors of poor outcomes [4].

In the pathogenesis of CMC, enhanced *STAT1* activation is related to increased JAK signaling [5, 11]. Therefore, in that disorder, ruxolitinib has been previously reported to treat alopecia, fungal infections, thrush, autoimmune cytopenias, and even diabetes, albeit with varied clinical responses [5-10]. However, we did not find any data on its application in aplastic anemia complicating CMC. Rosenberg *et al.* [11] recently described an 18-year-old man with aplastic anemia and *STAT1* GOF mutation, who was successfully treated with itacitinib, a new, investigational JAK1 inhibitor. That medication resulted in the prompt recovery of hematopoiesis. Therefore, it might be a therapeutic option in bone marrow lesions related to CMC and other autoimmune or immunodeficiency cases.

Conclusions

We present this case to increase CMC awareness and as a reminder that it is an immune disease, not only a dermatologic one. It may refer to the *STAT1* GOF gene pathological variant, or it may be de novo with no familiar history, like in our case. This disease also requires a specific type of treatment, such as JAK inhibitors and not only antifungal medications. However, choosing appropriate medication requires further experimental and clinical studies since ruxolitinib was ineffective in our case. We may only speculate that its earlier administration, i.e., before the severe bone marrow lesion, would be more efficient. In addition, in some severe CMC complications, such as aplastic anemia, itacitinib, a new selective JAK1 inhibitor, may raise some hopes. Since itacitinib does not block JAK2, erythropoietin and thrombopoietin receptors downstream, it may be more effective in hematologic disorders related to autoimmune diseases or immunodeficiencies.

The authors declare no conflict of interest.

References

1. Schwarz J, Cooper D, Schuelke M, et al. (2014): Mutation-Taster2: mutation prediction for the deep-sequencing age. *Nat Methods* 11: 361-362.
2. Adzhubei IA, Schmidt S, Peshkin L, et al. (2010): A method and server for predicting damaging missense mutations. *Nat Methods* 7: 248-249.

3. Lee PP, Lao-Araya M, Yang J, et al. (2019): Application of flow cytometry in the diagnostics pipeline of primary immunodeficiencies underlying disseminated *Talaromyces Marneffei* infection in HIV-negative children. *Front Immunol* 10: 1-13.
4. Toubiana J, Okada S, Hiller J, et al. (2016): Heterozygous *STAT1* gain-of-function mutations underlie an unexpectedly broad clinical phenotype. *Blood* 127: 3154-3164.
5. Moriya K, Suzuki T, Uchida N, et al. (2020): Ruxolitinib treatment of a patient with steroid-dependent severe autoimmunity due to *STAT1* gain-of-function mutation. *Int J Hematol* 112: 258-262.
6. Weinacht KG, Charbonnier LM, Alroqi F, et al. (2017): Ruxolitinib reverses dysregulated T helper cell responses and controls autoimmunity caused by a novel signal transducer and activator of transcription 1 (*STAT1*) gain-of-function mutation. *J Allergy Clin Immunol* 139: 1629-1640.e2.
7. Bloomfield M, Kanderová V, Paračková Z, et al. (2018): Utility of ruxolitinib in a child with chronic mucocutaneous candidiasis caused by a novel *STAT1* gain-of-function mutation. *J Clin Immunol* 38: 589-601.
8. Higgins E, Al Shehri T, McAleer MA, et al. (2015): Use of ruxolitinib to successfully treat chronic mucocutaneous candidiasis caused by gain-of-function signal transducer and activator of transcription 1 (*STAT1*) mutation. *J Allergy Clin Immunol* 135: 551-553.
9. Mössner R, Diering N, Bader O, et al. (2016): Ruxolitinib induces interleukin 17 and ameliorates chronic mucocutaneous candidiasis caused by *STAT1* gain-of-function mutation. *Clin Infectious Diseases* 62: 951-953.
10. Chaimowitz NS, Ebenezer SJ, Hanson IC, et al. (2020): *STAT1* gain of function, type 1 diabetes, and reversal with JAK inhibition. *N Engl J Med* 383: 1494-1496.
11. Rosenberg J, Hughes T, Peters J, et al. (2021): An N-of-1 trial of Itacitinib for a patient with aplastic anemia associated with a gain-of-function variant in *STAT1*, 08 January 2021, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-139401/v1].