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LETTER TO EDITOR

A 1-Year-Old Girl with a Gain-of-Function *STAT1* Mutation Treated with Hematopoietic Stem Cell Transplantation

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We report the case of a 1-year-old Peruvian girl who displayed recurrent infections by *Candida albicans* and pyogenic bacteria from the neonatal period onward. Our patient was born to non-consanguineous Mestizo parents. There was no family history suggestive of Primary Immunodeficiencies (PIDs). The patient suffered from *Candida albicans* infections since 3 days of age, predominantly affecting body skin, oral cavity and oropharynx, which required systemic antifungal therapy. Without antifungals the patient developed dysphonia and persistent cough, suggestive of laryngeal and respiratory tract involvement, which completely resolved when antifungal therapy was resumed. Computer tomography of the chest at 3 months of age revealed signs of residual inflammatory process in upper and medium lobes of right lung. Several chest X-rays taken later were not compatible with pneumonic processes. Alveolar lavage was not performed.

From the age of 1 month onward the patient presented with recurrent diarrhea. Stool culture grew enteropathogenic *Escherichia coli* and *Klebsiella pneumoniae* on different occasions. Diarrhea improved after intravenous antibiotic therapy. As the patient grew older, diarrhea episodes were less frequent. At 1 year old, failure to thrive was remarkable; patient's weight was persistently below third percentile. There were no clinical and immunological signs of endocrine or autoimmune disease.

Available hematologic, metabolic and immunologic work up performed when the patient was 4 months old did not reveal significant abnormalities, except for hypergammaglobulinemia.

Patient's blood samples were analyzed and a heterozygous mutation (N397D) located in the DNA binding domain of the transcription factor *Signal Transducer and Activator of Transcription 1 (STAT1)* was found. Further DNA sequencing in patient's parents, brother and sister revealed wild type *STAT1*, implying that the mutation had occurred *de novo*. This mutation was biochemically shown to be gain-of-function. The patient displayed low proportions of interleukin (IL)-17 producing T cells.

Candida resistance to antifungal therapy developed over time. When the patient was 13 months, clinical resistance was noted to Itraconazole, Posaconazole and Amphotericin B.

Due to the poor prognosis and quality of life of the patient we performed a reduced-intensity-conditioning Hematopoietic Stem Cell Transplantation (HSCT) from her 9-year-old 6/6 HLA-matched brother. The conditioning regimen and graft-versus-host disease (GVHD) prophylaxis that we used is detailed in Table I. Antifungal treatment with Caspofungin was indicated all over the procedure.

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Table I Details of the HSCT procedure

- Source: bone marrow
- Donor: 9-year-old 6/6 HLA-matched brother (wild type *STAT1*)
- Patient's weight: 7 kg
- Number of stem cells infused: 6.56×10^6 CD34+ cells/kg
- Conditioning regimen:
  - Fludarabine 30 mg/m^2/day from days −8 to −3
  - Melphalan 140 mg/m^2/day on day −3
  - Antithymocyte globulin 5 mg/kg/day on days −3 and −2
- GVHD prophylaxis:
  - Methotrexate 7.5 mg/m^2/day on day +1; 5 mg/m^2/day on days +3, +6 and +11
  - Cyclosporine 5 mg/kg/day on day −1; 3 mg/kg/day from days +1 to +32
- Date when Caspofungin was withdrawn: day+18 after transplant
- Date of myeloid engraftment (neutrophils >500 per μL): day+15 after transplant
- Discharge date from the hospital: day+25 after transplant

Fifty-two days after HSCT the patient was admitted to our hospital with a suspected diagnosis of pneumonia. She received intravenous Caspofungin, Vancomycin and Imipenem for 7 days, with excellent response. The patient kept clinically well for 4 months after HSCT without requirement of antifungal therapy and with a weight gain of 2 kg. IL-17 producing T cells were not measured at that time because of unavailable methods in Peruvian laboratories.

Four months after HSCT oral candidiasis recurred. Chimerism analysis at days+104 and+130 after transplant showed progressive loss of the donor cells (Table II). Weekly oral antifungal therapy with Fluconazole was indicated.

Five months after HSCT the patient developed severe thrombocytopenia, probable of autoimmune origin, unresponsive to intravenous immunoglobulin (2 g/kg). Prednisone (7.5 mg/kg/day) was required to maintain platelet levels above 15,000/μL. Liver enzymes (AST, ALT) were 4-to-10-fold elevated, probably secondary to Fluconazole therapy or an autoimmune disorder.

Ten months after HSCT, while we were planning a second HSCT, the patient developed cough, fever and dyspnea, which markedly worsened through few hours. Chest X-rays revealed diffuse pulmonary infiltrates. Patient was admitted to the Intensive Care Unit, but died by a probable fulminant interstitial lung infection. Causal microorganisms were not identified. Autopsy was not performed.

STAT1 gain-of-function (GOF) mutations reduce the dephosphorylation of activated STAT1 protein, leading to accumulation of phosphorylated STAT1 in the nucleus [1, 2]. Persistently activated STAT1 may shift the immune response toward STAT1-dependent interleukin-17 inhibitors and away from STAT3-mediated induction of IL-17 T cell generation [3, 4].

GOF mutations affecting *STAT1* lead to defective IL-17 T cell development, characterized by reduced production of IL-17, and IL-22; these cytokines are crucial for the antifungal defense of skin and mucosa [2, 5–8].

Patients with GOF *STAT1* mutations present with autosomal dominant (AD) chronic mucocutaneous candidiasis (CMC) [2]. Clinical manifestations include chronic oropharyngeal candidiasis, cutaneous dermatophytosis, and autoimmune phenomena, such as hypothyroidism and autoimmune hepatitis [3, 6]. Treatment of patients with this disease includes the use of long-term antifungal and antibacterial therapy or prophylaxis [2]. A 34-year-old patient with AD CMC underwent HSCT due to severe disease; however, she died 1 month later from the rupture and bleeding of a pre-existing cerebral aneurism (Liu et al., unpublished data). Hoh et al. [9] reported the case of a 12-year-old boy with CMC, Coomb's positive haemolytic anaemia and recurrent bronchopneumonia who was successfully treated with a HLA-identical sibling HSCT. Deeg et al. [10] reported a successful HLA-identical sibling HSCT in a 7-year-old girl with CMC and severe aplastic anemia. We performed HSCT in our patient due to the severity of the disease. Our patient's disease is the most severe clinical presentation of GOF STAT1 and CMC ever reported [11–19]. After a good response in the first months, donor cells were apparently rejected and the disease recurred. A myeloablative-conditioning regimen might have lead to a better outcome.

HSCT might be considered as a treatment option for patients with GOF *STAT1* mutations, especially for the rare patients with antifungal resistance and an apparently poor prognosis. Other treatments could be considered, including G-CSF and GM-CSF.

Table II Chimerism analysis after HSCT

N° of days after HSCT	Sample	XY karyotype (donor cells)	XX karyotype (recipient cells)	N° of metaphases	Type of banding
+ 21 days	Peripheral blood	15 %	85 %	20	GTG
+ 62 days	Peripheral blood	12 %	88 %	8	GTG
+ 78 days	Peripheral blood	50 %	50 %	20	GTG
+ 104 days	Peripheral blood	0 %	100 %	20	GTG
+ 130 days	Peripheral blood	0 %	100 %	20	GTG

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Conflict of Interest The authors declare that they have no conflict of interest regarding the contents of this article.

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