LETTER TO EDITOR

Fatal and Unresponsive Cytomegalovirus Infection in a New Homozygous FOXN1 Gene Variation Causing Nude SCID

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To the Editor

Human inborn errors of immunity (IEI) are caused by monogenic germline mutations resulting in loss or gain of function of the encode protein [1]. There are now 430 single-gene IEI and this number is increasing faster in the last years [1, 2]. Severe combined immunodeficiency (SCID) is the most severe form of IEI with a failure of functional T cell development, with or without accompanying defects in the production of B and/or NK cells [3].

Since the discovery of FOXN1 deficiency, the human counterpart of the nude mouse, a growing body of evidence investigating the role of FOXN1 in the thymus and skin has been published [4]. The FOXN1 (Forkhead Box N1) deficiency, also known as the nude SCID, is a very rare autosomal recessive form of SCIDs. It has a unique phenotype with severe T cell immunodeficiency with normal B and NK cells, thymus dysgenesis, congenital alopecia, and nail dystrophy [4].

We have read with special attention the recently cohort described 18 patients (11 homozygous, 2 compound heterozygous, and 5 heterozygous) with severe infections from nine countries in Europe, Middle East, and Asia. All, except one heterozygous patient, had signs of CID or SCID [5].

A 3-month-old Brazilian girl was admitted to our department due petechiae and purpuric lesions in the last month with no erythrodermic rash. She presented a remarkable phenotype with alopecia universalis and nail dystrophy since birth and actual small hepatosplenomegaly (Figs. 1 and 2). She was born full term, from healthy consanguineous parents (first-degree cousins) without ectodermal dystrophy or lymphopenia. Her parents had a child with similar phenotype who died at age 3 months of pneumonia and meningitis, without any investigation for immunodeficiency or other disorders (Fig. 3).

Due the uncommon phenotype, laboratorial work-up was initiated showing an absence of the thymus in the chest radiography and thrombocytopenia (32,000/mm3) and eosinophilia (1,275/mm3) in the total blood count. Serum immunoglobulins were elevated: IgG = 1329 mg/dL (338–698 mg/dL), IgM = 220 mg/dL (25–52 mg/dL), IgA = 70 mg/dL (4–27 mg/dL), and IgE = 43 UI/mL. Lymphocyte subpopulation showed remarkable lower levels of CD3+ = 489 cells/μL (1919–5368 cells/μL), CD4+ = 295 cells/μL (1358–3375 cells/μL), CD8+ = 164 cells/μL (523–1798 cells/μL), and CD19 = 373 cells/μL (955–2596 cells/μL), while CD16-56 = 3978 cells/μL (199–731 cells/μL) was elevated. Trec, CD4RA/RO, and CD8RA/RO were not available, so we were not able to rule out maternal engraftment.

Due the low levels of CD3, absence of thymus, alopecia, and nail dystrophy, the hypothesis of FOXN1 deficiency was performed and she started prophylaxis for bacterial and fungal infections with sulfametoxazol + trimethoprim and fluconazole in prophylactic doses and monthly immunoglobulin replacement. She presented a remission of petechiae, purpuric lesions, and thrombocytopenia subsequently. During the follow-up, she presented right axillar lymphadenopathy with local BCGitis diagnosis treated with rifampicin, isoniazid, and ethambutol. At age 8 months, IgE levels were extremely elevated (9,779 UI/mL).

Proceeding with the investigation, a genetic study (Invitae Primary Immunodeficiency Panel, including 407 immunity genes) was performed in partnership with Jeffrey Modell Foundation, identifying homozygous in the c.814C > A (p.Pro272Thr) variant of FOXN1 gene. Proline residue is highly conserved and this variant is not present in databases (GnomAD, ExAC). Algorithms (SIFT, PolyPhen-2, Align-GVGD) all suggest that this variant is likely to be disruptive and clearly clinically related with nude SCID by homozygous FOXN1 deficiency, which is expressed in

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the thymic epithelial cells, skin, hair, and nails. Subsequent genetic analysis of the parents’ FOXN1 gene showed that both were carriers of the variant found homozygous in the patient. Thymus transplant was indicated, but was not available in our country.

The patient was on immunoglobulin replacement without other complications, until 16 months old when she started to have recurrent fever, with nausea, and inappetence, being admitted to the hospital after shortness of breath presenting a huge hepatosplenomegaly. Investigation found a positive PCR for cytomegalovirus (CMV). No other microorganisms were found in any culture. Ganciclovir was started for the patient to treat an active CMV infection. In the first exam, a number of 5,340,000 copies were detected. After completed in 6 weeks, she was asymptomatic and the number of copies was 258,293. Ganciclovir was stopped to observe how the patient was responding after all the time combating the CMV infection.

On the fifth day off medication, the patient had a worsening in general condition, needing oxygen at night again and not eating properly as well. The number of copies of the CMV increased to 1,241,666 and ganciclovir was reinitiated. Despite antiviral medication and all medical support, the patient presented a progressive worsening in the subsequent weeks. She was admitted in the intensive unit care on the seventh week of re-treatment, with acute kidney injury, low oxygen saturation, and anasarca, and died after 3 days of intensive care.

Human nude SCID with FOXN1 mutation is a rare autosomal recessive IEI showing congenital athymia, alopecia, and nail dystrophy. We describe the first patient with nude SCID, to date, with a novel homozygous FOXN1 mutation from Americas. A homozygous mutation located at position chr17: 26,856,226 c.814C>A (p.Pro272Thr) was identified, and although no functional validation was performed, clinical and genetic data are highly compatible.

The clinical phenotype of our patient is like the previously described homozygous patients, characterized by congenital athymia, alopecia, and nail dystrophy. She also presents Omenn syndrome phenotype as described in 50% of patients.

![Fig. 1 Alopecia universalis in a nude SCID infant](image1)

![Fig. 2 Nail dystrophy in a nude SCID infant](image2)
However, she had lymphopenia with NK cells very high and hypergammaglobulinemia. The immunological phenotype of this patient is T-B-NK+, different to the most cases that have T-B+NK+ phenotype. Low B cell levels were described in one patient and in a second patient marked lymphopenia which resulted in T-B-NK-phenotype [5].

Homozygous was related to bad prognosis comparing with compound heterozygous and heterozygous mutation. Thymus transplantation could be the chance for our patient; unfortunately, it is not available in Brazil and the transfer to another country was extremely hampered by the COVID-19 pandemic situation. This patient developed a severe CMV lung infection at 16 months treated with long-term antiviral; however, she was non-responsive and the infection was fatal.

In conclusion, we report here a patient with nude SCID carrying a novel homozygous mutation in the FOXN1 gene. The awareness of clinical spectrum of disease is very important for physicians to think, diagnose, and adequately treat nude SCID patients. More thymus transplantation centers are needed around the world to help and make these patients survive.

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**Declarations**

**Conflict of Interest** The authors declare no competing interests.

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