The first patient reported with X-linked severe combined immunodeficiency in Peru

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Case report

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The first patient reported with X-linked severe combined immunodeficiency in Peru

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ABSTRACT

Background

X-linked severe combined immunodeficiency (X-SCID) is a life-threatening immune disorder caused by pathogenic mutations in the *IL2RG* gene. We report the first patient with genetically confirmed X-SCID in Peru.

Case presentation

Diagnosis was suspected before patient's birth because of family history. At birth, blood immunophenotype was compatible with X-SCID and genetic analysis revealed a pathogenic mutation in *IL2RG*. Intravenous immunoglobulin and antibiotic prophylaxis were initiated until patient's referral for an available novel treatment: gene therapy.

Conclusions

Family background is a key point to suspect X-SCID, allowing a timely diagnosis and treatment. X-SCID requires prompt immune reconstitution. However, HSCT is frequently not available to treat newborns in developing countries.

Keywords

X-linked severe combined immunodeficiency, X-SCID, Hematopoietic Stem Cell Transplantation, Gene therapy, Primary immunodeficiency.

41 BACKGROUND

42
43 X-linked severe combined immunodeficiency (X-SCID) is a potentially fatal primary
44 immunodeficiency characterized by profound impairment of both cellular and humoral
45 immunity, leading to an increased susceptibility to serious infections by many kinds of
46 microbes including opportunistic [1].

47
48 We report the first patient with genetically confirmed X-SCID in Peru.
49

50 CASE PRESENTATION

51
52
53 A 33-week-pregnant woman carrying a male fetus was referred for an immunological
54 evaluation because her previous two male children had deceased at early age due to severe
55 infections. She also had an apparently healthy 8-year-old daughter.

56
57 The first deceased boy was born at 36 weeks of gestation. At 6 months of age he presented
58 with failure to thrive and pneumonia requiring management at intensive care unit. However,
59 he evolved with chronic diarrhea, dying at 8 months of age due to intestinal perforation,
60 peritonitis and sepsis.

61
62 The second deceased boy was born at 32 weeks of gestation. At 5 months of age he presented
63 with chronic diarrhea, failure to thrive and *Pneumocystis jirovecii* pneumonia. Laboratory work
64 up showed hypogammaglobulinemia and absence of T cells. Despite therapy with
65 intravenous immunoglobulin, the boy died at 11 months of age due to systemic infection by
66 *Mycobacterium tuberculosis* and cytomegalovirus.

67
68 On account of the family history, we suspected a diagnosis of X-SCID in the coming male
69 baby, with a disease probability of 50%. Therefore, we decided to manage him as potentially
70 sick with the following recommendations: programmed Cesarean delivery, strict isolation,
71 breastfeeding avoidance, Bacille Calmette-Guérin (BCG) vaccine avoidance, immediate
72 immunologic testing to confirm the diagnosis, and urgent hematopoietic stem cell
73 transplantation (HSCT) if the diagnosis was confirmed.

74
75 Six weeks later, the patient was born through programmed Cesarean delivery, with a
76 gestational age of 39 weeks and a birth weight of 3500 g. Although the patient looked
77 apparently healthy, immediate immunologic testing was performed. Total leukocyte
78 (16,490/ μ L), lymphocyte (2,800/ μ L) and neutrophil (10,550/ μ L) counts were within normal
79 values, the same as hemoglobin (19.5 g/dL), platelets (313,000/ μ L) and serum
80 immunoglobulins. However, flow cytometric analysis revealed a virtual lack of T cells and
81 NK cells, with a normal B-cell count (97% of lymphocytes).

82
83 The presence of a T-B+NK- immunophenotype was highly suggestive of X-SCID. Therefore,
84 we proceeded to sent blood samples to Children's Hospital Boston, USA for genetic testing,
85 which confirmed the disease-causing mutation c.270-15a>g in the interleukin 2 receptor
86 subunit gamma (*IL2RG*) gene. In the meantime, the patient was in strict isolation while
87 receiving prophylaxis with intravenous immunoglobulin, cotrimoxazole and itraconazole.
88 BCG was not administered and breastfeeding was avoided.
89

The patient required an urgent potentially-curative therapy with HSCT. Nevertheless, there are several limitations to perform HSCT in Peru, such as the lack of a bone marrow national registry to look for human leukocyte antigen (HLA)-matched unrelated donors, and a lack of well-trained transplantation teams for primary immunodeficiencies. Our reported patient did not have an HLA-matched related donor, so he was referred to the United States of America for a novel treatment: gene therapy.

DISCUSSION AND CONCLUSIONS

X-SCID is a life-threatening primary immunodeficiency characterized by profound impairment of both cellular and humoral immunity [1]. Pathogenic mutations in the *IL2RG* gene lead to absent production or abnormal function of the common gamma chain protein, also called CD132 [2,3]. Defects in this protein result in a virtual absence of T and NK lymphocytes, with a normal B-lymphocyte count (T-B+NK- immunophenotype) [4]. Immunoglobulin production is impaired despite the presence of normal B-cell numbers. This is explained by the lack of T cell collaboration for antibody production and the presence of abnormal growth factor receptors on B cell surface [5].

X-SCID patients typically present in the newborn period with chronic diarrhea, failure to thrive and severe, recurrent infections by any kind of microbe including opportunistic ones. Some patients have an atypical milder presentation [7-9]. Asymptomatic children with abnormal newborn screening for SCID or family history of X-SCID should be fully evaluated.

Regarding our case, patient's family history allowed us to suspect X-SCID and to establish an appropriate management since birth. Our patient had a classical immunophenotype of X-SCID. As we expected, a pathogenic mutation was found in the *IL2RG* gene.

Primary treatment for X-SCID is HSCT [10,11]. The best timing for this procedure is immediately after birth. It has been established that better outcomes (>90% survival) are achieved in patients who receive transplantation in early infancy, below 3.5 months of age [10]. Provisional management includes immunoglobulin administration and antibiotic prophylaxis against *Pneumocystis jirovecii* and fungal infections [12]. The role of gene therapy is being investigated; there is evidence of effectiveness, but potential of oncogenic insertions should be considered [13].

We report the first patient with genetically confirmed X-SCID in Peru. Diagnosis was suspected before birth because of his family history. Early diagnosis allowed an adequate management until his referral to a gene therapy protocol.

Family background is a key point to suspect X-SCID, allowing a timely diagnosis and treatment. This severe life-threatening disease requires prompt immune reconstitution. However, HSCT is frequently not available to treat newborns in developing countries due to medical and administrative limitations. What should we do if SCID is confirmed in these newborns? Are they condemned to die?

List of abbreviations

X-SCID:	X-linked severe combined immunodeficiency
BCG:	Bacille Calmette-Guérin
HSCT:	Hematopoietic stem cell transplantation
HLA:	Human leukocyte antigen
IL2RG:	Interleukin 2 receptor subunit gamma
SCID:	Severe combined immunodeficiency

DECLARATIONS

Ethics approval and consent to participate

No approval was needed from the ethics committee.

Consent for publication

Parents of the patient gave consent to publish the current manuscript.

Availability of data and materials

Data from the patient is available in his physical clinical history at Edgardo Rebagliati Martins National Hospital (Lima, Peru).

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

All authors contributed to the evaluation, diagnosis, and management of the patient. JCA and JC were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Baker MW, Grossman WJ, Laessig RH, Hoffman GL, Brokopp CD, Kurtycz DF, et al. Development of a routine newborn screening protocol for severe combined immunodeficiency. *J Allergy Clin Immunol* 2009; 124(3):522-7.
2. Noguchi M, Yi H, Rosenblatt HM, et al. Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. *Cell* 1993; 73:147.
3. Schmalstieg FC, Goldman AS. Immune consequences of mutations in the human common gamma-chain gene. *Mol Genet Metab* 2002; 76(3):163.
4. Noguchi M, Yi H, Rosenblatt HM, Filipovich AH, Adelstein S, Modi WS, et al. Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. *Cell* 73: 147- 157. 1993. *J Immunol* 2008; 181(9):5817-27.

5. Kalman L, Lindegren ML, Kobrynski L, Vogt R, Hannon H, et al. Mutations in genes required for Tcell development: IL7R, CD45, IL2RG, JAK3, RAG1, RAG2, ARTEMIS, and ADA and severe combined immunodeficiency: HuGE review. *Genet Med* 2004; 6(1):16-26.
6. Conley ME. Molecular approaches to analysis of X-linked immunodeficiencies. *Ann Rev Immunol.* 1992;10:215–238.
7. Wada T, Yasui M, Toma T, et al. Detection of T lymphocytes with a second-site mutation in skin lesions of atypical X-linked severe combined immunodeficiency mimicking Omenn syndrome. *Blood* 2008; 112:1872.
8. Slatter MA, Angus B, Windebank K, et al. Polymorphous lymphoproliferative disorder with Hodgkin-like features in common γ -chain-deficient severe combined immunodeficiency. *J Allergy Clin Immunol* 2011; 127:533.
9. Conley ME. Molecular approaches to analysis of X-linked immunodeficiencies. *Ann Rev Immunol.* 1992;10:215–238.
10. Filipovich A. Hematopoietic cell transplantation for correction of primary immunodeficiencies. *Bone Marrow Transplant* 2008; 42 Suppl 1:S49.
11. Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. *Blood.* 2002;99:872–8.
12. Allenspach E, Rawlings DJ, Scharenberg AM. X-Linked Severe Combined Immunodeficiency. 2003 Aug 26 [Updated 2016 Apr 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1410/>
13. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M. Gene therapy for primary immunodeficiencies. *Immunol Allergy Clin North Am* 2010; 30:237.