

Clinical Pearls

Hypomorphic interleukin-7 receptor α -chain mutations and T-cell deficiency: a delay in diagnosis



Clinical Presentation

A 10-year-old white girl was referred for evaluation of chronic oxygen-dependent lung disease associated with recurrent pulmonary infections and digital clubbing. She was born at term to non-consanguineous parents. At a young age, she developed frequent cough and wheezing episodes diagnosed as asthma and frequent episodes of otitis media, including 1 episode at 6 years of age yielded *Bordetella bronchiseptica* from ear drainage and required 4 months of antibiotic treatment. Small tonsils and adenoids were noted during myringotomy tube placement. Immunologic evaluation at 6.5 years showed lymphopenia, normal immunoglobulin levels, and normal antibody responses to vaccines. Chronic otitis media persisted with pathogens, including *Haemophilus influenzae*, *Pseudomonas* species, *Alcaligenes xylosoxidans*, and yeast. At time of evaluation, she had cough and wheeze associated with hypoxia, diffuse bronchiectasis (Fig 1), restrictive pulmonary function test results (forced expiration volume in 1 second 21% predicted and force vital capacity 28% of predicted), and evidence for failure to thrive. Fluid obtained from bronchoalveolar lavage yielded *Serratia marcescens*. Sputum cultures yielded *Acinetobacter lwoffii*, *Pseudomonas aeruginosa*, *A. xylosoxidans*, *Aspergillus fumigatus*, and non-tuberculous mycobacteria. Immunologic evaluation (Table 1) performed in the absence of corticosteroid or other immunosuppressive treatment showed profound T-cell lymphopenia and decreased lymphocyte proliferation to mitogens and antigens. Most CD4 T cells were memory T cells (CD45RO⁺) and T-cell receptor excision circles were absent. No maternal T-cell engraftment was detected. B cells were modestly depressed, whereas natural killer (NK) cells were normal. Serum IgG and IgM levels were normal; IgA level was elevated. Tetanus toxoid and pneumococcal polysaccharide serum antibody responses were normal. Despite elevation in CD4CD45RO⁺ memory T cells, she displayed no features of Omenn syndrome, including hepatosplenomegaly, rash, eosinophilia, or elevated IgE.

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Clinical Outcome

Based on the degree of T-cell lymphopenia and dysfunction with the history of unusual infections and failure to thrive, the concern for “leaky” severe combined immunodeficiency (SCID) was raised.¹ The T⁺B⁺NK⁺ phenotype directed mutation analysis for an interleukin-7 receptor α chain (IL-7R α) defect and 2 novel frameshift mutations were identified in the IL-7R α gene, 1 10-basepair deletion in exon 5 (c.589_598del10, p.P197fsX44) and 1 single base deletion in exon 8 (c.993delA, p.Q331fsX2). Compound heterozygosity was confirmed by finding each parent was heterozygous for 1 of these 2 mutations. Then, the specific protein expression that showed significantly decreased protein levels by immunoblotting (Fig 2A) and flow cytometry (data not shown) was examined. In addition, IL-7R α mRNA levels were significantly decreased compared with control cells (Fig 2B). Evaluation of signal transducer and activator of transcription 5 (STAT5) phosphorylation demonstrated functional impairment of IL-7R α by a markedly lower response to IL-7 compared with control cells but a normal response to the alternative stimulus, interleukin-2 (Fig 2C).

Severe combined immunodeficiency is a genetically heterogeneous disorder characterized by profound immune defects, with a recently reported frequency of 1 of 58,000 live births.² Currently, 13 different genetic defects have been described leading to a SCID phenotype.³ Children with typical SCID have absent or extremely low naive T-cell numbers, with variable decreases in B and NK cells based on the specific genetic defect.^{1,2} Patients with SCID are susceptible to life-threatening infections that require immune reconstitution for survival. Mutations in the IL-7R α gene cause autosomal recessive SCID, leading to a T⁺B⁺NK⁺ phenotype, and account for approximately 6% to 12% of SCID cases.^{2,4} However, as with most SCID genotypes, “leaky” or hypomorphic mutations have been observed and lead to a less severe phenotype, often delaying diagnosis.¹ IL-7 signaling is essential for survival and proliferation of T-cell precursors signaling through STAT3 and STAT5.⁵ Patients with complete IL-7R α deficiency have profound T-cell lymphopenia and abnormal T-cell function, whereas B-cell levels are typically normal but immunoglobulin production is usually decreased. NK cell production and ex vivo function are typically normal.^{5,6} However, the present had evidence for some T-cell lymphopoiesis with very low circulating T cells and evidence for some T-helper cell function based on normal immunoglobulin levels and protein antigen-specific antibody production. The hypomorphic nature of this patient's mutations allowed for some residual IL-7R α protein expression evidenced by a decreased but not absent IL-7-induced STAT5 phosphorylation (with normal response to interleukin-2).

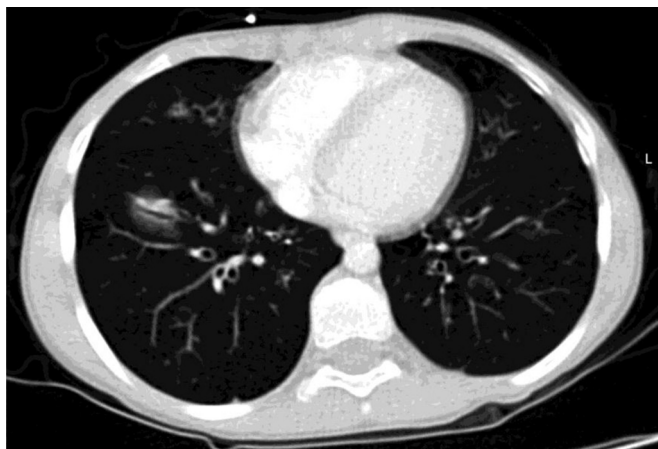


Figure 1. Computed tomogram at middle chest level of patient deficient in interleukin-7 receptor α chain shows diffuse bronchiectasis.

Despite her profound lymphopenia, this patient's diagnosis was delayed by more than 10 years, leading to irreversible respiratory failure. Review of her history and prior laboratory studies showed multiple signs of immunodeficiency, including failure to thrive, infections with unusual organisms, decreased lymphoid tissue, and chronic lymphopenia. However, primary immunodeficiency was considered unlikely because her pulmonary symptoms were ascribed to asthma and her lymphopenia was attributed to long-term steroid use. However, as noted by the immunologic evaluation, she was profoundly lymphopenic in the absence of corticosteroids or other immunosuppression. With an increasing appreciation of “leaky” or hypomorphic SCID, this diagnosis should be a part of the differential when evaluating any child with a history of unusual infections, failure to thrive, and/or depressed lymphoid numbers or function. Despite the mixed picture of immune dysfunction, this patient had findings consistent with hypomorphic SCID.⁷ In addition, her progressive pulmonary disease would be unusual owing to asthma, and in the absence of cystic fibrosis, bronchiectasis in a pediatric patient should raise the possibility of a primary immunodeficiency.⁸ Recent data from SCID newborn screening have shown that the T-cell receptor excision circle assay is

Table 1
Immunologic evaluation of patient

IgG (mg/dL) (608–1,572)	783
IgA (mg/dL) (45–236)	896
IgM (mg/dL) (52–242)	183
IgE (IU/mL) (<25)	<2
Tetanus titer (IU/mL) (>0.1)	0.59
Diphtheria titer (IU/mL) (>0.1)	0.07
Post-pneumococcal titer (IU/mL) (>1.3)	>50% serotypes protective
Absolute lymphocyte count cells/ μ L (1,900–3,700)	363
Absolute CD3 ⁺ cells/ μ L (1,200–2,600)	70
Absolute CD4 ⁺ cells/ μ L (650–1,500)	35
Absolute CD8 ⁺ cells/ μ L (370–1,100)	18
Absolute CD19 ⁺ cells/ μ L (270–860) ^a	62
Absolute CD56 ⁺ cells/ μ L (100–480)	224
CD4 ⁺ CD45RA ⁺ (51%–67%)	2%
CD4 ⁺ CD45RO ⁺ (33%–49%)	98%
Lymphocyte stimulation to mitogens (counts/min)	
Phytohemagglutinin (>93,000)	4,904
Concanavalin A (>76,000)	10,127
Pokeweed (>85,000)	31,207
Lymphocyte stimulation to antigens (SI)	
Tetanus (>3)	13.1
Candida (>3)	1.7

Abbreviation: SI, stimulation index.

^aB-cell quantity increased after treatment with antimicrobials to 161 cells/ μ L.

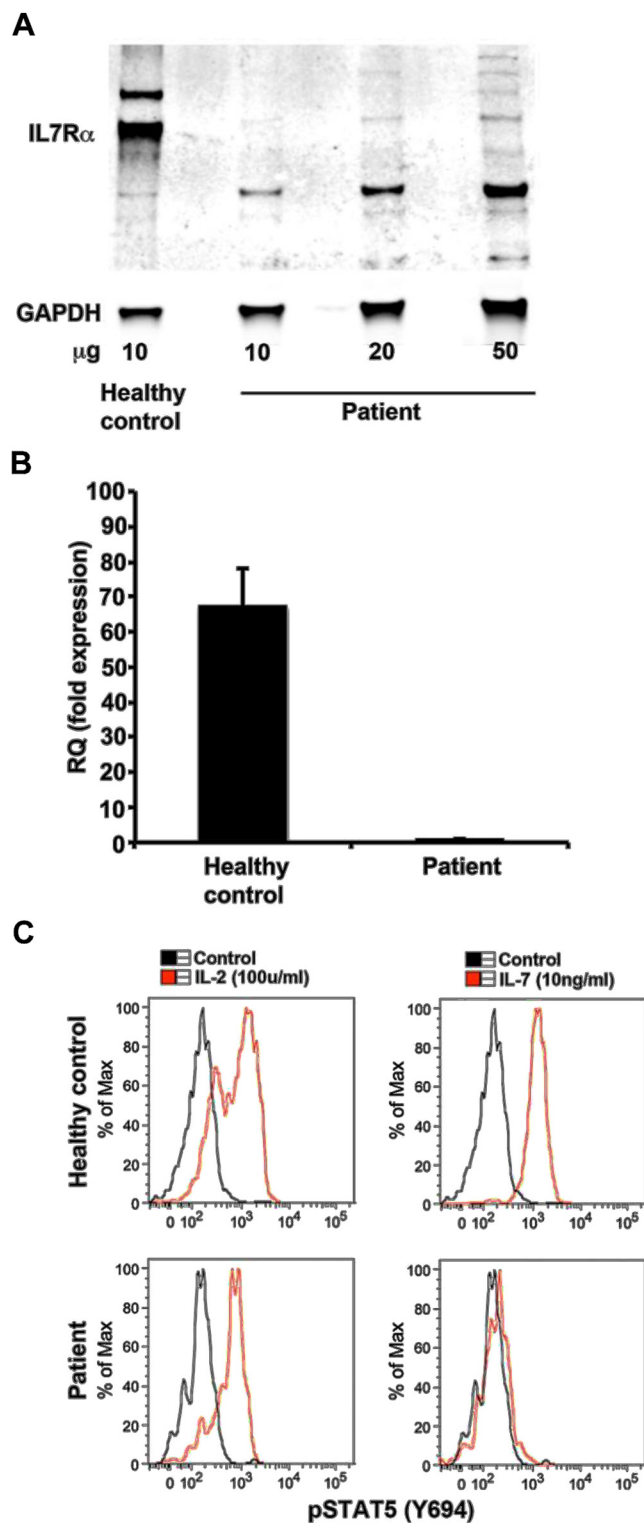


Figure 2. In vitro evaluation of patient deficient in interleukin-7 receptor α chain (IL-7R α). (A) Immunoblotting of cell lysates from a healthy donor and increasing amounts of lysate (10, 20, and 50 μ g) from the patient with an anti-IL-7R α antibody shows significantly decreased levels of IL-7R α . (B) Expression of IL-7R α mRNA in the patient and the healthy control. IL-7R α mRNA levels were normalized to levels of B2M. Mean $\pm$ SEM ($n = 5$) is expressed as fold difference with the patient level set arbitrarily to 1. (C) Significantly lower signal transducer and activator of transcription 5 phosphorylation (pSTAT5) in response to IL-7 (10 ng/mL; Cell Signaling Technology, Danvers, Massachusetts) was observed in CD4⁺ T cells from the patient compared with the healthy control. Response to interleukin-2 (IL-2; 100 U/mL) signaling in CD4⁺ T cells led to normal STAT5 phosphorylation in the patient and the healthy control. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; RQ, relative quantification.

effective in identifying patients with hypomorphic SCID² and likely would have identified the present patient at birth. Unfortunately, because of irreversible lung disease, this patient will require lung transplantation before definitive treatment with hematopoietic stem cell transplantation. This case points to the importance of early diagnosis of primary immunodeficiency with initiation of appropriate therapy to prevent long-term and potentially irreversible complications.

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