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LETTER TO THE EDITOR

Monoclonal IgG Kappa gammopathy previous to hematopoietic stem cell transplantation in an infant with severe combined immunodeficiency

KEYWORDS
Monoclonal IgG Kappa gammopathy;
Severe combined immunodeficiency (SCID);
Hematopoietic stem cell transplantation

1. Introduction

Severe combined immunodeficiency (SCID) comprises a group of genetic disorders characterized by impaired cellular and humoral immunity due to a block in T lymphocyte differentiation, variably associated to abnormal development of other lymphocyte lineage. The estimated incidence is 1 in 75,000–100,000 births. It is characterized by early onset infections that can be caused by low-virulence pathogens [1]. Spontaneous engraftment of maternal T-cells through transplacental transfer occurs in approximately 50% of the cases, and is mostly asymptomatic [1,2]. The most common curative therapy for all forms of SCID is hematopoietic stem cell transplantation (HSCT) [3]. Without immune reconstitution, SCID is inexorably fatal, mostly within the first year of life [4].

Benign monoclonal or polyclonal gammopathies and lymphoprolipherative diseases have been described in malignancies, auto-immune diseases, aplastic anemia and after HSCT in patients with primary or secondary immunodeficiencies. It is thought that they are secondary to monoclonal B-cell proliferation, as a consequence of an abnormal regulatory T-cell function [5–7].

In SCID patients, there is only one case report of monoclonal IgA gammopathy prior to HSCT in a T-B-SCID with maternal B-lymphocyte engraftment, and uncontrolled proliferation [4].

To our knowledge, this is the first published case of an infant with T-B+NK-SCID (X-linked) who developed a monoclonal IgGK gammopathy derived from self B-cells prior to HCT that completely resolved after HCT when full engraftment of donor T-cells occurred.

2. Case report

A 17-days-old boy was admitted to a 3rd level Hospital near Lisbon, due to an upper respiratory tract infection for which he completed 7 days of erythromycin. *Moraxella catharralis* was isolated in blood cultures. The differential leukocyte count demonstrated severe lymphopenia (700 cells/μL). The child was born at term by an uncomplicated, spontaneous vaginal delivery. The birth weight and head circumference were on 50th percentile and length on 25th percentile. The child was vaccinated at birth with bacilli Calmette Guérin and anti Hepatitis-B-Virus vaccines. He is the second child of non-consanguineous parents and has a healthy four years-old sister.

Three weeks later he was readmitted for fever and respiratory distress. His leukocyte count was: 17,900 leukocytes/μL, of which 2600 lymphocytes/μL. Prompt antibiotherapy with vancomycin and gentamicin was initiated. The chest X-ray showed bilateral interstitial fullness and absence of thymic shadow. The immunological evaluation led to a presumptive diagnosis of SCID (Table 1), later genetically characterized (hemizygous for G→A mutation at positioning 98 exon 5, leading to a Cys231Tyr amino acid substitution in the common cytokine gamma chain protein).

Chimerism studies were performed to assess for the presence of exogenous maternal lymphocytes. The results confirmed that 90% of T-cells were of maternal origin, and that all the B-cells were self (Table 1).

He started prophylaxis with cotrimoxazol, fluconazol, isoniazid, rifampicin and ethambutol, as well as regular infusions of intravenous human immunoglobulin (IVIG), while waiting for HSCT. Due to high levels of IgG, along with the appearance of a monoclonal peak in the protein electrophoresis, the presence of a B-cell clone was suspected. The immunofixation confirmed the presence of a monoclonal IgG Kappa fraction (Table 1) resulting from an expansion of the patient's B lymphocyte clone. Chimerism studies confirmed the absence of maternal B-cell engraftment. The viral load of EBV and other viruses remained negative. The child was submitted to HSCT from HLA-matched sibling donor without conditioning at the age of 4 months.

There was full engraftment of the infused cells, with complete immune reconstitution and no major complications post-HSCT. Two months after HSCT, laboratory workout revealed the disappearance of the previous gammopathy, with polyclonal B-cell population and normal serum immunoglobulins (Table 1).

3. Discussion

It is known that both primary and secondary immunodeficiencies predispose to lymphoprolipherative disorders, generally of B-cell origin [8].

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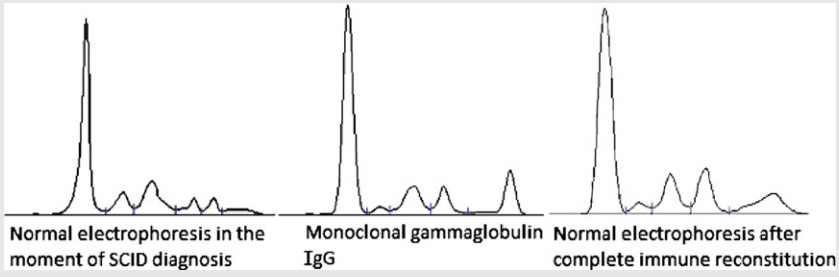
Table 1 Laboratory tests results.

Laboratory test	Prior to transplantation	2 months after transplantation	10 months after transplantation	Reference value
IgA (mg/dL)	<8	<25	18	0–75
IgG (mg/dL)	121	914	970	660–1050
IgM (mg/dL)	19	206	95	50–220
Immunofixation	Monoclonal IgG Kappa fraction		–	
Total Lymphocyte count	2500	7830	7450	3700–9000
CD3+(cells/μL)	102	6106	6513	2300–6500
CD3+CD4+(cells/μL)	88	763	2503	1500–5000
CD3+CD4+CD45RA (%)	1	11	72	64–92
CD3+CD8+(cells/μL)	0	5131	3664	500–1600
CD3+CD8+CD45RA (%)	0	6	11	53–88
CD16/56+(cells/μL)	35	544	491	100–1000
CD19+(cells/μL)	1750	1124	1384	600–1300
Lymphocyte proliferation				
Phytohemagglutinin (SI)	0	40	51	
PMA+ionomicin (SI)	0	52	63	
PPD (SI)	0	70	20	
Chimerism (locked in T lymphocytes)	90% maternal	100% donor	100% donor	
Viral load and PCR CMV, EBV, HSV, HIV1/2, HBV, HCV HHV6/7, VZV Enterovirus Rotavirus	All negative		All negative	
Electrophoretic patterns	Positive		Negative	



Monoclonal gammopathy [MG] in children is a rare disorder that is defined as a monoclonal B-cell proliferative disorder accompanied by an electrophoretically homogeneous immunoglobulin component (H-Ig) of a single isotype, allotype and idiotype in the serum [8].

Benign gammopathies have been reported in several conditions, such as hematological malignancies [8], autoimmune diseases [8], aplastic anemia [8], in bone marrow or renal transplant recipients [5], or in patients with primary immunodeficiencies, like SCID, auto-immune lymphoproliferative syndrome, Wiskott–Aldrich syndrome or ataxia–telangiectasia [4,9].

Follow-up analysis revealed that most of these MG were transient [8]. Most cases of monoclonal or oligoclonal gammopathies in infants with SCID occurred after HSCT, before T-cell immune reconstitution was complete [4,10]. Mechanisms leading to gammopathy are speculative. The hypothesis that diminution of T-cell mediated immune surveillance might temporarily allow B-cell proliferation is the most accepted and supported by animal experiments [4,8]. As a rule, control would later be regained, with subsequent stabilization or regression of the expanded clones [3]. Nevertheless, if control remained suppressed for a prolonged period of time, progression to lymphoma or myeloma might ensue [3,10]. Epstein–Barr virus may be responsible for the activation and evolution of B-cells into malignant monoclonal B-cell lymphomas [3]. Normal B-cell reconstitution post-HSCT appears to be a recapitulation of normal ontogeny and an impaired T-cell regulation may lead to an asynchronous, clonally dysregulated reconstitution [3,10]. Clones which recover faster than others can cause gammopathy, even though the overall system remains controlled. These clones are, most frequently, of donor origin [3]. To our knowledge, there is only one published case of MG in children with SCID previous to HSCT, and it was an IgA gammopathy, due to maternal B-cell engraftment and lack of T-cell surveillance [4].

In this report we describe a case of monoclonal gammopathy of Ig G Kappa producing self B-cells in a child with SCID previous to HSCT. There was no evidence of malignancy nor EBV or

other virus infections responsible for clonal activation. Chimerism analysis demonstrated that all the B-cells belonged to the patient. The persistence of this B-cell clone can be explained by the absence of normal T-cell function regulating the proliferation and activation of this B-cell clone, as described above. Restoration of T-cell function by HSCT enabled the host to suppress this aberrant B-cell proliferation, leading to spontaneous resolution, as described in other case reports [4].

Conflict of interest statement

The author(s) declare that there are no conflicts of interest.

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Inês Simão*
Ana Isabel Cordeiro
Primary Immunodeficiencies Unit, Department of Pediatrics, Hospital de Dona Estefânia, Centro Hospitalar de Lisboa Central, EPE Lisbon, Portugal
*Corresponding author.
E-mail address: isvs1@sapo.pt (I. Simão).

Luís Miguel Borrego
Catarina Martins
Primary Immunodeficiencies Unit, CEDOC, NOVA, Faculdade de Ciências Médicas, Immunnology, Lisbon, Portugal

Conceição Neves
João Farela Neves
Primary Immunodeficiencies Unit, Department of Pediatrics, Hospital de Dona Estefânia, Centro Hospitalar de Lisboa Central, EPE Lisbon, Portugal

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