Latin American Society for Immunodeficiencies

III LASID School & Registry Meeting

The Jeffrey Modell Centers for Immunodeficiencies in Latin America

Brazilian Group for Primary Immunodeficiencies

Date: May 14-17, 2014

Venue: The Royal Palm Plaza Hotel, Campinas-SP

(http://www.royalpalm.com.br/**)**

Brazil

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THE LASID SCHOOL

Welcome to the III LASID School & Registry Meeting !

The primary aim of this school is to promote education on the diagnosis, pathogenesis, and treatment of Primary Immunodeficiencies (PIDs), giving special attention to clinical cases and particularities in the Latin American Environment. Secondary aims are to attract and develop future scientists in academic medicine and to enhance the awareness of clinical immunology and its importance in scientific discoveries and clinical applications. As well the program should also stimulate future collaborations between young investigators in different medical centers and countries, and between young investigators and experienced physician/scientists in the field.

The LASID School is primarily directed at medical residents, post-graduate or clinical fellows-in-training, or junior faculty members. Each attendee presents a clinical case, which is followed by a group discussion of the appropriate management or diagnostic strategies. It provides an opportunity for fellows and junior faculty to gain important expertise before launching their own careers.

Considering the relevance of the LASID Registry in order to better know our patients, develop collaborations, evaluate regional characteristics and difficulties, a special focus has been included on the registry of cases.

The LASID Registry aims are:

1) Practical training for registering cases at the on-line data base of LASID Registry.
2) Provide tools for quality control of available data
3) Present the current statistics of the available data
4) Present the results of the ongoing clinical epidemiological investigations
5) Discuss proposals for future clinical epidemiological investigations on PIDs in Latin America.
6) Discuss the perspectives of molecular diagnosis of Primary Immunodeficiencies in Latin America
7) Create a Latin American Consortium for molecular diagnosis and bioinformatics of Primary Immunodeficiencies.

We stress that this is an international event congregating LASID, CIS, and ESID faculty members, Latin American physicians, and the Jeffrey Modell Centers of Latin America.

We wish you a pleasant stay in Campinas, SP-Brazil and a very productive course.

May, 2014

The Organizing Committee.

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Thais Sterza

Taj Ali Khan

Tatiane Pavan

Tatiana Lawrence

Walmir Cutrin Aragão Filho

PROGRAM

May 14

11:30 – 13:30 hs: Opening and lunch

13.30 hs: Issues with the Assessment of Specific Antibody Deficiency (SAD)" Prof. Lily Leiva

14.00 hs: Interpretation of pneumococcus vaccine response – Prof. Ricardo Sorensen

14:30 -15:30 hs: Moderator – Prof Jose Luis Franco

14:30 hs: 3 cases + discussion (*Cecilia Korol, Jesus Alvarez, Maria Gabriela de Belke)*

15:30 hs: Agammaglobulinemia: LASID database - Prof. Liliana Bezrodnik

16:00 – 16:30 hs: Moderator Prof Lilian Bezrodnik

16:00 hs: 2 cases + discussion (*Gabriel Velez, Myrian Esquivel)*

16.30: Coffee

17:00 -18:00 hs: Moderator – Prof Francisco Espinosa

17:00: 3 cases + discussion (*Ana Carolina Nápolis, Astrid Faure, Estefania Echeverri)*

18:00 – 19:00 hs: Moderator Prof Ricardo Sorensen

18.00: 3 cases + discussion (*Edgar M Guzman, Carlos Furiotti, Mariana G Pereira*)

19.30: Dinner

May 15

8.30: Pathogenesis of Common variable immunodeficiency – Prof. Klaus Warnatz

9.00 – 10:00 hs: Moderator - Prof Klaus Warnatz

9:00 hs : 3 cases + discussion *(Fabiane Pimenta, Syomara Angulo, Maria Esnaola Azcoiti)*

10.00: Severe combined immunodeficiencies and transplantation in Latin

America. Prof. Alejandra King

10.30: Coffee

11.00 – 12:00 hs: Moderator Prof Alejandra King

3 cases + discussion (*Anna Navarro, Ana Rozalem, Eunice Rocha)*

12.00: Bone marrow transplantation and Gene therapy in primary immunodeficiencies. Prof. Bobby Gaspar

12.30: Lunch

14.00: SCT: Brazil experience Prof. Juliana Folloni

14.10 – 14:40: Diseases of immune dysregulation – Prof. Troy Torgerson

15:10 – 15:40: Hemophagocytic Syndromes – Prof Jose Luis Franco

15.40 – 16:30: Overview of the LASID Registry program and proposals for collaborative work. Prof. Antonio Condino-Neto – Prof. Edith Gonzalez – Prof. Ricardo Sorensen

16.30: Coffee

17.00: Practical training for LASID registry Edith Gonzalez

19.30: dinner

May 16

8.30 – 9:00 hs: Subcutaneous immunoglobulin: how and when to use- Prof. Liliana Bezrodnik

9.00: - 10:00 hs Moderator Prof Antonio Condino Neto

3 cases + discussion *(Juan Ogando, Nuria Zurro, Rodolfo Vizcaino)*

10.00 – 10:30 hs: Clinical manifestations in adult patients with common variable immunodeficiency – Prof. Klaus Warnatz

10.30: Coffee

11.00 – 12:00 hs Moderator Prof Beatriz Costa Carvalho

3 cases + discussion (*Ana Fabro, Paula Palacio, Karol Burlamaqui)*

12.00: Laboratory diagnosis of primary immunodeficiency – Prof. Troy Torgerson

12.30: Lunch

14.00: Overview of bioinformatics and molecular diagnosis. Prof. João Carlos Setubal,

14:30: Molecular diagnosis and genetic studies of rare diseases in Brazil. Prof. Mayana Zatz and Prof. Maria Rita Passos

15.00: Overview on NGS and detection of genetic alterations. . Prof. Michal Okoniewsk

15.30: An approach to molecular analysis in next generation sequencing - Prof. Carolina Prando and Prof. Edgar Borges de Oliveira Junior

16.00: Gene regulation studies. Prof. Michal Okoniewsk

16.30: Coffee

17:00: Discussion on a Molecular Diagnosis Consortium - Prof. Ricardo Sorensen

19.30: Dinner

May 17

8.00: Mendelian susceptibility to mycobacterial infections: Prof. Francisco Espinosa

8.30: Conscious strategy to evaluate AIRE gene: Prof. Silvia Danielian

9:00 – 10:00 hs Moderator Prof Anete S Grumach

3 cases + discussion *(Blanca Olivier, Elsy Alcocer, Andrea Delgado)*

10.00: Autoinflammatory disorders: Prof. Alessandra Pontillo

10.30: Aim: to discuss current data and proposals to continue collaborative work on primary immunodeficiencies at LASID. Prof. Ricardo Sorensen

11.30: Closing

CLINICAL REPORTS

NAME: Korol Cecilia, Fortunatti, Daniela; Oleastro, Matias; Perez, Laura.
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INSTITUTION: Hospital J. P. Garrahan.

Clinical case:
Activation-induced cell death (AICD) is a key mechanism of T lymphocyte homeostasis in humans. The Fas/FasL and the cytolytic granule pathways have been described as essential actors of AICD. Autoimmune Lymphoproliferative Syndrome (ALPS) and Hemophagocytic Lymphohistiocytosis (HLH) are two forms of lymphoproliferative disorders in patients expressing defective Fas pathway or defective cytotoxic granule function respectively. It has been shown that in a setting of Fas deficiency, the cytolytic granule pathway may compensate the Fas defect (Mateo et al, Blood 2007; 110:4285-42922007)[a]. According with that, since ALPS T cells were found to overexpress lytic-granule content in the periphery, we decided to explore the extent of Fas expression and Fas- induced apoptosis of T cells genetically deficient in perforin in order to broaden the characterization of the cross-talking between both pathways.
Patient: 2-year-old girl with familial lymphohistiocytosis type-2 (FLH2) carrying 2 heterozygous *Perforin* mutations (H347Q and Q446P), leading to impaired cytotoxicity. She had not experienced accelerated phase and she was not under treatment at the moment of this study. Her brother, harvoring the same mutations, did experience the accelerated phase of the disease.
Methods: Fas expression on T-cell blasts and Fas induced apoptosis was carried out as in [a]
Results:

Day	Subset	Fas MIF	
		Patient	Control
4	CD3+ CD4+	253	373
	CD3+ CD8+	262	381
6	CD3+ CD4+	108	112
	CD3+ CD8+	109	136

FasexpressiononPHA/IL2activatedT-cellblasts:

Fas expression on T-cell blasts from the patient did not reach the values of the control cells at any activating time.

APO 1-3 (ng/ml)	Percentage of hypodiploid nuclei	
	Patient	Normal values (Mean +/- SEM)
25	71	57 +/- 15
2.5	6	7.1 +/- 3.2

Fasinducedapoptosis

Fas induced Apoptosis at 25 and at 2.5 ng APO1-3 (anti CD95)/ml was not significantly different to 30 normal controls.

Conclusion: The evaluated parameters in this patient do not show evidence of potential compensation in any extent from Fas pathway to perforin deficiency.

NAME: Jesús Armando Álvarez Álvarez, Isaura P. Sánchez, Camilo A. Pérez-Romero, Jose L. Franco- Restrepo, Claudia M. Trujillo-Vargas.
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INSTITUTION: Universidad de Antioquia

Clinical case: Familial Hemophagocytic Lymphohistiocytosis Type Ii (Fhl---Ii) Associated A Novel Mutation In Prf1 Gene.

Introduction: Familial hemophagocytic lymphohistiocytosis type II (FHL-II) is a recessive autosomal disorder characterized by uncontrolled activation of lymphocytes and macrophages infiltrating multiple organs, associated to fever, cytopenia, hepatosplenomegaly and hypertriglyceridemia. This disorder is caused by mutations in the PRF1 gene, which encodes perforin, a protein that participate in the granule-dependent cytotoxic function of NK and T cells. We report here two patients with FHL-II carrying a novel mutation in PRF1 gene in a heterozygous form associated with a common haplotype in the second allele.
Methods: Immunophenotyping of NK cells subpopulations and perforin detection was performed by flow cytometry. NK cells cytotoxicity against target cells (K562) was evaluated using the 5-(and-6)-carboxyfluorescein diacetate succinimidyl ester (CFSE)/Propidium Iodide mortality assay in peripheral blood mononuclear cells (PBMC). The entire coding region and exon/intron boundaries of exons 2 and 3 of PRF1 were amplified and sequenced from the genomic DNA. To predict the functional effect of the p.47G>V variant in the structure of the protein, we analyzed the mutated sequence using PolyPhen-2 and PROVEAN measuring the free energy change induced by the mutation (ΔΔG) upon folding. Finally, we used the Site Directed Mutator (SDM) software to calculate the stability score of the wild type and mutated proteins. Results: P1 and P2 were 4 years and 4 months old at the time of the diagnosis respectively, and had no family history of FHL. Both patients fulfilled the diagnostic criteria or FHL according to the Histiocyte Society. Evidences of hemophagocytosis were observed in P1 only after of the cerebrospinal fluid examination. Conversely, in bone marrow aspirates (BMA) from P1, occasional histiocytes in multiple microscopic fields were revealed only after the third sample analysis. No evidences of hemophagocytosis in BMA were observed in P2. P1 finally died due to sepsis secondary to peritonitis. Presently, P2 remains under the HLH 2004 protocol therapy and accomplishes the criteria for Hematopoietic Stem Cell Transplantation. Intracellular perforin expression was absent in the NK cells from both patients. They exhibited also null NK cell cytotoxic response even after IL-2 or IL-15 cell stimulation. Sequencing of exon 2 PRF1 gene revealed that both patients were compound heterozygous for a previously reported haplotype c.160C>T/272C>T (p.54R>C/91A>V) (paternally inherited) and the variant c.140G>T (p.47G>V) (maternal origin). We found that Glycine 47 is located in a protein domain of high relevance for function, called MACPF, implicated in the pore formation. It provides flexibility to the various loops and strands comprising the domain. On the contrary, Valine 47 might imply a disruption in the hydrophobicity of the domain and a reduction of the distance among the surrounding amino acids. Interestingly, the torsion seems not to be affected by this variation. POLYPHEN consider the p.47G>V as pathogenic and our results suggest reduction in the energy profile of the protein

thus increasing its stability.
Conclusion: We report here, the new PRF1 variant p.47G>V associated with two cases of FHL that confers, together with the haplotype p.54R>C/91A>V, perforin deficiency and absent NK cell cytotoxicity. The presence of hemophagocytosis was only demonstrated after the cerebrospinal fluid examination in one of the cases. In Silico analysis predicted the pathogenic role of the new variant suggesting an increase in the protein stability affecting function.

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Clinical case

A NK expansion in an Argentinean patient with chronic EBV infection: a primary immunodeficient patient?

The patient is a 7 year old Argentinean boy, with neither consanguineous parents, nor family history of primary immunodeficiencies, presenting with chronic EBV infection since 5 years of age. His clinical history included; recurrent bronchospasms, pneumonia at two years of age, persistent generalized lymphadenopathy and hepatosplenomegaly, accompanied by intermittent fevers starting at 3,2 years of age. Abdominal ultrasound showed homogeneous splenomegaly. Serology tests were negative for HIV, Parvovirus, Chagas, Bartonella, HAV, HBV, CMV IgM and EBV IgM; while positive for IgG to CMV (1/400) and IgG to EBV (1/200). The EBV viral load detected was 40000 copynumber/ml and the early antigen 1/50, so the patient was diagnosed with infectious mononucleosis. Laboratory evaluation at 5 years of age demonstrated an elevation of the hepatic enzymes and absence of autoantibodies. A bone marrow aspiration and liver biopsy revealed detectable EBV by PCR without malignancy signs. Initial immunology tests were performed to rule out X-linked lymphoproliferative disease: NKT cells were present but in a low number (0.02%) and SAP expression by flow cytometry was comparable to that of the normal control. In addition, no mutations were detected in SH2D1A and BIRC4 genes. Flow cytometry revealed NK-cell lymphocytosis (38%) with NK expressing three different populations: CD56bright/CD16 negative (1%), CD56dim/CD16 positive (37%) and also a CD56 negative/CD16 positive subpopulation. In order to characterize phenotypically and functionally the expansion of NK cells we completed the laboratory studies and observed high HLA-DR expression on NK cells and diminished perforin in terms both of percentage (63% vs 96% in a normal control) and mean fluorescence intensity (MFI: 31 versus 125). In addition, CD57 was negative and CD94 was highly expressed 100%, MFI: 454 than a normal control (72% MFI: 121). Furthermore, an abnormal expression of NK receptors like KIRP70 (0%), CD158b (1%) and CD159 that was highly expressed (95%) compared with normal controls. In the CD107a NK functional assay, there was no response to the K562 cell line but they responded normally after IL2 addition. No mutation in the perforin gene was found in this patient.

This patient with a chronic EBV infection and this atypical NK profile in which a definitive diagnosis was not reached leads to some questions: first, is this phenotype a consequence of the EBV infection or is the characteristic of an immunodeficiency condition? On the other hand, could this NK expansion be the manifestation of Large granular lymphocyte lymphoproliferation?

NAME: Gabriel Vélez[1], Luis Miguel Sosa[2], Estefanía Vásquez[1], Lucía Erazo[1], Diego Góngora[1], Julio Cesar Orrego[1], José Luis Franco[1].
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X-linked agammaglobulinemia in a patient with *Aspergillus fumigatus* infections: Case report.

ntroduction: Primary immunodeficiencies (PID) affecting antibody production leading to high susceptibility to infection by extracellular microorganisms. X-linked agammaglobulinemia (X-LA) is characterized by the decrease in all immunoglobulins and circulating B lymphocytes. Affected patients exhibit recurrent pyogenic infections such as pneumonia, otitis, sinusitis, pyoderma and conjunctivitis caused by capsulated bacteria such as *S. pneumoniae, S. pyogenes, H. influenzae and S. aureus*. Fungal infections are rare. This IDP results from mutations in the gene encoding the BTK enzyme located on the X chromosome (Xq21.3) that have an essential role in the maturation of B lymphocytes. The case presented is about a child with X- LA with *Aspergillus fumigatus* infections. Methods: Data were collected from clinical and laboratory data. Laboratory tests include peripheral blood tests, serum immunoglobulins measurement by nephelometry and subpopulations of T, B and NK cells by flow cytometry. Molecular diagnosis of X-LA was done by genomic DNA sequencing of BTK (OMIM # 300300). Results: Male patient, 4 years old. Non consanguineous parents. Multiple infections including infectious gastroenteritis whit unknown etiology at 6 months, at 12 months he was hospitalized for acute diarrheal disease and sepsis with bacterial culture of Salmonella spp. At the age of 15 and 18 months he presented suppurative otitis. At 16 and 19 months presented pneumonia. At 21 months of age, he required prolonged hospitalization and 6 days of ICU by sepsis accompanied by abscesses. *A. fumigatus and P. aeruginosa, E. faecium* was isolated in peritoneal fluid and urine blastoconidias and resolved with antibiotic treatment. He was referred to the PID Group at 26 months of age for diagnosis of recurrent infections and hypogammaglobulinemia with immunoglobulins IgA values 5.2 mg/dL (35-333 mg/dl), IgG 111.8 mg / dL (749 -2682 mg/dl) and IgM 53.1 mg/dL (36-457 mg/dl) , the patient was already being treated with 333 mg/kg Gammaglobulin IV every 3 weeks. The peripheral blood tests revealed anemia (Hb9 g/dL , hematocrit 30.7%) leukopenia (total WBC : 3400/uL , 1400 neutrophils /uL and lymphocytes : 1200/uL) and platelets 347000/uL (with a previous result at 20 months: 996000/uL). The results of total leukocyte subpopulations revealed 5115 cells/uL (6800-10000 cells/uL) with a percentage of CD3+ T lymphocytes from 90.5% (VR : 43-76 %) , CD19 Lymphocytes 0.67% (VR : 14-44 %) and NK lymphocytes 6.27 % (VR : 4-23 %). Mutational analysis of the BTK gene mutation was detected nonsense c. 1573C > T that has been associated with X -LA, in addition a silent mutation was not linked to X -LA (c. 1899C > T) was evidenced.
Conclusion: We report the case of a child diagnosed with X-LA and molecular characterization by mutation c. 1573C> T in BTK. In addition to bacterial infections, the child had *Aspergillus fumigatus* infection that is uncommon in these patients. After gammaglobulin replacement therapy the patient has shown improvement IgG immunoglobulins (774 mg / dL) and IgA (<15 mg / dL). Finally a silent mutation in the BTK gene has not yet been associated with X-LA was identified.

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Recurrent meningitis in a patient with X-linked agammaglobulinemia.

S is a 6-year-old boy. He was born of non-consanguineous marriage, full term, and completely immunized. He has history of recurrent otitis since 3-months-old, and at 9-months-old he presented with sepsis by *Pseudomonas aeruginosa* with pneumonia, persistent effusive otitis and right mastoiditis. He had right peripheral facial nerve palsy as a sequelae. He has not relevant family background. After that episode, he was referred to our center and XLA was diagnosed (mutation in exon 6 of BTK) and he started with intravenous IG (IVIG). No bacterial infections since then. In April 2013 he started with subcutaneous IG (SCIG) with a dose of 160 mg/k/wk. Serum IgG levels were always higher than 800 mg/dl. In September 2013 he was admitted to hospital with fever, headache and abdominal pain. Blood and urine cultures were negative. He received 7 days of parenteral antibiotics. In October 11th he presented again an episode of fever with severe headache and vomits. The basal IgG level was 984 mg/dl. The CSF was abnormal (230 cells 52% MN glu 34 mg/dl and proteins 164 mg/dl) and a positive latex test for N. meningitides was obtained. The blood and CSF bacterial and fungal cultures and viral PCRs were all negative. Normal cerebral CT scan. Meningitis was diagnosed. He received 8 days of IV cefotaxime and 1g/k of intravenous IG. He restarted with fever and headache 15 days later. At this time (Nov 2nd) the CSF had 705 cells 51% MN glu 329 mg/dl and proteins 160 mg/dl and **enterovirus PCR was positive** but the virus did not grow in cultures. CSF bacterial and fungal cultures and other viral PCRs were all negative. Normal cerebral CT and MR. Enteroviral recurrent meningitis was diagnosed and he started with IVIG 1gr/kg/wk. The symptoms disappeared rapidly and he has an improved CSF in Nov 13th (47 cells 90% MN). On Nov 29th similar symptoms restarted and was re-admitted to hospital. On neurological examination, he was conscious, oriented but presented with a mild paresis on right arm and leg The CSF was worse again (435 cells 54% MN glu 29mg/dl and proteins 122mg/dl) but all cultures and viral PCRs were negative. Normal cerebral TC and MR. IVIG was started to be administered 1g/k every 48hs (reaching serum IgG levels of 5000 mg/dl) and finally the Dec 18th started with daily intrathecal IG (ITIG) 300mg/day and daily IVIG 500 mg/k/day. The CSF started to improve and he had not clinical symptoms since the first day of hospitalization. In Dec 28th it had 2 cells glu 42mg/dl and proteins 139mg/dl so the intrathecal IG treatment was spaced to 300 mg every 48 hs. On Jan 8th he presented again an episode of fever and intense headache and the CSF had 41 cells 88% MN glu 26mg/dl and proteins 71mg/dl. The intrathecal IG was started again to be administered 300mg daily, the symptoms and CFS improved. Currently, our plan is to continue this treatment while we are trying to import *Pocapavir*, an antiviral agent against enteroviruses. To date Feb 22nd, S is still hospitalized. His neurological status is stable, he has not repeated symptoms an CFS has improved (2 cells, glu 44mg/dl, proteins 84mg/dl) but he has presented with neutropenia that required stem cell stimulators and a new episode of effusive otitis that responded to

antibiotics.

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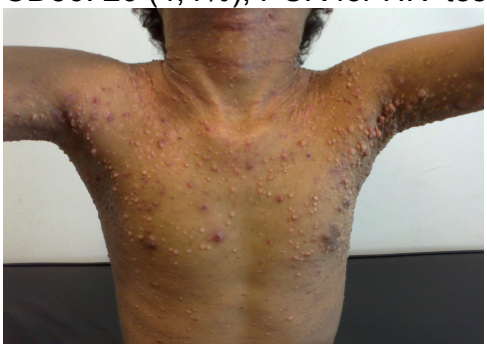
Clinical Case:

R. I. M., 10 year-old boy, referred with recurrent otitis media, sinusitis, and multiple episodes of pneumonia, palmo-plantar warts, and severe contagious molusco. He also had history of severe atopic dermatitis, asthma and food allergies. On evaluation he was noted to have persistent eosinophilia, lymphopenia, normal IgG levels, decreased CD4 and CD8 T cells. He started the use of cotrimazol daily and intravenous immunoglobulin (500 mg/kg), monthly. At age 11 year, 2 weeks after a viral disease, he developed weakness involving the arms, legs, and truncal muscles, which had a rapid progression (less than 24 hs). He performed an investigation with a normal magnetic resonance and the study of nerve conduction showed specific findings consistent with demyelination characteristic of classical Guilain-Barre Syndrome. He was treated with gammaglobulin (2g/kg) and evolved with resolution of the neurologic symptoms. Nowadays, he is receiving immunoglobulins monthly and cotrimazole daily.

Immunologic evaluation

IgG: 2072 mg/dL; IgA: 359 mg/dL; IgM:137 mg/dL; IgE:17.730 UI/ml
Specific IgG against tetanus: negative; Specific IgG against varicella: negative
IgG titers against specific pneumococcal serotypes: 4, 6B, 9V, 18C : undetectable; 14: 0,5; 19F:0,6; 23F:0,9
CD3: 512/mm3 (44%); CD4: 456/mm3 (39,2%); CD8: 31 (2,7%); CD19: 493 (42,4%); CD56: 20 (4,4%); PCR for HIV testing: negative; DHR: mild reduced activity



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Clinical case

The patient is a 3 years old girl, born in Argentina to non consanguineous parents.
One sister died at birth because of multiple malformations without diagnosis.
One brother presents recurrent wheezing. Incomplete vaccination.
She suffered recurrent wheezing and recurrent otitis during first year of life. At one year old she was hospitalized with gastroenteritis and severe dehydration. Anemia was diagnosed. She received oral treatment with iron during one year without response leading to the hematologist evaluation. At physical examination she had severe splenomegaly, bilateral cervical lymphadenopathy and urticarial rash. Laboratory´s results showed anemia and eosinophilia. A lymph node biopsy was performed with Lymphoblastic Lymphoma diagnosis.
Previously at the beginning of chemotherapy she was referred to our Immunology Unit.
With the suspicion of Lymphoproliferative Autoimmune Syndrome the following lab test were performed: IgG 606mg/dl IgA 46 IgM 36 IgE 5 (hypogammaglobulinemia), poor response to vaccines; CD3 57% CD4 15% CD8 28% NK 3% CD20 29%;
α/β DN 12% vitB12 >1500 sFasL >500pg/ml; Fas Expresion in CMNT diminished mother and girl; Apoptosis via Fas: patient 63%, mother 53%
Mutation in FAS gene confirmed the diagnosis: Exon 3 FAS p Cys 107 Tyr. Heterozygous.
Hematologist repeated lymph node biopsy showing: paracortical diffuse expansion, follicular hyperplasia, sinusoidal histiocytosis. Immunotypification: LT TCR α/β DN 27%
Short course of oral steroids was enough to improve anemia and temporary diminished splenomegaly and lymphadenopathies. She was completely vaccinated and reevaluated showing profound hypogammaglobulinemia with poor response to vaccines: IgG 354 IgA 26 IgM 8 IgE:1 IgG measles , IgG mumps, IgG hepatitis A and B: negatives; tetanus toxoid Antibodies: 0.2
CD 27- D+ 97%; CD27+ D+ 1%; CD27+ D- 2%
Gammaglobulin therapy was indicated at 500mg/kg/dose every month and patient is doing well without infections. Splenomegaly and lymphadenopathy remain without changes.

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Clinical case

Recurrent sinopulmonaryinfections,exocrine pancreatic insufficiency, neutropenia and skeletal defects in a patient with Schwachman-Diamond Syndrome (SDS)

Estefanía Vásquez E[1], Julio César Orrego[1], Jorge Rivera[2], José Luis Franco[1].1Group of PID and Jeffrey Modell Diagnostic and Research Center, University of Antioquia, 2Dept of Gastroenterology, Hospital Pablo Tobón Uribe, Medellín (Colombia)

Introduction. Schwachman-Diamond Syndrome (SDS) (OMIM 260400) is an autosomal recessive disorder characterized by bone marrow failure, skeletal abnormalities and pancreatic exocrine insufficiency. Mutations in the SBDS gene are present in most patients. Neutropenia is the most common hematologic abnormality conferring susceptibility to recurrent bacterial and fungal infections, mainly of the respiratory tract; leukemia is the main cause of death. Primary skeletal defects are related to abnormal development of the growth plates in the metaphysis. SDS is a diagnosis of exclusion along with cystic fibrosis (CF) since both disorders involve exocrine pancreatic ducts defects, however, SDS patients present with normal iontophoresis. Supportive care for SDS patients includes enzyme replacement as well as and antimicrobial therapy. The only curative therapy for the bone marrow failure is hematopoietic cell transplantation (HSCT).
Methods. Data were collected from clinical, radiologic and laboratory records. Other studies included peripheral blood tests(PBT), sweat tests, serum immunoglobulins, rheumatological, liver function tests, GI endoscopy, liver and bone marrow biopsies, pelvis and knees X rays and lung HR-CT scans. Genetic analysis included karyotype, panel for mutations in the CF gene and mutational analysis of the SBDS gene. Results. The patient was a female child born from non-consanguineous parents who developed recurrent sinopulmonary infections, intermittent neutropenia, hepatosplenomegaly, failure to thrive and chronic malabsorption syndrome since the age of three months. She was referred to our outpatient clinic at 2.9 years of age due to hypogammaglobulinemia and chronic lung disease. At physical examination we found underweight 12kg (weight for age between 0 y -2), unsteady gait, lower limb external rotation and joint hyperelasticity. Repeated blood tests showed intermittent neutropenia and increased transaminases. Rheumatological studies and as well as sweat tests were negative; however, serum IgG was normal, IgA<3.7mg/dl; 2.7 years (44-313mg/dl) and IgM 39mg/dl; 2.7 years (64-328mg/dl) were low. The GI endoscopy and biopsies showed chronic inflammation in the gastric mucosa. Lung CT scans showed normal thymus and lungs with attenuation of the fat absorption coefficient in the pancreas suggestive of cystic fibrosis. Pelvis and knee X- rays showed decreased density of the femur and tibia affecting the metaphyses along with irregularities and sclerosis. Liver biopsy showed chronic hepatitis with scattered plasma cells while bone marrow biopsy showed 70% cellularity, with increased hypergranular promyelocytes and hemophagocytosis in histiocytes. Cultures of tracheal aspirate from a pneumonia episode that triggered sepsis were positive to *S. pneumoniae* and *Haemophilus spp*. Genetic analysis ruled out a

chromosomopathy and mutations related with cystic fibrosis. Finally, the heterozygous mutations c.183_184 TA> CT and c. 258+2 T>C were demonstrated in exon 2 and intron 2 of the SBDS gene, respectively. Conclusion: Diagnosis of SDS should be considered in patients suspected of suffering from CF and who exhibit unsteady gait, pancreatic exocrine insufficiency, neutropenia and bone marrow failure, but that present with normal iontophoresis and negative CF genetic panel.

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Clinical case

Ocular complications in Wiskott Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is a primary immunodeficiency included within the well- defined syndromes, X-linked autosomal recessive inheritance, due to a mutation in the WASP gene, which encodes a key protein in the signaling pathway in cytoskeleton organization actin, characterized by eczema, thrombocytopenic purpura, infections by opportunistic pathogens and bleeding. These patients present various ophtalmologic manifestations that can affect the ocular surface or can be intraocular and are the direct cause of a hemorrhagic diathesis or increased susceptibility to infection, including conjunctivitis, blepharitis, corneal ulcers, episcleritis, necrotizing ulcerative keratitis Eruptions of the eyelids and eyelid eczema, acute retinal necrosis related to varicella zoster virus. Although these patients present with cytomegalovirus infections, there aren't any case associated with CMV ocular infection. We report 3 cases of eye disease including 2 cytomegalovirus and herpes virus in WAS.

CASE 1: 2 year-old male patient who started at 20 days of age with upper respiratory tract infections and non-suppurative otitis. Intermittently, he had stools with fresh blood that spontaneously remitted. At 7 months presented a dermatosis characterized by xerosis, and thrombocytopenia. WAS diagnosed by flow cytometric diagnosis with absence of WASP expression on CD3+ cells. A MMUD (umbilical cord blood) transplant was performed that got complicated with disseminated herpes simplex infection on day +3 and +7. Eye herpes infection was corroborated by PCR, characterized by corneal debridement in the left eye and right eye small ulcer in addition to infection with Eipsten Barr virus in day +23 corroborated by positive viral load of 1,000,000 copies which conditioned graft failure.

CASE 2: 2 years-old male with a history of a late brother at 9 months who was diagnosed with Wiskott Aldrich. He presented gastrointestinal bleeding at the age of 14 months, a month after he developed chickenpox. Wiskott Aldrich syndrome was diagnosed based on the history of a sibling with the same pathology and clinical manifestations. CMV infection was confirmed by PCR. Hematopoietic progenitor stem cell transplantation was performed at the age of 2 years 9 months old from maternal haploidentical donor. On day +14 presented low gastrointestinal bleeding diagnosed as ulcerative colitis, gastritis, colitis and thrombocytopenia with conjunctival hemorrhage. He was evaluated by ophthalmology who diagnosed cytomegalovirus retinopathy level I.

CASE 3: 5 years-old male presented with recurrent epistaxis difficult to control. He was referred to our hospital at the age of 9 months. Wiskott Aldrich syndrome was confirmed by gen sequencing. A HSCT was performed at the age of 2 years from a MMUD (cord blood), but it failed to engraft. 3 years later the patient presented decreased visual acuity, left eye deviation, with left eye vitreous hemorrhage, pale optic nerve and retinal whitish upper and lower.

CONCLUSION: These are the first two patiens reported with ocular CMV complications associated with WAS. Clinicians should be aware of these complications to star appropriate treatment.

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Clinical case

Patient male, 6 month of age. Mother controlled during pregnancy. All ITS by serology negative.
Maternal history: 11 pregnancies, 2 misbirth, 9 alive.
Pathologic History: 4 hospitalizations for Respiratory and Gastrointestinal symptoms at another hospital. Derived at Children Hospital of Córdoba City with presumptive diagnosis of Cystic Fibrosis. Lab: WBC: 12.740 (N:78% [9937.2], L:15% [1911], M:7% [891.8], Plat 1.066.000/mm3. Sweat test: Negative. Low cytometry: Total Lymphocytes: 900/mm3; CD3: 0.8% [7], CD4: 0.2% [2], CD8: 0.4% [4], Ratio CD4/CD8: 0.5, CD19: 86.4% [778]
Diagnosis: Severe Combined Imunodeficiency.
Treatment: Ceftriaxone and Klarithromicin, Prophylaxis with TMP-SMX. EV Gammagloblulin. Prophylaxis with Isoniazide, Rifampicin and Pyrazinamide for gastric wash positive for TBC. Prophylaxis with Fluconazol for *Candida albicans*.
Molecular assay informed: SCID by IL-2 Receptor Deficiency.
A sample for Histocompatibility was taked from patient and his brothers and sisters. 2 are compatible for Bone Marrow Transplantation. It was performed and well tolerated by patient. No conditioning regimen and prophylaxis was performed to avoid GvHD.

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Clinical case

MPN, male, was born full-term at 39 weeks, delivered by Cesarean section with a birth weight of 3.6 kg. Newborn screening test was normal (hemoglobin disorders, PKU, congenital hypothyroidism, cystic fibrosis, congenital adrenal hyperplasia and galactosemia). At 15 days of life, receiving cow's milk infant formula associated with breast feeding , he presented with mild diarrhea, associated with vomiting and failure to thrive. Initially, he was treated for gastroesophageal reflux disease and cow´s milk protein allergy. Ranitidine and omeprazole were initiated, the mother was under cow´s milk exclusion diet associated with extensively hydrolyzed formula.

At about 1 month of age he started to present with eczema and severe diarrhea. Extensively hydrolyzed formula was switched to amino acid-based formulas, with no clinical response. At this time, he was hospitalized with severe dehydration and metabolic acidosis with the need of intensive care. Parenteral nutrition and formulas for inborn errors of metabolism were tried with no clinical response. Screening for inborn errors of metabolism was negative.

The eczema didn't respond to oral steroids and it got worse progressively. The skin acquired an aspect of icthyosis and antibiotics were needed to treat secondary infections. Skin biopsy showed a mononuclear inflammatory infiltrate with lymphocytes and histiocytes around the vessels of the superficial plexus permeated by eosinophils.

Imaging studies performed during the investigation, including chest X-ray, echocardiogram and abdominal ultrasound were all normal. Complete blood counts showed lymphopenia and eosinophilia. No abnormalities were found in red blood cells or platelets. All immunoglobulin levels were low. Immunophenotyping showed a very low naïve T CD4+ (0.7%) and T CD8+ (31%) lymphocyte counts as well as low B lymphocyte counts (0.7%).

The patient was started on IVIG at about 8 months of age, along with cotrimazole and isoniazid (he had received BCG vaccine with no adverse reactions). Cephalexin was needed to treat skin secondary infections. Then he started to gain weight progressively, the diarrhea resolved and he had no more hospitalizations.

Currently he is 3 years old, continues to have eczema and he´s only receiving IVIG. Now he presents a new clinical feature: high TSH with a normal T4.

FOXP3 mutation wasn´t found. A heterozygous H249R mutation was identified in RAG1, but this mutation isn´t predicted to be pathogenic.

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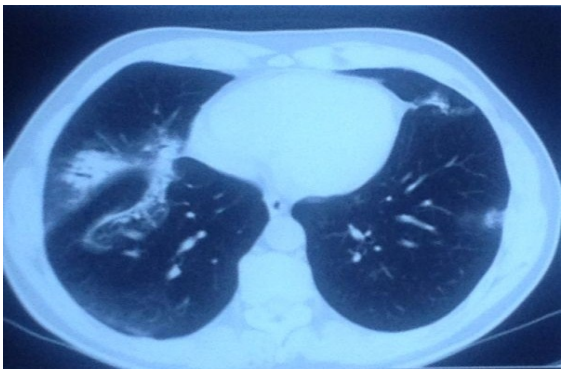
Clinical report

SJBG, 60, male, married, born in Santo André, SP, with two episodes of pneumonia, one just after the other. The first episode was treated with clarithromycin and prednisone for ten days. One month later, he felt asthenia and dyspnea and opacification of the basal lobe of the right lung was identified. *P jiroveci* was isolated from culture of bronchoalveolar lavage (BAL). He had received the first cycle of therapy with sulfamethoxazole-trimethoprim (SMZ-TMP) and prednisone for 14 days. He did not improve and a second round with smz-tmp, prednisone and moxifloxacin had been introduced for 7 days. Physical examination was normal, tonsils were absent due to tonsillectomy. Normal blood pressure. Absence of cervical lymphonodes, no hepatosplenomegaly and no lymphadenopathy. He had no recurrent infections previously. Left knee meniscus was removed by arthroscopy at age 56; he has bilateral osteoarthritis of femoral head. Family history: No consanguinity; brother died of Amyotrophic Lateral Sclerosis, no report of immunodeficiency in the family.

CT: No signs of thromboembolism, there is no evidence of pleural effusion, multiple consolidations in the upper, middle and lower lobes of the right lung with inflammatory aspect.

Immunological evaluation: IgA= 86 mg/dl; IgM= 68 mg/dl; IgG= 546 mg/dl; IgE=21 UI/dl; Isoagglutinins (anti-B)=¼; HIV=Negative; Hepatitis B=Negative; CMV=IgG positive IgM negative; EBV=IgG positive, IgM negative; Rubella=IgG positive IgM negative; FAN=Negative; Total lymphocytes: 620-1270 cells/mm^3; CD19+=69 (2,29%); CD3+=2200 (44%); CD4+=1714 (34,28%); CD8+=847 (16,94%); CD16+\56+=264 (18,46%)

He was referred to the specialized outpatient group of Immunology and hypogammaglobulinemia was identified. Tmp-smz was introduced for prophylaxis as well as intravenous gamma globulin monthly (500mg/kg). It's been one year and he is asymptomatic.



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Clinical case

LRBA mutation in a girl with interstitial lung disease and common variable immunodeficiency.

Common Variable Immunodeficiency (CVID) comprises an heterogeneous group of conditions characterized by severe infections often associated with autoimmunity or immune dysregulation. To date, only 10% of cases have been associated with genetic defects (*ICOS, CD19, CD21, CD81, TACI* and *LRBA*). Mutations in *LRBA* (LPS-responsive and beige-like anchor) were recently described, and patients are associated with impaired antibody production, infections, autoimmunity and immune dysregulation. The underlying mechanisms have yet to be explored in detail. We present an 11-year old female from consanguineous parents diagnosed with common variable immunodeficiency, with mutation in LRBA who presented interstitial lung disease

CASE REPORT:Patient was diagnosed at 7 years of life with complicated infections of the lower respiratory tract, long recurrent hospitalizations, with low serum immunoglobulins IgG 42.7 mg/dl, IgM 11.4 mg/dl , IgA 6.06 mg/dl , IgE 17.1 UI /ml, and low levels of B cells (CD19, 3.17%, 70 mm^3). CVID was diagnosed and treatment was started with intravenous gammaglobulin every 21 days, with poor response. Bronchoscopy was performed and tracheobronchitis was found, cytology for bronchial lavage presented inflammatory cells. Lung plethysmography reported restrictive lung pattern. High resolution CT scan showed chronic lung damage, with fibrosis of the lung, bronchiectasis, compatible with interstitial pneumopathy. Bronchial cultures were negative for bacteria and fungus. A mutation in the *LRBA*, consisting of 15 nucleotides insertion in mRNA sequence was found. Additionally, there was a reduction in total memory B cells with an increase of $CD21^{low}$ cells. She received treatment with steroids and rituximab, with clinical improvement. She is on steroids (prednisone) and immunosuppressive (hydroxychloroquine, mofetil mycophenolate), and regular IVIG every 21 days with fungal and bacterial prophylaxis with a favorable outcome.

Discussion: *LRBA* encodes a large cytoplasmic protein that is expressed in many diverse cell types, including lymphoid and myeloid lineage immune cells. Although the protein function remains broadly unknown, data from limited studies of LRBA and homologous proteins suggest that LRBA may play a role in vesicular transport. B-cells from *LRBA*-deficient patients demonstrate defective autophagy and apoptosis that affect B cell survival. While these findings start to explain defects of antibody production seen in patients, however there is much work to be done to investigate other aspects of the clinical phenotype and so far, nothing is known about the importance of LRBA for the function of other immune cell types. To our knowledge, this is the first LRBA defect patient with interstitial lung disease described to date.

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Clinical case

Full term newborn, male, from Paraguay without relevant perinatal history. Third child of non-consanguineous parents. His brother died at 17 years old with a medical record of unstudied hypogammaglobulinemia, brain abscesses and chronic diarrhea and hepatosplenomegaly since birth. His sister and parents are healthy. Personal History: He presented chronic diarrhea since birth with dysentery. At 18 months, he was diagnosed with hypothyroidism and he started levothyroxine treatment. He presents failure to thrive with decreased bone age and shows a saddle nose, macrocephaly, brachycephalic, hypertelorism and a wide flattened forehead. He exhibited hipogammaglobulinemia and impaired response to protein and polysaccharide antigens, so that, at 4 y.o. he started treatment with IVIG. In September 2011 he presented prolonged fever, hepatosplenomegaly and abdominal pain. Abdominal ultrasound revealed anechoic images on the spleen. Due to fungal suspicion he was treated with amphotericin. In January 2012, he was admitted at Ricardo Gutierrez Children's Hospital in Argentina. HIV, EBV and CMV polymerase chain reaction were negative. A complete immunological evaluation was performed. T cells compartment showed an activation phenotype with increased CD4+CD45RO+ population and impaired proliferative response to PHA, iono + PMA, SEB, CONA and PWM. Pre and post-switched memory B cells were diminished with an augmentation of transitional B subpopulation. NK cells function assays and DHR test were normal. CD4+CD25hiCD127low Treg cells were severely diminished. He presented a normal CD25 and CD40L expression and a low production of IL-10 and IL-8 after stimulation with different agonists compared with healthy donors. Autoantibodies were negative. Stool cultures were performed because of his persistent diarrhea with isolation of *Entamoeba histolytica* and *Candida albicans*. He completed treatment with Metronidazole and fluconazole with partial improvement. He presented a perianal lesion, the biopsy showed psoriasiform dermatitis without germ isolation. The colonoscopy revealed multiple ulcers covered with fibrin, pseudopolyps and decreased colonic caliber. No isolation of germs. He began treatment with mesalazine 2 g/day and prednisone 1 mg/kg/day with good response. When the corticoid dose was decreased, diarrhea appeared again. A new colonoscopy was performed, reveling ulcers covered with fibrin with greater compromise of sigmoid colon. Currently he is receiving prednisone and Sirolimus and he started treatment with ganciclovir after positive CMV PCR in intestinal biopsy with partial improvement. His family history and his personal background lead us to think in an X-linked immunodeficiency, so that; we performed molecular studies for NEMO, CD40L and IKBα with negative results. γ chain studies remain to be done Thinking in an atypical combined immunodeficiency RAG1, RAG2 and ARTEMIS where evaluated, also with negative results. Under suspicion of combined immunodeficiency with immune deregulation, he is currently in bone marrow transplantation plan.

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Clinical case

Autoimmune Thrombocytopenia In A T-B-NK+SCID Patient

Case Report: ASM, male, DOB 01/30/13, at age 2mo started to develop a severe erythematous rash over his entire body, along with ulcer formation/exudation at the BCG vaccination site. He also started to have recurrent URIs. At 6mo he was referred to our hospital in severe respiratory distress. Chest X-ray showed an infiltrate in the left lower lobe and absent thymus shadow. Nasal swab was Rhinovirus +. ICU care was needed. Immunological work-up showed normal ALC and T CD3+ lymphocyte counts, (3,220cels/mm3) and low number of naïve T cells: CD4+= 2,289cels/mm3; naive CD4+ (CD45+RA/CCR7+)=5.7cels/mm3; CD8+ 257cels/mm3; naïve CD8+ (CD45+RA/CCR7+) 0.3cels/mm3. B CD19+ lymphocyte count was extremely low (22.7cels/mm3/ 0.4%). NK count was normal (1,861 cels/mm3). IgG levels (76mg/dL) were low but IgM levels were very high (1,791mg/dL). TREC was 0/ul. Diagnosis of T-B-NK+ SCID was made. At 8mo, a month after recovery, he developed disseminated petechiae/purpura, but no bleeding. Platelet counts reached a minimum of 3,000/mm3. CMV antigenemia was negative. Anti-platelet antibodies were present (reactivity to glycoprotein IIb/IIIa, antigenic specificity HPA-3b – BAKb – most likely). He was given two doses of rituximab 375mg/m2 a week apart. A month later his platelet count was still 13,000/mm3, but after a high dose of intra-venous immunoglobulin (2g/kg, divided in two doses) his platelets reached 134,000/mm3. At 11 mo the patient was submitted to a haploidentical hematopoietic stem cell transplantation (his father was the donor). Conclusion: T-BNK+ SCID patients can produce autoantibodies despite their low B cell counts, suggesting the presence of abnormal clones.

Statement letter

During my fellow in Allergy/Immunology I realized that Immunology is my greatest field of interest. I really like studying it and trying to understand this complex system. Once I´m beginning now to study Immunology deeper I am looking for opportunities to improving my knowledge. That ´s why I really want to participate of this summer-school. I think that it will help me to consolidate some concepts and to open my mind to new ones.

Currently, I´ve just finished my residency but I keep following the service of Immunology from a referral center in Brazil - Hospital São Paulo. My goal in this area is to continue my studies and participate in a research project. I want to learn more about the methods of characterization of immunodeficiencies, including immunophenotyping, Elispot, evaluation of B cell function and even genetic sequencing. I believe that the appropriate and directed use of immune function testing provides not only critical diagnostic information but also directs decisions regarding prediction of complications and the most appropriate therapy.

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Clinical case

MAF, male, who presented at 15 months of age Juvenile Xanthogranulomatosis, with spontaneous remission in 6 weeks. At 17 months of age, he was admitted with bilateral pneumonia and pleural effusion. After this first episode, he presented recurrent viral and/or bacterial "bronchitis" until 4 years of age, totaling 15 episodes and 2 pneumonias with pleural effusion; *Haemophilus influenza* was isolated once. At 28 months of age: viral encephalitis, 12 days after being vaccinated for yellow fever. One week after receiving the varicella vaccine, at 4 years old, he presented herpes zoster. He also had, at 5 years old, 45 days of Diarrhea, Rotavirus + (patient had been vaccinated). At 5 1/2 years old, he was diagnosed with calcaneus osteomyelitis. Biopsy and PCR demonstrated granulomatous disease. Tendon biopsy showed caseous necrosis and an empirical combination of tuberculostatic drugs was initiated. PPD was negative, as well as search for *Blastomycosis* and *Bartonella*. After 2 months a non tuberculosis mycobacterium was identified on tendon biopsy (PCR for *Mycobacteria*: positive for Mycobacterium sp; negative for M. tuberculosis). At 6 years old, he was admitted for 15 days due to multiply hepatic abscesses. A month later again, he was admitted for 5 days due to headache, dizziness and prostration. After 2 weeks from last admission he presented with acute hearing loss and audiometry showed total hearing loss on the left side and partial loss on the right side. Viral infection or drug toxicity was questioned. CMV IgM/IgG negative. Despite, multiple combination of tuberculostatic drugs, he evolved with a new fistula at the left calcaneous. A tendon biopsy was performed with no mycobacterial growth, BAAR negative. One year ago, at 6 years and 2months of age he presented with two episodes of chorea (CBC and ASLO normal), presumed adverse reaction to SMZ/TMP. At 6 ½ years old he started to present fatigue, generalized pain, weakness and pale skin. In few days he was admitted with acute anemia, CT showed splenomegaly, Hb reached 5,5 mg/dL, Coombs positive, very increased LDH. Auto-immune Hemolytic Anemia was attributed to levofloxacin or pyrazinamide, both drugs used for Mycobacterial treatment and thus, being withdrawn. Laboratory tests findings included persistent leukopenia, reaching 533 cells/mm3, normal immunoglobulin's count. Immunophenotyping showed low absolute and relative number of T and B lymphocytes population (CD3+ 255---41,9% and CD20+ 42---7%) with decreased number of Naïve CD4+ and CD8+ Lymphocytes (4---0,57% and 13---2,26%, respectively) and increased percentage of NK lymphocyte population (51,1%). HLA was performed and the sister matches.

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Clinical case

SEVERE COMBINED IMMUNODEFICIENCY

Name: CKR, Female, 11 months, born in Pueblo Nuevo, Guanajuato. Third pregnancy, born at 37 weeks by cesarean indicated by oligohydramnios, birth weight 2850 g, microtia detected at birth. Breast fed until 4 months, with supplemental milk formula, weaning at 4 months. Omphalorexis 12 days. Normal psychomotor development

Death of paternal and maternal uncles in early age. Brother died at 14 months of age after several upper recurrent infections and encephalitis. Brother's autopsy showed encephalitis, pericarditis, myocarditis, endocarditis, gastritis with candida.

At two month old, she presented erythematous purpuric petechiae. At 4 months presented skin lesions treated with antibiotics. Diarrhea after 6 months old. Complete immunization up to 6 months without complications. At 7 months, she presented erythematous skin lesions and fever of 38 degrees, not responding to drugs. There was worsening of the lesions and the child was hospitalized with conjunctival hyperemia, cheillitis, erythema of palms, discrete desquamation of inguinal region and feet, hepatomegaly. Diagnosis was Kawasaki disease, treated with intravenous gamma globulin. Urine cultures isolated *Klebsiella* and *Enterococo fecalis*. At 9 months, she was hospitalized with fever, leucopenia, lymphopenia and eczema. Peripheral blood smear showed thrombocytopenia, decreased granulocytes and few young cells. Bone marrow aspirate: no malignity, megakaryocytes at the expense of increased cellularity, decreased red cell, diffuse basophilia. During the hospitalization, she presented pneumonia, sepsis and autoimmune hemolytic anemia. Primary immunodeficiency was suspected.

Laboratory test: 18/12/13: TREC: presumptive positive. IgA=7 mg/dL, IgG=883 mg/dL, IgM 136 mg/dL, IgE 69.9UI/mL; C3=94.2mg/dL; C4=21.93 mg/dL, Hb=11.3; Hct=35%, VCM=79.7, HCM=25.7, Leukocytes=4320mm/3, Neutrophils=1180mm/3, Lymphocytes 2270mm/3; Monocytes=700mm/3; Eosinophils=150mm/3; Basophils 20mm/3

FLOW CYTOMETRY: T-B+NK+; Leukocytes 6200 mm/3; Lymphocytes 42%: 2604 mm/3; Neutrophils 32%: 1984 mm/3; Monocytes 13%: 806 mm/3; CD19+ 35% (911mm/3); CD 16+ 56+= 41% (1067 mm/3); CD3+= 9% (234/mm3); CD4+= 69% (162/ mm3); CD8+= 30% (70/ mm3).

Diagnosis: Severe combined Immunodeficiency due to IL7RA

Comment: patient with family history of early death of brother with diagnosis severe infection and encephalitis. She presented chronic diarrhea and autoimmune diseases. Isolates from urine cultures of *Enterococo* and *Klebisiella.* At 9 months had fever and lymphopenia. Immunophenotye of flow cytometry T-B+Nk+, TRECs low levels, performing diagnosis of alteration IL7Ra.

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Clinical Case

Does Amphotericin B exacerbate lung inflammation in Chronic Granulomatous Disease?

Chronic Granulomatous Disease (CGD) is a primary immunodeficiency caused by the lack of function of the phagocyte NADPH oxidase, which generates reactive oxygen species (ROS) and participate in the microbicidal activity of phagocytes. CGD patients are prone to recurrent life-threatening infections, and they also suffer from increased inflammatory responses, causing morbidity like granuloma formation, Crohn-like disease, pulmonary fibrosis, among others. While infection susceptibility mechanisms are well defined, the underlying reasons for the hyperinflammatory reactions in CGD remain poorly undestood. Upon stimulation with TLR2 or TLR4 ligands, leukocytes from CGD patients yield an increased production of pro-inflammatory cytokines which is, surprinsingly, independent of NADPH oxidase activity. The role of diverse immunological mediators and pathways causing excessive inflammation in CGD have been demonstrated: impaired neutrophil apoptosis and esferocytosis, innate immune receptors (TLR`s), ROS-Dependent oxidization of T-cell membrane proteins, Th17 lymphocytes activation, Inflammasome activation, among others. Neutrophils, macrophages and circulating blood monocytes from CGD patients produce larger amounts of pro-inflammatory cytokines and adhesion molecules compared with healthy control subjects. ROS are implicated in many other functions instead of pathogens killing and they have a role in: metabolism, cell death, apoptosis regulation, induction of host defense genes, oxidative signaling and regulation of inflammatory response.

Systemic fungal infections, mainly Candida spp. and Aspergillus spp. are common in patients with CGD and these patients frequently need antifungal drugs. Amphotericyn B (AmpB) is a polyene antifungal agent introduced in clinical practice since 1950; it binds to ergosterol in fungal lipid bilayer membranes. This drug has been the gold standard treatment for systemic mycosis for many years despite causing severe adverse events mainly renal failure, but others like fever, chills, arthralgias are described and related to intravenous infusion. Even though there are newer antifungal drugs, they are expensive and not always available in developing countries. Mechanism of action for Ampothericyn B has not been completely understood and it is known this drug has immunomodulatory effects: promotes neutrophil aggregation and pulmonary leukostasis (neutrophil-dependent injury), stimulates IL-1β, TNF- α, PGE2 production, and probably activates Toll-like receptors (TLR´s), leading to a pro-inflammatory state. Rarely, it has been described severe acute lung damage with AmpB infusion (tachypnea, respiratory distress, hemoptisis, ARDS, stridor); it has been proposed and demonstrated in experimental studies this drug cause inflammatory mediators release (IL-1, IL-6, TNF-alpha, PGE2) which probably are responsible for symptoms, local tissue inflammation, leucocyte migration, activation, and increased vascular permeability. We report four patients with CGD who developed varied inflammatory conditions; they got fungal infections and developed pulmonary complications after Amphotericin

B was administered.
Case 1. 12-years old male with CGD diagnosed since 2003. He was admitted in 2011 because of two-week fever history, pneumonia was diagnosed. During hospitalization he continued with intermittent high-grade fever in spite of antibiotic treatment; he developed sepsis with systemic inflammatory response and required intensive care unit admission with mechanical ventilation. Bronchoscopy was performed finding *Penicillum* in bronchial sample and AmpB was initiated the same day. Twenty-four hours after bronchoscopy procedure he developed severe hypoxemia, bilateral pulmonary hemorrhage and shock. Voriconazole and posaconazole were added and treatment with cyclosporin, steroid pulse therapy and GGIV was initiated suspecting autoimmune pulmonary vasculitis. Patient didn´t improve and died one week later.
Case 2. 8-year old male. He was diagnosed with CGD (CYBB mutation) since 2006. In 2012 he was admitted for 1- month fever history and treated with meropenem + vanchomycin without improvement; AmB (lipid complex) was started and twenty-four hours later he started with respiratory distress, hemoptysis and hypoxemia requiring mechanical ventilation, new bilateral infiltrates appeared in chest X-ray. We started intravenous immunoglobulin (IVIG) 1 gr/kg/do and methylprednisolone 1 mg/kg/do; Amphoterycin B was discontinued and Voriconazole plus caspofungin started, Rituximab course was administered for suspected pulmonary vasculitis. He weaned mechanical ventilation after six days and lung infiltrates resolved, he was discharged. He developed sepsis and died in 2013 outside our unit.
Case 3. 14-years old male. He was diagnosed with CGD (Gp91phox defect) cince 2003. In June/2012 was admitted to our unit with 1-month lasting fever of unknown etiology, antibiotics were initiated without clinical improvement. Laboratory work-up demonstrated positive result for Candida antigen in blood, AmpB was initiated. Approximately twelve hours after first dose, he abruptly developed fever, nausea, vomiting and twenty- four hours later hemoptysis, respiratory distress, tachypnea, tachycardia and hypoxemia requiring mechanical ventilation and vassopressors, bilateral lung infiltrate appeared in chest X-ray; AmpB was changed for caspofungin plus voriconazole. IVIG, cyclosporin and steroid pulse therapy were given with rapidly clinical improvement; mechanical ventilation stopped 4 days later. He was transplanted in 2013 from 100% compatible related-donor; now he is on treatment for GVHD with mycophenolate.
Case 4. 9-years old male with CGD diagnosed since 2007. In 2012 he was admitted with long-term fever and severe pain in right shoulder, with no respiratory symptoms; antibiotics were given without clinical improvement. We demonstrated hepatic and kidney fungomas, and initiated AmpB treatment . Five days after AmpB was initiated he abruptly presented with tachypnea, tachycardia, dyspnea, hypoxemia and new bilateral lung infiltrates in chest X-ray. AmpB was changed for caspofungin plus voriconazole. Steroid pulse therapy + IVIG was given with respiratory symptoms resolved. It was later confirmed right humerus fungal osteomyelitis (*Aspergillus* spp.). He was discharged with oral posaconazole treatment and is now waiting for HSCT.
DISCUSSION. We describe four patients with CGD who developed acute pulmonary adverse events when AmpB was administered. It is noteworthy highlighting they improved with anti-inflammatory treatment (high-dose steroids plus IVIG). The hyperinflammatory state of CGD patients and the immunomodulatory and proinflammatory effect produced by AmpB , are known. While uncommon, pulmonary complications during AmpB therapy have been reported in neutropenic patients

with systemic mycoses, but we didn´t find reports specifically in PID´s patients. Based in literature reports and pathophysiologic understanding, it is possible that CGD patients are at higher risk for severe adverse reactions with AmpB therapy than patients without immune dysregulation. Assuming this, it would be necessary to change our clinical practice and to use alternative antifungal drugs as first-line treatment in this patients. It will probably be more expensive to treat pulmonary and hemodynamic complications than use newer drugs like Voriconazole and Posaconazole. It is difficult to know in this patients which one is the main pathogenic stimuli for lung damage: infectious agent, AmpB or CGD immune dysregulation itself, but the short period of time between AmpB infusions and respiratory symptoms suggests an important role for this drug. We should have in mind all of this pathogenic variables to develop better treatment strategies. Interestingly, patients 2, 3 and 4 improved with steroid pulse therapy and immunosupresive agents. Early and aggressive anti-inflammatory treatment should be considered in these patients in addition to antimicrobials and supportive care.

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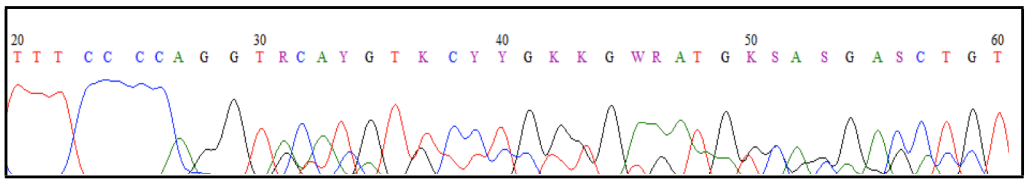
Clinical case

Bronchopumlmonary and osteoarthritis caused by *Aspergillus fumigatus* as the primary clinical manifestation of a girl with Autosomal Chronic Granulomatous disease.

Introduction: Phagocytic cells play a central role in the celular host defense system due to their ability to release large amount of superoxide in the respiratory burst. The multicomponent enzime NADPH oxidase is largely responsible for this antimicrobial defense system clarly demostrated in patients suffering a rare inherited disorder know as chronic granulomatous disease (CGD). The second most common form of CGD is due the deficiency of the p47-phox (A47°) encode for NCF1 gene, a dinucleotide delection within GTGT repeat at the beginning of exon 2, predict a frameshift and premature stop codon. Several studies claim that there are two p47-phox homologous pseudogene co-localize with the funtional gene, the recombination within genes lead to the incorporation the ΔGT into NCF1. Objective: Our aim is determine the genetic relationship-phenotype of patients with deficiency of the p47-phox. Methods: The diagnosis of CGD was preformed blood samples stored in heparin by direct measurement of superoxide production for dihydrorodamine oxidation (DHR) test for superoxide free radical. DNA genomics was isolated from whole blood stored in EDTA using a DNA kit (Wizard® Genomic DNA Purification Kit) and Polymerase chain reaction was performed using Taq polymerase (Invitrogen), PCR fragment were purified and sequenced using Purification Kit (Life Technology) and BigDye® Terminator v3.1 Cycle Sequencing Kit respectivelly. Results: A mutation analyses of the A47° CGD shown a single mutation, a GT deletion at the beginning of exón 2. Conclusion: A47° CDG patients the sequence homozygous for the deletion GT suggest one more than one p47-phox related sequence might be present in normal genomic.

A



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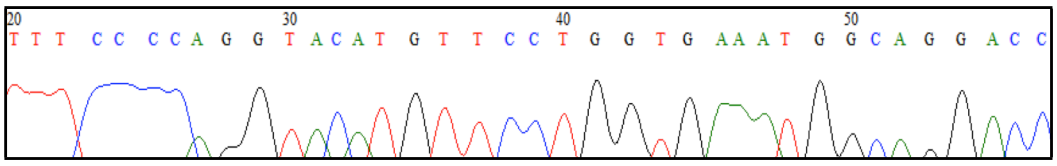

Figure 1: Sequence analysis of the intron 1/exon 2 of p47-phox. A) Normal individual B) A47° CGD patient.

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Clinical Case

Fulminant Aspergillosis In A Patient With Chronic Granulomatous Disease

A 7 y old female patient had familial history of one healthy brother, deceased maternal uncle at 4 months of age due to not specified infection and maternal cousin with Dx of Chronic Granulomatous Disease. She was evaluated at 2 years for intestinal obstruction and acute abdomen; exploratory laparotomy was performed finding severe generalized peritonitis and hepatomegaly, diagnosed as nonspecific peritonitis. After complete antibiotic schedule she was discharged. A month later, she had partial bowel obstruction and she was admitted for conservative management. At 5 years, she was admitted with pneumonia, splenomegaly (10cm), X-ray showed solitary nodule, suspected of tuberculosis. Pulmonary CT showed alveolar nodule occupancy with an image suggestive of cavitation in right upper lobe and right pleural effusion. Tuberculosis was suspected. It was positive for *H capsulatum* treated with Amphotericin B. Bronchoscopy biopsy was performed: acute and chronic nonspecific inflammation. Continued hospitalized with poor outcome, with control CT lung lesions decreased in number, with necrosis inside, bronchoalveolar occupation zone probably right with necrosis inside. Treatment was started with clarithromycin for suspected Mycoplasma, Linezolid is added to the handling and cefepime. Liver biopsy was performed with data likely reactive hepatitis. Lung biopsy was repeated and granulomas were compatible with CGD, with abnormal NBT (<5% of control) and Dihydrorhodamine (DHR) Flow Cytometric Assay showed an autosomal recessive pattern with two cell populations, one with normal and other with abnormal activities. It was started interferon gamma, continuous antimicrobial and antifungal therapy. At 6 y old, she was admitted with a 6 day fever, 5 day cough, wheezing, respiratory distress of 4 days duration. On admission with respiratory rate of 40, sat O_2=79% at environment air, intercostal and suprasternal retractions, thoracoabdominal dissociation, paleness, hypoventilation lung fields with bilateral fine crackles predominantly in left chest without dullness to percussion, with systemic inflammatory response. Requires placement of nasal noninvasive ventilation. CT lung with linear bronchiectasis, multiple areas of confluent alveolar type consolidation with air bronchogram occupying almost both lung. It was introduced Cefotaxime and Dicloxacilline and continuous IFN-gamma. For persisting fever, it was added cefepime + amikacin. For persistent fever despite 4 days with antibiotics, Vancomycin was added two days later. Due to poor outcome trimethoprim-sulfamethoxazole was initiated. After a bronchoalveolar lavage, Aspergillosis was suggestive and Voriconazole was introduced with systemic glucocorticoids. She improved in the first 10 days, however respiratory distress recurred. Nosocomial pneumonia was suspected and antibiotics were reintroduced but the disease progressed. It was discarded a macrophage activation syndrome. Cyclosporine (5mg/kg) was started as immunomodulation therapy. She evolved with urinary bleeding and massive alveolar hemorrhage, dying of pulmonary hemorrhage and respiratory failure. In the pathology report of bronchial fluid obtained during resuscitation, *Mucor* was isolated.

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Clinical case

LNS, male, born to non consanguineous parents, was admitted at 2-month-old with popliteal abscess from *S. aureus*, requiring three surgical procedures, urinary tract infection from *E. coli*, bacteremia from *K. pneumoniae* and interstitial pneumonia. At 6-month-old he was admitted because of suppurative acute otitis media with secondary facial palsy from *S. aureus* and *C. parapsilosis,* besides bilateral pneumonia with lung abscess followed by septic shock from *S. aureus,* requiring surgical treatment, intravenous antibiotics and oral Isoniazid, Riphampicin and Ethambutol for 6 months for lung improvement. At 15-month-old he was admitted again with urinary tract infection and bacteremia from *K. pneumoniae,* and bloody diarrhea. He also presented chronic diarrhea, eczema, conical teeth, hypohydrosis, hyperthermia, recurrent mucocutaneous candidiasis and extensive lesion on the BCG site. Positive family history: male brother died at 3-month-old from pneumonia and a maternal brother died in the first year of life.

Laboratory tests findings: persistent leukocytosis (WBC >20,000 cells/µl), IgG=147mg/dl (<P3), IgM=25-91mg/dl (P3-P97), IgA=15mg/dl (P50) and IgE=197UI/ml at 4 months-old. Normal CD3, CD4, CD8 and CD19 expression. Normal bone marrow aspiration and normal neutrophil superoxide production. Skin biopsy showing *Ichthyosis vulgaris*.

The patient has been treated with intravenous human immunoglobulin (725mg/kg/month) in addition to Trimethoprim-Sulfamethoxazole for *P. jiroveci* prophylaxis.

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Case Report (ML)

Pre term female newborn hospitalized since birth due to neonatal septicemia. She was the 4th child from non consanguineous parents. No familial history. At 2 months old, she was referred to our hospital with fever and tumefaction in right ankle with diagnosis of septic arthritis. Laboratory's results showed WBCs 38000 (N61%) and PCR 74 (mg/l) and isolation of *Pseudomonas* at central blood culture treated with meropenem and vancomycin (14 days). At the same time, she developed resistant antifungal muget. During hospitalization, she developed multiple infections (arthritis, myositis, thigh abscess, chronic osteomyelitis in tibia). At physical examination, she was malnourished, with oral and cutaneous candidiasis, and ectodermal dysplasia.

Laboratorial evaluation: GB 29200 (N21/L64/M14/E1), Hb 10,8g/l; Platelets 590000; PCR 19 (mg/l); uric acid 1,23 (mg %). Humoral assessment showed agammaglobulinemia (IgG: 0,67 g/l, IgA: < 0,07 gr/l, Ig M: < 0,04 gr/l, IgE <5 UI/ml). Cellular assessment (lymphocyte subsets) and DHR assay were normal. Lymphocyte subsets CD3+= 77%; CD4+= 53%, CD8+= 23%, CD19%, NK+= 8% CD4RA 97%; CD4 RO < 1%

Lymphocyte proliferation and NEMO were requested.

Lymphocyte proliferation showed lower response to PHA / OKT3/ TT / PPD

Expression of NEMO protein was normal, no production of TNF-α in response to LPS. IKBα gen was sequenced and showed a heterozygous mutation D31G.

Gammaglobulin was indicated at 500mg/kg/ dosis every month reaching protective IgG values (IgG 6.13 g/l).

At eight months old, she died of meningoencephalytis and sepsis by *Acinetobacter* while HLA studies were in process.

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Clinical case

PHSN, age 5, male, living in Sao Bernardo do Campo. At three years old, was hospitalized after ten days of high fever (40°C),pancytopenia,hepatosplenomegaly, hypertriglyceridemia and hypo-fibrinogenemia after trip to the Northeast. It was suspected of Hemophagocytic Sd. Subsequently discarded after a bone marrow biopsy and MO. Antibiotic therapy was started with ceftriaxone for four days, with no improvement. Treatment was changed to Vancomycin and Cefepime and held for 14 days without fever subsides. He visited an endemic region for Leishmania, then it was searched for this disease; two serologies were positive. Amphotericin was infused for 24 dyas without improvement. It was changed to liposomal amphotericin, kept for 28 day. He evolved with bilateral pneumonia, anasarca, mild pericardial effusion, central catheter infection by *Klebsiella* sensitive to Meropenem. Cellulitis was treated with teicoplanin for 14 days. Due to complications and new febrile episode with poor clinical condition, PPD test was performed and resulted negative. He developed axillary and epitrochlear lymphonode enlargement and further drainage. Empirically, we started treatment with RIPE regimen (rifampicin, isoniazid, pyrazinamide and ethambutol) for 10 months. After two months of treatment, there was 2-3 daily peaks of fever, hepatosplenomegaly but with clinical improvement. He was referred for immunologic evaluation. The child was a preterm infant, born by cesarean section, (P=2800g). He had neonatal pneumonia requiring hospitalization in ICU with intubation for 7 days. He was admitted at 2 years of age after contact with sheep, developing fever and red spots in the body, requiring antibiotic therapy. No relevant familial history.

-Myelogram: mild hyperplasia of the megakaryocytic series, with a slight increase of immature forms; 3% blasts

- Bone Marrow Biopsy: normal

After two years of follow up, the patient showed no new bacterial infections and keeps without antibiotics.

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Clinical case

Macrophage Activation Syndrome Complicating Stat-1 Defect.

Introduction: The absence of STAT-1 in a rare condition that occurs in only 5% of patients identified in the group of MSMD, STAT-1 is a protein transduction and transcription functions of intracellular signaling plays an important role in the production proinflammatory cytokine**.** MAS is characterized unrestricted proliferation of macrophages and T-lymphocytes, resulting in an exaggerated inflammatory response, characterized by continuous fever, cytopenias, hepatosplenomegaly, mental status alterations, coagulation disorders, hypofibrinogenemia and increased erythrocyte sedimentation rate. There are no reports of STAT-1 defect complicated with hemophagocytic syndrome.

Clinical Case: 5 year-old male, history of endogamy, mother deceased at age 21 years after meningeal TB, a 8 y old sister with pulmonary TB and diagnosed with STAT-1 defect. The patient presented with intestinal obstruction, persistent fever, and malaise. Exploratory laparotomy was performed with intestinal resection, and multiple intestinal perforations leading to enterocutaneous fistula. Histopathology reported positive Ziehl-Nielsen with granulomas, PCR positive for TB in retroperitoneal tissue and pleural fluid. Treatment with antituberculosis drugs was started (rifampin, isoniazid, ethambutol and pyrazinamide). One month after, he was referred with severe malnourishment. Anti-TB drugs were started with isoniazid, rifampicin, ethambutol, pyrazinamide, amikacin, levofloxacin, clarithromycin, plus meropenem and linezolid, trimethoprim and fluconazole. Gamma Interferon was started. The patient had improved with remission of fever and weight gain; *M. bovis* was isolated as the causative. Three weeks, he presented evidence of SIRS, with high-grade fever, abdominal focus, anemia, neutropenia, lymphopenia and low platelet limit (Hb 10 hto 29.3, Leuc 4000 , NT 700, LT200, Plaq 122,000, Bn 43%). For sepsis, it was administered immunomodulatory doses of gamma globulin (1g/kg/day) and Neupogen 5 mcg/kg/d, restarting antimicrobial therapy with carbapenem (meropenem), maintaining parenteral nutrition. The patient was stabilized. Three weeks after, he presented persistent high fever, clinical deterioration. Meropenem and gammaglobulin (2g/kg/day) was introduced and hemophagocytic parameters were performed. The tests showed: anemia, lymphopenia, thrombocytopenia, elevated acute phase reactants, and elevated ferritin (Blood count: hb 8.9, hto 25, 2400 Leuc, NT 1700, LT 600, Plaq 125 000, triglycerides 180, Fibrinogen 324, Ferritin 3637, ESR 50, CRP 17). He evolved with hepatosplenomegaly; he needed supportive care with mechanical ventilation, dexamethasone and cyclosporine IV (3 mg/kg/d), with clinical improvement. He was maintained with treatment antituberculosis 1st, 2nd and 3rd line and progression scheme antibiotics piperacillin tazobactam, caspofungin and Meropenem. Increased ferritin up to 11 057; fibrinogen 243; persistent neutropenia (700); anemia 8.9; hypertriglyceridemia (415). Liver function tests: ALT128, AST 142, GGT 366. The defect in STAT-1 is a rare alteration; this has not been associated with macrophage activation syndrome.

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Clinical case

CHRONIC CUTANEOUS VASCULITIS IN A PATIENT WITH INTERLEUKIN-12/ RECEPTOR β1 DEFICIENCY

INTRODUCTION: The Mendelian susceptibility to mycobacterial diseases, is a primary immunodeficiency caused by mutations in 7 autosomal genes (IFNGR1, IFNGR2, IL12B, IL12BR1, STAT1, ISG15, and IRF8) and an X-linked gene (NEMO). This syndrome presents a high degree of allelic heterogeneity and variable penetrance. Patients are predisposed to present severe disseminated infections by non tuberculous environmental mycobacteria, Bacille Calmette Guérin (BCG) and non typhoidal Salmonella, which can present clinically with lymphadenopathy, liver or spleen infection, osteomyelitis, skin or lung infection, adenitis, osteitis or sepsis. Autoimmunity can complicate several primary immunodeficiencies. Leukocytoclastic vasculitis can complicate patients with defects in IL-12Rb1. We report a patient with a defect in IL-12RP1 and chronic recurrent cutaneous leukocytoclastic vasculitis.

CASE REPORT: We present a 4 year-old female. She has 3 healthy siblings. No history of consanguinity or inbreeding. From the first year of life, she suffered from several episodes of gastroenteritis requiring hospitalization. In addition, at 1 year 3 months old, she had an axillary abscess treated with dicloxacillin and her first pneumonia. She had a history of 4 pneumonia requiring hospitalization. At 2 years 3 months old, she was hospitalized due to cervical abscess treated with dicloxacillin, and cefotaxime. At 2½ years old, she had seizures associated with fever, generalized tonic-clonic, lasting approximately 2 minutes. Eight months later, she had new event of same characteristics, of approximately 40 seconds. Normal brain MRI. At 3 and half years old, returns to 4 events seizure about 1minute long, no trigger. The reported EEG was discrete low activity for age, no epileptiform activity, started treatment with levetiracetam 30mg/kg /day to date.

She presented anemia and fever for one month, diagnosed in stool with Salmonella. She had more than 4 events of gastrointestinal Salmonella isolated in stool cultures and blood cultures, treated with ceftriaxone with improvement. Later, she was hospitalized for anemia and skin lesions on the lower extremities, red-violet color, which did not disappear to the touch, not itchy, compatible with purpura Henoch Schonlein. She was treated with prednisone 10 mg/d for a week with improvement. At 2 years 8 months old, she was referred to a tertiary hospital for the presence of hepatosplenomegaly, fever, lymphadenopathy, arthralgia and back skin lesions purpuric type, where Autoimmune hemolytic anemia was diagnosed with positive direct Coombs pathology chronic lung and arthritis.

Laboratory studies, was performed: Serology for hepatitis A, B and C, cytomegalovirus, Ebstein Barr Virus, ELISA and PPD all negative. Serology for Leishmania, AntiDNAn, ANA and anticardiolipin were negative. Immunoglobulins: IgA146, IgE374, IgM 235, IgG 3040.Positive direct Coombs1:2 on 2 determinations. Flow cytometry: Total Lymphocytes 7860, CD3 51% (2459 total), CD8 18% (863 total), CD430% (1452Total), CD19 38%, CD16/56 5.5%.

At 3 years old, she presented persistent cervical lymphadenopathy, cervical node biopsy was done, which was reported positive PCR for Mycobacterium

tuberculosis, treatment with isoniazid, pyrazinamide, ethambutol, and rifampin were started for 6 months with improvement of the lymphadenopathy. She received prophylactic treatment with trimethoprim-sulfamethoxazole, fluconazole and interferongamma1 (50mgm2SC) at doses 3 times a week. Two months later, same purpuric skin lesions returned, a skin biopsy reported leukocytoclastic vasculitis in papillary dermis, and perivascular infiltrate of neutrophils, which destroy vascular walls, karyorrhexis and follicular edema in dermis and subcutaneous tissue unaltered without report of IgA deposit. Featured events over two dermal lesions same features, one with fever and last event at 3 years 11 months old, treated with steroid and ciprofloxacin for isolation in blood cultures and stool cultures of Salmonella group D with improvement of skin lesions. Currently she is asymptomatic in treatment with steroid to 0.7mgkgd and hydroxychloroquine, with adequate evolution and remission of skin lesions.
Conclusions: We report the case of a 3-years-old diagnosed with defect in IL-12/IFN- gamma axis (mutation in the gene IL12Rβ1) and presented initially with a severe recurrent gastroenteritis and subsequently infected with Histoplasma, lymphadenopathy and tuberculosis, as well as the presence of autoimmune hemolytic anemia. Characteristically presented skin lesions since 2 years old, of same characteristics on 4 times, with report of leukocytoclastic vasculitis in skin biopsy and reporting of positive blood cultures and stool cultures for Salmonella, and good response with treatment with steroid and cyprofloxacin, remitting the frequent events of leukocytoclastic vasculitis. The leukocytoclastic vasculitis in patients with defect axisIL-12 IFN gamma, is rare and could be the first manifestation.

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Clinical case

Hyper IgM syndrome with upper airway obstruction due to lymphoid hyperplasia

Hyper IgM syndrome (HIGM) is a heterogeneous group of disorders characterized by normal or elevated IgM levels associated with absent or decreased IgG, IgA and IgE due to defects of immunoglobulin class switch recombination (CSR). Some types are autosomal recessive HIGM caused by mutations in CD40 or by B cell-intrinsic defects of CSR due to mutations in activation – induced cytidine deaminasa (AICDA), uracil-DNA glycosylase (UNG) and mutations in the post meiotic segregation 2 gene (PMS2).This patients have recurrent bacterial infections of the upperand lower respiratory tracts. Lymphoid hyperplasia (especially tonsils and cervical lymph nodes) is a prominent feature and is due to the massive enlargement of the germinal centers that are filled with actively proliferating B cells.

Clinical Case

This is a 16 year old girl, born from unrelated parents, with HIGM (probably type 3) who was diagnosed in August 30th, 2007, based on: recurrent cervical lymphadenopathies and parotitis, recurrent otitis media and productive cough, serum immunoglobulin's (age 9 years): IgA 22 mg/dl, IgG 146 mg/dl, IgM 368 mg/dl, peripheral blood lymphocytes: lymphocytes 4953/ul, Tcells 3417/ul, CD3+CD4+ 692/ul, CD3+CD8+ 2175/ul, CD19+ 149/ul, NK 1287/ul. A lymph node biopsy showed lymphoid hyperplasia. She had recurrent upper respiratory tract infections, with persistent cough, without fever or respiratory distress. Since diagnosis, she had been receiving monthly intravenous immunoglobulin and prophylactic TMP/SMX. A molecular study has not been done.

One year ago (May 2013), she was admitted with purulent tracheitis and treated with clindamycin and cefotaxime. A normal chest CT scan in August 2013 showed absence of bronchiectasis. Since then she had persisted with respiratory symptoms (productive cough) and received clarithromycin during 7 days without any improvement. On February, 2014 a chest X-rays revealed atelectasia of the middle right lobe and that prompted an evaluation with the otolaryngologist and pneumologist. The physical examination showed two tumors on the basis of the tongue (whitish and soft). Hepato-splenomegaly was not found, but she had multiple cervical lymphadenopathies. All laboratories were normal including blood count, biochemistry, hepatic function tests, CRP and blood cultures.

During a bronchoscopy, for bronchoalveolar lavage, an enlarged soft tissue producing obstruction of the upper airway was found. The epiglottis and arytenoids were totally deformed by infiltration. Trachea and bronchi were not explored due to the airway obstruction in supine position. Trachea was filled with purulent material. She was treated with clindamycin and cefotaxime. An otolaryngologist did a tracheostomy due to airway obstruction. Further, a direct laryngoscopy, bronchoscopy and biopsy were done. Histology of the lesions is pending.


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