Primary Immune Deficiencies, Atypical Lymphoproliferative Disorders, Immuno-Hematology Disorders

PID_ALP_ID-1_V1.1

A NOVEL CONGENITAL B CELL LYMPHOCYTOSIS DISEASE: BENTA DISEASE RESULTS OF GAIN-OF-FUNCTION MUTATION IN CARD11

Ankit Kumar Parmar, Prasad Taur, Purva Kavinde, Naseer, Maya Gupta, Sangeeta Mudaliar, Archna Swami, Nitin Shah, Bharat Agarwal, Manisha Madkaikar, Mukesh Desai. *Division of Pediatric Hematology-Oncology, Bai Jerbai Wadia Hospital for Children, Mumbai, India*

Abstract

Background: Congenital B cell lymphocytosis is a rare clinical syndrome. Recently, two activating germ line mutations in *CARD11* have been identified as driving disease in patients with what we now refer to as BENTA (B cell Expansion with NF-κB and T cell Anergy). Here we report a new patient with BENTA disease who was found to have a heterozygous, germ line *de novo* G123D *CARD11* mutation.

Case report: 1 year male presented with fever, loose motion since & respiratory distress 1month. He has history of NICU stays for respiratory distress for 20 days. On examination significant lymphadenopathy with hepato-spleenomegaly. Investigation: - CBC s/o of Bicytopenia in form of HB 4.3 gm. % & PLT 72000 with lymphocytosis TLC 26.3, 36%poly, 48% lypmho, & high retic. P/S:-NCNC anemia, lymphocytosis (atypical), decreased PLT. Renal and liver function test and LDH (244) & Uric acid (2.6) within normal limits. Chest x ray s/o B/L minimal pleural effusion. Bone marrow aspiration s/o absent megakaryocytes, few myeloid cells & blast like cells present. Treatment given: ventilator support with blood products and IV antibiotics. After 15 days of hospital stay: worsening of bicytopenia with same size organomegaly with symptomatic improvement.

On further Ix CMV & EBV PCR negative. CT Thorax: areas of consolidation in B/L lung parenchyma of infective etiology. Repeat BMA with FLOW Cytometry negative for malignancy.BM biopsy s/o normo cellular marrow with normal trilineage cells. Majority of lymphoid cells are B cells, (CD 20, CD 79& focally CD 10: positive). Cd 34 & Tdt is Negative.

Considering differential of autoimmune lympho-proliferative disease (ALPS): -DCT positive, LSSA s/o B cell high- CD19+ 70% with normal T cell & NKcells. Immunoglobulin level: - high IgG with normal IgA IgM. **DNT (double negative T cell) was negative 3%.**

For rare causes of ALPS with B cell lymphocytosis: Perforin, CARD 11 and Fas ligand was sent. Patient CARD 11 G123D germ line mutation was present. Hence patient labeled as BENTA disease and started on sirolimus. Patient responded well in form of recovery from cytopenia and resolving organomegaly. No episode of respiratory disease after starting treatment.

Discussion: A novel congenital B cell-specific lymph proliferative disorder termed B cell Expansion with NF-κB and T cell Anergy (BENTA) disease characterized by excessive B cell lymphocytosis presenting in early childhood, with associated splenomegaly and lymphadenopathy. BENTA disease is genetically defined by germ line-encoded, heterozygous GOF mutations in CARD11. CARD11 is expressed primarily in lymphocytes and functions as a scaffold molecule that bridges engagement of the antigen receptor. Phenotyping reveals accumulation of both immature transitional and mature naïve polyclonal B cells, while T cell fall within normal pediatric ranges. BENTA patients exhibit several hallmarks of primary immunodeficiency with Sino pulmonary and ear infections other "opportunistic" viral infections with insufficient humeral immune responses in response to polysaccharide-based vaccines.

Conclusion: BENTA disease represents different spectrum of ALPS disorder with similar presentation but different molecular mechanism and lack of typical feature of autoimmune phenomenon. Also traditional test DNT not useful for a diagnosis of BENTA disease hence to diagnose such a disease precise molecular tests are require if clinical background firmly suggestive of disease.

References

1) J Clin Immunol. 2015 Jan;35(1):32-46. doi: 10.1007/s10875-014-0106-4.
2) Current Opinion in Allergy & Clinical Immunology:December 2015 - Volume 15 - Issue 6 - p 533–538.

PID_ALP_ID-1_V1.2

HYPER IGD SYNDROME: A CASE REPORT

Mohammed Naseer, P. Taur, A. Parmar, P. Kanvinde, S. Mudaliar, N. Dighe, P. Keni, A. Pandrowala, M. Madkaikar, A. Dalvi, A. Mishra, B. Agarwal, Y. Amdekar, M. Desai. *Bai Jerbai Wadia Hospital for Children, Mumbai, India*

Background: Hyper IgD syndrome (HIDS) is a rare autosomal recessive inflammatory genetic disorder characterized by periodic attacks of fever associated with joint pain, skin rash and abdominal pain. It is caused by inherited mutations in Mevalonate kinase gene that leads to decreased activity of the enzyme mevalonate kinase (MVK)[1]. Patients have MVK enzymes with reduced but not abolished activity. The prevalence is unknown but the estimated incidence is around 200 patients worldwide.

Objective: To describe Clinical and Laboratory features of a case of Hyper IgD syndrome

Methodology: Case study at a Tertiary care centre, Mumbai

Case: 11 months male infant 2nd BO, BONCM, brought with complaints of fever since day 15 of life, recurring every 8-15 days, lasting for 3-4 days in each episode. Fever is associated with skin rash which is maculopapular, generalized and decreases when fever subsides. Fever is also associated with cough and enlargement of cervical lymph nodes. Lymph nodes would regress to normalcy once the fever subsided. Child had episodes of recurrent anal abscess with fever (at 3 months), 3 episodes of dactylitis (at 5 months) and 1 episode of pneumonia. Birth and developmental history is insignificant. No significant family history was observed. Child was treated symptomatically with paracetamol during attacks. On examination, child had erythematous skin rash and cervical lymphadenopathy. Systemic examination revealed no abnormality. Child was primarily investigated for immunodeficiency disease. Investigations revealed high leukocyte count with elevated ESR. Serum IgA levels were normal. Blood sample sent to Maryland for immunodeficiency work up was positive for Hyper IgD with a novel pathogenic mutation in MVK gene (1097A>G, D366G homozygous). Patient is currently under follow up with acute episode being treated with paracetamol, steroids and planned for Anakinra.

Discussion: HIDS is caused by genetic mutation of MVK gene. This mutation is uncommon and most patients are Caucasians living in western European countries. It begins in first year of life with bouts of fever lasting for 3-7 days. HIDS may be associated with diffuse skin rash, joint pain, petechie, purpura and enlarged cervical lymph nodes. During the symptom flares child is non infectious and the flares taper within a few days. One of the differentials is Cryopyrin associated periodic syndrome (CAPS) which has longer duration of flares. HIDS patients have attacks throughout life with the greatest frequency being in childhood and adolescence.

Conclusion: Hyper IgD syndrome should be suspected in a child with early onset "attacks" of fever associated with skin rash and lymphadenopathy. With increased inflammatory markers (raised ESR and CRP) during flares, a raised IgD levels (N <100 IU/ml) is helpful in diagnosis. Various anti cytokine treatment modalities are available (Anakinra, Etanercet, Anti-TNF agents[2], lenalidomide, NSAIDS), the efficacy of whom has not been completely established.

PID_ALP_ID-1_V1.3

CHRONIC GRANULOMATOUS DISEASE: CASE SERIES

Purva Kanvinde [1], Prasad Taur [1], Ankit Parmar [1], Naseer [1], Mukesh Desai [1], Manisha Madkaikar [2], Manasi Kulkarni [2], Mrinal Joshirao [1], Sangita Mudaliyar [1], Archana Swami [1], Nitin Shah [1], Bharat Agrawal [1]. [1] *Division of Immunology, Bai Jerbai Wadia Hospital, Mumbai, India;* [2] *National Institute of Immunohaematology (NIIH), K.E.M. Hospital, India*
E-mail address: purvakanvinde@gmail.com (P. Kanvinde).

Abstract

Summary: There is a paucity of data on CGD from developing countries. We aim to study the clinical profile, microbiological spectrum, treatment approach and response in children diagnosed with CGD in a tertiary care hospital over a span of 9 years.

Introduction: Chronic granulomatous disease (CGD) is a rare inherited immunodeficiency disorder with an incidence of 4-5 per 1 million individuals; it is caused by 4 genes, 1 X-linked and 3 autosomal recessive in