A Novel Homozygous Deletion Mutation in Recombination Activating Gene 1 in Saudi Infant with atypical Omenn Syndrome

*Mohammed A. Al-Suhaibani[1]

ABSTRACT

Omenn syndrome is a form of severe combined immunodeficiency associated with erythrodermia, hepatosplenomegaly, lymphadenopathy, diarrhea, alopecia, and failure to thrive. The recombination activating enzymes RAG1 and RAG2 have a crucial role in both B and T cells development. The majority of mutations are missense mutations in recombination activating genes RAG1 and RAG2. We report a 4 months old Saudi girl with a novel homozygous deletion mutation in recombination activating gene 1.

الملخص

متلازمة أومن هي حالة لنقص المناعة المركب الشديد وتكون مصاحبة لاحمرار في الجلد وتضخم في الكبد والطحال وتضخم في العقد اللمفاوية والإسهال والثعلبة وفشل في نمو الجسم. الجينات (RAG1) و(RAG2) لها دور حاسم ومهم في نمو وتطور الخلايا المناعية التائية والبائية. معظم الطفرات في هذه المتلازمة هي طفرات مغلطة في الجينات (RAG1) و(RAG2). نعرض هنا حالة رضيعة سعودية لديها متلازمة أومن ولديها طفرة جينية متماثلة غير مألوفة في الجين (RAG1).

INTRODUCTION

Omenn syndrome is an autosomal recessive form of sever combined immunodeficiency (SCID) characterized by erythroderma, desquamation, alopecia, persistent diarrhea, failure to thrive, lymphadenopathy and hepatosplenomegaly [1]. The immunologic defects are characterized by hyperesinophilia, hypogammaglubenimia, high level of IgE and virtual absent of circulating B cells. The T cells can be normal in number, but they present oligoclonal and nonfunctional. Most of the Omenn syndrome patients have mutation in recombination activating genes RAG1 and RAG2 which have been mapped to chromosome 11p13 [2].

An early diagnosis within the first three months of life will provide better protection for Omenn syndrome patients from infection and improve transplantation outcome [3]. Omenn syndrome is potentially fatal disease if untreated. The patients are prone to have bacterial, viral and fungal infections as in other forms of severe combined immunodeficiency. Allogeneic hematopoietic stem cell transplant has treated the condition successfully [4]. Here, we describe a 4 months old Saudi female infant with atypical feature of Omenn syndrome. The patient was shown to have a novel homozygous deletion in recombination activating gene 1.

CASE REPORT

We report the case of the 4 months old girl a product of uncomplicated pregnancy, born at full term by spontaneous vaginal delivery and with birth weight of 3.3 kg. She was born for consanguineous parents with a family history of older sibling who died due to congenital anomaly at neonatal period. She has received BCG and hepatitis B vaccines at birth.

She was admitted to our hospital at age of 4 months because of fever and skin rash. The patient had generalized scaly erythematous skin rash since birth, which involve the whole body and the scalp. Subsequently, she started to have hair loss, diarrhea and fever.

The physical examinations revealed unwell looking, dehydrated, tachypnic and febrile baby .she had generalized erythematous maculpopular rash with scaly scalp and skin. There were generalized lymphadenopathy, hepatomegaly with no splenomegaly. Overall, the cardiovascular and neurological exam were normal.

Received on: May 12, 2014 *Accepted on: June 14, 2014*

*Correspondence: suhaibani7@gmail.com
[1]Pediatric Resident in King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia

The initial CBC the following result: leukocyte count of 44×10^9/l, of which the neutrophil count was 5.3×10^9/l, and lymphocyte count was 29.6×10^9/l. The eosinophil count was 7.22×10^9/l. Hemoglobin count was 8.15g/dl and the platelet count was 343. Lymphocyte marker revealed an absolute lymphocyte count of 28 $\times10^9$/L, absolute CD3+ 26.5 $\times10^9$/L (95%), absolute CD4+ 2 $\times10^9$/L (7.3%), absolute CD8+ 14.5 $\times10^9$/L (51.4%), absolute CD19+ 0.01 $\times10^9$/L (0.04%), and absolute CD16+/CD56+ 1 $\times10^9$/L (4.6%). IgG, IgM and IgA were low with normal serum IgE levels (30.2 Ku/L).

The patient's Blastogenesis showed marked depression in lymphocytes response to phytohemagglutinin (RR 41%), concanavalin A (RR 25%), pokeweed mitogen (RR 32%) and pooled allogeneic cells (RR 14%).

TORCH screening for congenital infections showed positive IgG and negative IgM immunoglobulin for Epstein Barr virus, cytomegalovirus virus, rubella and toxoplasmosis. HIV was negative.

On the other hand, a computed tomography of the chest showed patchy consolidation bilaterally, nodular opacities in both upper lobes and minimal left pleural effusion. In addition, there are multiple enlarged lymph nodes seen in both axillae. (Figure 1)

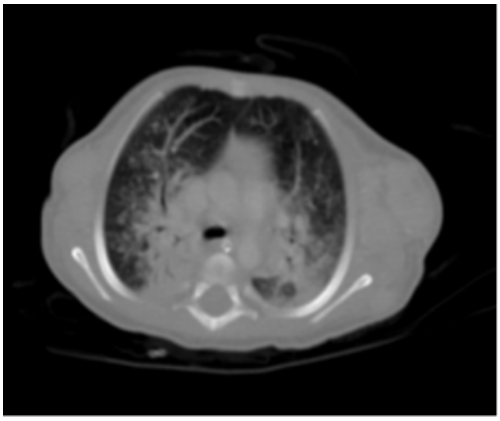

Figure 1: Chest CT scan showed consolidation of the posterior segment of the right and left upper lobe. There is patchy ground-glass opacification with Multiple nodular opacities in both upper lobes more on the right side .also, it showed multiple enlarged axillary lymph nodes.

Histopathological examination of the lung was consistent with CMV infection. The inguinal Lymph node biopsy PCR was positive for mycobacterium tuberculosis and it showed non necrotizing granulomatous lymphadenitis. (Figure 2) (Figure 3)

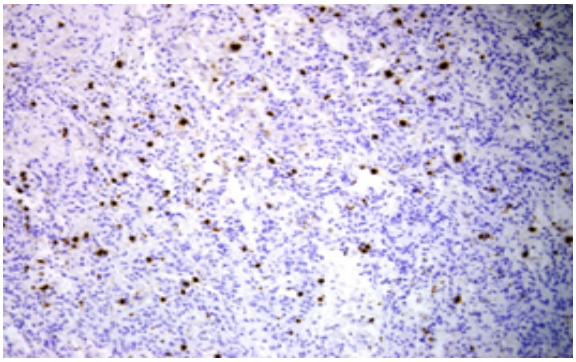

Figure 2: Sections from an intraoperative lung biopsy Immunohistochemistry stains for CMV infection was done and showed strong nuclear positivity.

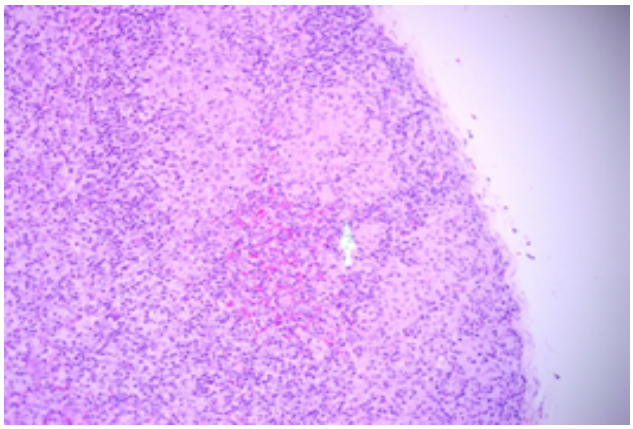

Figure 3: Sections from an excised lymph node show a reactive process exhibiting several non-caseating ill-defined granulomas.

The sequence analysis of RAG1 gene identified two copies of a single nucleotide deletion (c.555delG) in the coding region of the RAG1 gene in this patient. This mutation (c.555delG) predicts a sequence frame shift due to juxtaposition of the first nucleotide of codon 186 to the second nucleotide of codon 185, inserting 14 amino acid and a premature termination codon (X) in exon 2 of RAG1 protein (p.K186SfsX15). The gene result indicates that our patient is likely affected with Omenn syndrome due to the presence of novel homozygous disease causing single nucleotide deletion (c.555delG) (p.K186SfsX15) in exon 2 of RAG1 gene.

The patient has been treated with broad spectrum antibiotics, intravenous immunoglobulins, anti-tuberculosis, anti-fungal and gancyclovir. She had persistent tachypnea, respiratory distress and recurrent fever. Therefore, she needed a pediatric

intensive care unit admission. She had a full match donor (her brother) but unfortunately she died at the age of 6 months due to respiratory failure and sepsis before bone marrow transplantation.

Discussion

Omenn syndrome was first described as "familial reticuloendotheliosis with eosinophilia" in 12 infants by Omenn1 in 1965. It is an autosomal recessive disease that manifest as exfoliative dermatitis, followed by lymphadenopathy, hepatosplenomegaly, alopecia, diarrhea, failure to thrive and recurrent life threatening infections. Usually they are presented within the first weeks of life with generalized dermatitis that may be misdiagnosed as eczema. However, the dermatitis has a pachydermatis appearance that progress to desquamation [5,6].

The differential diagnosis of the Omenn syndrome include severe atopic dermatitis, graft vs. host disease (GVHD), Hyperimmunoglobulin E (HIE) syndrome, and histiocytosis X. Laboratory findings include hypereosinophilia and hypogammaglobulinemia. IgE serum levels are usually increased in the absence of detectable B lymphocytes in peripheral blood, skin and lymph node tissues. Lymphocyte stimulation with mitogens, phytohaemagglutinin (PHA), concavalin A (con A) and Pokeweed Mitogen (PWA) are absent or profoundly reduced [7].

On the other hand, the skin biopsy in Omenn syndrome usually revealed epidermal basal vacuolization, apoptosis of keratinocytes, acanthosis and parakeratosis [8,9]

The recombination activating enzymes RAG1 and RAG2 are mandatory in the assembly of V (D) and J segments. The gene comprises 2 exons; encodes 1043 amino acid protein with ATG start codon present with exon 2. Most of the Omenn syndrome patient has mutation in recombination activating genes RAG1 and RAG2 which have been mapped to chromosome 11p13. This enzyme plays an important role in process of assembling the V (D) and J (Variable, Diversity, and Joining) segments which led to generation and development of both B and T cells. So, impaired effective V (D) and J recombination will lead to markedly reduced number of T and B lymphocyte [10].

Recently, there were many cases of Omenn syndrome have been reported to have DCLRE1C, LIG4, IL7RA, ADA, RMRP, and CHD7 gene mutation which are responsible of this peculiar immunodeficiency [11-16].

In Saudi Arabia, there were many cases of Omenn syndrome reported to have S401P and R396H mutations in RAG1 gene, and a novel I444M mutation in RAG2 gene [17,18].

This is the first report in the literature showing a novel homozygous deletion mutation causing single nucleotide deletion (c.555delG) (p.K186SfsX15) in exon 2 of RAG1 gene. This mutation is expected to result in sever reduction of the nonfunctional recombination activating protein due to either nonsense mediated mRNA decay and /or rapidly degraded truncated protein.

Our patient is presented with a progressive diffuse erythrodermic scaly skin rash since first week of life. Also, she had some clinical manifestations of Omenn syndrome that are characterized by hepatomegaly, generalized lymphoadenopathy and alopecia. The white blood cell count was elevated mainly lymphocytosis with elevated eosinophil and the IgE level was normal .all lymphocytes were CD3+. There were oligoclonal predominance of activated memory cells CD4 and marked depression in the lymphocyte response to phytohemagglutinin PHA. Our patient had several atypical characteristics of Omenn syndrome like normal spleen and normal IgE level.

Conclusion

There is variability in the clinical and laboratory characteristics of Omenn syndrome .many gene mutations have been discovered recently .Early diagnosis of Omenn syndrome is very important to initiate appropriate treatment .the delay in the diagnosis can be lethal. After all, Genetic counseling should be considered for family future planning.

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