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Transfusion Dependent Anemia, and Cytopenia Secondary to Parvovirus B19 Infection as the First Manifestation of X-linked Hyper IgM Immunodeficiency Syndrome in Two Male Patients in Their Third Decade of Life

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ABSTRACT

We describe two male patients with unique mutation of CD40L gene, unlike classic presentation of X-linked hyper IgM immunodeficiency syndrome (XHIGM syndrome), both were healthy until presenting in their early twenties with a challenging symptomatic transfusion-dependent anemia, investigations confirmed XHIGM syndrome with concurrent chronic Parvovirus infection.

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Background

Hyperimmunoglobul in-M(HIGM) syndromes are a rare heterogeneous group of primary immunodeficiency disorders characterized by defects of immunoglobulin class switch recombination (CSR), with or without defects of somatic hypermutation (SHM) [1]. This leads to lowlevels of IgG, IgA, and IgE with normal or elevated levels of IgM, and poor antibody function [2]. HIGMsyndromes are genetically determined and are further subdivided into 5 sub-groups based on the affected gene: CD40L deficiency (XHIGM), activation induced cytidine deaminase (AID) deficiency (HIGM2), CD40 deficiency (HIGM3), HIGM4, Uracil N-glycosylase (UNG) deficiency (HIGM5).

The most common form of HIGM is XHIGM, which is inherited in an X-linked manner, constitutes around 70% of cases, with an estimated prevalence of 1:1,000,000 males, and is caused by defects or deficiencies in CD40 ligand (CD154) [3,4]. The disease-causing gene of XHIGM is CD40L, located on Xq26.3-Xq27 [5]. CD40L is expressed primarily on activated CD4+T cells, and interacts with CD40 expressed on B- cells, monocytes, macrophages, and dendritic cells. CD40L-CD40 interactions stimulate germinal center development of B-cells and is essential for the initiation of CSR and SHM [1]. These interactions also provide a co-stimulatory signal for T-cells, and lead to T-cell activation and thus gene mutation leads to impairment of NK- and T-cell cytotoxicity, reduced or absent antigen-specific responses [6]. The combined T and B immunological defect is clearly illustrated by the susceptibility of patients with XHIGM to recurrent infections, autoimmune disorders and malignancies [4].

Half of the males develop symptoms by year one of age, and by year four of age more than 90% are symptomatic [6]. The most common infections include recurrent upper and lower respiratory tract bacterial infections, opportunistic infections like Pneumocystis jirovecii, fungal infections, and infectious or non-infectious protracted diarrhea that can lead to failure to thrive. Liver manifestations are prognostically important since chronic CMV and cryptosporidium infection can lead to cirrhosis and cholangiocarcinoma [7,8]. Other reported long term complications are malignancies including hepatocarcinoma, neuroectodermal tumor of gastrointestinal tract and pancreas, as well as lymphoma, and autoimmune disorders like inflammatory bowel disease and chronic arthritis. Hematologic manifestations of the syndrome include chronic neutropenia, anemia and less commonly, thrombocytopenia. Neutropenia could be chronic, episodic, or cyclic, and is usually related to infections. Anemia when it occurs could be multifactorial and might be caused by one or more of the following factors: anemia of chronic disease, iron deficiency, rarely aplastic and/or Coomb's positive hemolysis [9].

Human Parvovirus-B19 belongs to the Erythro-parvovirus genus within the Parvo-viridae family, and among this family, B19 is the only known Parvovirus to be pathogenic to humans, clinical manifestations vary depending on the immunologic status of the affected host [10]. Parvovirus-B19 infection in children with intact immune system is considered a common, self-limited disease and usually causes a mild febrile illness known as erythema infectiosum while in adults it may cause arthritis. On the other hand, when immunocompromised patients get exposed to Parvovirus-B19, their immune system is unable to produce neutralizing antibodies, viremia persists and might lead to aplastic anemia and RBCs aplasia which is usually seen in bone marrow biopsy in addition to the characteristic giant pro normoblast with viral inclusions [10].

Rarely, certain CD40L mutations can result in mild phenotypes of XHIGM, these patients remain asymptomatic and undiagnosed

with the disease manifesting only after exposure to Parvovirus-B19 infection [11].

Case Presentation

Case 1 is a 20-year-old male, who had completely normal childhood with no recurrent infections, presented with intermittent transfusion dependent anemia of unknown cause despite extensive laboratory, radiological, infectious and autoimmune investigations over 6 years. He had cyclic episodes of fever of unknown origin, weight loss and night sweating accompanying the drop in hemoglobin with hepatosplenomegaly. Despite relatively prolonged periods of spontaneous remissions for almost 3 years the patient relapsed and became progressively transfusion-dependent, needing transfusion almost every 2-3 weeks with thrombocytopenia, and neutropenia (Table-1-A). His initial bone marrow biopsy only showed evidence of ineffective erythropoiesis. A repeat bone marrow biopsy showed erythroid hyperplasia with maturation arrest. The immature erythroid precursors appear enlarged with occasional cytoplasmic blebbing and intranuclear viral inclusions (Figure-1-A). Frequent large, disintegrated cells seen in the background with large nucleus, pale chromatin and eosinophilic nucleoli like inclusions (Figure1-B). The trephine biopsy revealed marked hypercellularity (~98%) with significant erythroid hyperplasia, reduced and left shifted granulopoiesis and adequate megakaryopoiesis. Multiple giant pronormoblasts with eosinophilic inclusions and peripheral chromatin condensation (Figure 1-C).

Molecular Myeloid Panel showed low level molecular abnormalities, all found in <10%, those abnormalities resolved in a subsequent bone marrow biopsy.

In view of the bone marrow biopsy findings Parvovirus PCR was sent and it detected Parvovirus genetic material (Table 1-B). It is very unlikely for Parvovirus-B19 to cause such a picture in immunocompetent patient. The infection with Parvovirus raised the possibility of an immunodeficiency, syndrome and led us to perform whole exome sequencing, the result of which revealed the presence of a mutation in the CD40 ligand (Table-1-C). He was born of a consanguineous marriage; his mother was negative for the same mutation with negative maternal family history of similar condition making his diagnosis as de novo XHIGM. Immunoglobulin levels were checked, and indeed, he had mildly elevated IgM 6.49 g/L, slightly low IgG 6.93 g/L and normal IgA.

The patient was treated with Intravenous immunoglobulins (IVIG) course for Parvovirus infection 1 gm/m2 for three days, then continued monthly IVIG of 400mg/kg. Shortly after the IVIG infusion, he had tremendous response in his CBC (Table-1-A) and complete normalization of symptoms.

Case 2 is a 22-year-old male, who also had completely normal childhood, with history of recurrent mild sinusitis and ear infections, presented with symptomatic anemia his hemoglobin has fallen to the low levels of 4.8g/dl and neutropenia (Table-1-A). He had hepatosplenomegaly, investigations ruled out hemolysis. He had severe reticulocytopenia and viral serology was positive for Parvovirus-B19 IgM (Table-1-B). Bone marrow examination showed similar features to case 1, based on our previous experience with the first patient, which raised the suspicion of immunodeficiency syndromes, whole exome sequencing was sent and showed CD40L gene mutation (Table-1-C), Immunoglobulins level showed mild elevation of IgM 3.7g/L with low IgG 1.13g/L and very low IgA <0.05 g/L. The patient required four transfusions and it took him around 30 days to become transfusion independent and another 60 days before normalization of his hemoglobin. Patient was born of a consanguineous marriage. Family members testing is currently being conducted.

The definitive therapy of the severe forms of this syndrome is bone marrow transplantation, but the benefit of transplant in our two patients is questionable given their mild phenotype and the absence of infections and other complications.

Table-1-A	**Case 1**		**Case 2**	
CBC Reference Value	**Pre- treatment**	**Post- treatment**	**Pre-treatment**	**Post treatment**
WBCs 4.0-11.0 x10^9/L	1.6	8.3	2.5	3.9
ANC 2.00-7.50 x10^9/L	0.64	2.62	0.62	1.03
Hemoglobin 13.0-18.0 gm/dL	5	16	4.8	13.3
Platelets 150-450 x10^9/L	62	94	245	130
Table-1-B	**Viral serology and PCR**			
Parvo B19 IgM	Positive		Positive	
Parvo B19 IgG	Positive		Negative	
Parvovirus B19 DNA (PCR)	Positive		Positive	
Table-1-C	Whole exome sequencing			
Gene	Mutation of CD40LG		Mutation of CD40LG	
Variant coordinates	ChrX(GRCh37):g.135730422C>A NM_000074 . 2: c.15C>A p.(Tyr5*)		ChrX: 135741549 c.761c>T p.(Thr254Met)	
Type and classification	Stop gain Likely pathogenic Class 2		Pathogenic	

All published cases with XHIGM and Parvovirus B19 induced anemia in adolescents and young adults

Table -2	Author	Age at presentation (years)	Clinical manifestation	Parvovirus B19 status	Mutation detected	Immunoglobulins level	Treatment received	Response	
Case 1(11)	Seyama	14	Fatigue, pallor (anemia, mild neutropenia)	B19 DNA detected in serum by polymerase chain reaction (PCR)	CD40L Thr 254 Met	IgG	214 mg/dl	IVIG	Anemia resolved
						IgA	<7 mg/dl		
						IgM	383 mg/dl		
Case 2(11)	Seyama	8	Pancytopenia, bone marrow resembling myelodysplasia	B19 demonstrated in the archived bone marrow smears	CD40L Arg 11 stop	IgG	160 mg/dl	IVIG	Anemia resolved, mild thrombocytopenia
						IgA	22 mg/dl		
						IgM	285 mg/dl		
Case 3(11)	Seyama	17	Fever, fatigue, abdominal pain splenomegaly (anemia) (right upper lobe pneumonia)	A banked bone marrow biopsy, using immunoperoxidas e staining, was found to have intranuclear inclusions positive for B19	CD40L IVS2 + 2 t > a	IgG	267 mg/dl	IVIG	Anemia resolved, splenomegaly disappeared
						IgA	71 mg/dl	IVIG	
						IgM	518 mg/dl		

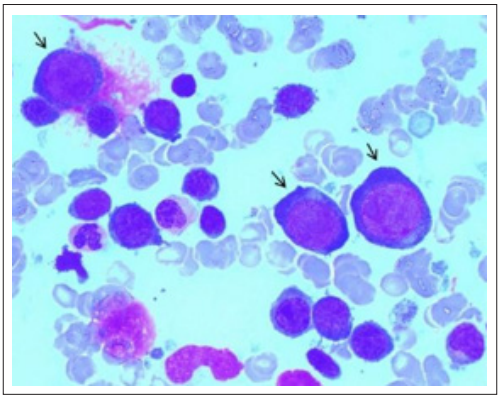

Figure 1A: Bone marrow aspirate showing erythroid precursors infected with parvovirus B19

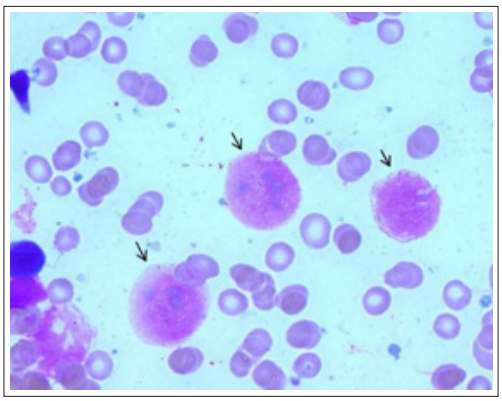

Figure 1B: Large disintegrated erythroblasts with viral inclusions

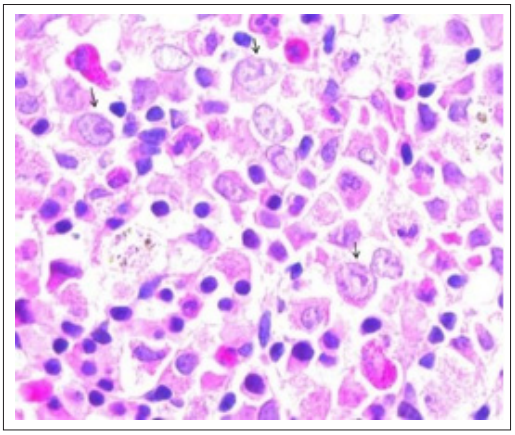

Figure 1C: Giant erythroblasts with eosinophilic viral inclusions in bone marrow trephine biopsy

Discussion

Classical XHIGM syndrome, presents in the early years of life, usually with different presentations mainly infectious, here we are reporting two unique patients with a rare presentation in regard to the age of presentation and to the presentation itself, as both presented with chronic anemia induced by Parvovirus-B19 infection manifested after the age of 20 years.

Case 1 had milder phenotype, but there was a delay in the diagnosis, while case 2 had severely low IgA level which explains recurrent sinusitis.

From a hemato-pathologic point of view despite the presence of typical morphological finding associated with Parvovirus-B19 infection in the first patient, this was masked by the marked hypercellularity and the associated dyserythropoesis. The picture further complicated by the low level myeloid molecular findings which diverted the differential diagnosis temporarily into the direction of myelodysplastic syndrome. Therefore, high index of

suspicion should be practiced in such cases with unexplained non-hemolytic anemia or pancytopenia looking for any morphological feature of Parvovirus-B19.

A national registry in the United States was developed to provide clinical information on patients from 60 unrelated families with XHIGM syndrome. In this report; 50% were symptomatic within their first year of age and 90% by age 4 years [3]. Later in life presentation has been reported; but has been mostly related to delayed diagnosis rather than delayed presentation [12,13].

Among the infections reported, pneumonia was the most prevalent, occurred in 80%, followed by upper respiratory tract infections which occurred in 49% including sinusitis and otitis media, and less frequently reported infections like CNS infection, skin and soft tissue infection, and osteomyelitis [3].

Mild phenotypes of XHIGM are reported, usually associated with hypomorphic mutations of CD40LG gene that don't eliminate protein function or expression, which results in milder phenotypes with atypical presentations, late onset presentation and less infections; making diagnosis more difficult [13]. There hasn't been in the literature a clear association between specific mutations and the clinical phenotype of the patients. In a retrospective analysis of 98 patients with XHIGM syndrome, only six had mild clinical phenotype, three out of the six patients presented with Parvovirus-B19 induced anemia, these three patients were completely asymptomatic until they developed chronic anemia caused by Parvovirus-B19 infection at the ages of 8, 14, and 17 respectively, and all the three patients responded well to IVIG [11]. (Table-2) One of the three mild phenotype presenting with Parvovirus infection induced anemia had the same mutation expressed by case 2 which is a missense mutation Thr 254 Met, while case 1 had a stop gain mutation which is a very rare variant that has not been published yet in any of the genetic databases and classified as likely pathogenic based on ACMG (American College of Medical Genetics) recommendations.

In conclusion we are reporting 2 cases of a late presentation of XHIGM. The similarity between the 2 cases is the occurrence of protracted anemia requiring blood transfusions from an unexpected relatively benign virus. The other point of similarity is their relatively late presentation probably indicating a milder form of disease from these 2 reported mutations. The occurrence of such a clinical scenario ought to raise a high index of suspicion of an underlying immunological disorder. We believe in the era of easily accessible molecular diagnostics more undiagnosed cases will come to light with heightened awareness of this condition.

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