CASE REPORT
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Neonatal Onset of Hemophagocytic Lymphohistiocytosis Due to Prenatal Varicella-Zoster Infection in a Neonate with Griscelli Syndrome Type 2

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ABSTRACT

Griscelli syndrome (GS) type 2 is an inborn error of the immune system classified as immune dysregulation. This autosomal recessive disease has three types with different genetic causes. In all variants, hypopigmentation is common, but neurological involvement or immunodeficiency varies in severity. The known genetic defects associated with GS include mutations in myosin 5 A (GS type1), guanosine triphosphate binding protein (GS type 2), and human melanophilin (GS type 3). Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition and is characterized by severe, ineffective, and uncontrolled inflammatory reactions. A HLH can be classified as primary or secondary, with secondary resulting from autoimmunity, malignancy, spontaneous or infectious causes. Many prenatal infections can cause long-term complications in the fetus, including toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis, parvovirus, and varicella zoster (known as TORCH syndrome). Prenatal infections have been associated with TORCH for a long time, but HLH is a rare complication. The report presents a case of HLH with symptoms of sepsis, organomegaly, and cytopenia from the time of birth. A genetic test confirmed Griscelli Syndrome Type 2, which was diagnosed during an immunologic consultation regarding partial albinism not seen in family members. Prenatal infection was the only approved finding in the investigation into the trigger of HLH in this patient starting in the first days of life. Accordingly, the patient was diagnosed with type 2GS syndrome with neonatal-onset HLH caused by a prenatal infection.

Keywords: Griscelli syndrome type 2; Hemophagocytic lymphohistiocytosis; Primary immunodeficiency diseases

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INTRODUCTION

Primary inborn errors of immunity refer to a set of diseases that, due to one or more genetic defects, the number or function of one or more components of this system is disturbed to different degrees. The site of infection, organism, age of onset, autoimmunity, allergy, and the presence of certain physical characteristics can be considered as a clue.[1]

In Griscelli syndrome type2, which is classified under the set of partial albinism with immunodeficiency, hair color can be considered as a clue for the approach.[2-3]

Griscelli syndrome has three different types with different genetic defects and different clinical manifestations. A range of immune defects, neurological disorders with pigmentation defects of varying degrees are the main clinical manifestation.[4-5] This syndrome, infections not only as a pathogen but also as a trigger of regulatory disorder in the immune system can cause fatal conditions named as HLH.[6]

In this article, we introduce a patient with Griscelli syndrome type2, who suffered from an intrauterine infection that caused HLH in the first days of birth.

Case Presentation

Infection, autoimmunity, allergy, cancer and immune regulation are mentioned as inborn error of immunity manifestations.

A Term neonate who was admitted to the hospital in the first hours of birth with petechiae, tachypnea, and pancytopenia was treated with an antibiotic with the diagnosis of sepsis. Our patient was the 3rd child born to consanguineous parents by cesarean section with normal APGAR. His birth weight was 2990g. Blood, urine, and cerebrospinal fluid (CSF) cultures were negative but neutropenia and thrombocytopenia were the only noticeable findings. TORCH study and maternal autoimmune screening were requested.

He was hospitalized and treated with a possible diagnosis of sepsis and was discharged in good general condition after 9 days. His mother had a good condition after a cesarean section. She had a history of two abortions and admission for viral pneumonia of ricella infection with antiviral therapy (Acyclovir) in the 3rd trimester at 34 weeks of gestational age. At the next follow-up visit, which took place 10 days after discharge, the patient was pale with hepatosplenomegaly, but the general condition was good. He was admitted for the second time and an antibiotic and acyclovir were started. Within the next week, the patient's general condition worsened and he was referred to our hospital due to a lack of response to treatment. At the beginning of hospitalization in our ward, he had a fever and oral candidiasis. Petechiae, tachypnea, hepatosplenomegaly, pallor, and oral candidiasis were remarkable in the physical exam. Bone marrow aspiration (BMA) was done for him due to pancytopenia. He fulfilled the HLH-94 diagnostic criteria (fever, splenomegaly, cytopenia, hypertriglyceridemia, high ferritin level, hemophagocytosis in bone marrow).[7] He had silvery gray hair on the face, scalp, eyelids, and eyebrows (Figure 1A), and had a different appearance from his parents and two sisters (They had brown skin color).

The direct Coombs test was negative. Varicella-Zoster IgG 2.9(more than 1.1 is positive), IgM 0.05 (less than 0.9 is negative) in the neonate and Varicella-Zoster IgG 3.2 (more than 1.1 is positive), IgM 0.23 (less than 0.9 is negative) in his mother. Blood, CSF, and urine culture were negative. chest radiography was normal. Ultrasonography of the abdomen revealed hepatosplenomegaly.

An echocardiography and brain CT were normal. Immunophenotyping showed normal flow (Table 1).

Cytometry of peripheral blood. Bone marrow aspiration showed hemophagocytic histiocytes (Figure 1B). A peripheral blood smear revealed no giant cytoplasmic granules in leukocytes. An uneven accumulation of large pigment granules was detected in hair shaft examination instead of the homogenous distribution of small pigment granules which is shown in normal hair. (Figure 1C and 1D). A whole-exome sequencing showed a homozygote frameshift deletion in Gene *RAB27A* NM_004580 in exon 4 of chromosome 15 (c.315_316delAA) OMIM 607624. This mutation was validated by Sanger sequencing in the parents but his sisters were not checked because of the unwillingness of his family. Griscelli syndrome was diagnosed and chemotherapy with etoposide-based treatment protocol HLH-94 consisted of 8 weeks of induction therapy and subsequent continuation therapy for 6 courses was started and after 14 courses, our patient achieved a good response, and treatment was continued with cyclosporine A and low dose prednisolone. The patient was referred for bone marrow transplantation at the age of 6 months. Here we introduced a term baby who was hospitalized with petechiae, anemia, and

tachypnea on the first day of birth. All infectious tests were negative and in the course of the disease, he developed hepatosplenomegaly, oral candidiasis, pancytopenia, and infiltration of hemophagocytic histiocytes in the bone marrow. Our patient fulfilled the HLH criteria[7] and the initial diagnosis of Griscelli syndrome was made based on a microscopic examination of hair follicles for characteristic abnormal melanin clumps.[8] The diagnosis of type 2 GS was confirmed by a genetic study that found frameshift deletion in the *RAB27A* gene.

In the prenatal history, the mother had chickenpox and pneumonia and the baby's silver hair color was noticeable on physical examination. The early diagnosis of GS is important because affected children are more susceptible to recurrent infection and/or hemophagocytic lymphohistiocytosis (HLH) both of which may lead to a fatal outcome. The type 2 GS caused by a mutation in the *RAB27A* gene is associated with a primary immunodeficiency due to dysfunction T-cell and impaired natural killer cytotoxic activity, which can enhance the susceptibility to repeated infections and life-threatening conditions diagnosed as HLH. Abnormal T-cell activation and inflammatory cytokine production due to cytotoxic deficiency are the main explained etiology in animal studies.[9] It is usually triggered by viral and bacterial infections, marked by periods of fever, hepatosplenomegaly, and pancytopenia. In this case, griscelli syndrome was the underlying disease and we think prenatal exposure to varicella virus led to early symptoms on the first day of life. This patient was not admitted to our hospital and because at the first and second admission HLH was not considered in the main differential diagnosis so we can't confirm HLH definitely at that time but we suggest that according to pancytopenia, fever, hepatosplenomegaly, and normal cultures our patient had HLH at the first admission, however in our hospital. He was exposed to viral infection when his mother was infected with varicella in the 3rd trimester consequently followed by an accelerated phase and positive criteria of HLH when he had one month old.

The clinical onset of GS occurs between 4 months to 7 years of age usually.[10] In a recent study on 12 patients with GS2, the age of onset ranged from less than 1 year to 21 years with a median of 9.5 years of age and the age at diagnosis ranged from 3 to 42 years with a median of 11. 5 years of age. In one case at the age of 11 years, he had a viral infection and died of HLH. Another case was also diagnosed with HLH with a prior EBV infection and died at the age of 39 years.[11] In a study in Turkey by Cetinkaya et.al, on 28 patients with HLH, the median age of the study population was 23 (4.3 to 117) months at the time of the diagnosis of HLH.[12]

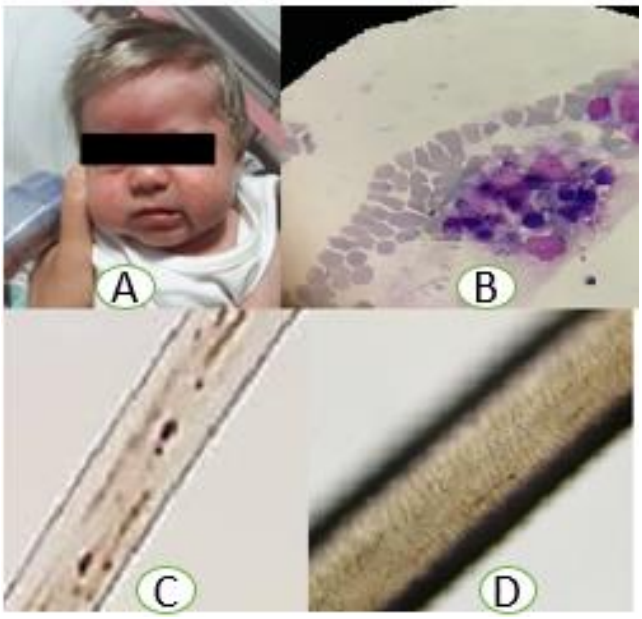

Figure 1. Patient appearance with silvery gray hair on the face, scalp, eyelids, and eyebrows (A). A hemophagocytic histiocyte in the bone marrow (B). Hair shaft of the patient with abnormal melanin clumps (C). Normal hair shaft (D)

Table 1. Laboratory findings

Test	First admission	Third admission	Normal
Leukocyte count	5400 Lymphocytes 65.8 Neutrophils 12.1 Monocytes 14% Basophils 0.6% Eosinophils 7.5%	5200 Lymphocytes 77% Neutrophils 4.4 Monocytes 15% Basophils 0.6 Eosinophils 3%	9000-30000 cells/mm^3
Total erythrocyte count	2.88	2.5	4-5.5×10^6 cells/mm^3
Hemoglobin	9.5	6.7	13.7-20.1 g/dL
Hematocrit	28.5	21.6	45-65 %
Platelet count	60000	50000	150-450 ×10^3 cells/mm^3
MCV	100	86.4	99-115 fl
MCH	33.5	28.4	33-39 pg/cell
MCHC	33.3	32.9	30-36 g/dl
*ESR	9	14	4-20 min 1st hour
**CRP	10.7	< 6	0-0.5 mg/dl
^PT	14.5	13.7	10.1-15.9 sec
^^PTT	37.9	35	31.3-54.3 sec
∞AST	262	35	15-60 µ/L
∞∞ALT	248	57	13-45 µ/L
Alkaline phosphatase	634	543	150-420 µ/L
Varicella-zoster virus Ab IgG	3.22 (positive)	-	<0.8 Negative 0.8-1.1 Border line ≥1.1 Positive
Varicella zoster virus Ab IgM	0.23 (negative)	-	<0.9 Negative 0.9-1.1 Border line ≥1.1 Positive
Fibrinogen	-	61	135-300 mg/dL
Ferritin	-	1785	200-600 ng/mL
LDH	-	600	180-430 µ/L
TG	-	607	<200 mg/dL
Cholesterol	-	109	<200 mg/dl
IgG	-	424	430 ∓119 mg/dL
IgM	-	60	30∓11 mg/dL
IgA	-	0.2	21∓113 mg/dL

IgE	-	4	21∓113 mg/dL
CD3	-	79% (absolute count: 4854)	2500-5500
CD4	-	52% (absolute count:3198)	1600-4000
CD8	-	23% (absolute count:1454)	560-1700
CD19	-	11% (absolute count:676)	300-2000
CD20	-	13% (absolute count:799)	773-1990
CD56	-	25% (absolute count:1537)	170-1100
CD16	-	37% (absolute count:2275)	170-1100

* Erythrocyte sedimentation rate
** C-Reactive protein
^ Prothrombin time
^^ Partial prothrombin time
∞ Aspartate aminotransferase
∞∞ Alanine aminotransferase
× Triglyceride

In a study in Egypt, 101 patients with HLH were enrolled and the median age at presentation was 13.1 months.[13] The most common causes of secondary HLH were viral infections (67%) of which Dengue was the most common (52%) followed by Epstein Barr virus (EBV) and HIV,[14] however, Griffin et al described that EBV is the most commonly identified infectious trigger of HLH.[15] Early-onset of symptoms on the first day of birth and prenatal infection with varicella virus are two points that distinguish our patient from other Griscelli syndromes in the literature. Early diagnosis is very critical and the appearance of the patient is an important clue. As a result, the finding of partial albinism in children should alert clinicians to consider GS since a simple method can confirm the diagnosis and early diagnosis is life-saving.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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