Case Report

Griscelli syndrome type 2 with deletion of entire RAB27A gene

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ABSTRACT

Griscelli syndrome (GS) type 2 is a rare autosomal recessive disorder caused by mutation of RAS-associated protein RAB27A gene located on chromosome 15. It is a hyper-inflammatory disorder with partial albinism and immunological impairment and/or severe neurological impairment. We describe the case of a 2.5-month-old boy with classic features of GS type 2 with early-onset hemophagocytic lymphocytic histiocytosis (HLH) and multiple recurrences. Genetic testing found homozygous loss of 68 kbp of RAB27A gene at chromosome 15 at cytoregion q21.3, suggestive of deletion of exons 1–5. This genotype of large deletion correlated with the clinical severity. He was managed as per HLH 2004 protocol and was awaiting bone marrow transplantation when he succumbed to his illness. The case is being presented not only as the disease is rare but also the mutation identified is extremely rare and awareness of it will help clinicians to manage the case appropriately.

Key words: Griscelli, HLH, Hypopigmentation

Griscelli syndrome (GS) is a rare autosomal recessive disorder that occurs due to the mutations of the genes involved in the transport of melanosomes in melanocytes. This disorder is classified into three subtypes (GS1, GS2, and GS3) based on the genetic loci involved. The genes involved are MYO5A (GS1), RAB27A (GS2), and MLPH (GS3). GS3 is limited to partial albinism alone, while GS1 also shows severe primary neurological impairment [1,2]. GS type 2 is due to mutations in the RAB27A gene which is located on chromosome 15q21.3. This gene encodes for a low molecular weight GTPase, RAB27A, which in addition to intracellular transport of melanosomes, plays an essential role in exocytosis of cytolytic granules in cytotoxic T lymphocytes and NK cells and secretory vesicles in endocrine cells [2]. The patients with GS-2 succumb to illness due to the accelerated hemophagocytic syndrome phase secondary to immunological impairment unless an early bone marrow transplant (BMT) is performed [3].

CASE REPORT

A 2.5-month-old boy, hailing from Bihar, fourth born of the non-consanguineous marriage, with a history of one sibling death in early infancy, presented with complaints of fever, cough, fast breathing, pallor, and abdominal distension for the 1-month duration. He was initially managed locally where he was found to have hepatosplenomegaly and bicytopenia. Fever used to be hectic with multiple spikes of 100–101 Fahrenheit daily. In view of persistent fever, organomegaly, and bicytopenia, the child was referred to our center for further management.

At presentation, the child had a fever, pallor, massive hepatosplenomegaly, and hypopigmentation of the skin and hair (Fig. 1). He had significant respiratory distress with refractory wheeze and was oxygen dependent for 3 weeks of the hospital stay.

Initial investigations included a complete blood count (CBC) and infective workup along with the nasopharyngeal aspirate and imaging to identify the cause of persistent fever, lower respiratory tract infection, and organomegaly. CBC showed hemoglobin of 5 g/dl, platelet count of 20,000/µL, and white cell count of 8400 cells/µL with relative lymphocytosis (65%). Peripheral smear showed no monocytosis. Infective workup including malaria antigen, dengue virus serology, Widal titers, blood culture, and nasopharyngeal aspirate for H1N1 was negative. TORCH IgM was also negative.

In view of persistent fever, cytopenia, and organomegaly, hemophagocytic lymphocytic histiocytosis (HLH) was suspected and serum ferritin, triglycerides, and fibrinogen were done which showed hypofibrinogenemia (182 mg/dl), hyperferritinemia (1036 ng/ml), and hypertriglyceridemia (307 mg/dl). Bone

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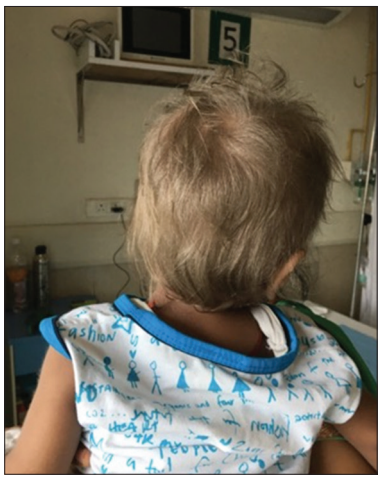

Figure 1: Hypopigmented hair of the 2.5-month-old boy

marrow examination showed dyserythropoietic changes with hemophagocytosis and there were no blasts. Ultrasonography of the abdomen showed hepatosplenomegaly and there was no other mass. Based on the clinical features and investigations, HLH was diagnosed. Hair mount examination was done in view of hypopigmentation of hair, which showed clumps of melanin. Perforin and Natural Killer (NK) cell degranulation were done to rule out the hypopigmentation syndromes with HLH predisposition.

On the basis of initial clinical presentation, differential diagnoses of acute leukemia, Juvenile myelomonocytic leukemia, HLH, and solid tumors were made. Later on, clinical history and examination along with laboratory findings pointed to a diagnosis of HLH. The diagnosis was made based on the HLH 2004 diagnostic criteria five out of the following nine diagnostic criteria for HLH: Fever, splenomegaly, cytopenias (affecting two or more of three lineages in the peripheral blood), hypertriglyceridemia, hypofibrinogenemia, elevated ferritin, hemophagocytosis in bone marrow/spleen/lymph nodes, low or absent NK cell activity, or elevated soluble CD25 (interleukin [IL]-2 receptor) [4].

In view of hypopigmented hair and HLH, the possibility of underlying hypopigmentation syndromes with HLH predisposition, such as Griscelli, Chediak-Higashi, or Hermansky-Pudlak syndrome was considered. Hair mount examination showed an irregular distribution of melanin clumps, based on which, the possibility of GS type 2 was entertained. Next-generation sequencing (NGS) report suggested homozygous deletion of a contiguous region corresponding to the entire RAB27A gene (exons 1-5) thus confirming the clinical diagnosis of GS Type 2. Since the sensitivity of NGS to detect large deletions is low, cytogenomic microarray analysis was done which indicated a homozygous loss of 68 kbp of RAB27A gene at chromosome 15 at cytoregion q21.3, suggestive of deletion of exons (1-5).

The child was started on HLH protocol with Dexamethasone at 10 mg/m^2/day. Intravenous immune globulin (IVIG) was given at 400 mg/kg/day for 2 consecutive days. He had significant respiratory distress with a refractory wheeze for which supplemental oxygen was given for 6 weeks. Injection etoposide was also given as per the HLH protocol. He was transfused two packed red blood cells (PRBC) as per requirement. After initial stabilization on HLH protocol, the child had multiple episodes of reactivation of HLH, usually triggered by viral respiratory infections.

At 2 years, he developed acute liver failure due to HLH reactivation; managed with dexamethasone and etoposide. At 2.5 years, he developed a central nervous system (CNS) reactivation which was managed with intrathecal methotrexate, along with systemic therapy for HLH for another episode of systemic reactivation. There was no human leukocyte antigen (HLA) matched related/unrelated donor identified and the family was making financial arrangements for haploidentical transplantation when he succumbed due to sepsis and aspiration pneumonia at 3 years of age.

DISCUSSION

It is well documented that GS type 2 is a rare, autosomal recessive disorder caused by mutations in the RAB27A gene located on chromosome 15q21.3. Location base-pair starts at 55202966 and ends at 5570922 consisting of 5 encoding exons (exon 2–6) [5]. Most common mutations found in GS 2 are generally substitution mutations and deletions, generally microdeletion, and large deletions involving 1 or 2 exons, in the exons or introns leading to nonsense and frameshift mutations [6,7].

A Hispanic child aged 1.5 years with immunodeficiency, liver dysfunction, and hemophagocytosis has been described with a novel 47 kb deletion [7]. However, deletion of the entire RAB27A gene (Exon 1-5) is very rare and there is only one such case report from a highly consanguineous Muslim Arab family from Israel [8]. Clinical diagnosis of GS2 can be considered in children who present with hypopigmentation and recurrent HLH [9]. The disease is fatal unless early bone marrow transplantation is done [10].

Our patient is similar in terms of the early onset of presentation, neurological deterioration with CNS hemophagocytosis, and liver failure described in the original kindred although our patient is from a non-consanguineous Hindu family. The case is being discussed for its rarity and to highlight that simple investigation such as hair mount and peripheral smear can help arrive at bedside diagnosis and that without bone marrow transplantation the outcome of these children is dismal.

CONCLUSION

Homozygous deletion of the contiguous region corresponding to the entire RAB27A gene (exons 1–5) is a rare mutation causing GS2. Clinical presentation of GS2 consists of a phenotypic presentation of hypopigmentation with recurrent HLH. The disease is fatal unless early bone marrow transplantation is done.

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