(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
GADIF IMPACT FACTOR: 1.49

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume2, Issue 1, Page No: 86-89
January-February 2019

Griscelli syndrome with Hemophagocytic Lymphohistiocytosis

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Type of Publication: Case Report
Conflicts of Interest: Nil

ABSTRACT

Background: Griscelli syndrome is a rare autosomal recessive disorder that results in pigmentary dilution of the skin and the hair (silver hair), the presence of large clumps of pigment in hair shafts, and an accumulation of melanosomes in melanocytes. It is characterized by partial albinism with common variable immunodeficiency and associated with hemophagocytic lymphohistiocytosis in accelerated phase of disease. Rare autosomal recessive disorder with about 60 cases reported worldwide[1,2]. The disorder is associated with profound cellular immunodeficiency and neurologic abnormalities such as seizures, ataxia and oculomotor abnormalities. Hemophagocytic lymphohistiocytosis (HLH) is an overwhelming activation of T lymphocytes and macrophages, leading to clinical and hematologic alterations. It is described as secondary HLH when seen in patients with systemic infection, immunodeficiency or underlying malignancy and may cause death in the absence of treatment.

Materials and Methods: A patient having silvery grey hair all over the body with repeated attacks of infection and splenomegaly was studied and literature was reviewed. Thorough investigations were carried out along with histopathological and genetic analysis.

Results: Griscelli syndrome with type 2 Hemophagocytic lymphohistiocytosis was diagnosed.

Conclusions: We present an unusual manifestation of immunodeficiency with characteristic phenotype of silvery grey hair all over body which should alert clinicians to consider Griscelli Syndrome. An early diagnosis and management may help prevent associated morbidities and mortality.

Keywords: Autosomal recessive, Griscelli syndrome, Hemophagocytic lymphohistiocytosis,Immunodeficiency.

INTRODUCTION

Griscelli and Prunieras [3] initially described Griscelli syndrome , or partial albinism with immunodeficiency, in 1978. Griscelli worked at Hospital Necker-Enfants Malades in Paris, France. Children with Griscelli syndrome caused by a defect in the *RAB27A* gene develop an uncontrolled T-lymphocyte and macrophage activation syndrome known as hemophagocytic syndrome (HS) or hemophagocytic lymphohistiocytosis (HLH) [4,5,6]. HS usually results in death unless the child receives a bone marrow transplant. Children with a defect in the *MYO5A* gene develop neurologic problems but no immunologic problems. Griscelli syndrome has got three types.

Griscelli syndrome type 1 is associated with pigmentary changes & neurological symptoms without immunodeficiency. The said mutation is in MYO5A gene. Griscelli syndrome type 2 manifests with diminished ability of cytotoxic T cells to kill target cells. The associated mutation is in RAB27A gene. Griscelli syndrome type 3 is associated with only pigmentary changes.

Background

4 year old male , second issue of second degree consanguineous marriage , presented with "being unwell " for 2 years. Recurrent episodes of fever and otitis media - treated with various antibiotics. Progressive abdominal distension (splenomegaly),

pallor and fever- treated with courses of antimalarials for last one and a half year. Multiple swellings in neck (cervical lymphadenopathy) – treated with antitubercular drugs for 3 months. Now patient was brought with high grade fever, jaundice, and tarry stools of 10 days duration.

On examination the child was malnourished (Protein energy malnutrition Grade III) ,febrile, pallor ++, icterus++ , clubbing+ , pedal edema +.Silvery grey hair all over the body, including eyebrows and eyelashes (Figure 1) . No petechiae, purpura or lymphadenopathy.

Systemic examination revealed splenomegaly of 9 cm ,firm, non tender. Firm hepatomegaly of 7cm, non tender (Figure 2). No evidence of free fluid.

Investigations

Haemogram : Hemoglobin 7.7 gm/dl ↓ , Total leukocyte count 6400/cu.mm, Differential Leucocyte Count : Neutrophils 34%, Lymphocytes 64%,Monocytes 1%,Eosinophils 1% . Platelets 20,000 /cu.mm ↓.

Peripheral blood smear showed absence of giant cytoplasmic granules in leucocytes thus excluding Chediak Higashi syndrome. Bone marrow smear (Leishman stain) showed haemophagocytosis (Figure 3) . Hair microscopy showed clusters of aggregated melanin pigment in medullary area of shaft (Figures 4 & 5).

Liver function and other tests: SGOT 183 IU / L ,SGPT 118 IU / L , serum alkaline phosphatise 745 IU / L ↑, Total bilirubin 5.9 mg % ↑ [Direct 3.9 mg % , Indirect 2.0 mg %], LDH 1394 IU / L ↑↑ , serum triglycerides 226 mg % ↑↑ , serum ferritin 1528 ng / ml ↑↑ , serum fibrinogen 286.7 mg / dl ↑ .

USG abdomen revealed hepatosplenomegaly with mild ascites.

Diagnostic criteria for HLH [7] : were fulfilled (5 out of the 8 criteria below).

A) Initial diagnostic criteria (to be evaluated in all patients with HLH)

Clinical criteria ✶ Fever ,✶ Splenomegaly . Laboratory criteria : ✶ Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood), ✶ Hypertriglyceridemia and/or hypofibrinogenemia.

Histopathologic criteria : ✶ Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy

B) New diagnostic criteria. : Low or absent NK-cell activity (according to local laboratory reference),

✶ Ferritin ≥ 500 microgram/L, Soluble CD25 (i.e. soluble IL-2 receptor) ≥ 2400 U/ml

[✶ Seen in our patient.]

Mutation Analysis

Mutation analysis revealed RAB27A mutation, diagnostic of Griscelli syndrome type 2.

RAB27A gene sequenced- homozygous for a C to T substitution leading to R184X mutation. Forward sequence shows T instead of a peak of C. Reverse sequence is the complementary strand showing A instead of G.

Father shows heterozygosity i.e. two peaks where there should be one; One allele has a normal C, other allele has T nucleotide at same position.

Final Diagnosis

Griscelli syndrome with type 2 Hemophagocytic lymphohistiocytosis

Course in Hospital : Otitis media treated with antibiotics. One unit of PCV transfused. Hemophagocytic lymphohistiocytosis (HLH) protocol (2004) of chemotherapy started. After 1 cycle of chemotheraphy child had a brief seizure which was possibly due to CNS involvement, known to occur in HLH. Patient had febrile neutropenia-, was treated with Vancomycin & Ceftriaxone. After treatment patient showed clinical improvement manifested by disappearance of fever, icterus, hepatosplenomegaly and no further convulsions or any neurodeficit.

Hematological and Biochemical improvement:

Hemoglobin 10.2 gm/dl , Total leukocyte count 12,200/cu.mm, Differential Leucocyte Count : Neutrophils 39%, Lymphocytes 54%, Monocytes 5%, Eosinophils 2% . Platelets 150,000 /cu.mm.

SGOT 134 IU / L ,SGPT 127 IU / L , serum alkaline phosphatise 301 IU / L ,Total bilirubin 1.28 mg % [Direct 0.85 mg % , Indirect 0.43 mg %]

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Last seen, the child was in clinical, biochemical and hematological remission. The patient was referred for Bone Marrow Transplantation.

Conclusions

We present an unusual manifestation of immunodeficiency with characteristic phenotype of silvery grey hair all over body , a presentation which should alert clinicians to consider Griscelli Syndrome. An early diagnosis and management can help prevent associated morbidities and mortality.

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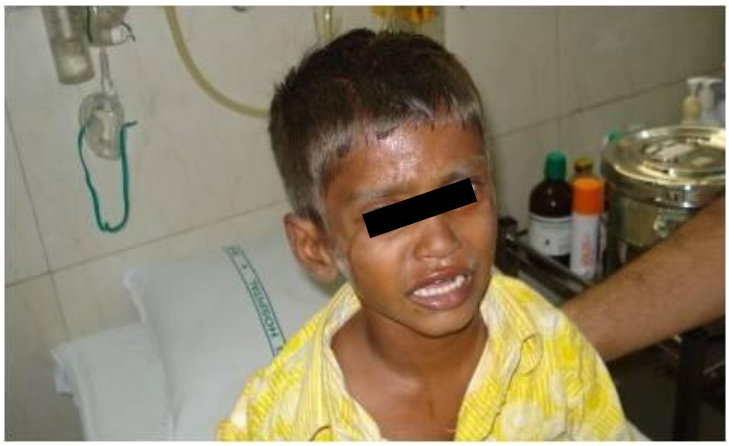

Figure 1 - Silvery grey hair all over the body, eyebrows and eyelashes

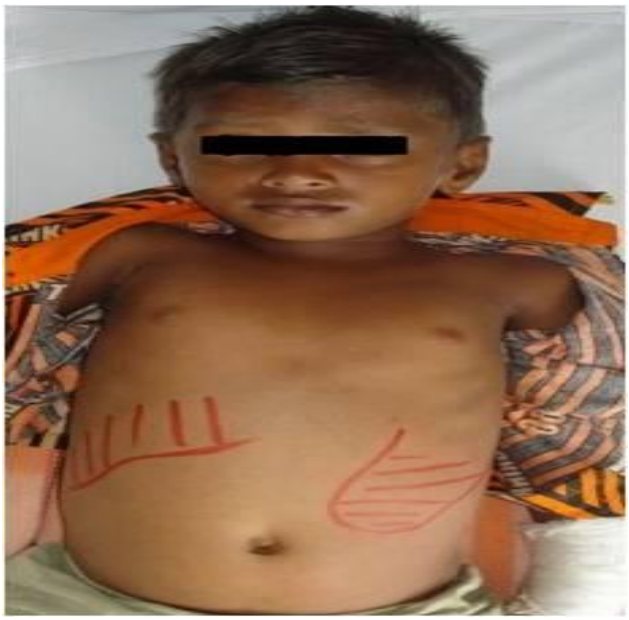

Figure 2 : Hepatosplenomegaly

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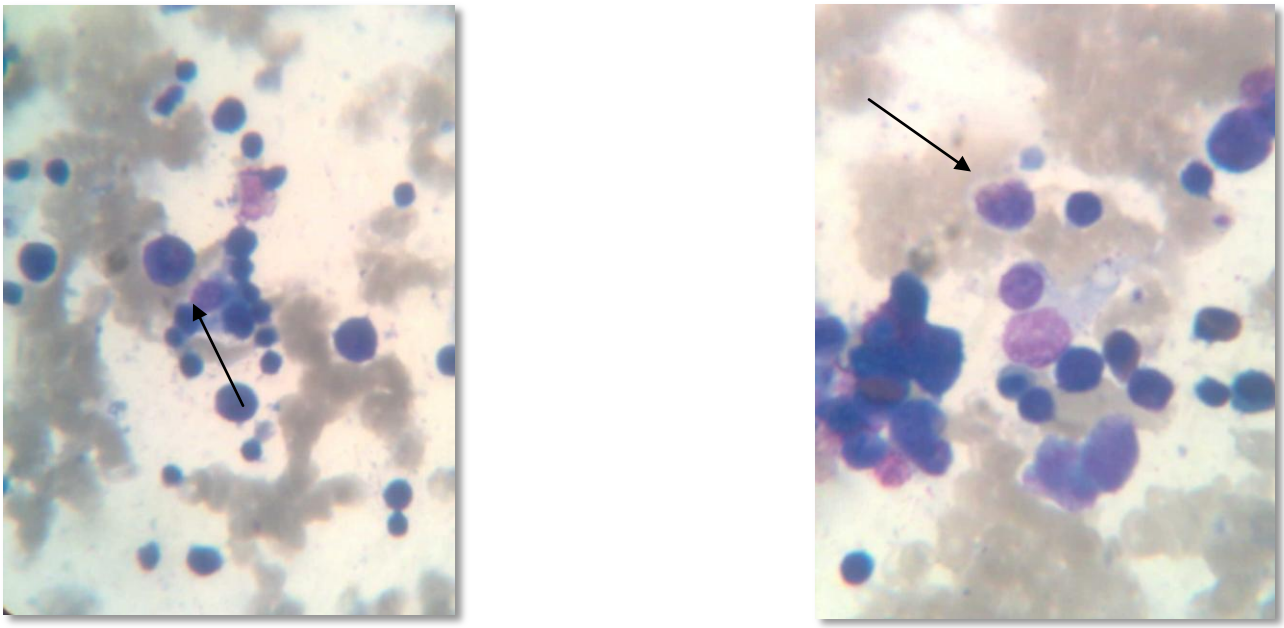
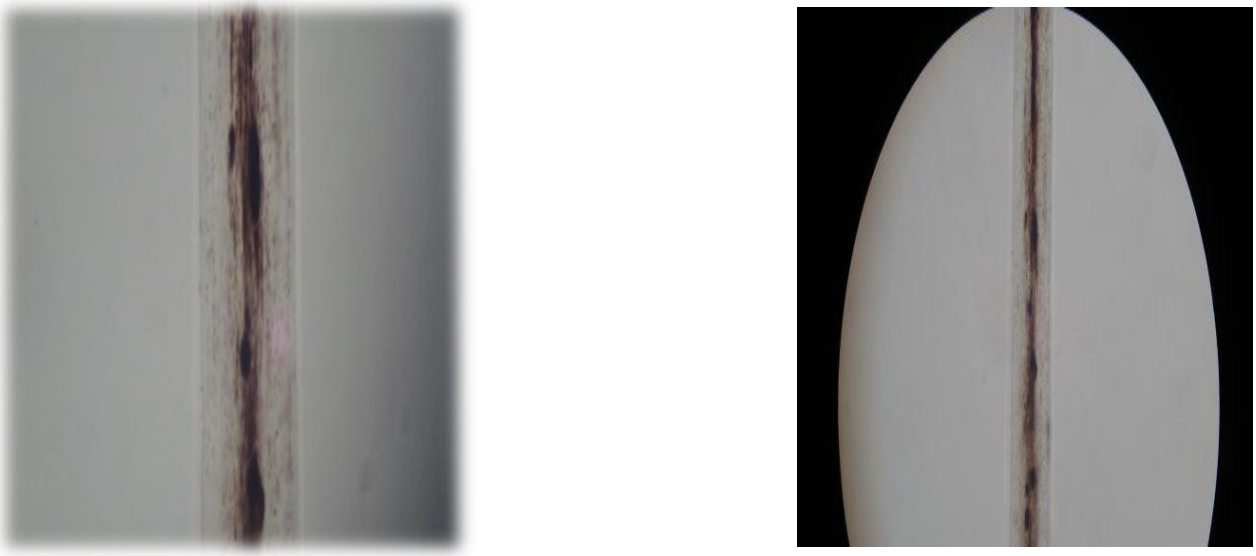


Figure 3 : Bone marrow smear (Leishman stain) showing haemophagocytosis



Figures 4 & 5 : Hair microscopy shows clusters of aggregated melanin pigment in medullary area of shaft

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