Journal of Medical Research and Health Sciences
Received 25 Mar 2021 | Revised 12 Apr 2021 | Accepted 10 May 2021 | Published Online 20 May 2021

DOI: https://doi.org/10.15520/jmrhs.v4i5.344
JMRHS 4 (5), 1253–1256 (2021)

ISSN (O) 2589-9031 | (P) 2589-9023

CASE STUDY

Open Access Journal

Unusual Presentation of Griscelli Syndrome type II, Case Report.

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Abstract

Griscelli syndrome (GS) is a rare autosomal recessive disorder caused by mutation in the MYO5A (GS1, Elejalde), RAB27A (GS2) or MLPH (GS3) genes. All three subtypes of this disease present by pigmentary dilution of the hair and skin with silvery-grey hair. Whereas this is the only feature in GS3 phenotype, GS1 patients also have primary neurological impairment and GS2 patients show severe immunological deficiencies leading to recurrent infections and hemophagocytic syndrome. We report here the case of GS2 in a10-year-old boy, with immunodeficiency and recurrent infections with hemophagositic lymphohistocytosis but without pigmentary changes.

Keywords: albinism, RAB27A, Hemophagocytic lymphohistiocytosis, Immunodeficiency

1 | INTRODUCTION

Griscelli Syndrome(GS) It is a rare hereditary syndrome due to genetic mutations leading to defective transport of melanosomes, with prevalence of less than 1 per million. The disease is usually diagnosed between 4 months and 7 years of age (1) . Characterized by pigmentary dilution of the skin and hair (silver colored hair) with partial albinism, hepatosplenomegaly, pancytopenia, hepatitis, immunologic, neurological abnormalities, and Hemophagocyitc lymphohistiocytosis (2) . Major differential diagnoses of GS are Chediak-Higashi syndrome, Elejalde syndrome, Hermansky-Pudlak syndrome, and neutrophil functional abnormalities conditions such as Wiskott Aldrich, chronic childhood granulomatosis, and hyper IgA syndrome. The disease flares up due to macrophage and T lymphocytes activation (3) .

GS was classified into three different subtypes, all of which show similar pigment dilution.

Type 1 Griscelli syndrome (GS1 [MIM 214450], Elejalde), caused by mutation in the MYO5A gene: Neurological dysfunction include changes in muscle

Supplementary information The online version of this article (https://doi.org/10.15520/jmrhs.v4i5.344) contains supplementary material, which is available to authorized users.

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tone or paralysis, seizures, and developmental delay. Type 2 Griscelli syndrome (GS2 [MIM 607624]), caused by mutation in RAB27A gene: Is associated with immunological deficiency and increased risk of infection due to uncontrolled T lymphocyte and macrophage activation leading to HLH.

Type 3 Griscelli syndrome (GS3 [MIM 609227]), caused by mutation in the melanophilin gene (MLPH): It presents with partial dilution of skin and hair pigment only, without systemic problems (4) .

2 | CASE REPORT:

We present a 10 years old Saudi boy from the South region of the kingdom with a history of recurrent otitis media presented to the emergency room with prolonged fever for 17 days, partially responding to antipyretics. He was initially admitted in another hospital and received antibiotics without improvement, investigation did not show any specific diagnosis. There were no associated symptoms except parents reporting subjective weight loss, but no associated night sweating or contact with TB patient. He underwent hypospadias repair and orchiopexy at 3 years of age and appendectomy at 4 years age. His uncle had leukemia and died at the age of 7 years, his consanguineous parents and two sisters are healthy.

Clinically at presentation patient was febrile, with tachypnea, tachycardia and desaturation, looking unwell, in average body built, pale skin color, dark black colored scalp hair and eyebrows with normal pattern, no distress or deformity noticed. He was conscious, alert, following commands, moving all four limbs with normal tone and power, well perfused, palpable peripheral pulses, warm extremity. He had normal cardiac examination. Chest examination revealed equal air entry with bilateral vesicular breath sounds in the upper and middle zone, and decreased in the lower zone, no added sounds. Head and Neck exam showed bilateral cervical and submandibular lymphadenopathy, non-tender, 3-4 cm in diameter. His abdomen was distended, but soft and lax, having hepatosplenomegaly (liver span ~14.5cm and spleen ~5 cm below costal margin), both firm, smooth surface and non-tender (Picture 1).

FIGURE 1:

Initial investigation (Table 1), (Table 2), (Table 3) showed pancytopenia with no blasts in blood smear, high LDH and ferritin and disturbed liver enzymes, prolonged coagulation with low fibrinogen, CXR showed RT sided pneumonia with effusion.

TABLE 1:

TEST	RESULT	UNIT
WBC	3.10	10e9/L
NEUTROPHIL ABSOLUTE	0.24	10e9/L
NEUTROPHIL %	7.80	%
LYMPHOCYTE ABSOLUTE	2.48	10e9/L
LYMPHOCYTE %	80.00	%
HEMOGLOBIN	8.40	g/dl
MCV	66.10	fl
MCHC	36.20	g/dl
MCH	23.90	pg
PLT	13.000	10e9/L
RDW	16.9	%
RETIC	1.9	%

TABLE 2:

TEST	RESULT	UNIT
PROTHROMBIN TIME (PT)	14.100	SEC
INR	1.270	INR
APTT	61.300	SEC
FIBRINOGEN	1.29	g/L
D-DIMER	1.26	µg/ml
FIRRITIN	5698	ng/ml

TABLE 3:

TEST	RESULT	UNIT
MAGNESIUM	0.86	mmol/L
LDH	498	U/L
URIC ACID	220	umol/L
SODIUM	126	mmol/L
POTASSIUM	4.29	mmol/L
CHLORIDE	93	mmol/L
CREATININE	30	umol/L
UREA	3.8	mmol/L
ALBUMIN	27.5	g/L
CALCIUM	2.03	mmol/L
ALKALINE PHOSPHATE	337	U/L
BILIRUBIN TOTAL	10.6	umol/L
ALT (SGPT)	255	U/L
AST (SGOT)	238	U/L
GGT	313	U/L
TRIGLYCERIDE	3.9	mmol/L

Lymph node biopsy showed infection by Epstein-Barr virus (EBV), Bone Marrow Biopsy showed evidence of Hemophagocytic lymphohistiocytosis (HLH) (Picture 2).

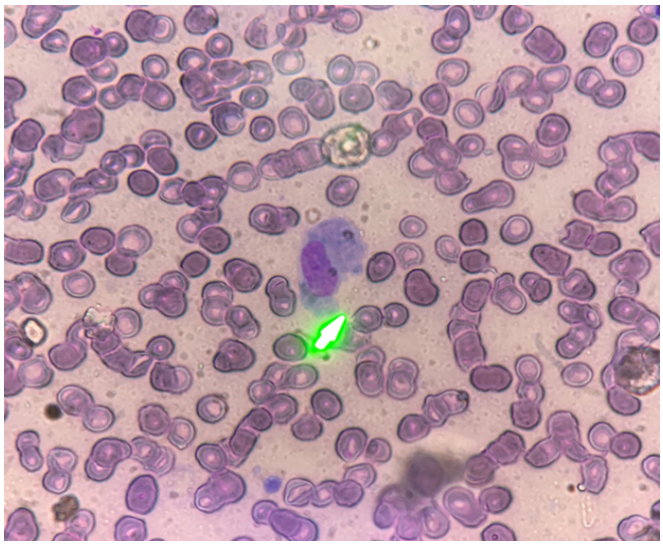

FIGURE 2:

He was admitted to intensive care unit for stabilization. He was started on HLH 2004 protocol and HLH gene panel was sent. He responded to the treatment while waiting for gene panel result which confirmed RAB27A gene mutation. He was then sent for Bone Marrow Transplantation (BMT) and is currently in remission post-transplant.

3 | DISCUSSION

GS is an autosomal recessive disorder with varied clinical manifestations. It was first reported by Griscelli *et al*. in two unrelated patients in 1978 France (5) . GS presents with variable phenotype and is categorized into 3 types. GS1 patients primarily present with neurological involvement without immune dysfunction. Hepatosplenomegaly, recurrent infection, hypomelanosis and silvery gray hair are consistent features of GS2 patients. GS3 is categorized by hypomelanosis with no immunologic or neurologic involvement. Presence of grayish hair is a hallmark of all the three types of GS patients. Genetic loci for three different phenotypes (GS1, GS2, and GS3) are MYO5A, RAB27A, and MLPH respectively (6) , (7) .

People with GS2 have unusually light skin and silver-colored hair.

The reason we are presenting this case is the conspicuous absence of pigmentary changes which delayed the diagnosis of GS thinking of it as a secondary HLH. If it was not the gene test the diagnosis might have been delayed even further.

We did not find any such case reported with GS2 (RAB27A mutation) with picture of immune deficiency and HLH and absent albinism.

This case highlights the difficulties in diagnosing a boy with GS who presented to clinicians with recurrent infection, fever, pancytopenia, lymphadenopathy, and hepatosplenomegaly with lacking of key feature of depigmentation of hair shaft, specially without reported cases with same presentation in literature.

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How to cite this article: M.A., Z.A, A.M. , **Unusual Presentation of Griscelli Syndrome type II, Case Report.**. Journal of Medical Research and Health Sciences. 2021;1223–1226. https://doi.org /10.15520/jmrhs.v4i5.344