Received: 30 December 2020 | Revised: 22 March 2021 | Accepted: 4 April 2021

DOI: 10.1002/ccr3.4212

CASE REPORT

Clinical Case Reports Open Access WILEY

Griscelli Syndrome in a seven years old girl

Borhan Moradveisi[1] | **Avat Karimi**[2] | **Shirin Behzadi**[2] | **Farima Zakaryaei**[3]

[1]Cancer and Immunology Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran

[2]Department of Pediatrics, Kurdistan University of Medical Sciences, Sanandaj, Iran

[3]Department of Emergency Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran

Correspondence
Farima Zakaryaei, Medical Doctor, Department of Emergency Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran.
Email: farima0258@gmail.com

Abstract

In this study, a case of Griscelli Syndrome (GS) in a 7 years old girl was reported. The patient initially presented with fever and pancytopenia in laboratory results; after ruling out the malignancies, she went under treatment with the diagnosis of infectious disease and was discharged after two weeks. Nevertheless, ten days after discharge, she developed new symptoms. Due to patient symptoms and general appearance, microscopic analysis of her hair shaft was done, and the abnormal distribution of pigments in the shaft was observed, indicating GS.

KEYWORDS

distribution of pigments in the shaft, griscelli syndrome, pancytopenia

1 | INTRODUCTION

Griscelli and Siccardi first reported Griscelli syndrome (GS) in 1978. Griscelli syndrome is also known as "partial albinism along with neurological and/or immunological defects." It is a rare autosomal-recessive (MIM 214 450 and 607 624) multisystem genetic disorder.[1]

GS is diagnosed at the age of 1-8 years with a mean of 17.5 months. It is characterized by partial pigmentary dilution and silvery gray hair, cellular immune deficiency, and neurological abnormalities. The prognosis of this disease is poor. Treatment with cyclosporine A and chemotherapy has shown remission in symptoms in these patients.[2]

In this study, a case of Griscelli Syndrome (GS) admitted to Besat Hospital in Sanandaj in September 2020 is reported.

2 | CASE REPORT

A seven-year-old girl was admitted to Besat Hospital with complaints of one-month history of low-grade fever and periodic abdominal pain.

She was the first child of the family born from parents with consanguineous marriage. She had a complete vaccination history and typical developmental milestones. Her birth weight was 3.8 kg; further, she congenitally had hell brown hair and gray eyelashes.

She had no past medical history of a specific disease. Her parents had a family relationship (they were cousins) but no past medical history of a specific disease. She was phenotypically normal (Figure 1); her weight was 20 kg at the admission time.

Her primary vital sign was normal. She had hell brown scalp hair. On physical examination, she had an ill appearance, and in the abdominal examination, splenomegaly and hepatomegaly were detected.

The initial laboratory results of the patient's examinations showed pancytopenia on complete blood count (CBC; Table 1).

Abdominal ultrasound was requested for her, and spleen (142mm) and liver (136mm) size enlargement were reported.

Due to pancytopenia and organomegaly, oncology consultation was performed to rule out malignancy and leukemia; peripheral blood smears (PBS) and bone marrow aspiration

(BMA) were done for her, and hemophagocytosis was seen (Figure 2). So, malignancy was ruled out, and infectious disease was suggested.

Laboratory test results were negative for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), adenovirus, and mycobacterium tuberculosis. Also, echocardiography was performed to rule out Kawasaki and endocarditis (both normal).

Treatment with FFP and intravenous immunoglobulin (IVIG), as well as empiric antibiotic therapy, started for the patient. After two weeks, her laboratory results became normal, and she was discharged from the hospital with following-up recommendations for hematological tests.

Ten days after discharge, she developed epistaxis, fever, generalized abdominal pain, weakness, loss of appetite, delusions, consciousness disturbances, and shortness of breath and thus was admitted to Besat Hospital's emergency department again. At the time of admission, she was ill, and her GCS was 11 out of 15. Periorbital edema and inflammation of the oral mucosa (Figure 3), respiratory distresses, besides massive splenomegaly and hepatomegaly, were detected on physical examination. A chest X-ray

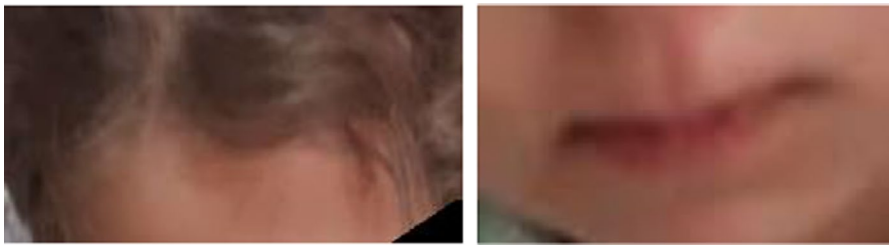

FIGURE 1 The phenotypic feature of the patients

BUN	24 mg/dl	CRP		+1			
Cr	0.8	Bs		91			
Uric acid	1.84 mmol/L	CBC		WBC	2700/ µl	Neut	42%
						lymph	53%
AST	128 U/L			Hb	8.1 g/dL		
ALT	99 U/L			Plt	57000/ µl		
ALK-P	528			MCV	77.1		
Na	128 mmol/L			MCH	20.4		
K	3.6 mmol/L			MCHC	26.8		
Ca	8.1 mg/dL	LDH		160 U/L			
PTT	60 s	Bili	T	1.4 mg/dL			
			D	0.8 mg/dL			
PT	13.3 s	INR		1.2			

TABLE 1 Laboratory results

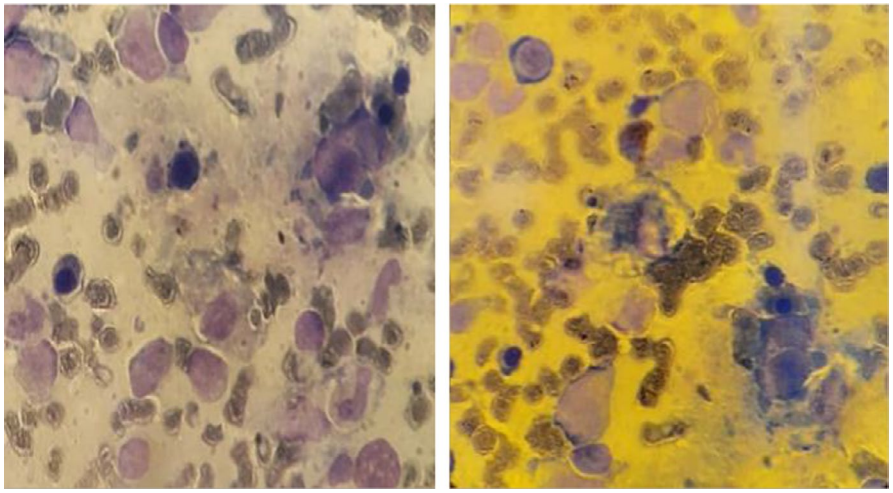

FIGURE 2 Bone marrow aspiration (hemophagocytosis were seen)

FIGURE 3 The phenotypic feature of the patients with eyebrows pigmentation

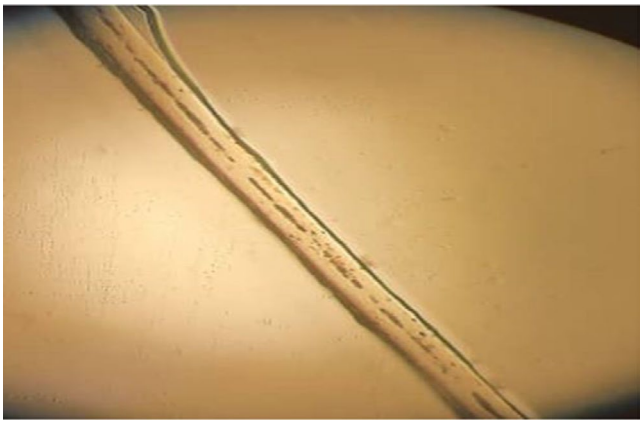

FIGURE 4 Accumulation of melanosomes in hair shafts

(Figure 5) and a brain CT scan were done for the patient, which were normal. The patient was transferred and monitored in PICU.

Due to fever, splenomegaly, pancytopenia, increased ferritin level, hypertriglyceridemia, hyponatremia, hyperbilirubinemia, and hypoalbuminemia (Table 2), HLH in the context of GS and Chediak-Higashi syndrome was suggested for her; however, since she had no previous history of any disease, Chediak Higashi syndrome was ruled out, and GS was diagnosed.

Oncology consultation was performed for the patient due to the diagnosis of HLH in the context of GS, and the oncologist did a microscopic evaluation of her hair shaft to rule out Griscelli Syndrome based on the patient's general appearance. A typical accumulation pattern of melanosomes instead of small homogenous was observed in hair shafts, indicating GS (Figure 4).

Antibiotic therapy was started along with dexamethasone, pack cell, as well as fresh-frozen plasma (FFP) and cryoprecipitate (Cryo); however, after one day, she experienced a tonic colonic seizure, and her GCS decreased to 9/15; she was intubated due to her low GCS and respiratory acidosis. The second CXR was done for the patient, and pulmonary hemorrhage was detected (Figure 5). A couple of hours later, she developed DIC symptoms and died.

The patient's parents did not allow genetic testing for their daughter. The patient also had a 2-year-old brother; he underwent microscopic evaluation of the hair shaft, and it was

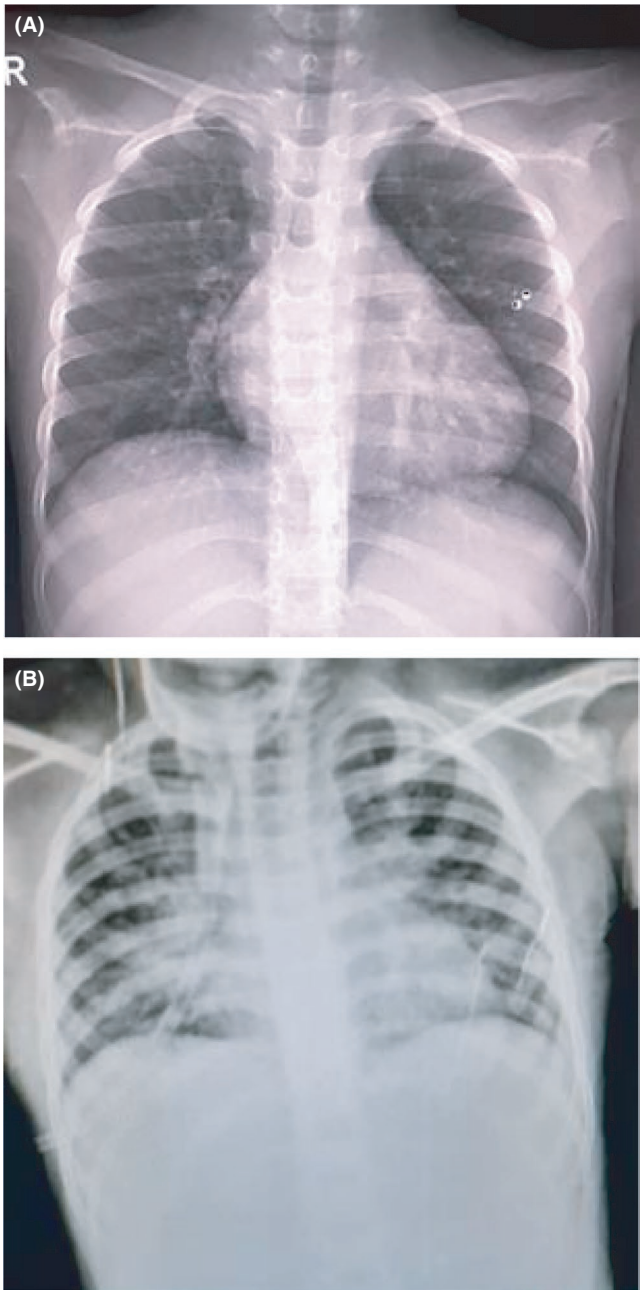

FIGURE 5 The first(A) and second(B) CXR of the patient

typical for GS; thus, he is undergoing genetic evaluation and complementary therapies. Also, the patient's mother is currently pregnant and has been given genetic counseling for further evaluation.

TABLE 2 Laboratory results

BUN		36 mg/dl	CRP	+1			
Cr		1.3	Bs	20			
Uric acid		10 mg/dL	CBC	WBC	1800/ µl	Neut	42%
						lymph	53%
AST		1132 U/L		Hb	7 g/dL		
ALT		319 U/L		Plt	17000/ µl		
ALK-P		187		MCV	87.9		
Na		128 mmol/L		MCH	25.8		
K		4 mmol/L		MCHC	31.5		
Ca		8 mg/dL	Alb	2.7 g/dL			
PTT		150 s	Total pro	4.1 g/dL			
PT		27 s	INR	4.1			
TG		310 mg/dl	ferritin	600ng/mL			
Bili	T	2.2 mg/dL	LDH	160 U/L			
	D	1.1 mg/dL					

3 | DISCUSSION

GS is an autosomal-recessive congenital disorder caused by mutations in 15q21. Based on the point of mutation, GS is divided into three types. Mutations of the Myosin-Va gene (MYO5A) can lead to GS type 1, characterized by neurological symptoms without immune dysfunction. Also, mutations in the RAB27A gene can lead to GS type 2, causing hypopigmentation of skin and hair and associating with immunological dysfunction. Moreover, the mutation in melanophilin can lead to GS type 3, presented with hypomelanosis without immunological and neurological manifestation.[3-6]

One of the differential diagnoses of GS in Chediak Higashi syndrome, both of these disease, can present with generalized skin hypopigmentation at birth, albinism, silvery gray hairs, and, more rarely, iris pigmentary dilution and hepatosplenomegaly.[7,8] GS is difficult to be diagnosed since it is rare.[9]

Delay in the diagnosis of these patients can decrease success. It is also essential to diagnose the type of disease in the patient at its early stage since each type requires different treatment. Palliative and supportive treatments are suggested in GS1 patients, and GS3 patients require no treatment, and it has a very good prognosis.[5,9,10]

Due to different mutations in the RAB27A gene, GS-II clinical symptoms can differ from case to case.[20] Gris celli syndrome type 2 clinical presentations are partial albinism, immunodeficiency, organomegaly, pancytopenia, and lymphohistiocytic infiltrates in various organs (GS2).[3,11-15]

GS-II can cause hemophagocytic lymphohistiocytosis (HLH), leading the immune system to produce too many activated immune cells called T lymphocytes and macrophages; these can damage body organs and tissues, causing life-threatening complications.[16] Therefore, GS-II has a poor prognosis and can cause death in early childhood. Bone marrow transplant is the only treatment for these patients,[5] and patients with GS who fail to be transplanted usually die within five years after diagnosis.[17]

Most of the GS-II reported cases are from parents with consanguineous marriages.[20] In the present study, the patient's parents were cousins; hence, she was born from parents with consanguineous marriage. Consanguineous marriages are common in Iran, and it is a risk factor for congenital autosomal-recessive diseases; thus, genetic counseling and education are necessary for these couples.[19]

The current case report is the fourth GS in Iran.[18-20] The patient had complained of fever, epistaxis, stomachache, weakness, losing appetite, and respiratory distress, and she was manifested with hepatosplenomegaly and pancytopenia. The diagnosis was delayed due to the attribution of general appearance (fair skin and light hair color) of the patient to her congenital, her symptoms to malignancy and infectious disease, thus being not suspicious to GS. Finally, she developed pulmonary hemorrhaging and DIC and died; hence, it could be suggested that she developed HLH resulting in DIC due to the overactivity of immune cells, thus damaging the body organs.

Due to the prevalence of consanguineous marriage in the country, autosomal-recessive diseases, including GS, should be considered in children with immunodeficiency, organomegaly, and pancytopenia; therefore, microscopic examination of hair and skin is recommended in these patients.

4 | CONCLUSION

GS is a rare disorder, thus being difficult to be diagnosed; it has the same clinical presentation as malignancies,

infectious disease, and immunodeficiency. Due to the poor prognosis of GS, it should be considered in pediatrics with pancytopenia, splenomegaly, and light hair color, especially in children born from parents with consanguineous marriage. Thus, the microscopic examination of hair and skin, as well as genetic tests, are recommended in these patients since early diagnosis and treatment of such patients may lead to survival.

ETHICS APPROVAL

Written consent was obtained from the patient's father, stating not showing the full face image of their child's face in the article. Also, this manuscript has been ethically approved by the ethics committee of Kurdistan University of Medical Sciences, Sanandaj, Iran. (ethical committee approval ID: IR.MUK.REC.1399.282). Available on https://ethics.research.ac.ir/IR.MUK.REC.1399.282

ACKNOWLEDGMENTS

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

Borhan Moradveisi (BM): designed the study and critically reviewed the manuscript. Farima Zakaryaei (FZ): was the major contributors in writing the manuscript; Avat Karimi (AK) and Shirin Behzadi (SB): collected the data; all authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

ORCID

Farima Zakaryaei https://orcid.org/0000-0003-0114-0788

REFERENCES

1. Griscelli C, Durandy A, Guy-Grand D, Daguillard F, Herzog C, Prunieras M. A syndrome associating partial albinism and immunodeficiency. *Am J Med*. 1978;65:691-702.
2. De saint basile G. Griscelli syndrome. Orphaned encyclopedia, 2003. https://www.orpha.net/data/patho/GB/uk-griscelli.pdf
3. Ménasché G, Pastural E, Feldmann J, et al. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. *Nat Genet*. 2000;25:173-176.
4. Pastural E, Ersoy F, Yalman N.,et al. Two genes are responsible for Griscelli syndrome at the same 15q21 locus. *Genomics*. 2000;63:299-306.
5. Singh A, Garg A, Kapoor S, et al. An Indian boy with griscelli syndrome type 2: case report and review of literature. *Indian J Dermatol*. 2014;59(4):394-397. https://doi.org/10.4103/0019-5154.135494
6. Durmaz A, Ozkinay F, Onay H, et al. Molecular analysis and clinical findings of Griscelli syndrome patients. *J Pediatr Hematol Oncol*. 2012;34(7):541-544.
7. Valente NY, Machado MC, Boggio P, et al. Polarized light microscopy of hair shafts aids in the differential diagnosis of Chédiak-Higashi and Griscelli- Prunieras syndromes. *Clinics (Sao Paulo)*. 2006;61:327-332.
8. Bellinati-Pires R, Araujo MIAS, Grumach AS. Deficiências do sistema fagocitário. In: Carneiro-Sampaio MM, ed. *Alergia e Imunologia em pediatria*, 1st edn. São Paulo: Sarvier; 1992:165-166.
9. Minocha P, Choudhary R, Agrawal A, et al. Griscelli syndrome subtype 2 with hemophagocytic lympho-histiocytosis: A case report and review of literature. *Intractable Rare Dis Res*. 2017;6(1):76-79. https://doi.org/10.5582/irdr.2016.01084
10. Mishra K, Singla S, Sharma S, Saxena R, Batra VV. Griscelli syndrome type 2: A novel mutation in RAB27A gene with different clinical features in 2 siblings: A diagnostic conundrum. *Korean J Pediatr*. 2014;57:91-95.
11. Inamadar AC, Palit A. Silvery hair with bronze-tan in a child: A Case of Elejalde disease. *Indian J Dermatol Venereol Leprol*. 2007;73:417-419.
12. Meschede IP, Santos TO, Izidoro-Toledo TC, Gurgel-Gianetti J, Espreafico EM. Griscelli syndrome-type 2 in twin siblings: case report and update on RAB27A human mutations and gene structure. *Braz J Med Biol Res*. 2008;41:839-848.
13. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. *Eur J Pediatr*. 2007;166:95-109.
14. Anikster Y, Huizing M, Anderson PD, et al. Evidence that Griscelli syndrome with neurological involvement is caused by mutations in RAB27A, not MYO5A. *Am J Hum Genet*. 2002;71:407-414.
15. Weitzman S. Approach to hemophagocytic syndromes. *Hematology Am Soc Hematol Educ Program*. 2011;2011:178-183.
16. Reddy RR, Babu BM, Venkateshwaramma B, Hymavathi CH. Silvery hair syndrome in two cousins: Chediak-Higashi syndrome vs Griscelli syndrome, with rare associations. *Int J Trichology*. 2011;3(2):107-111.
17. Cesaro S, Locatelli F, Lanino E, et al. Hematopoietic stem cell transplantation for hemophagocytic lymphohistiocytosis: a retrospective analysis of data from the Italian Association of Pediatric HematologyOncology (AIEOP). *Haematologica*. 2008;93(11):1694-1701.
18. Shamsian BS, Nikoufar M, Esfahani SA, et al. A 10-year single center survey of pediatric patients with histiocytic disorders in Iran. *Turk J Pediatr*. 2011;53(1):34-42.
19. Nejad M, Ebrahim S, et al. Griscelli syndrome: a case report. *Iran J Child Neurol*. 2014;8(4):72-75.
20. Bahrami A, Nateghian A, Salehi S, et al. Griscelli syndrome type 2: a rare case with apparently normal skin and hair pigmentation. *Acta Med Iran*. 58(1):38-42.

How to cite this article: Moradveisi B, Karimi A, Behzadi S, Zakaryaei F. Griscelli Syndrome in a seven years old girl. *Clin Case Rep*. 2021;9e04212. https://doi.org/10.1002/ccr3.4212