Case Report

Griscelli Syndrome Type 3 with Coexistent Universal Dyschromia—An Uncommon Association of a Rare Entity

Abstract

Griscelli syndrome type 3 is an autosomal recessive disorder caused by mutations in the melanophilin gene and does not have any mucocutaneous or systemic abnormalities other than a pigmentary dilution of skin and hair. We report a case of an 8-year-old girl who presented with silvery grey hair of scalp, eyebrows, eyelashes, and entire body surface with associated universal dyschromia of the skin. After establishing a definite diagnosis of Griscelli syndrome 3, the prognosis was explained and counseling was given. A review of the literature revealed only 27 cases of Griscelli syndrome type 3 in the English language of which only one case by Batrani *et al*. has reported an associated dyschromia. We report this case to add to the existing literature on this rare condition and to highlight the coexistence of universal dyschromia with Griscelli syndrome type 3.

Keywords: *Grey hair, Griscelli syndrome, universal dyschromia*

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Introduction

Griscelli syndrome (GS), first described by Griscelli in 1978, is a rare autosomal recessive disorder characterized by partial pigmentary dilution of skin and hair.[1] Three types of this disorder have been described with loss of function of three distinct genes.[2] The three genes together encode a tripartite protein complex mediating the melanosome transport pathway thereby distributing melanin from melanocytes to the surrounding keratinocytes. Mutation of these genes will result in perinuclear accumulation of melanosome within the melanocytes and is considered to be the hallmark of the disease.[3] Among the three subtypes of GS, types 1 and 3 are rare.[4] Here, we report a case of an 8-year-old girl who presented with silvery grey hair of scalp, eyebrows, eyelashes, and entire body surface with associated dyschromia of the skin. A review of the literature revealed only 24 cases of GS type 3 in the English language of which only one case by Batrani *et al*. has reported an associated dyschromia.[5]

Case Report

An 8-year-old Indian girl born out of a nonconsanguineous marriage presented to our outpatient department with chief complaints of light-colored scalp and body hair along with light-colored spots distributed all over the body surface. On examination, she had silvery grey hair over the scalp (predominantly over the frontal and temporal region) and the eyebrows and eyelashes [Figure 1]. Several discrete hypopigmented macules on a background of diffuse hyperpigmentation were present all over the body surface covered with fine grey hair [Figure 2]. The hypopigmented macules were remarkably predominant over the face, trunk, and the lower limbs. The rest of the physical and systemic examination was within normal limits and no other family member was involved. There was no history of any recurrent infections or failure to thrive.

A trichogram revealed coarse unevenly distributed clumps of melanin pigment in the medulla of the hair shaft [Figure 3]. Skin biopsy from the hypopigmented macule revealed enlarged hyperpigmented melanocytes with sparsely pigmented adjacent keratinocytes in the basal layer of the epidermis [Figure 4]. Immunohistochemistry with HMB-45 showed an enlarged and increased number of pigment laden melanocytes [Figure 5]. Masson Fontana stain from the

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Table 1: Close differential diagnosis of Griscelli syndrome type 3 (GS3) and dyschromia along with its clinical features, histopathology, hair microscopy, and management[2,5]

	GS3	FGM	DUH	ACD	CHS
Inheritance	AR	AD	AD, occasionally AR	AD, occasionally AR	AR
Gene involved	*MLPH* or *MYO5a*	Not identified	*ABCB6* gene on 2q35	*DSARD*	*LYST*
Clinical features	Pigmentary dilution of skin and hair with or without dyschromia	Generalized hyperpigmentation with raindrop (guttate) hypopigmentation, mainly on sun-exposed areas	Reticulate pigmentation of the whole body associated with developmental defects, nail pterygium, cataract, glaucoma, seizures and mucosal pigmentation	Reticulate pigmentation (trunk > photo-exposed site) Freckles, poikiloderma, atypical parkinsonism	Silvery gray hair, hemophagocytic syndrome, polyneuropathy, parkinsonism, dementia, and ataxia
Histopathology of skin	Hyperpigmented melanocytes with sparsely pigmented adjacent keratinocytes in the basal layer	Enlarged melanocytes with increased or decreased keratinocyte melanin and variable melanin incontinence	Normal-sized melanocytes, epidermal melanin increased or decreased, variable melanin incontinence	Amyloid deposits in the papillary dermis	Large melanosomes in both melanocytes and keratinocytes
Light microscopy of hair	Small and large clumps of melanin in an irregular pattern	Irregularly distributed melanin along the hair shaft	Nil	Nil	Small clumps of melanin in a regular pattern
Treatment	Nil	Nil	Nil	Acitretin, topical steroids, keratolytic, CO2 laser	Bone marrow transplantation

GS3=Griscelli syndrome; FGM=Familial gigantic melanocytes; DUH=Dyschromatosis universalis hereditaria; ACD=Amyloidosis cutis dyschromia; CHS=Chediak-Higashi syndrome; AR=Autosomal recessive; AD=Autosomal dominant

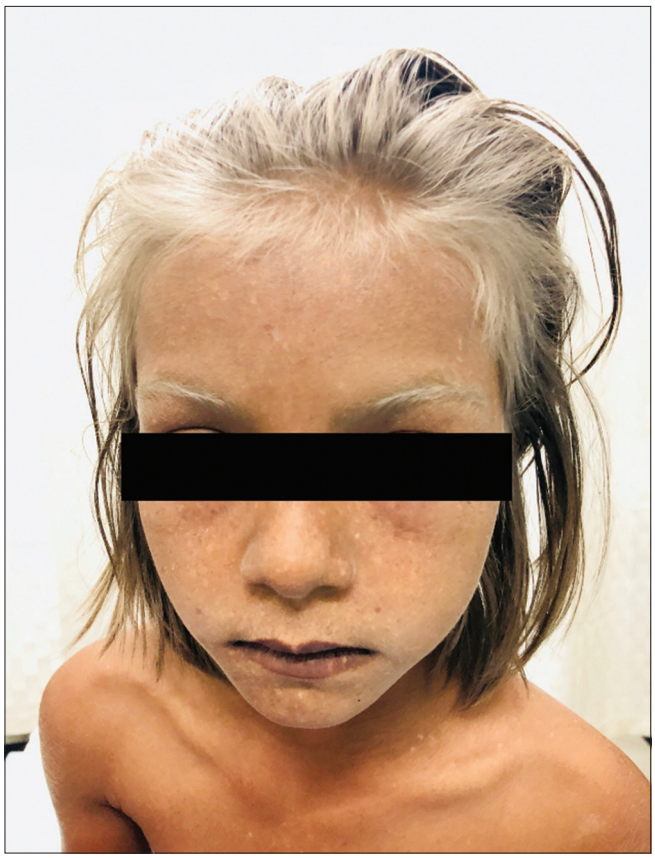

Figure 1: 8-year-old girl with silvery grey hair including eyelashes and eyebrows with dyschromia of face

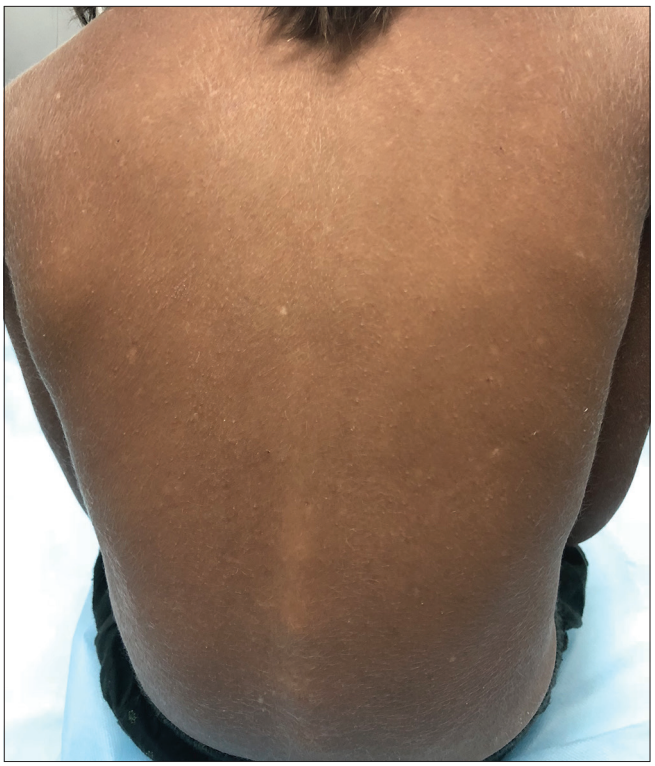

Figure 2: Hypopigmented macules with diffuse hyperpigmentation and fine grey hair on the trunk

hyperpigmented lesion showed uniform prominence of enlarged hyperpigmented melanocytes [Figure 6] and from the hypopigmented lesion showed patchy prominence of enlarged hyperpigmented melanocytes [Figure 7]. The hematological and neurological evaluation was done from the respective departments and was normal. Further, the patient was also referred to the department of pediatrics

Table 2: Cases of GS3 reported so far with associated additional features

Author and year of publication	GS 3	Silvery hair	Hypopigmented skin	Dyschromia (both hyper and hypopigmentation)	Other additional features
Sanal *et al*., 2002[8]	Two cases	yes (one case with MYO5a F-exon del)	yes	no	no
Al-Idrissi *et al*., 2010[11]	One case	yes	yes	no	Preterm delivery, respiratory distress, and intracerebral hemorrhage
Westbroek *et al*., 2011[3]	Seven cases	yes	yes	no	Recurrent lung disease, psychomotor retardation, recurrent infection in 3 patients
Çağdaş *et al*., 2012[4]	Two cases	yes	no	no	nil
Kaur *et al*., 2014[6]	Two cases	yes	yes	no	nil
Yilmaz *et al*., 2014[9]	One case	Yes(MYO5a F-exon del)	no	no	Eczema and diaper dermatitis
Khemka *et al*., 2015[2]	One case	yes	Was present at birth	no	Generalized bronze discoloration of the skin
Akgun *et al*., 2015[12]	One case	yes	no	no	One tooth bud was absent, and two teeth were microdontic, a deeply arched palate, deficient hygiene, and gingivitis.
Nouriel *et al*., 2015[13]	Two cases	yes	yes	no	Hypoplastic left heart syndrome
Alonazi *et al*., 2016[1]	One case	yes	no	no	nil
Shah *et al*., 2016[7]	One case	yes	yes	no	Bronze tan hyperpigmentation over fair skin
Hemalata *et al*., 2017[14]	One case	yes	yes	no	nil
Kassem *et al*., 2018[15]	One case	yes	yes	no	nil
Batrani *et al*., 2018[5]	One case	Present over the body surface and partially over beard eyebrow, eyelashes. Scalp hair was normal	no	yes	nil
KY Dagnewu[16]	Two cases	yes	yes	No	Macular patchy hypopigmentation on the limbs and trunk
Gupta M[17]	One case	yes	No	No	Tanning over face
Our case	One case	yes	no	yes	nil

for the assessment for any developmental/growth delay and was found normal. On the basis of clinical examination, absence of neurological or immunological abnormalities, typical findings on hair trichogram and skin biopsy, a diagnosis of GS3 was made. Mutational analysis for confirmation could not be done as it was not available in our center and the patient could not afford it elsewhere.

Discussion

GS is a rare autosomal recessive congenital disorder characterized by a mutation in genes encoding RAB27A/melanophilin/myosin 5a tripartite protein complex which is required for the capture of matured melanosomes by the peripheral actin network of the melanocytes and their transfer to the surrounding keratinocytes.[6] Mutation in each member of this complex will result in three different forms of GS with skin and hair hypopigmentation as a common feature of all subtypes. GS type 1 caused by a mutation in the myosin 5a gene is characterized by neurological manifestations in addition to skin and hair changes. There is no curative treatment for GS type 1 other than palliative care.[2] GS type 2 is caused by the *RAB27A* gene mutation. Predominant features of GS2 are immunological dysregulation and life-threatening hemophagocytic syndrome caused by activated T cells and macrophages infiltrating various organs (including the brain) and causing massive tissue damage, organ failure, pancytopenia, and (in the absence of immunosuppressive treatment) death thereby requiring early intervention. Bone marrow transplantation is the only curative treatment for this condition.[2]

GS3 is caused by mutations in the melanophilin gene and does not have any mucocutaneous or systemic abnormalities other than a pigmentary dilution of skin and hair; thus, it has a good prognosis and needs little or no treatment.[7] In addition to melanophilin gene mutation, two cases of GS3 with MYO5a F-exon deletion have been reported.[8,9] Close differential diagnoses for silvery/grey hair syndromes are GS type 1 and type 2, Chediak–Higashi syndrome (CHS).[2] However, except for GS3, all other conditions are associated with variable hematological, neurological, and

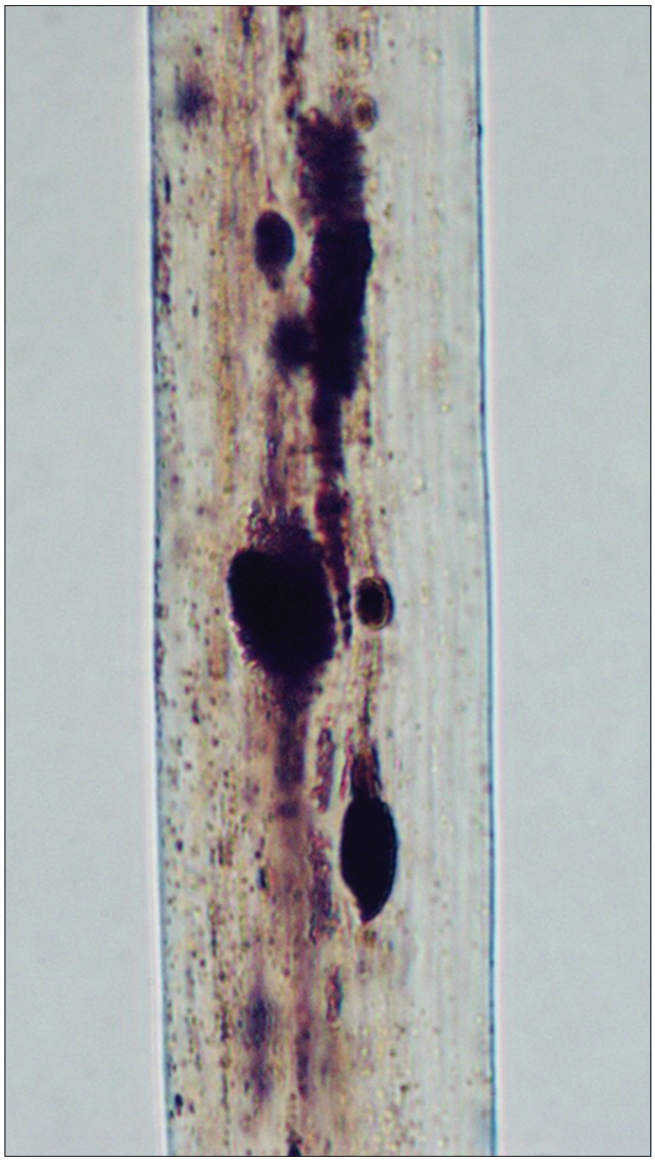

Figure 3: Whole-mount of patient hair showing large unevenly distributed clumps of melanin pigment in the medulla of the hair shaft (unstained ×400)

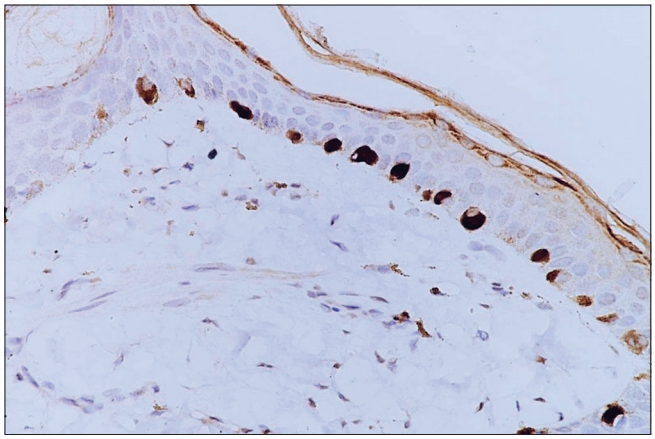

Figure 5: Human melanoma black (HMB-45) immunohistochemical highlights enlarged pigment-laden melanocytes which appear increased in number

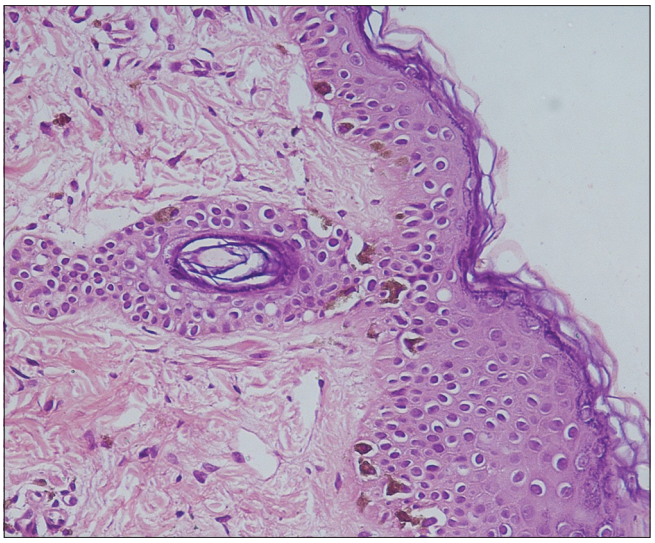

Figure 4: Histopathology of both hypo- and hyperpigmented lesion showing enlarged hyperpigmented basal melanocytes with sparsely pigmented adjacent keratinocytes (H and E ×200)

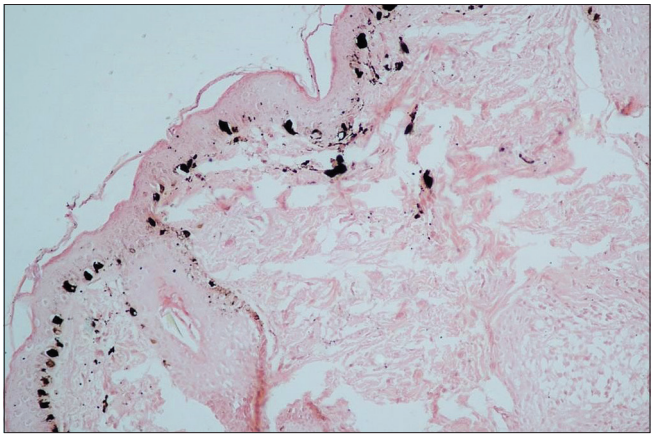

Figure 6: Mason-Fontana stain on hyperpigmented lesion showing uniform prominence of enlarged hyperpigmented melanocytes (H and E ×200)

immunological abnormalities, which were absent in our patient. When it comes to silvery-white hair with dyschromia, familial melanopathy with gigantic melanocytes (FGM) is different, however, it is almost impossible to differentiate them without a genetic analysis and needs further scientific studies. Other differentials for the universal dyschromia in our patient are dyschromatosis universalis hereditaria (DUH) and amyloidosis cutis dyschromia. However, in cases of DUH and ACD abnormal melanocytes and grey hair are not seen as in GS3.[10] Close differential diagnosis of GS3 and dyschromia along with its clinical features, histopathology, hair microscopy, and management are given in Table 1.[2,5]

Most reported cases of GS are from the Turkish and Mediterranean populations. To our knowledge, a total of 27 cases of GS3 have been reported so far.[1-9,11-17] An association with dyschromia has been reported in a case report by Batrani *et al*. in 2018.[5] Two cases with diffuse bronze hyperpigmentation in GS3 have also been reported.[2,7] We report this case to add to the existing

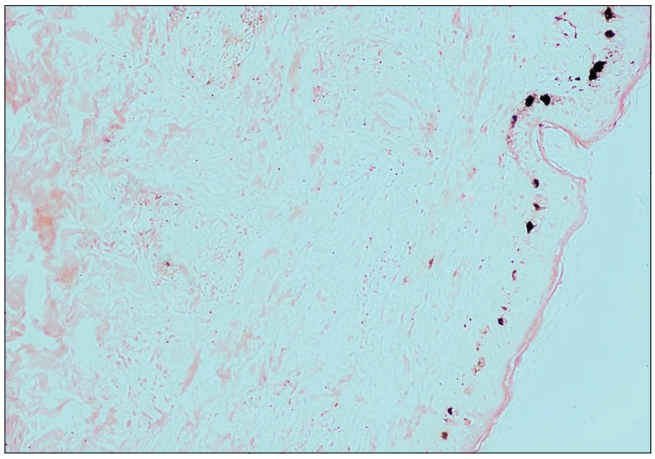

Figure 7: Mason Fontana stain on hypopigmented lesion showing patchy prominence of enlarged hyperpigmented melanocytes (H and E ×200)

literature on this rare condition and to highlight the coexistence of universal dyschromia with GS3. Cases of GS3 reported so far with associated additional features are summarized in Table 2.[1-9,11-17]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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