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Case Report

Griscelli syndrome: Erdheim-Chester disease-like local presentation progressing to accelerated phase

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ABSTRACT

Background. Griscelli syndrome (GS) is a rare genetic disorder characterized by oculocutaneous albinism and variable immune dysfunction. Among three distinct types of GS, occurring due to different genetic mutations; GS type 1 presents with neurological manifestations, hemophagocytic lymphohistiocytosis (HLH) generally develops in GS type 2, and GS type 3 primarily exhibits oculocutaneous albinism. HLH, a life-threatening condition with excessive immune activation, may occur secondary to various triggers, including infections, and develop in different tissues, as well as in the testis, similar to Erdheim-Chester disease.

Case. After referral at 19 days of age with restlessness, left testicular swelling, and erythema, an infant was diagnosed with bilateral hydrocele with left testicular torsion by testicular ultrasound, leading to a left orchiectomy. Pathology showed testicle and spermatic cord hemorrhagic necrosis. A week later, the infant presented with right testicular swelling and hepatosplenomegaly. He had silvery gray hair. We administered broad-spectrum antibiotics for increased acute phase reactants. Viral panels, including cytomegalovirus and Epstein-Barr virus, were negative. Laboratory findings indicated cholestasis and disseminated intravascular coagulation. Bone marrow aspiration revealed hemophagocytosis and increased histiocytes. Microscopic hair examination supported the diagnosis of GS. Sanger sequencing revealed the homozygous mutation c.217T>G (p.W73G) in *RAB27A*.

Conclusion. Prompt diagnosis and treatment of HLH are crucial to prevent progression to multi-organ failure and death. This case highlights the diverse tissue involvement and diagnostic challenges in Griscelli syndrome type 2.

Key words: griscelli syndrome, testicular torsion, newborn, *RAB27A*, hemophagocytic lymphohistiocytosis, local HLH.

Griscelli syndrome (GS) is a rare genetic syndrome associated with oculocutaneous albinism.[1,2] The cause of this syndrome was understood with the discovery of mutations of myosin Va, Rab27a, and melanophilin in the years 1997, 2000, and 2002, respectively.[1-3] The clinical phenotype in GS type 1 (OMIM #214450) includes primarily developmental neurological problems. In GS type 2 (OMIM #607624), hemophagocytic lymphohistiocytosis (HLH), cutaneous hypopigmentation, immunodeficiency, and neurological

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involvement due to HLH are primary manifestations. In GS type 3 (OMIM #609227), oculocutaneous albinism is the only symptom.[3]

HLH mainly presents with persistent fever, hepatosplenomegaly, lymphadenopathy, and hemophagocytosis. It can be seen secondary to infections like Epstein-Barr virus (EBV) or cytomegalovirus (CMV), in immunodeficiency syndromes like GS type 2 or Chediak–Higashi syndrome, in lymphoma, autoimmune diseases, and in perforin (*PFR1*), Munc 13-4 (*UNC13D*), syntaxin 11 (*STX11*), syntaxin binding protein 2 or Munc 18-2 (*STXBP2*) deficiencies. For HLH diagnosis, intermittent renewal of criteria occurs due to diagnostic developments.[4] If not treated, uncontrolled inflammation progresses into multiple organ failure and death.[3]

In this report, we present a GS type 2 case who presented in the early neonatal period with testicular torsion and HLH.

Case Presentation

We present an infant who was referred to our clinic on the 19th day of his life with restlessness, swelling, and erythema of the left testicle. He was born as the first child of consanguineous parents. Testicular ultrasound showed left testicular torsion with bilateral hydrocele, and the patient underwent left orchiectomy (pathology presented in Fig. 1A and 1B). We could not perform magnetic resonance imaging or computerized tomography because anesthesia would be required in the newborn period. The pathological specimen showed hemorrhagic necrosis of the testicle and spermatic cord. A week after, during admission for right testicular swelling, clinicians noted silvery gray hair, fever, cytopenia, and hepatosplenomegaly on physical examination (Fig. 1C, Table I). We started broad-spectrum antibiotics (vancomycin, meropenem, and amikacin). Viral panels, including CMV and EBV PCR, were within normal limits. Gamma glutamyl transferase (GGT) and bilirubin levels (direct and total) were slightly high, which may have indicated cholestasis due to drugs or hepatic HLH involvement. High international normalized ratio (INR) and D-dimer levels were compatible with disseminated intravascular coagulation, and vitamin K was administered. Bone marrow aspiration showed hemophagocytosis and increased histiocytes.

Hair microscopy of the patient showed large pigment clusters compatible with GS (Fig. 1D). There was no intracranial involvement, and cerebrospinal fluid parameters were within normal range. We confirmed the GS type 2 accelerated phase diagnosis by Sanger sequencing, which revealed the homozygous mutation c.217T>G (p.W73G) in exon 3 of *RAB27A*. This mutation in *RAB27A* was reported before as a cause of GS.[5]

After the HLH-2004 protocol, the patient underwent an allogeneic hematopoietic stem cell transplantation (HSCT) from his HLA-identical father. Myeloablative regimen was given to the patient. Eight days after HSCT, he developed CMV-related pneumonia and heart failure. With fluconazole, voriconazole and foscarnet treatment, the clinical course regressed. Eighteen months after HSCT, the chimerism was 95% (Table I).

During follow-up, steroids were tapered at the 4th month of HSCT. His evaluation showed hypothyroidism with increased thyroid stimulating hormone. When he was 15 months old, on physical examination, macrocephaly and mild developmental delay (by Denver-II Developmental Screening Test) were detected. Cranial magnetic resonance imaging (MRI) showed increased T2-weighted signal intensity in centrum semiovale and bilateral periventricular regions. The audiological test was bilaterally symmetric, and he achieved his developmental steps late. Now, he attends primary school, and his development is appropriate for his age. He is euthyroid with thyroid hormone replacement.

The family gave written consent for this publication.

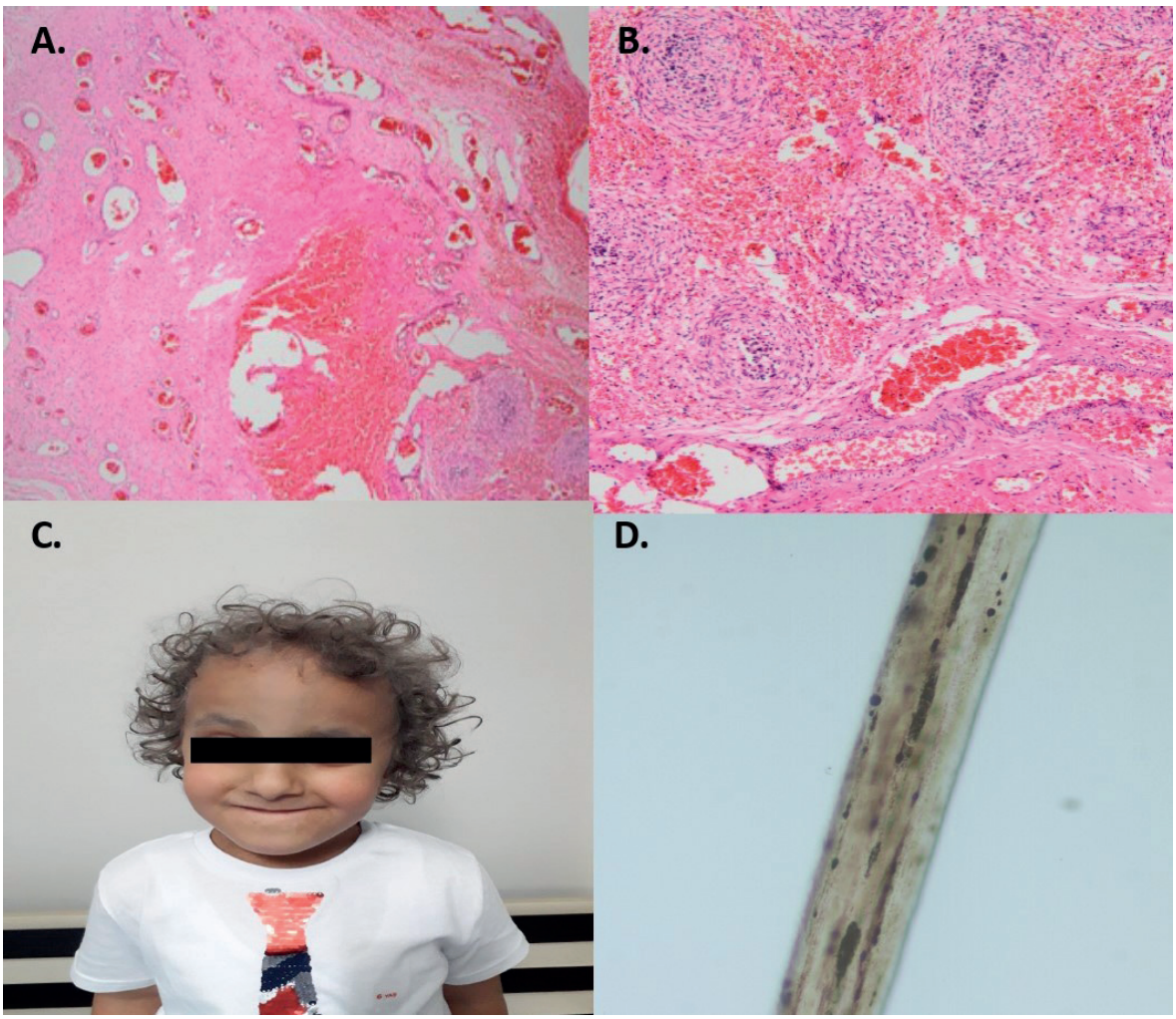

Fig. 1. A and **B)** Light microscopic findings show diffuse hemorrhagic necrosis in left orchiectomy material (Hematoxylin & eosin staining, x10 and x20 magnification, respectively) **C)** Child with obvious grey hair and brows, picture taken by his parents when he was 6-years-old **D)** Microscopic examination of patient's hair, x20 magnification, was compatible with Griscelli syndrome

Discussion

We presented a newborn diagnosed after orchiectomy and a previously reported gene defect for GS type 2.[6]

This case was interesting from two points: He is one of the youngest GS patients whom developed HLH in the literature, and presented with probable testicular involvement not reported before in the medical literature. One study reported testicular involvement in HLH but lacked patient characteristics.[7]

The HLH-2004 protocol (steroids, cyclosporine a, intravenous immunoglobulin, etoposide) and antimicrobial prophylaxis were used to treat GS type 2 as valid treatment at the time of patient presentation. The scheme should be applied until remission occurs, and HSCT should be performed as curative therapy.[3,4] In the current case, after the patient was diagnosed with GS type 2 and HLH by diagnostic criteria, he was treated first for HLH and then with HSCT as curative treatment. We did not find any central nervous system (CNS) involvement. When a

Table I. Laboratory parameters of the patient.

Laboratory parameters	On admission	18 months after HSCT
Hemoglobin (g/dL)	6.2 (9.5-16)	13.9 (11-13.9)
WBC (x10^6/L)	4,400 (6,000-18,000)	9,700 (5,500-12,000)
ALC (x10^6/L)	2,800 (900-8,800)	6,000 (5,000-6,000)
ANC (x10^6/L)	600 (1,200-7,500)	2700 (1,500-6,300)
AEC (x10^6/L)	100 (100-1,700)	300 (100-750)
Platelets (x10^9/L)	21 (60-600)	296 (225-470)
Erythrocyte sedimentation rate (mm/h)	2	-
C-reactive protein (mg/dL)	9.87 (0-0.5)	-
Ferritin (mg/dL)	14.4 (20-336)	44.4 (20-336)
Fibrinogen (mg/dL)	253 (180-350)	-
Triglyceride (mg/dL)	88 (<150)	43 (<150)
IgA (mg/dL)	72.9 (11-14.01)	-
IgG (mg/dL)	626 (603-1466)	-
IgM (mg/dL)	74.8 (22-87)	-
CD3 (% - /mm^3)	81 (53-84)	54 (53-75)
	2,270 (2,500-5,500)	3,250 (2,100-6,200)
CD4 (% - /mm^3)	46 (35-64)	28 (32-51)
	1,288 (1,600-4,000)	1,700 (1,300-3,400)
CD8 (% - /mm^3)	41 (12-28)	29 (14-30)
	1,150 (560-1,700)	1,750 (620-2,000)
CD16/56 (% - /mm^3)	9 (4-18)	24 (3-15)
	250 (170-1,100)	1,450 (180-920)
CD19 (% - /mm^3)	7 (6-32)	12 (16-35)
	200 (300-2,000)	700 (720-2,600)

Values in parenthesis for hemoglobin, WBC, ALC, ANC, AEC, AMC and platelet count indicate 5th and 95th percentiles in first column and 25th and 90th percentiles for second column, respectively. Values in parenthesis for immunoglobulin values indicate 15th and 85th percentiles, respectively. Values in parenthesis for lymphocyte subsets indicate 10th and 90th percentiles, respectively. AEC, absolute eosinophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; ANC, absolute neutrophil count; CD, cluster of differentiation; HSCT, hematopoietic stem cell transplantation; Ig, immunoglobulin; WBC, white blood count.

patient with GS presents with a neurological symptom, CNS involvement in HLH should be excluded.

After HSCT, hypothyroidism was observed, which was related to long-term corticosteroid treatment. MRI showed increased T2-weighted signal intensity in centrum semiovale and bilateral periventricular regions. It may be related to possible CNS involvement of HLH, which was in the beginning phase and had not progressed but was cured during the HLH follow-up after HLH 2004 therapy was started.[8]

Testicular torsion may develop in the early newborn period. Intravaginal testicular torsion usually occurs in adolescents, and the extravaginal testicular tortion generally occurs in prenatal and neonatal periods. Although the most commonly detected etiology of intravaginal torsion is the bell clapper deformity, extravaginal torsion's etiology is still unknown.[9,10] Our patient's specimen was necrotic, and we could not determine the torsion type, which might be an extravaginal torsion according to the medical literature.[9]

We thought that the testicular torsion may be the result of testicular involvement due to HLH. However, we could not confirm this as we could not show hemophagocytosis in the testis

biopsy, as it was necrotic. Hence, testicular torsion in our patient may have been due to the involvement of the testis in the subclinical phase of HLH.

Testicular involvement in this patient is a novel finding. There may be a link between testicular torsion and histiocytic infiltration. Confirmation to this from the medical literature may be the Erdheim-Chester disease, which is characterized with local histiocytic infiltration of the testis and is one of the causes of testicular torsion.[11] Thyroid, CNS, and testicular involvement did not occur at the same time. Central nervous system involvement in HLH can be subtle, as seen in this patient. In a patient with partial albinism, cranial imaging should be conducted before HSCT with a conditioning regimen since intracranial HLH involvement may be the case.

Thyroid function tests were not performed before HSCT and we do not know whether the hypothyroidism that developed after transplantation was autoimmune. The thyroid replacement therapy needed in the course of the disease may be due to thyroid involvement, which may be directly due to the infectious agent triggering the HLH or secondary to the HLH thyroid involvement. We suggest that the local tissue involvement in this disease is step by step and testicular involvement may be the first sign of gradual HLH development as seen in the present case.

Cytopenia and hepatosplenomegaly are common features of HLH in patients with partial albinism. However, various tissues may be affected locally during the progressive course of HLH. Therefore, if a patient with partial albinism presents with atypical local involvement, histiocytosis and HLH may be on the top of the differential diagnosis list.

Ethical approval

Informed consent was obtained from the family for publication of this brief report.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: DC, FİT; data collection: TS, GS, AKT; analysis and interpretation of results: HA, HTA; draft manuscript preparation: TA, GS, AKT, DC. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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