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Case report

Successful bone marrow transplantation in a case of Griscelli disease which presented in accelerated phase with neurological involvement

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Summary:

Griscelli disease (GD) is a rare disorder characterized by pigment dilution, immunodeficiency and occurrence of accelerated phase consisting of hemophagocytosis, pancytopenia and neurological manifestations. Allogeneic BMT in the early period is an important modality of treatment for GD. We carried out an alloBMT from an HLA-identical sibling donor on a 4-year-old girl who presented in accelerated phase with neurological manifestations including convulsions, strabismus, severe dysarthria, ataxia and clonus. She was treated with etoposide, methylprednisolone and intrathecal methotrexate for 8 weeks and underwent alloBMT after receiving a conditioning regimen including ATG (rabbit, 10 mg/kg × 5 days), Bu/Cy. 8×10^8/kg nucleated bone marrow cells were given. Engraftment occurred early and the post-BMT period was uneventful. Currently, she is at 18 months post BMT with sustained engraftment and with a normal neurological examination except for minimal clonus. Long-term follow-up will determine the prognosis regarding the neurological findings.

Keywords: Griscelli disease; bone marrow transplantation; neurological involvement

Griscelli disease (GD) is a rare autosomal recessive disorder characterized by silvery-gray hair, eyebrows and eyelashes, diffuse skin hypopigmentation, variable cellular immunodeficiency and occurrence of uncontrolled lymphocyte and macrophage activation leading to an accelerated phase consisting of hepatosplenomegaly, pancytopenia and in some patients, neurological manifestations.[1–3] Recently, the gene for GD has been mapped to chromosome segment 15q21, a region for human myosin-Va gene.[4] Myosin-Va is responsible for actin-dependent activities which are important in determining cell shape, cytokinesis and intracellular transport of organelles.[5] Defects in intracellular trafficking thus account for the defective transport of melanosomes from melanocytes to keratinocytes and defective protein secretion by cytotoxic T and NK cells resulting in skin hypopigmentation and defective cytototoxicity, respectively. Myosin-Va may also play a role in the intracellular distribution of membranous organelles in neurons.

The prognosis of patients with GD is poor unless allogeneic hematopoietic stem cell transplantation is performed before progression to accelerated phase. We report a GD patient in accelerated phase with neurological involvement who was successfully treated by allogeneic bone marrow transplantation.

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Case report

A 4-year-old girl was first referred to Hacettepe Children's Hospital for further evaluation of persistent fever, hepatosplenomegaly and neurological manifestations including strabismus, dysarthria, ataxia and loss of sphincter control. Five months prior to her referral, she had a prolonged febrile illness, and convulsions, strabismus, ataxia, dysarthria, enuresis, encopresis and was hospitalized in a local medical center and investigated for her progressive neurological disease. Cerebrospinal fluid analysis revealed a mononuclear leukocytosis with a high protein level and sterile culture. EEG showed frontotemporal abnormal ties. MRI showed multiple nodular foci with increased signal intensities in the white matter of the cerebellum. She was the second child of third-degree consanguineous parents. The older sister was healthy with normal pigmentation. On physical examination, silvery-gray hair, eyebrows, eyelashes and skin hypopigmentation were present. The liver was palpable 4 cm and the spleen 5 cm below the respective costal margins. Neurological examination showed strabismus (esotropia), ataxia, intention tremor, dysmetry, dysdiadokokinesia, dysartric speech, bilaterally increased deep tendon reflexes, positive Babinsky and clonus of 20–25 beats. The hemoglobin was 6.7 g/l (1.03 mmol/l) and white blood count 2000/mm^3 (2×10^9/l) with no giant granules in the leukocytes and the platelet count was 57 000/mm^3 (57×10^9/l). Serum fibrinogen was 100 mg/dl (1 g/l) (N: 200–400 mg/dl), triglycerides 213 mg/dl (2.13 g/l) (N: 32–

99 mg/dl), ferritin 140 ng/dl (140 μg/l) (N: 7–140 ng/dl). Liver function was normal. Bone marrow aspirate showed no hemophagocytosis. Light microscopy of hair shaft showed clumped pigment granules throughout. Linkage analysis of the patient's DNA showed a linkage to chromosome 15q21. Medical history, physical examination and laboratory data were consistent with the diagnosis of GD in accelerated phase with neurological involvement. A combination of high-dose methylprednisolone (30, 20, 10, 5 each dose for 1 week and 2.5 mg/kg/ day for 4 weeks, total 8 weeks), etoposide (150 mg/m^2, i.v., once a week for 8 weeks), and IT methotrexate 15 mg/m^2 once a week for 8 weeks was started. She improved rapidly with the disappearance of organomegaly, strabismus and regression of the intention tremor and ataxia. BMT was then carried out from her HLA-identical sister. Conditioning consisted of ATG (rabbit) 10 mg/kg/day from days −14 to −10; Bu 5 mg/kg/day days −9 to −6 (total 20 mg/kg) and CY 50 mg/kg on days −5 to −2 (total 200 mg/kg). She was given 8×10^8 bone marrow nucleated cells/kg from her sibling and received cyclosporin A (3 mg/kg/day i.v.) and short-course MTX (10 mg/m^2 on days +1, +3 and +6) as GVHD prophylaxis. She received GM-CSF, intravenous immunoglobulins (IVIG) (weekly 150 mg/kg), antibiotics, antiviral and antifungal prophylaxis and gut decontamination. She had a febrile episode in the neutropenic period and was treated with antibiotics. Neutrophils reached 0.5×10^9/l by day +15 and platelets 20×10^9/l by day +26. The neurological abnormalities gradually resolved over the following days and she was discharged from hospital on day +30 with normal physical findings except for clonus of 2–3 beats on the right side.

Follow-up magnetic resonance imaging (MRI) of the central nervous system, at +4.5 months, revealed multiple foci of increased signal intensity involving the left cerebellar hemisphere, bilateral periventricular area and centrum ovale (Figure 1a). Language development and motor functions developed normally. There was no sign of GVHD and CsA was stopped at 6 months post BMT. Another follow-up MRI study at +1 year revealed a decrease in the size of the previous foci with the disappearance of the cerebellar lesions (Figure 1b). Currently, she is 18 months post BMT, remains well with a stable hematological picture, full donor-type engraftment, and no systemic signs of accelerated phase or neurological abnormalities.

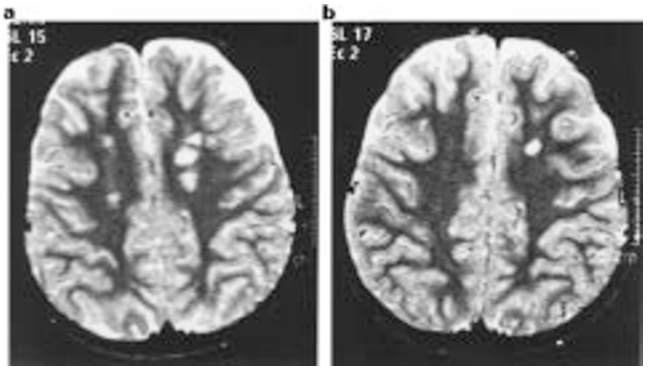

Figure 1 Brain MRI images 4.5 months (**a**) and 1 year (**b**) after BMT showing disappearance and decreasing of signal intensities of the lesions.

Discussion

The clinical signs and findings in this patient were consistent with Griscelli disease. Linkage analysis of the patient's DNA showed a linkage to chromosome 15q21. The spectrum of neurological involvement in GD may range from an early onset severe neurological disorder similar to the neuroectodermal melanolysosomal disease described by Elejalde *et al*[6] to the form that accompanies the accelerated phase as observed in our patient. Late presentation of neurological manifestations, their synchronized appearance with the accelerated phase, and regression of the neurological findings after cytoreductive therapy confirm the abnormality has an infiltrative nature related to the accelerated phase (AP). The lesions on MRI may be caused by cellular infiltrations during AP. The accelerated phase is attributed to a defect in immunomodulation with uncontrolled activation and accumulation of mononuclear leukocytes in different organs associated with hypercytokinemia. GD patients can enter the accelerated phase at any age and this is mostly responsible for the fatal outcome in patients, 20–50% of whom also have neurological involvement.[7–9] Hematopoietic stem cell transplantation seems to be effective in GD with neurological involvement due to AP. Mouse studies with dilute mutation (Myosin-Va deficiency) which is equivalent to GD in humans, show that myosin-Va is involved in the transport of melanosomes in melanocytes and smooth endoplasmic reticulum in cerebellar Purkinje cells. It has been shown that Myo-Va may be mutated in such a way that only coat color or both coat color and the nervous system are affected.[10] Although the relationship between the defect and the accelerated phase is not yet clear, the pathogenesis of the neurological findings in the accelerated phase has been suggested as due to cellular infiltration and inflammation in the central nervous system.

The prognosis in GD patients without hematopoietic stem cell transplantation is known to be very poor.[11,12] Out of three patients who received BMT in the accelerated phase of the disease, two died while another patient who was diagnosed by the characteristic pigmentary dilution, before overwhelming infection and progression to accelerated phase, was transplanted successfully.[2,11] In our patient, we first attempted to control the accelerated phase and then used a conditioning regimen including ATG, Bu and CY for BMT. Currently, she is 18 months after an uneventful BMT and has age-matched motor and mental development. Success of BMT, even in a patient with neurological abnormalities due to accelerated disease as in our patient, indicates that uncontrolled activation of lymphohistiocytic cells is responsible for the fatal outcome in this syndrome, as suggested previously. Long-term follow-up of the patient will define further prognosis of the neurological involvement in GD.

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