SUCCESSFUL ALLOGENEIC HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR GRISCELLI SYNDROME TYPE 2 MANIFESTED AS LONG-TERM CNS AND LUNG INJURY.

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Background

Griscelli syndrome type 2 (GS2) is a rare disease with typical combination of hypopigmentation and haemophagocytic lymphohistiocytosis (HLH). It is a life-threatening disease caused by mutations in RAB27A gene and may be treated by allogeneic haematopoietic stem cell transplantation (alloHSCT). We present a case with unusual clinical presentation, novel genetic mutation and successful alloHSCT.

Case report

Previously healthy 5 year old boy presented with an acute demyelinating encephalomyelitis (Fig. 1A). Several months later a focal confluent infiltration in the lungs (Fig. 1B), enlarged mediastinal lymph nodes and granulomatous dermatitis (Fig. 1C) appeared. Diagnostic work-up was unspecific. Due to recurrent CNS and lung attacks the patient has been steroid-dependent for 4 years. Attempts to taper steroids or acute upper respiratory infection provoked dyspnoea, progression of lung infiltrates and deterioration of CNS symptoms. At the age of 9 he developed classical HLH symptoms. The patient displayed no signs of oculocutaneous albinism (Fig. 1D). Abnormal degranulation assay suggested primary HLH. No HLH mutations were found by whole exome sequencing. Breakpoint PCR sequencing revealed a complex structural rearrangement at the 5'UTR of RAB27A in homozygous state. Reduced RAB27A transcription and expression was confirmed by RT-PCR and Western blot analyses (Fig. 2). GS2 was confirmed.

Severe cushingoid, impaired renal function and residual neurologic symptoms were present prior to HSCT. AlloHSCT from HLA-identical healthy sibling using fludarabin (180 mg/m^2) and melphalan (140 mg/m^2) based reduced intensity preparative regimen was performed. Cyclosporin and mycophenolat mofetil were used for GvHD prophylaxis. Bone marrow derived stem cells were infused (CD34+ 7.01 x 10^6/L, CD3+ 0.46 x 10^8/L) infused. Rapid hematologic recovery with full donor chimerism ocurred. IAcute GvHD Grade II (skin +++, liver+) followed by chronic cutaneous GvHG ocurred (Fig. 3). GvHD was successfully managed with steroids, extracorporeal photopheresis and psoralen with UVA radiation. Currently the patient is full chimera, steroid-free and in a stable, improving clinical condition 21 months after HSCT.

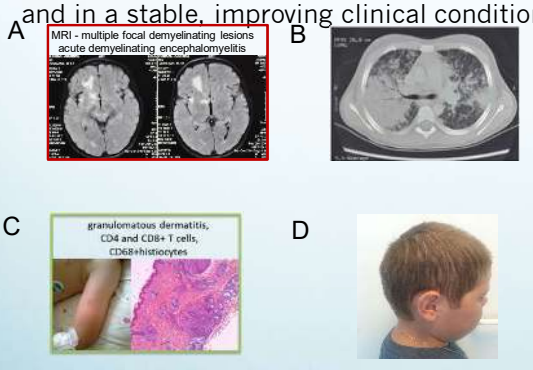

Fig.1. Clinical presentation. CNS lesions at first presentation (A). Pulmonary infiltarion (B). Skm granulomas (C). Normal hair (D).

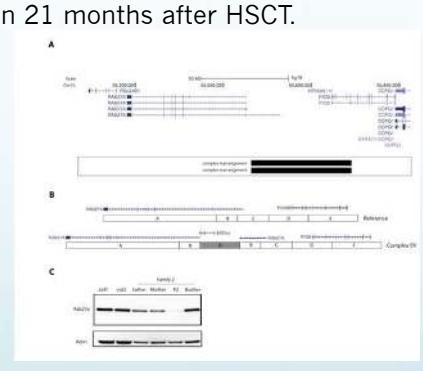

Fig. 2. Genetic analysis. A complex structural rearrangement at the 5'UTR of *RAB27A* was found (A). The rearrangement involved two duplication and one inversion (B). Reduced RAB27A protein expression (C).

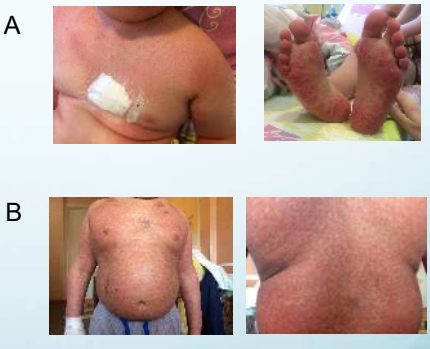

Fig. 3. Cutaneous GvHD: acute (A), chronic (B).

Conclusion

GS2 can present as isolated CNS and lung involvement without hypopigmentation. If no mutations are found in the exons, mutations in non-coding regions should be pursued by whole genome sequencing. AlloHSCT using RIC is feasible and should be offered to these patients.

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