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Allogeneic stem cell transplantation-A curative treatment for paroxysmal nocturnal hemoglobinuria with PIGT mutation: A case report

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Abstract

BACKGROUND

Patients with paroxysmal nocturnal hemoglobinuria (PNH) have a clonal population of blood cells deficient in glycosylphosphatidylinositol-anchored (GPI-anchored) proteins, most of the time resulting from a mutation in the X-linked gene PIGA. We report a patient with PNH resulting from a rare biallelic PIGT mutation on chromosome 20.

CASE SUMMARY

A 47-year-old man was referred to our hospital for febrile pancytopenia. The patient reported a history of recurrent urticaria and arthralgia and he presented during 3 mo recurrent acute dermo-hypodermatitis and aseptic meningitis. Based on clinical cases published with PIGT-PNH, with clinically typical PNH and autoinflammatory symptoms, we treated our patients with repeated infusions of eculizumab to decrease autoinflammatory symptoms and then we performed an allogeneic stem cell transplantation (allo-SCT) with a mismatched unrelated

donor. Our patient experienced no acute Graft *vs* Host disease (GvHD) and a moderate chronic GvHD and is now considered cured at 24 mo after allo-SCT.

CONCLUSION

This case report suggests that allo-SCT should be considered to cure PIGT-PNH patients.

Key Words: Paroxysmal nocturnal hemoglobinuria; Allogeneic stem cell transplantation; PIGT mutation; Recurrent meningitis; Autoinflammatory symptoms; Case report

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Core Tip: Paroxysmal nocturnal hemoglobinuria with autoinflammatory symptoms has been described in 4 cases with PIG-T mutations (PIGT-PNH entity). We report the fifth case in the world. For the first time we treated him with an allogeneic hematopoietic stem cell transplantation (allo-SCT) after repeated infusions of eculizumab to decrease autoinflammatory symptoms. Allo-SCT was performed with a mismatched unrelated donor and no excess of alloreactivity or toxicity was observed. We think that this new case report with a review of literature will help physicians to have a focus on PIGT-PNH. It suggests that allogeneic SCT should be considered as a curative treatment option for this disease.

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INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hematopoietic stem cell (HSC) disorder. Deficient HSCs give rise to a clonal population of blood cells deficient in proteins anchored with glycosylphosphatidylinositol (GPI-anchored), a glycolipid moiety that secures 100 different proteins to the cell surface[1]. In 2019, 4 patients with typical PNH and autoinflammatory symptoms, including recurrent aseptic meningitis, were found to have a germline point mutation in one *PIGT* allele, with the other *PIGT* allele being removed by somatic deletion of a 20q region implicated in hematological malignancies. Analyses of patient leukocytes revealed free GPI expressed on the cell surface, triggering autoinflammation through increased IL-1 β secretion, activation of the lectin pathway of complement and production of C5b-9 complexes[2]. Therefore, eculizumab treatment abrogates not only intravascular hemolysis but also autoinflammation. We report the fifth case of PIGT-PNH and the first time that allogeneic hematopoietic stem cell transplantation has been applied as treatment. This procedure was readily feasible with no excess alloreactivity or toxicity.

CASE PRESENTATION

Chief complaints

A 47-year-old man was referred to our hospital for pancytopenia with PNH cloning and meningitis and urticaria.

History of present illness

Upon admission to our hospital, he presented with fever, sudden brownish urine and altered consciousness with mild pancytopenia (hemoglobin 93 g/L, platelets 137.109/L and leukocytes 2.109/L).

History of past illness

The patient reported a history of recurrent urticaria and arthralgia since he was 30-years-old. Three months and one month prior, he was hospitalized for acute dermatohypodermatitis with pancytopenia and no documented microbiologic agent. He was successfully treated with piperacillin and tazobactam for 14 d.

Personal and family history

No special family history was reported.

Physical examination

Examination revealed urticaria and symptoms of meningitis including headache and stiff neck. His meningitis symptoms were resolved at 3 d after initiation of meropenem. During hospitalization, he experienced 4 episodes of aseptic meningitis and general fatigue, arthralgia and urticaria preceded each episode. He recovered quickly within 3 d from the last episode of meningitis with corticosteroids and without antibiotics. The patient developed severe chronic hemolysis after the first meningitis episode.

Laboratory examinations

C reactive protein levels were mildly elevated at 20 mg/L. Examination of lumbar cerebrospinal fluid showed 307 polymorphonuclear leukocytes/mm³. No bacteria, fungi, viruses or mycobacteria were identified, nor were autoantibodies. A biopsy from one urticarial lesion revealed mixed inflammatory (neutrophils and monocytes) infiltrate. Flow cytometric analysis of both erythrocytes and granulocytes indicated deficiency of GPI-anchored proteins (Figure 1); complement system dosing showed a normal CH50 Level. Factor H and Factor I plasma concentrations and anti-Factor H antibodies were also normal. Examination of cellular morphology based on bone marrow aspiration revealed multilineage dysplasia with no excess blasts (< 2%). Medullary cytogenetic analysis detected a 20q deletion in the karyotype, and Sanger sequencing highlighted a deletion of 4 nucleotides (NM_015937.6:c.766_769del) in exon 6 (p. Lys256ThrfsTer38) leading to a frameshift and a premature stop codon. This mutation was found in the heterozygous state in both T lymphocytes and in the negative cellular fraction, suggesting a constitutional anomaly. These results were confirmed using another sample consisting of DNA extracted from fibroblast culture cells collected after skin biopsy. This finding is reported only once in the ClinVar database (RCV000735856.1). According to the CGH array, we detected a large somatic deletion of 18 Mb from 20q11.21 to 20q13.13, an area including the entire PIGT gene. This 20q deletion associated with heterozygous constitutional mutation of PIGT leads to biallelic inactivation of the gene (Figure 2).

Imaging examinations

Cerebral magnetic resonance imaging results were normal.

FINAL DIAGNOSIS

PIGT-PNH.

TREATMENT

All the patient's symptoms, including urticaria, arthralgia, headache/meningitis and hemolysis, completely disappeared after eculizumab was administered regularly. Finally, after 8 mo on eculizumab treatment, the pancytopenia worsened (hemoglobin 90 g/L, platelets 67.10⁹/L and leukocytes 1.10⁹/L), and the patient presented a sepsis secondary to a catheter-related bacteremia of staphylococcus epidermidis resistant to methicillin. Bone marrow tests revealed 8% blast. We decided to transplant the patient because of the episode of severe infection and bone marrow smear results. The decision of transplantation was difficult, because in common PNH caused by mutation of PIGA, there is a high risk of developing GVHD, especially in patients older than 40-years-old with no sibling donors. No data were available about transplantation in PNH caused by mutation of PIGT, and our patient had no sibling or matched unrelated donors. However, recent retrospective studies demonstrated promising results with HLA-mismatched/haploidentical hematopoietic stem cell transplantation after reduced intensity conditioning and GVHD prophylaxis with post-Transplant cyclophosphamide in refractory severe aplastic anemia patients. Moreover, inflammatory symptoms in our patient were totally controlled by eculizumab. We hypothesized that it could be a good time for transplantation. Therefore, allogeneic hematopoietic stem cell transplantation with peripheral blood stem cells from an HLA-mismatched unrelated donor was carried out after a reduced-intensity conditioning regimen consisting of thiotepa (5 mg/m² at day -7), a total fludarabine dose of 150 mg/m² (30 mg/m² from day -5 to day -1), and total intravenous (i.v.) busulfan 6.4 mg/kg (3.2 mg/kg/d on days -4 and -3). Graft vs host disease (GVHD) prophylaxis consisted of posttransplant cyclophosphamide (50 mg/kg/j on days +3 and +4), cyclosporine A (starting on day +5 at 3 mg/kg/day) as a continuous i.v. infusion, and i.v. MMF (starting on day +5 at 15 mg/kg every 12 h). A dose of 6×10⁶ CD34⁺/kg body weight was infused.

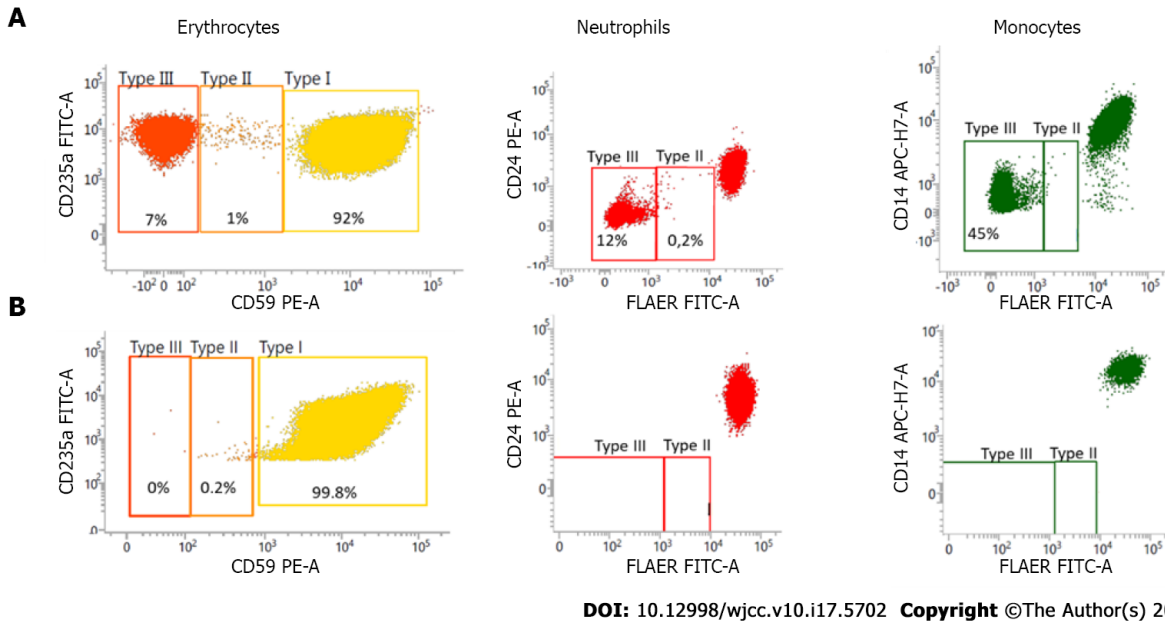


Figure 1 Expression of GPI-anchored proteins in patient peripheral blood cells before and after allo-HSCT. A: Before transplantation: expression of (left) CD59 on red cells, (center) CD24/FLAER on neutrophils, and (right) CD14/FLAER on monocytes. There is a mosaic of cells with normal expression of GPI-anchored proteins and cells with reduced (type II) or completely lacking expression (type III) of GPI-anchored proteins; B: After transplantation, CD59 was expressed on 99.8% of red cells (left), CD24/FLAER on 100% of neutrophils (center) and CD14/FLAER on 100% of monocytes (right).

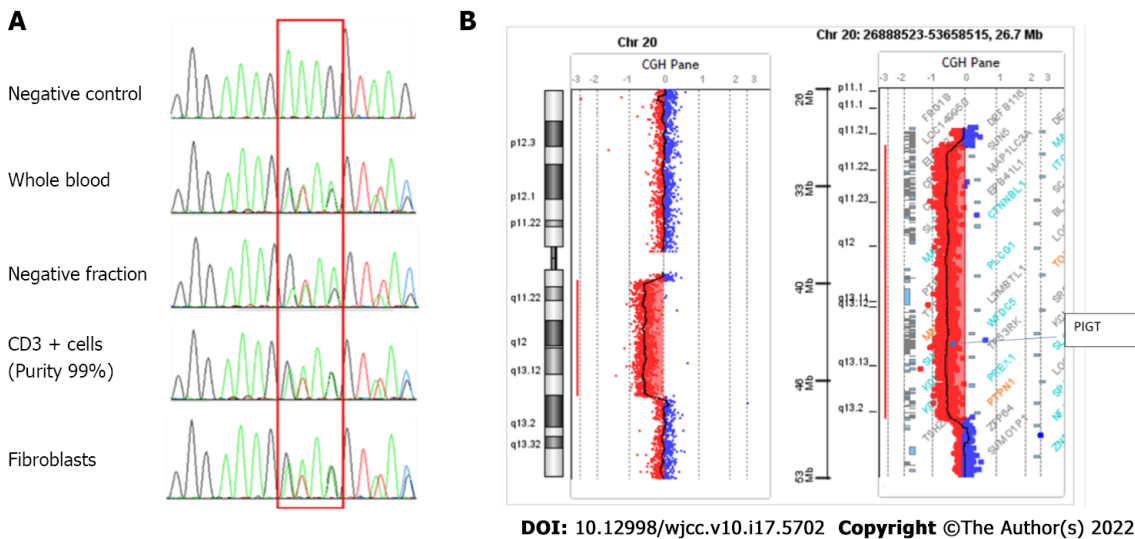


Figure 2 Genetic analysis. A: Genetic sequencing. Cell sorting was performed on blood samples (*Robosep, Easy sep CD3 whole blood positive selection kit*[®]). The positive fraction consisted of a T lymphocyte population (purity: 99%), and the negative fraction included B lymphocytes, natural killers, monocytes and polymorphonuclear cells. DNA was extracted from these two fractions using a Qiagen DNA minikit[®]. The entire *PIGT* gene was sequenced by the Sanger method (*Big Dye Terminator v3.1, Life Technologies*) using primers for each exon; B: CGH array (*Agilent, Sure Print G3 Human CGH Microarray 4x180K*) performed on DNA extracted from bone marrow samples highlights a large somatic deletion of 18 Mb from 20q11.21 to 20q13.13, removing the entire *PIGT* gene.

OUTCOME AND FOLLOW-UP

We observed rapid myeloid engraftment, with a time for neutrophils $> 0.5 \times 10^9/L$ and platelet recovery ($> 20.10^9/L$) of 15 d and 16 d, respectively. Chimerism was complete donor at 1, 3, 12 and 18 mo posttransplant. No acute GvHD was observed. Six months after transplantation, he developed moderate chronic hepatic and skin GvHD that improved by enhancing the calcineurin inhibitor and starting 1 mg/kg/d corticosteroid therapy. At the time of writing, at 24 mo after transplantation, chronic GvHD is in complete remission with no immunosuppressant.

DISCUSSION

PNH is a clonal disorder involving blood cells deficient in glycosylphosphatidylinositol-anchored (GPI-anchored) proteins[1,3], which is often caused by a deficient initial step in GPI anchor synthesis, as catalyzed by the GPI-GlcNAc transferase encoded by the X-chromosomal gene *PIGA*[4-6]. However, 22 *PIG* genes participate in the biosynthesis and protein attachment of GPI[7,8]. The *PIGT* gene on chromosome 20, at position 20q13.12 with 12 exons, encodes phosphatidylinositol-glycan biosynthesis class T protein (PIG-T), a subunit of the heteropentameric GPI transamidase complex that facilitates attachment of GPI anchors to proteins[9]. Four cases of PHN with recurrent inflammatory symptoms have been reported[2] with PIGT defects and successfully treated with eculizumab. In 2013, PNH due to 2 mutation events was reported: a germline splice site mutation and a somatic deletion in *PIGT* (c.1401-2A>G), as identified by next-generation sequencing[10]. In 2018, a second patient with long-term severe urticaria and joint pain before developing PNH harbored similar mutations in *PIGT* (c.250G>T) and exhibited recurrent aseptic meningitis in addition to inflammatory symptoms[11]. Both cases clearly improved with eculizumab treatment. In 2019, 2 additional patients with PHN and inflammatory symptoms were reported: one had chronic lymphocytic leukemia, and the other carried the *JAK2*-V617F mutation. Both patients harbored germline mutations in one *PIGT* allele (one patient with c.761_764delGAAA and the other with c.197delA) associated with somatic deletions, including the entire *PIGT* gene in the second allele without *PIGA* gene abnormalities[2]. In known cases of PHN with *PIGT* disruption, one of the *PIGT* alleles is removed due to a somatic deletion of varying size, including the common deleted region (CDR) of 1.9 Mb, which is close to the centromeric region, often described in myeloid malignancies with 20q deletion. Based on a family segregation study, *PIGT* haploinsufficiency is not sufficient for the development of autoinflammatory symptoms. In our case, the development of MDS with 20q deletion was an indispensable additional abnormality resulting in biallelic inactivation of *PIGT*, explaining the PNH. If mutations in both *PIGA* and *PIGT* can induce PNH, recurrent inflammatory symptoms, including meningitis, are in particular found with *PIGT* mutations. Therefore, some authors have proposed creating a new entity named PIGT-PHN[2]. In PNH-PIGT syndrome, cytokine dosing suggests that increased free GPI might over activate NLRP3 inflammasomes in mononuclear cells with strong IL-1 β and IL-18 responses. IL-18 is produced by activated inflammasomes[12,13] and is also produced during clinical GvHD. NLRP3 is known to play a role in enhancing GvHD[14]. Our case report is the fifth published case of PIGT-PNH. Among 4 patients previously described, 3 patients were partially controlled with corticosteroids, colchicine, diphenhydramine, cromoglycin, azathioprine, mycophenolate mofetil, dapsone, anakinra and canakinumab. Only eculizumab treatment abrogates autoinflammation for one patient. We confirm that eculizumab is the best treatment to abrogate intravascular hemolysis and autoinflammation. Because we know that complement activation and inflammatory dysregulation before allo-SCT might be associated to a higher incidence of severe acute GvHD in patients, our main concern was about the toxicity of this procedure. We report for the first time that allogeneic hematopoietic stem cell transplantation is a readily feasible procedure with no excess alloreactivity or toxicity.

CONCLUSION

Allogeneic stem cell transplantation has not been reported for treating PIGT-PNH, yet this therapy addresses the concern regarding a high risk of alloreactivity and toxicity in patients with activated NLRP3 inflammasomes in mononuclear cells. Our case is the first to be successfully treated with allo-SCT, and no toxicity (especially GvHD) was observed.

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FOOTNOTES

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