

Paroxysmal nocturnal hemoglobinuria and liver transplantation: a new paradigm with proximal complement inhibition

Hemoglobinuria paroxística nocturna y trasplante hepático: un nuevo paradigma con inhibidores proximales del complemento

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Abstract

Paroxysmal nocturnal hemoglobinuria (PNH) is caused by an acquired somatic mutation of the phosphatidylinositol glycan class A gene. It is characterized by complement-mediated intravascular hemolysis, an increased risk of thrombosis, and varying degrees of bone marrow failure. Budd-Chiari syndrome is a rare but severe thrombotic complication associated with PNH. We present the case of a 57-year-old man with a history of aplastic anemia who developed classic PNH, complicated by multiple thrombotic events and two liver transplants. Despite treatment with eculizumab, with adequate therapeutic levels and effective blockade of the terminal complement pathway, he presented persistent anemia with transfusion dependence and elevated hemolysis markers such as lactate dehydrogenase (LDH). Given the suspicion of extravascular hemolysis, treatment with pegcetacoplan, a proximal complement inhibitor, was initiated, achieving normalization of LDH and significant improvement in hemoglobin levels, reaching transfusion independence. However, due to the recurrence of severe hemolytic crises, treatment was ultimately switched to iptacopan, resulting in remission of the crises and clinical and laboratory stability of the patient. This case illustrates the usefulness of proximal complement blockade with anti-C3 agents in PNH patients with liver transplantation and suboptimal control under anti-C5 therapy.

Keywords: Hemolysis. Anemia. Liver transplants. Complement.

Resumen

La hemoglobinuria paroxística nocturna (HPN) se debe a una mutación somática adquirida del gen PIG-A. Se caracteriza por hemólisis intravascular mediada por el complemento, elevado riesgo trombótico y diferentes grados de insuficiencia medular. El síndrome de Budd-Chiari es una complicación trombótica grave y poco frecuente asociada a la HPN. Presentamos el caso de un varón de 57 años con antecedente de aplasia medular que desarrolla una HPN clásica, complicada con múltiples eventos trombóticos y doble trasplante hepático. A pesar del tratamiento con eculizumab, con niveles terapéuticos adecuados y bloqueo efectivo de la vía terminal del complemento, presenta anemia persistente con dependencia transfusional y elevación de parámetros de hemólisis como LDH. Ante la sospecha de hemólisis extravascular, se decide iniciar tratamiento con pegcetacoplan, inhibidor proximal del complemento, logrando normalización de LDH y mejoría significativa de la hemoglobina alcanzando la independencia transfusional. Sin embargo, por reaparición de crisis hemolíticas severas recurrentes se cambia finalmente a iptacopan, consiguiendo la nueva remisión de las crisis y la estabilidad clínica y analítica del paciente. Este caso ilustra la utilidad en pacientes con HPN y trasplante hepático con control subóptimo con anti-C5 del bloqueo proximal del complemento con fármacos anti-C3.

Palabras clave: Hemolisis. Anemia. Trasplante Hepático. Complemento.

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Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare hematologic disorder characterized by complement-driven intravascular hemolysis, severe thrombophilia, and bone marrow failure, resulting from the clonal expansion of hematopoietic stem cells harboring a somatic mutation in *phosphatidylinositol glycan class A (PIG-A)*. *PIG-A* is essential for the synthesis of glycosylphosphatidylinositol, which anchors a variety of proteins to the cell surface, including key regulators of the complement pathway such as CD55 and, especially, CD59. The absence of these molecules leads to activation of the alternative pathway, resulting in intravascular hemolysis and other manifestations of PNH, the most clinically significant being thrombosis due to its associated morbidity and mortality.¹

Budd-Chiari syndrome (BCS) is a rare condition caused by obstruction of hepatic venous outflow, which may occur as a thrombotic complication of PNH. The underlying pathophysiology linking PNH and BCS involves the release of free hemoglobin, activation of the coagulation cascade, and endothelial dysfunction leading to platelet activation. This prothrombotic state substantially increases the risk of developing BCS, highlighting the importance of careful thrombotic risk assessment and management in patients with PNH.²

Case report

We report the management of a complex case of PNH complicated by significant thrombotic events and liver transplantation, treated with both terminal (anti-C5) and proximal (anti-C3) complement inhibition.

The patient was a 57-year-old man diagnosed with aplastic anemia in 1993, who subsequently developed classical PNH in 2000, with transfusion-dependent anemia and multiple thromboembolic complications, including BCS. The patient initially received anti-C5 therapy with eculizumab, a first-in-class monoclonal antibody that inhibits terminal complement activation. Treatment with eculizumab was initiated in 2009, resulting in a good response, with improvement in anemia and resolution of intravascular hemolysis. However, from 2014 onward, his condition progressively worsened, with persistent intravascular hemolysis and frequent breakthrough hemolysis (BTH), even after dose escalation to 1200 mg weekly, without clinical improvement.

In 2019, liver function deteriorated, leading to portal hypertension and multiple life-threatening episodes of

gastrointestinal bleeding. He underwent liver transplantation that year; however, control of BTH with eculizumab was inadequate, and he subsequently developed hepatic artery re-thrombosis and ischemic cholangiopathy, resulting in graft failure.

Later in 2019, he underwent a second liver transplantation. Since then, no further thrombotic events have occurred; however, he continued to require high doses of eculizumab (1200 mg every 7–10 days). Despite this, he experienced persistent intravascular hemolysis (lactate dehydrogenase [LDH] > 2–3 times the upper limit of normal), anemia, and significant transfusion requirements. Moreover, he exhibited elevated reticulocyte counts but showed no evidence of extravascular hemolysis, as confirmed by repeatedly negative direct antiglobulin tests using different techniques (gel immunoagglutination and anti-C3b flow cytometry).

Functional complement studies were performed and showed discordant results, with elevated plasma eculizumab levels, undetectable CH50 activity, and C5 levels < 5 mcg/mL (indicative of effective terminal pathway blockade). However, elevated C5b-9 levels (233 ng/mL) suggested ongoing membrane attack complex formation, consistent with the patient's clinical course and inadequate response to anti-C5 therapy.

Recent studies suggest that extensive opsonization of red blood cells promotes extravascular hemolysis through opsonophagocytosis, but may also contribute to persistent intravascular hemolysis and BTH. This occurs because C5 inhibitors fail to fully block the terminal complement pathway when C3b deposition on opsonized red blood cells is markedly increased.³

Flow cytometry was regularly performed to quantify PNH clones in leukocytes and erythrocytes. Leukocytes were stained with CD33 and FLAER, while erythrocytes were stained with CD55, CD59, and CD235a. Samples were processed and analyzed immediately using a calibrated flow cytometer, and data were evaluated with specialized software following a defined gating strategy.

PNH clonality studies consistently revealed a discrepancy between leukocyte and red blood cell clonality, attributed to ongoing hemolysis (Fig. 1).

Therefore, we present a complex case of PNH with thrombotic complications. Despite anti-C5 therapy, the patient showed persistent LDH elevation, with adequate eculizumab levels and no evidence of extravascular hemolysis, indicating ongoing complement activation and treatment failure.

Following the approval in 2021 of pegcetacoplan as the first C3-targeted therapy for adult patients with PNH with persistent anemia after at least 3 months of C5

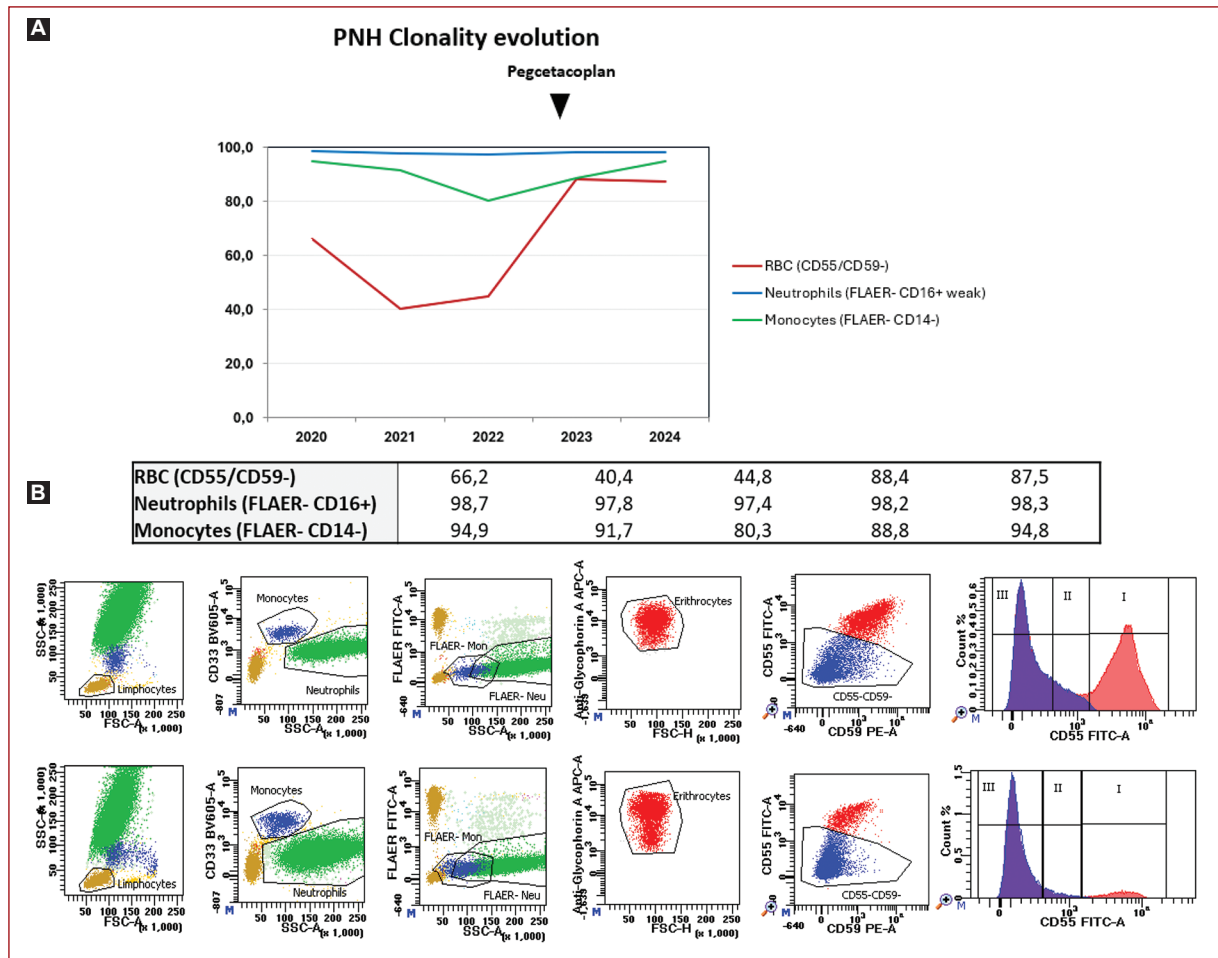


Figure 1. A: clonality evolution before and after treatment with pegcetacoplan. A sign of treatment effectiveness and hemolysis control is the increase in clone size in RBC, equal to that of leukocytes. **B:** flow cytometry analysis of the leukocyte and erythrocyte PNH clones. Lymphocytes were gated in a FSC/SSC dotplot as low-FSC/SSC cells, monocytes and neutrophils in a CD33/SSC dotplot as CD33high SSClow and CD33dim SSC-high, respectively. PNH leukocyte clones were identified as FLAER negative in a FLAER/SSC dotplot. Erythrocytes were gated in a CD235a/FSC dotplot, and negative CD55/CD59 clones identified in a CD55/CD59 dotplot. Type I, II y III erythrocytes were identified in a CD55 histogram. Upper line represents patients previous to treatment, and the lower plots after treatment. RBC: red blood cells; UNL: upper normality limit.

inhibitor treatment, the patient initiated pegcetacoplan in April 2023 (1080 mg twice weekly). This resulted in rapid and significant control of intravascular hemolysis (LDH levels normalized), near-resolution of anemia (hemoglobin increased by 3.5 g/dL from a baseline of 8 g/dL) (Fig. 2), and achievement of transfusion independence. Until May 2025, the patient remained on biweekly pegcetacoplan, maintaining normal LDH levels, transfusion independence, and hemoglobin levels between 10 and 11 g/dL (Table 1).

From May 2025 onward, the patient experienced frequent BTH episodes associated with intercurrent infections, mainly urinary and respiratory. In January 2026, due to persistent severe hemolytic crises with hemoglobinuria, treatment was switched to iptacoplan (Fig. 3).

Since then, the patient has not experienced new BTH episodes, maintains normal LDH levels, and remains transfusion-independent.

Discussion

At present, terminal complement inhibition is the initial treatment of choice for patients with severe manifestations of PNH and has been shown to modify the natural course of the disease, offering patients with PNH a close to normal life expectancy. However, a substantial percentage of patients with anti-C5 therapy show data of insufficient disease control, such as persistence of hemolysis and/or anemia, causing organ damage and impairing quality of life. It is essential to

Table 1. Evolution of hemolysis parameters after the initiation of pegcetacoplan

Analyzed data	T 13 apr	M 17 apr	T 20 apr	T 27 apr	11 May	25 May	22 Jun	27 Jul	31 Aug	5 Oct	9 Nov	7 Dec	11 Jan	15 Feb
Hb (g/dL)	7.5	5.5	7.1	9.9	9.6	10.8	10.7	10.2	10.7	11.1	11.3	10.6	11.6	11.4
LDH (U/L)	412	747	495	246	187	190	174	149	160	152	169	206	194	162
Retic. (×10/uL)	166.6	120	139	106	77.9	107	82.3	106,7	106,1	87.8	103.1	88.7	118.4	116.8
Pegcetacoplan	No	1080 mg	1080 mg	1080 mg infusion on Mondays and Thursdays at home (2 infusion sites)										
Haptoglobin (mg/dL)	< 7				< 7		19	22	23	29	12		< 7	29
Hemopexin (mg/dL)	69.9				79		81.6	78.8	79.7	77.6	79.9		88.7	85.8
Eculizumab	1200 mg			1200 mg										
pRBCs		2												

Hb: hemoglobin; LDH: lactate dehydrogenase; pRBCs: Packed red blood cells.

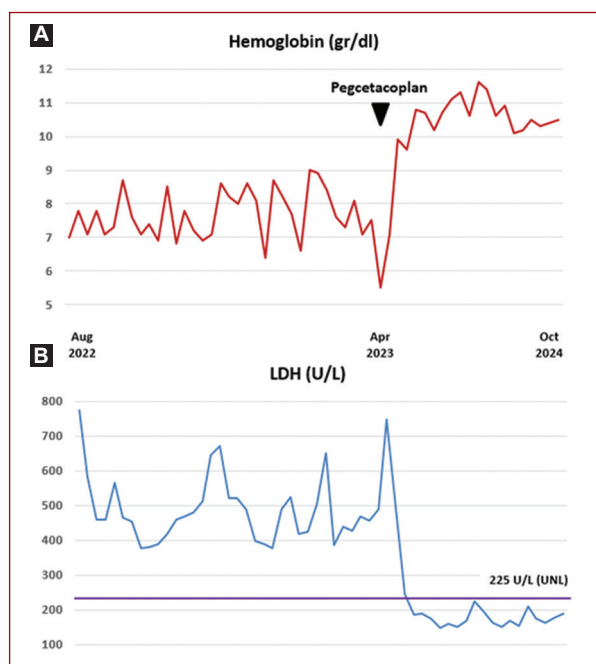


Figure 2. A: evolution hemoglobin levels, B: LDH levels before and after treatment with pegcetacoplan. UNL: upper normality limit.

identify patients with anti-C5 treatment failure, not only with residual anemia but also with suboptimal hemolysis control,⁴ and all situations that may contribute to a persistent (pharmacodynamics BTH) or transient (pharmacokinetics BTH) amplification of the complement system.

In our case, after suboptimal control of intravascular hemolysis with anti-C5 treatment following the first liver transplant, a second transplant was necessary. In our patient, the presence of an allogeneic organ (liver) and all that it entails (immunosuppression, recurrent infections, etc.) leads to persistent activation of the complement system (pharmacodynamics BTH). In this context, C5 inhibition is probably insufficient to control hemolysis, and it is necessary to intensify the inhibition of the complement system by inhibition at the proximal level.

The inhibition at the proximal level resulted in an immediate and significant improvement in hemoglobin levels and intravascular hemolysis control (normal LDH levels and clonality in red blood cells similar to clonality in leukocytes, Figs. 1 and 2). Our case highlights the efficacy of proximal complement inhibitors in preventing liver post-transplant complications, challenging the traditional view that PNH is a contraindication for liver transplantation in the era of proximal complement inhibition.

This case demonstrates the successful use of proximal complement inhibitors in a patient with PNH who developed BCS and subsequently underwent liver transplantation. These treatments target the complement system, which plays a critical role in the pathogenesis of both PNH and BCS, effectively reducing complement-mediated hemolysis and thrombotic complications. These treatments highlight the potential of complement inhibition as a therapeutic strategy for managing complex thrombotic events in PNH patients with persistent hemolysis and pharmacodynamics BTH, particularly those requiring liver transplantation.

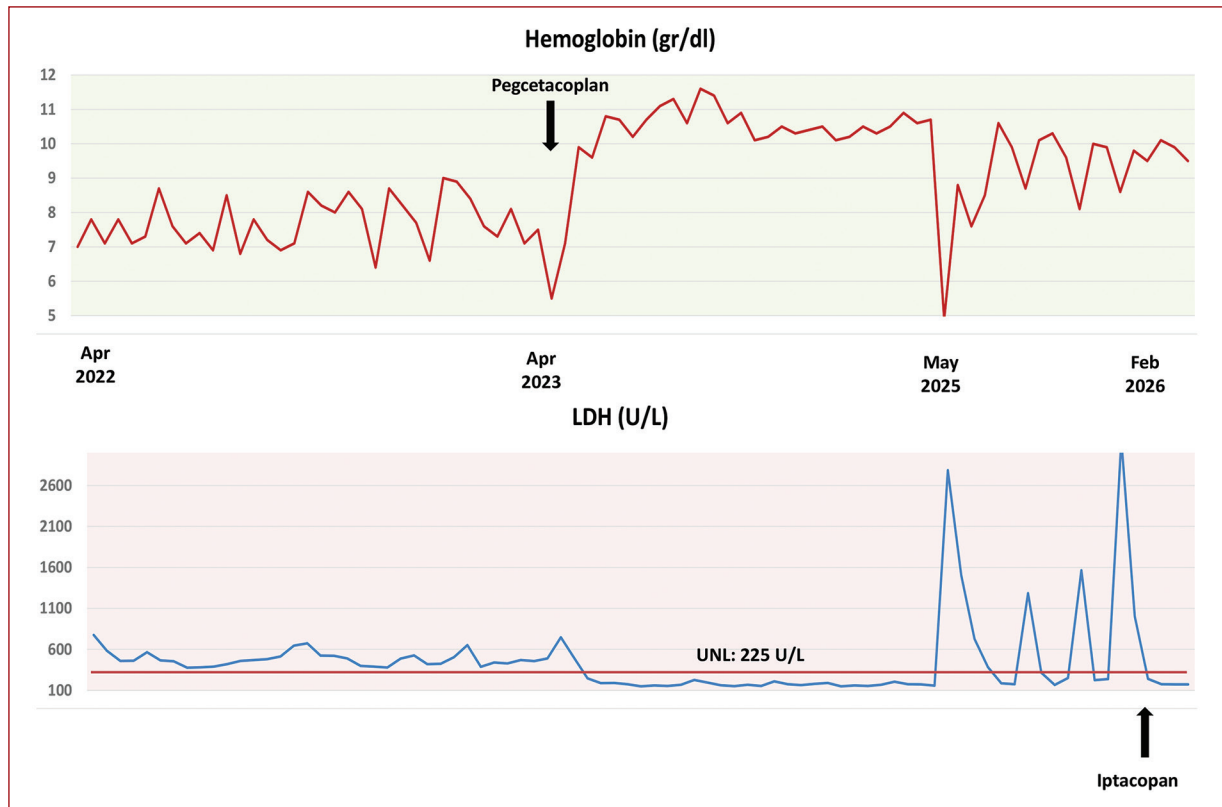


Figure 3. Long-term outcomes of the patient treated with pegcetacoplan.

Table 2. Case reports of liver transplantation in patients with PNH

Authors	Country	Year	Patients	Ecuzumab	Complications and outcomes
Halff et al. ⁶	USA	1990	1	NO	Repeated HAT, retransplant, and death.
Schattenfroh et al. ⁷	Germany	1993	1	NO	Life-threatening GI bleeding during anticoagulation with warfarin, late HAT after anticoagulation withdrawal, retransplantation and death.
Rückert et al. ⁸	Germany	1999	1	NO	Late recurrent BCS.
Bahr et al. ⁵	Germany	2003	1	NO	Chronic subdural hematoma during anticoagulation with warfarin, late recurrent BCS, and PVT after anticoagulation withdrawal. Alive 4 years after transplant.
Vivarelli et al. ⁹	Italy	2003	1	NO	Repeated HAT, 5 retransplant and death.
Chang et al. ¹⁰	USA	2007	1	NO	PVT with refractory ascites treated with splenic artery embolization. Late leukemic transformation.
Singer et al. ¹¹	USA	2009	1	YES	1,5 years post-transplant without complications.

BCS: Budd-Chiari syndrome; GI: gastrointestinal; HAT: hepatic artery thrombosis; PNH: paroxysmal nocturnal hemoglobinuria; PVT: portal vein thrombosis.

Proximal complement inhibitors are indicated as a second-line treatment for anemic patients who have not achieved adequate control with C5 inhibitor therapy.

While its primary clinical benefit is observed in patients with extravascular hemolysis following anti-C5 treatment, C3 inhibition has proven highly effective in

controlling both extravascular and intravascular hemolysis. This makes pegcetacoplan an excellent alternative for patients who do not achieve sufficient control of intravascular hemolysis with anti-C5 therapy, regardless of the degree of anemia.

Notably, PNH should not be considered an absolute contraindication for liver transplantation in the complement inhibitors era, especially with the new inhibitors. However, if transplantation is undertaken, meticulous patient monitoring is critical. Effective management and control of intravascular hemolysis is essential, and the use of available anti-complement therapies is crucial to optimize patient outcomes and prevent complications.

As shown in the literature, only one case of PNH performed without anti-complement treatment survived⁵ (Table 2). Our case is the second described treated with anti-complement treatment and the first with long-term follow-up with proximal complement inhibitors.⁵⁻¹¹ At present, 5 years have passed since the transplant, the patient has no complications and leads a normal life.

This experience underscores the importance of adapting complement inhibition strategies to achieve better control of intravascular hemolysis and reduce thrombotic risks, particularly in patients requiring aggressive procedure that amplifies the complement system, such as liver transplantation.

Conclusion

This case highlights the potential role of proximal complement inhibition in patients with PNH who have suboptimal disease control despite adequate terminal complement blockade with anti-C5 therapy. In this patient, treatment with pegcetacoplan led to rapid control of hemolysis, improvement in hemoglobin levels, and transfusion independence. However, an increase in hemolytic episodes during follow-up ultimately prompted a switch to iptacopan, resulting in sustained clinical and laboratory stability.

Importantly, this experience suggests that PNH should not be considered an absolute contraindication to liver transplantation in the era of complement inhibitors. However, transplantation requires careful monitoring and effective control of complement-mediated hemolysis, particularly because the presence of an allogeneic liver and associated factors, such as immunosuppression and infections, may amplify complement activation.

Overall, proximal complement inhibition represents a valuable therapeutic strategy for patients with PNH and persistent hemolysis despite anti-C5 therapy, including those undergoing or having undergone liver transplantation. Further experience and longer-term follow-up are needed to define the optimal complement inhibition strategy in these patients.

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