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CASE REPORT

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Complement inhibitor eculizumab in thrombotic microangiopathy: Single-center case series

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Abstract

Our case series showed that eculizumab is efficacious and safe in treating thrombotic microangiopathy, as well as it has positive effects on quality of life. Further extensive studies are required to develop unified treatment guidelines.

KEYWORDS

atypical hemolytic uremic syndrome, complement, eculizumab, nephrology, thrombotic microangiopathy

1 | INTRODUCTION

Hemolytic uremic syndrome (HUS) is a form of thrombotic microangiopathy (TMA) mainly characterized by Coombs-negative hemolytic anemia, non-immune thrombocytopenia, and acute renal damage.[1,2] International Hemolytic Uremic Syndrome group classification divides HUS into four categories: (a) infection-associated (typical) HUS mostly due to Shiga toxin-producing *Escherichia coli* (STEC); (b) HUS secondary to autoimmune diseases, malignancies, solid organ or bone marrow transplantation and drugs; (c) cobalamin C defect-related HUS; and (d) atypical HUS (aHUS) due to dysregulation of the alternative complement pathway and mutations of diacylglycerol kinase ε(DGKE) gene.[1,3-5] Secondary TMA due to autoimmune diseases accounts for 24% of all cases, whilst aHUS constitutes about 10% of HUS cases with an incidence rate in Europe varying from 0.23 to 1.9 per million annually.[6-10] Defects in regulation of the complement system may be inherited, acquired or both, and are detected in 40%–60% of patients.[6,7,11] Whilst genetic background predisposes patient to the disease, a trigger, such as pregnancy, medical treatment, infection, organ transplantation or cancer, is necessary for aHUS to appear.[1,4]

Supportive therapy, including maintenance of electrolyte and fluid balance, timely initiation of dialysis and treatment of underlying cause, is the cornerstone of HUS treatment.[4,12] Steroids, anti-platelet agents, and heparin were not superior to supportive therapy alone. However, high doses of steroids may be associated with faster recovery of renal function.[13-15]

Historically, plasma therapy (PT), either exchange (PE) or infusion (PI), was the first-line treatment for aHUS. Although PT may temporarily maintain hematological parameters, it does not address complement dysregulation; therefore, microangiopathic processes persist.[11,16-18] PT

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failed to ensure renal remission in up to 75% of patients.[19] In addition, Noris et al. study showed that 67% of adults and 48% of the children with aHUS treated with PT progressed to an end-stage renal disease (ESRD) or died at 3 years' follow-up.[20]

Eculizumab is a humanized chimeric monoclonal antibody that binds to the human C5 complement protein and hinders the generation of proinflammatory C5a and terminal complement complex. Primary approved for the treatment of paroxysmal nocturnal hemoglobinuria, eculizumab demonstrated the efficacy in treating both transplanted and non-transplanted patients with aHUS.[11,21-26] It has tremendously improved renal and hematological outcomes, in addition to ceasing TMA events, and elimination or reduction of PT and dialysis.[27-29]

We here describe the effect of eculizumab in the treatment of three patients with TMA in Vilnius University Hospital Santaros Klinikos Nephrology and kidney transplantation department.

2 | METHODS

This is a single-center report of three patients who received eculizumab, one of which for systemic lupus erythematosus (SLE) associated hemolytic uremic syndrome, and two for aHUS. The diagnosis of HUS was considered in the presence of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury. A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) level was checked to exclude thrombotic thrombocytopenia purpura (TTP). The diagnosis of SLE was confirmed based on American College of Rheumatology (ACR) classification criteria.[30] In addition, factors that may cause secondary HUS, such as systemic autoimmune disease, DIC, metastatic cancer or Shiga toxin, were eliminated for two patients with aHUS. Mutations in genes encoding ADAMTS 13, complement component C3, complement regulatory protein CD46, complement factor B (CFB), complement factor H (CFH), complement factor H-related protein 5 (CFHR5), complement factor I (CFI), diacylglycerol kinase-ε (DGKE), and thrombomodulin (THBD) were checked by PCR method.

Demographic characteristics, clinical history, and treatment modalities before starting eculizumab therapy are summarized in Table 1. Laboratory tests (complete blood count (CBC), peripheral smear, lactate dehydrogenase (LDH), haptoglobin, ferritin, liver and renal function tests, C-reactive protein, C3, C4, ANA, dsDNA) were performed (Table 2).

TABLE 1 Demographic, clinical data, and treatment modalities in aHUS patients

Parameters	Case #1	Case #2	Case #3
Sex	Female	Female	Male
Age	26	46	47
Presenting symptoms	Fatigue, nausea, anorexia, oliguria	None (arrived as a potential recipient for cadaveric kidney transplantation)	None (hospitalized due to progressive kidney graft failure for further examination and treatment)
Initial physical examination findings	Facial redness and swelling, body rash, *livedo reticularis*, tachycardia	Physical findings on admission were normal	Blood pressure – 180/106 mmHg, other physical findings were normal
Initial diagnosis	Agranulocitosis, acute kidney injury (AKI)	NA	Suspected graft failure
Previous TMA episodes	None	Yes (2 episodes)	None
Genetic screening	Negative	Heterozygous missense variant of CFB (c.967A>G, p.(Lys323Glu))	Heterozygous nonsense variant of CFH (c.3572C>A, p.(Ser1191*)); Heterozygous missense variant of CFHR5 (c.1702T>C, p.(Cys568Arg))
Meningococcal vaccine	Before eculizumab	Before eculizumab	Before eculizumab
Pneumococcal vaccine	Before eculizumab	Before eculizumab	Before eculizumab
Treatment during hospitalization before eculizumab:			
Hemodialysis (number of sessions)	45	NA	49
Plasmapheresis (number of sessions)	21	NA	22
Steroids	Yes	Yes	Yes

Abbreviation: NA, not applicable

TABLE 2 Laboratory data of HUS patients

Parameters	Normal range	Case #1	Case #2	Case #3
Serum creatinine (μmol/L)	49–90	408	641	237
Urea (mmol/L)	2.5–7.5	32.5	11	19.1
CRP (mg/L)	≤5	2.44	1.71	5.25
AST (U/L)	≤40	84	18	40[b]
ALT (U/L)	≤40	48	11	55[b]
Haptoglobin (g/L)	0.3–2.0	<0.08	0.70	0.45
Ferritin (μg/L)	10–200	470.44	ND	ND
D-dimers (μg/L)	<250	3305	990[a]	1115.4[c]
ADAMTS 13 (IU/ml)	0.40–1.50	0.86	ND	>1.50[c]
C3 (g/L)	0.9–1.8	0.22	ND	0.66
C4 (g/L)	0.15–0.57	0.03	ND	0.24
Coombs		+	ND	–

Abbreviations: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C3, complement component 3; C4, complement component 4; CRP, C-reactive protein; IU, international unit; ND, not determined during current hospitalization.

[a]On day 4 after kidney transplantation.

[b]On hospital day 27.

[c]On hospital day 17.

Patients failed to respond to plasmapheresis, corticosteroid, and hemodialysis treatments, and were given eculizumab intravenous (IV) induction dose of 900 mg once a week for 4 weeks, followed by maintenance dose of 1200 mg IV per 2 weeks (standard schedule).

3 | RESULTS

3.1 | Case 1

A 26-year-old female patient was admitted to the hospital because of leukopenia, anemia, and thrombocytopenia detected two weeks ago. On admission day, complete blood count (CBC) showed white blood cell count (WBC) of 1.23×10^9/L ($4.0–9.8 \times 10^9$/L), hemoglobin (Hgb) of 88 g/L (117–145 g/L), and platelet count (PLT) of 62×10^9/L ($140–450 \times 10^9$/L), along with acute kidney injury, oliguria, increase in lactate dehydrogenase (LDH), and D-dimers (Table 2). Urinalysis detected proteinuria 6 g/l, red blood cells 527/hpf, and white blood cells 34/hpf. Medical history raised suspicion of SLE (arthralgia, *livedo reticularis* and malar rash, in addition to positive ANA, anti-dsDNA assays were documented 3 years ago). The patient did not receive SLE treatment 3 in this timeline. Hemodialysis due to progressing anuria and azotemia followed the initial treatment with empiric antibiotics and methylprednisolone. The patient was positive for anti-double-stranded DNA (anti-dsDNA), anti-extractable nuclear antigen (anti-ENA) (SS-A, Ro-52, nucleosomes, histones, DFS70), and the anti-nuclear antibody (ANA) was positive at 1:600 in a nucleolar pattern. Kidney biopsy showed chronic membranoproliferative glomerulonephritis (lupus nephritis class IV-S (A/C)[31]), along with active thrombotic microangiopathy. ADAMTS 13 level was normal, allowing to differentiate TTP and HUS. Due to the presence of microthrombi on renal biopsy, plasmatherapy was initiated on hospital day 6. Moreover, to address the lupus nephritis, EUROLUPUS treatment protocol with cyclophosphamide and methylprednisolone pulse therapy was administered on day 7. Despite given treatment, patients' condition deteriorated rapidly, she developed posterior reversible encephalopathy syndrome (PRES) with hypertensive crisis on hospital day 12, and febrile neutropenia on day 25. Platelet count continued to decrease in the face of plasmatherapy to a nadir of 20×10^9/L, followed by a rise in the LDH to a peak of 488 U/l on day 42. After a multi-disciplinary discussion, eculizumab was considered. Following meningococcal and pneumococcal vaccination along with ciprofloxacin prophylaxis (500 mg four times a day), eculizumab was initiated on day 60. Eculizumab reduced the hemolytic pace, allowing hemoglobin levels to recover, LDH levels to decrease, also platelet count started to rise. However, significant renal recovery was not evident (Table 3). She was discharged following the third eculizumab dose on day 77.

3.2 | Case 2

The patient presented with clinical features of aHUS at the age of 35 years. She was negative for anti-dsDNA, ANA, and anti-neutrophil cytoplasmic antibody (ANCA); also,

TABLE 3 Outcomes in HUS patients before and after eculizumab treatment

Parameters	Normal range	Case #1	Case #2	Case #3
Hemoglobin (g/L)				
Before starting eculizumab	117–145 (F)	89	144	95
After eculizumab				
At week 4	128–160 (M)	91[a]	70	121
At week 12		NA	115	139
Platelet count ($\times 10^9$/L)				
Before starting eculizumab	140–450	51	233	212
After eculizumab				
At week 4		93[a]	107	192
At week 12		NA	232	161
LDH (U/L)				
Before starting eculizumab	125–243	412	148	196
After eculizumab				
At week 4		294[a]	273	218[b]
At week 12		NA	273	170[c]
eGFR (CKD-EPI) (ml/min/1.73 m^2)				
Before eculizumab	>90	<15	<15	<15
After eculizumab				
At week 4		<15[a]	<15	71
At week 12		NA	50	81
Dialysis dependency				
Before eculizumab		Yes	Yes	Yes
On eculizumab		Yes[a]	No	No

Abbreviations: F, for females; M, for males.

[a]At week 3 of eculizumab therapy.

[b]At week 2 of eculizumab therapy.

[c]At week 8 of eculizumab therapy.

C3 and C4 levels were checked (0.216 g/L and 0.275 g/L, respectively). Renal biopsy showed TMA. Kidney function did not recover; therefore, hemodialysis was started. A year later, she underwent deceased donor kidney transplantation. Three years afterward, antibody-mediated rejection (ABMR) occurred (borderline changes according to Banff classification) and plasmapheresis has been done; anaphylaxis and clinical death were observed. She returned to hemodialysis therapy due to recurrent TMA; transplantectomy was performed. At the age of 42 years, the patient received second cadaveric renal transplant. Graft functioned for one year, then ABMR (Banff class IIA) occurred (rituximab, intravenous immunoglobulin (IVIG) and methylprednisolone were administered). Renal biopsy showed pronounced glomerulitis and C4d2 depositions with no signs of TMA. At the age of 45 years, she underwent second transplantectomy due to acute graft rejection. Moreover, genetic analysis detected a mutation in CFB gene. aHUS diagnosis was proved, and she was included in active transplant waiting list. Prior to her third transplantation, eculizumab was indicated for the prevention of recurrent TMA in renal graft. During her last hospitalization (Tables 1-3), eculizumab was initiated the same day as she underwent cadaveric kidney transplantation. Because of delayed graft function, methylprednisolone pulse therapy was administered on day 6; serum creatinine and urea were 755 μmol/L and 16.7 mmol/L, respectively; histologically diffuse C4d deposition in peritubular capillaries was detected (approached as ABMR; IVIG and plasmapheresis were started). On day 18, hemolysis occurred (Hgb decreased in three days from 87 to 76 g/L, haptoglobin 1.68→0.35 g/L, LDH increased from 143 to 289 U/L). Due to hemolysis, additional plasmapheresis sessions were added, making a total of 10 sessions. To evaluate eculizumab efficacy, CH50 and SC5b-9 levels were tested at week 4 of eculizumab therapy (36.6 U Eq/ml (55–75 U Eq/ml) and 224.2 mg/ml (200–325 mg/ml), respectively); therefore, it was decided to continue eculizumab therapy. The patient was discharged following the sixth eculizumab dose on day 46. Significant hematologic

and renal recovery was documented (Hgb showed no negative dynamics (87 g/L), haptoglobin was 1.98 g/L; serum creatinine, urea and PLT were: 195 μmol/L, 8.6 mmol/L, and 251 × 10^9/L, in given order).

3.3 | Case 3

A 47-year-old male patient was diagnosed with chronic glomerulonephritis at the age of 12 years. He started hemodialysis at the age of 23 years shortly before his first living-related kidney transplantation; the graft functioned for 2.5 years. Later, the patient underwent three more cadaveric kidney transplantations at the age of 29, 37, and 45 years. Initially, he was hospitalized 23 months earlier, due to mild grade ABMR (renal allograft protocol biopsy showed focal C4d deposition in peritubular capillaries; serum creatinine was 101 μmol/L (62–115 μmol/L) and eGFR 77 ml/min/1.73 m^2 (>90 ml/min/1.73 m^2)); four sessions of plasmapheresis were applied. Fifteen months after, he was re-admitted to the hospital due to progressive kidney graft failure (at this time, serum creatinine was 237 μmol/L, urea 19.1 mmol/L (2.5–7.5 mmol/L), eGFR <15 ml/min/1.73 m^2; Tables 1-2); methylprednisolone pulse therapy was administered. On hospital day 8, he tested positive for parainfluenza virus type 3, which triggered Coombs-negative hemolysis (Hgb decreased from 107 g/L to 87 g/L, PLT 179→154 × 10^9/L with schistocytes present, LDH was 290 U/L (125–243 U/L)). Kidney biopsy showed membranoproliferative changes with focal IgA and IgM deposition. Plasmapheresis was started on day 17. His microangiopathic hemolytic picture progressed in the face of plasmapheresis, with development of red cell transfusion necessity and hemolysis to a nadir hemoglobin of 75 g/L by hospital day 53 and nadir PLT of 57 × 10^9/L by day 56. LDH peak of 710 U/L was seen by day 24. Due to deteriorating kidney graft function, hemodialysis was initiated on day 21. On hospital day 36, second graft biopsy revealed active ABMR (Banff class IIA) along with membranoproliferative changes with local signs of glomerulitis; additional 4 sessions of plasmapheresis, and IVIG were administered. Furthermore, third and fourth graft biopsies showed chronic TMA (on day 67), and graft fibrosis increasing in time (on day 100); transplantectomy was indicated. Genetic testing detected mutations in CFH and CFHR5 genes; aHUS was confirmed. Five days after transplantectomy, the patient started hallucinating (suspected PRES); therefore, haloperidol was given. After a multi-disciplinary discussion, it was decided to prepare the patient for eculizumab therapy and the fifth kidney transplantation. He was discharged on day 135 (Hgb 105 g/L, PLT 188 × 10^9/L). Eight months later, the patient underwent cadaveric kidney transplantation along with first infusion of eculizumab (at this point, serum creatinine was 421 μmol/L, urea 8.0 mmol/L, PLT 212 × 10^9/L, Hgb 95 g/L). Four days later, he developed type-II myocardial infarction (troponin was 36809 ng/L (≤35 ng/L)); after the condition improved, he was discharged following his fifth eculizumab dose on day 26 post-transplantation. The graft functioned well, as well as a slight hematological improvement was visible (Table 3). On the day of the discharge, serum creatinine and urea were 106 μmol/L and 7.7 mmol/L, respectively.

4 | DISCUSSION

Atypical HUS is a severe orphan disease, occurring due to complement dysregulation, and resulting in increased formation of C3 convertase on cell surfaces, generating the anaphylatoxins C3a and C5a, and initiating membrane attack complex (MAC) C5b-9 formation.[1,6,11,32] This uncontrolled activation of alternative complement pathway results in deposits of granular C3 in the glomeruli and arterioles eventually causing microvascular thrombosis.[1,33,34] aHUS primarily affects kidney function, appearing as mild proteinuria, hematuria, azotemia, and hypertension.[1,35] However, extra-renal features are seen in 20% of patients, the most common of which is involvement of the central nervous system, presenting with seizures, vision loss, hemiparesis, headache, and encephalopathy.[1,35,36] In Case 1, the patient developed PRES on hospital day 12, and her symptoms resolved with control of blood pressure. Moreover, in Case 3, the patient developed hallucinations 5 days after transplantectomy, suggesting plausible diagnosis of PRES. PRES may manifest similarly to cerebral TMA, therefore must be differentiated. Moreover, both of these conditions may be interrelated in aHUS, since TMA, over-activation of complement and excessive C5a might increase vascular permeability and worsen cerebral edema resulting in PRES.[37,38]

Defects in regulation of the complement system are caused by mutations in genes encoding complement regulatory proteins: Factor H (CFH), Factor I (CFI), membrane cofactor protein (MCP), complement 3 (C3), Factor B (CFB) or thrombomodulin. Moreover, about 10% of patients have autoantibodies directed against FH.[1,4,21] Whilst genetic testing for complement abnormalities is recommended but not required to start eculizumab therapy, it can provide significant information about both, the disease process and long-term renal outcomes, crucial to determine optimal duration of treatment.[39-41] CFH-related aHUS is considered to have the most severe outcomes, as 70% of patients die, need dialysis, or have permanent renal damage at 1-year.[7,20,42] In addition, Fakhouri et al. found that up to 72% of patients with CFH variants experienced

aHUS relapse after eculizumab discontinuation (median time to relapse was 6.5 months).[39] CFH, CFB, and C3 variants are major risk factors for post-transplant recurrence (>90%).[20,43] Caprioli et al. showed that 83.3% of grafts in patients with CFH mutations were lost due to disease recurrence within the first year.[42] Our patients exhibited a heterozygous CFB mutation (Case 2) and compound heterozygous CFB and CFHR5 mutations (Case 3). Consequently, graft loss due to TMA recurrence was documented in Case 2.

Coombs-negative hemolytic anemia is a part of HUS triad; however, positive result for direct Coombs' test (direct antiglobulin test (DAT)) does not exclude the diagnosis of HUS. On the contrary, positive DAT is considered as T-antigen antibody reaction and may suggest the diagnosis of HUS secondary to neuraminidase producing organisms, such as *Campylobacter*, influenza A (H_1N_1) or *Streptococcus pneumoniae*.[44-47] TMA is observed in 3% to 9% of patients with SLE.[48] We present a case (Case 1) of Coombs-positive HUS secondary to SLE. SLE and HUS have overlapping clinical characteristics, including hemolytic anemia. Therefore, SLE-associated HUS may present with hemolytic anemia in the absence of schistocytes accompanied by positive Coombs' test.[44] Treatment of secondary TMA focuses on the management of underlying autoimmune disorder. Glucocorticoids, immunosuppression, anticoagulation, anti-platelet agents, and PT are used. However, 50% of patients fail to respond to treatment.[49-51] Eculizumab is usually administered as an off-label agent in severe cases of secondary TMA and its use is based solely on a limited number of case reports. A recent publication showed hematologic improvement within the first week of after eculizumab initiation in secondary TMA patients. Moreover, eGFR improved by 25% in half of the patients, and proteinuria reduced in 43% by week 4.[48] In most cases, eculizumab therapy led to discontinuation of dialysis within 6 months, in addition to reduced levels of serum creatinine.[52]

In the pre-eculizumab era, aHUS prognosis was poor: risk of serious TMA-associated morbidity and mortality rates varied by genotype, and renal transplantation was linked to poor graft survival and high rates of disease recurrence.[7,29,42,43] Current guidelines recommend immediate initiation of eculizumab after diagnosis of aHUS is made, as early initiation was associated with a markedly greater renal improvement.[11,26,53] However, the particular mechanism, by which eculizumab leads to improved renal function remains undetermined, but it may include sustaining controlled blood pressure, kidney remodeling, continuous dissolution of thrombi, or restoration of endotheliocyte function and structure.[29,54,55] Legendre et al., showed that eculizumab therapy significantly increased the platelet count and eGFR, along with decrease in proteinuria from baseline to week 26. Moreover, a significant increase in platelet count was seen earlier, by day 7 ($p = 0.03$).[11] Consequently, *Menne* et al., discovered that eGFR improved rapidly on eculizumab and remained stable for up to 6 years for patients who continued eculizumab treatment.[28] The favorable therapeutic effects of eculizumab include elimination or reduction of dialysis and PT.[11,29] A recent study on TMA reported that 60% of patients improved by at least one CKD stage after 6 months of eculizumab therapy.[52] In our study, hematological response to eculizumab therapy was seen by week 4, whilst kidney function improvement prolonged (Table 3). Dialysis was eliminated in Case 2 and 3; however, Case 1 cannot be fully assessed due to the shorter surveillance time (3 weeks).

The issue of eculizumab cessation has been rising through the past years.[56-58] As aHUS is an episodic disease, triggered by an environmental trigger in genetically predisposed patients, a period of time when complement inhibition is unnecessary appears plausible.[59] However, relapses occur in up to 33% of aHUS patients shortly after eculizumab treatment discontinuation (within 6 weeks).[56,57] It is suggested that cessation of eculizumab therapy might be considered on a case-by-case basis after no less than 6–12 months of treatment and at the minimum of 3 months of normalization of kidney function (in non-transplanted patients over the age of 3 years).[3,58,60] According to Ardissino et al., hemoglobinuria detected by urine dipstick test at home was able to identify disease relapse.[56] Despite possible false-positive results, it is an easy and affordable test worth to be performed as a relapse warn.[57]

Noteworthy, eculizumab treatment is safe but not without substantial risk.[22] The most prominent risk factor is the susceptibility to an infection with encapsulated bacteria, specifically *Neisseria meningitidis* (meningococcus) from 1000-fold to 2000-fold compared to normal population.[11,22,61] Therefore, meningococcal vaccines must be received at least 2 weeks prior the first dose of eculizumab. In case of an urge of immediate initiation, two weeks of antibiotics (penicillin V or ciprofloxacin) are necessary along with vaccinations.[62] All 3 of our patients received meningococcal vaccination prior to eculizumab initiation. Moreover, in Case 1, due to life-threatening situation, ciprofloxacin was administered in addition to meningococcal vaccination. Hypertension, diarrhea, upper respiratory tract infection, headache, and fever are the most frequently reported adverse events of eculizumab.[63,64] However, usually all serious adverse effects related to eculizumab resolve without interruption of the treatment.[11,65] Moreover, Legendre et al., showed that no new adverse events were reported after week 26 of treatment.[11] No adverse events were observed in our patients.

5 | CONCLUSIONS

Monoclonal antibody eculizumab is beneficial for treating paroxysmal nocturnal hemoglobinuria, neuromyelitis optica and atypical hemolytic uremic syndrome. Our small case series demonstrate that eculizumab is efficacious and safe, as well as it has positive effects on quality of life. As the data are limited to only small cohort studies and case reports, there are no unified recommendations for vaccination, maintenance, reduction, or discontinuation of eculizumab therapy. Vigilance and early treatment of meningococcal infection are crucial for all patients receiving treatment with eculizumab, despite their vaccination and antimicrobial prophylaxis status. Therefore, extensive prospective studies on this topic are necessary.

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CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
All authors contributed equally to this work.

ETHICAL APPROVAL
All information related to the identity of the patients will remain confident.

CONSENT
Obtained.

DATA AVAILABILITY STATEMENT
The authors confirm that the data supporting the findings of this study are available within the article.

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