Segmental citrate anticoagulation for double-filtration plasmapheresis: A case report and literature review

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Abstract. Regional citrate anticoagulation (RCA) has been widely used in patients with high-risk bleeding for anticoagulation in renal replacement therapy. However, scientific reports on the use of RCA in double-filtration plasmapheresis (DFPP) are limited. In the available reports, anticoagulation was not performed in the plasma component separator. However, as demonstrated in the present study, during the treatment of a patient with anti-neutrophil cytoplasmic antibody-associated vasculitis, although RCA was used for DFPP, coagulation occurred in the plasma component separator, resulting in the interruption of treatment. Thus, segmental citrate anticoagulation (SCA) was used and the filter was successfully prevented from clotting again. The present study demonstrates that SCA can more effectively prevent the clogging of the plasma separator and the plasma component separator, thereby maintaining the continuity of treatment and avoiding treatment interruption.

Introduction

Double-filtration plasmapheresis (DFPP) is a blood purification process that uses specific filters to remove pathogenic substances from the blood, such as immunoglobulin, immune complexes, lipoproteins, etc. The DFPP system includes two parts of filters. At the beginning of the surgery, the blood passes through the first filter (plasma separator), which is used to separate white blood cells, red blood cells and platelets from plasma. Subsequently, the plasma without cellular components passes through a second filter (plasma component separator) where macromolecules are selectively removed and discarded (1).

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Regional citrate anticoagulation (RCA) is an anticoagulant regimen used for patients who are at a high risk of bleeding. It provides excellent anticoagulation without increasing the risk of bleeding and significantly reduces the occurrence of clotting in the filter during treatment (2). At present, when RCA is performed for DFPP, it is generally considered that only the first filter needs to be anticoagulated, while the risk of coagulation in the second filter is very rare, and anticoagulation is not required (2,3).

The present study describes the case of a patient with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) treated with DFPP. During the course of treatment, when conventional RCA was used for DFPP, the second filter became clotted. Thus, segmented citrate anticoagulation (SCA) was then performed and the treatment was successfully completed.

Case report

A 78-year-old Chinese female patient was admitted to the Department of Cardiology, Chonggang General Hospital (Chongqing, China), with a 3-day episode of dyspnea. A physical examination revealed a temperature of 36.3˚C, a breathing rate of 22 breaths/min, a heart rate of 85 beats/min and a blood pressure of 167/90 mmHg. She had edema of the lower limbs. A computed tomography (CT) scan revealed patchy opacities and shadows in the bilateral lungs (Fig. 1A). The laboratory test findings of the patient at the time of admission are presented in Table I.

The patient had a 2-month history of hypertension (of which the highest blood pressure value was 150/90 mmHg) and a 2-month history of renal disease (the serum creatinine level was 90 μmol/l, and the estimated glomerular filtration rate was 55 ml/min/1.73 m^2). At the time of admission, the patient was clinically diagnosed with the following: i) Grade 2 hypertension (severe); ii) heart failure (cardiac function grade III); and iii) chronic kidney disease and renal anemia.

Following admission, the patient received anti-hypertensive treatment (felodipine) and furosemide in the Department of Cardiology, Chonggang General Hospital; however, the symptoms did not markedly improve. On day 3, the patient was transferred to the Department of Nephrology for further treatment due to renal insufficiency. Considering that the patient presented with rapidly deteriorating renal function,

severe microscopic hematuria and lung lesions, Goodpasture syndrome or ANCA-AAV was suspected.

On day 4, the patient's dyspnea worsened, and hemoptysis occurred. A re-examination of CT scan revealed the rapid deterioration of bilateral lung lesions (Fig. 1B). The laboratory findings revealed that hemoglobin decreased rapidly, renal function deteriorated, and cytoplasmic pattern ANCA (C-ANCA, analyses performed by the Guangzhou Kingmed Center For Clinical Laboratory, Co., Ltd.) and anti-proteinase 3 ANCA (PR3-ANCA, analyses performed by the Guangzhou Kingmed Center For Clinical Laboratory, Co., Ltd.) test results were positive. Anti-glomerular basement membrane and anti-nuclear antibody levels were normal (Table I). Combined with the clinical manifestations, the imaging examination and laboratory test results, a diagnosis of AAV was made.

There are currently no validated diagnostic criteria for AAV and no precise or specific diagnostic tests (4). Classification criteria were established in 1990 by the American College of Rheumatology (5). The 1994 Chapel Hill Consensus Conference produced disease definitions for vasculitis and the definitions were updated in 2012 (6); however, it should be noted that these are classification criteria and nomenclature definitions, respectively, for use in clinical trials and teaching.

A positive biopsy is strongly supportive of vasculitis and the European League Against Rheumatism (EULAR) recommend the procedure to assist diagnosis and further evaluation for patients suspected of having vasculitis (7). However, the patient described herein refused to undergo a tissue biopsy.

Despite the lack of tissue biopsy support, the patient had a positive test result for a C-ANCA determined using immunofluorescence and PR3-ANCA specificity determined using ELISA (performed by the Guangzhou Kingmed Center For Clinical Laboratory, Co., Ltd.), which has a high sensitivity and specificity for the diagnosis of AAV (8). In addition, the patient developed severe hematuria and proteinuria, and the renal function deteriorated rapidly within two months. Diffuse hemorrhage occurred in the lungs in a short period of time. Other diseases, such as systemic lupus erythematosus, anti-glomerular basement membrane disease and IgA vasculitis are not commonly associated with the aforementioned symptoms. Therefore, it was considered that the patient's condition was caused by AAV.

The patient was immediately treated with daily intravenous methylprednisolone (500 mg) for 3 days. Considering the critical condition of the patient, DFPP was initiated. The amount of plasma per treatment was 1.5-fold the plasma volume of the patient. The pulp waste was 400-500 ml. Sodium citrate (4%) was used as the anticoagulant with a speed of 150 ml/h in the first filter and 50 ml/h in the vein ampulla for DFPP. The second filter was clogged at ~1.5 h following the commencement of DFPP, and it was found that a large number of fibrin clots were formed in the second filter and plasma ampulla (Fig. 2A). As the coagulation of the second filter hindered the treatment process, citrate was administered to the first filter, the second filter and vein ampulla at the same time. Sodium citrate (4%) was administered at a speed of 150 ml/h in the first filter, 50 ml/h in the second filter and 50 ml/h in the vein ampulla (Fig. 3). After adjusting the anticoagulant regimen, no coagulation occurred in the second filter or plasma ampulla (Fig. 2B).

Following the initiation of treatment, 0.9 g calcium gluconate (10%) was administered intravenously every hour. Fresh, frozen plasma was added during the treatment to maintain the stability of blood volume and osmotic pressure. Following continuous treatment with methylprednisolone and DFPP for 3 days, the patient's lung lesions markedly improved (Fig. 1C). However, the patient developed marked water and sodium retention; thus, DFPP was discontinued and hemodialysis was initiated (three times) to remove the excess water and sodium from the body. Following methylprednisolone pulse therapy, intravenous cyclophosphamide (400 mg, every 15 days, 6 times in total) and oral prednisone (60 mg/day for 7 days) were administered. After 1 week, the prednisone dosage was reduced to 40 mg/day for 7 days; after 1 week, the prednisone dosage was reduced to 30 mg/day for 15 days; the drug was then tapered by 2.5 mg every 15 days. On the 25th day post-admission, the patient's pulmonary hemorrhage further improved (Fig. 1D), and her kidney function also partially improved (Table I).

Discussion

AAV is complicated by diffuse alveolar hemorrhage in ~10% of patients, and once AAV is combined with pulmonary hemorrhage, the risk of mortality significantly increases (9). The MEPEX study demonstrated that although plasma exchange did not reduce the risk of mortality, it increased the rate of renal recovery in patients with AAC that presented with renal failure when compared with intravenous methylprednisolone alone (10). Another meta-analysis on 387 patients with AAV demonstrated that plasma exchange may reduce the risk of progression to end-stage renal disease or death in renal vasculitis (11). However, the PEXIVAS study found that plasma exchange did not reduce the incidence of mortality or end-stage renal disease among patients with severe AAV (12).

Although the efficacy of plasma exchange for AAV is controversial, the 2021 update of the KDIGO guidelines still recommends that plasma exchange should be considered in patients with rapid deterioration of renal function and diffuse alveolar hemorrhage (13). Therefore, in the present study, considering the rapid deterioration of renal function and diffuse alveolar hemorrhage in a short period of time, DFPP we initiated for the patient.

For DFPP, the first issue to be resolved is the selection of anticoagulation. As plasma exchange will rapidly separate blood cells and plasma, it will easily coagulate in the first filter; thus, some form of anticoagulation is necessary. Heparin and low-molecular-weight heparin are commonly used anticoagulant drugs; however, they can affect the coagulation system (2,3). The patient had a rapid and severe alveolar hemorrhage (Fig. 1 and B), and hemoglobin levels also rapidly decreased (from 71 to 50 g/l in 4 days). At this time, the use of heparin or low-molecular-weight heparin poses a risk of aggravating the pulmonary hemorrhage.

The question remains of whether regional heparinization combining a prefilter dose of heparin with post-filter neutralization with protamine can be used for anticoagulation. Previous studies have indicated that regional heparinization anticoagulation is a simple and safe procedure that prevents increases in hemofilter transmembrane pressure and increases circuit

Table I. Laboratory data of the patient upon admission and on the 4th and 25th days after admission.

Parameter	Upon admission	Day 4 after admission	Day 25 after admission
Complete blood count			
Hemoglobin (g/dl)	7.1	5.0	6.4
White blood cells (/mm^3)	9.65x10^3	8.21x10^3	7.69x10^3
Platelets (/mm^3)	57x10^3	69x10^3	86x10^3
hs-CRP (mg/l)	106	117	4.69
Blood chemistry tests			
Alanine aminotransaminase (IU/l)	16	17	25
Aspartate aminotransferase (IU/l)	16	14	42
Total protein (g/l)	74.1	58.8	64.1
Albumin (g/l)	36.0	27.5	32.7
Total cholesterol (mmol/l)	3.82		
Low-density lipoprotein Cholesterol (mmol/l)	2.1		
High-density lipoprotein Cholesterol (mmol/l)	1.36		
Triglycerides (mmol/l)	1.29		
Scr (mg/dl)	5.07	5.63	3.90
eGFR (ml/min/1.73m^2)	8.65	7.75	11.84
Urinalysis			
pH	6.0		6.0
Protein	(++)		(++)
Glucose	(-)		(-)
Red blood cells (/U/l)	503.85		16.92
Urine protein to creatine ratio (mg/g creatinine)	647.1		1387.9
Serum immunological			
C3 (g/l)		1.1	
C4 (g/l)		0.3	
P-ANCA		Negative	
C-ANCA		Positive	
Myeloperoxidase-ANCA		Negative	
Proteinase 3-ANCA		Positive	
Anti-GBM antibody		Negative	
Anti-nuclear antibody		Negative	
Anti-dsDNA antibody		Negative	
Anti-SM antibody		Negative	

hs-CRP, high sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate; Scr, serum creatinine; ANCA, anti-neutrophil cytoplasmic antibodies; c-ANCA, cytoplasmic pattern anti-neutrophil cytoplasmic antibody; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; dsDNA, double-stranded DNA; anti-SM, anti-Smith antibody.

lifetime (14,15). However, in clinical practice, regional heparinization does not appear to be an ideal choice. First, the use of regional heparinization for anticoagulation may expose the patient to the side-effects of both heparin and protamine. Second, heparin has a much longer half-life than protamine, and it is difficult to titrate the optimal protamine dose required to neutralize heparin (16). In view of this, the 2012 KDIGO guidelines for AKI directly recommended that local heparin anticoagulation should be avoided in patients who are at a high risk of bleeding and who need continuous renal replacement therapy (17). Therefore, RCA was selected for the patient described herein.

Citrate binds to ionized calcium in plasma and induces local hypocalcemia, which inhibits the conversion of prothrombin to thrombin, thereby inhibiting activation of the coagulation cascade *in vitro*. When the blood is returned to the patient, the citrate chelating calcium can release the same amount of ionized calcium through the tricarboxylic acid cycle metabolic pathway. Losses of calcium ions and citrate-chelating calcium are then replenished to restore coagulation properties (3,18-20).
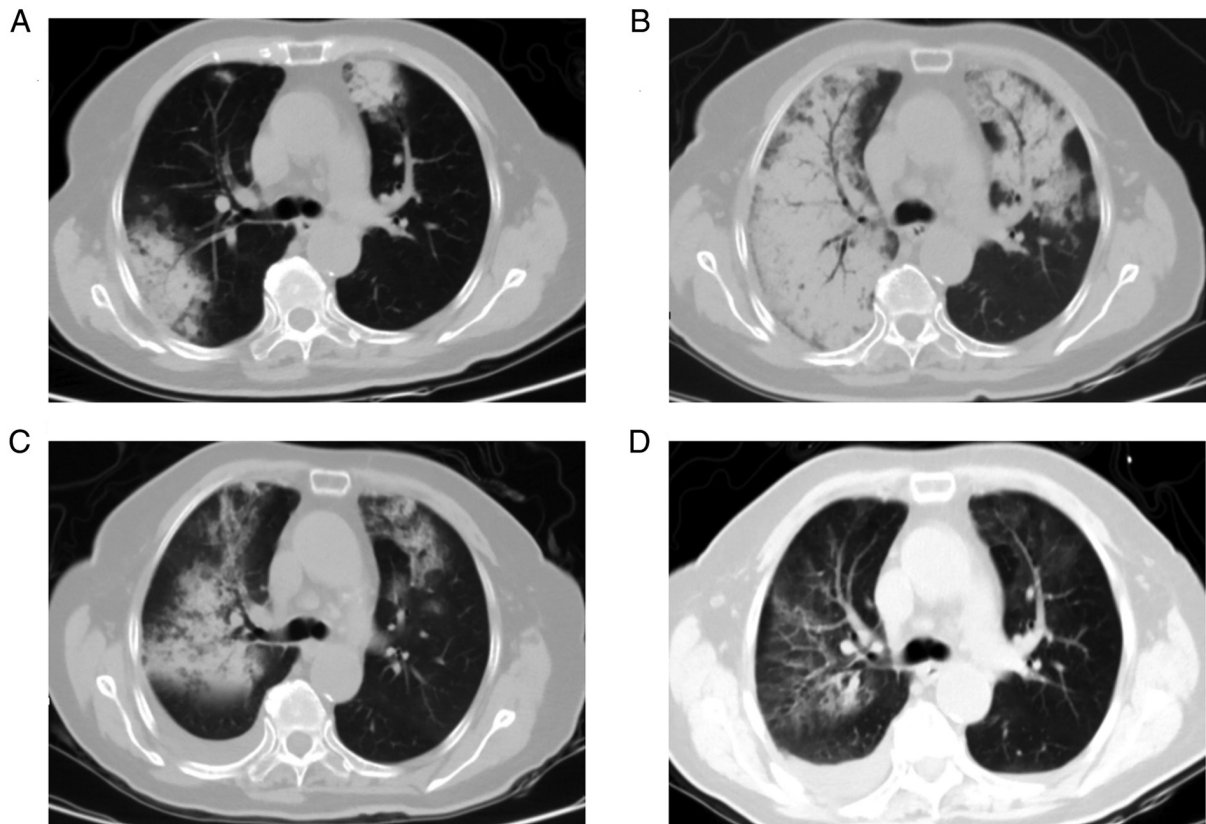
Figure 1. CT images. (A) CT scan illustrating patchy opacity shadows of bilateral lungs. (B) CT scan illustrating the rapid deterioration of bilateral lung lesions. (C) CT scan illustrating that the lung lesions improved significantly. (D) CT scan illustrating that the pulmonary hemorrhage further improved. CT, computed tomography.

Figure 2. Fibrin clot in plasma ampulla. (A) A large aggregate of fibrin clots was formed in the plasma ampulla when the second filter was not anticoagulated. (B) No apparent fibrin clot formation was observed in the plasma ampulla following the anticoagulation of the second filter.

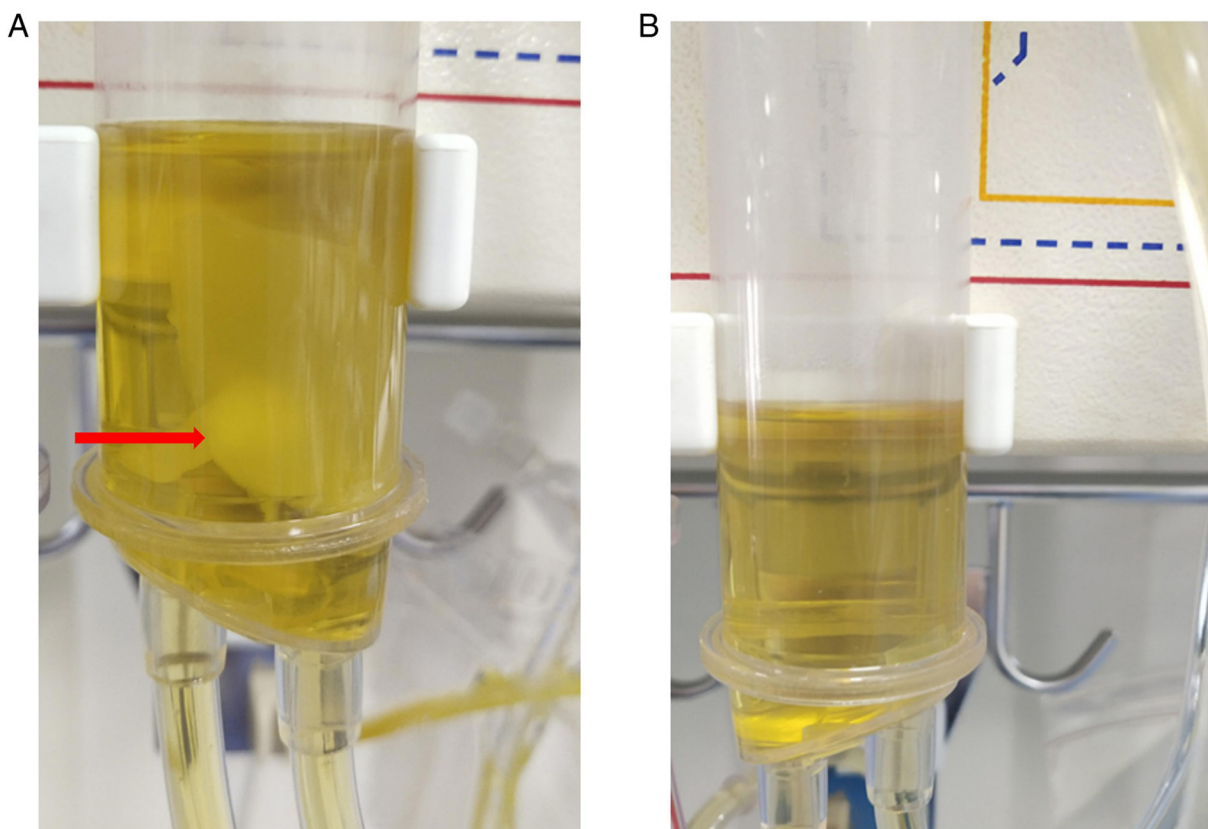Figure 3. Segmental citrate anticoagulation. (A) Arrow indicates the administration of citric acid before the blood entered the first filter to prevent the filter from clogging. (B) Arrow indicates the administration of citric acid before the plasma entered the second filter to prevent the filter from clogging. (C) Arrow indicates the administration of citric acid when the blood entered the vein ampulla to prevent the ampulla from clogging.

When RCA is used for DFPP, citrate is generally only administered in the first filter. This is due to the fact that thrombus formation in the second filter is difficult due to the absence of platelets and red blood cells in plasma (3). In addition, in the present study, fresh-frozen plasma was used as the replacement fluid, which also contains citrate as an anticoagulant. Therefore, in the initial treatment, anticoagulation was performed only in the first filter and the vein ampulla, which

Table II. Electrolyte changes before and after DFPP.

Electrolyte	Before DFPP	After the first DFPP	After the second DFPP	After the third DFPP
Serum calcium (mmol/l)	1.91	1.96	2.06	2.02
Serum potassium (mmol/l)	4.52	3.72	3.32	3.37
Serum sodium (mmol/l)	131.8	137.8	147.5	155.3
Serum chlorine (mmol/l)	98.9	95.1	92.2	94.7
Bicarbonate (mmol/l)	15.90	25.10	36.65	43.70

DFPP, double-filtration plasmapheresis.

is also a site prone to coagulation in extracorporeal circulation devices (21). However, the second filter was clogged ~1.5 h after the first DFPP treatment commenced. When examining the circuit, it was found that a large number of fibrin clots were formed in the second filter and plasma ampulla.

For the fibrin clot in the second filter and plasma ampulla, it was initially speculated that the insufficient dose of citrate may have caused the ionic calcium level in plasma not to fall to the appropriate range (0.2-0.4 mmol/l), resulting in thrombin activation and cleavage of fibrinogen to form a fibrin clot (22). Indeed, it has been reported that fibrin clots may be formed when the amount of anticoagulant is deficient in the collection of blood by plasmapheresis from normal donors (23). However, in this case, both filters should be clotted at the same time (the risk of clotting of the first filter is much greater than that of the second filter), and no fibrin clots were found in the plasma separated from the first filter in the case described herein. Therefore, it may be possible that the membrane surface of the second filter plays a role similar to platelets and cooperates with calcium ions and other coagulation factors to form prothrombin activators, resulting in the formation of fibrin clots. Therefore, citrate was administered to the first filter, second filter and vein ampulla at the same time. Following the adjustment of the anticoagulation regimen, no fibrin clots were formed during the subsequent treatment.

It should be emphasized that this is the first time SCA was used for DFPP, at least to the best of our knowledge. In addition, there are no scientific reports on the use of SCA in DFPP; thus, determining the dose of citric acid is difficult. A research team proposed a new protocol that enables the individualization of the use of RCA during therapeutic plasma exchange: $CiWB=(1-Hct) \times (8.035 \times pCai3-22.89 \times pCai2+24.68 \times pCai-5.361)$, where CiWB represents the whole blood citrate concentration in mmol/l, Hct represents the hematocrit, and pCai represents the plasma concentration of ionized calcium in mmol/l)] (24). However, this method is not suitable for DFPP, and the calculation process is cumbersome. Therefore, we refer to the protocol for RCA in critically ill patients undergoing continuous renal replacement therapy; that is, citric acid is infused at a fixed speed (25,26). Combined with the authors' own experience in using citric acid, the citric acid dose was set at 150 ml/h [first filter, 1.2-fold the blood flow rate (130 ml/min)], 50 ml/h [second filter, 0.4-fold the blood flow rate (130 ml/min)] and 50 ml/h [vein ampulla, 0.4-fold the blood flow rate (130 ml/min)].

During the course of treatment, certain unexpected evets occurred due to the lack of experience. First, the use of SCA increases the input of citrate, which poses the risk of overloading water and sodium. In fact, after the third DFPP treatment, severe sodium and water retention occurred (Table II). Thus, emergency dialysis had to be initiated to relieve the water overload. Second, a large amount of citrate input will increase the risk of hypocalcemia or metabolic alkalosis (24). Although there was no severe hypocalcemia following the calcium supplementation, the patient developed an alkaline overload due to the use of citrate (Table II). Therefore, the changes in serum calcium and bicarbonate in patients need to be strictly monitored to adjust the dose of citrate over time.

When a patient requires DFPP for treatment, it often means that the patient is in critical condition. At this time, the use of SCA can not only ensure the successful completion of DFPP, but may also avoid the bleeding tendency caused by the use of heparin or low-molecular-weight heparin. There is a risk of sodium and water retention, as well as hypocalcemia and metabolic alkalosis when performing SCA. However, the hazard caused by citrate can be reduced through appropriate measures, such as the use of diuretics, calcium supplements or lowering the dose of citrate, and if necessary, blood purification.

In conclusion, to the best of our knowledge, the present reports for the first time that SCA can be used for anticoagulation in DFPP. The regimen can more effectively prevent clogging of the first and second filters, thereby maintaining the continuity of treatment and avoiding treatment interruption and increased treatment costs caused by filter replacement.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JH, CM and FW conceived the case report, wrote the initial manuscript and reviewed the final manuscript. JH interpreted and created the images and reviewed the final manuscript. All

authors have read and approved the final manuscript. JH, CM and FW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The patient provided informed consent for her involvement in the present study.

Patient consent for publication

The patient provided informed consent for the publication of all the relevant clinical data.

Competing interests

The authors declare that they have no competing interests.

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