The possible usefulness of a medium *cut-off* dialyzer in a patient with cardiomyopathy of unclear origin

Prawdopodobna użyteczność dializatora typu medium cut-off u pacjenta z kardiomiopatią o nieznanym pochodzeniu

Bartłomiej A. Szewczyk[1], Kamila Hołownia[1], Andrzej Jaroszyński[1,2]

[1]Medical College, Jan Kochanowski University, Kielce Poland
Head of the Collegium: Prof. Marianna Janion MD, PhD
[2]Department of Nephrology, Institute of Medical Science, Jan Kochanowski University, Kielce, Poland
Head of the Institute: Prof. Andrzej Jaroszyński MD, PhD

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Słowa kluczowe: dializator typu medium *cut-off,* kardiomiopatia, duże średnie cząstki.

Abstract

The large middle molecules are a specific class of uremic toxins, which includes compounds like interleukins 1β, 6, 18, tumor necrosis TNF-β, and free light chains (FLCs). Accumulation of these molecules is associated with cardiovascular complications in end-stage renal disease (ESRD). Medium cut-off (MCO) membrane provides the ability to remove large middle molecules effectively with marginal albumin leak. We present the case of 59-year-old male patient with ESRD. He was admitted to the Nephrology Clinic because of deteriorating heart failure. Moreover, the patient suffered from unclear origin cardiomyopathy. He underwent percutaneous coronary intervention. Due to worsening outcome, an attempt to use MCO treatment was made. After 6 months of MCO treatment, the patient's clinical condition improved spectacularly. This is the first case report of the use of MCO treatment in a patient with a cardiomyopathy of unclear origin. Our study suggests that using MCO treatment in such cases may be advisable.

Streszczenie

Duże średnie cząstki to specyficzna klasa toksyn mocznicowych, która obejmuje takie związki, jak interleukiny 1β, 6, 18, czynnik martwicy nowotworu (TNF-α) oraz wolne łańcuchy lekkie. Gromadzenie tych cząsteczek w organizmie wiąże się z powikłaniami sercowo-naczyniowymi w schyłkowej niewydolności nerek (SNN). Membrany typu medium *cut-off* (MCO) mają zdolność do skutecznego usuwania dużych średnich cząsteczek przy marginalnej ucieczce albumin. Przedstawiamy przypadek 59-letniego mężczyzny z SNN. Został przyjęty do kliniki nefrologii z powodu narastającej niewydolności serca. Ponadto pacjent cierpiał na kardiomiopatię o nieznanym pochodzeniu. Dalsze postępowanie terapeutyczne obejmowało przezskórną interwencję wieńcową. Ze względu na pogorszenie wyników podjęto próbę zastosowania leczenia dializatorem typu MCO. Po 6 miesiącach terapii tym dializatorem stan kliniczny mężczyzny uległ spektakularnej poprawie. Jest to pierwszy opis przypadku zastosowania dializatora typu MCO u pacjenta z kardiomiopatią o niejasnym pochodzeniu. Przedstawiony opis przypadku sugeruje, że zastosowanie dializatora typu MCO w takich przypadkach może być zalecane.

Introduction

Cardiomyopathy of unclear origin is a difficult diagnostic issue, especially in the chronic renal failure population due to increased accumulation of large middle molecules. The levels of pro-inflammatory molecules including interleukins 1β, 6, 18, and tumor necrosis factor (TNF-α) increase progressively with chronic kidney disease (CKD) stage and are the highest in haemodialysis patients [1, 2]. Molecules such as IL-6, free light chains (FLCs), α1-microglobulin, and YKL-40 are potentially associated with increased mortality [2]. Cardiovascular mortality is estimated to be higher in the CKD population [3] due to elevated levels of proinflammatory and procoagulant biomarkers [4]. Proinflammatory molecules and FLCs are a potential treatment target via dialysis techniques [2].

Medium cut-off (MCO) dialyzers have potential efficiency benefits over conventional haemodialysis (HD) and haemodiafiltration [5]. The MCO type dialyzer expanded the perspective into removing large middle molecules. The new class of membranes extended the clearance of medium-sized molecules between 11.6 and 45 kDa, including FLCs [6].

Aim of the research

We present a unique case of unclear origin cardiomyopathy that has been treated successfully with an MCO dialyzer.

Case report

A 59-year-old Caucasian male patient with end-stage renal disease (ESRD), hypertension, and congestive heart failure was admitted to the Nephrology Clinic because of deteriorating heart function. He suffered from membranoproliferative glomerulonephritis, which ultimately resulted in ESRD. For this reason, the patient had been receiving peritoneal dialysis until he got a kidney transplantation. Unfortunately, T-cell–mediated rejection developed 3 months after the transplantation, and graft removal was necessary. Finally, conventional HD was applied to the long-term treatment.

During his stay at the Nephrology Clinic his general condition was stable, although he complained of dyspnoea. The physical examination showed a marked lower extremity swelling and suspicion of bilateral pleural effusion. His left ventricular ejection fraction (LVEF) at the time of initial assessment was 38% (Table 1), and he was classified with functional III class according to New York Heart Association. A reduction of weight did not improve the patient's outcome. Coronary angiography was performed because ischaemic aetiology was the most likely cause of the deteriorating heart failure. He underwent percutaneous coronary intervention in the left anterior descending artery (LAD) with implantation of a stent and plain balloon angioplasty due to restenosis in LAD. After 6 months the patient's state deteriorated. The lack of treatment improvement excluded ischaemic aetiology with a high probability and suggested different causes. The patient underwent sigmoidoscopy and gastroscopy, but no significant changes were observed. Pulmonary congestion was found on chest X-ray. A transthoracic echocardiography (TTE) revealed a dilated left ventricle (LV) with left ventricular hypertrophy. Proteinogram presented raised levels of α2-globulin (4.68 g/l) and γ-globulin (16.51 g/l) (Table 1). Immunofixation showed a high κ free light chain level of 4.26 g/l and a λ free light chain level of 2.25 g/l (Table 1) – a ratio of 1.89. HCV and HIV tests were negative. Due to the discordance results, cardiac amyloidosis was considered as a possible aetiology of the cardiomyopathy.

The patient was transferred to the Cardiomyopathy Clinic for further diagnosis. The laboratory tests showed that particular parameters were higher: increased level of: T-troponin 84.970 ng/l, NT-proBNP > 35,000 pg/ml, κ free light chain level 339.04 mg/l, λ free light chain level 143.64 mg/l (Table 1), and a ratio of 2.36. There was no sign of M-protein in urine or blood. It was difficult to compare accurate levels of κ and λ FLCs because of discordant methodologies. Immunofixation tests were performed in different laboratories. TTE findings were characteristic for cardiac amyloidosis. Cardiac magnetic resonance (CMR) did not reveal any typical findings in cardiac amyloidosis, although left ventricular anterior wall thickness increased up to 16 mm; this cardiac manifestation differentiates between hypertrophic cardiomyopathy with constrictive pericarditis and chronic kidney disease-related cardiomyopathy. Moreover, transthoracic echocardiography revealed that LVEF was reduced by 30% and left ventricle mass index (LVMI) increased to 237 g/m^2 (Table 1), which was evidence of gradually increasing heart failure. Amyloidosis was eliminated due to the following: labial salivary gland biopsy, bone marrow biopsy, large intestine biopsy, and transthyretin mutation analysis.

Afterwards, the patient was hospitalized in the same Nephrology Clinic as previously with indications to haemodialysis. Treatment was initiated with a Theranova 400 MCO dialyzer 3 times a week. The patient's state of health began to normalize after regular haemodialysis. Ailments began to subside after 3 months. Heart failure and antihypertensive drug therapy was adjusted to patient health state (Table 2). After 1 year, the patient was qualified as eligible for kidney transplantation. The ejection fraction increased to 45%, and LVMI decreased to 189 g/m^2. T-troponin (66.9 ng/l) and NT-proBNP (1198 pg/ml) reduced significantly (Table 1). Furthermore, the patient did not complain of any ailment and was in good health.

Discussion

We believe that there has been no previously described case of unclear origin cardiomyopathy treated with an MCO dialyzer. In this, light chain cardiac amyloidosis was widely suspected due to echocardiography findings prompting deposit storage disease and increased rate of FLCs. The CMR confirmed the findings of severe left ventricular dysfunction although the image has not normal for amyloidosis. Nonetheless, light chain cardiac amyloidosis transpired to be a misdiagnosis. The patient does meet the criteria of hypertrophic cardiomyopathy, although heart failure aetiology is uncertain due to CKD [7, 8]. Progressive signs and symptoms of heart failure occurred, although the patient received standard cardiac treatment. The patient complained of increasing breathlessness and deteriorating state of health.

Patients with chronic kidney disease have elevated levels of κ and λ FLCs [9] that might be stored in organs and cause kidney or heart dysfunction [10]. It is noteworthy that there was no evidence to classify the disorder as a monoclonal gammopathy of undetermined significance (MGUS). The patient did not meet the reference criteria of light chain MGUS, and the ra-

Table 1. Laboratory test, echocardiogram and cardiac magnetic resonance values

Variable	Nephrology Clinic	Cardiomyopathy Clinic	After 6 months of MCO treatment	Reference range
Creatinine [mg/dl]	5.11	8.9	9.17	0.70–1.30
Phosphor [mg/dl]	3.9	–	5.1	2.50–4.80
Uric acid [mg/dl]	4.6	3	4.5	3.40–7.00
Folic acid [mg/dl]	14.8	–	–	3.10–19.90
HGB [g/dl]	8.1	8.7	11.2	13.00–17.20
MCV [fl]	94.7	96.4	96.3	80.0–97.00
Ferritin [ng/ml]	658	–	692	20–300
Vitamin B_{12} [pq/ml]	1357	–	–	180–914
Calcium total [mEq/l]	4.06	–	4.91	4.50–5.50
Troponin T [ng/l]	86.7	84.97	66.9	0.00–14.00
NT-proBNP [pg/ml]	29600	>35000	1198	0.00–125.00
β2 microglobulin [mg/l]	46.09	–	15.7	0.80–2.20
M-protein [g/dl]	0	0	0	–
Total protein [g/dl]	7.2	7.7	7.8	6.00–8.00
Proteinogram:				
Albumin [g/l]	34.33	37	42.9	40.20–47.60
Alpha1 [g/l]	4.68	4	3.2	2.10–3.50
Gamma [g/l]	16.51	18	18.1	8.00–13.50
Echocardiogram values:				
Ejection fraction (%)	38	30	45	52–72
Left ventricle mass index [g/m²]	224	237	198	49–115
Cardiac magnetic resonance – left ventricular adjusted values:				
EDV/BSA [ml/m²]	–	170	–	62–97
ESV/BSA [ml/m²]	–	100	–	15–37

BSA – body surface area, EDV – end-diastolic volume, ESV – end-systolic volume, HGB – haemoglobin, MCV – mean corpuscular volume.

Table 2. Heart failure and antihypertensive drug therapy

Generic name	Before initiation of MCO treatment	After 6 months of MCO treatment
Acetylsalicylic acid	75 mg × 1	75 mg × 1
Doxazosin	4 mg × 1	4 mg × 1
Bisoprolol	10 mg × 1	2.5 mg × 2
Ramipril	10 mg × 3	2.5 mg × 1
Clopidogrel	75 mg × 1	–
Amlodipine	10 mg × 2	–
Ivabradine	5 mg × 2	–

Therapy is presented at a dose in milligrams and number of times per day. Route of administration: oral tablets.

tio of FLCs between 1.65 and 3.1 can be attributed to renal impairment in the CKD population [11]. High levels of IL-6, FLCs, α1-microglobulin, and YKL-40 are connected with higher morbidity and mortality observed in CKD [2]; therefore, the aforementioned symptoms could be caused by elevated levels of large middle molecules.

Standard haemodialysis has limited functionality in removing middle and large molecules. MCO membranes are able to remove an extended range of molecules such as myoglobin, α1-microglobulin, YKL-40, β2-microglobulin, and κ and λ FLCs [6], and that was the reason for applying MCO. After several weeks, the patient's condition improved, the NT-ProBNP level decreased significantly, and LVEF increased to 45%, which suggests that his heart function improved [12].

LVMI decreased noticeably, which leads us to suspect that paraproteins were successfully removed by the MCO dialyzer. This case report highlights the possibility of using MCO dialyzers in disorders such as cardiomyopathies of mainly unknown aetiology, which could bring substantial benefits for patients. It should also be considered that medium cut-off dialyzers may be regarded as a new course of treatment of disorders correlated with unclear aetiology of heart failure in the CKD population. It is worth attempting to use the MCO dialyzer in the case of unclear origin cardiomyopathy, due to the possible positive clinical outcome. Further studies and selection of patients for MCO treatment are essential to confirm the data.

Conflict of interest

The authors declare no conflict of interest.

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Address for correspondence:

Prof. **Andrzej Jaroszyński**
Medical College
Jan Kochanowski University
al. IX Wieków Kielc 19A
25-317 Kielce, Poland
Phone: +48 604 968 724
E-mail: jaroszynskiaj@interia.pl