Acute chest pain and dyspnoea as clinical presentation of primary membranous nephropathy. A case report and literature review

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Abstract. Membranous nephropathy (MN) is the commonest cause of nephrotic syndrome (NS) in adult male patients worldwide. Most of the cases (80%) are idiopathic (primary MN, PMN), whereas about 20% are associated with autoimmune diseases, malignancies or exposures (secondary MN). PMN is a kidney-specific autoimmune glomerular disease mediated by antibodies to the M-type phospholipase A2 receptor (anti-PLA2R) (85%), thrombospondin type 1 domain containing 7A (THSD7A) (3–5%), or by other still unidentified mechanisms (10%). Most of the patients with PMN present with NS (80%). Clinical course of PMN is characterised by spontaneous remissions (40%) and relapses (15-30%). One third develop end-stage renal disease (ESRD) within 5 to 15 years from the onset. Anti-PLA2R/THSD7A antibodies levels correlate with proteinuria, clinical course, and outcomes. The treatment still remains matter of debate. Hypertension, proteinuria, and hyperlipidaemia must be treated in all patients. Immunosuppressive therapy is indicated in patients with elevated anti-PLA2R/THSD7A levels and proteinuria >3.5 g/d at diagnosis. With proper management, only 10% or less will develop ESRD over the subsequent 10 years. Here we report a case of a 34-year-old male patient with a ten-year history of asymptomatic PMN, treated with ACE-inhibitors, who presented to our emergency room for acute chest pain and exertional dyspnoea due to ESRD that required urgent dialysis. (www.actabiomedica.it)

Key words: membranous nephropathy, proteinuria, PLA2R, THSD7A, renal transplant, acute renal failure, end stage renal disease, dialysis

Introduction

A 34-year-old male presented to our emergency room complaining of acute chest pain started at rest and increased in few hours, associated with fatigue, general malaise, and exertional dyspnoea in the last week. He had a diagnosis of primary membranous nephropathy (PMN) at the age of 24 years, following the detection of proteinuria during a medical examination for a certificate of fitness for soccer, and treated with ACE-inhibitor (ramipril 2.5 mg daily). His mother was affected by PMN in regular follow-up and treated only with supportive therapy. Since he was in good clinical condition, he missed regular medical controls until the presentation to our ED. He denied smoke, loss of weight, fever, nausea, vomiting and abuse of NSAIDs. On admission he was apyretic, displaying dry skin and mucous membranes. Blood pressure, heart rate, peripheral oxygen saturation and respiratory rate were 150/90 mmHg, 118 bpm, 98% while breathing in room ambient air, and 18 breaths/min, respectively. Heart sounds were normal. On chest exam bibasilar

fine crackles were heard. Electrocardiogram showed sinus tachycardia and complete right bundle branch block. Point-of-care ultrasonography showed bilateral B lines in the middle fields and slight bilateral pleural effusion with dilated inferior vena cava partially collapsible with inspiration, and atrophic kidneys, with no signs of hydronephrosis. Echocardiography excluded pericardial effusion and right heart dilatation, showing left ventricular hypertrophy with normal ejection fraction. Venous blood gas analysis showed metabolic acidosis (pH 7.15, HCO3 11, BE -18 mmoL/L) with hyperkaliemia (7.1 mEq/L), decreased calcium level (3.34 mg/dL) and normal lactates and glucose. Urine dipstick resulted positive for proteins (3+), glucose (1+) and blood (3+). Results of laboratory tests are reported in table 1, confirming acute renal

Table 1. Patient's laboratory findings at admission and discharge. WBC, white blood cells; RBC, red blood cells; Hb, haemoglobin; Hct, haematocrit; MCV, mean cell volume; MCH, mean cell haemoglobin; PLT, platelet; CHr, reticulocyte haemoglobin content; BNP, Brain Natriuretic Peptide; HS, high-sensitive; PTH, parathyroid hormone; Ig, immunoglobulin. Normal range values are in brackets, altered values in bold.

	At Admission	At Discharge
WBC (4-10 x 10⁹/L)	9.7	5.96
Neutrophil Count (2-8 x 10⁹/L)	**8.2**	4.23
Lymphocyte Count (1.5-4 x 10⁹/L)	**0.7**	**1.1**
RBC (4.3-5.7 x 10⁶/L)	**1.82**	**2.89**
Hb (13.2-17.3 g/dL)	**5.4**	**8.7**
MCV (82-98 fL)	94	93.4
Hct (39-49%)	**17.1**	**27**
MCH (27-32 pg)	29.7	30.1
PLT Count (150-450 x 10⁹/L)	268	360
Serum iron (53-167 mcg/dL)	90	–
Serum ferritin (12-300 ng/mL)	294	–
Transferrin saturation (15-45%)	41	–
Folate (3-10 ng/mL)	4.6	3.6
B12 (180-914 pg/mL)	360	308
CHr (29-35 pg)	33	35
BNP (0-100 pg/mL)	**1930**	**588**
HS Troponin (2.3-20 pg/mL)	14.1	–
Creatinine (0.6-1.2 mg/dL)	**20**	**9.9**
Blood urea nitrogen (10-50 mg/dL)	**448**	**132**
Potassium (3.5-5.0 mEq/L)	**7**	4.8
Sodium (135-146 mEq/L)	138	139
Chloride (97-110 mEq/L)	105	101
Calcium (8.1-10.4 mg/dL)	**5.73**	**7.81**
Phosphate (2.6-4.5 mg/dL)	**7.5**	**5.4**
PTH (14.5-87.1 pg/mL)	**672**	**616**
Vitamin D3 (>10 ng/mL)	12.8	–
Proteinuria (g/d)	**2.4**	**1.7**

	At Admission	At Discharge
Beta 2 microglobulin (0.8-2.4 mg/L)	**19.37**	–
C3 (93-188 mg/dL)	117	–
C4 (15-48 mg/dL)	42	–
IgA (70-400 mg/dL)	142	–
IgG (700-1800 mg/dL)	**382**	–
IgM (40-230 mg/dL)	**32**	–
IgG1 (382-928 mg/dL)	**153.9**	–
IgG2 (242-700 mg/dL)	**119.6**	–
IgG3 (22-176 mg/dL)	72.1	–
IgG4 (3.9-8.6 mg/dL)	**3.1**	–

failure (creatinine 20 mg/dL, normal value 0.6-1.2; blood urea 448 mg/dL, normal value 10-50) with severe hyperkaliemia (7 mEq/L, normal value 3.6-5), hypocalcemia (5.73 mg/dL, normal value 8.1-10.4) and hyperphosphatemia (7.5 mg/dL, normal value 2.6-4.5), and severe normochromic normocytic anemia (hemoglobin 5.4 g/dL, hematocrit 17.1%, MCH 29.7 pg, MCV 94 fL) with normal serum iron assessment (ferritin 294 ng/mL, normal value < 300; iron 90 mcg/dL, normal value 53-167; transferrin saturation 41%, normal value <45%), reticulocyte haemoglobin content, haptoglobin, folate and B12 vitamin levels. Ultra-sensitive cardiac troponin resulted in the normal range (14.1 pg/mL, normal value <20), while BNP was elevated (1930 pg/mL, normal value 0-100). White blood count, platelets, liver and thyroid function, coagulation tests, fibrinogen, and C-reactive protein were within normal limits. Urinalysis confirmed the protein loss and renal damage with markedly increased proteinuria (2.4 g/d), albuminuria (>15 mg/dL, normal value 0-2.5), and glycosuria (50 mg/dL, normal value 0-15) without evidence of urine infection at repeated urine cultures and negative urinary cytology. Autoimmune diseases and infections were excluded using a comprehensive autoimmune (ENA, ANA, p- and c-ANCA) and infectious disease panel (HBV, HAV, HCV, HIV, CMV, EBV). A RT-PCR nasopharyngeal swab for SARS CoV-2 ruled out COVID-19. C3 and C4 complement fractions were in the normal range. Beta2 microglobulin was elevated (19 mg/L, normal value 0.8-2.4), but with normal serum free light chains, negative urine and serum immunofixation, and

reduced IgG1, IgG2 and IgG4 as observed in severe renal failure.

Supportive therapy, including 2 blood units, furosemide iv (40 mg), sodium bicarbonate 8.4% iv and orally sodium polystyrene sulfonate (Kayexalate® 15 grams) was immediately administered in the emergency room. Severe acute renal failure required urgent hemodialysis. The patient was hospitalized in the nephrology unit and treated with daily hemodialysis with a progressive amelioration of serum creatinine and normalization of serum potassium level. He was discharged after 7 days of hospitalization with a three-times-per-week hemodialysis regimen and supportive therapy based on dietary protein restriction, ACE-inhibitor, beta-blocker, furosemide, calcium carbonate and calcitriol, provided that a kidney transplant was planned.

Discussion

Membranous nephropathy (MN) is the most common cause of idiopathic nephrotic syndrome (NS) in non-diabetic adults worldwide (1,2) and one of the most common and challenging causes of NS among older males (3). Peak incidence occurs in the fourth and fifth decades of life, and overall incidence in adults is estimated at 1.2 per 100,000 per year (4). PMN is rare in children (1–7% of biopsies) (5). It is an organ-specific autoimmune disease due to immune complex deposition and complement activation, histologically characterized by the uniform thickening of the

glomerular capillary wall, caused by subepithelial deposits of immune complexes, which appear with a pathognomonic pattern of injury in glomeruli as granular deposits of immunoglobulin G (IgG) with immunofluorescence, and as electron-dense deposits on electron microscopy (6). Clinically, proteinuria is the hallmark of the disease, usually non-selective and associated with microscopic haematuria. Among 70% to 80% of patients with MN refers to hospital because of NS at presentation (7). Hypertension and different degree of renal failure may be present at clinical onset in a variable number of patients (1), and 30% of patients can develop end- stage renal disease (ESRD) within 5 to 15 years of onset (8). Mortality is high due to several complications, such as infections, malignancies, or cardiovascular events (9).

The etiology

MN can be classified as primary (PMN) or secondary depending on its etiology. Approximately 80% of MN cases are idiopathic (10). The frequency and etiology of secondary MN vary in different geographic areas (1). Secondary MN can occur after exposure to drugs, such as penicillamine, captopril at high dose and nonsteroidal anti-inflammatory drugs, as well as toxic agents, including formaldehyde, mercury, or gold. It can also be secondary to infections, such as malaria, hepatitis B and C, HIV, and tuberculosis, or be related to autoimmune diseases (systemic lupus erythematosus, SLE; rheumatoid arthritis) or cancers (lung, kidney, stomach, colon) (1). In some cases, the cause of MN can remain occult. Immunohistology and disease course can differ considerably between primary and secondary MN (11).

The pathophysiology

The understanding of the pathogenesis of MN has dramatically improved in the last decade, even if MN is a well-known distinct clinical entity since 1940s (12). The history of MN started with the construction of a rat model nearly 60 years ago by Heymann and coll. (13). In this model, rats developed nephrotic syndrome when immunised with crude kidney extract plus Freund's adjuvant, secondary to the damage of podocyte

foot processes due to complement fixing antibodies. Since then, our knowledge has deeply progressed, and recent studies have demonstrated that PMN is a kidney-specific autoimmune glomerular disease with a pathognomonic pattern of injury in the glomeruli. As recently clarified by Akiyama and coll., the antigenic proteins involved in human PMN express themselves on the cell membrane of podocytes, the antibodies bind to the target proteins at the base of the podocyte membrane, thereby forming immune deposits in situ, and immune complexes induce complement activation, resulting in podocyte injury and disease progression (14). As confirmed by several researchers, the target autoantigen is represented by two multi-domain transmembrane glycoproteins composed by multiple repeating domains called M-type phospholipase A2 receptor (PLA2R) and thrombospondin type 1 domain-containing 7A (THSD7A) (10, 15-19).

The discovery of PLA2R and THSD7A antibodies has given new perspectives in understanding the pathogenesis of the disease process and has dramatically changed the diagnostic and therapeutic approach. PLA2R is a 185 kDa glycoprotein which belongs to the mannose receptor protein family, but its function in podocytes is currently unknown. Antibodies against PLA2R belong to IgG4 isotype and the presence of other subclasses of IgG on biopsy makes secondary MN more likely (20). Most cases of PMN have circulating IgG4 autoantibody to the podocyte membrane antigen PLA2R (70%), and biopsy evidence PLA2R staining indicating recent immunologic disease activity despite negative serum antibody levels (15%), and notably no patients with secondary MN were positive for the same (15). More importantly, PLA2R antibodies have also been reported to be of prognostic significance (16). Patients with positive PLA2R antibody titres at the time of biopsy have a lower rate of complete remission (21), while decreasing antibody titres suggest immunological remission (22, 23), and become undetectable prior to complete remission of proteinuria (24).

THSD7A is 250 kDa transmembrane glycoprotein expressed by podocytes, that triggers IgG4-predominant antibody response like PLA2R. THSD7A antibodies were identified in a smaller percentage of patients with PMN who were anti-PLA2R negative (2-5%) (18,25).

Genetics may play a role in the pathogenesis of PMN. Interestingly, several studies reported that the prevalence of anti-PLA2R antibodies in Japanese patients with PMN is lower than in other countries, probably due to several reasons, including genetic differences, or environmental and dietary factors (26-28). A genome-wide association study done by a European consortium revealed that an HLA-DQA1 allele on chromosome 6p21 is most closely associated with PMN in Caucasians, and this allele may facilitate an autoimmune response against targets such as variants of PLA2R1 (29). In Chinese population, a risk locus was found within the nearby DR-B locus in idiopathic MN (30). Familial PMN is rare and usually diagnosed in children (5,31).

The remaining 10% without demonstrable anti-PLA2R/THSD7A antibody or antigen likely have PMN probably secondary to a different, still unidentified, anti-podocyte antibody (32,33).

As recently reported by Akiyama and coll., the pathogenesis of PMN is an autoantibodies-driven mechanism which leads to the development of a PLA2R-associated membranous nephropathy based on 5 phases. First, the plasma cells are initiated to produce antibodies against PLA2R (phase A), which bind to podocytes. The first clinical sign of the disease, i.e., proteinuria begins to develop (phase B). In this phase no antibodies or only a low level of antibodies is detected in circulation. In the phase C or active phase, proteinuria starts to increase, and antibodies are detected in the serum. Then, in the phase D, the disease starts to resolve, antibodies production stops and disappears from circulation but not from the glomeruli. Finally, in the remission phase (phase E) podocyte injury is restored, and proteinuria is no more detected (14).

The immunological process which leads to the activation of this autoimmune mechanism still remains unclear. It is possible that the immunological activation can be induced by environmental factors, such as air pollution as reported in China (34), which leads to the loss of B-cell tolerance, IgG4 antibodies generation and deposition on glomerular basement membrane. Complement activation is demonstrated to play a crucial role in the pathogenesis of PMN, at least in animal models (35). However, a clinical study using the anti-C5 antibody, eculizumab, failed to show

significant effects (36). In contrast, recent studies successfully demonstrated that the anti-CD20 antibody, rituximab, depleted B cells, which led to proteinuria remission in patients with MN (37-39). Although the precise pathophysiology of PMN is not completely clear, there is no doubt that B cells play a crucial role in the development of the disease.

In conclusion, anti-PLA2R and THSD7A antibodies are 100% specific in terms of MN diagnosis and as consequence, they can be classified as excellent biomarkers to diagnose MN and to prognosticate the course of the disease. Their presence or absence help clinicians to classify patients with MN as primary or secondary cases. Moreover, PLA2R antibodies levels identify patients with immunologically active disease who can be promptly treated to avoid irreversible damages such as ESRD, based on the evidence that the antibodies titer correlates with poor prognosis, treatment failure and renal failure (32,40).

Clinical features

PMN can have an extremely heterogeneous presentation. It can occur in both sexes and all ethnic groups, but it is more common in white males after 40 years with a peak incidence between 50 and 60 years. Clinical course of PMN is characterised by spontaneous remissions and relapses. Approximately about 40% undergo spontaneous complete or partial remission, while 15-30% have relapses, and about 50% continue to have nephrotic syndrome. Among them, 30% progress to ESRD (41,42). Female gender and Japanese ancestry have a milder disease and a better prognosis (43). Proteinuria, initial serum creatinine and rate of change of creatinine are the most important factors in predicting progression to chronic kidney disease than initial proteinuria alone (44).

The most common clinical feature of PMN at diagnosis and during the clinical course is NS. For this reason, all adult patients with idiopathic NS should be screened initially for anti-PLA2R/THSD7A antibodies as well as for the common causes of secondary MN including hepatitis B and C, SLE, and malignancies, being the specificity of the anti-PLA2R assay for PMN 100%. Hypertension, peripheral oedema, hypoalbuminemia, and hyperlipidaemia can be the

first clinical manifestation of NS (45). About 80% of patients present with nephrotic-range proteinuria (< 3.5 g/d) and the remaining 20% have sub nephrotic proteinuria, even if most of them (61%) develop a NS usually within the first year from the diagnosis (46). Renal function is normal at presentation in almost all the cases (> 90%) (47). Spontaneous remissions occur in about 30% in an average of 14 months and up to 60% by 5 years and are more commonly in patients with low levels of anti-PLA2R/THSD7A antibodies. Anti-PLA2R/THSD7A levels generally correlate with proteinuria, clinical course, and outcomes (16).

Laboratory findings show normal complement values in PMN; hypocomplementemia suggests SLE or hepatitis B infection. Antinuclear antibodies, rheumatoid factor, and cryoglobulins are absent in PMN. Urinary excretion of the C5b-C9 terminal complement complex is elevated in some patients and can be correlated with disease activity and prognosis (48). Microscopic haematuria occurs in 50% of the patients, while macroscopic haematuria is rare (1).

The clinical consequences of PMN can be considered as both short and long term. In the short term, they include complications of NS, such as development of venous thrombotic and thromboembolic events (VTE), that are proportional to the degree of hypoalbuminemia and increase significantly below albumin levels of about 2.8 g/L (49,50). There is also an increased risk of infection, due primarily to urinary loss of immunoglobulins, and of cardiovascular diseases (51). An association with malignancies is well documented. Cancer may be seen within 3 years in up to 20% of patients over 60 years and may be more common in the anti-THSD7A group, where up to 20% have had a malignancy detected within 3 months (52). The most feared long-term consequence of PMN is progressive loss of renal function as occurs in 60% of untreated patients with about 35% eventually developing ESRD within 10 years (46). Patients who never become nephrotic virtually never progress. Other established risk factors for progression include age, male sex, decreased glomerular renal fraction on presentation, increased excretion of some low molecular weight markers, such as beta 2 microglobulin and persistent elevated anti-PLA2R levels after therapy (46, 51).

Diagnosis

The diagnosis of PMN requires renal biopsy and histopathological examination by immunofluorescence and electron microscopy (53, 54). Renal biopsy may be deferred in patients in whom immunosuppressive treatment is not a reasonable option, including those with advanced renal failure, with sub-nephrotic proteinuria, in whom the prognosis is excellent and specific treatment is not offered, and elderly patients in whom the risks of therapy are felt to be prohibitive. Diagnostic evaluation should always include:

- Antinuclear antibodies and complement C3, C4, which are normal in PMN. Low complement levels are suggestive of other glomerulopathies.
- Hepatitis B and C serologies to rule out secondary MN.
- Age-appropriate cancer screening as malignancies are well-known triggers for secondary MN.
- In selected patients with rapid worsening of renal function, renal vein dopplers, computed tomography with contrast or angiography are necessary to early identify renal vein thrombosis.
- PLA2R1 antibody.

Management

The first step is differentiating between primary and secondary MN, since in secondary MN immunosuppression can impair host responses to malignancies or enhance viral replication, which results in a severe damage for the patient. In secondary MN the therapy must be directed at the underlying cause, while supportive and targeted therapies with immunosuppression are the gold standard for PMN. Considering the primary form, the treatment still remains controversial and heavily debated (55,56). Supportive care should be initiated in all patients at the time of diagnosis and continued for the course of the disease. Hypertension, proteinuria, and hyperlipidaemia must be always treated. Salt restriction and diuretics help to control oedema, a low protein diet allowing for replacement of urinary protein losses, angiotensin-converting enzyme

inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) can reduce proteinuria and enhance chances of a spontaneous remission; statins are indicated for hyperlipidaemia (57,58). KDIGO guidelines recommend blood pressure of 130/80 mmHg for the treatment goal (59). It is known that the ACEIs or ARBs decrease proteinuria and attenuate renal progression in patients with diabetic and non-diabetic proteinuric renal diseases, but their beneficial effect in improving the long-term prognostic outcome in patients with PMN still remains to be proven. Venous thromboembolic events (VTE) are rare and varies widely but are more common in patients with hypoalbuminemia, which is the only independent predictor of a venous thromboembolism at diagnosis (60). Standard guidelines for anticoagulation do not exist (49) and prophylactic anticoagulation treatment should be tailored for each patient (61). KDIGO guidelines recommend a prophylactic anticoagulation with warfarin if serum albumin is below 2.5 g/d (59). Duration of anticoagulation is still a matter of debate. Given the low frequency of VTE, a well-powered clinical trial would be challenging to achieve. The great challenge for the clinicians is the timing to start immunosuppression. Data reported in literature about the natural history of PMN are divergent, and it is not unreasonable to delay immunosuppression since spontaneous remission occurs in up to 30% of patients (62). However, up to 30% of patients with persistent NS progress to ESRD over 10 years (41) and need more aggressive therapy. There is evidence that treatment-induced remission is associated with improved prognosis. Therapy has been largely evaluated in several studies. Goals of therapy are the complete or partial remission, preserving renal function as more as possible. Treatment regimens are based on immunosuppressive agents, including steroids, alkylating agents, calcineurin inhibitors, mycophenolate, and rituximab (6). The identification of parameters that bear poor prognostic outcome is pivotal for selecting patients to receive immunosuppressive therapy. Male gender, increasing age, nephrotic-range proteinuria, the ratio of IgG to α1-microglobulin excretion in urine, focal segmental glomerulosclerosis, and impaired renal function at presentation are predicting factors for risk of renal progression (41). One of the most shared and logical approach is based on

proteinuria/GFR-based guidelines, that divide patients into three categories based on the risk of progression, as proposed in the algorithm by Cattran and coll. (63). Low-risk patients have normal serum creatinine and creatinine clearance values, and a peak proteinuria < 4 g/d over 6 months of observation. Medium-risk patients have normal or nearly normal serum creatinine and creatinine clearance values, and proteinuria > 4 g/d but <8 g/d over 6 months of observation. Finally, high-risk patients have either abnormal or deteriorating serum creatinine and creatinine clearance values, and/or persistent proteinuria > 8 g/d over 6 months of observation. The long-term prognosis for low-risk patients is excellent, therefore immunosuppressive drugs are not recommended. Individual classified as medium risk does not benefit from corticosteroids as a single agent (64), but when corticosteroids are combined with a cytotoxic agent, such as chlorambucil (65). In a randomized study by Ponticelli and coll. both cyclophosphamide (2.5 mg/kg/day) and chlorambucil (0.2 mg/kg/day) have been resulted equally efficacious and showed to be safe in a six-month therapy (66). The infection profile of cyclophosphamide might be slightly better than chlorambucil, but cyclophosphamide therapy is associated with significant cancer risk (bladder and haematologic). Thus, tacrolimus (FK506) can be used as an alternative to alkylating agents if the latter therapy is poorly tolerated (67). As the percentage of high-risk patients with PMN is small, very few trials have been conducted. Long-term oral cyclophosphamide with or without prednisone has been used in two small, non-randomized, case-controlled studies (68,69). Although both studies showed a benefit, the main limit of the therapy is related to the prolonged cytotoxic effects which can cause infertility, infection, and malignancies. In a randomized controlled trial by Cattran and coll. (70), one year of cyclosporine significantly reduced proteinuria and slowed the rate of disease progression. However, the main limits of the study were the small size of the enrolled patients, and the cost and the cytotoxicity of the drug.

The main limit of proteinuria/GFR-based guidelines is that there was no way to distinguish patients with immunologically active disease from those with inactive disease who have persistent proteinuria

despite immunologic remission. For this reason and the evidence that immunosuppressive therapies have been shown to decrease the titres of anti-PLA2R1 antibodies, treatment of PMN should be based on a new antibody-guided algorithm as proposed by Couser WG (6), that can be summarized as follows: patients with elevated anti-PLA2R/THSD7A levels and proteinuria >3.5 g/d at diagnosis (active PMN), and those who fail to reduce proteinuria to < 3.5 g/d after 6 months of supportive care or have complications of NS, should be considered for immediate immunosuppressive therapy. Patients who are negative for anti-PLA2R/THSD7A in the serum but have PLA2R or THSD7A antigen staining in the biopsy sample, and usually predominately IgG4 deposition in glomeruli, have inactive anti-PLA2R/THSD7A–mediated PMN and should be treated with supportive care while monitoring anti-PLA2R levels for 4–6 months. Patients with elevated anti-PLA2R levels (with positive PLA2R staining and predominantly IgG4 in the biopsy sample) and proteinuria < 3.5 g/d have active anti-PLA2R/THSD7A–mediated PMN but would receive supportive care with monthly anti-PLA2R monitoring, because most of these patients will undergo spontaneous remission. Immunosuppressive treatment should be selected on the basis of characteristics of individual patients with dose and duration of therapy guided by regular monitoring of anti-PLA2R levels. New therapies should be based on B-cell depleting agents and complement inhibitors. In a recent pilot study of belimumab, an inhibitor of B cell activation, the authors reported a significant reduction in anti-PLA2R levels and proteinuria in 14 patients with PMN receiving up to 2 years belimumab monotherapy (10 mg/kg, every 4 weeks) (71). Several new trials are targeting complement inhibition to treat renal diseases showing promising preliminary results, and complement-based therapies could represent the new targeted therapy for PMN (72).

Renal transplantation is indicated in patients with ESRD and results effective in 10-20% of patients with PMN (6). About 2% of renal transplant recipients can develop *de novo* anti-PLA2R/THSD7A negative MN with a mechanism not completely clear (73), probably due to IgG1 deposits or related to graft rejection (74–76). Treatment regimens for *de novo* MN are considered in patients with nephrotic-range proteinuria (> 4 g/d) post-transplant and are based on rituximab added to regular immunosuppressive protocol at different doses with monitoring of CD20 counts. In patients resistant to rituximab, cyclophosphamide at the dose of 2 mg/kg per day is usually employed (73,75).

Conclusion

PMN can represent a real challenge for the clinicians not only for its diagnosis, but more importantly for its management. As reported in our case report, the patient has developed an irreversible renal failure after many years from the diagnosis of PMN, that required urgent dialysis and blood transfusion. Surprisingly the patient presented to our emergency room complaining about acute chest pain, fatigue and exertional dyspnoea due to congestive heart failure and severe anaemia related to a chronic untreated renal disease, in absence of peripheral oedema, elevated blood pressure and haematuria. The clinical course of PMN and the development of severe complications in our patient confirm the data reported in literature and strengthen the importance of a close follow-up of all the patients with PMN with a tailored approach for the early detection and management of complications and the prompt starting of supportive and/or immunosuppressive therapy.

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