Nephrotic syndrome in the course of type 1 diabetes mellitus and systemic lupus erythematosus with secondary antiphospholipid syndrome – diagnostic and therapeutic problems

Aleksandra Graca, Dorota Suszek, Radoslaw Jeleniewicz, Maria Majdan
Department of Rheumatology and Connective Tissue Diseases, Medical University of Lublin, Poland

Abstract
Nephrotic syndrome (NS) can be a symptom of many autoimmune, metabolic, or infectious diseases. Kidney involvement is often observed in the course of diabetes mellitus (DM) and systemic lupus erythematosus (SLE). The development of NS with coexisting SLE and DM generates serious diagnostic problems. In this paper, the authors present diagnostic and therapeutic dilemmas in a patient with long-lasting DM, SLE, and secondary antiphospholipid syndrome, in whom NS symptoms appeared. Histopathological examination of the kidney confirmed the diagnosis of lupus nephritis. Immunosuppressive and anticoagulant drugs were used.

The authors demonstrated that the character of morphologic lesions in the kidney biopsy can help in diagnosis, nephropathy classification, and further therapeutic decisions, which are distinct in both diseases.

Key words: nephrotic syndrome, diabetes mellitus type 1, systemic lupus erythematosus.

Introduction
Nephrotic syndrome (NS) is a clinical condition characterized by daily loss of protein in the urine > 3.5 g/1.73 m²/day, hypoalbuminemia, hyperlipidemia, and the presence of edema. Most often, it is caused by primary glomerulonephritis (70%) [1]. In other patients, secondary glomerulopathies might be the cause of NS and are associated with [1]:
• diabetes,
• amyloidosis,
• autoimmune diseases: systemic lupus erythematosus (SLE), systemic vasculitis,
• infectious diseases: HIV, HBV, HCV, CMV, toxoplasmosis, parvovirus B19,
• drug effects: gold salts, nonsteroidal anti-inflammatory drugs,
• cancer,
• renal vessel thrombosis: thrombotic microangiopathy, renal vein thrombosis.

Systemic lupus erythematosus is a chronic autoimmune disease that is associated with disturbances of acquired and innate immunity caused by various environmental factors and genetic predispositions. Lupus nephritis (LN) occurs in 35–75% of patients with SLE and manifests most commonly as glomerulonephritis [1, 2]. Proteinuria > 500 mg/day is the main symptom of LN. Also, NS may occur in the course of this disease. Lupus nephritis can also manifest as urinary changes such as granular casts, hematuria, and sterile leukocyturia, as well as acute kidney injury (AKI) or chronic kidney disease (CKD). In addition to clinical symptoms, kidney biopsy plays a key role in determining the diagnosis of LN. Based on the histopathological image, changes in kidneys can be classified into one of six classes (Table I) [3, 4].

Diabetic nephropathy is a functional and structural malfunctioning of the renal parenchyma due to chronic hyperglycemia. Diabetic nephropathy is a microangiopathic complication of diabetes and affects approximately 40% of diabetics. Microalbuminuria is an early symptom of diabetic nephropathy. 80% of patients with...
type 1 diabetes mellitus have overt proteinuria after 6–14 years of disease duration [5]. Diabetic kidney disease is currently the most common cause of end-stage renal disease (ESRD) [6]. Based on the histopathological image, diabetic nephropathy can be divided into four classes according to glomerular lesions (Table II) [7].

### Material and methods

As a background for discussion a case of nephropathy which was initially treated as a complication of poorly controlled long-lasting type 1 diabetes (DMT1) is presented. In the described patient apart from kidney involvement, no other signs of systemic connective tissue disease were observed. Diagnosis for autoimmune diseases was carried out due to the progressive nature of nephropathy despite constant diabetes treatment and an episode of thrombosis. The results of serological tests supported the diagnosis of systemic disease: SLE/APS.

Such a coincidence of events prompted the search for other descriptions and answers to the described clinical problem. Therefore the literature was analyzed using key words: diabetes mellitus type 1 and lupus erythematosus, nephrotic syndrome, lupus nephritis.

### Case report

A 28-year-old female patient with type 1 diabetes was diagnosed at the age of 13 (2004) and at the age 22 (2012) with onset of proteinuria (1.5 g/day) and eGFR 90 ml/min/1.73 m²; therefore DMT1 treatment was started using a personal insulin pump. In 2015 the patient was admitted to the Endocrinology Clinic due to weight gain and massive swelling of lower limbs. Laboratory tests revealed microcytic anemia (Hb 10.2 g/dl), leukopenia (3790/ml) with lymphopenia (1000/ml), hypoproteinemia with dysproteinemia (total protein – 5.7 g/dl, albumin – 3.18 g/dl), proteinuria (6.5 g/day), and hypercholesterolemia. Renal function parameters remained normal.

Additionally, immunological studies showed a reduced concentration of complement components C3 and C4, an anticardiolipin antibodies (ANA) presented in titer 1 : 2560 with speckled staining pattern, whereas pANCA and cANCA antibodies were absent. In abdominal ultrasound, the kidneys had normal size and structure. The patient also had an episode of deep vein thrombosis in the left upper limb.

At the age of 26 (2016), the patient was admitted to the Department of Rheumatology and Systemic Connective Tissue Diseases. The patient denied skin, mucosal and joint symptoms. The immunoassay tests were repeated: ANA 1 : 2560, speckled staining pattern, SS-A (++), SS-B (+++), Rib P (++) present in the ENA panel, anti-dsDNA borderline, anti-cardiolipin antibodies present in the IgM class – aCL-IgM (160.4 MPL; norm < 20 MPL) and in the IgG class – aCL-IgG (38.1 GPL; norm < 20), lupus anticoagulant was absent, but Factor V Leiden mutation was present.

Based on the clinical image and the results of additional tests, SLE was diagnosed. Hydroxychloroquine at a dose of 200 mg/day was recommended for treatment. Three months later, the anti-phospholipid antibody assay was repeated. High-aCL-IgM and aCL-IgG were detected, and anti-beta2-glycoprotein I antibodies present in the IgM and IgG class (anti-beta2-glycoprotein I antibodies present in the IgM and IgG class) were present.

Antiphospholipid syndrome (APS) was diagnosed, and warfarin anticoagulation was initiated. Due to the unclear etiology of nephropathy (diabetic? in the course of SLE? APS?), the patient was qualified for kidney biopsy.

The pathomorphological image corresponded to class IV lupus nephropathy. Glucocorticosteroid and cyclophosphamide (CYC) pulses were used in the Euro-Lupus regimen. After 3 g CYC administration, partial remission of
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Analyzing the secondary nephrotic syndrome causes

Nephrotic syndrome is a common symptom of autoimmune diseases, especially SLE. The percentage of patients with lupus nephritis who have NS ranges from 30% to 70%. The presence of NS significantly worsens the prognosis in patients with SLE [8]. Epidemiological studies indicate the coexistence of various autoimmune diseases in one patient, most commonly Hashimoto’s disease, type 1 diabetes, albinism, or inflammatory joint diseases. The co-occurrence of one or more autoimmune diseases in one patient increases the risk of damage to organs they have involved, including kidney damage. About 30% of patients with SLE develop another autoimmune disease [9].

Patients with SLE are at an increased risk of developing diabetes. The comorbidity of SLE and type 1 diabetes is relatively rare. In the Kota et al. study [10], SLE was diagnosed in 3 out of 260 patients with type 1 diabetes. Cortes et al. [11] analyzed a group of 485 patients with SLE. Type 1 and type 2 diabetes were diagnosed in 3 (0.61%) and 6 (0.82%) patients with SLE, respectively. Some patients with type 1 diabetes with insulin resistance associated with insulin receptor antibodies are more likely to develop SLE. In these patients, a variety of antibodies are found, including SLE marker antibodies against dsDNA [11]. Anti-insulin antibodies were found in 5 out of 27 (19%) patients with SLE [12, 13].

In the group of metabolic diseases, the most common cause of NS is diabetes, especially long-term and poorly controlled. Many studies show the co-morbidity of diabetes and kidney disease, which is not a consequence of diabetes but another associated disease [14–17]. Both SLE and diabetes can lead to the development of NS and ESRD in a variety of mechanisms. The comorbidity of type 1 diabetes in patients with SLE significantly increases this risk [18, 19].

Renal involvement is associated both with primary and secondary APS. Antiphospholipid syndrome causes various pathophysiological effects concerning the kidneys [20, 21]. Antiphospholipid associated nephrophy (APSN), acute or chronic with nephritic or nephrotic syndrome, may be presented in kidney biopsy specimens as:

- thrombotic microangiopathy (TMA),
- fibrous intimal hyperplasia (FIH),
- focal cortical atrophy (FCA).

However, the renal biopsy was a decisive test that allowed the diagnosis of lupus nephropathy and the exclusion of thrombotic changes in the course of APS. Only intensive immunosuppressive treatment with cyclophosphamide made it possible to achieve NS remission, which was maintained by introducing MMF in long-lasting treatment. Performing kidney biopsies in patients with nephropathy and diabetes should be considered particularly in patients with a short duration of diabetes, presence of hematuria, NS, or another systemic disease [2, 14–17].

Conclusions

The comorbidity of SLE and diabetes and the symptoms of nephropathy can pose significant diagnostic difficulties and require a specific diagnostic approach. Differentiation of the underlying causes of kidney damage is crucial in undertaking the appropriate treatment. The nature of morphological changes in kidney biopsy may help in the diagnosis, classification of nephropathy, and further therapeutic decisions, which are different in diabetic nephropathy and lupus nephritis (diabetic kidney disease and lupus nephritis).

The authors declare no conflict of interest.
References

1. Kodner C. Diagnosis and management of nephrotic syndrome in adults. Am Fam Physician 2016; 93: 479-485.
2. Reddy V, Isenberg D. Clinical presentation and assessment of disease activity in lupus nephritis. In: Rheumatology and the Kidney. Adu D, Emery P, Madaio M (eds.). Oxford University Press, 2012: 1-10.
3. Weening JJ, D’Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revised. J Am Soc Nephrol 2004; 15: 241-250, DOI: 10.1097/01asn.0000108969.21691.5d.
4. Bajema IM, Wilhelmus S, Alpers ChE, et al. Revision of the International Society of Nephrology/Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney Int 2018; 93: 789-796, DOI: 10.1016/j.kint.2017.11.023.
5. Bakris GL, Moltch M. Microalbuminuria as a risk predictor in diabetes: the continuing saga. Diabetes Care 2014; 37: 867-875, DOI: 10.2337/dc13-1870.
6. Sanchez-Niño MD, Benito-Martín A, Ortiz A. New paradigms in cell death in human diabetic nephropathy. Kidney Int 2010; 78: 737-744, DOI: 10.1038/ki.2010.270.
7. Tervaert TWC, Mooyaart AL, Amann K, et al. Pathologic classification of diabetic nephropathy. J Am Soc Nephrol 2010; 21: 556-563, DOI: 10.1681/ASN.2010010010.
8. Gomez Mendez LM, Cascino MD, Katsumoto TR, et al. Outcome of participants with nephrotic syndrome in combined clinical trials of lupus nephritis. Lupus Sci Med 2019; 6: e000308, DOI: 10.1136/lupus-2018-000308.
9. Chambers SA, Charman SC, Rahman A, Isenberg D. Development of additional autoimmune diseases in a multiethnic cohort of patients with systemic lupus erythematosus with reference to damage and mortality. Ann Rheum Dis 2007; 66: 1173-1177, DOI: 10.1136/ard.2006.062984.
10. Kota SK, Meher LK, Jamnula S, et al. Clinical profile of coexisting conditions in type 1 diabetes mellitus patients. Diabetes Metab Syndr 2012; 6: 70-76, DOI: 10.1016/j.dsx.2012.08.006.
11. Cortes S, Chambers S, Jerónimo A, Isenberg D. Diabetes mellitus complicating systemic lupus erythematosus – analysis of the UCL lupus cohort and review of the literature. Lupus 2008; 17: 977-980, DOI: 10.1177/0961203308091539.
12. Heras P, Mantzioros M, Mendrinos D, et al. Autoantibodies in type 1 diabetes. Diabetes Res Clin Pract 2010; 90: e40-42, DOI: 10.1016/j.diabres.2010.08.015.
13. Lidar M, Braf A, Givol N, et al. Anti-insulin antibodies and the natural autoimmune response in systemic lupus erythematosus. Lupus 2001; 10: 81-86, DOI: 10.1191/09612030169081314.
14. Teng J, Dwyer KM, Hill R et al. Spectrum of renal disease in diabetes. Nephrology (Carlton) 2014; 19: 528-536.
15. Grujic M, Salapura A, Basta-Jovanovic G, et al. Non-diabetic kidney disease in patients with type 2 diabetes mellitus – 11-year experience from a single center. Med Arch 2019; 73: 87-91, DOI: 10.5455/medarch.2019.73.87-91.
16. Zhuo L, Ren W, Li W, et al. Evaluation of renal biopsies in type 2 diabetic patients with kidney disease: a clinicopathological study of 216 cases. Int Urol Nephrol 2013; 45: 173-179, DOI: 10.1007/s11255-012-0164-6.
17. Kveder R, Kajtna-Koselj, Rott T, Bern A. Nephrotic syndrome in patients with diabetes mellitus is not always associated with diabetic nephropathy. Nephrol Dial Transplant 2001; 16 (Suppl 6): E6-E7, DOI: 10.1093/ndt/16.suppl_6.86.
18. Jiang MY, Hwang JC, Feng L. Impact of diabetes mellitus on the risk of end-stage renal disease in patients with systemic lupus erythematosus. Sci Rep 2018; 8: 6008, DOI: 10.1038/s41598-018-24529-2.
19. Munoz C, Isenberg DA. Review of major endocrine abnormalities in patients with systemic lupus erythematosus. Clin Exp Rheumatol 2019; 37: 791-796.
20. Bienaime F, Legendre Ch, Terzi F, et al. Antiphospholipid syndrome and kidney disease. Kidney Int 2017; 91: 34-44, DOI: 10.1016/j.kint.2016.06.026.
21. Majdan M. Kidney involvement in antiphospholipid syndrome – current diagnostic and management problems. Reumatologia 2017; 55: 213-214, DOI: 10.5114/reum.2017.71626.