

## Membranous nephropathy secondary to bladder cancer

Membranous nephropathy (MN) is one of the most common cause of the nephrotic syndrome in adults and occurs in 10% secondary to neoplasm. Treatment of the primary cause of MN is associated with clinical remission and slowing of progression of kidney disease.

We describe a case report of 51-year-old male who presented with peripheral edema, urinary protein loss of 13 grams per day, hypoalbuminemia, lipid disorders and normal glomerular filtration rate. In evaluation of nephrotic syndrome kidney biopsy was performed and histopathological examination revealed MN. Blood test for anti-phospholipase A2 receptor autoantibodies (anti-PLA2R) was negative, so secondary MN was suspected and patient underwent computed tomography of abdomen and pelvis which showed a tumor in the bladder. Patient underwent transurethral resection of bladder tumor (TURBT). Because of histopathological examination result (urothelial cancer, pT1HG+Cis) restaging resection (reTURBT) was performed with histopathological examination revealing residual disease (pT1HG). Patient was qualified for BCG intravesical therapy (scheme 6+3). Daily proteinuria was 5 grams at that time. 10 months later BCG failure was observed and the patient underwent TURBT (pT1HG). Due to high risk of recurrence, progression and understaging, patient underwent radical cystectomy. After surgery, improvement of urinary protein loss was observed. In four-year follow-up, no recurrence nor distant metastases were observed; patient has normal glomerular filtration rate and trace proteinuria.

(NEPROL. DIAL. POL. 2018, 22, 27-29)

## Nefropatia błoniasta wtórna do raka pęcherza moczowego

Nefropatia błoniasta (NB) jest jedną z najczęstszych przyczyn zespołu nerczycowego u osób dorosłych. Około 10% przypadków NB ma charakter wtórny do nowotworów. Leczenie pierwotnej przyczyny NB prowadzi do ustąpienia objawów i spowolnienia postępu glomerulopatii.

Opisano przypadek 51-letniego mężczyzny, który zgłosił się do kliniki z powodu obrzęków obwodowych, białkomoczu 13 g/dobę, hypoalbuminemi, zaburzeń gospodarki lipidowej przy prawidłowej filtracji kłębuszkowej. W celu dalszej diagnostyki zespołu nerczycowego wykonano biopsję nerki. W badaniu histopatologicznym stwierdzono cechy nefropatii błonistej (NB). Ujemny wynik autoprzeciwciała skierowanych przeciwko receptorowi fosfolipazy A2 (anti-PLA2R) w surowicy pacjenta nasunął podejrzenie wtórnej NB. Wykonano wielofazowe badanie tomografii komputerowej jamy brzusznej i miednicy. Badanie uwidocznilo w pęcherzu moczowym guzową zmianę. Wykonano przezcewkową elektroresekcję guza (transurethral resection of bladder tumor – TURBT). W badaniu histopatologicznym rozpoznano raka urotelialnego pęcherza moczowego nienaciekającego błonę mięśniową pT1HG+Cis, co spowodowało zakwalifikowanie pacjenta do restagingowej resekcji (reTURBT). W badaniu histopatologicznym wycinków z łoży po guzie odnaleziono utkanie nowotworowe pT1HG. Pacjent został zakwalifikowany do immunoterapii BCG w schemacie 6+3. Utrata białka z moczem wynosiła w tym czasie 5 g/dobę. 10 miesięcy później zaobserwowano niepowodzenie immunoterapii BCG, pacjent został poddany TURBT (pT1HG). Z powodu wysokiego ryzyka wznowy i progresji procesu nowotworowego oraz ryzyka zaniżenia stopnia zaawansowania klinicznego nowotworu, pacjenta poddano radykalnej cystektomii. Po zastosowaniu leczenia urologicznego zaobserwowano zmniejszenie dobowej utraty białka. W 4-letniej obserwacji nie zauważono wznowy procesu nowotworowego ani odległych przerzutów. Pacjent ma prawidłową czynność nerek i obserwuje się jedynie śladowy białkomocz.

(NEFROL. DIAL. POL. 2018, 22, 27-29)

Lukasz BIAŁEK  
Julia MRÓZ  
Jolanta GOZDOWSKA  
Dorota MISZEWSKA-SZYSZKOWSKA  
Anna SADOWSKA  
Magdalena DURLIK

Department of Transplantation Medicine,  
Nephrology and Internal Diseases, Medical  
University of Warsaw, Warsaw, Poland  
Head:  
Prof. Magdalena Durlik, MD, PhD

### Key words:

- membranous nephropathy
- bladder cancer
- anti-phospholipase A2 receptor autoantibodies

### Słowa kluczowe:

- nefropatia błoniasta
- rak pęcherza moczowego
- autoprzeciwciała przeciwko receptorowi fosfolipazy A2

Conflict of interest: not declared

Received: 04.01.2018

Accepted: 19.01.2018

### Address for correspondence:

Jolanta Gozdowska  
phone: +48 605 532 525  
email: jolanta.gozdowska@wum.edu.pl

## Background

Membranous nephropathy (MN) is one of the most common cause of the nephrotic syndrome in adults [1]. In the management of MN it is crucial to identify whether it is idiopathic or secondary. Uncovering the underlying cause of MN may not always be easy, because it may be associated with many diseases, out of which the most often ones are neoplasms (which are responsible for 10% of MN; mainly solid tumors e.g. lung cancer, prostate cancer, colon cancer [2,3], systemic lupus erythematosus, HBV or HCV infection, drug therapy (penicillamine, NSAIDs, captopril, gold) or less common syphilis or sarcoidosis [4]. In idiopathic MN, the glomerular lesions are mainly caused by autoantibodies against a podocyte membrane protein, the M-type of phospholipase A2 receptor 1 (anti-PLA2R). For this reason the positive result of anti-PLA2R antibodies confirms with high specificity the idiopathic character of MN, and the negative results force to search for the secondary MN [5,6]. Removal of underlying causes of MN is associated with clinical remission and slowing of progression of kidney disease in some cases.

Bladder cancer is the most common urinary tract malignancy and fourth the most common cancer in males in Poland. In Europe, more than 90% of bladder cancers are urothelial carcinomas, which risk factors are age, male sex and smoking. At the time of the diagnosis in Poland 78% of the patients are affected by non-muscle invasive bladder cancer (NMIBC) [7]. In patients with high-risk NMIBC management is based on transurethral resection of bladder tumor (TURBT) with adjuvant intravesical chemotherapy and BCG-immunotherapy [8]. However, in selected cases of T1HG tumors radical cystectomy should be considered [9,10].

## Case Report

51-year-old male was admitted to the nephrology ward for the diagnostic evaluation of nephrotic syndrome. Patient reported peripheral edema for a few weeks. Laboratory tests revealed urinary protein loss of 13 grams per day, microscopic hematuria, hypoalbuminemia and lipid disorders. Kidney function was within normal limits – serum creatinine level was 0.86 mg/dl, glomerular filtration rate 100 ml/min/1.73 m<sup>2</sup>. He had a history of untreated hypertension, smoking (60 pack-years) and alcohol abuse. During first hospitalization patient underwent chest and sinus X-rays and abdominal ultrasound examination but it did not reveal any pathologies. Patient received nephroprotective treatment. After obtaining informed consent kidney biopsy was performed. In the histopathological examination of the specimen MN was diagnosed, thus the patient's blood was tested for anti-PLA2R antibodies and the result was negative.

Due to high percentage of secondary MN in anti-PLA2R-negative patients further diagnostics was conducted. The patient had negative results for HBV, HCV and HIV. Computed tomography of ab-

domen and pelvis showed a 11 mm contrast-enhancing lesion protruding into the bladder lumen without lymphadenopathy. Proposed surgical treatment was transurethral resection of bladder tumor (TURBT) with adjuvant intravesical doxorubicine. In the days following the surgery daily proteinuria decreased to 7 grams. Histopathological examination after TURBT revealed non-muscle invasive bladder cancer – urothelial type pT1HG+Cis. According to the EAU Guidelines on NMIBC in all T1 tumors restaging resection (reTURBT) should be performed within 2-6 weeks. Histopathological examination of the tissue obtained after reTURBT revealed residual disease pT1HG. Due to high risk of recurrence and progression of the bladder cancer the patient was qualified for BCG intravesical therapy (scheme 6+3). Patient had still daily proteinuria of 5 grams. 10 months later (6 months after finishing BCG therapy) the recurrence of the tumor was observed and the patient underwent cystoscopy with subsequent TURBT (pT1HG). Due to BCG failure, high risk of progression, possibility of understaging and insufficient effect of MN treatment, patient was qualified to radical cystectomy with Bricker ileal conduit urinary diversion. Histopathological examination did not reveal cancer tissue in the bladder – also in the detrusor muscle layer- what confirmed the completeness of last TURBT. After surgery, improvement of urinary protein loss was observed. One-year after surgery. In four-year follow-up no recurrence nor distant metastases were observed, kidney function was within normal limits (serum creatinine 0.95 mg/dl, eGFR=82.6 ml/min/1.73 m<sup>2</sup>) and urinalysis did not reveal proteinuria.

## Discussion

Membranous nephropathy, which is one of the most common cause of nephrotic syndrome in adults, in one fourth of patients is secondary to other factors [1,4,11]. It has a recognizable association with neoplasms. Leeaphorn et al. underline that only 20% of patients had a diagnosis of the cancer before a diagnosis of MN, while the remainder of patients had a diagnosis of the cancer following the MN [3], what seems to be especially important during diagnostics and management of patients with MN.

According to Lefaucheur et al. patients with MN secondary to malignancy are older and more often heavy smokers. More importantly, the number of inflammatory cells infiltrating glomeruli was significantly higher in the group of patients with cancer-associated MN [2]. Another important factor which helps in distinguishing the idiopathic from the secondary cause is measuring anti-PLA2R antibodies [9]. Positive anti-PLA2R antibodies seem to be pathognomonic for the idiopathic MN while negative result increases the risk of MN secondary to malignancy [10]. Described patient was a smoker and had a negative result of anti-PLA2R, what also confirms the secondary type of MN. In such cases the immu-

nosuppressive treatment (e.g. steroids and cyclosporin A) is not recommended, as it does not cause clinical remission. Patient management should be focused on active searching and treatment of the primary disease [4].

Authors suggest that cancers may be responsible for 10% of all MN out of which the most common are solid tumors, such as lung cancer, prostate cancer, renal cancer and colorectal cancer, but hematologic malignancies were also a significant group [2,3,12]. However, reporting the association between bladder cancer and MN is seldom. This is to our best knowledge the third case report of MN secondary to urothelial carcinoma. Reshi et al. presented a case report of a 50-year-old male, whose tumor resection entailed the disappearance of proteinuria in 4 weeks [13]. Fabbian et al. reported a case report of a 75-year-old patient, who suffered from recurrent bladder tumor and MN. Improvement of proteinuria was observed in 3-4 weeks after each of four TURBTs, whilst the steroid treatment was unrelated to this improvement [14]. Our patient had an improvement in daily urinary protein excretion after initial TURBT and during the BCG therapy, however it was not satisfactory (5 grams per day after BCG therapy). In our case satisfactory daily proteinuria was not achieved until radical treatment (radical cystectomy).

However, the decision of radical cystectomy was not the easy one. Histopathological examination result after first TURBT (pT1HG+Cis) effected in placing our patient in the subgroup of highest risk tumors [6]. According to the EORTC scoring system patient had 24% and 46% of probability of recurrence at 1 and 5 years respectively and 17% and 45% of probability of progression to muscle-invasive bladder cancer at 1 and 5 years respectively [15]. Moreover, in patients with high grade tumor there is the highest risk of residual disease [16]. Our patient underwent reTURBT and had a positive histopathological examination of reTURBT specimen. After BCG failure, which is defined as any recurrence of high-grade tumor after completion of BCG therapy [6], radical cystectomy should be offered to the patient [6,17] because the cancer specific survival is better in this group than in patients who underwent radical cystectomy after the progression to muscle invasive bladder cancer [18]. Though radical cystectomy is a kind of treatment which significantly impacts patients quality of life. One should remember that bladder preservation strategies should be considered oncologically inferior to radical cystectomy [19]. Furthermore, in the presented case report patient still did not achieve the satisfactory daily proteinuria level, so he agreed for the proposed surgical treatment, which not only relieved him from the bladder cancer, but also removed the proteinuria.

To conclude, this is to our best knowledge the third case report of MN secondary to bladder cancer. While diagnosing MN, one should always remember that it may be secondary to cancer, especially when patient is a heavy smoker or has

a negative result of anti-PLA2R antibodies. Treating the primary cause may conduce to the improvement of proteinuria.

#### References

1. **Glassock RJ:** Diagnosis and natural course of membranous nephropathy. *Semin Nephrol.* 2003; 23: 324-332.
2. **Lefaucheur C, Stengel B, Nochy D, Martel P, Hill GS. et al:** Membranous nephropathy and cancer: Epidemiologic evidence and determinants of high-risk cancer association. *Kidney Int.* 2006; 70: 1510-1517.
3. **Leeaphorn N, Kue-A-Pai P, Thamcharoen N, Ungprasert P, Stokes MB, Knight EL:** Prevalence of cancer in membranous nephropathy: A systematic review and meta-analysis of observational studies. *Am J Nephrol.* 2014; 40: 29-35.
4. **Ponticelli C, Glassock RJ:** Glomerular diseases: membranous nephropathy -a modern view. *Clin J Am Soc Nephrol.* 2014; 9: 609-616.
5. **Beck LH Jr, Bonaglio RG, Lambeau G, Beck DM, Powell DW. et al:** M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med.* 2009; 361: 11-21.
6. **Timmermans SA, Ayalon R, van Paassen P, Beck LH Jr, van Rie H. et al:** Anti-phospholipase A2 receptor antibodies and malignancy in membranous nephropathy. *Am J Kidney Dis.* 2013; 62: 1223-1225.
7. **Poletajew S, Biernacki R, Buraczynski P, Chojnacki J, Czarniecki S. et al:** Stage of bladder cancer in Central Europe - Polish perspective. *Neoplasma* 2016; 63: 642-647.
8. **Babjuk M, Böhle A, Burger M, Capoun O, Cohen D. et al:** EAU Guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2016. *Eur Urol.* 2017; 71: 447-461.
9. **Segal R, Yafi FA, Brimo F, Tanguay S, Aprikian A, Kassouf W:** Prognostic factors and outcome in patients with T1 high-grade bladder cancer: can we identify patients for early cystectomy? *BJU Int.* 2012; 109: 1026-1030.
10. **Willis DL, Fernandez MI, Dickstein RJ, Parikh S, Shah JB. et al:** Clinical outcomes of cT1 micropapillary bladder cancer. *J Urol.* 2015; 193: 1129-1134.
11. **Karkoszka H, Więcek A, Perkowska-Ptasińska A:** [Membranous nephropathy. Pathophysiology, morphology and recommendations concerning diagnosis and treatment]. *Nefrol Dial Pol.* 2016; 20: 62-70.
12. **Bacchetta J, Juillard L, Cochat P, Droz JP:** Paraneoplastic glomerular diseases and malignancies. *Crit Rev Oncol Hematol.* 2009; 70: 39-58.
13. **Reshi AR, Mir SA, Gangoo AA, Shah S, Bandy K:** Nephrotic syndrome associated with transitional cell carcinoma of urinary bladder. *Scand J Urol Nephrol.* 1997; 31: 295-296.
14. **Fabbian F, Rizzioli E, Catalano C:** Membranous glomerulonephritis and transitional cell carcinoma, improved proteinuria after each tumor resection. *G Ital Nefrol.* 2003; 20: 65-68.
15. **Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffieux C. et al:** Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol.* 2006; 49: 466-475.
16. **Bialek Ł, Zapala P, Niewczas A, Poletajew S, Dybowski B, Radziszewski P:** Identification of patients who benefit most from restaging resection of bladder cancer. *Europ Urol Suppl.* 2016; 15: 1478-1479.
17. **Zehnder P, Thalmann GN:** Timing and outcomes for radical cystectomy in non-muscle invasive bladder cancer. *Curr Opin Urol.* 2013; 23: 423-428.
18. **Herr HW, Sogani PC:** Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol.* 2001; 166: 1296-1299.
19. **Yates DR, Brausi MA, Catto JW, Dalbagni G, Rouprêt M. et al:** Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer. *Eur Urol.* 2012; 62: 1088-1096.