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ASSOCIATION BETWEEN MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS AND COLORECTAL CANCER – A CASE REPORT

Galina Severova[1], Vlatko Karanfilovski[1], Ljupka Naunovska[1], Sabir Suleyman[1], Zaklina Sterjova Markovska[1], Nikola Gjorgjievski[1], Ana Stojanoska Severova[1], Pavlina Dzekova-Vidimliski[1], Vesna Ristovska[1], Irena Rambabova-Bushljetik[1], Ljuben Arsenkov[2], Gordana Petrushevska[3]

[1] University Clinic of Nephrology, Faculty of Medicine, "Ss. Cyril and Methodius", University in Skopje, RN Macedonia

[2] Department of Abdominal Surgery, University Surgery Hospital "St. Naum Ohridski", 1000 Skopje, RN Macedonia

[3] Institute for Pathology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Skopje, RN Macedonia

Corresponding author:Vlatko Karanfilovski, MD, University Clinic of Nephrology, Str. Mother Teresa 17, 1000 Skopje, Republic of N. Macedonia, Phone number: 00389 71 380 466, e-mail: vlatko1994@live.com

ABSTRACT

Membranoproliferative glomerulonephritis (MPGN) is a rare glomerular disease characterized by mesangial hypercellularity and thickening of the glomerular basement membrane (GBM). MPGN can be idiopathic or associated with malignancy, systemic immune complex disorders and chronic infections. It has rarely been associated with solid organ tumors, such as lung, gastric, breast or prostate cancer. We report a patient with MPGN and coexisting colorectal carcinoma.

A 48-year-old man presented with anemia, loss of weight, hypertension, and nephrotic syndrome. The renal biopsy findings were compatible with type 1 MPGN. The antineutrophilic cytoplasmic antibodies, antinuclear antibodies, anti-GBM, serologic markers of hepatitis B and hepatitis C and tumor markers were negative. After ruling out the secondary causes of MPGN, the patient was treated with pulse doses of methylprednisolone and a single dose of cyclophosphamide. However, due to the worsening anemia and rectal bleeding, a colonoscopy was performed, which established a diagnosis of adenocarcinoma of the descending colon. The patient was treated with left hemicolectomy and oral corticosteroids. Within a year after the cancer treatment, the patient experienced a complete resolution of the proteinuria and improvement of the kidney function.

Although rare, MPGN can be associated with hematologic malignancies and solid organ tumors. The most common causes of secondary MPGN should be ruled out before starting specific treatment. In our patient, cancer treatment has led to a subsequent remission of the nephrotic syndrome, which indicated that this association was not coincidental but rather causal. In patients with a tumor and concomitant glomerulopathy which is suspected to be paraneoplastic in etiology, the treatment of the underlying malignancy should be prioritized.

Keywords: Membranoproliferative glomerulonephritis; nephrotic syndrome; colorectal carcinoma

BACKGROUND

Glomerular disorders are common in cancer patients and may occur as a paraneoplastic condition or as a result of treatment with different chemotherapeutic agents [1]. Malignant or lymphoproliferative disease has been reported in up to 11% of adult patients with nephrotic syndrome either

at the time of diagnosis or during the follow-up period [1,2]. Membranous glomerulonephritis (MGN) is the most common malignancy-related glomerular disease, found in approximately 75% of the patients with solid tumors and glomerulopathy [1-3]. Membranoproliferative glomerulonephritis (MPGN) is characterized by mesangial hypercellularity and thickening of the glomerular basement membrane (GBM) [2]. Etiologically, MPGN can be idiopathic or secondary to malignancies, systemic immune complex disorders and chronic infections. It could be divided into three pathohistological types: type I (subendothelial and mesangial deposits), type II (intramembranous deposits) and type III (subendothelial and subepithelial deposits) [2]. MPGN has rarely been associated with solid organ tumors, such as lung, gastric, breast or prostate cancer [3-5]. To our knowledge, MPGN related to colon cancer has been reported only in few cases [6]. Here, we present a patient with MPGN and coexisting colorectal carcinoma. The treatment of the colon cancer led to improvement of the kidney function.

CASE PRESENTATION

A 48-year-old man presented with anemia, loss of weight, worsening hypertension, and bilateral pedal edema. Initial laboratory findings revealed normal serum creatinine level and nephrotic syndrome with 24-hours proteinuria of 15 g/day (reference range <0.2 g/day), serum albumin of 22g/L (reference range 35-50 g/L), hyperlipidemia (total cholesterol 7.37 mmol/L; reference range <5.5 mmol/L) and hypocomplementemia (serum C3 level of 0.35 g/L; reference range 0.8-1.4 g/L). These findings along with the clinical presentation indicated a necessity of performing a renal biopsy. The histopathological analysis showed lobular appearance of the glomeruli with mesangial expansion, hypercellularity and endocapillary proliferation, without hyaline deposits in capillary loops and no segmental sclerosis. The light microscopy and subsequent electron microscopic evaluation set the diagnosis of type 1 MPGN (Figure 1).

Other relevant investigations including antineutrophilic cytoplasmic antibodies (p-ANCA and c-ANCA), antinuclear antibodies (ANA), anti-double-stranded DNA, anti-GBM, serologic markers of hepatitis B and hepatitis C and tumor markers: PSA – 1.47 µg/L (reference range <4 µg/L), CYFRA 21-1 – 3.51 µg/L (reference range <3.3 µg/L), CA 19-9 – 14.17 U/mL (reference range <37 U/mL) resulted negative. ChestX-ray scan was made because of the slightly elevated CYFRA 21-1, but it showed no pathological findings.

After excluding the most common causes of secondary MPGN, the patient was diagnosed

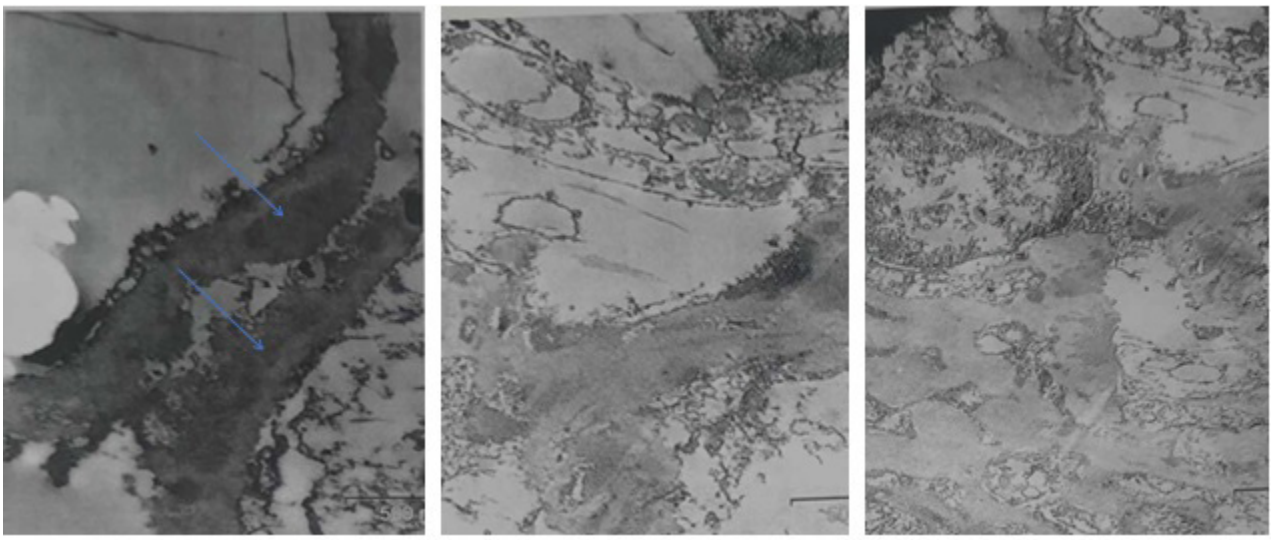


Figure 1. *Electron microscopic analysis showed increased mesangial cellularity with irregularly thickened glomerular basement membrane (GBM) with interposed cells and double contours of GBM (blue arrows in the left image, magnification 1500x). Ultrastructurally, a smaller number of subendothelial and subepithelial deposits are also present (Image in the middle, magnification 1500x, and image on the right, mag 1500x)*

Table 1. *Dynamics of biochemical findings during treatment and follow-up period*

	first appointment	renal biopsy	pulse doses of MP for 3 consecutive days	single dose of CTX		control appointment
Laboratory parameters	15th January 2022	15th March 2022	12th April 2022	18th April 2022	10th May 2022	14th November 2023
Hemoglobin (ref. 120-180g/L)	107	96	86	88	60	137
Erythrocytes (ref. 4.2 – 5.5 x 10^{12}/L)	4.47	3.59	3.04	3.13	2.34	4.67
Leukocytes (ref. 4 – 9 x 10^{9}/L)	8.1	8.9	9.5	12.9	13.5	11.2
Thrombocytes (ref. 150 – 450 x 10^{9}/L)	540	510	462	447	469	291
Albumin (ref. 35 – 50g/L)	22	23	22	20	26	47
Total proteins (ref. 63 – 83g/L)	45	45	38.95	36	47	73
Urea (ref. 2.7 – 7.8 mmol/L)	3	5.2	6.56	9.9	10	5.7
Creatinine (ref. 45 – 109 umol/L)	84.5	90.8	103.99	86	99	77
24h – proteinuria (ref. 0.2- g/L)	15.02		5.306	21.096	11.42	0.299
Triglycerides (ref. <2mmol/L)	2.54					1.08
Total cholesterol (ref. <5.5mmol/L)	7.37					4.6
HDL cholesterol (ref. 0.9 – 2.0 mmol/L)	1.40					1.70
LDLcholesterol (ref. 2.2 – 3.7 mmol/L)	4.82					2.4
Glucose (ref. 3.5 – 6.1mmol/L)	5.6		9.6	4.47	5.8	8.7
D – dimers (ref.<0.50mg/L)	4.02					
Complement C3 (ref. 0.8 – 1.4g/L)	0.35					
Complement C4 (ref. 0.2 – 0.5g/L)	1.49					
CRP (ref. <6mg/L)	1.69	2.8	2.6	0.8	0.5	0.80
PSA (ref. <4.0 µg/L)	1.47					
CYFRA 21-1 (ref. <3.3 µg/L)	3.51					
CA-19-9 (ref. <37.0U/mL)	14.17					

as primary type 1/3 MPGN at that time, and was treated with pulse doses of methylprednisolone combined with cyclophosphamide. One month after the initiation of the treatment and before the second dose of cyclophosphamide, the patient presented with melena and worsening anemia (hemoglobin of 60g/L; reference range 120-189 g/L). A colonoscopy with biopsy was performed which established the diagnosis of adenocarcinoma of the descending colon. The patient was surgically treated with left hemicolectomy and creation of preventive colostomy, without a need of additional radiotherapy or chemotherapy.

After the surgical intervention, the treatment with oral corticosteroids continued with gradually decreasing the dosage. Within a year after the cancer treatment, the patient experienced a complete resolution of the proteinuria and improvement in the clinical status (Table 1).

DISCUSSION

Glomerular lesions manifested with nephrotic syndrome are well described in association with various malignant diseases [1]. Nephrotic syndrome appeared prior to the diagnosis of cancer in approximately 40% of patients, at the time of diagnosis in 40% of patients, and after diagnosis in 20% of patients [7]. Although it is difficult to estimate the true prevalence of glomerular lesions among cancer patients, Birkeland et al. in a retrospective analysis of 1958 patients from Danish renal biopsy registry and oncological registry found that 102 patients (5.2%) with biopsy-proven glomerulonephritis developed cancer during the 5-years follow-up period. The risk of cancer among patients with glomerulonephritis was 2.5 and 3.5 times higher than in the general population at 1 and 2 years, respectively, but it was the same at 5 years after biopsy, which might suggest that this association is not related to applied immunosuppressive therapy, but rather secondary to a complex interplay between oncogenesis and glomerular pathology [8].

Membranous nephropathy was the most common cause of paraneoplastic nephrotic syndrome in patients with solid tumors, but with minimal disease change, MPGN, IgA nephropathy, focal and segmental glomerulosclerosis, amyloidosis, and thrombotic microangiopathies might be also seen [7]. The association between MPGN and solid tumors is very rare, although there are several reports of various carcinomas, including prostate, lung, and thyroid carcinoma related to MPGN [3-5,7]. The most commonly associated malignancy with MPGN is chronic lymphatic leukemia [9]. Although colorectal cancer is relatively common, in the literature, there are only several reports of colorectal carcinoma associated with MPGN: one of them was in a patient with non-metastatic colon cancer, and the other two were in patients with metastatic disease [1,6,7]. Our case describes a patient who was diagnosed with colorectal cancer shortly after the diagnosis and initiation of the treatment for biopsy-proven MPGN.

There are three theories that have been suggested to explain the possible pathogenesis of tumor-associated glomerulonephritis: 1) an undiagnosed malignancy associated with antigen deposition may have caused glomerular disease-like paraneoplastic syndrome; 2) immunosuppressive therapy used in glomerular disease may trigger carcinogenesis; and 3) viral infection may have induced both glomerulopathy and cancer by: intrinsic viral oncogenic activity; disrupted renal clearance of the biological mediators associated with carcinogenesis; or both [1]. In our patient, MPGN could have occurred idiopathically or in association with colorectal carcinoma. However, remissions of proteinuria after the treatment of the carcinoma suggest that there was an etiologic association between the colorectal cancer and MPGN rather than an incidental finding.

Clinically, it is difficult to differentiate primary MPGN from secondary MPGN associated with solid tumors. In significant number of patients with malignancy-associated nephropathy, nephrotic syndrome appears prior to the diagnosis of malignancy and it is the reason to search for possible occult underlying malignancies [8,9]. This is the reason why secondary MPGN should be ruled out before starting a specific treatment. In our case, none of the initial tests indicated a secondary form of MPGN, however, the persistence of anemia and gastrointestinal complaints prompted us to perform a colonoscopy which set the diagnosis of colorectal cancer.

Previous reports have shown that curing the malignancy remains the first option for treating an associated nephropathy. In cases with persistent nephrotic syndrome after cancer treatment or in cases with an inoperable tumor, immunosuppression can be the alternative treatment [3,6]. Our

patient was treated with left hemicolectomy combined with the usage of oral corticosteroids. The treatment of the cancer has led to a subsequent remission of the nephrotic syndrome.

CONCLUSION

We report a case of primary adenocarcinoma of the colon associated with biopsy-proven MPGN presented with nephrotic syndrome. The diagnosis of both conditions was made in a short period and the treatment of cancer led to the resolution of MPGN, which suggested a close etiological interplay between both diseases. The most common causes of secondary MPGN should be ruled out before starting a specific treatment. Clinicians should always think about the possible paraneoplastic nature of the presenting nephropathy. In patients with a tumor and concomitant glomerulopathy, which is suspected to be paraneoplastic in etiology, the treatment of the underlying malignancy should be prioritized. If curing of the cancer is impossible, then prednisolone is an appropriate treatment for resolution of the proteinuria.

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Резиме

АСОЦИЈАЦИЈА НА МЕМБРАНОПРОЛИФЕРАТИВЕН ГЛОМЕРУЛОНЕФРИТИС И КОЛОРЕКТАЛЕН КАРЦИНОМ – ПРИКАЗ НА СЛУЧАЈ

Галина Северова[1], Влатко Каранфиловски[1], Љупка Науновска[1], Сабир Сулејман[1], Жаклина Штерјова Марковска[1], Никола Ѓорѓиевски[1], Ана Стојаноска Северова[1], Павлина Џекова Видимлиски[1], Весна Ристовска[1], Ирена Рамбабова Бушљетиќ[1], Љубен Арсенков[2], Гордана Петрушевска[3]

[1] Универзитетска клиника за нефрологија, Медицински факултет, „Св. Кирил и Методиј“, Скопје, РС Македонија

[2] Одделение за абдоминална хирургија, Универзитетска хируршка болница „Св. Наум Охридски“ Скопје, РСМакедонија

[3] Институт за патологија, Медицински факултет, „Св. Кирил и Методиј“, Скопје, РС Македонија

Мембранопролиферативниот гломерулонефритис (МПГН) е ретко гломеруларно заболување, кое се карактеризира со мезангијална хиперцелуларност и задебелување на гломеруларната базална мембрана (ГБМ). Етиолошки МПГН може да биде идиопатски или асоциран со малигнитет, системски заболувања на имуни комплекси или хронични инфекции. Ретко МПГН е засоцирана со тумори на солидните органи, како белодробен, желудочен, карцином на дојка и простатичен карцином. Овде даваме приказ на пациент со МПГН и истовремено присутен колоректален карцином.

48-годишен маж се презентираше со анемија, губиток на тежина, хипертензија и нефротски синдром. Бубрежната биопсија беше со наод во прилог на МПГН тип I. Антинеутрофилните цитоплазматски антитела, антинуклеарните антитела, анти-ГМБ, како и серолошките маркери за хепатит Б и хепатит Ц беа негативни. Откако се исклучија најчестите причини за секундарен МПГН, пациентот беше третиран со пулсни дози на метилпреднизолон и единична доза циклофосфамид. Сепак, поради влошување на анемијата и појава на ректално крвавење, беше направена колоноскопија и се постави дијагноза за аденокарцином на десцендентен колон. Кај пациентот беше направена хемиколектомија лево и се продолжи со орални кортикостероиди. Во периодот на една година од третманот на малигномот, кај пациентот имаше комплетно повлекување на протеинуријата и подобрување на бубрежната функција.

Иако ретко, МПГН може да биде асоцирана со хематолошки малигнитети и тумори на солидните органи. Најчестите причини за секундарна форма на МПГН треба да бидат исклучени пред да се започне со специфична терапија. Кај нашиот пациент лекувањето на карциномот доведе до истовремена ремисија на нефротскиот синдром, што укажува дека оваа асоцијација не е случана, туку повеќе причинско-последична. Кај пациентите со тумор и истовремено присутна гломерулопатија, за која постои сомнение дека е со паранеопластична етиологија, треба да се даде приоритет на лекување на малигнитетот.

Клучни зборови: мембранопролиферативен гломерулонефритис; нефротски синдром; колоректален карцином