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Case report

Membranous Nephropathy as a Paraneoplastic Syndrome in A Patient with Ovarian Serous Cystadenofibroma - Case Report

Ana Stojanoska[1], Nikola Gjorgjievski[1], Stojanoska-Godjoska Simona[2], Svetlana Pavleska-Kuzmanovska[1], Galina Severova[1], Lada Trajceska[1], Irena Rambabova-Bushljetic[1], Vladimir Pushevski[1], Biljana Gerasimovska[1], Vesna Ristovska[1] and Goce Spasovski[1]

[1]University Department of Nephrology, [2]Institute of Pathology, Faculty of Medicine, Ss. Cyril and Methodius University of Skopje, Skopje, Republic of North Macedonia

Abstract

The nephrotic syndrome (NS) has been associated with a variety of malignancies in several numbers of literature reports but has been reported in only nine cases associated with ovarian neoplasms so far. Particularly, the ovarian serous cystadenofibroma has not been described so far anywhere in the literature. We describe a case of a 46-year-old woman presented in our Nephrology Department, with biopsy-proven membranous nephropathy, most probably secondary to ovarian serous cystadenofibroma. The surgery (bilateral adnexectomy) and pulse treatment with corticosteroids, led to remission of the NS. To the best of our knowledge, this is the first report of an ovarian serous cystadenofibroma associated with membranous nephropathy, with remission of the NS after tumor removal and pulse steroid treatment.

Keywords: nephrotic syndrome, membranous nephropathy, paraneoplastic syndrome, resolution of nephrotic syndrome

Introduction

The nephrotic syndrome (NS) has been associated with a variety of malignancies in several reports in the literature but has been reported in only nine cases associated with ovarian neoplasms so far. The relationship between glomerulopathy and tumor pathology was first described in 1922 by Galloway [1] in a patient with Hodgkin's disease who developed massive proteinuria. This association was confirmed in 1966 by Lee *et al.* who found 11 patients with cancer in a cohort of 101 patients with a nephritic syndrome [2]. The most common renal pathology in these patients was membranous nephropathy (MN) with deposition of the immune complex [3].

Tumors as an important source of antigens may induce the production of specific antibodies forming immune complexes subsequently deposited in the kidneys. Another hypothesis is that antigens with a high affinity for basement membrane constituents can get implanted directly into the renal tissue and induce the formation of immune complexes with circulating antibodies [2]. These two mechanisms would explain the role for chemotherapy or surgery in the reversal of the glomerular injury in these settings.

We present a patient with a benign ovarian tumor (serous cystadenofibroma) who suffered from nephrotic syndrome. To the best of our knowledge, nephrotic syndrome has not been described so far in association with serous cystadenofibroma.

Case-report

A 46-year-old woman presented recently in our Nephrology Department with a history of progressive edema of lower extremities and ascites of 7 weeks' duration. From the comorbidities, she had arterial hypertension well controled with one antihypertensive drug for the last 10 years (Nifedipine 20-40 mg/day), and bronchial asthma since 2013. She was prescribed diuretics at the first consultation with her doctor because of the lower extremities swelling, but with no positive results at all. At her second consultation, the laboratory analysis were in favor of hypoalbuminemia (albumin 17 g/l), normal levels of serum creatinine (creatinine 51 μmol/l), normal markers od inflammation (CRP 1.3, Le 7.2), and elevated levels of tumor markers (CA 125-536.5 U/ml, CA 15-3-45.5 U/ml). The abdominal echotomography showed normal-sized kidneys with bilateral, hyperechogenic cortical texture, and also, an ascites presentation. The abdominal CT showed abnormal mass finding on the right ovary. Thereafter, she was hospitalized in the Gynecology and Obstetrics Department, where bilateral adnexectomy was performed as per protocol. Postoperative course was uneventful. During the hospitalization, massive proteinuria was confirmed twice before surgery (30 g/24h; 46 g/dU). The anti-glomerular basement membrane antibodies (anti-GBM) were nega-

Correspondence to: Ana Stojanoska, University Department of Nephrology, "Mother Teressa" 17 str, 1000 Skopje, R. N. Macedonia; Mobile : +38978355944 ; E-mail: stojanoska.ana@hotmail.com

tive, and the results from the anti-nuclear antibodies (ANA) and anti-neutrophil cytoplasmatic antibodies (ANCA) were in reference values. The chest X-ray showed no abnormality. Serous cystadenofibroma was the histological diagnosis obtained from the Pathology department. The persistence of edema and massive proteinuria after surgery indicated further need for evaluation and treatment in our Nephrology Department. After a careful nephrological workup, a decision for renal biopsy (RB) to determine the precise direction of further treatment, was considered. A diagnosis of NS, most probably MN was suspected. While waiting for the histopathological renal biopsy finding, the patient received pulse treatment of 500 mg of methylprednisolone (for 3 consecutive days, tapering the dose in the following days). She was initially treated with diuretics and supplemented with albumin/plasma due to the persistent hypoproteinemia and hypoalbuminemia. After the corticosteroid pulses, the levels of proteinuria slowly reduced being 11.5g/24h at the hospital discharge. During hospitalization, the histology confirmed features of membranous nephropathy, and the patient continued with oral corticosteroids (Decortin 40 mg/day). Within three weeks of the tumor resection, edema disappeared and serum albumin started to improve. We strongly advised further follow up under treatment of this patient, and anticipate the remission of her nephrotic status in around 6 months after surgery.

Discussion

Different types of glomerular diseases may be associated with tumors. Paraneoplastic NS could be due to MN as presented in our case, minimal change disease, focal segmental glomerulosclerosis, or amyloidosis [4]. Despite the hypothesis of tumor proteins presenting as antigens inducing antibodies to immune complexes formed in the basement membrane, it could not have been certainly established. Additionally, an enhanced immune reaction triggered by the tumor itself may be required in the development of MN. Another hypothesis is that certain antigens with a high affinity for the basement membrane get implanted in situ and form immune complexes with circulating antibodies. On the other hand, a theory of persistent virus load causing primarily glomerulonephritis and then malignancies, perhaps through common pathogenesis has been also established. Several histological characteristics by immunofluorescence and electron microscopy may help to distinguish between idiopathic and secondary forms of membranous nephropathy [4]. Presence of immunoglobulin G, IgG1 and IgG2 subtypes, is more marked in the kidneys of patients with paraneoplastic membranous nephropathy than in those with idiopathic membranous nephropathy due to activation of both Th1 and Th2 cytokines which may be activated by tumor antigens or other stimulants, resulting in the unique pattern of IgG subtype and increased numbers of inflammatory cells [5]. That glomerulopathy is due to the malignancy and supported by the fact that remission occurs after treatment of the primary etiology (surgical excision or chemotherapy) and relapse of proteinuria occurs after a recurrence of the tumor [5]. Remission of the paraneoplastic nephrotic syndrome was described at various times after the resection of tumors, which is connected with immunological dysregulation in the course of neoplastic disease [6]. Ovarian tumors can be associated with membranous nephropathy, as described in Table 1.

Based on this literature, remission of the NS was seen in 6 cases that experienced successful treatment of an ovarian tumor. In only 3 cases, the association of the paraneoplastic syndrome was with a benign form of a neoplasm [2,9,12], among the other 5 that are connected and explained by the presence of malignancy [2,7,8, 10,11] One out of five patients having the malignant type, obtained remission of NS only by excision and steroid treatment [1]. On the other hand, two out of three patients having the benign form reached to remission by extracting the tumor together with corticosteroids [9,12], without the need of chemotherapy as well. In contrast to these findings, remission of the NS was not achieved in two patients with ovarian tumor (adenocarcinoma and benign teratoma) even though one of them was treated with prednisone and tumor excision as per recommendations [2]. In our patient, the surgical resection of the ovarian tumor and corticosteroid treat-

Table 1. Evidence of ovarian tumors associated with MN

Authors	Age	Kidney histology	Ovarian tumour type	Treatment			Response of NS
				Surgery	Steroid	Chemotherapy	
Lee *et al*. [2]	65	MN	Adenocarcimona	No	No	No	No
Lee *et al*. [2]	28	MN	Benign teratoma	Yes	No	Yes	No
Torres *et al*. [7]	N/A	MN	Adenocarcinoma	Yes	N/A	Yes	Yes
Hoyt *et al*. [8]	65	MN	Papillapy serous carcinoma	Yes	Yes	N/A	Yes
Jeroydi *et at*. [9]	36	MN	Benign mature cyst teratoma	Yes	No	Yes	Yes
Forgy *et al*. (10)	68	MN	Serous adenocarcinoma	Yes	Yes	No	Yes
Ata *et al*. [11]	65	MN	Clear cell carcinoma	Yes	Yes	Yes	Yes
Kilis-Pstrusinka *et al*. [12]	16	MN	Benign mature teratoma	Yes	No	Yes	Yes

ment [13] resulted in brisk remission of the nephrotic syndrome although we would underline that methylprednisolone alone is not supported by evidence, or by KDIGO guidelines with good effect in MN. The possibility of a coincident occurrence of these conditions cannot be completely ruled out. However, considering the patient's age, the lack of other causes of nephrotic syndrome, the consecutive association between tumor diagnosis and the onset of symptoms as well as the remission of the NS following treatment of the ovarian mass seems to be a reasonable consideration.

Conclusion

Association of the NS with benign ovarian tumors is very rare, with currently available reports from three cases. Ovarian serous cystadenofibroma precisely has not been described so far anywhere in the literature. Paraneoplastic NS has membranous glomerulonephritis as its most common pathology. Possible hypotheses include immune complex reactions induced by either tumor antigen or viral infection. In our case, remission of the NS occurred after excision of the tumor along with the corticosteroid treatment, support to a certain extent the etiological role of the tumor. Finally, the treatment of this kind of patients is a great challenge requiring a multidisciplinary approach.

Conflict of interest statement: None declared

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