Triple negative breast cancer and immunoglobulin A nephropathy: A case report and literature review

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Abstract. The association between malignant tumors and the occurrence of glomerular disease has been well documented in previous studies. The most common types of malignant tumor include Hodgkin's lymphoma with minimal change glomerular nephritis, solid tumor with membranous nephropathy and renal cell carcinoma with immunoglobulin (Ig)A nephropathy. The present case study describes a case of a 31-year-old Chinese female patient who was hospitalized with chronic glomerulonephritis. The patient self-administered unknown traditional Chinese medicine; however, protein excretion/24-h remained increased compared with normal levels. After 34 months, a tumor was identified in the patient. Subsequently, the patient was administered breast-conserving surgery and sentinel lymph node biopsy, which validated the diagnosis of triple negative breast cancer at stage IA (T1cN0M0). The patient received chemotherapy and radiotherapy. Following the review of the relevant studies within the last 30 years, it was demonstrated that the present report was the second documented case of breast cancer associated with IgA nephropathy. Thus, the present study hypothesized that IgA nephropathy may be a tumor manifestation in breast cancer.

Introduction

In 1922, Galloway introduced the concept of paraneoplastic glomerulopathy (1). In 1966, the association between malignant tumors and nephrotic syndrome was initially identified (2). There is a strong association between solid tumors and membranous nephropathy, Hodgkin's lymphoma and minimal kidney disease (3). Lung, gastric, breast and colorectal tumors are the most common types of malignant tumor in association with renal glomerular diseases (4). Immunoglobulin A (IgA) nephropathy is the most common type of primary

glomerulonephritis, and represents a major health challenge worldwide (5,6). In the present report, to the best of our knowledge, the second case of breast cancer associated with IgA nephropathy within the last 30 years was described. A case of triple negative breast cancer combined with proteinuria, pathologically validated focal proliferative IgA nephropathy and Lee grading III was presented. The present case was analyzed using relevant studies. The present case study was approved by the Ethics Committee of The Fourth Hospital of Hebei Medical University (Shijiazhuang, China) and the patient provided informed written consent.

Case report

History of renal disease. A 31-year-old Chinese female was hospitalized at The First Hospital of Hebei Medical University (Shijiazhuang, China) in April 2012 experiencing fever (38-39°C; normal, 36.7-37.2°C), gross hematuria and proteinuria (400 mg/24 h; normal, <150 mg/24 h), and there were no abnormalities identified on physical examination; thus, a diagnosis of chronic glomerulonephritis was validated. Between June 2012 and March 2013, the patient administered self-treatment using unknown traditional Chinese medicine and the 24-h proteinuria returned to the normal value (<150 mg/24 h). During the patient's pregnancy in June 2013, the patient experienced swollen limbs and increased blood pressure. The blood pressure increased to 180/120 mmHg (normal, <130/90 mmHg) and the highest proteinuria determined was 7 g/24 h (normal, <150 mg/24 h). All symptoms were relieved following the child's birth and the proteinuria decreased to <2 g/24 h. Over frequent monitoring (every 3 months for 2 years), no abnormalities were observed. A renal biopsy was performed on the patient in December 2014, as the proteinuria increased to 2 g/24 h.

The renal biopsy (performed in December 2015) was observed using scanning electron microscopy, which revealed capillary endothelial cell vacuolar degeneration, presence of red blood cells in the individual lumen, endothelial cells with no hyperplasia and capillary loops under stress. In addition, it was identified that the majority of the basement membrane was thickened, corrugated and coiled, and the foot processes of visceral epithelial cells were fused. Mesangial and stromal hyperplasia was accompanied with a limited number of electron dense deposits with high density. Furthermore, lymph and mononuclear cell infiltration, partial renal tubular atrophy and renal interstitial collagen fiber hyperplasia were observed.

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Red blood cells were observed in the lumens of capillaries. In addition, arteriole walls were thickened and a stenosis was identified in the lumen (Fig. 1).

Optical microscopy performed on renal biopsy sections (magnification, x400) revealed eight glomeruli, one of which was sclerotic (hematoxylin-eosin staining; Fig. 2A) and another one was segmental sclerotic (periodic acid-silver methenamine; Fig. 2B). In the remaining six glomeruli, glomerular mesangial cells were observed with mild-to-moderate stromal hyperplasia (periodic acid-Schiff; Fig. 2C). Furthermore, focal segmental exacerbation, vacuolization and granular degeneration of renal tubular epithelial cells, focal atrophy, renal interstitial focal necrosis and inflammatory cell infiltration were observed. The results of immunofluorescent staining were as follows: IgA positive (2+); and IgM, IgG, C3, C1q negative (Fig. 2D).

The patient was administered piperazine ferulate tablets (200 mg, oral, three times a day), irbesartan (150 mg, oral, once a day) and 'corbrin capsule', a traditional Chinese medicine drug made from herbs (648 mg, oral, three times a day). Subsequently, the 24-h proteinuria was controlled and levels returned to normal (<150 mg/24 h).

History of breast cancer. A tumor was initially identified by the patient in February 2015, with a diameter of 2 cm. The blood pressure of the patient was 137/91 mmHg following hospitalization at The Fourth Hospital of Hebei Medical University, but no other abnormalities were identified during physical examination. The body mass index (BMI) was calculated to be 32.95 kg/m^2 (meaning she was classified as obese) and the results of urinalysis were as follows: Proteinuria, 1.0 g/l; the number of erythrocytes was 5 times higher than normal; the number of leukocytes was within the normal range; urinary cast examination was negative; serum albumin and serum globulin ratio, 1.58 (normal value, 1.20-2.40); blood urea nitrogen, 3.7 mmol/l; (normal value, 2.8-7.1 mmol/l); and serum creatinine, 54.5 μmol/l (normal value, 44.2-132.6 μmol/l).

The patient accepted breast-conserving surgery and sentinel lymph node biopsy in February 2015. The post-surgical pathological manifestation revealed that the diameter of the left breast tumor was 1.8 cm, and that the patient exhibited breast metaplastic cancer without vascular tumor thrombus or metastasis of sentinel lymph nodes with negative margins. Immunohistochemistry results were as follows: Estrogen receptor, 0; progesterone receptor, 0; human epidermal growth factor 2, 0; p53, 60%; Ki-67 protein, 50%; type II topoisomerase, 30%; cytokeratin+; vimentin+; S-100 protein+; synaptophysin; and cluster of differentiation 56$^{-/+}$. The diagnosis of triple negative breast cancer was validated and the tumor was staged IA (T1cN0M0), according to the Tumor-Node-Metastasis staging system (7). The patient consultation at the Chinese Academy of Medical Sciences (Beijing, China), revealed that the left breast exhibited an invasive breast cancer with considerable necrosis. The patient was treated with paclitaxel (90-120 mg/m^2) for 12 weeks, followed by cyclophosphamide treatment (200 mg/m^2) for 12 weeks.

Diagnosis and treatment. The patient was initially treated with paclitaxel liposome (180 mg, intravenously, day 1).

Protein excretion increased from 121 mg/24 h prior to treatment with paclitaxel to 679 mg/24 h, which is higher than the normal level (<150 mg/24 h), for half a month. The chemotherapy was suspended and radiotherapy was administered. For the left breast and the organ at risk, the following parameters were applied: Double lung V10 (i.e., the proportion of the lung receiving 10 Gy), ≤50%; V20, ≤25-28%; and V30 ≤15-18%. The target dose was 90% CTV ≥50 Gy in 25 fractions, combining with 12-Mevβ electron beam; the dose was 1,600 cGy in 8 fractions. Following radiotherapy, seven cycles of chemotherapy with paclitaxel liposome (180 mg, intravenously, day 1) were performed. The proteinuria (≤523.5 mg/24 h) was occasionally higher than normal values during this period. At the point of writing, no recurrence of tumors was observed.

Discussion

The majority of patients with carcinomas may be complicated by glomerular diseases (4). The combined occurrence of cancer with membranous nephropathy is common (8), whereas tumors associated with IgA nephropathy have been rarely studied. The present study identified only 10 cases of malignant tumors with IgA nephropathy in a review of previous studies performed in the last 30 years. To the best of our knowledge, the first patient with breast cancer and atypical IgA nephropathy was identified in 1986 (3). Other studies included patients with IgA nephropathy with renal cell carcinoma (5,9), bronchial carcinoma (6), small cell lung carcinoma (10,11), basaloid squamous cell carcinoma (12), mesothelioma (13), rectal cancer (14) and gastric adenocarcinoma (15) identified in 1991, 1996, 1998, 2008, 2009, 2012 and 2013, respectively (Table I).

In spite of the limited number of identified cases, an association between solid tumors and IgA nephropathy has been demonstrated. The reason for this association may be the following: i) Detection bias as patients with membranous nephropathy are likely to be screened for cancer; ii) similar demographic characteristics of the population, as membranous nephropathy and cancer exhibit a higher incidence in the elderly and/or smokers; and iii) the majority of the drugs administered to treat glomerular disease may be oncogenic, which may lead to subsequent malignancy (4). Thus, these factors may lead to the lack of information about the epidemiology of cancer-associated membranous nephropathy.

The pathogenesis of tumor-associated IgA nephropathy remains unknown. A previous study demonstrated that the abundance of IgG deposits and the loss of glomerular foot processes may lead to proteinuria and glomerular damage in tumor-bearing animals (16). Previous studies using mouse models revealed that minor glomerular abnormalities may be associated with the immune response of malignant tumors (17,18). Associated antigens were released from the surface of tumor cells, thus stimulating the production of antibodies (19). Subsequently, antigen-antibody immune complexes may be formed (19). The most common type of antigen-antibody immune complex observed was self-polymeric IgA 1 in IgA nephropathy, or as a joint auto-antigen complement C3 (20). The IgG and/or IgM antibody complexes may be formed

and deposited in the glomerular mesangium. The affinity of the latter for the extracellular matrix may be increased, thus leading to glomerular lesions (20).

Although membranous nephropathy possesses similarities to solid tumors and there is a close association between minimal change disease and Hodgkin's lymphoma, there are numerous exceptions (21). Other types of glomerular damage, including glomerulonephritis, IgA nephropathy and rapidly progressive glomerulonephritis, may be associated with solid tumors (21). In addition, minimal nephrosis, membranous nephropathy, mesangioproliferative glomerulonephritis, focal segmental glomerulosclerosis and IgA nephropathy may be associated with certain types of hematological malignancy (22).

In the present case study, the principal clinical manifestation was hematuria and increased 24-hour proteinuria. Immunofluorescence staining revealed IgA deposits and inflammatory infiltration was observed in renal interstitial cells. Using our present understanding of the pathogenesis of IgA nephropathy, the present study hypothesized that the patient may exhibit a breast cancer in the early stage of IgA nephropathy, without experiencing specific symptoms. The antigen may be released from the breast tumor cells and lead to continuous antigenemia. Subsequently, the antigens may stimulate the production of antibodies and form immune complexes which are deposited in the glomeruli, resulting in glomerulonephritis. This process is likely to progress in the subclinical phase of cancer. In spite of this, due to the lack of tumor-associated antigen detection in the present and previous studies, the specific antigens involved in IgA-associated breast cancer remain unknown.

The identification of tumor-associated antigens in the glomerular lesion is required for the diagnosis of tumor-associated glomerular diseases. This diagnosis cannot be validated in the present case study on the basis of the clinical and pathological information, and may be due to the following reasons: i) The patient cannot be diagnosed with breast cancer-associated IgA nephropathy due to the absence of examination results; ii) it remains unclear whether the patient exhibited breast cancer prior to experiencing glomerular problems and whether malignancy developed due to the renal disease; and iii) tumor-associated glomerular disease can be taken into account only when tumour and renal glomerular damage concurrence and other factors which could cause glomerular damage are excluded. The diagnosis could not be determined on the basis of the initial symptoms experienced by the patient prior to kidney biopsy. The patient's initial symptoms returned after 2 years; however, although the IgA nephropathy was pathologically diagnosed, the return of symptoms may be due to reasons other than breast cancer, which were not eliminated.

The patient exhibited triple negative breast cancer and IgA nephropathy, which may exhibit a poor prognosis. Triple negative breast cancer is defined as the absence of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 gene expression (23). The principal characteristics of triple negative breast cancer are as follows: i) More aggressive with higher probability of brain metastases and recurrence during the first and third year following diagnosis than other types of breast cancer; and ii) decreased survival rate following the first metastatic event, compared
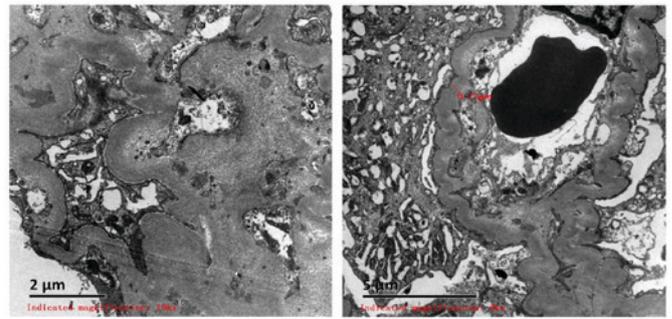

Figure 1. Focal proliferative IgA nephropathy (Lee grading, III) (27) was diagnosed using electron microscopy. In accordance with the Oxford classification (28) of IgA nephropathy, it was equivalent to M1 E0 S1 T0. IgA, immunoglobulin A.
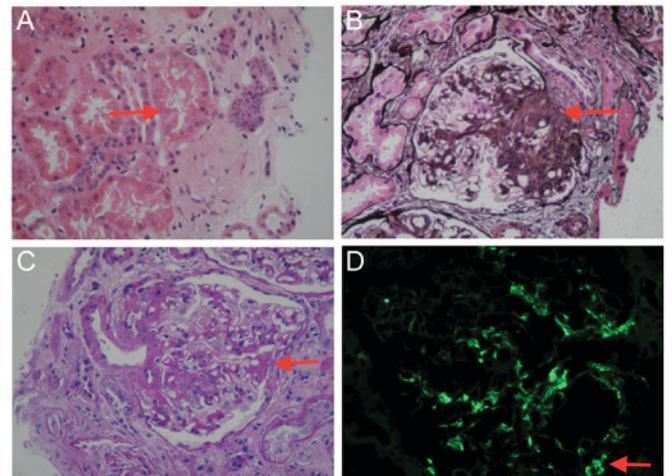

Figure 2. Pathological examination or renal tissue using optical microscopy. (A) Glomerular sclerosis indicated by hematoxylin and eosin staining. (B) Glomerular segmental sclerosis indicated by periodic acid-silver metheramine. (C) Glomerular balloon adhesion indicated by periodic acid-Shiff staining. (D) Immunoglobulin A deposition indicated by immunofluorescence detection of paraffin-embedded sections. Points of interest pertaining to each description are indicated with a red arrow. Magnification, x400.

with other subtypes of breast cancer (23). The 5-year survival rate of patients with triple-negative breast cancer was <15%, and prognosis-associated factors include the tumor size and lymph node status (23). Between 5 and 25% of patients with IgA nephropathy may develop end-stage renal disease within 10 years of the initial diagnosis. Severe obesity, hypertension, renal injury and proteinuria are associated with the prognosis of patients with breast cancer (24). The following parameters observed in the present patient indicated a risk of recurrence of breast cancer: BMI of 32.95 kg/m^2, validation of triple negative breast cancer diagnosis post-surgery, tumor size of 1.8 cm and Ki-67 positive staining of 50%. The patient was administered paclitaxel chemotherapy combined with radiotherapy, and regular monitoring of renal functions and primary diseases were performed during treatment. In addition, physical exercises and weight loss were advised by a physician to minimize the controllable risk factors, such as obesity or hypertension.

The IgA nephropathy may develop prior to, in parallel with, or following malignancy'. Certain investigators recommended

Table I. Cases of cancer associated with IgA nephropathy in the past 30 years.

Case	Author (year)	Age, years	Sex	Tumor type	Nephrosis	IHC	Sequence of two diseases	Symptoms	Therapy	Sequelae	(Refs.)
1	Yin et al (1986)	57	F	Breast cancer	IgA nephropathy (diffuse mesangial proliferative glomerulonephritis)	IgA deposits in mesangial area	ST	Hypertension, proteinuria	S	No further examination	(3)
2	Tanaka et al (1991)	61	M	Kidney cancer	IgA nephropathy	IgA, C3 and fibrin deposits	ST	Proteinuria	S	Nephrosis recovery	(5)
3	Schütte et al (1996)	45	-	Bronchial cancer	IgA nephropathy	-	NC	-	-	-	(6)
4	Tomoda et al (1998)	66	M	Small cell lung cancer/gastric cancer	IgA nephropathy	-	CN	Edema, proteinuria	S and C	Nephrosis recovery	(10)
5	Lam et al (1998)	70	M	Basaloid squamous cell carcinoma of the oesophagus	IgA nephropathy (mesangial proliferative glomerulonephritis)	IgA, C3 and IgM deposits in mesangial area	NC	Erythra, proteinuria, microscopic hematuria	S	-	(12)
6	Yacoub et al (2008)	55	M	Small cell lung cancer	IgA nephropathy	-	NC	Hypertension, microscopic hematuria	S	Succumbed	(11)
7	Mimura et al (2009)	58, 66, 59	M	Kidney cell cancer (3 cases)	IgA nephropathy	1, IgA^{++}, IgG$^-$, IgM$^-$ and C3$^+$; 2, IgA^{++}, IgG$^-$, IgM$^+$ and C3$^+$; 3, IgA^{++}, IgG$^-$, IgM$^-$ and C3$^+$	1, NC; 2, NC; 3, S	All have microscopic hematuria, proteinuria	1, C and S; 2, C and S; 3, S	1 and 3, nephrosis recovery; 2, renal failure	(9)
8	Fawole et al (2012)	65	M	Mesothelioma	IgA nephropathy	IgA^{++}, C3^{++}	CN	Short breath, dry cough, microscopic hematuria, proteinuria	CH and C	Succumbed	(13)
9	Yahata et al (2013)	68	M	Rectal cancer	IgA nephropathy	IgA^{+++}, C3^{+++}, IgG$^+$, IgM$^+$ and C1q$^+$	CN	Hematuria, proteinuria	S, CH and T	Nephrosis recovery	(14)
10	Kocyigit et al (2013)	58	M	Gastric cancer	IgA nephropathy (focal segmental glomerulosclerosis)	IgA deposits	CN	abdominal distention, loss weight	S, CH, R and C	Nephrosis recovery	(15)

Ig, immunoglobulin; IHC, immunohistochemistry; F, female; M, male; ST, simultaneous; NC, nephrosis then cancer; CN, cancer then nephrosis; S, surgery; CH, chemotherapy; R, radiotherapy; C, corticosteroids; T, targeted therapy.

that any patient with kidney lesions should be screened for cancer (11). The occurrence of malignant and membranous nephropathy should be well-documented in medical studies, particularly those associated with cancer. The strongest association was observed between membranous glomerulonephritis and solid tumors (3). A previous study estimated that ~25% patients >60 years of age with membranous glomerulonephritis experienced an associated cancer and the overall incidence of cancer in patients with membranous glomerulonephritis was 7.9% (25). However, a previous study revealed that 0.36% of patients with nephrotic syndrome exhibited an underlying malignancy (26). Additionally, it has been recommended that any patient with nephrotic syndrome >40 years of age should be screened for cancer (16). No associated guideline has been published by the Scientific Association of Nephropathy (4).

It was difficult to elucidate whether the association between breast cancer and IgA nephropathy in the present patient was a coincidence or an etiological association. In addition, whether patients with IgA nephropathy should receive cancer screening, and whether kidney disease is associated with specific types of cancer remains unknown and requires additional study.

With the approaching of precision medicine, genomics will serve an essential role in diagnosis and disease therapy. Drugs have been developed that target specific genes, enable advancements in medical technology and improve the quality of lives for patients. There is a limited number of studies that focus on kidney-disease-associated cancer treatment, in spite of targeted drugs being developed for other types of cancer. Further research into cancer genomics and identification of targeted drugs is urgent. Additional studies are required to determine the association between IgA nephropathy and cancer, and the underlying molecular mechanism. This would enable the genomics underlying IgA nephropathy-associated cancer to be determined and novel therapeutic strategies to be developed.

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