Anti-Neutrophil Cytoplasmic Antibody-Associated Glomerulonephritis and Malignancy: A Case of a Patient Diagnosed with Renal Failure and Pulmonary Carcinoma Concurrently

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ABSTRACT: A 70-year-old man presented with proteinuria, microscopic hematuria, and an increased level of serum creatinine. A systemic workup revealed that the patient had bronchogenic carcinoma and anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis concurrently. Despite the increase in the cumulative number of publications on paraneoplastic glomerulopathies, an awareness of the link between cancer and ANCA-associated glomerulonephritis is lacking. We strongly recommend the accumulation of more cases similar to our own, thereby allowing us to clarify the management strategies as well as the nature of this disease condition more precisely.

KEYWORDS: ANCA, crescentic glomerulonephritis, malignancy, paraneoplastic glomerulopathy, bronchogenic carcinoma

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There is a lack of information on anti-neutrophil cytoplasmic antibody-associated glomerulonephritis as a comorbidity in patients with malignancy. We herein report our experience with a man who was found to have the disease and bronchogenic carcinoma concurrently.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis is a characteristic clinical entity presenting with rapidly progressive deterioration of the renal function.[1] Its pathogenesis appears to be multifactorial, involving environmental exposure, infections, genetic predispositions, and the intensity and duration of the injuries as well as innate and adaptive characteristics of the immune system,[2,3] although the disease may occasionally manifest as a renal phenotype of paraneoplastic syndrome in patients complicated by malignancies.[4,5] While this pathology has been studied through multipronged approaches,[6,7] information on the link between cancer and ANCA-associated glomerulonephritis remains insufficient.[4,5]

We herein report our experience with a man who was revealed to have renal disease and bronchogenic carcinoma concurrently.

Case Report

A 70-year-old man presented at a regional general hospital because of a protracted cough and hemoptysis manifesting for the last 2 months. He had a 98-pack-year history of cigarette smoking but had quit smoking at 67 years of age. At the presentation, he was found to have 3+ proteinuria and microscopic hematuria with an increased serum creatinine (sCr) level of 3.3 mg/dL despite having no apparent history of renal disease. Ten days later, he showed an increase in the titer of anti-myeloperoxidase-ANCA (MPO-ANCA) to 33.2 U/ml, but no increase in anti-proteinase 3-ANCA or anti-glomerular basement membrane antibodies was revealed, so he was referred and admitted to our hospital for a further workup. Other medical histories included hypertension and emphysema, for which he had received sporadic medical care, while the renal parameters had not been monitored on a regular basis. No exposure to a specific environment or activity was noted.

At the time of the admission (clinical day 1), the patient had a temperature of 36.9°C, a pulse of 98 beats/minute, and a blood pressure of 155/88 mmHg. There were no rashes or petechiae. Renal sonography of both kidneys revealed the preservation of the size with slightly elevated renal cortex echogenicity, while a chest radiograph showed a round circumscribed solitary lesion at the right pulmonary hilar region, and subsequent chest computed tomography (CT) revealed a solid mass in the right upper lobe anterior segment with distinct lymphadenopathy (Figure 1). The laboratory data on admission are summarized in Table 1. A 24-hour urine specimen contained 2.4 g of protein, and his Cr clearance was 24.0 mL/minute.

A renal biopsy performed on clinical day 1 (Figure 2) revealed 3 cores of renal parenchyma with 10 glomeruli, 3 of

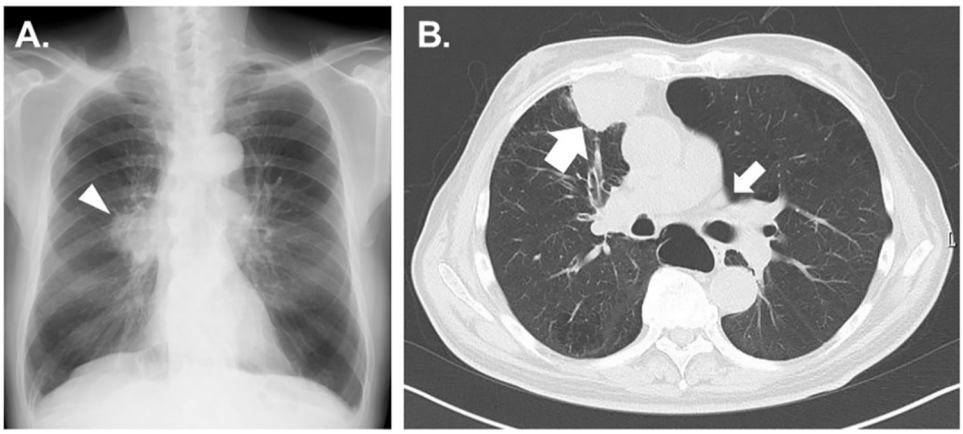

Figure 1. The radiographic findings. A conventional chest radiograph showing a solitary circular opacity (white arrowhead) in the right pulmonary hilar region (A). A chest CT image showing a well-marginated soft-tissue nodule in the right upper lobe anterior segment (wide arrow) with distinct lymphadenopathy (narrow arrow) (B).

Table 1. Laboratory data on admission.

White blood cells	9500/μL	(3900-9800)
Hb	9.8 g/dL	(13.5-17.6)
Platelet count	28.1×10^4/μL	(13.0-36.9)
Blood urea nitrogen	36 mg/dL	(8-20)
Creatinine	3.23 mg/dL	(0.63-1.03)
Total protein	8.4 g/dL	(6.9-8.4)
Albumin	3.4 g/dL	(3.9-5.1)
Sodium	140 mmol/L	(136-148)
Potassium	4.4 mmol/L	(3.6-5.0)
Chloride	104 mmol/L	(96-108)
Calcium	9.0 mg/dL	(8.8-10.1)
Phosphorus	4.1 mg/dL	(2.4-4.6)
C-reactive protein	1.14 mg/dL	(0-0.14)
IgG	2437 mg/dL	(870-1700)
IgA	565 mg/dL	(110-410)
IgM	53 mg/dL	(33-160)
C3	138 mg/dL	(86-160)
C4	33 mg/dL	(17-45)
Squamous cell carcinoma related antigen	22.4 ng/mL	(<2.1)
CEA	7.4 ng/mL	(<4.5)
NSE	34 U/mL	(<12)
CYFRA	4.6 ng/mL	(<3.5)
Pro-gastrin-releasing peptide	204 pg/mL	(<81)

The reference ranges for each parameter used at our institute are indicated in parentheses.
Abbreviations: Hb, hemoglobin; Ig, immunoglobulin; CEA, carcinoembryonic antigen; NSE, neuron-specific enolase; CYFRA, cytokeratine-19 fragments.

which were globally sclerotic. Although no evidence of vasculitis was confirmed in the blood vessels, the glomeruli showed cellular crescents with focal segmental necrotizing lesions. Marked interstitial infiltration of inflammatory cells was also noticed. An immunofluorescence analysis revealed no significant staining for C1q or fibrinogen or immunoglobulins, while electron microscopy failed to demonstrate the presence of deposits in the biopsy specimens. Thus, a diagnosis of MPO-ANCA-associated crescentic glomerulonephritis accompanied by a presumed right pulmonary neoplasm was made.

Thereafter, fluctuation in the patient's sCr level, ranging from 2.77 mg/dL to 3.00 mg/dL was noted until clinical day 11, when the patient showed a sCr level of 2.74 mg/dL and started to receive oral prednisolone (PSL) at 30 mg/day, while a transbronchial lung biopsy performed on clinical day 14 led to a clinical diagnosis of stage IIIC (T4N3M0) squamous cell lung carcinoma in accordance with the American Joint Committee on cancer-tumor-node-metastasis classification (8th edition).[8] The patient was subjected to chemotherapy consisting of paclitaxel and carboplatin on clinical day 52. Although no favorable responses were noted for the pulmonary disease, the MPO-ANCA titer became negative approximately 4 months after the renal biopsy while he was still being treated with oral PSL (10 mg/day). His sCr levels finally settled around 1.94 mg/dL, so he was never on renal replacement therapy. However, the patient ultimately died of respiratory failure 13 months after the initial presentation.

Discussion

The link between neoplasms and glomerulopathies has been recognized for decades. Solid tumor-associated membranous nephropathy and Hodgkin lymphoma-related minimal change disease have received focus as classic phenotypes of this clinical entity, but several other diseases, including membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and immunoglobulin A nephropathy, have been described as well.[4-7] The association of rapidly progressive glomerulonephritis and/

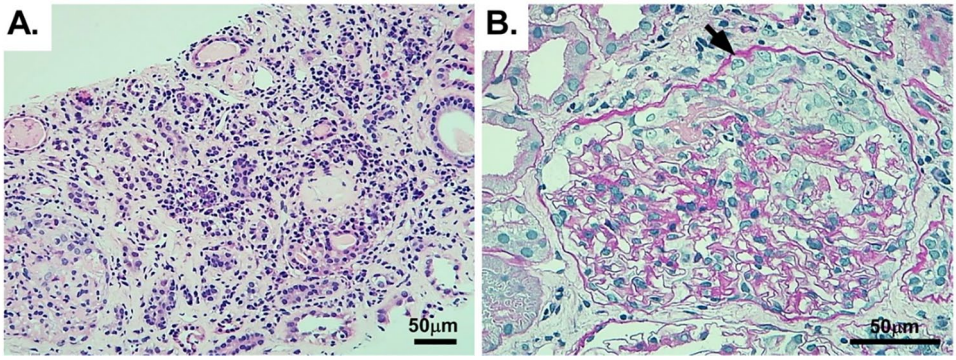

Figure 2. The renal biopsy finding. Light micrographs showed marked interstitial inflammatory infiltrates (A) and glomerulus with cellular crescent (arrow) (B). Right panel, Hematoxylin and Eosin staining, left panel, Periodic acid-Schiff staining. The scale bar is indicated in each panel.

or ANCA-associated glomerulonephritis with malignancies has also been reported anecdotally.[9-17] In this regard, the clinical scenario of the current patient, characterized by a set of conditions including a deteriorated renal function because of ANCA-associated glomerulonephritis and pulmonary carcinoma, may not be surprising. However, we feel an awareness of the link between ANCA-associated glomerulonephritis and malignancy is lacking among physicians. Furthermore, systematic studies on this topic are rare, and distinct clinical and/or pathological features that might help us differentiate the paraneoplastic subtype from primary disease have yet to be clarified, so we strongly recommend accumulating further cases similar to our own, thereby allowing us to establish optimum management strategies as well as to clarify the nature of this pathology more precisely.

The malignancies most frequently found among overall patients with paraneoplastic glomerulopathies have been adenocarcinomas of the lung and gastrointestinal tract, although other neoplastic diseases can be seen.[4,5,7,18] In contrast, a wide variety of diseases, including hematological neoplasms as well as solid tumors, such as cancers of the prostate, bladder, lung, and stomach, have been associated with ANCA-associated glomerulonephritis, with renal cell carcinoma numerically being the most common.[4,5,18] Paraneoplastic renal abnormalities and malignancies often manifest themselves within 12 months of each other,[7,18] while pulmonary cancer may appear even years after the diagnosis of ANCA-associated glomerulonephritis has been made.[17] Why ANCA-associated glomerulonephritis can occur in a paraneoplastic manner is poorly understood; however, a dysregulated inflammatory-cell response, elevation of various cytokines, and the cross-reactive nature between cancer cells and vascular endothelium in terms of antigen complementarity have been proposed as candidate mechanisms leading to this pathology.[14,16,17,19] Alternatively, or in addition, such a link may result from patient exposure to an as-yet-unidentified common risk factor shared by these 2 disease states.[17]

Given the differential diagnosis of hemoptysis,[20] we should always bear in mind that underlying diseases, including neoplasms and/or infections in the pulmonary system, can occasionally mimic ANCA-associated disease characterized by pulmonary-renal syndrome in patients with kidney failure,[21] although the diagnostic process in the present patient was straightforward. Taken together, the present and previous findings[9-17,19] actually highlight the need to explore the potential existence of underlying but as-yet-undisclosed neoplasia that later may be detected among some subsets of patients with the disease, although how thorough the search should be remains to be clarified. At present, experts recommend empirically that basic routine cancer screening procedures, including chest radiography, an occult blood survey of stool specimens, and colonoscopy, be included in the diagnostic evaluation, especially in patients with newly developed membranous nephropathy without any other obvious causes.[7,18] Sex-specific surveys, including the measurement of the prostate-specific antigen level, a careful breast examination, a mammogram, and cervical cytology as well as further investigations, including bronchoscopy, gastroscopy, and CT, may be in order after the first-line assessment.[7,18]

Decisions on the treatment for malignancy-associated renal disease should be based on the patient's general condition, and management policies are sometimes complicated;[7,22] thus, it is not surprising that the optimal therapeutic strategy remains to be established. The surgical removal of the tumor bulk may lead to remission from renal manifestations in some subsets of patients with paraneoplastic kidney injury,[7,23] although whether or not this is also the case in patients with ANCA-associated glomerulonephritis has not been explored thoroughly.[5] In contrast, it has been recommended that the administration of immunosuppressive agents be avoided when treating paraneoplastic glomerular diseases, as this may exacerbate the concurrent malignancy.[4,7] Although we failed to assess in detail whether or not the corticosteroid had an adverse effect in terms of the concomitant malignant disease in the present patient, it should be noted that there have been few systemic studies on this subject. Furthermore, there are several previous examples wherein immunosuppressive therapy successfully led to remission of ANCA-associated glomerulonephritis in patients with untreatable cancers.[10,12] Until the validity of such a policy is sufficiently evaluated, adopting individualized approaches and management is necessary. The current empirical arguments justifying the use

of immunosuppressive agents in this population may include rescuing subjects with life-threatening-conditions and/or restriction of the standard treatment approach using low dosages for several months combined with oncology consultations.[24]

Consent

Written informed consent was obtained from the patient to publish this case report and any accompanying images. The clinicians at our university are not required to obtain institutional review board approval for case reports of a single patient.

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REFERENCES

1. Berti A, Cornec-Le Gall E, Cornec D, et al. Incidence, prevalence, mortality and chronic renal damage of anti-neutrophil cytoplasmic antibody-associated glomerulonephritis in a 20-year population-based cohort. *Nephrol Dial Transplant*. 2019;34:1508-1517.
2. Charles Jennette J, Falk RJ. L1. Pathogenesis of ANCA-associated vasculitis: observations, theories and speculations. *Presse Med*. 2013;42:493-498.
3. Xiao H, Hu P, Falk RJ, Jennette JC. Overview of the pathogenesis of ANCA-associated casculitis. *Kidney Dis (Basel)*. 2016;1:205-215.
4. Bacchetta J, Juillard L, Cochat P, Droz JP. Paraneoplastic glomerular diseases and malignancies. *Crit Rev Oncol Hematol*. 2009;70:39-58.
5. Lien YH, Lai LW. Pathogenesis, diagnosis and management of paraneoplastic glomerulonephritis. *Nat Rev Nephrol*. 2011;7:85-95.
6. Akimoto T, Otani N, Takeshima E, Saito O, Kusano E, Nagata D. Do we have to perform a renal biopsy? Clinical dilemmas in a case with nephrotic syndrome. *Clin Med Insights Case Rep*. 2014;7:67-70.
7. Nagayama I, Akimoto T, Ono Y, Ueda Y, Nagata D. Remission of nephrotic syndrome after surgical intervention for bronchogenic carcinoma: the 10-year follow-up of a patient with membranous nephropathy. *Int Med Case Rep J*. 2018;11:167-171.
8. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151:193-203.
9. Biava CG, Gonwa TA, Naughton JL, Hopper J Jr. Crescentic glomerulonephritis associated with nonrenal malignancies. *Am J Nephrol*. 1984;4:208-214.
10. Edgar JD, Rooney DP, McNamee P, McNeill TA. An association between ANCA positive renal disease and malignancy. *Clin Nephrol*. 1993;40:22-25.
11. Navarro JF, Quereda C, Rivera M, Navarro FJ, Ortuño J. Anti-neutrophil cytoplasmic antibody-associated paraneoplastic vasculitis. *Postgrad Med J*. 1994;70:373-375.
12. Hruby Z, Bronowicz A, Rabczyński J, Kopeć W, Szewczyk Z. A case of severe anti-neutrophil cytoplasmic antibody (ANCA)-positive crescentic glomerulonephritis and asymptomatic gastric cancer. *Int Urol Nephrol*. 1994;26:579-586.
13. Tatsis E, Reinhold-Keller E, Steindorf K, Feller AC, Gross WL. Wegener's granulomatosis associated with renal cell carcinoma. *Arthritis Rheum*. 1999;42:751-756.
14. Baschinsky DY, Baker PB, Niemann TH, Wilmer WA. Pauci-immune ANCA-positive crescentic glomerulonephritis associated with metastatic adenocarcinoma of the lung. *Am J Kidney Dis*. 2000;36:E24.
15. Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2004;43:1532-1535.
16. von Vietinghoff S, Schneider W, Luft FC, Kettritz R. Crescentic glomerulonephritis and malignancy—guilty or guilt by association? *Nephrol Dial Transplant*. 2006;21:3324-3326.
17. Chemouny JM, Pagnoux C, Caudwell V, et al. ANCA-associated diseases and lung carcinomas: a five-case series. *Clin Nephrol*. 2014;81:132-137.
18. Ronco PM. Paraneoplastic glomerulopathies: new insights into an old entity. *Kidney Int*. 1999;56:355-377.
19. Folci M, Ramponi G, Shiffer D, Zumbo A, Agosti M, Brunetta E. ANCA-associated vasculitides and hematologic malignancies: lessons from the past and future perspectives. *J Immunol Res*. 2019;2019:1732175.
20. Earwood JS, Thompson TD. Hemoptysis: evaluation and management. *Am Fam Physician*. 2015;91:243-249.
21. McCabe C, Jones Q_, Nikolopoulou A, Wathen C, Luqmani R. Pulmonary-renal syndromes: an update for respiratory physicians. *Respir Med*. 2011;105:1413-1421.
22. Ito C, Akimoto T, Nakazawa E, et al. A case of cervical cancer-related membranous nephropathy treated with radiation therapy. *Intern Med*. 2011;50:47-51.
23. Pai P, Bone JM, McDicken I, Bell GM. Solid tumour and glomerulopathy. *QJM* 1996;89(5):361-368.
24. Lionaki S, Marinaki S, Panagiotellis K, et al. Glomerular diseases associated with malignancies: histopathological pattern and association with circulating autoantibodies. *Antibodies (Basel)*. 2020;9:18.