Antineutrophil cytoplasmic antibody-positive pauci-immune glomerulonephritis associated with mantle cell lymphoma

Kana N. Miyata1,3, Nazia A. Siddiqi1, Lawrence P. Kiss2, Nikolas B. Harbord1, and James F. Winchester1

1Department of Internal Medicine, Division of Nephrology and Hypertension, 2Department of Pathology, Mount Sinai Beth Israel, New York, NY, and 3Department of Internal Medicine, Division of Nephrology and Hypertension, Harbor UCLA Medical Center, Torrance, CA, USA

Abstract. Renal involvement in non-Hodgkin lymphoma, especially mantle cell lymphoma (MCL) is rare. A 77-year-old man presented with acute kidney injury (AKI), which rapidly progressed to dialysis dependence. Kidney biopsy revealed patchy B-cell lymphocytic aggregates in the interstitium, which were positive for cyclin D1, consistent with atypical CD5-negative MCL as confirmed by the detection of translocation t(11;14) by FISH. Crescents were noted in 3 of 26 glomeruli; while PR-3 antineutrophil cytoplasmic antibody (ANCA) positivity and negative immunofluorescence suggested an additional pauci-immune (rapidly progressive) glomerulonephritis pattern of injury. Patient received chemotherapy (cyclophosphamide, vincristine, and prednisone), which improved his renal function and allowed for discontinuation of hemodialysis. However, he died from pulmonary hemorrhage 8 months after initial presentation. This is the first reported case of a patient with coexistence of renal MCL infiltration and ANCA-positive pauci-immune glomerulonephritis.

Case

A 77-year-old Filipino man presented with worsening kidney function. His medical history was significant for chronic kidney disease, hypertension, hypothyroidism, and bladder cancer (low-grade urothelial tumor) for which he underwent transurethral resections 3 times until 4 months prior to this admission. He had a 10-pack-year smoking history but denied any alcohol or drug use. Two months prior, he was noted to have a 2.2 × 1.7 cm right lung mass on chest X-ray, and a CT scan showed diffuse lymphadenopathy in the neck, chest, abdomen, and pelvis. The result of bronchoscopy with biopsy was inconclusive.

He was found to have acute kidney injury (AKI) (serum creatinine of 4.5 mg/dL from 2.2 mg/dL 1 week prior) by his primary care physician and was sent to our medical center. Two months prior, he was noted to have a 2.2 × 1.7 cm right lung mass on chest X-ray, and a CT scan showed diffuse lymphadenopathy in the neck, chest, abdomen, and pelvis. The result of bronchoscopy with biopsy was inconclusive.

He was found to have acute kidney injury (AKI) (serum creatinine of 4.5 mg/dL from 2.2 mg/dL 1 week prior) by his primary care physician and was sent to our medical center. Two months prior, he was noted to have a 2.2 × 1.7 cm right lung mass on chest X-ray, and a CT scan showed diffuse lymphadenopathy in the neck, chest, abdomen, and pelvis. The result of bronchoscopy with biopsy was inconclusive.

Introduction

Mantle cell lymphoma (MCL) is predominantly a disease of elderly men and is characterized by its aggressive form of non-Hodgkin lymphoma (NHL) with short median survival of 3 – 4 years [1].

Lymphoma can involve the kidneys in various ways. Acute kidney injury (AKI) related to lymphoma can be from direct obstruction of the ureters or renal artery, renal vein thrombosis, lymphomatous infiltration of the kidneys, or paraneoplastic glomerulonephritis. It can also be from the indirect effect of hypercalcemia, bone invasion, paraproteinemia, and amyloid, or from treatment such as radiation nephritis and uric acid nephropathy [2, 25].

We present a case of AKI with biopsy-proven concomitant MCL infiltration to the kidneys and paraneoplastic antineutrophil cytoplasmic antibody (ANCA)-positive pauci-immune glomerulonephritis with crescent formation.

Key words

acute kidney injury – mantle cell lymphoma – crescent – lymphomatous infiltration of the kidney
thin old man in no acute distress. Physical examination revealed II/VI holosystolic murmur, mild crackles at left lower lung base, palpable nontender submandibular and right axillary lymph nodes, no peripheral edema, and no skin rash. Urinalysis showed protein 1+, blood 2+, WBC 3/HPF, RBC 73/HPF with many dysmorphic RBCs, positive eosinophils, and granular casts. Urine protein/creatinine ratio was 2.9 g/gCr. Laboratory studies showed serum hemoglobin of 8.3 g/dL, urea nitrogen of 43 mg/dL, and creatinine of 5.3 mg/dL. HIV and hepatitis panel were negative. He had low C3 49 mg/dL and C4 16 mg/dL, positive ANA 1 : 160, negative MPO-ANCA, and positive PR-3 ANCA (5.5 AU/mL). Serum and urine protein electrophoresis were unremarkable. Kidney ultrasound showed slightly enlarged kidneys for his height (right 12.4 cm and left 11.4 cm) with increased echogenicity. Hospital course was complicated by pulmonary edema associated with a non-ST-elevation myocardial infarction. Kidney function continued to decline requiring hemodialysis on hospital day 16.

The kidney biopsy contained 26 glomeruli, of which 2 were globally sclerosed. Three glomeruli showed cellular crescent formation with epithelial cells and admixed inflammatory cells with scanty fibrin (Figure 1). The remaining glomeruli were roughly normal in size with normal cellularity. The mesangial areas had normal amounts of matrix and cellularity. There was no evidence of endocapillary proliferation, glomerulitis, or double contour formation. There was moderate tubular atrophy and interstitial fibrosis occupying ~ 20 – 40% of the cortical area. There were patchy dense monotonous lymphocytic aggregates and many separate areas with mixed inflammation including frequent plasma cells, occasional eosinophils, and no neutrophils (Figure 2). The lymphoid aggregates consisted of atypical mature lymphoid cells with irregular nuclear contours that were predominantly B-cells, positive for CD20 and cyclin D1, negative for CD3, CD5, and CD 10 (Figure 3). The findings supported a diagnosis of atypical CD5-negative mantle cell lymphoma confirmed by the detection of translocation t(11;14) by FISH (fluorescence in situ hybridization). Immunofluorescence and electron microscopy did not show immune complex deposits.

Subsequent bone marrow biopsy did not show bone marrow involvement by lymphoma. The patient was diagnosed with stage 4EB mantle cell lymphoma (diffuse lymphadenopathy, splenic and kidney involvement, lung lesions) with coexistence of renal infiltration by MCL and pauci-immune glomerulonephritis.

Given his age and multiple comorbidities, the patient received 6 cycles of palliative chemotherapy (IV cyclophosphamide 325 mg/m² on day 1, IV vincristine 1.4 mg/m² on day 1,
ANCA-positive AKI with MCL

and oral prednisone 100 mg daily on days 1–5; every 3 weeks). After the completion of chemotherapy, he was noted to have regained some renal function, and hemodialysis was discontinued. However, he died from pulmonary hemorrhage at 8 months from the initial presentation.

Discussion

We present a rare case of AKI caused by MCL rapidly leading to end-stage renal disease. An interesting point of this case is the coexistence of the two possible causes of AKI; lymphoma infiltration into the interstitium and PR3-ANCA-positive pauci-immune glomerulonephritis likely as a paraneoplastic manifestation.

The differential diagnosis of AKI related to malignant lymphoma is broad. Direct obstruction of the ureters, renal arteries, and veins by tumor masses can be diagnosed by imaging tests, and treatment-related AKI is usually obvious from the treatment history. The enlargement of kidneys bilaterally may be seen with the direct lymphomatous infiltration as in this case. However, kidney biopsy is usually helpful for the accurate diagnosis of the lymphoma subtypes and the clarification of the extent and location of the infiltration, which may influence the prognosis [3]. Paraneoplastic glomerulonephritis typically requires kidney biopsy for the diagnosis. Da’as et al. [8] reported that 83 patients out of 700 patients with NHL or chronic lymphocytic leukemia (CLL) had manifestations of renal failure. The overall incidence of kidney involvement in MCL is not known, likely because MCL is a rare disease, occurring only in 3–7% of NHLs in United States and Europe [26].

In a previously published large case series, Richmond et al. [4] identified lymphoma

Figure 3. Kidney biopsy showing atypical lymphocytes in interstitium (A: H & E stain; 100×). Immunohistochemistry markers were positive for CD20 (B: 100×) and cyclin D1 (D: 100×), and negative for CD5 (C: 100×).
| Case | Age (years) | Gender | Lymphomatous infiltration to tubulointerstitium | ANCA | Renal manifestations of mantle cell lymphoma in previous case reports |
|------|-------------|--------|-----------------------------------------------|------|-----------------------------------------------------|
| 1    | 72          | F      | Yes                                           | No   | Prednisone, vincristine, mitoxantrone               |
| 2    | 77          | M      | No                                            | Neg  | Prednisone                                          |
| 3    | 52          | M      | Yes (AN with predominant B lymphocyte infiltration) | No   | Prednisone, vincristine, mitoxantrone               |
| 4    | 69          | M      | Yes                                           | No   | Prednisone                                          |
| 5    | 75          | M      | No                                            | Neg  | Prednisone                                          |
| 6    | 68          | M      | Yes (AIN with predominant B lymphocyte infiltration) | No   | Prednisone                                          |
| 7    | 80          | M      | No                                            | Neg  | Prednisone                                          |
| 8    | 68          | M      | No                                            | Neg  | Prednisone                                          |
| 9    | 76          | M      | Yes                                           | No   | Prednisone                                          |
| 10   | 69          | M      | No                                            | Neg  | Prednisone                                          |
| 11   | 69          | M      | Yes                                           | No   | Prednisone, vincristine, mitoxantrone               |
| 12   | 59          | M      | Yes                                           | No   | Prednisone                                          |
| 13   | 68          | M      | Yes                                           | No   | Prednisone                                          |
| 14   | 65          | M      | No                                            | Neg  | Prednisone                                          |
| 15   | 55          | M      | No                                            | Neg  | Prednisone                                          |
| 16   | 56          | M      | Yes                                           | No   | Prednisone                                          |
| 17   | 46          | M      | Yes                                           | Neg  | Prednisone                                          |
| 18   | 54          | M      | Yes                                           | No   | Prednisone                                          |
| 19   | 77          | M      | No                                            | Neg  | Prednisone                                          |
| 20   | 58          | M      | No                                            | Neg  | Prednisone                                          |

ANCA: Different antibodies (e.g., ANCA, ENA) detected in some cases.

Reference: Baldus et al. 1996 [6], Rerolle et al. 1999 [7], Daías et al. 2001 [8], Wu et al. 2002 [9], Karmi et al. 2004 [10], Hill et al. 2004 [11], Colak et al. 2004 [12], Lee et al. 2012 [15], Le et al. 2013 [16], Chu et al. 2013 [16], Li et al. 2014 [17], Khow et al. 2014 [18], Kofman et al. 2014 [19], Peddi et al. 2015 [21], Sekulic et al. 2015 [22], Abeysekera et al. 2015 [23].
ANCA-positive AKI with MCL

ANCA-positive AKI with MCL 13
cells’ renal parenchymal infiltration in 34% of
all the lymphoma autopsy cases, but clinically
significant renal failure was observed in less
than 10% of the patients with renal lympho-
ma infiltrate. Although rare, AKI, leading to
ESRD, can be caused solely by lymphoma in-
filtration as reported by Lee et al. [5].

To our knowledge, this is the first report
of biopsy-proven ANCA-positive pauci-im-
une glomerulonephritis with crescent for-
mation associated with MCL. To date, there
are 21 reported cases of MCL with renal in-
volvement; 10 cases with renal MCL infiltr-
ation, 3 cases with proliferative glomerulone-
phritis, 4 cases with membranoproliferative
glomerulonephritis, 2 cases with minimal
change disease, 2 cases with focal segmen-
tal glomerulosclerosis, 1 case with immune
complex-mediated glomerulonephritis, and 5
cases with ANCA-negative crescent for-
mation (Table 1). Out of 5 cases with crescents,
3 cases had concomitant lymphomatous in-
filtration of tubulointerstitium as seen in our
case [15, 20, 21]. Out of the 21 cases report-
ed, 15 cases mention the result of ANCA and
all were reported negative.

It is known that the risk of malignancies
is increased in patients with ANCA-associat-
ed vasculitis compared to the general popu-
lation [27]. The association of solid tumor
malignancies, such as kidney, lung, or colon
cancer, and paraneoplastic ANCA-associat-
ed vasculitis has been published sporadically
in case reports [28]. Li et al. [17] identified
20 NHL patients with renal involvement,
among which 2 patients had positive PR3-
ANCA (1 patient with T/NK cell lymphoma
and another with chronic lymphocytic leu-
kemia/small lymphocytic lymphoma). In
those studies, ANCA-associated vasculitis
occurred concurrently or preceded the can-
cer diagnosis. Pathophysiological mecha-
nism of paraneoplastic glomerulonephritis
remains largely undetermined. Hypotheses
include dysregulation of T-cell immunology,
vascular endothelial growth factor (VEGF)
and VEGF-receptor dysregulation, increased
cytokine levels, antibody production by the
neoplasm, and deposits of malignancy-relat-
ed antigens [20, 28, 29].

It is important to note that the current
standard treatment option for ANCA-associ-
ated vasculitis is a part of the chemotherapy
regimen for MCL. Cyclophosphamide or
rituximab in addition to corticosteroids are usually used for both diseases, though the dosing may be different. Renal recovery in our case might be attributed to the resolution of both of the histologic findings by his chemotherapy regimen. Interestingly, most of the case reports of MCL-related kidney disease have good renal outcomes after the treatment of MCL, though it tends to recur when MCL recurs (Table 1). This is another clue that shows renal injury is a paraneoplastic feature and not de-novo kidney disease.

Learning points of this case are (1) lymphoma infiltration and/or glomerular disease associated with lymphoma should be suspected as a differential diagnosis for AKI with an underlying hematologic disease, and (2) early detection by kidney biopsy and initiation of cancer treatment can possibly change the patients’ renal and/or overall outcomes.

Conflict of interest

Authors declare no conflict of interest.

References

[1] Weisenburger DD, Vose JM, Greiner TC, Lynch JC, Chan WC, Bierman PJ, Dave BJ, Sanger WG, Armitage JO. Mantle cell lymphoma. A clinicopathologic study of 68 cases from the Nebraska Lymphoma Study Group. Am J Hematol. 2000; 64: 190-196.

[2] Coggins CH. Renal failure in lymphoma. Kidney Int. 1980; 17: 847-855.

[3] Luciano RL, Brewster UC. Kidney involvement in leukemia and lymphoma. Adv Chronic Kidney Dis. 2014; 21: 27-35.

[4] Richmond J, Sherman RS, Diamond HD, Craver LF. Renal lesions associated with malignant lymphomas. Am J Med. 1962; 32: 184-207.

[5] Lee HJ, Seo JW, Cho HS, Kang Y, Bae EJ, Lee DW, Jeon DH, Lee JS, Chang SH, Park DJ. Renal involvement of mantle cell lymphoma leading to end stage renal disease. Hemodial Int. 2012; 16: 104-108.

[6] Balfus M, Klopper K, Kress S, Waldherr R, Möller P, Brass H. Primary bilateral renal centrocytic non-Hodgkin’s lymphoma as a cause of renal failure. Nephron. 1996; 73: 86-90.

[7] Revolle JP, Thervet E, Beaubois H, Vincent F, Rousselot P, Pillebout E, Legendre C. Crescentic glomerulonephritis and centrocytic lymphoma. Nephrol Dial Transplant. 1999; 14: 1744-1745.

[8] Da’as N, Polliaci A, Cohen Y, Amir G, Darmon D, Kleinman Y, Goldfarb AW, Ben-Yehuda D. Kidney involvement and renal manifestations in non-Hodgkin’s lymphoma and lymphocytic leukemia: a retrospective study in 700 patients. Eur J Haematol. 2001; 67: 158-164.

[9] Wu Q, Jinde K, Yanagi H, Endoh M, Sakai H. Acute interstitial nephritis with polyclonal B cell infiltration and development of mantle cell lymphoma. Intern Med. 2002; 41: 1158-1162.

[10] Karim M, Hill P, Pillai G, Gatter K, Davies DR, Winearls CG. Proliferative glomerulonephritis associated with mantle cell lymphoma – natural history and effect of treatment in 2 cases. Clin Nephrol. 2004; 61: 422-428.

[11] Hill P, Somerville C. An 80-year-old man with renal insufficiency, proteinuria, hematuria, hemiparesis, and pleuritis. Am J Kidney Dis. 2004; 44: 1121-1125.

[12] Colak N, Dede F, Canbakhan B, Odabas AR, Akyürek N. Acute tubulo-interstitial nephritis associated with mantle cell lymphoma presented as acute renal failure. Nephrology (Carlton). 2007; 12: 107-108.

[13] Wong CF, Mohiteshhamzadeh M, Arsalanianzadeh B, Dutt T, Shawki H, Khine MM, Rustom R. Successful treatment of focal segmental glomerulosclerosis in association with mantle cell lymphoma. Ren Fail. 2007; 29: 363-366.

[14] Davies J, Healey DA, Wood KM, Jones K, Kanagasundaram NS. Acute renal failure due to mantle cell lymphoma – a case report and discussion of the literature. Clin Nephrol. 2007; 67: 394-396.

[15] Lubas A, Mrzíć A, Smoszna J, Niemczyk S. Membranoproliferative glomerulonephritis, mantle cell lymphoma infiltration, and acute kidney injury. Int Urol Nephrol. 2013; 45: 1489-1494.

[16] Chu JR, Dierksen JE, Glass WF, Aisenberg GM. Association of membranoproliferative glomerulonephritis with mantle cell lymphoma. BMJ Case Rep. 2013; 2013.

[17] Li SJ, Chen HP, Chen YH, Zhang LH, Tu YM, Liu ZH. Renal involvement in non-Hodgkin lymphoma: proven by renal biopsy. PLoS One. 2014; 9: e95190.

[18] Khow KS, Yong AS, Yong TY, Kass BJ, Barbara JA, Li JY. Minimal change disease associated with newly diagnosed mantle cell lymphoma. Ren Fail. 2014; 36: 634-637.

[19] Kofman T, Zhang SY, Copie-Bergman C, Moktefi A, Raimbourg Q, Francois H, Karras A, Plaisier E, Painchart B, Favre G, Bertrand D, Gyan E, Souid M, Roos-Weil D, Desvaux D, Grimmert P, Hailou C, Lang P, Sahali D, Audard V. Minimal change nephrotic syndrome associated with non-Hodgkin lymphoid disorders: a retrospective study of 18 cases. Medicine (Baltimore). 2014; 93: 350-358.

[20] Wang J, Li L, Chen F, Yin Q, Zhang X, Liu F. Antineutrophil cytoplasmatic antibody-negative pauci-immune crescentic glomerulonephritis and mantle-cell lymphoma: a case report and review of the literature. WIMJ Open. 2014; 1: 114-116.

[21] Peddi S, Ram R, Kataru SR, Chenmu KK, Nandyala R, Kottu R, Kumar VS. Acute renal failure in a patient with mantle cell lymphoma. Hemodial Int. 2015; 19: E12-E15.

[22] Sekulic M, Stanek J, Crosson JT, Kim Y, Dolan M, Krigman H, Linden MA. Parenchymal infiltration and lymphoma-associated membranoproliferative pattern of glomerular injury: an unusual
presentation of mantle cell lymphoma. Clin Nephrol. 2015; 84: 173-180.

[23] Abeysekera RA, Wazil AW, Nanayakkara N, Ratnatunga N, Fernando KM, Thinnarachchi J. Mantle cell lymphoma first presenting as immune complex-mediated glomerulonephritis: a case report. J Med Case Reports. 2015; 9: 115.

[24] Hindocha S, Gopaluni S, Collins GP, Shenbaga-raman P. Focal segmental glomerulosclerosis in a patient with mantle cell lymphoma. BMJ Case Rep. 2015.

[25] Prakash J, Behura SK, Ghosh B, Singh S, Usha. Usha. Renal amyloidosis: A rare presenting manifestation of Hodgkin’s disease. Hong Kong Journal of Nephrology. 2011; 13: 74-76.

[26] Zhou Y, Wang H, Fang W, Romaguer JE, Zhang Y, Delasalle KB, Kwak L, Yi Q, Du XL, Wang M. Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004. Cancer. 2008; 113: 791-798.

[27] Pankhurst T, Savage CO, Gordon C, Harper L. Malignancy is increased in ANCA-associated vasculitis. Rheumatology (Oxford). 2004; 43: 1532-1535.

[28] Bacchetta J, Juillard L, Cochot P, Droz JP. Paraneoplastic glomerular diseases and malignancies. Crit Rev Oncol Hematol. 2009; 70: 39-58.

[29] Lien YH, Lai LW. Pathogenesis, diagnosis and management of paraneoplastic glomerulonephritis. Nat Rev Nephrol. 2011; 7: 85-95.