CASE REPORT

Association of membranoproliferative glomerulonephritis with mantle cell lymphoma

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SUMMARY

Mantle cell lymphoma (MCL) is a rare and aggressive lymphoid neoplasm. It can involve the kidney, either by direct lymphomatous infiltration or by a paraneoplastic glomerulonephritis. We present here the case of a man with rectal bleeding and rapidly progressive renal failure, who had MCL in the gastrointestinal tract and paraneoplastic membranoproliferative glomerulonephritis, and whose renal dysfunction normalised after chemotherapy.

BACKGROUND

Mantle cell lymphoma (MCL) is a rare and aggressive lymphoid neoplasm that comprises 4–10% of non-Hodgkin's lymphoma cases.¹ It can involve the kidney, either by a direct lymphomatous infiltration² or by a presumed paraneoplastic glomerulonephritis.³ Features supporting a paraneoplastic mechanism are: (1) no obvious alternative cause; (2) time relationship between the cancer and the presumed secondary manifestation; (3) clinical (and histological) remission after complete surgical removal of the tumour or after full remission achieved by chemotherapy; (4) recurrence of symptoms along with the tumour relapse.⁴

We present here the case of a man with rectal bleeding and rapidly progressive renal failure, who had MCL in the gastrointestinal tract and presumably paraneoplastic membranoproliferative glomerulonephritis (MPGN).

CASE PRESENTATION

A 68-year-old Hispanic man presented with a 2-week history of reduced urine output with dark urine, swelling in all four extremities and shortness of breath. He also reported of rectal bleeding, nausea and abdominal distention for 8 days. His medical history was significant for a transurethral prostate resection 6 years earlier to treat benign prostatic hyperplasia. He smoked 20 cigarettes daily for 45 years until 7 years prior to this admission. He had also consumed one case of beer each weekend for approximately 20 years. He was not taking any medications at the time of his admission, and was not under routine medical care.

On admission his blood pressure was 172/105 mm Hg, temperature 37.1°C, pulse 82/min, respiratory rate 20/min and oxygen saturation 97% on room air. Physical examination revealed crackles in the lung bases, abdominal distention, 2+ pitting oedema in both lower extremities and 1+ pitting oedema in both upper extremities. Haemorrhoids were noticed on rectal examination.

INVESTIGATIONS

Laboratory studies showed serum haemoglobin of 11.7 g/dL, serum creatinine of 3.2 mg/dL and blood urea nitrogen of 94 mg/dL. The anion gap was 14 mEq/L, serum albumin was 2.2 g/dL and serum globulins were 3.9 g/dL. Lactate dehydrogenase levels were 199 U/L (normal). Urinalysis showed 4+ protein (urine protein/creatinine ratio 2.75), 64 red blood cells and 35 white cells/high power field. No abnormalities were noted on renal ultrasound.

Over the next 5 days his urine output remained minimal, his creatinine increased to 4.8 mg/dL and his blood urea nitrogen increased to 104 mg/dL. His potassium rose to 5.7 mEq/L, and his phosphate levels to 8.8 mg/dL. Consequently haemodialysis was started.

Colonoscopy showed large internal and external haemorrhoids without evidence of bleeding, and nodular friable mucosa in the rectum and caecum. Biopsy of the rectal mucosa showed neoplastic cells arranged in lymphoid aggregates that were cyclin D1, CD5 and CD20 positive; these findings were diagnostic of MCL (figure 1). Congo red stain of the biopsied mucosa was negative for amyloid. CT scans of the chest, abdomen and pelvis revealed enlarged internal iliac, axillary and mildly prominent superior mediastinum lymph nodes at the base of the neck. Positron emission tomography-CT scan showed numerous hypermetabolic centimetre and subcentimetre lymph nodes throughout the neck, chest and pelvis consistent with active lymphoma. Upper endoscopy showed sessile polyps along the greater curvature of the stomach and the distal oesophagus. Biopsy of the polyps showed atypical lymphoid proliferation morphologically consistent with MCL in a background of intestinal metaplasia. Bone marrow biopsy showed CD5, CD20, λ and cyclin D1 positive, λ -restricted B-cell lymphocytes consistent with MCL. Expression of κ , CD23, CD10, CD103, CD11c, CD56, CD16, CD15, CD13, CD11b, CD64, CD36, CD34, CD117, CD33, CD14 were negative. MIPI score was not evaluated.

Renal biopsy (figure 2) showed mild, diffuse mesangial matrix expansion and mesangial hypercellularity with focal segmental thick capillary walls, but without endocapillary hypercellularity. Mild acute tubuloe epithelial injury was also present. Immunofluorescence showed diffuse mesangial and segmental capillary, granular staining for IgG, κ light chain and λ light chain (1+) and IgM (2+). IgA was essentially negative with very focal segmental trace staining. C3 and C1q were also not detected in paraffin sections, and were trace in a single glomerulus present in frozen sections.

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Figure 1 Rectal biopsy showing distinct lymphoid aggregates within the mucosa. The cells are monomorphic with irregular nuclear contours and unremarkable nucleoli in H&E magnifications at $\times 10$ (A) and $\times 40$ (B). Immunohistochemical stain demonstrates cyclin D1 positivity (C).

Electron microscopy showed mesangial and subendothelial electron dense deposits and segmental duplication of the basement membrane with mesangial interpositioning consistent with MPGN. There was no evidence of lymphomatous infiltration of the kidney. Serum complement C3 was 69.5 mg/dL (normal 90–180 mg/dL). Serum antiglomerular membrane antibody, rheumatoid factor and anti-neutrophil cytoplasmic antibody were negative, and serum complement C4 levels were normal. Hepatitis and HIV serology panel were negative.

TREATMENT

The patient received chemotherapy 2 weeks after his initial admission, including fractionated cyclophosphamide $\times 6$ doses

over 3 days, rituximab $\times 1$ dose on day 4 and dexamethasone 40 mg daily for 10 days.

OUTCOME AND FOLLOW-UP

The patient was asymptomatic at discharge, and planned for haemodialysis three times weekly. One week later, when the patient was readmitted for his second round of chemotherapy, his creatinine was 1.0 mg/dL and his urine output had also improved. Consequently, haemodialysis was put on hold. He received a total of three cycles of the same chemotherapy, and once his renal function was fully recovered (fourth cycle) his therapy was switched to protocol rituximab-Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone). His last documented serum creatine was 0.5 mg% and

Figure 2 Renal biopsy. (A) This glomerulus demonstrates mesangial expansion with mild mesangial hypercellularity (H&E). (B) Periodic Acid-Schiff staining demonstrates segmental basement membrane duplication. (C) Immunofluorescence microscopy highlights the granular deposition of IgG in the mesangium and segmentally along the capillary walls. (D) Electron microscopy shows subendothelial electron dense, immune complex-type deposits associated with basement membrane duplication and mesangial interpositioning.

the urine protein/creatinine ratio was 1.4. The urinalysis was then normal but for protein 1+. No further ultrasound or complement level was checked. One month later the patient moved to a different town and became lost to our follow-up.

DISCUSSION

We present a case of acute glomerulonephritis with segmental mesangial interpositioning characteristic of MPGN associated with MCL that fulfils most of the necessary features to support a paraneoplastic pathogenesis. The findings are consistent with very early MPGN since endocapillary hypercellularity is not present and basement membrane duplication is only segmental. Although we cannot prove renal histological resolution in the absence of a biopsy, we did show that renal function and urinalysis improved after chemotherapy targeting MCL. The ability to ascertain sustained remission of the underlying neoplasm and concomitant normal kidney function requires longer follow-up.

Extranodal manifestations are frequent in MCL (unlike other types of non-Hodgkin's lymphoma); they are accompanied by nodal involvement, as in our patient, in 85–96% of the reported cases.¹ Microscopic compromise of the gastrointestinal mucosa seems to be the rule, but it seldom changes the therapeutic approach.⁵

Lymphomas have been tied to renal dysfunction in a variety of ways. The tumour mass can cause an extrinsic obstruction of the ureters, leading to hydronephrosis, or can obstruct the renal arteries or veins. Lymphoma can also present as a primary extranodal renal lymphoma with acute kidney failure. Such a presentation accounts for 0.7% of all extranodal lymphomas in North America, and carries a grim prognosis.⁶ Primary renal involvement is seldom reported in MCL.² More commonly, advanced nodal lymphomas infiltrate the kidney, sometimes with no associated signs or modification of the urinalysis.⁷ Tumour lysis syndrome or direct renal toxicity following chemotherapy can similarly produce nephrotoxicity.^{4, 6}

We found reports of two other cases of MCL causing MPGN as a paraneoplastic phenomenon. Both patients in these cases were dialysis-dependent, and regained renal function following treatment of the lymphoma, ultimately dying of relapsed disease.³ Our patient presented with renal failure. We could not determine whether chronic kidney disease played a role in his presentation because we had no evidence of his baseline renal function; however, his rapid and continued decline in renal function while on our service met the diagnostic criteria for acute kidney loss.⁸ A renal biopsy was subsequently indicated to establish the aetiology of the renal dysfunction.⁹ His kidney function began to improve following chemotherapy targeting the lymphoma, allowing haemodialysis to be put on hold.

The mechanism behind paraneoplastic glomerulopathy is unproven, though various hypotheses exist that involve dysregulation of T-cell immunology, impaired glomerular permeability due to vascular endothelial growth factor -receptor dysregulation, malignancy-derived antibodies aimed against specific glomerular antigens, and malignancy-related antigen deposition in the glomeruli.⁴ Another hypothesis is that tumour-induced cytokines lead to complement activation and subsequent deposition in the glomeruli, causing glomerular inflammation and MPGN.

The scarce casuistic on the association of MCL and MPGN prevents full understanding of the underlying pathophysiology of this process. The absence of specific therapies for primary MPGN¹⁰ suggests that our patient's kidney function improved only after his MCL responded, rather than as a response to the chemotherapeutic agents.

Learning points

- ▶ Mantle cell lymphoma is a rare and aggressive lymphoid neoplasm.
- ▶ Kidneys can be affected either by direct lymphomatous infiltration or by a paraneoplastic glomerulonephritis.
- ▶ Paraneoplastic mechanism is suspected when there is no obvious alternative cause; time relationship between the cancer and the presumed secondary manifestation; there is clinical (and histological) remission after complete surgical removal of the tumour or after full remission achieved by chemotherapy; or recurrence of symptoms along with the tumour relapse.
- ▶ The prognosis of this form of lymphoma is worse than other non-Hodgkin's lymphoma, and that warrants close follow-up of renal function in this setting.

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Competing interests None.

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REFERENCES

- 1 Jares P, Campo E. Advances in the understanding of mantle cell lymphoma. *Br J Haematol* 2008;142:149–65.
- 2 Lubas A, Mróz A, Smoszna J, *et al.* Membranoproliferative glomerulonephritis, mantle cell lymphoma infiltration, and acute kidney injury. *Int Urol Nephrol* Published Online First: 1 Jul 2012. doi:10.1007/s11255-012-0210-4
- 3 Karim M, Hill P, Pillai G, *et al.* Proliferative glomerulonephritis associated with mantle cell lymphoma—natural history and effect of treatment in 2 cases. *Clin Nephrol* 2004;61:422–28.
- 4 Bacchetta J, Juillard L, Cochat P, *et al.* Paraneoplastic glomerular diseases and malignancies. *Crit Rev Oncol Hematol* 2009;70:39–58.
- 5 Romaguera JE, Medeiros LJ, Hagemeister FB, *et al.* Frequency of gastrointestinal involvement and its clinical significance in mantle cell lymphoma. *Cancer* 2003;97:586–91.
- 6 Da'as N, Polliack A, Cohen Y, *et al.* Kidney involvement and renal manifestations in non-Hodgkin's lymphoma and lymphocytic leukemia: a retrospective study in 700 patients. *Eur J Haematol* 2001;67:158–64.
- 7 Kowalewska J, Nicosia RF, Smith KD, *et al.* Patterns of glomerular injury in kidneys infiltrated by lymphoplasmacytic neoplasms. *Human Pathol* 2011;42:896–903.
- 8 Bellomo R, Charlotte R, Kellum JA, *et al.* the ADQI workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004;8:R204–12.
- 9 Korbet SM. Percutaneous renal biopsy. *Semin Nephrol* 2002;3:252–67.
- 10 Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med* 2012;366:1119–31.

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