CASE REPORT

Antineutrophil Cytoplasmic Antibody-negative Pauci-immune Crescentic Glomerulonephritis and Mantle-cell Lymphoma

A Case Report and Review of the Literature

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ABSTRACT

Mantle-cell lymphoma (MCL) is an aggressive lymphoid neoplasm of non-Hodgkin's lymphoma (NHL). Crescentic glomerulonephritis associated with NHL has rarely been reported. In this report, we present a case of antineutrophil cytoplasmic antibody (ANCA)-negative pauci-immune crescentic glomerulonephritis (GN), presenting with the coexistence of proteinuria, haematuria, progressive renal failure and MCL infiltration in the kidney, in the setting of newly-diagnosed MCL. Following the chemotherapy, there was a resolution of renal function. To the best of our knowledge, this is the first report of ANCA-negative pauci-immune crescentic GN and MCL. The pathophysiologic relationship between ANCA-negative pauci-immune crescentic GN and MCL should be investigated further.

Keywords: ANCA, antineutrophil cytoplasmic antibody, mantle-cell lymphoma, pauci-immune crescentic glomerulonephritis

WIMJ Open 2014; 1 (3): 114

INTRODUCTION

Renal involvement associated with non-Hodgkin's lymphoma (NHL) has occasionally been reported (1). The diversity of lymphoma-associated renal lesions makes diagnosis difficult, while recurrence of proteinuria and deterioration of renal function may be the first signs of underlying malignancy. The most common glomerular injury reported in association with NHL is membranoproliferative glomerulonephritis (GN), followed by membranous GN (1), while crescentic GN has rarely been reported with NHL (2−4). Mantle-cell lymphoma (MCL) is an aggressive lymphoid neoplasm accounting for 3%−7% of NHL in the United States of America (USA) and Europe (5). However, reports with kidney involvement are extremely rare. Here, we report a case of antineutrophil cytoplasmic antibody (ANCA)-negative pauci-immune crescentic GN, presenting with proteinuria, haematuria, progressive renal failure and MCL infiltration in the kidney, in the setting of newly-diagnosed MCL.

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CASE REPORT

A 46-year old female was referred to our hospital in November 2012 with skin rash and renal failure. One year prior, she had been admitted to the local hospital with progressive renal failure. Laboratory investigation then revealed an elevated serum creatinine of 725.0 μmol/L. A renal biopsy at that time was compatible with crescentic GN. During steroid therapy (prednisone at the dose of 1 mg/kg/day) and cyclophosphamide pulse therapy (1 g/month) for six months, serum creatinine decreased to normal level, but in the tapering phase of prednisone, there was a relapse of renal failure. Six months ago, her creatinine increased to 320 μmol/L with onset of skin rash.

On admission, physical examination showed a temperature of 36.5 °C, respiratory rate of 20 beats per minute (bpm), heart rate of 80 bpm and blood pressure of 104/72 mmHg. There was erythematous skin eruption with nonpalpable petechiae and purpurae on her lower extremities. Widespread cervical, axillary and inguinal lymph node enlargement and moderate oedema of both the lower legs was noted. The laboratory investigations were as follows: the leukocyte count was 28.22 × 10^9/L with elevations of neutrophilic granulocyte, lymphocyte and monocyte, haemoglobin was 43 g/L with direct antiglobulin test positive and platelets were 365 × 10^9/L. Erythrocyte sedimentation rate was 116.0 mm/hour (Westergren). Serum electrolytes and liver function tests were normal. The creatinine was 312.0 μmol/L, with estimated glomerular filtration rate 23.12 ml/min/1.73 m^2. Urin-

 DOI: 10.7727/wimjopen.2014.198

alysis showed 30 red blood cells per high-power field. The 24-hour urinary protein excretion was 1.0 g/24 hour, with decreased serum albumin at 23.1 g/L. Antistreptolysin O titre and serum complement levels were within normal limits. There was no evidence of hepatitis B virus, hepatitis C virus, human immunodeficiency virus, human T-cell lymphotropic virus Type I, or Epstein-Barr virus infection. There was a marked polyclonal hyperimmunoglobulinaemia (IgA 20.10 g/L, IgG 87.50 g/L, IgM 3.23 g/L, IgE > 3000.00 IU/mL). Serum protein electrophoresis, immunofixation electrophoresis of both serum and urine were normal. Antineutrophil cyto-plasmic antibody, antinuclear antibody (ANA) and anti-glomerular basement membrane antibody were negative. Cryoglobulin was not detected. Bilateral renal morphology was normal on ultrasonography. Total body computed tomography scan confirmed the involvement of cervical, axillary and inguinal regions, and additionally revealed enlarged mediastinal and retroperitoneal lymph nodes as well as a mild hepatosplenomegaly.

The other laboratory investigations were as follows: skin biopsy was unremarkable. Bone-marrow aspirate, trephine biopsy and flow cytometry revealed only reactive plasma cells with no evidence of lymphoma. An inguinal lymph node biopsy was taken (Fig. 1). Immunohisto-

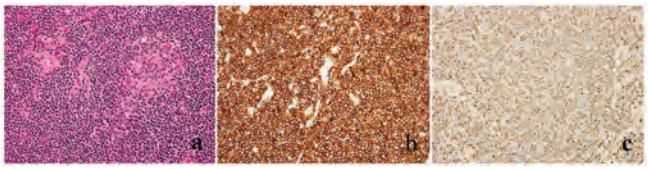

Fig. 1: Findings from inguinal lymph node biopsy of the patient with mantle-cell lymphoma.
(a) lymph node with lymphoid infiltrate composed predominantly of small cleaved cells (H&E stain, 400×); (b) CD20 was stained positive (400×); (c) cyclin D1 was stained positive (400×).

chemistry of lymphoid infiltration with cells of the following immunophenotype: CD20(+), CD5(+), CD3ε(-), CD2(-), CD4(-), CD8(-), CD10(-), CD23(-), CD43(+), CD56(-), cyclin D1(+) and Ki-67 proliferation index was 5%−8%. B-cell receptor rearrangements were found on molecular examination. The morphology and immunohistochemistry correlated with MCL.

A repeat percutaneous renal biopsy was performed and light microscopy specimen contained 14−16 glomeruli, large fibrous crescentic formations in most glomeruli, 4−6 of which were sclerosed, and glomeruli without crescents appeared normocellular (Fig. 2). There were many tubules exhibiting atrophy or necrosis of epithelial cells with the presence of protein in the lumina, and a group of lymphoid cell infiltrate in the interstitium. Immunohistochemical studies revealed positive expression of CD20 and cyclin D1 (Fig. 3). Immunofluorescence showed no deposition of immune complexes in the glomeruli. These findings defined the diagnosis as MCL and ANCA-negative pauci-imune crescentic GN.

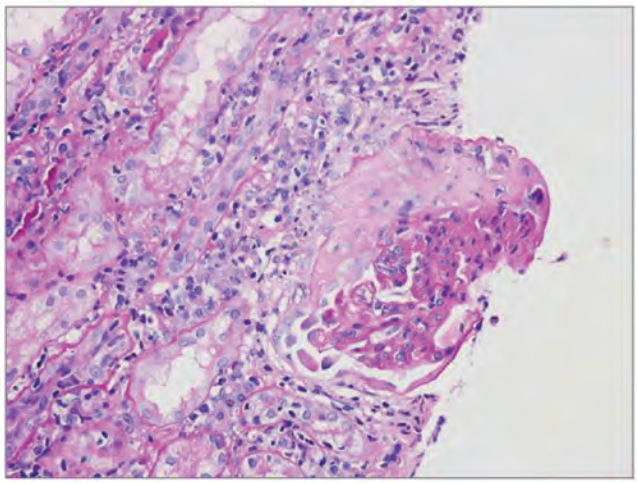

Fig. 2: Findings from renal biopsy specimens of the patient.
Periodic acid-Schiff (PAS) staining shows large fibrous crescentic formations partly covering the glomerular tuft in most glomeruli with mild mesangial and endothelial proliferation, and there were many tubules exhibiting atrophy or necrosis of epithelial cells with the presence of protein in the lumina, and a group of lymphoid cell infiltrate in the interstitium (PAS stain, 400×).

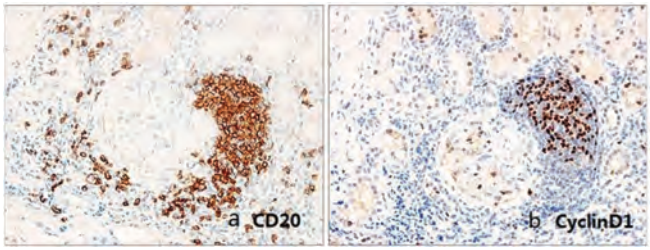

Fig. 3: Immunohistochemical studies for renal biopsy specimens of the patient with mantle-cell lymphoma.
(a) infiltration of CD20 positive lymphoid cells surrounding the glomeruli; (b) infiltration of cyclin D1 positive lymphoid cells surrounding or in the glomeruli (400×).

Being diagnosed with stage IIIA NHL, the patient was put on a chemotherapy regimen COP, consisting of cyclophosphamide 750 mg/mWan^2 on day one, vincristine 1.4 mg/m^2 on day one, and prednisone 60 mg/m^2 on days one to five. (Because of financial constraints, the patient did not take rituximab, a monoclonal anti-CD20 antibody.) After six cycles of chemotherapy, creatinine fell to 113.6 μmol/L, with the gradual improvement of oedema and anaemia.

DISCUSSION

Mantle-cell lymphoma is a rare aggressive B-cell lymphoma with a characteristic balanced translocation t (11;14) [q13;q32] which results in overproduction of cyclin D1. The onset of MCL is usually insidious and most patients are diagnosed with stage III or VI at their first visit. Many patterns of GN associated with NHL have been reported before, but MCL was included only in a few reports (6−8). Renal injury associated with MCL can present with isolated

proteinuria or haematuria or both, or more commonly with renal failure, as described in this case. In the majority of reports, the nephropathy is usually diagnosed simultaneously with or develops after the diagnosis of lymphoma. But in a few reports, clinical presentation of nephropathy has preceded and even revealed the diagnosis of lymphoma. In the index patient, crescentic glomerulonephritis was diagnosed preceding the diagnosis of lymphoma. When steroid was tapered, the recurrence and deterioration of renal function led to a biopsy diagnosis of MCL.

Renal manifestations usually improve after treatment of the underlying lymphoma (1, 6−8). Moreover, the evolution of GN can be used as a marker of lymphoma progression, because a relapse of GN can precede the diagnosis of recurrence of lymphoma (8). In this case, we had the opportunity to repeat the renal biopsy, which showed large fibrous crescentic formation in most glomeruli. This suggested that steroids might hardly reverse most or all crescentic lesions, although we cannot entirely exclude the possibility that the sampling was not representative of the overall glomerular lesions.

Malignant lymphomas can affect the kidneys by several potential mechanisms, including direct infiltration of the renal parenchyma by malignant cells, cryoglobulin deposition, obstruction of urinary outflow by tumour mass, biochemical abnormalities such as hypercalcaemia and hyperuricaemia following antitumour therapy, and finally, effects of paraneoplastic glomerulonephritis. The presence of lymphomatous infiltration in the renal biopsy detected around the glomeruli might suggest that the renal damage and the deterioration of renal function in our patient was partially mediated by the infiltration of MCL.

Interestingly in our case, immunofluorescence of the kidney biopsy specimen without deposition of immune complexes in the glomeruli defined the diagnosis as pauci-imune crescentic GN, which is most common in ANCA-associated crescentic GN. Until now, all of the reported cases have illustrated the mechanism of the association of active MCL and renal disease, and the mechanisms proposed to explain the paraneoplastic phenomenon include immune complex deposition, tumour antigens and viral antigens (9). However, the pathophysiological association between lymphoma and ANCA-negative pauci-immune crescentic GN remains poorly understood, even though it is postulated that the cause could be T-cell dysfunction with abnormal secretion of cytokines, altering the permeability of the glomerular basement membrane (10) with crescent formation. The pathophysiologic relationship between ANCA-negative pauci-immune crescentic GN and MCL should be investigated further.

In conclusion, we have presented an unusual case of ANCA-negative pauci-immune crescentic GN and renal failure associated with MCL, which widens the spectrum of GN in connection with this type of lymphoma and implies that MCL can induce glomerular injury or crescent formation. Moreover, this case illustrates that chemotherapy may improve the outcome and kidney function.

Authors' note

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal. The authors declare that they have no competing interests.

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Submitted 28 Aug 2014
Accepted 08 Sep 2014
Published 22 Dec 2014
Online: http://myspot.mona.uwi.edu/wimjopen/article/1611