CASE REPORT

Focal segmental glomerulosclerosis in a patient with mantle cell lymphoma

Sumeet Hindocha,¹ Seerapani Gopaluni,² Graham P Collins,³ Packiam Shenbagaraman⁴

¹Oxford University Hospitals, Oxford, UK

²Royal Berkshire Hospital, Reading, UK

³Department of Haematology, Churchill Hospital, Oxford, UK

⁴Oxford Kidney Unit, Churchill Hospital, Oxford, UK

Correspondence to

Dr Sumeet Hindocha, sumeet.hindocha@gmail.com

Accepted 28 August 2015

SUMMARY

Mantle cell lymphoma (MCL) is a rare lymphoid neoplasm occurring in about 6% of all non-Hodgkin's lymphomas. Although nephrotic syndrome due to various glomerulopathies is well described in patients with lymphomas, focal segmental glomerulosclerosis (FSGS) with MCL has been reported only once before. We present a second case of FSGS associated with MCL that was resistant to standard treatment of FSGS but resolved when the underlying MCL was treated.

BACKGROUND

Focal segmental glomerulosclerosis (FSGS) is a histological lesion rather than a diagnosis and it can be either idiopathic or secondary to infections, drugs, obesity or previous kidney injury. Patients with primary FSGS typically present with nephrotic syndrome while those with secondary FSGS present with non-nephrotic range proteinuria and develop renal insufficiency over time.

We present a case of a man who presented with nephrotic syndrome due to FSGS who responded to treatment given for mantle cell lymphoma (MCL). FSGS is rarely reported as a paraneoplastic glomerulopathy in haematological malignancies and has only been reported in one other patient with MCL prior to this case.¹

CASE PRESENTATION

A 67-year-old Caucasian man presented with a 1-month history of progressive lower limb swelling, nausea and shortness of breath. He had been fit and well previously.

On presentation, he was hypertensive with a blood pressure of 185/110 mm Hg. Examination revealed marked peripheral pitting oedema and small bilateral pleural effusions.

INVESTIGATIONS

Urinalysis showed 3+ blood and 4+ protein. Laboratory investigations revealed renal impairment with elevated creatinine of 272 µmol/L (3.08 mg/dL) and urea of 27.8 mmol/L (77.85 mg/dL). Serum albumin was low at 28 g/L and 24 h urine protein was measured at 10 g/day. The patient's haemoglobin was 13.7 g/dL and his white cell count was $8.19 \times 10^9/L$, with a normal differential cell count (the lymphocyte count measured $2.1 \times 10^9/L$). The serum immunoglobulins, complements, vasculitic screen and serum protein electrophoresis were normal. A renal ultrasound scan was normal. The patient underwent a renal biopsy.

Renal histology was consistent with early FSGS, with 5 of the 27 glomeruli reported as segmental lesions with epithelial hypertrophy and hyperplasia, endocapillary foam cells and focal hyalinosis, along with tip lesions, and with 10% of the interstitium showing fibrosis and tubular atrophy.

TREATMENT

The patient was started on prednisolone 60 mg once a day. Within 8 weeks, his creatinine had improved to 108 µmol/L (1.22 mg/dL) and serum albumin level had increased to 33 g/L. Urine protein creatinine ratio had also improved to 116 mg/mmol. Prednisolone was tapered off over a period of 8 months. However, the patient relapsed within a fortnight of finishing the course.

When he relapsed, he was started on ciclosporin as a second-line agent, along with prednisolone 30 mg/day, which was weaned to 15 mg/day within 4 weeks and then gradually weaned off completely over 6 months. He responded well to this treatment with a fall in proteinuria within 4 weeks. Urine protein creatinine ratio had improved from 1242 to 93 mg/mmol. Further follow-up over the next few months showed a persistent, rising lymphocyte count ($3.8 \times 10^9/L$ at 5 months and $5.4 \times 10^9/L$ at 11 months from initial presentation) and the patient's nephrotic syndrome began to relapse in spite of him being on an adequate dose of ciclosporin (ciclosporin levels were between 120 and 150 µg/L). His renal function began to deteriorate again with worsening nephrosis. His serum creatinine had risen to 192 µmol/L (2.17 mg/dL) and serum albumin had fallen to 25 g/L.

OUTCOME AND FOLLOW-UP

A haematology opinion was sought. Immunophenotyping of the peripheral blood revealed a significant increase in the number of CD19+ B cells. Fluorescence in situ hybridisation (FISH) analysis was positive for t(11:14), consistent with a diagnosis of MCL. The patient had reported of tiredness but did not have B symptoms and there was no lymphadenopathy or hepatosplenomegaly on examination. CT imaging demonstrated a borderline mediastinal lymph node of 1 cm but with no other lymphadenopathy. Lymphocyte count at this point (13 months following initial presentation) was $17.4 \times 10^9/L$.

Ciclosporin was stopped and the patient was started on three cycles of R-CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone and rituximab) chemotherapy, to which he

CrossMark

To cite: Hindocha S, Gopaluni S, Collins GP, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-211765

responded well. The R-CHOP regimen was given every 21 days for six cycles. On day 1 of each cycle he received: rituximab 375 mg/m² given as an intravenous infusion, cyclophosphamide 750 mg/m² given as an intravenous bolus, hydroxydaunorubicin 50 mg/m² given as an intravenous bolus and vincristine 1.4 mg/m² given as an intravenous infusion. Oral prednisolone was given for the first 5 days of each cycle at a dose of 100 mg/day. By the end of this treatment, the patient's renal function improved to a creatinine level of 107 µmol/L (1.21 mg/dL), serum albumin to 33 g/L and his urine protein creatinine ratio had also improved significantly to 127 mg/mmol.

He has remained in partial remission for 2 years following his treatment for MCL. His creatinine is stable and his proteinuria is just over 100 mg/mmol. He is under regular haematology follow-up.

DISCUSSION

FSGS is the most common histological lesion in adult idiopathic nephrotic syndrome, accounting for 35% of all cases and over 50% of cases among African-American.² It is important to differentiate between primary and secondary FSGS, as the treatment is distinctly different.

The cause for primary FSGS may be related to a circulating factor causing injury to visceral epithelial cells or podocytes. Secondary FSGS usually results from glomerular hypertrophy and hyperfiltration, and is seen in a number of conditions such as obesity, HIV infection, previous renal injury, nephron loss, etc.

MCL, a mature B-cell lymphoma, constitutes around 6% of all non-Hodgkin's lymphomas (NHLs). Around 20–30% of patients have a leukaemic component at presentation.³ The genetic hallmark of MCL is the translocation t(11;14)(q13;q32) leading to aberrant expression of cyclin D1, which is not typically expressed in normal lymphocytes. MCL is one of the most difficult B-cell lymphomas to treat.

In our case, the renal diagnosis predated the diagnosis of MCL by almost a year. We propose that a paraneoplastic manifestation does not necessarily follow the neoplasm, and can predate the illness, therefore requiring a high degree of suspicion and vigilance. In a retrospective study of 700 patients with NHL, it was shown that glomerulonephritis may precede, coexist or even follow the diagnosis of lymphoma by several years.⁴ In our patient, renal biopsy at presentation showed that 10% of the cortex had established interstitial fibrosis and tubular atrophy. We hypothesise that, with prolonged heavy proteinuria, he may have sustained more interstitial fibrosis and tubular atrophy, which would explain the persistent non-nephrotic range proteinuria. The fact that the FSGS was not very responsive to standard immunosuppressive therapy, yet showed a good response following successful treatment of MCL, supports their relationship. The patient remains in remission from an MCL and a nephrosis perspective to this day, after successful treatment of MCL.

Only one other case of FSGS in association with MCL has been described.¹ Lymphocytosis was the key to diagnosis in both cases (including ours). Neither of the cases had other clinical features of lymphadenopathy, hepatosplenomegaly or B symptoms, and CT imaging revealed only a borderline mediastinal lymph node. FISH analysis showed an 11:14 translocation, which is a pathognomonic feature of MCL. Patients responded well to R-CHOP chemotherapy, with improvement in renal function and nephrotic syndrome.

Even though ciclosporin has been linked to NHL, our patient had only been on it for slightly over a year, and the ciclosporin levels were modest.⁵ The lymphocyte count was seen to rise soon after starting ciclosporin, arguing against this possibility.

The mechanism behind the causation of FSGS in Hodgkin's lymphoma is thought to be related to altered T-cell function causing abnormal secretion of cytokines (vascular endothelial growth factor, transforming growth factor-β) leading to enhanced glomerular permeability.^{6–8} However, such evidence found in Hodgkin's lymphoma is not found in cases of NHL.

Da'as *et al.*,⁴ in their review of 700 patients with NHL and chronic lymphocytic leukemia, found 83 patients with renal involvement. Of these, 66 patients had NHL and only 4 patients had glomerulonephritis. The authors also reported that a search of the literature showed glomerular lesions in only 37 patients with NHL. Of these, only three patients had FSGS.⁴ Only eight patients with MCL have been reported to show kidney involvement. Four patients had proliferative glomerulonephritis, one had FSGS, two cases had renal infiltration and one case developed tubulointerstitial nephritis.⁹

Learning points

We want to emphasise the following key points:

- ▶ This is the second case to be reported showing an association between focal segmental glomerulosclerosis (FSGS) and mantle cell lymphoma (MCL).
- ▶ There is a need to maintain a high clinical index of suspicion for haematological malignancies in patients presenting with nephrotic syndrome and lymphocytosis and/or lymphadenopathy, and who fail to respond to standard FSGS therapy.
- ▶ FSGS related to MCL may respond well to treatment of MCL.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Wong CF, Mohteshamzadeh M, Arsalanzadeh B, *et al.* Successful treatment of focal segmental glomerulosclerosis in association with mantle cell lymphoma. *Ren Fail* 2007;29:363–6.
- 2 Haas M, Meehan SM, Karrison TG, *et al.* Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976–1979 and 1995–1997. *Am J Kidney Dis* 1997;30:621–31.
- 3 Pérez-Galán P, Dreyling M, Wiestner A. Mantle cell lymphoma: biology, pathogenesis, and the molecular basis of treatment in the genomic era. *Blood* 2011;117:26–38.
- 4 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.
- 5 Durnian JM, Stewart RMK, Tatham R, *et al.* Cyclosporin-A associated malignancy. *Clin Ophthalmol* 2007;1:421–30.
- 6 Doussis-Anagnostopoulou IA, Talks KL, Turley H, *et al.* Vascular endothelial growth factor (VEGF) is expressed by neoplastic Hodgkin-Reed-Sternberg cells in Hodgkin's disease. *J Pathol* 2002;197:677–83.
- 7 Mallouk A, Pham P-TT, Pham P-CT. Concurrent FSGS and Hodgkin's lymphoma: case report and literature review on the link between nephrotic glomerulopathies and hematological malignancies. *Clin Exp Nephrol* 2006;10:284–9.
- 8 Newcom SR, Gu L. Transforming growth factor beta 1 messenger RNA in Reed-Sternberg cells in nodular sclerosing Hodgkin's disease. *J Clin Pathol* 1995;48:160–3.
- 9 Lubas A, Mróz A, Smosna J, *et al.* Membranoproliferative glomerulonephritis, mantle cell lymphoma infiltration, and acute kidney injury. *Int Urol Nephrol* 2013;45:1489–94.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow