Glomerulonephritis preceding late relapse of Hodgkin's disease

W.A. Lynn and R.E. Marcus¹

Departments of Medicine and ¹Haematology, Hillingdon Hospital, Uxbridge, Middlesex UB8 3NN, UK.

Summary: We report a case of focal sclerosing glomerulonephritis which developed 11 years after successful treatment of nodular sclerosing Hodgkin's disease. Hodgkin's disease relapsed 7 months later and responded completely to combination chemotherapy with simultaneous improvement in renal function. This case shows that relapse of Hodgkin's disease may occur after a 10 year interval and furthermore it may be preceded by nephrotic syndrome. Renal disease in such cases may not recover until the underlying Hodgkin's disease is treated.

Introduction

Glomerulonephritis is a well recognized complication of Hodgkin's disease,¹ and non-Hodgkin's lymphoma.^{2,3} In some reports it has preceded clinical Hodgkin's disease,⁴ in others it has occurred at the time of presentation.¹ It has also been described after successful induction of remission.⁵ We present a patient in which late relapse of Hodgkin's disease was preceded by glomerulonephritis which resolved only after combination cytotoxic chemotherapy.

Case report

A 62 year old female schizophrenic presented in September 1975 with malaise, weight loss and axillary lymphadenopathy. Clinical examination revealed hepatomegaly. Renal function was normal and there was no proteinuria. Axillary node biopsy showed nodular sclerosing Hodgkin's disease, and she was treated with MOPP (mustine, vincristine, procarbazine and prednisolone).⁶ She entered complete remission after two courses and received a total of four cycles of therapy.

She remained well until April 1986 when she developed ankle oedema with proteinuria. Investigations at that time showed: blood pressure 140/90 mmHg, haemoglobin 12.4 g/dl, erythrocyte sedimentation rate (ESR) 70 mm/h, sodium 136 mmol/l, potassium 4.6 mmol/l, urea 18.2 mmol/l, creatinine 648 μ mol/l, albumin 16 g/l, 24-hour urinary protein 20.4 g/l (non-selective pattern) and

creatinine clearance 4 ml/min. Her renal function deteriorated and haemodialysis was instituted. Renal biopsy consisted of 12 glomeruli of which 4 showed hyaline sclerosis with granular deposition of IgM and C3 within the abnormal glomeruli consistent with a diagnosis of focal sclerosing glomerulonephritis. She was dialysed for 6 weeks with improvement in renal function. However, her serum creatinine remained elevated and she continued to have proteinuria. In June 1986 she received a 6-week course of oral prednisolone starting at 60 mg daily and reducing by 10 mg per week.

In November 1986 she again presented with axillary lymphadenopathy. Haemoglobin was 13.2 g/dl, ESR 67 mm/h, serum albumin 30 g/l, creatinine 253 μ mol/l, 24-hour urinary protein 2.6 g/l and creatinine clearance 17 ml/min. Computerized tomography also showed mediastinal lymphadenopathy. Biopsy of the axillary mass confirmed recurrent nodular sclerosing Hodgkin's disease. She was given LOPP (vincristine, chlorambucil, procarbazine and prednisolone).⁶ She entered complete remission after two courses and in view of her frailty only four cycles of therapy were given. Renal function improved steadily during this period and at follow-up 3 months later there was no evidence of Hodgkin's disease, her serum creatinine was 96 μ mol/l, creatinine clearance 85 ml/min and the proteinuria less than one gram in 24 hours.

Discussion

Late relapse of Hodgkin's disease is extremely rare. The majority of patients relapse within the first 2

Correspondence: W.A. Lynn, M.B., B.S., M.R.C.P.

Accepted: 4 December 1987

years, with smaller numbers between 2 and 5 years. In the Stanford series of 1225 consecutive patients treated between 1961 and 1977 39% relapsed overall. Of these only six relapsed after remaining disease-free for more than 5 years, and in only one case did Hodgkin's disease recur after more than 10 years.⁷ Other series confirm this pattern of disease recurrence.^{8,9} In a recent analysis of 692 patients with stage III or IV Hodgkin's disease, submitted to the British National Lymphoma Investigation (BNLI), only seven patients relapsed after more than 5 years of complete remission and in only one case relapse occurred after a disease-free interval of 10 years (BNLI, personal communication).

Glomerulonephritis associated with Hodgkin's disease is well described although uncommon. The renal histology of 24 cases was reviewed in 1976,¹⁰; 66% of cases showed minimal change glomerulonephritis, 20% were membranous glomerulonephritis and 14% were not classified. Another series¹¹ reveals a similar distribution, but crescentic glomerulonephritis¹² and focal sclerosing glomerulonephritis^{13,14} have also been described. The renal condition occurs most frequently at the time of presentation with Hodgkin's disease.¹ It may, however, precede clinically detectable Hodgkin's disease, although only two cases have been reported where this interval was more than one year.^{4,15} Two cases have also been reported where glomerulonephritis developed after clinical remission of Hodgkin's disease.⁵ However, both cases subsequently received immunosuppressive therapy for their glomerulonephritis and therefore suppression of subclinical Hodgkin's disease cannot be excluded.

In our case renal function was normal until her presentation with the nephrotic syndrome. The episode of acute renal failure was probably due to acute tubular necrosis. This would explain her partial recovery in renal function after a short period of haemodialysis. However, her renal function remained abnormal until treatment of recurrent Hodgkin's disease when it rapidly returned to normal. It is also possible that the oral prednisolone given during June and July had a temporary suppressing effect on her nephrotic

syndrome or under underlying Hodgkin's disease or both.

Moorthy in 1976¹⁶ reviewed 33 cases of nephrotic syndrome associated with Hodgkin's disease. Twenty-one patients received chemotherapy with remission of the nephrotic syndrome in all cases, 9 cases received radiotherapy alone with resolution of renal disease in 7, in 2 patients surgical excision of nodes was the only treatment and the nephrotic syndrome resolved in both cases. This would suggest that the renal lesion depends upon the presence of active Hodgkin's disease. Effective therapy is then followed by recovery in renal function.

The mechanism of renal damage is unclear but direct tumour infiltration or amyloid deposition were not seen in these series. It has been proposed that renal damage may result from a nephrotoxic substance released by Hodgkin's disease cells,¹ by local effects of abnormal T lymphocytes¹⁶ or by tumour antigens inducing immune-complex mediated glomerular damage.¹⁷ It is of interest that focal sclerosing glomerulonephritis without associated Hodgkin's disease generally responds poorly to therapy and tends to lead to progressive renal impairment.¹⁸ In this case and others^{13,14} there was recovery of renal function after treatment of the Hodgkin's disease. This suggests that focal sclerosing glomerulonephritis may have a different prognosis when associated with Hodgkin's disease. Alternatively, removing the stimulus for further renal damage may allow recovery of kidney function.

The combination of nephrotic syndrome and Hodgkin's disease is rare. Nevertheless this possibility should be entertained and excluded when a patient with a past history of treated Hodgkin's or non-Hodgkin's lymphoma presents with renal disease, especially in those patients where renal replacement therapy might not otherwise be contemplated.

Acknowledgements

Our thanks to Dr L. H. Sevit and Dr R. Britt for permission to report on their patient.

References

1. Plager, J. & Stutzman, L. Acute nephrotic syndrome as a manifestation of active Hodgkin's disease. *Am J Med* 1971, **50**: 56-66.
2. Belghiti, D., Vernant, J., Hirbec, G., Gubler, M., Andre, C. & Sobel, A. Nephrotic syndrome associated with T-cell lymphoma. *Cancer* 1981, **47**: 1878-1882.
3. Giron Gonzalez, J.A., Yebra Bango, M., Merino Morales, F., Menezes Caro, J.L., Diego Marin, F.J. & Durantez Martinez, A. The association of non-Hodgkin's lymphoma with glomerulonephritis. *Postgrad Med J* 1986, **62**: 1141-1145.

4. Huisman, R.M., de Jong, P.E., de Zeeuw, D., van Imhoff, G.W. & van der Hem, G.K. Nephrotic syndrome preceding Hodgkin's disease by 42 months. *Clin Nephrol* 1986, **26**: 311–313.
5. Shapiro, C.M., Vander Laan, B.F., Jao, W. & Sloan, D.E. Nephrotic syndrome in two patients with cured Hodgkin's disease. *Cancer Res* 1972, **31**: 1828–1833.
6. Hancock, D.W. Randomised study of MOPP against LOPP in advanced Hodgkin's disease. *Radiother Oncol* 1986, **7**: 215–221.
7. Kaplan, H. In: *Hodgkin's Disease*. Harvard University Press, 1980. pp 549–597.
8. Frei, E. & Gehan, E.A. Definition of a cure for Hodgkin's disease. *Cancer Res* 1972, **31**: 1828–1833.
9. de Vita, V.T., Simon, R.M., Hubbard, L.M. *et al.* Curability of advanced Hodgkin's disease – long term follow up of MOPP treated patients at the National Cancer Institute. *Ann Intern Med* 1972, **92**: 587–595.
10. Gagliano, R.G., Costanzi, J.J., Beathard, G.A., Sarles, H.E. & Bell, J.D. The nephrotic syndrome associated with neoplasia: an unusual paraneoplastic syndrome. *Am J Med* 1976, **60**: 1026–1031.
11. Routledge, R.C., Hann, I.M. & Jones, P.H. Hodgkin's disease complicated by the nephrotic syndrome. *Cancer* 1976, **38**: 1735–1740.
12. Petzel, R.A., Brown, D.C., Staley, N.A., McMillen, J.J., Sibley, R.K., & Kjellstrand, C.M. Crescentic glomerulonephritis and renal failure associated with malignant lymphoma. *Am J Clin Pathol* 1979, **71**: 728–732.
13. Phillips, M., Neild, G.H., Cameron, J.S., Williams, D.G. & Amlot, P. Hodgkin's disease and focal glomerulosclerosis (letter). *N Engl J Med* 1983, **309**: 1389–1390.
14. Watson, A., Stachura, I., Fragola, J. & Bourke, E. Focal glomerulosclerosis in Hodgkin's disease. *Am J Nephrol* 1983, **3**: 228–232.
15. Kramer, P., Sizoo, W. & Twiss, E.E. Nephrotic syndrome in Hodgkin's disease. *Neth J Med* 1981, **24**: 114–119.
16. Moorthy, A.V., Zimmerman, S.W. & Burkholder, P.M. Nephrotic syndrome in Hodgkin's disease. *Am J Med* 1976, **61**: 471–477.
17. Froom, D.W., Franklin, W.A., Hano, J.E. & Potter, E.V. Immune deposits in Hodgkin's disease with nephrotic syndrome. *Arch Pathol* 1980, **94**: 547–553.
18. Glasscock *et al.* Primary glomerular diseases. In: *The Kidney*, 2nd edition. Saunders, W.B., Philadelphia, 1981.