The association of non-Hodgkin's lymphoma with glomerulonephritis

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Summary: Paraneoplastic glomerulonephritis is an infrequent complication in the course of non-Hodgkin's lymphoma (21 cases to date). We report a modality not previously described: mesangioproliferative glomerulonephritis and mixed lymphocytic lymphoma, and review the literature on the subject. The onset of the two processes was simultaneous. Antitumour treatment induced simultaneous remission of the lymphoma and glomerulonephritis.

Introduction

The nephrotic syndrome is a paraneoplastic manifestation in 10% of all adult cases in some series (Lee *et al.*, 1966; Eagen & Lewis, 1977). Hodgkin's disease has been the most commonly associated tumour, but cases have also been described in connection with other haematological diseases and carcinomas (Fer *et al.*, 1981; Richmond *et al.*, 1962).

There are only a few publications which associate glomerulonephritis (GN) with non-Hodgkin's lymphomas (NHL). We report a case of NHL presenting with nephrotic syndrome and renal failure due to mesangioproliferative GN.

Case report

A 67 year old white woman was admitted to our hospital because of generalized oedema for 8 months.

On physical examination, the only positive findings were inguinal lymphadenopathy and anasarca. Laboratory data showed a normal haemogram; erythrocyte sedimentation rate, 110 mm in the first hour; urine protein excretion, 6.60 g/24 h; hyaline-cellular and granular casts; 9 to 10 erythrocytes and 15 to 20 leucocytes per high power field; serum total proteins, 41 g/l; albumin, 21 g/l; creatinine clearance, 15 ml/minute. The following results were either normal or negative: urine culture, immunoelectrophoresis, antistreptolysin titre, hepatitis B virus serology, VDRL, antinuclear antibodies, complement, cryoglobulin and circulating immune complexes.

Lymph gland biopsy showed mixed diffuse lym-

Figure 1 Lymph gland biopsy showing abnormal architecture with diffuse cellularity and loss. Evident destruction of the ganglion with diffuse cellularity and loss of the marginal sinus (light microscopy). (H & E $\times$ 400)

phocytic lymphoma (Figure 1). Chest X-ray, pedal lymphogram and hepatic and bone marrow biopsies were normal.

Kidney biopsy was performed from which eight glomeruli were obtained, some of them augmented in size and with an elevated number of nuclei. Deposits of fuchsinophilic material were detected in the basement membrane and the mesangium. No signs of amyloidosis, vasculitis or infiltration by lymphoma were observed (Figure 2). Granular deposits of IgM and C₃ were detected by immunological techniques in mesangium and capillaries.

The patient was treated with CVP (cyclophosphamide, vincristine and prednisone) and diuretics. The treatment was continued for a total of 12 months.

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Figure 2 Glomerulus with augmented mesangial matrix, occupying the entire capsular area. (a) Haematoxylin-eosin $\times 400$ and (b) haematoxylin-eosin and silver stain $\times 800$.

There was complete remission of tumour and nephropathy which continued 7 years after presentation.

Discussion

We have found 22 cases of NHL and different types of GN, including our own. We have excluded the six cases described by Gupta (1973) and one of those described by Muggia & Ultmann (1971) given the absence of precise histological data. The remaining 15 cases are shown in Table I.

The average age of the patients was 47 years, range 7–74 years and the male: female ratio was 10:4. The patient's sex is not mentioned in one case (Gluck *et al.*, 1973).

The presentation of GN and NHL was simultaneous in seven cases. Four cases presented with clinical manifestations of nephropathy (nephrotic syndrome in two and nephrotic syndrome plus kidney failure in the other two). Lymphadenopathy was the first mani-

festation in the three cases. There is no information regarding the presentation sequence in the remaining case.

The pathology of NHL is difficult to compare due to the diversity of the nomenclature employed in the classification. The majority (9 cases) were in stage IV, according to the Ann Arbor staging system (Carbone *et al.*, 1971), at the time of diagnosis.

A wide range of histological glomerular lesions was detected as shown in Table I. In cases 12 and 13, besides GN, renal infiltration by lymphoma was observed. It is not possible to establish a relationship between the histological types of NHL and GN.

In ten cases the evolution of both processes is mentioned explicitly. Eight of them (cases 2, 7, 8, 9, 10, 11, 12 and 15) presented parallel courses in that the progression or remission of the tumour was accompanied by a similar course in the kidney disease. The clinical course was independent in cases 6 and 13. In the case described by Hyman *et al.* (1973) (case 6), GN appeared 4 months after the appearance of the lymphoma, which was at that time in complete remission. Banks *et al.* (1984) (case 13) describe the onset of focal proliferative GN in a patient who had been diagnosed as having a lymphoma 13 years earlier. Partial remission of the nephropathy was achieved and maintained by means of a specific treatment, despite the progression of the lymphoma.

Minimal change glomerulonephritis has been the most common histological type of nephropathy associated with Hodgkin's disease (Eagen & Lewis, 1977). However, proliferative (Lowry *et al.*, 1971), membranous (Row *et al.*, 1975) and focal segmental sclerosis (Powderly *et al.*, 1985) glomerular lesions have been described. There is, however, no predominant histological type associated with non-Hodgkin's lymphoma.

Glomerulonephritis can appear before, simultaneously or after the appearance of the lymphoma, whether it be Hodgkin's or non-Hodgkin's. When glomerular disease occurs at the same time as lymphoma, treatment of the neoplasia may suppress associated nephropathy. Although the antineoplastic drugs might act directly on the glomerulus, the regression after radiation therapy to extrarenal areas suggests that a direct effect of therapy on the glomerulus is not always the cause of the therapeutic response of the nephropathy.

The pathogenesis of GN in this type of patient is not clear. Alteration of T lymphocytes in patients with neoplasms (Shalhoub, 1974; Moorthy *et al.*, 1976) has been mentioned as the disorder responsible for minimal-change nephropathy. In other histological types, the occasional finding of tumoral antigens and antibodies and of antigen-antibody complexes in serum and renal eluate (Costanza *et al.*, 1973; Mendes Da Costa *et al.*, 1974; Couser *et al.*, 1974; Sutherland *et*

Table I Non-Hodgkin's lymphoma and glomerulonephritis

Case	Histological types NHL	GN	Mode of onset of nephropathy NS	RF	Presentation sequence	Response of GN to treatment of NHL	Reference
1	Lymphosarcoma	Minimal-change	+		Onset of NHL 12 months later	No treatment of NHL	Ghosh & Muehrcke (1970)
2	Reticulum-cell	Membrano-proliferative	+		Simultaneous	PR initial Recurrence of NHL: no response	Muggia & Ullmann (1971)
3	Well differentiated diffuse lymphocytic	Diffuse proliferative with crescents	+	+	Simultaneous	No response	Sagel <i>et al.</i> (1971)
4	Lymphosarcoma	Membranous	+		Onset of NHL 8 months later	No treatment of NHL	Rabkin <i>et al.</i> (1973)
5	Lymphosarcoma	Membranous	+		ND	ND	Gluck <i>et al.</i> (1973)
6	Burkitt	Membrano-proliferative	+	+	Onset of GN 4 months later	No relation	Hyman <i>et al.</i> (1973)
7	Well differentiated diffuse lymphocytic	Minimal-change	+	+	Simultaneous	CR	Gagliano <i>et al.</i> (1976)
8	Well differentiated diffuse lymphocytic	Diffuse proliferative with crescents		+	Simultaneous	PR	Petzel <i>et al.</i> (1979)
9	Well differentiated diffuse lymphocytic	Diffuse proliferative with crescents		+	Simultaneous	Death 3 days after diagnosis	Petzel <i>et al.</i> (1979)
10	Lymphoma T	Segmentary and focal sclerosis	+	+	Simultaneous	PR	Belghiti <i>et al.</i> (1981)
11	Diffuse convoluted T cell lymphocytic	Segmentary and focal sclerosis	+	+	Onset of NHL several weeks later	CR	Herskowitz <i>et al.</i> (1982)
12	Well differentiated diffuse lymphocytic	Focal proliferative with crescents; invasion by lymphoma	+		Onset of NHL 18 months later	PR	Banks <i>et al.</i> (1984)
13	Well differentiated diffuse lymphocytic	Focal proliferative with crescents; invasion by lymphoma		+	Onset of GN 13 years later	No relation	Banks <i>et al.</i> (1984)
14	Lymphocytic	Rapidly progressive (Type III)		+	Onset of GN 1 year later	PR	Biava <i>et al.</i> (1984)
15	Mixed diffuse lymphocytic	Mesangial	+	+	Simultaneous	CR	Present case

NHL: non-Hodgkin's lymphoma; GN: glomerulonephritis; NS: nephrotic syndrome; RF: renal failure; CR: complete remission; PR: partial remission; ND: no data.

al., 1974; Pascal *et al.*, 1976), suggests an immune complex-mediated mechanism. Helin *et al.* (1980), in a study of 24 patients with different types of neoplasms without clinically manifested kidney disorder, demonstrated the existence of glomerular electron-dense complexes in 11 of them and a significant correlation with the presence of circulating antibodies. From the group of patients dealt with in our review, only one had circulating immune complexes and cryoglobulins were detected in two. Finally, it is possible that the association between neoplasms and GN is a coincidence, with independent evolution presented in some

cases (Hyman *et al.*, 1973; Banks *et al.*, 1984). However, the discovery of a greater incidence of neoplasms in some types of GN (Lee *et al.*, 1966; Gluck *et al.*, 1973; Biava *et al.*, 1984; Row *et al.*, 1975) would lend support to a causal relationship.

In conclusion, we have presented a case of non-Hodgkin's lymphoma associated with nephrotic syndrome and kidney failure which widens the spectrum of glomerulonephritis in connection with this type of lymphoma, extending it to include mesangioproliferative glomerulonephritis, an association which had not been described previously.

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