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CASE REPORT

Small cell lung cancer with paraneoplastic nephrotic syndrome

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Small cell lung cancer with paraneoplastic nephrotic syndrome. E.S. Boon, A.A. Vrij, C. Nieuwhof, J.A. van Noord, E. Zeppenfeldt. ©ERS Journals Ltd 1994.

ABSTRACT: We present a case of nephrotic syndrome, associated with small cell lung carcinoma. Renal biopsy revealed membranous glomerulonephritis, probably due to immune complex deposition with tumour antigen.

Complete remission of the small cell lung carcinoma after chemotherapy was followed by regression of the nephrotic syndrome. This regression persisted even when brain metastases developed, without simultaneous relapse of tumour outside the central nervous system.

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The association of nephrotic syndrome with malignancy has been previously reported [1]. Neoplasm and nephrotic syndrome may occur concomitantly, although the time interval between them may be a year or more [2].

If a nephrotic syndrome presents in an adult patient, underlying malignancy should be considered. It may be found in 10–22% of cases, being more prevalent in the older age group. Bronchogenic carcinoma is rarely associated with nephrotic syndrome [1, 3–6], and may be encountered in 3% of patients initially presenting with nephrotic syndrome [4].

Case report

A 64 year old male patient was admitted to the hospital with progressive weight gain and generalized oedema during the previous four weeks. His medical history included gout and duodenal ulcer. He had smoked 40 pack-years. Several days before admission he had moderate haemoptysis. On physical examination, gross oedema of the periorbital region, hands and legs was present. His body weight was 97 kg. Blood pressure was 170/94 mmHg and pulse 72·min^{-1}. Central venous pressure was not elevated. Heart sounds were normal, without a murmur. On auscultation of the lungs, crackles were present over the left lower lobe. Laboratory results were as follows: erythrocyte sedimentation rate (ESR) 111 mm·h^{-1}, haemoglobin 8.2 mmol·l^{-1}, white cell count 5.5×10^{9}·l^{-1}, sodium 140 mmol·l^{-1}, potassium 5.0 mmol·l^{-1}, serum creatinine 126 µmol·l^{-1} and urea 10.9 mmol·l^{-1}. Creatinine clearance was 63 ml·min^{-1}. Serum albumin was 13.5 g·l^{-1} and immunoelectrophoresis did not reveal paraprotein.

Tests for antinuclear antibody, anti-double-stranded deoxyribonucleic acid (ds-DNA), circulating immune complexes, hepatitis B serum antigen, cryoglobulins, and cold agglutinins were negative. The urine sediment was free of casts and erythrocytes, but the 24 h urine collection revealed proteinuria of 19 g daily. A chest X-ray showed a consolidation in the left lower lobe and a computed tomographic (CT)-scan of the chest disclosed a tumour with mediastinal lymph node enlargements. On fibreoptic bronchoscopy, a tumour was seen at the division of left upper and lower lobe. Biopsies revealed small cell lung carcinoma. Subsequently, a renal biopsy was performed, disclosing membranous glomerulonephritis stage I, with subepithelial deposition of immunoglobulin G (IgG) and complement component C3 (fig. 1). Amyloid deposition could not be demonstrated, and

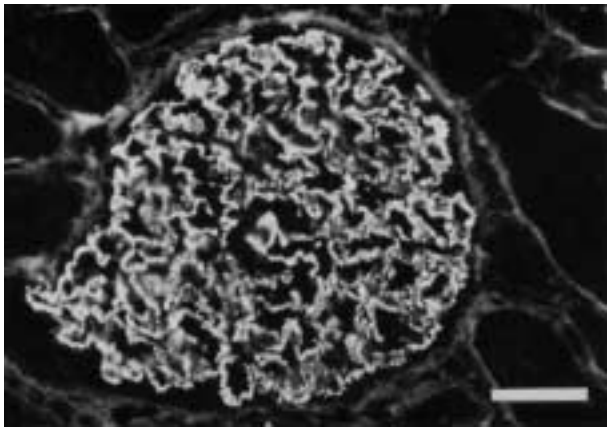

Fig. 1. – Diffuse glomerular granular capillary deposition of immunoglobulin G (IgG), demonstrated by the immunofluorescent technique. (Bar = 50 µm).

renal vein thrombosis was excluded by ultrasound with colour flow mapping. Liver and bone scintigraphy were normal.

Paraneoplastic nephrotic syndrome was diagnosed associated with small cell lung carcinoma (limited disease). Symptomatic treatment consisted of salt restriction, furosemide 40 mg in combination with captopril once daily. Indomethacin was added, without relief of symptoms. Chemotherapy was started with cyclophosphamide 2000 mg, doxorubicin 100 mg and etoposide 200 mg on the first day intravenously, followed by 400 mg etoposide orally on days 3 and 5. After five courses, complete remission was achieved, assessed by fibreoptic bronchoscopy and chest X-ray. Proteinuria decreased during chemotherapy to 1.0 g daily, and serum albumin increased to 29.3 $g \cdot l^{-1}$. Body weight decreased to 92 kg, with disappearance of oedema.

However, the patient was readmitted 5 months later, with headaches and an unsteady gait. CT-scan of the cerebrum revealed multiple brain metastases, for which radiotherapy was given. At that time, proteinuria was 1.7 g in the 24 h urine collection. Chest-X ray and ultrasonography of the liver were normal. Clinical and biochemical signs of bone metastases were absent. The patient died two months later from brain metastases. Postmortem examination was not performed.

Discussion

Nephrotic syndrome, associated with malignancy may be due to amyloidosis, renal vein thrombosis or neoplastic infiltration. However, in most cases, including bronchogenic carcinoma, membranous glomerulonephritis is found. In membranous glomerulonephritis, subepithelial deposition of circulatory immune complexes with tumour antigen damages the glomerular basement membrane, leading to protein leakage. IgG and complement can predominantly be demonstrated. Elution of kidney tissue may yield IgG, specifically reacting with tumour tissue of the lung [3, 7]. Carcinoembryonic antigen (CEA) could also be demonstrated in glomeruli in cases of colonic carcinoma. Some authors report cases of bronchogenic carcinoma with glomerular deposition of immunoglobulin A (IgA), which is intriguing, as it may be encountered in other tumours arising from mucosal areas [8]. Minimal change glomerulonephritis is the principal cause of nephrotic syndrome in Hodgkin's disease. The hypothesis is that T-cell dysfunction leads to cytokine release, which may damage the glomerular basement membrane [2].

The clinical course of patients with nephrotic syndrome associated with bronchogenic carcinoma will be determined by tumour behaviour. Renal insufficiency is rare, and complete regression of the nephrotic syndrome can be expected in 25% of cases in which the tumour can be successfully treated. In half of these patients, improvement of proteinuria can be achieved [9].

In our patient, complete remission of small cell lung carcinoma was followed by regression of the nephrotic syndrome. Chemotherapy probably played a pivotal role by stopping the formation of immune complexes, although the role of the co-medication and the direct effect of cyclophosphamide on the nephrotic syndrome cannot be completely ruled out [10].

Some authors suggest that the reappearance of proteinuria can be used as a marker for tumour recurrence [3]. Despite multiple brain metastases, without tumour relapse outside the central nervous system (CNS), proteinuria did not recur. In our case, this can be explained by the impermeability of the blood-brain barrier for tumour-containing immune complexes. As tumour relapse outside the CNS was not completely ruled out because of the limited restaging examination, an alternative explanation is clonal heterogeneity. The biochemical and immunological characteristics of tumour cells may have been changed during chemotherapy.

We conclude that, particularly in older patients presenting with nephrotic syndrome one should be aware of underlying malignancy, including bronchogenic carcinoma. Successful treatment of the bronchogenic carcinoma leads to improvement or disappearance of proteinuria in 75% of cases.

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