Case Report

Nephrotic syndrome as the presenting feature of malignant thymoma

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Introduction

Nephrotic syndrome is a well-established manifestation of neoplastic disease, but its association with thymoma is rare. Only 18 cases have been reported in the literature and 17 biopsied [1–14]: minimal-change lesions were present in 10 cases, focal segmental glomerulosclerosis in four, proliferative glomerulonephritis in two, and membranous glomerulopathy in one case.

We report two further cases with minimal-change lesions and membranous glomerulopathy respectively. The patients presented with a nephrotic syndrome complicated, in the second case, by pure red cell aplasia.

Case report

Case 1

A 65-year-old male was admitted in June 1994 for generalized oedema with shortness of breath. He presented severe anasarca with a weight gain of 14 kg. He had been well until 1 month before, when swelling was noted after an amarilie vaccination. He had a history of well-treated hypertension, angora pectoris, and asthma.

Renal investigations showed a 24-h proteinuria of 13 g (selectivity 78%); serum total protein: 45 g/l, albumin: 17 g/l; cholesterol: 13.2 mmol/l; creatinine: 220 µmol/l; creatinine clearance: 33 ml/min; there was a small microscopic haematuria. Immunology showed a decrease of IgG but no changes in other immunoglobulins; antinuclear antibody, rheumatoid factor levels, cryoglobulinaemia and ANCA were negative. There was no monoclonal band either in serum or in urine. Haematological parameters and liver tests were normal. An echo-Doppler eliminated renal-vein thrombosis. Percutaneous renal biopsy showed a minimal-change glomerulonephritis: at light-microscopy all glomeruli appeared normal, there were a few epithelial alterations of the proximal tubules and moderate parietal fibrosis of the vessels; with immunofluorescence there was a moderate staining of the mesangium with C3. Renal failure was attributed to the tubular lesions.

The patient was treated with salt restriction, diuretics, and oral steroids after three boluses of 1 g methylprednisolone. Because of steroid resistance, a new renal biopsy was performed 4 months after the first; it confirmed the minimal-change lesions associated with a peritubular lymphocytic infiltration. After three new steroid boluses, oral cyclophosphamide was introduced and steroids slowly tapered, without any response after 3 months. All immunosuppressive agents were then discontinued.

At February 1995 renal failure was aggravated: creatinine was 350 µmol/l, creatinine clearance 20.6 ml/min, and nephrotic syndrome persisted; 24-h protein was 12 g, serum protein 45 g/l, serum albumin 19 g/l; hypertension reappeared; an ACE inhibitor was introduced and proteinuria fell to 5 g/24 h. In August 1995 a superior vena cava syndrome appeared; a mediastinal tumour was discovered on chest X-ray and confirmed on CT. After a mediastinoscopy with biopsy in favour of a thymoma, a surgical resection was performed and removed a 140-g tumour; it was an epithelial cell type of malignant thymoma. The patient did not tolerate this operation; he presented a chylothorax and infectious complications and died rapidly.

Case 2

A 60-year-old female was admitted in April 1994 because of a full-blown nephrotic syndrome: generalized oedema, abdomen swelling, and bilateral pleural effusion, with a weight gain of 12 kg, associated with hypertension 170/100 mm Hg. The patient’s history was unremarkable, except for a diabetes mellitus which had appeared 4 years previously, and for a recent laparotomy for an appendicular peritonitis. Chest X-ray confirmed bilateral pleural effusion. Pleural fluid had 3900 cells/mm³, with 88% lymphocytes. Total protein, LDH in the fluid were 32 g/dl and 499 IU/l respectively. Cultures and pathology of sputum, pleural

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Renal investigations showed a 24-h protein excretion of 7–10 g (selectivity 80%), serum total protein 50 g/l, albumin 17 g/l, cholesterol 6.04 mmol/l, triglyceride 2.31 mmol/l, creatinine 63 μmol/l, creatinine clearance 138 ml/min, blood counts, other haematological parameters, and liver tests were normal. Urine analysis did not reveal haematuria or leukocyturia. Immunology showed no changes in immunoglobulin levels; antinuclear factor, rheumatoid factor, ANCA, and cryoglobulinaemia were negative; there was no monoclonal band in urine, nor in serum; and no plasmocyte proliferation on myelogram. Echocardiography, abdominal echography, and eye ground examination were normal. Percutaneous renal biopsy was performed and showed a stage 1 membranous glomerulonephritis.

The patient was treated with salt restriction and diuretics, and when pleural effusion diminished, right parietal and pleural nodules appeared, as well as mediastinal adenopathies. A CT scan disclosed a mediastinal lobulated mass spread to the left lung field. The biopsy of this mass revealed a lymphoepithelial cell type of malignant thymoma. The right pleural biopsy showed a secondary localization of the thymoma. Chemotherapy associating cisplatinum, cyclophosphamide, epirubicin and methylprednisolone was started, and despite a bad digestive tolerance, continued with a total of 6 monthly courses, from October 1994 to March 1995.

In June 1995, the nephrotic syndrome had remitted: 24-h protein excretion was 1.25 g; serum total protein was 61 g/l, and serum albumin 32.2 g/l. Serum creatinine remained constant at about 100 μmol/l. On CT scan the pleural and mediastinal lesions were dramatically ameliorated but did not disappear. At this time a severe normocytic normochromic anaemia (haemoglobin 7.5 g/dl) appeared with a selective erythroid aplasia in the marrow, necessitating multiple monthly transfusions.

The check-up realized in February 1996 showed an aggravation of the mediastinal and of the pleural lesions, leading to a radiation therapy with a total dose of 64 Gy. At this date, 24-h proteinuria was 0.25 g and serum albumin: 32.7 g/l; creatinine was 138 μmol/l, and creatinine clearance 103 ml/min. Because of the recurrence of anaemia (haemoglobin 5.5 g/dl), cyclosporin A was introduced at a daily dose of 3 mg/kg, aiming at whole blood levels between 100 and 150 ng/ml, and maintaining haemoglobin between 9 and 11 g/dl without transfusion.

In February 1997, after 12 months of cyclosporin A treatment, the patient was admitted for recurrence of anaemia (haemoglobin 5 g/dl), without blood spoliation. Proteinuria was absent, serum protein 65 g/l, serum albumin 34.8 g/l; renal failure was present (creatinine 176 μmol/l, creatinine clearance 35 ml/min), but cyclosporin blood levels were only at 101 ng/ml. CT scan found no evolution of the mediastinal and pleural lesions. The patient received blood transfusions, and the daily dose of cyclosporin A was increased to 4 mg/kg. One month later renal function had not changed; haemoglobin was 7.4 g/dl and cyclosporin blood level at 129 ng/ml.

Discussion

Our two cases document that a nephrotic syndrome may be the presenting feature of a thymoma; this is unusual [5,8], as in most previous reports, thymoma had been known before the nephrotic syndrome appeared after a delay of 1–15 years (average 3.4 years) following thymectomy or medical treatment, often without evidence of recurrence. Our first case, manifesting a steroid-resistant nephrotic syndrome, had minimal-change lesions, as found in most such cases [3–5,7,10–12,14]. Our second had membranous glomerulopathy, which remitted after treatment of the thymoma: this is reminiscent of what had previously been observed in cases of membranous glomerulonephritis related to solid tumour. In the only other case of membranous glomerulonephritis and thymoma [3], the nephrotic syndrome occurred 3 years after thymectomy with no evidence of recurrent thymoma.

In patients with thymoma, nephrotic syndrome is rare: only two cases were reported in a review of 960 cases of thymoma [15]. Overall 20 cases have been reported, including our observations; only 19 had renal biopsy; histological lesions are given in Table 1. The histological type of the thymoma was noted in 14 cases and was lymphocytic in three, epithelial in six and lymphoepithelial in five (Table 1).

Moreover, the presence of elevated antinuclear antibodies titres in up to 50% of thymic neoplasia patients [16], as well as the presence of pure red-cell aplasia as in our second case, of hypogammaglobulinaemia, or of myasthenia gravis point to frequent presence of T-cell dysfunction. This may also be related to the genesis of the nephrotic syndrome, via production of a lymphokine increasing glomerular basal membrane permeability. This hypothesis could explain the high proportion of minimal-change lesions and focal segmental glomerulosclerosis in patients with a nephrotic syndrome associated with thymoma. On the other hand, the occurrence of membranous glomerulonephritis, as in our second case, is consistent with autoimmunity or an antigen–antibody complex deposition, as is commonly seen in solid tumours. Scadding et al. [4] suggested that azathioprine may be responsible for the occurrence of glomerulonephritis because 9% of their patients with thymoma receiving this drug developed a nephrotic syndrome. This observation was probably the result of coincidence, since the majority of patients including ours had not received azathioprine.

The renal outcome of the reported cases was variable (Table 1). When the nephrotic syndrome was the presenting feature or when it appeared at the time of a recurrence of thymoma, its resolution depended on whether treatment of the thymoma was successful or not. In the other cases, an occasional response to
treatment with steroids alone or in combination with other immunosuppressive agents was noted. The incidence of pure red-cell aplasia in thymoma is close to 5%. It is an indicator of poor prognosis [17–19]. Thymectomy, corticosteroids, immunosuppressive therapy, and high-doses of intravenous gammaglobulins are the most effective forms of treatment, but therapeutic failures and relapses are frequent. Cyclosporin A has been used successfully, as was also the case in our second patient, after other treatment had failed [19–21]. In the future cyclosporin A should be considered as a first-line treatment.

### References


### Table 1. Reported cases with thymoma and nephrotic syndrome

<table>
<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Thymoma</th>
<th>Renal histology</th>
<th>Delay (years)</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>1977</td>
<td>Yoshinaga</td>
<td>64</td>
<td>M</td>
<td>EC</td>
<td>PGN</td>
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<td>Dead</td>
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<td>LC</td>
<td>MGN</td>
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<tr>
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<td>MC</td>
<td>MCN</td>
<td>3.5</td>
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<td>Scadding</td>
<td>64</td>
<td>F</td>
<td>EC</td>
<td>FSGS</td>
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<td>1986</td>
<td>Adachi</td>
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<td>F</td>
<td>–</td>
<td>FSGS</td>
<td>4</td>
<td>Dead</td>
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<tr>
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<td>Hirokawa</td>
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<td>Oriso</td>
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<td>–</td>
<td>MCN</td>
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<tr>
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<td>M</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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<tr>
<td>1990</td>
<td>Chan</td>
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<td>F</td>
<td>–</td>
<td>MCN</td>
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<td>1992</td>
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<tr>
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<tr>
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<tr>
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</tbody>
</table>

M, male; F, female; LC, lymphocytic cell type; EP, epithelial cell type; LE, lymphoepithelial cell type; MCN, minimal-change nephropathy; FSGS, focal segmental glomerulosclerosis; MGN, membranous glomerulonephritis; PGN, proliferative glomerulonephritis.