# MINIMAL CHANGE GLOMERULOPATHY IN TWO PATIENTS AFTER THYMECTOMY

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## ABSTRACT

**Two myasthenia gravis patients developed nephrotic syndrome due to minimal change glomerulopathy 3 to 14 years after thymectomy for malignant thymoma. Impaired cellular and humoral immunity has been documented in patients with thymoma and persists after thymectomy. The occurrence of minimal change disease lends support to the hypothesis that the glomerulopathy is secondary to T-cell dysfunction, resulting in production of a lymphokine which increases glomerular basement membrane permeability.**


**Keywords:** Thymoma, minimal change glomerulopathy, myasthenia gravis

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## INTRODUCTION

The first case of minimal change glomerulopathy associated with malignant thymoma was reported by Varsano et al (1). Scadding et al (2) described several patients developing various forms of glomerulonephritis after thymectomy for epithelial thymoma and myastenia gravis. Here we report 2 patients with myasthenia gravis who developed minimal change glomerulopathy 3 to 14 years post-thymectomy for malignant thymoma. The possible mechanism for the association will be briefly discussed.

## CASE REPORTS

**Case 1 :** MD, a 57-year-old woman, had thymectomy in 1973 for malignant thymoma, and underwent pleurectomy in 1984 for secondaries. She subsequently developed myasthenic symptoms and was treated with a course of radiotherapy and chemotherapy, then maintained on pyridostigmine and steroid. All treatments were discontinued in July 1986. She remained relatively well till January 1987. When she presented to us, she had generalized oedema, with tender superficial leg veins. She had heavy proteinuria of 27 G daily. Investigations revealed normal blood counts, urea = 18.3 mmol/l; creatinine = 0.136 mmol/l; albumin = 21 g/l; globulin = 23 g/l; cholesterol = 9.8 mmol/l; antinuclear factor was 1:250; anti-DNA and rheumatoid factor were negative; C3 = 118 mg/dl (normal range established in our laboratory 60-130); C4 = 35 mg/dl (normal 13-60); IgG = 400 mg/dl (normal 700-1850); IgA = 180 mg/dl (normal 90-450); IgM = 146 mg/dl (normal 50-300); IgE = 6 IU/ml (normal <100). A renal venogram performed showed patent renal veins and inferior vena cava. Renal biopsy showed eight glomeruli in paraffin sections: one had capsular fibrosis; the rest had occasional segmental increase in mesangial matrix and cells. Tubules, interstitium and vessels were unremarkable. Cryostat sections showed 5 glomeruli with negative immuofluorescent staining for IgG, IgA, IgM, Clq, BIC and fibrin. There was extensive effacement of foot processes on electron microscopy. Minimal change glomerulopathy was diagnosed and prednisolone started at a dose of 60 mg per day. However, renal function continued to deteriorate. She became dyspnoeic, and chest X-ray showed diffuse hilar shadows. Despite continuous arteriovenous haemofiltration, ceftazidime and high-dose cotrimoxazole and later ventilator support, she died. Autopsy could not be obtained.

**Case 2:** LKL, a 37-year-old-woman, had myasthenia gravis in 1984. At thymectomy, thymoma deposits were found in the thymus, the chest wall and the diaphragm, and she received postoperatively radiotherapy to the mediastinum. Her myastenic symptoms were controlled with pyridostigmine. In February 1987, she presented to our hospital because of generalised oedema. Investigations revealed the following: urea = 4.2 mmol/l; creatinine = 0.069 mmol/l; albumin = 15 g/l; globulin = 32 g/l; cholesterol = 11.4 mmol/l; antinuclear factor and rheumatoid factor were negative; C3 = 152 mg/dl; C4 = 52 mg/dl; IgG = 1352 mg/dl; IgA = 205 mg/dl; IgM = 221 mg/dl. Urine microscopy did not reveal active urinary sediments and 24-h urinary protein excretion was 7 g. A renal biopsy was performed. 5 glomeruli were seen in paraffin sections. All appeared normal by light microscopy. A few convoluted tubules were atrophic. The cryostat sections showed 5 glomeruli displaying a weak peripheral interrupted immunofluorescent staining for IgG and IgM. Electron microscopy showed extensive foot process effacement and slight increase in mesangial matrix. The picture was that of minimal change glomerulopathy. She was given prednisolone 60 mg per day and

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her nephrotic syndrome remitted within one week. The dose of prednisolone was tapered off over 4 weeks and at last follow-up she remained in remission. Before the initiation of steroid therapy, immunological tests on the patient's T and B lymphocytes were performed. The results are as follows: total lymphocyte count = 7.6 x $10^8$/1 (normal 8-34 x $10^8$/1); OKT4 = 1.38 x $10^8$/1 (normal 5-13.6 x $10^8$/1); OKT8 = 2.81 x $10^8$/1 (normal 2.9-10.3 x $10^8$/1) OKT4:OKT8 = 0.49 (normal range: 0.9-2.7). PHA stimulation: 76875 cpm/$10^6$ cells (normal range: 41000-225000); ConA stimulation: 29905 cpm/$10^6$ cells (normal range = 7500-64000). Spontaneous and pokeweek mitogen(PWM)-induced plague forming cells (PFC) were measured by a previously described technique (3). Spontaneous immunoglobulin secreting cells (PFC/$10^6$ cells): IgG producing cells = 1125 (normal range: 50-800), IgA-producing cells = 1325 (normal range = 200-1750); IgM-producing cells = 925 (normal range = 25-700). PWM-induced (0.5 ug/ml) PFC/$10^6$ IgG = 840 (normal range = 2000-22000): IgA = 280 (normal range = 1000-23000): IgM = 560 (normal range = 2000-35000).

## DISCUSSION

Thymoma has been associated with other types of glomerulonephritis (2, 3), but the association with minimal change disease is most interesting in that it seems to support the hypothesis that minimal change glomerulopathy is caused by T-cell dysfunction resulting in production of a lymphokine which increases glomerular basement membrane permeability (5). Impaired cellular and humoral immunity is well-documented in patients with thymoma and persists despite thymectomy (6). As shown in case 2, there was a marked reduction in CD4+(helper-inducer) cells; the increased spontaneous Ig-secretion suggested in-vivo B-cell activation. Recently, a soluble immune response suppressor, a lymphokine produced in vitro by ConA-activated T-suppressor cells, was isolated in the serum and urine of steroid-responsive nephrotic patients (6). It is interesting to speculate whether thymectomised patients who develop the nephrotic syndrome also produce such a immune response suppressor(s).

One of our patients had had chemotherapy; both had had local radiotherapy. Scadding et al (2) reported an incidence of 9% of their myasthenic patients developing glomerulonephritis post-thymectomy after being on azathioprine for 2 years or more. They postulated a contributory role of chronic immunosuppression towards development of glomerulonephritis, which varied from focal segmental glomerulosclerosis, focal proliferative to minimal change glomerulopathy.

It was interesting to note that LKL, whose myasthenia was easily controlled with pyridostigmine while nephrotic,noticed pronounced worsening of symptoms after proteinuria abated. It supported previous observation (2) that loss of anti-acetylcholine receptor antibodies in urine resulted in improvement of myasthenia.

The death of case 1 remained uncertain. Acute renal failure associated with minimal change disease had been reported by several authors (8 - 10). Hypovolemia, acute tubular necrosis and severe renal interstitial oedema were listed as the possible causes. Still the relentless clinical course, despite active treatment, suggested that focal glomerulosclerosis might be the primary lesion, rather than minimal change disease. Also, the immunocompromised state of the patient - being nephrotic, on steroid treatment albeit for a short period, and thymectomized would render her prone to opportunistic infections such as pneumocystis carinii. It was unfortunate that a post-mortem could not be obtained.

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