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# The syndrome of autoimmune interstitial nephritis and membranous nephropathy

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**Abstract.** A 2-year-old male patient was evaluated for Fanconi syndrome with hypertension and failure to thrive. Renal biopsy revealed autoimmune interstitial nephritis with membranous nephropathy. The patient developed autoimmune hemolytic anemia and intractable diarrhea with villous atrophy of the jejunum. He progressed to end-stage renal disease and was transplanted without recurrent disease. Immune work-up done prior to immunosuppressive therapy showed marked elevation of IgE. Studies of T lymphocyte cytokine production showed normal production of interleukin-4 but depressed levels of interferon-γ. The simultaneous occurrence of autoimmune interstitial nephritis and membranous nephropathy in a young male represents a unique syndrome. Abnormalities of T lymphocyte subpopulations and their cytokines may be involved in the pathogenesis of this disorder.

**Key words:** Autoimmune interstitial nephritis – Membranous nephropathy – Autoimmunity – Interferon-γ

## Introduction

Autoimmune interstitial nephritis and membranous nephropathy are distinct pathological entities. The simultaneous occurrence of these two pathological findings in the same patient is rare. However, several reports of this unusual nephropathology in young male children suggest the existence of a distinct syndrome rather than a random association [1–10]. The patients present with renal tubular dysfunction and failure to thrive. The renal disease usually progresses to chronic renal failure [4]. Extrarenal disorders, such as enteropathy with intractable diarrhea [4, 5, 10] and pulmonary hemorrhage [2], have been reported in some cases. This paper reports clinical, pathological, and immunological findings in a young male patient with autoimmune interstitial nephritis and membranous nephropathy.

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## Case report

The patient developed generalized lymphadenopathy and eczema at age 6 months. Cellulitis in the right leg and sinusitis occurred at age 9 months. Work-up for failure to thrive at 2 years revealed renal glycosuria and hypertension. Renal arteriogram was normal.

Reevaluation at age 2 years 6 months showed Fanconi syndrome with acidosis, renal glycosuria, hypouricemia, hypophosphatemia, and generalized aminoaciduria. Urine protein excretion was 430 mg/24 h. Heavy metal screen, white cell cysteine, plasma amino acids, antinuclear antibody, and human immunodeficiency virus status were normal.

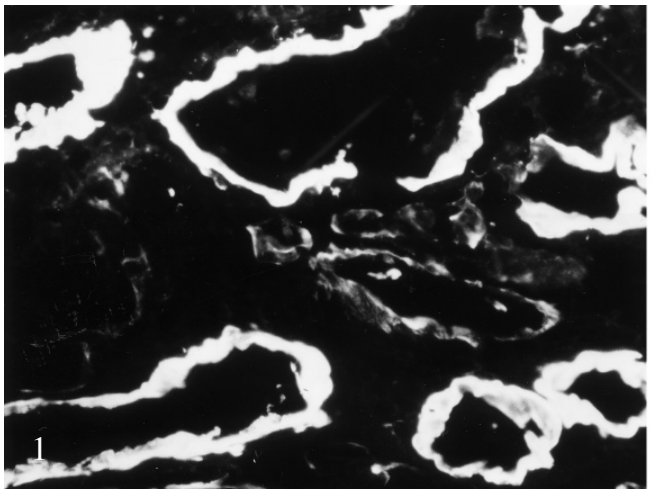
Renal biopsy showed interstitial nephritis with lymphocytic infiltration and some fibrosis. The glomeruli were normal. Immunofluorescence findings were equivocal in tubules and glomeruli. Electron-dense deposits were not seen on electron microscopy.

At age 3 years 5 months he developed Coombs'-positive autoimmune hemolytic anemia with a hematocrit of 14%. The hemolytic process and the positive Coombs' test resolved with corticosteroid therapy.

Repeat renal biopsy, performed at age 3 years 6 months because of rising serum creatinine, showed prominent tubulointerstitial nephritis with tubular atrophy. Linear staining of IgG along the tubular basement membrane (TBM) was demonstrated by immunofluorescence (Fig. 1). Staining for C1q was negative. The glomeruli revealed focal segmental sclerosis by light microscopy and focal capillary deposits of IgG and C3 complement by immunofluorescence. Electron microscopy revealed glomerular capillary subepithelial electron-dense deposits (Fig. 2).

Lymph node biopsy displayed severe cortical and paracortical lymphocyte depletion, increased medullary histiocytes, and a paucity of germinal centers. The patient was noted to have acanthosis nigrans.

The patient was treated with prednisone, 2 mg/kg per day, without improvement in renal function. At age 3 years 10 months, peritoneal dialysis was started and steroids were tapered to 0.2 mg/kg per day. One month later he developed severe diarrhea. Cultures and stool for ova and parasites were negative. Biopsy of the jejunum obtained at age



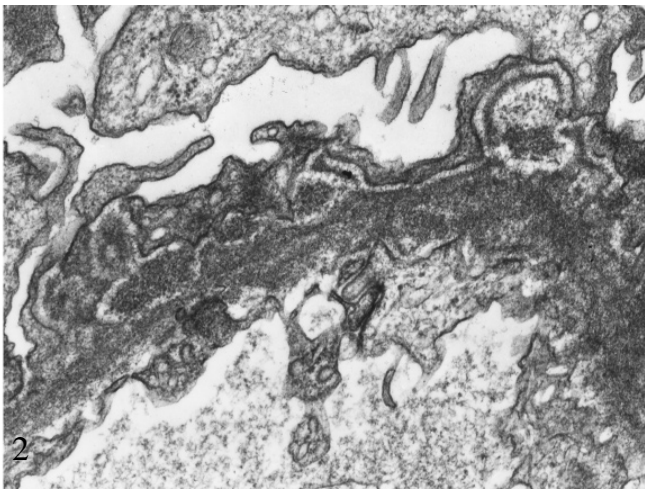


**Fig. 1.** Linear staining along the tubular basement membranes is detected with antisera against IgG

**Fig. 2.** Subepithelial deposits are present in the glomerular capillary wall. Some deposits are covered by neolamina. The peripheral lucency suggests resorption of the deposit material. Podocyte effacement is also present

**Table 1.** Immunoglobulin levels in our patient with autoimmune interstitial nephritis and membranous nephropathy

| | Serum level (mg/dl) | Normal range |
|---|---|---|
| IgG | 771 | (518–1,447) |
| IgA | 46 | ( 23– 137) |
| IgM | 69 | ( 43– 198) |
| IgG1 | 537 | (360– 810) |
| IgG2 | 295 | ( 60– 310) |
| IgG3 | 12 | ( 9– 160) |
| IgG4 | 215 | ( 9– 160) |
| IgE | 11, 014 U/ml | (<130) |

**Table 2.** Lymphokine secretion by T lymphocytes[a]

| | Patient | | Control range |
|---|---|---|---|
| | A | B | |
| IL-4 | 320 | 401 | (159 – 486) |
| IFN-γ | 1,585 | 927 | (4,571–14,300) |

IL-4, Interleukin-4; IFN-γ, interferon-γ

[a] IL-4 and IFN-γ secretion by isolated T cells activated with 1 μM ionophore and 10 ng phorbol myristate acetate/ml. Units are pg/ml. Patient sample A at age 2 years 10 months and sample B at 3 years 3 months, both prior to therapy with cyclosporin A and prednisone

4 years revealed severe villous atrophy and infiltration with plasma cells and lymphocytes. Diarrhea improved with intravenous nutrition and intravenous corticosteroid therapy.

Renal transplant was performed with the mother as a donor at age 4 years 9 months. Postoperatively the levels of cyclosporin were inconsistent, suggesting poor gastrointestinal absorption of cyclosporin, and he had an episode of rejection which was treated with murine monoclonal anti-CD3 antibody (OKT3). He was placed on intravenous cyclosporin treatment.

**Table 3.** Anti-tubular basement membrane nephritis and membranous nephropathy – cases from the literature

| Author | Year | Sex | Age | Nephrotic | Fanconi | Extrarenal | Autoimmune |
|---|---|---|---|---|---|---|---|
| Tung and Black [1] | 1975 | M | 6 months | Yes | Yes | – | – |
| Levy et al. [2] | 1978 | M | 3 years | No | Yes | Pulmonary hemorrhage | Antialveolar |
| Levy et al. [3] | 1979 | M | 5 years | Yes | | Enteropathy | – |
| Wood et al. [4] | 1982 | M | 1 year | Yes | | – | – |
| | | F | 10 years | Yes | Yes | – | – |
| Martini et al. [6] | 1983 | M | 2 years | Yes | No | Enteropathy | Antiintestinal |
| Ellis et al. [5] | 1982 | M | 6 months | Yes | | Enteropathy TTP | Antiintestinal |
| Katz et al. [8] | 1992 | M | 4.5 years | Yes | | – | – |
| | | M | 6 months | Yes | | – | – |
| | | M | 2 years | No | No | – | – |
| Gallego et al. [7] | 1990 | M | 2 years | Yes | | Diabetes mellitus pulmonary hemorrhage | – |
| Habib et al. [10] | 1993 | M | 4 months | Yes | ? | Diabetes mellitus enteropathy | Antiintestinal, antirenal brush border |
| Current | | M | 2 years | No | Yes | Enteropathy anemia | Anti-RBC |

TTP, Thrombotic thrombocytopenia purpura; RBC, red blood cell

Jejunal biopsy obtained 5 months after the transplant was normal. Biopsy of the transplanted kidney showed no evidence of membranous nephropathy or autoimmune interstitial nephritis. Therapy was converted to oral cyclosporin without problems. The acanthosis nigrans has resolved.

The patient is now 2.5 years post renal transplant. His serum creatinine is 1.0 mg/dl and blood urea nitrogen 20 mg/dl. Serum phosphorus, urine glucose, and serum bicarbonate are normal.

## Materials and methods

*Lymphokine secretion*. Interferon-γ (IFN-γ) and interleukin-4 (IL-4) secretion by isolated T cells was determined as previously described [11]. Briefly, T cells were isolated from peripheral blood mononuclear cells by sheep erythrocyte rosetting. T cells, $2\times10^6$/ml, were activated with 1 μM ionophore and 10 ng phorbol myristate acetate. The IFN-γ and IL-4 levels in the T cell supernatants 72 and 20 h after T cell activation, respectively, were measured by radioimmunoassays. The patient was studied prior to therapy with cyclosporin A or prednisone at age 2 years 10 months and again at 3 years 3 months. Isolated T cells from three healthy 3-year-old children served as controls.

## Results

### *Immunological studies*

Results of immunological tests are shown in Table 1. Serum IgE was markedly elevated. Antibody response to tetanus and pneumococcal vaccines was normal. Isohemagglutinins were positive against type A and B (patient type O). Complement levels for C1q, C2, C5, C6, and properdin were normal. The nitroblue tetrazolium test was normal.

Lymphocyte responses to phytohemagglutinin (PHA) and tetanus toxoid were normal. Lymphocyte surface markers CD3, CD4, CD8, and CD19 were normal. IFN-γ secretion by isolated T cells was markedly lower than that of T cells of the age-matched controls (Table 2). In contrast, IL-4 secretion was within the range of the controls. The HLA type of the patient was A2, A3, B60, B72, C3, C7, DR3, and DR13.

## Discussion

The syndrome of autoimmune interstitial nephritis and membranous nephropathy in a young male is a rare, but distinct disorder. A summary of patients described in detail in the medical literature is shown in Table 3. Of 13 reported cases, 12 are males less than 5 years of age. Patients present with failure to thrive, renal tubular dysfunction, and proteinuria.

The pathogenesis of the autoimmune interstitial nephritis has been studied by Katz et al. [8], who found that an antibody from serum of these patients reacts with a 58-kilodalton antigen isolated from the renal TBM. The finding of autoantibodies to renal tubular epithelium in some patients [10] suggests the possibility of a renal lesion analogous to Heymann nephritis. This hypothesis is supported by the finding of the Heymann nephritis antigen in the glomeruli of a patient with this disorder [12].

Several extrarenal complications of the syndrome have been described (Table 3). Gastrointestinal disease, presenting with intractable diarrhea and malabsorption, has been seen in some cases. Biopsy of the small intestine shows villous atrophy [3]. Diabetes mellitus, thrombotic thrombocytopenia purpura, and pulmonary hemorrhage have also been reported. Autoantibodies besides anti-TBM have been reported, including antibody to intestinal epithelium and pulmonary membranes. The finding of autoantibodies suggests that the extrarenal manifestations may have an autoimmune basis.

There are limited immunological data regarding this disorder. Elevated serum IgE levels have been reported in 1 patient [5]. T lymphocyte function studies have not been previously reported. In our patient, the lymphocyte response to PHA was normal. Studies of lymphocyte cytokine secretion showed a normal level of IL-4, but depressed level of IFN-γ. IFN-γ is associated with the TH1 lymphocyte subpopulation, while IL-4 is associated with TH2 cells. The high levels of serum IgE are consistent with overactivity of the TH2 lymphocyte subpopulation, as this immunoglobulin class is known to be induced by TH2 cells and downregulated by TH1 cells [13]. There is evidence from animal models that a TH1/TH2 imbalance can be associated with autoimmunity [14]. These findings suggest that abnormalities in T lymphocyte subpopulations and their cytokines may be involved in the pathogenesis of this syndrome.

A familial pattern has been recognized [5, 8]. The overall preponderance of males with this syndrome would be consistent with a genetic disorder linked to the X chromosome. An association between the HLA B7 and DR-8 in 2 patients with the syndrome was reported by Katz et al. [8]. Our patient has neither of these antigens. He does have HLA DR-3, which is associated with membranous nephropathy [15], but this was not seen in other cases of this syndrome [8].

There are additional cases in the literature which may represent variations of the syndrome. Colletti et al. [16] reported a male infant with membranous nephropathy and autoimmune enteropathy who did not have anti-TBM antibodies. Ellis et al. [5] described a second case in a male infant, who was a maternal cousin of the first case, with anti-TBM antibodies and enteropathy, who did not have membranous nephropathy.

Treatment of this disorder is difficult. Corticosteroids have improved proteinuria in some cases [4,12], but others have shown progressive loss of renal function despite this therapy [2]. Corticosteroids may be useful in treating the extrarenal manifestations of autoimmune disease. For example, the autoimmune hemolytic anemia in our patient responded to corticosteroid therapy. Drug malabsorption should be considered in patients with enteropathy who do not respond to pharmacological therapy.

A possible beneficial effect of cyclosporin A in the treatment of these patients has been suggested by Levy [9]. Our patient has done well since cyclosporin A was started and has not had evidence for further autoimmune phenomena while on this drug. More data on treatment with cyclosporin A prior to transplantation would be useful.

Recurrent nephropathy in the renal transplant has been reported in 1 patient [8]. Two other cases were successfully transplanted after a course of plasmapheresis. The successful renal transplant in our patient shows that pretreatment plasmapheresis is not required in all patients.

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# Literature abstract

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## Dominantly transmitted glomerulocystic kidney disease: a distinct genetic entity

**Cindy K. Sharp, Suzanne M. Bergman, John M. Stockwin, Michelle L. Robbin, Carlos Galliani, and Lisa M. Guay-Woodford**

Glomerulocystic kidney disease (GCKD) is a relatively rare condition with both a sporadic and familial occurrence. Pathologically, GCKD is characterized by cystic dilatation of Bowman's space and the initial proximal convoluted tubule. As a heritable disorder, GCKD has primarily been recognized in infants with a family history of classic, autosomal dominant polycystic kidney disease (ADPKD). Dominantly transmitted GCKD associated with either hypoplastic or normal-sized kidneys has also been reported in older children and adults. A large, three-generation African-American family with familial GCKD is characterized. Of the 20 individuals available for study, seven affected individuals were identified by renal sonogram or renal histopathology. GCKD in this family segregates as an autosomal dominant trait as evidenced by its apparent transmission from a father to his sons. A set of directed linkage strategies indicates that the distinctive GCKD phenotype in this family results from a dominantly acting mutation that disrupts a genetic locus distinct from the ADPKD loci, *PKD1* and *PKD2*, as well the human homologue of mouse jcpk mutation, a newly described murine GCKD. These analyses are the first known genetic studies conducted in a family with heritable GCKD and postinfantile age of onset.