Minimal Change Nephrotic Syndrome with IgM Deposits in Kimura’s Disease: A Case Report and Literature Review

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Kimura’s disease is a rare condition of unknown etiology. It has been reported to be associated with nephrotic syndrome, but the causal relationship and etiological mechanism have not been confirmed. We report a case of steroid-responsive minimal-change nephrotic syndrome with immunoglobulin M deposits 2 years after the diagnosis of Kimura’s disease. A review of the English-language literature from 1998 to May 2004 revealed a total of eight cases of nephrotic syndrome in patients with Kimura’s disease. Six had nephrotic syndrome before the diagnosis of Kimura’s disease was made, four of whom needed dialysis. The relationship between Kimura’s disease and nephropathy is discussed.

Key words: Kimura’s disease, eosinophilia, nephrotic syndrome, minimal-change nephrotic syndrome, immunoglobulin M

Although cytologic features have been described previously, excisional biopsy of the lump is essential to exclude malignancy [17]. The diagnostic gold standard for Kimura’s disease essentially involves histology of excised specimens: follicular lymphoid hyperplasia, heavy eosinophilic infiltration with or without eosinophilic abscess formation, proliferation of post-capillary venules, vascularization of germinal centers, frequent occurrence of Warthin-Finkeldey polykaryocytes, and sclerosis [2,10,18]. Immunohistochemistry may show IgE reticular networks in germinal centers and IgE-coated non-degranulated mast cells [18,19].

While the pathogenesis has not been established, Kimura’s disease is commonly regarded to be associated with proteinuria [20]. We report a case of minimal-change nephrotic syndrome with IgM deposits developing 2 years after the diagnosis of Kimura’s disease.
CASE REPORT

A 24-year-old male first presented with bilateral cervical lymphadenopathy in August 2000. Fine needle aspiration cytology showed reactive changes and subsequent excisional biopsy confirmed the diagnosis of Kimura’s disease (Figure 1). There was no further treatment and a few small subcutaneous lymph nodes persisted over the neck.

The patient presented to our unit in June 2003 with generalized edema of a few days’ duration. There was no family history of renal or autoimmune disease. He took no regular medication. Physical examination revealed a well-built man with gross lower-limb edema. There was no skin rash or arthritis, and blood pressure was normal. Multiple bilateral lymph nodes were palpable over the cervical area, the largest one being up to 1 cm in diameter. There were no other palpable regional lymph nodes.

The patient was eosinophilic (1.9 × 10^9/L; reference range, 0.04–0.44 × 10^9/L). Electrolytes were normal. Albumin and globulin concentrations were 20 g/L and 28 g/L, respectively. The erythrocyte sedimentation rate was 36 mm/hour and total cholesterol was 11.24 mmol/L. Urinalysis revealed albuminuria (+++), microscopic hematuria (1–4/μL), and the presence of granular and hyaline casts. Creatinine clearance was 76.39 mL/min/1.73 m^2 and urinary total protein was 6.79 g/day. Tests for hepatitis B surface antigen and anti-hepatitis C virus antibody were negative. C3 and C4 levels were only marginally elevated. The antinuclear factor titer was 1:80 and the test for anti-double-stranded DNA was negative. The antistreptolysin O titer was less than 200 U/mL. Ultrasound assessment showed normal-sized kidneys with increased echogenicity.

The renal biopsy specimen was 8 mm long with 23 well-preserved glomeruli. Glomerular cellularity, basement membrane, tubules, and vessels were all normal apart from hyaline droplet change in the proximal tubules. There was no interstitial fibrosis or tubular atrophy (Figure 2). Immunofluorescence of the specimen revealed IgM(+) deposits in the glomerular mesangium in a focal segmental and finely granular pattern; there were no other immunodeposits. Electron microscopy revealed diffuse fusion of epithelial processes and microvilli formation. There was also a small to moderate amount of mesangial and paramesangial deposits. A few giant mitochondria were noted in the tubules. The focal pattern of IgM deposition and the absence of diffuse mesangial expansion or cell proliferation support the pathologic diagnosis of minimal-change nephrotic syndrome rather than IgM nephropathy.

The patient was subsequently started on diuretics and prednisolone 1 mg/kg/day. IgE was still elevated at 3 weeks (227 IU/mL; reference range, < 100 IU/mL). Other immunoglobulins were not elevated. CT of the thorax, abdomen, and pelvis showed no evidence of lymphadenopathy in other regions.

He responded dramatically to prednisolone. Proteinuria fell to 0.14 g/day after only 3 weeks of steroid treatment. At 5 months, there had been no recurrence of proteinuria despite a tailing dose of prednisolone 5 mg daily. Eosinophilia improved but persisted. The neck lymph nodes fluctuated in size but never disappeared.

Figure 1. Lymph node featuring vascularized germinal center (right upper corner), eosinophilic infiltrate (left upper corner), abundant postcapillary venules (left center), and a traversing fibrous band (hematoxylin & eosin, original magnification × 200).

Figure 2. Renal biopsy showing a glomerulus with normal cellularity, no mesangial expansion, and basement membrane of normal thickness (hematoxylin & eosin, original magnification × 600).
**DISCUSSION**

Kimura’s disease is commonly regarded as associated with proteinuria. In spite of limited available data, at least three pathogenic mechanisms have been proposed (Figure 3). It is thought that an as yet unknown stimulus triggers an aberrant immune response [18,19], manifested as an imbalance between T helper 1 and T helper 2 cell activity [21–23]. The first proposed mechanism highlights the importance of skin lesions in the pathogenesis of nephropathy in Kimura’s disease. Katagiri et al noted a drop in the levels of interleukin (IL)-4, IL-5, and IL-13 mRNA in peripheral blood mononuclear cells of affected patients when the mass was removed or treated with radiotherapy [22]. Unfortunately, this mechanism cannot explain why some patients develop nephropathy prior to the development of subcutaneous lumps, though one may argue that the lumps are subclinical. In the second proposed mechanism, cytokines play pivotal roles in causing both the nephrotic syndrome and clinical manifestations of the disease. Different permeability factors appear to be implicated in causing abnormal glomerular permeability in nephrotic syndrome [24]. Different cytokines may modify production of these factors [25]. In the third proposed mechanism, a common etiologic factor causes both direct damage to the kidney and an aberrant immune response. However, no identifiable antigen in renal biopsies has so far been reported. Alternatively, nephropathy and other clinical features of Kimura’s disease may be part of a systemic atopic phenomenon that may not be temporally related [26].

According to previous reviews, 12–16% of patients with Kimura’s disease have proteinuria, among whom, 62–79% reach the nephrotic range [20,27]. On the other hand, in a reported series of 40 cases from Hong Kong, only one patient developed nephrotic syndrome [10].

Membranous glomerulonephritis is the most common renal lesion reported in patients with Kimura’s disease [28]. Other reported renal lesions include minimal-change nephrotic syndrome [29], mesangio-proliferative glomerulonephritis [30,31], focal segmental glomerulosclerosis [32], and IgA nephropathy [28].

**Figure 3.** Proposed pathogenic mechanisms of Kimura’s disease. (A) The first proposed mechanism highlights the importance of skin lesions in the pathogenesis of nephropathy in Kimura’s disease. (B) In the second proposed mechanism, cytokines play pivotal roles in causing both the nephrotic syndrome and clinical manifestations of the disease. (C) The third proposed mechanism, a common etiologic factor causes both direct damage to the kidney and an aberrant immune response. PBMC = peripheral blood mononuclear cell; PF = permeability factor; IL = interleukin.
Renal disease typically follows the appearance of skin lesions, though this chronologic sequence is not necessary [20].

Up to 1982, 21 cases of nephropathy in patients with Kimura’s disease had been reported in the literature, all involving male patients [20]. A subsequent review covering the period from 1981 to 1998 found an additional 12 cases, 10 of which involved male patients [28]. Our search of the English literature from 1998 to May 2004 (including our case) revealed eight more cases of Kimura’s disease with nephropathy (Table). Reported patients were 9 to 35 years of age and male. It is intuitive to speculate that male gender is a risk factor for renal involvement in Kimura’s disease, but a conclusion cannot yet be reached, given the small number of reported cases. In contrast to a previous review [28], in most of the recently reported cases (6 of 8), nephrotic syndrome preceded the diagnosis of Kimura’s disease, and four patients needed dialysis. Although one may speculate that the presence of nephropathy preceding soft-tissue masses in Kimura’s disease is associated with poor prognosis due to some unidentified factor, end-stage renal failure in these cases may be better accounted for by the natural progression of the renal pathology itself (Table).

Although Kimura’s disease is commonly regarded as associated with nephrotic syndrome, readers are reminded that this impression originates from a literature review by Yamada et al [20], who noted a high prevalence of proteinuria among all cases of Kimura’s disease that had been reported in the literature by 1982. This might, at least partly, be attributed to under-reporting of uncomplicated Kimura’s disease and/or over-reporting of coincidental nephropathy (i.e. report bias). Isolated case reports of different renal lesions developing in patients with Kimura’s disease have since been published [28]. Concomitant response of the subcutaneous mass and nephropathy to treatment might seem to offer further evidence of the association [33], when it is equally probable that steroid may treat reactive lymphenadopathy and nephropathy independently. Nevertheless, not only has a causal

### Table. Reported cases of nephrotic syndrome in patients with Kimura’s disease in the English literature since 1998

<table>
<thead>
<tr>
<th>Year</th>
<th>Ethnicity</th>
<th>Age (yr)/Sex</th>
<th>Onset of proteinuria*</th>
<th>Serum creatinine (μmol/L)</th>
<th>Peak IgE level (normal range)</th>
<th>Peak eosinophil (%) total WCC</th>
<th>Renal pathology</th>
<th>Treatment</th>
<th>Response to treatment</th>
<th>Need for dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998 [32]</td>
<td>Brazilian (Caucasian) 9/M 17/M</td>
<td>1 year before Lump improved</td>
<td>4.32 &gt; 3 106 Normalized</td>
<td>– 55% Normal</td>
<td>FSGS FSGS, chronic rejection</td>
<td>Prednisolone Cyclosporine, azathioprine, prednisolone</td>
<td>No No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998 [28]</td>
<td>Vietnamese</td>
<td>24/M</td>
<td>7-8 years before</td>
<td>5.4 80 Normalized</td>
<td>– 16%</td>
<td>IgA nephropathy</td>
<td>Pulsed methyl-prednisolone and prednisolone</td>
<td>Yes No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 [33]</td>
<td>Japanese</td>
<td>11/M</td>
<td>–1 year after</td>
<td>18 27 1,000 U/mL (&lt; 500)</td>
<td>23% N/A</td>
<td>Prednisolone/ cyclosporine</td>
<td>Yes No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 [31]</td>
<td>Vietnamese</td>
<td>14/M</td>
<td>5 years before</td>
<td>4 62 Normalized</td>
<td>– 11%</td>
<td>MPGN Prednisolone (transiently also chlorambucil)</td>
<td>Poor Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001 [34]</td>
<td>Chinese (Taiwan) 32/M</td>
<td>1 year 8 months before</td>
<td>&gt; 300 mg/dL 2,705</td>
<td>17,300 IU/mL 57% N/A</td>
<td>Prednisolone (for the lump)</td>
<td>N/A Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002 [30]</td>
<td>Thai</td>
<td>12/M</td>
<td>4 years before</td>
<td>7 71 210 IU/dL (30-140)</td>
<td>37% MPGN</td>
<td>Prednisolone/ cyclophosphamide</td>
<td>Poor No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003 [35]</td>
<td>Chinese (Taiwan) 35/M</td>
<td>&gt; 10 years before</td>
<td>– 1,017 1,350 mg/L (30-280)</td>
<td>20% FSGS</td>
<td>Steroid (for the lump)</td>
<td>N/A Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004 [this paper] (Hong Kong) 24/M</td>
<td>3 years after</td>
<td>6.79 86 227 IU/mL (&lt; 100)</td>
<td>18% MCNS</td>
<td>Prednisolone</td>
<td>Yes No</td>
<td></td>
<td></td>
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*Related to the time of first appearance of subcutaneous lesion(s); †the case report described recurrence of FSGS in the same child after kidney transplantation. WCC = white cell count; FSGS = focal segmental glomerulosclerosis; N/A = data not available or not applicable; MPGN = mesangioproliferative glomerulonephritis; MCNS = minimal-change nephrotic syndrome. (Note: to convert serum creatinine in μmol/L to mg/dL, multiply by 0.0113.)
relationship never been established, but the exact prevalence and incidence of nephropathy among patients with Kimura’s disease are not known. To determine the exact prevalence of nephropathy, one needs to gather a group of patients with Kimura’s disease and screen them all for proteinuria. In the few case series that are available, proteinuria was uncommon [10–12,18].

Coronary artery spasm [21], myocardial infarction [36], asthma [37], ulcerative colitis [38], and lichen amyloidosis [39] have also been associated with Kimura’s disease. These associations should be viewed with skepticism for similar reasons.

Steroids are effective in inducing remission of subcutaneous masses and lymphadenopathy in Kimura’s disease, although relapse may occur when treatment is stopped [33]. Surgical excision is commonly performed to exclude malignancy. Radiotherapy is effective [40], but may not be appropriate for a benign condition. Non-steroidal anti-inflammatory drugs [41], pentoxifylline [42], cyclosporine [22], interferon-alpha [40], and all-trans-retinoic acid [44] have all been used with variable success. It is uncertain if these treatments are also effective against concomitant nephrotic syndrome.

Optimal treatment regimens and long-term prognosis for renal lesions in patients with Kimura’s disease are largely unknown due to the rarity of these lesions and the lack of long-term follow-up data in the literature. Usual standard treatment protocols should be adopted and patients offered dialysis, if necessary. There is no evidence that nephropathy in Kimura’s disease carries an exceptionally poor outcome. Steroid treatment, particularly with prednisolone, is commonly used as first-line treatment (Table).

In this article, we have described a typical case of steroid-responsive minimal-change nephrotic syndrome in a patient with Kimura’s disease. Although a wide range of renal lesions have been reported in patients with Kimura’s disease, risk of progression to end-stage renal failure is probably predicted by the renal pathology itself. Even if Kimura’s disease and nephropathy are associated, the link is more likely to be non-specific and to depend on individual susceptibility. The pathogenesis of Kimura’s disease is obscure and treatment is anecdotal. More research into the natural history of the disease and its pathogenesis and associations is warranted.

ACKNOWLEDGMENTS

We thank Dr. Mansha Hari Khemlani for proofreading the article and Mr. Yuen Sze Chun for his computer support.

REFERENCES


