

Case Study

Nephrotic syndrome during the tapering of oral steroids after pathological diagnosis of Kimura disease from a lacrimal gland mass: case report and review of 10 Japanese patients

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A 42-year-old man with eosinophilia and high serum immunoglobulin E (IgE) developed a lacrimal gland mass on the left side. Excisional biopsy revealed hyperplasia of lymphoid follicles, and infiltration with lymphocytes and eosinophils around lacrimal gland acini, leading to the pathological diagnosis of Kimura disease. IgE-positive cells were mainly found along follicular dendritic cells, and a small number of IgG4-positive cells was present. One month after oral prednisolone was started at 40 mg daily and tapered to 10 mg daily, he developed lower leg edema on both sides and marked proteinuria (10.8 g/day). Renal biopsy showed no glomerular abnormalities, no immunoglobulin deposition, and no tubulointerstitial infiltration with eosinophils, leading to the diagnosis of minimal change nephrotic syndrome. Proteinuria subsided in response to an increased dose of prednisolone to 30 mg daily. Proteinuria relapsed three times in the following 5 years when oral prednisolone was tapered. In conclusion, Kimura disease manifested as an orbital mass and did not relapse. However, nephrotic syndrome relapsed frequently with background eosinophilia and high serum IgE. This study reviewed the clinical features of 10 Japanese patients with Kimura disease associated with proteinuria.

Keywords: Kimura disease, nephrotic syndrome, lacrimal gland, IgG4, renal biopsy

INTRODUCTION

The ocular adnexa are supporting tissues for the eye globe, comprising the eyelid, lacrimal gland and sac, extraocular muscles, and orbital interstitial tissue. These sites are frequently affected by lymphoma¹ and inflammatory diseases such as IgG4-related disease.² Magnetic resonance imaging of ocular adnexal masses cannot differentiate inflammatory diseases from lymphoma. Therefore, excisional biopsy is required to establish the diagnosis and decide the treatment strategy.

Kimura disease predominantly occurs in young Asian males and presents as soft subcutaneous granulomas, which are frequently seen in the head and neck. Lymphoid follicular hyperplasia and marked eosinophilic infiltration are the pathological characteristics of Kimura disease, and blood examination commonly reveals eosinophilia and high serum immunoglobulin E (IgE).³⁻⁶ Kimura disease rarely manifests as orbital tumors such as lacrimal gland masses.⁷⁻⁹

Pathologically, it remains controversial whether Kimura disease in Asian reports and angiolymphoid hyperplasia with eosinophilia in Western reports are the same entity.⁶

In this study, we report a patient with Kimura disease who initially presented with a lacrimal gland mass and then developed nephrotic syndrome one month after the tapering of oral prednisolone. We also reviewed 10 reported Japanese patients with Kimura disease associated with proteinuria.¹⁰⁻¹⁸

CASE REPORT

A 42-year-old man noticed upper eyelid swelling on the left side that subsided spontaneously 5 months ago. He again developed left eyelid swelling with left exophthalmos 2 months ago, and was referred to an ophthalmologist. In his past history, he underwent bilateral tonsil extirpation due to otitis media at the age of 5 years. He developed systemic urticaria lasting a week after eating sashimi 3 years ago, and

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was found to have eosinophilia and a right renal cyst during a physical checkup 2 years ago. He was also allergic to cedar pollen.

At the referral visit in August 2010, his best-corrected visual acuity was 1.5 in both eyes, and he had full eye movement. He had clear ocular media and normal fundi in both eyes. The upper eyelid on the left side was swollen and no mass was palpable. Magnetic resonance imaging demonstrated a lacrimal gland mass on the left side with an anteroposterior length of 2 cm (Fig. 1). The mass had the same internal signal as cerebral gray matter and had irregular staining on contrast enhancement. Serum IgE was elevated to 735 IU/mL, and his white blood cell count was 5,560/ μ L with 9.4% eosinophils. Renal function was normal, and urinalysis detected no proteinuria.

Excisional biopsy of the left lacrimal gland mass demonstrated hyperplasia of lymphoid follicles, and infiltration with lymphocytes and numerous eosinophils around lacrimal gland acini (Fig. 2A), leading to the pathological diagnosis of Kimura disease. Immunohistochemically, IgE-positive cells in lymphoid follicles were mainly found along follicular dendritic cells (Fig. 2B). Some areas were infiltrated exclusively with eosinophils, presenting as an eosinophilic granuloma or abscess (Fig. 2A). The structure of the lymphoid follicles surrounded and infiltrated by eosinophils was mostly obscured, indicative of eosinophilic folliculolysis (Fig. 2D). There were few IgG4-positive cells (Fig. 2C), and no predilection was noted on Ig κ and Ig λ staining.

Oral prednisolone was then tapered from 40 mg daily. At the dose of 10 mg daily in mid-September, one month after the start of oral prednisolone, the patient developed lower leg edema on both sides. Serum total protein decreased to 5.1 g/dL, serum albumin decreased to 2.4 g/dL, and urinalysis revealed 4+ proteinuria. Daily total urinary protein was 10.8 g/day. In the beginning of October, no histopathological change in glomeruli or tubulointerstitial tissue, nor infiltration with inflammatory cells, including eosinophils, was found on renal biopsy (Fig. 3). Immunohistochemical staining of the frozen sections detected no glomerular

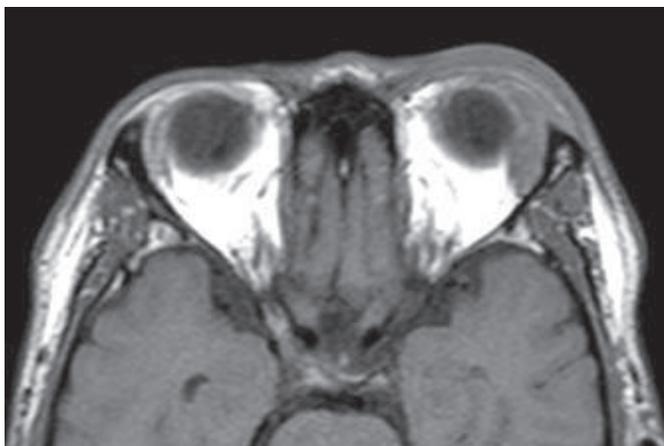


Fig. 1. Magnetic resonance imaging at the initial visit in August 2010. A mass with an anteroposterior length of 2 cm arose from the lacrimal gland on the left side.

deposition of IgG, IgA, IgM, C3, C1q, or fibrinogen. With the diagnosis of minimal change nephrotic syndrome, oral prednisolone was increased to 40 mg daily, and proteinuria subsided in 2 weeks.

Oral prednisolone was gradually tapered in the following 3 months. In the beginning of January 2011, he developed proteinuria again at the dose of 17.5 mg daily (Fig. 4). Oral prednisolone was increased to 30 mg daily and combined with oral cyclosporine at 75 mg daily. In the following 2 years, oral prednisolone was gradually tapered in combination with oral cyclosporine at 100 mg daily. In December 2013, proteinuria relapsed for the second time at 5 mg daily of prednisolone and 75 mg daily of cyclosporine. Oral prednisolone was increased to 30 mg daily and gradually tapered. In August 2015, proteinuria relapsed for a third time at 7 mg daily of prednisolone and 100 mg daily of cyclosporine. At the last visit in June 2017, he was stable with no proteinuria at 7.5 mg daily of prednisolone and 125 mg daily of cyclosporine. Serum IgE was 811 IU/mL, and the white blood

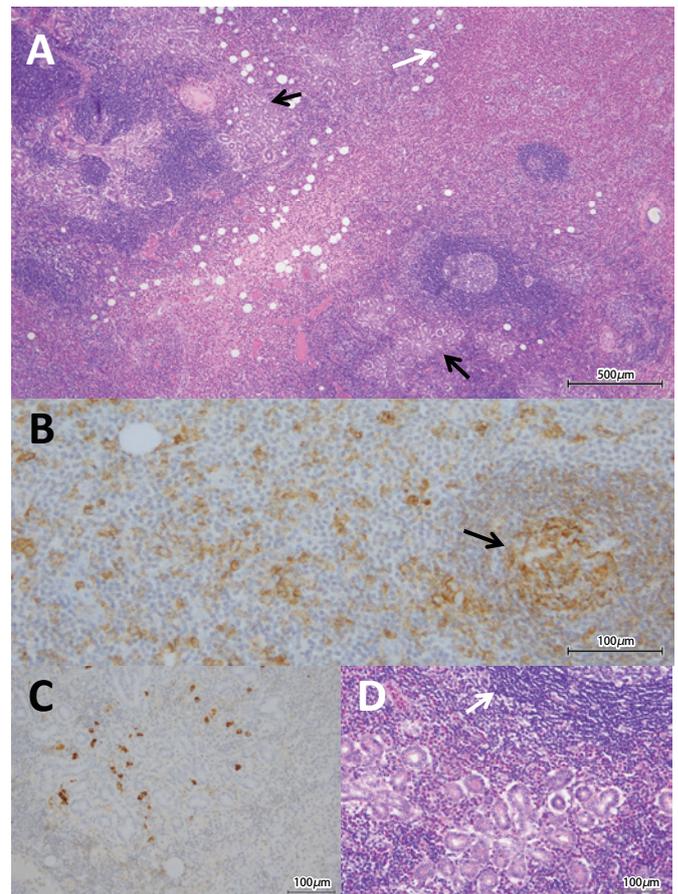


Fig. 2. Excisional biopsy of the lacrimal gland mass on the left side in August 2010. Lymphoid follicular hyperplasia, and marked infiltration with eosinophils and lymphocytes around lacrimal acini (black arrows) were observed on hematoxylin-eosin staining (A). Note the area exclusively with eosinophils, referred to as an eosinophilic granuloma or abscess (white arrow in A). The obscured structure of the lymphoid follicle was infiltrated with eosinophils, indicative of eosinophilic folliculolysis (white arrow in D). IgE in the lymphoid follicle was stained mainly along follicular dendritic cells (black arrow in B). There were few IgG4-positive cells (C). Bar = 500 μ m in A, Bar = 100 μ m in B, C, and D.

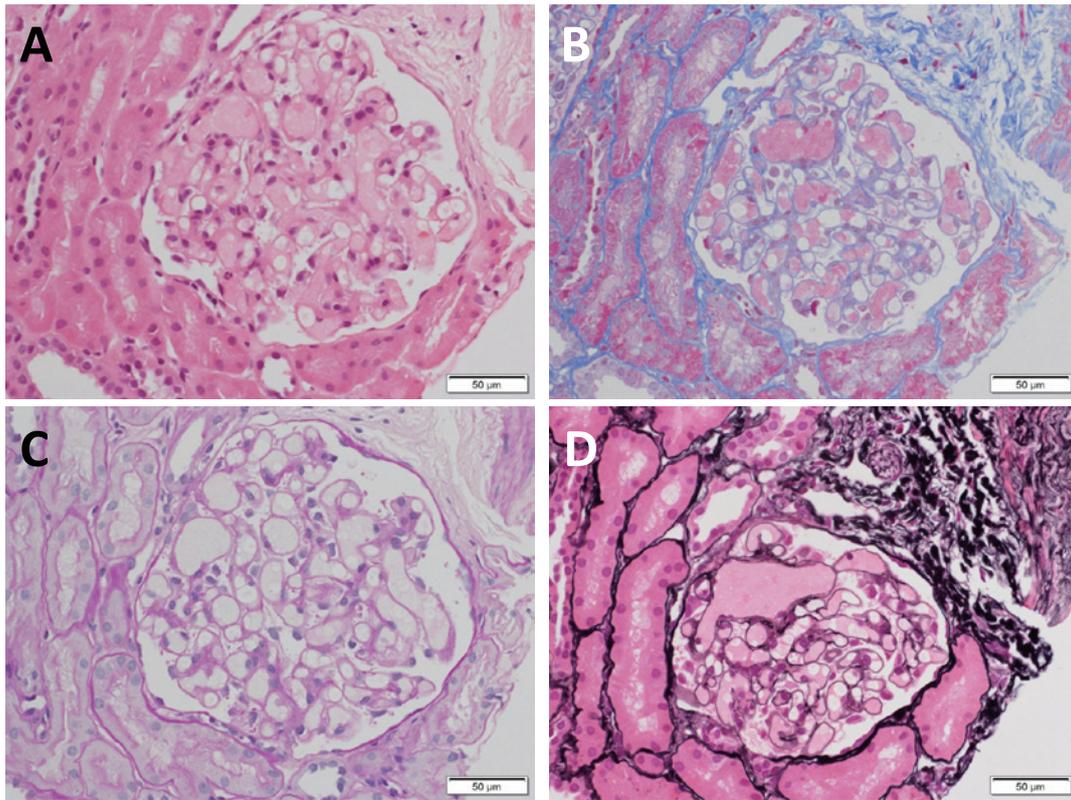


Fig. 3. Renal biopsy at the time of development of nephrotic syndrome during tapering of oral prednisolone to 10 mg daily in October 2010. No glomerular change was noted on hematoxylin-eosin (HE, **A**), Masson trichrome (**B**), periodic acid-Schiff (PAS, **C**), or periodic acid methenamine silver (PAM, **D**) staining. Bar = 50 μm .

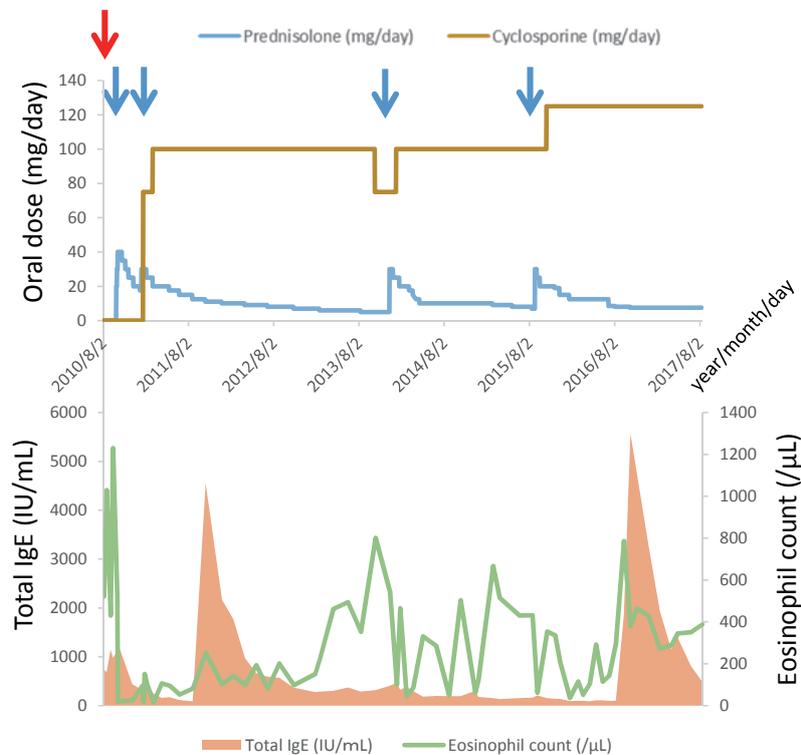


Fig. 4. Blood eosinophil counts and serum IgE levels in the current patient with Kimura disease associated with nephrotic syndrome. Onset and relapse of proteinuria (blue arrows) did not appear to be related with IgE elevation or eosinophilia. Red arrow indicates the timing of excisional biopsy of the lacrimal gland mass. Initial prednisolone from 40 mg to 10 mg daily is not visualized in the chart due to short scale of time axis.

cell count was 5,400/ μ L with 6.5% eosinophils (Fig. 4). Serum IgG4 was in the normal range at 18.3 mg/dL. The patient exhibited no relapse of the orbital lesion during follow-up.

DISCUSSION

Nephrotic syndrome has been reported as a complication of Kimura disease.^{4,11-13,19} Ten Japanese patients with Kimura disease associated with proteinuria who have been reported since 1981 are summarized in Table 1. All 11 patients, including the present patient, were male and developed proteinuria associated with a subcutaneous mass, which was confirmed pathologically by excisional biopsy as Kimura disease. Three of these 11 patients did not satisfy the criteria for nephrotic syndrome, i.e., proteinuria equal to and greater

than 3.5 g/day.²⁰ Since the year 2000, nephrotic syndrome with Kimura disease has been frequently reported in Chinese patients.²¹⁻²⁶

In the review of 10 Japanese patients with Kimura disease associated with proteinuria, renal biopsy confirmed glomerular IgE deposition in only one patient (Case 1 in Table 1) who exhibited a low level of proteinuria (0.6 g/day), and glomerular endocapillary and mesangial proliferation. In this patient (Case 1), interstitial lymphoid follicles with eosinophilic infiltration were also noted.¹⁰ The other patients in the review (Cases 3, 6, 7, 8 in Table 1) were found to have no glomerular IgE deposition. The role of glomerular IgE deposition in the development of nephrotic syndrome remains undetermined in Kimura disease.

The present patient is unique in that nephrotic syndrome developed during the tapering of oral prednisolone one

Table 1. Summary of 11 Japanese patients of Kimura disease with proteinuria after the year 1981 including the present patient (Patient No. 11)

Patient/Sex/ Age at onset of nephrotic syndrome	Duration before pathological diagnosis of Kimura disease	Location of biopsy- confirmed mass	Onset of proteinuria relative to diagnosis of Kimura disease	Prednisolone at onset of proteinuria	Daily amount of urinary protein	Renal biopsy	Renal pathological diagnosis and immunohistochemistry	IgE glomerular deposition	Treatment for nephrotic syndrome	Author (Year)
1/M/31	19 years	Both thighs	Simultaneous	No	0.6 g/day#	Yes	Endocapillary and mesangial proliferative glomerulonephritis IgE, IgG, IgM, C3, C5 deposition	Yes	No description	Konishi ¹⁰ (1981)
2/M/48	6 years	Left retroauricular region	Simultaneous	Yes	20 g/day	Yes	Membranous nephropathy IgG, IgA, C1 capillary granular deposition	Unknown	Prednisolone 40 mg daily	Yamada ¹¹ (1982)
3/M/12	1 month	Left retroauricular region	Simultaneous	No	21.8 g/day	Yes	No glomerulus on light microscopy IgG, IgA, C3 mesangial deposition	No	Prednisolone 2 mg/kg daily	Furuse ¹² (1982)
4/M/57	17 months	Right retroauricular region	Simultaneous	No	0.89 g/day#	Yes	Membranous nephropathy IgG capillary granular deposition	Unknown	Prednisolone 30 mg daily	Kimura ¹³ (1985)
5/M/29	19 years	Neck	Simultaneous	No	11.1 g/day	Yes	Minimal change No deposition	Unknown	Prednisolone 40 mg daily	Matsumoto ¹⁴ (1988)
6/M/68	2 years	Bilateral retroauricular regions	Simultaneous	No	4 g/day	Yes	Membranous nephropathy IgG capillary granular deposition	No	Prednisolone 40 mg daily	Matsuda ¹⁵ (1992)
7/M/59	3 years	Right retroauricular region	Simultaneous	No	19 g/day	Yes	Minimal change No deposition	No	Prednisolone 60 mg daily	Matsuda ¹⁵ (1992)
8/M/49	6 years	Right cheek	Later	No	11.6 g/day	Yes	Mesangial proliferation with segmental sclerosis No deposition	No	Prednisolone 60 mg daily	Moriya ¹⁶ (1994)
9/M/11	9 months	Left cheek	Simultaneous	No	18 g/day	No	Not applicable	Unknown	Prednisolone 2 mg/kg daily initially Prednisolone or cyclosporine 5 mg/kg daily on relapse	Nakahara ¹⁷ (2000)
10/M/15	13 years	Left hip	Later	No	2.1 g/day#	Yes	Membranous nephropathy IgG, C3, C1q granular deposition	Unknown	Prednisolone 30 mg daily	Obata ¹⁸ (2010)
11/M/42	5 months	Left lacrimal gland	1 month later	Yes	10.8 g/day	Yes	Minimal change No deposition	Unknown	Prednisolone 40 mg daily initially Prednisolone and cyclosporine on relapse	Matsuo (current)

All patients show eosinophilia and high levels of serum IgE. #Urinary protein level does not satisfy criteria of nephrotic syndrome.²⁰

month after the pathological diagnosis of Kimura disease from the lacrimal gland mass. Nephrotic syndrome was controlled well by increasing oral prednisolone. The patient experienced three relapses of proteinuria in the following 5 years when oral prednisolone was tapered to a low dose. Currently, nephrotic syndrome is well controlled by a low dose of oral prednisolone combined with oral cyclosporine. Low-dose cyclosporine combined with low-dose prednisolone is a recent trend in the treatment of nephrotic syndrome.^{17,20}

Renal biopsy demonstrated minimal glomerular change on light microscopy and no glomerular deposition by fluorescent immunohistochemistry in the present patient. Glomerular IgE deposition in this patient remains unknown because routine fluorescent immunohistochemical staining did not include IgE. Thus, there is no pathological explanation as for why nephrotic syndrome occurred. The orbital lesion caused by Kimura disease never relapsed after oral steroid administration, whereas proteinuria repeatedly relapsed during tapering in this patient. Immunological aberration or inflammatory propensity initiated by Kimura disease may cause nephrotic syndrome with background eosinophilia and continuous high serum IgE levels.

Pathologically, the small number of IgG4-positive cells was found among infiltrating cells around lacrimal acini in the excised mass arising from the lacrimal gland. The present patient did not satisfy the criteria for IgG4-related disease. A few recent studies have addressed the relation of Kimura disease with IgG4-related disease.²⁷⁻²⁹ Kimura disease in the lacrimal gland, as noted in the present patient, may aid in understanding the relation with IgG4-related disease because the lacrimal gland is frequently affected in IgG4-related disease.

This study described repeated episodes of proteinuria during the tapering of oral prednisolone in a patient with Kimura disease involving the lacrimal gland. Rises in serum IgE levels in this patient mainly occurred in autumn, and were therefore seasonal fluctuations. Furthermore, the relapse of proteinuria was not related with the rise in serum IgE or eosinophilia. In previous reports, elevated serum IgE was found to play a role in the onset and relapse of minimal change nephrotic syndrome.³⁰⁻³³ Continuous high levels of serum IgE, even if fluctuating, and eosinophilia may underlie the development of Kimura disease and nephrotic syndrome.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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