

## Original Article

# Successful treatment of Kimura's disease with leflunomide and methylprednisolone: a case report

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**Abstract:** Kimura's disease (KD) is an uncommon, chronic inflammatory disease characterized by tumor-like lesions in the soft tissue and lymph nodes and increased peripheral blood eosinophil counts and serum immunoglobulin E (IgE). Prednisone is widely used to treat the disease. Here, we reported a 59-year-old KD patient failed to response to prednisone. Leflunomide combined with methylprednisolone (Medrol) were carried out to treat KD and encouraging outcome was obtained during the medication and 1 year follow up period.

**Keywords:** Kimura's disease, eosinophilia, leflunomide, effect

## Introduction

Kimura's disease (KD) is an uncommon, chronic inflammatory disease characterized by tumor-like lesions in the soft tissue and lymph nodes, elevated peripheral blood eosinophil count and serum immunoglobulin E (IgE). In recent years, it has suggested that T cell and interleukin family had engaged in the course of KD. Systemic corticosteroids and immunosuppressive agents may be the most popular therapeutic options of KD. But unfortunately the effect was discouraged since relapse after dose reduction was usually observed. Corticosteroids in combination with leflunomide was reported to treat KD in two individuals and yielded good outcome [1]. In the present report, we introduced leflunomide in combination with methylprednisolone to treat a KD patient who failed to response to corticosteroid.

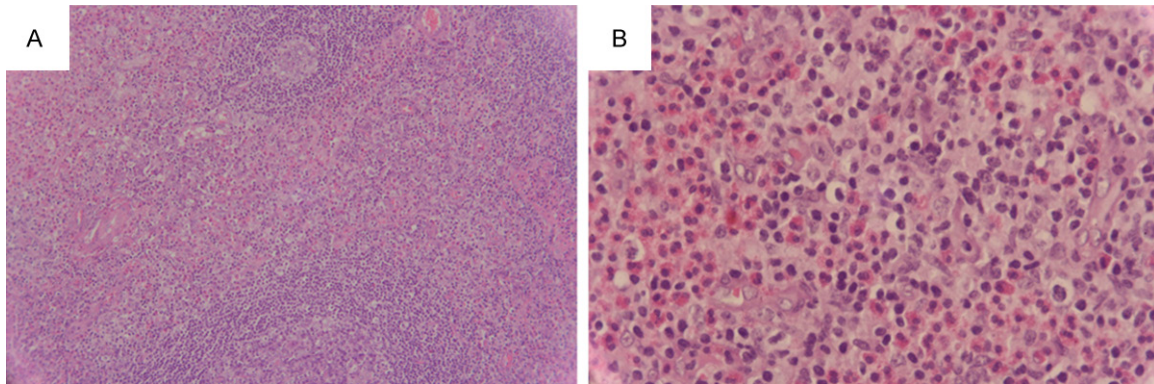
## Case report

59-year-old man, a fish farm worker, complained to us about the enlarged subcutaneous masses located in bilateral fossa axillaris and neck. It has been more than 20 years since he

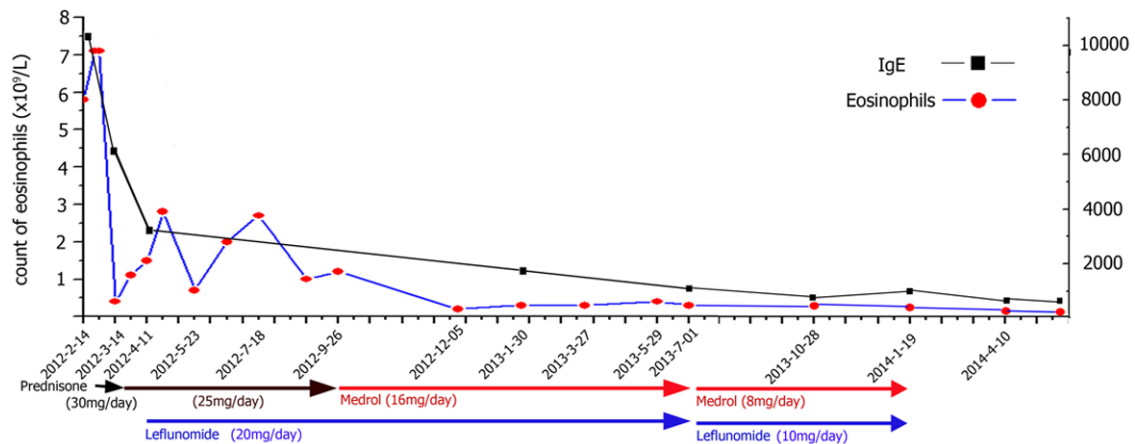
found the enlarged subcutaneous masses while they enlarged in the recent several months. Another main symptom the patient complained was pale color and pain of the left digitus annularis and the fourth and fifth toes. Chronic cough persisted for more than 30 years since the patient started to smoke in his second decade. Severe generalized pruritus also persisted for more than 20 years without any treatment.

Physical examination, we found fused lymphonodus, about 2 cm in diameter, with soft property in the bilateral fossa axillaris and enlarged lymphonodus in bilateral inguinal region and neck. Paleness, sensation of cold and numbness was found in the affected extremities. Ulcer on the fifth toe could be observed.

Blood examination showed increased eosinophil ( $5.25 \times 10^9/L$ , 52.7% of white blood cell), elevated IgE (9740 IU, normal  $<100$  IU/mL), normal level of IgA (3.51 g/L), IgG (11.4 g/L), IgM (0.59 g/L), complement-C3 (1.03 g/L) and complement-C4 (0.24 g/L). Antinuclear antibody (ANA), Anti-Sm antibody, Anti-SSA antibody, Anti-Scl-70 antibody, Anti-Jo-1 antibody, Anti-GBM antibody, SSB, PM-Scl, CENP B, PCNA,



**Figure 1.** Biopsy specimen of the lymph node revealing lymphoid follicles with germinal centres (A,  $\times 100$ ) and extensive eosinophil infiltration (B,  $\times 400$ ).



**Figure 2.** The therapeutic modality and the eosinophil and IgE variation.

dsDNA, nucleosome, histone, ribosomal P protein and AMA-M2 are negative. SM/RNP was slight positive. Erythrocyte sedimentation rate (ESR) was 3 mm/h. Liver, kidney, blood electrolyte and blood coagulation function was normal. Plasmodium was negative to rule out parasitic infection. Urinalysis was negative.

B-ultrasound found enlarged lymph nodes in bilateral fossa axillaris, inguinal region, neck and left supraclavicular region. No obvious mass was found in posterior peritoneum region. There was no abnormality found in the liver, kidney, spleen and pancreas by ultrasound examination. Vascular ultrasound revealed vasculitis of bilateral lower extremity and right anterior tibial arteries was embolized, no blood flow signal could be detected. Plaque formed in left superficial femoral artery. Deep venous of bilateral lower extremity showed no abnormal echo.

To make a definite diagnosis, lymphonodus excision biopsy was performed. Histopathological examination showed lymphoid follicles with germinal centers and extensive eosinophil infiltration (**Figure 1**). Based on the above findings, the diagnosis of KD was established.

Balloon angioplasty was carried out to treat the vascular obliterans of the left lower limbs. Digital subtraction angiography found multiple angiostenosis of both legs. After balloon angioplasty, aspirin (100 mg/day) and cilostazol tablet (50 mg/day) was administered for anticoagulant therapy.

Prednisone (30 mg/day) was carried out to treat the disease. Omeprazole and alfacalcidol capsule were taken to protect gastric ulcer and calcium loss. Blood examination showed eosin-

ophils dramatically dropped from 52.7% to 3.9% of white blood cell as well as IgE from 9740 IU to 5960 IU in the first two weeks. Thus, we tapered prednisone to 25 mg/day. However, the outcome discouraged us for increasing eosinophils ( $1.10 \times 10^9/L$ , 13.7% of white blood cell) in the next two weeks. Since most authors reported that prednisone was effective to treat KD, we persevered to use prednisone for another two weeks. Unfortunately, eosinophil count continued to increase to  $1.50 \times 10^9/L$  (20.5% of white blood cell). But serum IgE gradually reduced to 3740 IU. Generalized pruritus improved markedly and enlarged lymph nodes masses in bilateral fossa axillaris dwindled. At this time point, we introduced leflunomide (20 mg/day) together with prednisone (25 mg/day). During the following 5 months, eosinophil count fluctuated between  $0.70 \times 10^9/L$  and  $2.80 \times 10^9/L$ . Thus, we introduced methylprednisolone (16 mg/day) instead of prednisone. The eosinophil count declined to normal level in the following 9 month. Serum IgE also declined to 1085 IU, even it exceeded the normal level (**Figure 2**). Dose de-escalation of methylprednisolone (8 mg/day) and leflunomide (10 mg/day) was performed during the following 6.7 months while both eosinophil count and serum IgE sustained at low level. ALT and AST were within the normal range during the whole therapy period. The patient is now still under follow-up. No enlarged lymph node was detected by palpation. No obvious adverse effects happened.

### Discussion

KD was first described as eosinophilic hyperplastic lymphogranuloma by Kim and Szeto in 1937 in China. In 1948, Kimura noted a change in the surrounding blood vessels and referred to it as unusual granulation combined with hyperplastic changes in lymphoid tissue. Interestingly, KD occurs predominantly in Asian young males, especially in China and Japan. Wang et al. [2] reviewed that there were 444 cases of KD reported between 1984 to 2007 in China and Ishii et al. [3] reviewed 429 cases of KD in 1982. KD is benign chronic inflammatory disease. It has multiple clinical features, including painless masses in the head and neck region, eosinophilia and raised serum IgE. Renal involvement were usually reported and resulted in proteinuria and nephrotic syndrome

Arthropathy and bronchial asthma have been noted. Other complications included ulcerative colitis, atopic dermatitis, aortitis syndrome, endocarditis, Buerger's disease-like vasculitis [4] and Raynaud's phenomenon [5]. The definite etiology of KD is unclear. In recent years, it has been found that autoimmunity, allergy, neoplasm, and parasite infestation are possible risk factors.

Although various therapeutic modalities have been used, treatment of KD is still an enigma. The most common therapy includes surgical excision or radiotherapy of enlarged masses, local or systemic corticosteroids, immunosuppressive agents as well as many other interventions. Surgical excision should be performed to make a pathological diagnosis or on KD patients who only developed localized masses as well as to pursue cosmetic result. Even some cases were reported that no relapse occurred 2 years after surgical removal of Kimura's associated masses in head and cervical region [6], relapse are frequent (about 51.7%). Irradiation is also limited to reduce the size of localized masses, but has no obvious effect on systemic disorder. Oral corticosteroid is extensively used. Most cases have initial response to oral corticosteroid but reoccurrence rate is high after medicine cessation (about 45.8%). Immunosuppressive agent cyclosporine was also chosen as the maintenance immunosuppressive therapy for KD patient with nephrotic syndrome. Soeria-Atmadja et al. [7] reported cyclosporine 2 mg/kg/day could maintain prolonged remission of KD with nephrotic syndrome. However, the side effects of cyclosporine, such as acral dysaesthesia, hypertension, headache, vertigo, gingival swelling, bleeding and mild gingival hyperplasia, made it unsuitable for long-time use.

Leflunomide is a novel immunosuppressant used for rheumatoid arthritis and lupus nephritis as well. It prevents the expansion of activated and autoimmune lymphocytes by interfering with their cell cycle progression while non-lymphoid cells are able to use another pathway to make their ribonucleotides by use of salvage pyrimidine pathway, which makes them less dependent on de novo synthesis. The antiproliferative effects on T and B lymphocytes have motivated two authors to use leflunomide in combination with steroids to treat KD patients

with or without renal involvement. The first patient was response to oral prednisone and pulse cyclophosphamide but still relapsed when prednisone was tapered, and failed to response to vincristine. Combination of leflunomide (20 mg/day) and prednisone (1 mg/kg/day) was effective [1]. The other patient took methylprednisolone (24 mg/day) and leflunomide (20 mg/day) initially, maintained with methylprednisolone (4 mg/day) plus leflunomide (10 mg/day) for two years and get satisfied outcome [8].

In our present study, the patient developed multiple classical features of KD, including chronic cough, generalized pruritus, subcutaneous masses, arteriitis, eosinophilia and elevated serum IgE. He was initially response to prednisone in the first two weeks, but quickly reoccurrence happened. In the following prednisone treatment period, even clinical manifestation such cough, pruritus and subcutaneous lymph nodes improved, eosinophil count persist at high level. We thought that prednisone should be effective but not sufficient. Thus we introduced leflunomide and methylprednisolone instead of prednisone lately. Blood analysis demonstrated no hepatic or renal impairment and the patient did not complain any discomfort during the treatment period. To our knowledge, this is the third published case treated by leflunomide and corticosteroids. We propose that the present therapeutic modality may be a good alternative for the KD patient who is unresponsive to corticosteroids or rapidly relapses. Larger-scale studies should be undertaken to further investigate the safety and efficacy of the present treatment.

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### Disclosure of conflict of interest

None.

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