

Kimura's disease or IgG4-related disease? A case-based review

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Abstract Kimura's disease usually presents with benign painless soft tissue swelling around the head and neck areas with eosinophilia and high immunoglobulin E (IgE) levels. IgG4-related disease is characterized by fibrosis and sclerosis of the involved organs, with infiltration of IgG4-positive plasma cells. There are some similar clinical manifestations of these two diseases, with eosinophilia or high IgE levels often found in patients with IgG4-related disease. However, the relation between these two diseases is not well known. We report a 23-year-old man who had multiple neck lumps for longer than 1 year. He had remarkable eosinophilia and elevated serum IgE levels. Biopsy of his lymph nodes suggested the diagnosis of both Kimura's disease and IgG4-related disease. In this article, we discuss the relationship between Kimura's disease and IgG4-related disease. We also suggest a possible model ("allergen-specific immunotherapy") to illustrate our view that an increase in IgG4-positive plasma cells is an epiphenomenon of Kimura's disease.

Keywords Allergen-specific immunotherapy · Eosinophil · IgE · IgG4-related disease · Kimura's disease

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Introduction

Kimura's disease is a rare and benign chronic inflammatory soft tissue disorder of unknown origin, which predominantly inflicts young male adults in Asia. Kimura's disease usually presents as subcutaneous masses around the head and neck with or without systemic symptoms. Laboratory investigations of this disease are characterized by eosinophilia ($>5\%$ of white blood cells or $>0.5 \times 10^9/L$ of blood) and high immunoglobulin E (IgE) levels [1, 2].

IgG4-related disease is a systemic disease that is characterized by extensive IgG4-positive plasma cells and T lymphocyte infiltration of various organs. Involvement of multiple organs, such as the pancreas, bile duct, gallbladder, salivary gland, retroperitoneum, kidney, lung, lymph nodes, and prostate, in which tissue fibrosis with obliterative phlebitis is pathologically induced has been previously reported [3].

Kimura's disease has been known by many rheumatologists. However, IgG4-related disease is a relatively new disease. A patient recently came to our clinic for multiple neck lumps. He appeared to suffer from both Kimura's disease and IgG4-related disease.

Case report

A 23-year-old man was referred to our hospital with multiple neck lumps for longer than 1 year duration. He had a history of asthma, psoriasis, urticaria, and superficial hemangioma. On physical examination, multiple cervical lymph nodes were palpable on both sides of the neck and bilateral inguinal regions. There was a red rash (2×2 cm in size) on his right ear. We also found typical psoriasis rashes on his scalp. A routine blood test showed elevated leukocytes counts ($14 \times 10^9/L$) and remarkable eosinophilia ($5.32 \times 10^9/L$, 38% of white blood cells). Serum IgE was higher than $3,000$ IU/L,

which was beyond the detection range of our hospital. His antinuclear antibody titer was 1:1,000 positive, but results for antineutrophil cytoplasmic antibody and perinuclear antineutrophil cytoplasmic antibody were negative. The laboratory results also showed normal liver and renal function. Neck and inguinal lymphadenomegaly, but not hepatosplenomegaly, was found by B-ultrasound. Chest and abdominal computed tomography was normal except for lymphadenomegaly. Bone marrow smears showed myeloid hyperplasia with an increased proportion of eosinophils. Finally, biopsy of one of the left cervical lymph nodes suggested follicular hyperplasia with reactive germinal centers, eosinophilic infiltrates involving the interfollicular areas, and proliferation of postcapillary venules, which are all signs of Kimura's disease. Immunohistochemistry showed the following: follicular area, Bcl-2(-), Bcl-6(+), CD10(+), CD20(+), CD79a(+), and Ki67(+) 80 %; interfollicular area, CD3(+), CD5(+), CD43(+), MPO(-), and Ki-67(+) 10 %; histiocytes, CD68(+); and follicular dendritic cells, CD21(+) and CD23(+). The pathological diagnosis, which was also the final diagnosis, was Kimura's disease.

Kimura's disease is rare in China, although it predominantly inflicts young male adults in Asia. We discussed this case with other rheumatologists in a regular rare case conference in our district. In this conference, some rheumatologists believed that our patient's clinical features had something in common with IgG4-related disease, such as elevated eosinophilia and serum IgE and lymphadenopathy. Based on these findings, we performed further research. His serum IgG4 level was 2.09 g/L. Additional immunohistochemistry (Fig. 1) showed that (1) abundant IgG+ and IgG4+ plasma cells were present, (2) there were greater than 10 IgG4+ cells per high power field, and (3) the IgG4/IgG ratio was above 40 %. The diagnosis of IgG4-related disease was considered.

Our patient was then treated with prednisone 15 mg/day and leflunomide 10 mg/day. His symptoms gradually improved. Serum IgE levels dropped to 2367 IU/mL and eosinophils decreased to $0.78 \times 10^9/L$ after 1 month.

Discussion

Kimura's disease, a chronic inflammatory disease, which is endemic to Asians has a male preponderance. Kimura's disease usually presents with benign painless soft tissue swelling around the head and neck area. Laboratory investigations for this disease are characterized by eosinophilia and high IgE levels [1, 2]. These symptoms characterize the clinical manifestations of Kimura's disease, suggesting that Th2 cells play a crucial role in the pathogenesis of this disease. Although the precise cause and pathogenesis of Kimura's disease are unclear, it has been speculated that a viral or parasitic trigger may alter T cell immunoregulation or induce IgE-mediated type I

hypersensitivity, resulting in the release of eosinophilotropic cytokines [4, 5]. In *in vitro* assays, activated CD4+ T cells of the Th2 phenotype have been shown to release interleukin (IL)-4 and IL-5, which in turn might contribute to marked eosinophilia and high serum IgE levels [6]. Abundant expression of eosinophilotropic cytokines, such as IL-4, IL-5, and IL-13, in peripheral blood mononuclear cells has also been reported in a patient with Kimura's disease [7]. Both of the class switches to IgG4 and IgE depend on IL-4/IL-13 [8–11], which are therefore considered to be part of the Th2 immune response for ensuring B cell proliferation and immunoglobulin class switching. In summary, antigens or abnormal immune factors that induce IgE and eosinophil responses are good inducers of IgG4.

In our case, biopsy of the lymph nodes showed coexistence of abundant eosinophils and IgG4-positive plasma cells. We then performed a review of published cases with Kimura's disease in which IgG4-positive plasma cells had also been studied (Table 1). Tsubouchi et al. recently reported numerous IgG4-positive cells in a lung biopsy of a Japanese man who had been treated for Kimura's disease [12]. Immunohistochemical staining of the lung specimens showed infiltration of IgG4-positive plasma cells (IgG4-positive/IgG-positive plasma cells=35 %). Another report documented a Caucasian who had been initially diagnosed as having epithelioid hemangioendothelioma and had experienced five recurrences. He was finally diagnosed with Kimura's disease by McKelvie et al. [13]. In their case, up to 150 IgG4-positive plasma cells per high power field were noted among all of the biopsies of the lymph nodes. Similarly, Hattori et al. reported two patients with Kimura's disease whose skin was involved [14]. Histopathological and immunohistochemical examination of skin specimens from these two patients showed abundant eosinophils and distinct fibrosis peculiar to Kimura's disease and an extremely high proportion of IgG4/IgG plasma cells (99.9 and 91.3 %). All of the cases mentioned above were definitely diagnosed with Kimura's disease. However, immunohistochemistry of either lymph nodes or skin lesions revealed abundant IgG-positive and IgG4-positive plasma cells.

Typical histological features of Kimura's disease in lymph nodes include germinal center hyperplasia, increased postcapillary venules in the mantle zones, vascularization of germinal centers, eosinophilic infiltration in the sinuses and paracortex occurring later in germinal centers, paracortical eosinophilic abscesses, and sclerosis of variable degrees [15]. IgG4-related lymphadenopathy shows a broad morphological spectrum, with five various histological patterns [16–19]. The type V pattern is the least common, featuring focal replacement of the nodal parenchyma by sclerothaline tissue, which shows variable infiltration of lymphocytes, plasma cells, and eosinophils [20]. Although lymph node involvement of Kimura's disease shares some similarities with those seen in the type V variant of IgG4-related disease, there are

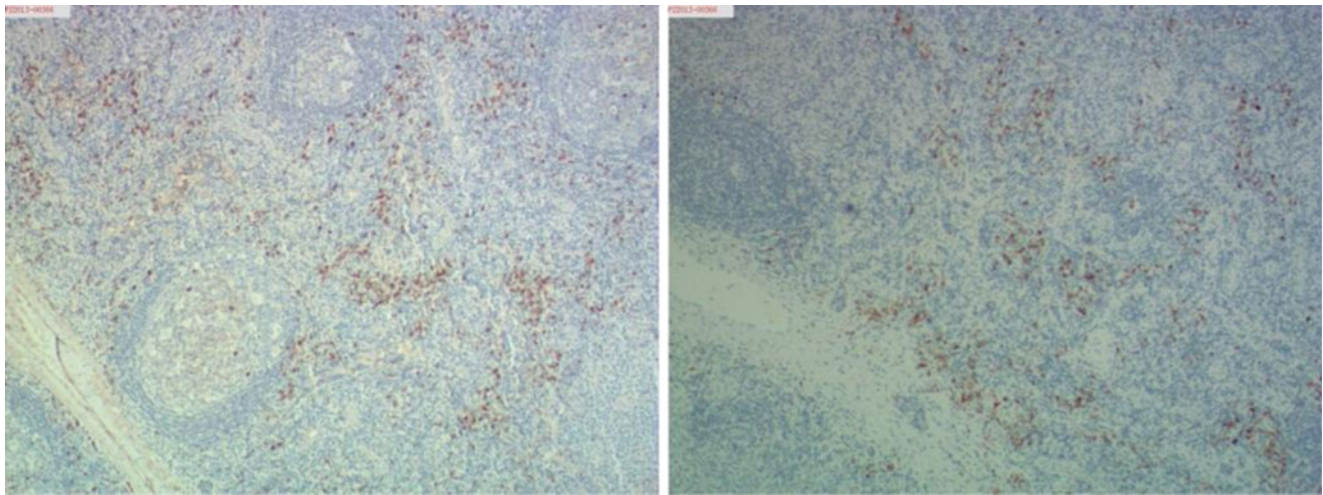


Fig. 1 Immunohistochemical staining of the lymph node. *Left:* plasma cells positive for anti-IgG antibody, *right:* plasma cells positive for anti-IgG4 antibody

still several morphological features that can be used for distinction of the two diseases. Kimura's disease is, to some extent, a type of hypersensitivity to an unknown or known allergen. However, IgG4-related disease is fibrosis and sclerosis of involved organs with infiltration of IgG4-positive plasma cells. Expression of IgE in follicular dendritic cells and eosinophilic microabscesses is routinely seen in Kimura's disease, but not in IgG4-related lymphadenopathy [13]. Tsubouchi and colleagues observed numerous IgG4-positive plasma cells in a lung biopsy of a patient with Kimura's disease, and they suggested the coexistence of the two diseases. We hold a different view that the presence of any IgG4-positive plasma cells in the peripheral blood, infiltration of IgG4-positive plasma cells in lymph nodes, and skin lesions are epiphenomena of Kimura's disease.

According to the possible pathogenesis, clinical, and pathological features of Kimura's disease, we searched for an appropriate model to illustrate our view. We propose "allergen-specific immunotherapy" as the model. Allergen-specific immunotherapy is based on repeated exposure of low-dose disease-causing allergens to modify allergen-specific immune responses in patients so that higher doses of the allergen can be tolerated [21]. The microenvironment and antigen-presenting

cells promote the differentiation of CD4⁺ T cells to Th2 cells during T cell priming after exposure to allergens [22–24]. Th2 cells produce a variety of cytokines, such as IL-4 and IL-13, which promote immunoglobulin class switching of B cells to IgE and IgG4. Th2 cells also produce IL-5 of which eosinophilic activity is dependent on. This immune response is particularly strong in individuals with a genetic predisposition towards allergies, but it can be found in everybody. Allergen-specific immunotherapy can alter the balance from allergen-specific Th2 to allergen-specific Th1 immunity, and it may induce the secretion of immune regulatory cytokines, such as IL-10 and T regulatory cell (Treg) responses [25, 26]. IL-10 interferes with class switching [27], which affects IgE and IgG4 production [28]. In addition, IL-10 is presumably needed to drive the differentiation of IgG4-switched B cells to IgG4-secreting plasma cells [29]. Treg cells are classified into two categories: naturally occurring Treg cells and induced Treg (iTreg) cells. These types of cells may be essential in the suppression of Th2-mediated inflammation and maintenance of immune tolerance [30]. Induced Treg cells acquire their suppressive activity under specific stimulatory conditions. Examples for iTreg cells consist of interferon- γ -producing Th1 cells and IL-10-producing Tr1 cells [31]. After

Table 1 Clinicopathological features of patients with Kimura's disease

Case	Age	Sex	Serum IgG4	Lesion for biopsy	IgG+ cells/HPF	IgG4+ cells/HPF	IgG4+/IgG
Tsubouchi et al. [12]	46	M	High IgG4 level	Lung	ND	ND	>35 %
McKelvie et al. [13]	30	M	ND	Lymph node	ND	150	0.6
Hattori et al. [14] (1) ^a	62	M	ND	Skin	136	135.8	0.999
Hattori et al. [14] (2)	57	F	ND	Skin	20.8	19	0.913

Numbers of IgG+ and IgG4+ cells are mean $\pm$ SD in the original article; we use mean here for comparison with other cases

HPF high power field, M male, F female, ND not done

^a Hattori et al. reported two cases

stimulation by allergens, IL-10 and transforming growth factor- β levels increase in peripheral blood mononuclear cells. This leads to active suppression of specific T cell responses, which are mediated by Tr1 cells or CD4⁺ CD25⁺ Treg cells [32, 33]. Tr1 cells and CD4⁺ CD25⁺ Treg cells suppress allergen-specific IgE and induce IgG4 in peripheral blood mononuclear cell cultures [28]. Patients with Kimura's disease, as we have mentioned above, may have a genetic predisposition towards allergies. Persistent or interrupted exposure to a known or unknown allergen could trigger the occurrence of Kimura's disease. Release of IL-4, IL-5, and IL-13 is mediated by the predominant Th2 immune response. As a result, elevated IgE and abundant eosinophils with mast cells and basophils cause type 1 hypersensitivity. We speculate that this is an initial immune response of Kimura's disease. IL-4 and IL-13 promote immunoglobulin class switching of B cells to IgE and IgG4. Therefore, IgG4-positive plasma cells have been found in almost all of the species we have studied. As the time of allergen exposure is extended, iTreg should be induced and Th2-mediated inflammation should be suppressed. IgG4 would be dominant instead of IgE, and clinical manifestations caused by type 1 hypersensitivity would gradually disappear. At this time, the lesion may be composed of IgG4-positive plasma cells and sclerosis of fibrous tissue with IgE and eosinophils. This model may not be realistic because doses and exposure time cannot be controlled in naturally occurring Kimura's disease and whether induction of suppression of the Th2 response really occurs is unclear.

We hope to study more cases of Kimura's disease to support our idea, but this could be difficult because it is rare. Immunohistochemistry of IgG4- and IgG-positive plasma cells and detection of IL-4, IL-5, IL-10, IL-13, and transforming growth factor- β could lead to a better understanding of the relationship between Kimura's disease and IgG4-related disease.

Disclosures None.

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