

## What do we know about Kimura disease?

### Co powinniśmy wiedzieć o chorobie Kimury?

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#### ABSTRACT

This article describes Kimura's disease as a rare case of lymphadenitis and reviews its epidemiology, clinical aspects, diagnosis and treatment methods. The role of surgical procedures was also underlined. Kimura disease is a rare and benign chronic inflammatory soft tissue disorder of unknown origin. The definitive histological description was published by Kimura et al. in 1948 and henceforth, the disease has born his name. Since that time, there has been a gradual increase in the number of reports. While most cases of Kimura disease have originated in China, Japan or Southeast Asia, there have been sporadic case reports from Europe and America. The data suggest that Kimura's disease should be included in the list of differential diagnoses for all neck lymph node involvements. If a otolaryngologist maintains a high index of suspicion, an early diagnosis can be made to contribute to a more successful outcome of the disease.

#### KEY WORDS

Kimura's disease, disease management, treatment

#### STRESZCZENIE

Artykuł opisuje chorobę Kimury – rzadką przyczynę limfadenopatii, jej epidemiologię, objawy kliniczne, diagnostykę i leczenie, w tym leczenie chirurgiczne. Choroba Kimury jest rzadkim, łagodnym, przewlekłym zapaleniem tkanki łącznej nieznanego pochodzenia. Cechy histologiczne tej choroby zostały po raz pierwszy opisane przez Kimurę i wsp. w 1948 r. i nazwane jego nazwiskiem. Większość przypadków choroby Kimury pochodzi z Chin, Japonii bądź południowo-wschodniej Azji, natomiast nieliczne z Europy i Ameryki. Obraz kliniczny choroby nakazuje uwzględnienie jej w diagnostyce różnicowej powiększenia węzłów chłonnych szyi. Daje to możliwość pomyślnego wyleczenia.

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choroba Kimury, przebieg choroby, leczenie

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## INTRODUCTION

The causes of neck lymphadenopathy include a wide variety of disorders from infectious diseases through autoimmune and allergic diseases, as well as benign and malignant neoplasms.

In most cases, cervical lymph node enlargement is associated with reactive changes in response to bacterial, viral, chlamydial or mycotic pathogens, or with the presence of primary haematological malignancies such as Hodgkin's disease and non-Hodgkin's lymphomas [1,2,3,4].

There are, however, some clinical entities associated with cervical lymphadenopathy that are very rarely seen, particularly in European countries, where they may cause substantial diagnostic difficulties. We present one of them – Kimura disease. This one is benign in the clinical course but may mimic aggressive malignant conditions and, when misdiagnosed, may lead to potentially harmful and unnecessary evaluations and treatments of patients.

### Definition

Kimura disease is a rare and benign chronic inflammatory soft tissue disorder of unknown origin. The disease was first described in 1937, in the Chinese literature by HT Kimm and C Szeto and termed "eosinophilic hyperplastic lymphogranuloma".

The definitive histological description was published by Kimura et al. in 1948 and henceforth, the disease has born his name. Since that time, there has been a gradual increase in the number of reports (as of 2007, about 300 reported cases) [3,4,5,6,7,8].

### Epidemiology

While most cases of Kimura disease have originated in China, Japan or Southeast Asia, there have been sporadic case reports from Europe and America. The disease is most prevalent in Asians, uncommon in Caucasians, and rare in Africans.

It has been suggested that the common factor is a degree of Asian ancestry. There is a marked male predominance, with a male/female sex ratio of 3.5 to 7.1. The peak age of onset is during the third decade [1,2,3,9,10,11].

### Aetiology and pathogenesis

The aetiology of Kimura's disease is not understood at this time, but it may relate to a disturbance in the normal rate of production of eosinophils and IgE, currently believed to be the product of an interaction between type 1 and 2 T helper cells [1,2,12,13].

Such an imbalance could result in the excessive production of eosinophilic cytokines such as interleukin 4. Patients with Kimura disease have been shown to have high levels of circulating eosinophil cationic proteins and major basic proteins, with heavy concentrations of IgE in their tissues.

The proposed theories include persistent antigenic stimulation following arthropod bites, and parasitic, candidal (especially *Candida albicans*) or viral infections. To date, none of these theories have been substantiated [1,2,14,15,16]. Complications such as atopic dermatitis, allergic rhinitis, asthma, and urticaria occur among patients [1,2,16,18,19].

### Clinical features and prognosis

The nature of Kimura's disease is mostly benign, with a good prognosis. The importance lies in its ability to mimic a number of other benign inflammatory and neoplastic conditions of the head and neck. Kimura's disease is a chronic inflammatory condition characterized by a triad of:

- painless subcutaneous masses in the head or neck region, accompanied by regional lymphadenopathy
- blood and tissue eosinophilia
- markedly elevated serum immunoglobulin E levels.

Clinically, subcutaneous soft tissue masses occur predominantly in the head and neck region (76%) and often involve parotid, submandibular (43%) or minor salivary glands as well as regional lymph nodes (31–100%).

Other sites – the eyelids, orbit, preauricular region, the groin, epicranium and lachrymal glands may be frequently involved, as well as the hard palate and larynx. The maxilla, oral cavity paranasal sinuses, nerves and sperm ducts are rarely affected [19,20].

The clinical course of Kimura's disease is usually benign. These observed subcutaneous masses, when left untreated, tend to slowly enlarge and may eventually become disfiguring.

Patients may complain of local or generalized pruritus and sub-acute or chronic dermatitis. Renal involvement, usually extramembranous glomerulonephritis, is found in about half of patients. They may develop isolated proteinuria (about 5% of patients), or demonstrate a full nephrotic syndrome (about 12% of patients) [1,2,3,4,21].

Approximately 67 to 100% of these patients develop regional lymphadenopathy, mainly of the cervical lymph nodes. Infrequently, axillary, inguinal or epitrochlear nodes may be affected; in a longstanding disease, this lymphadenopathy may become generalized [2,3,4,5]. In the long term, patients seem to do well.

## DIAGNOSIS: LABORATORY AND HISTOLOGICAL FEATURES

### Laboratory findings

Laboratory investigations will invariably reveal peripheral eosinophilia and increased serum immunoglobulin E (IgE) levels. They may have elevated erythrocyte sedimentation rates (ESR) and mild hyperleucocytosis; however, hiperleucocytosis has been more rarely observed [1,2,3,4,5,14]. In patients with Kimura's disease eosinophilia is almost always present while raised IgE is always the case (which can be helpful in differential diagnosis versus angiolymphoid hyperplasia with eosinophilia).

### Imaging diagnostic methods

In the course of Kimura's disease, masses should also be assessed by imaging methods like Computed Tomography (CT), Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET). Computed tomography imaging of KD is non-specific. In CT scans with contrast enhancement, the lesions appear as homogeneous, slightly hyperattenuated lymph nodes and swollen salivary glands. Enlarged ill-defined subcutaneous masses occupying the salivary gland region were also detected. Magnetic resonance imaging can differentiate its precise nature from other soft tissue tumours. These lesions tend to be heterogeneous, hypointense, sometimes slightly hyperintense in T1-weighted and T2-weighted imaging. The discrepancies in the degree of enhancement may be attributable to differing degrees of fibrosis and vascular proliferation. The image of F-2-deoxy-2-fluoro-d-glucose – positron emission tomography in KD can closely resemble that seen in neoplastic disorders, such lymphoma or metastatic lymphadenopathy. It should be taken into consideration as a differential diagnosis for a generalized lymphadenopathy [8,16,17].

### Histological features

The histopathological picture of Kimura's disease is characterized by the presence of tight fibrosis, lymphocytic infiltration with follicle formation, and mixed inflammatory infiltration with the presence of eosinophils. Some authors describe the changes as a component of three elements: cellular, fibrocollagenous and vascular. The cellular element of follicle formation is built mainly from lymphocytes. The fibrocollagenous part is combined from eosinophilic cells and eosinophilic "micro abscesses" (Fig. 1). Giant cells and plasma cells are also present but in small amounts. Fibrosis is also present, even in the initial period. The vascular component consists of

a proliferation of enlarged endothelial cells. There are no atypical cell nuclei or enlarged cytoplasm. In enlarged regional lymph nodes, follicular hypertrophy with increased amounts of eosinophils, with or without fibrosis, is affirmed (Fig. 2). The deposition of IgE in the germinal centers can be readily demonstrated with immunohistochemistry. The lymph node architecture is preserved [3,4,5,6].

Pathologically, this picture is most difficult to distinguish from angiolymphoid hyperplasia with eosinophilia (ALHE), and for a long time, these two conditions were thought to represent one and the same pathology; however, the current consensus is that they represent two ends of a spectrum of similar diseases [1,2,3,4,5,6].

### Figure captions

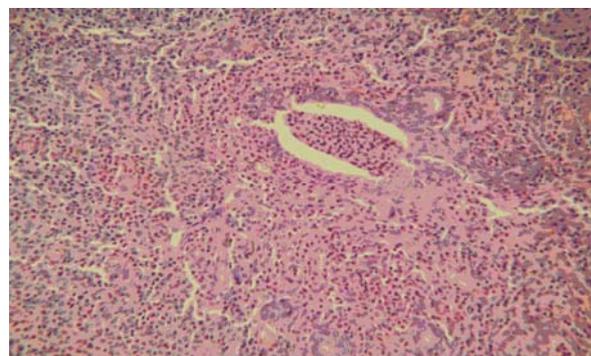


Fig. 1. Kimura disease. Parotid gland. Dense eosinophilic infiltrations forming "micro abscesses".  
Ryc. 1. Choroba Kimury. Ślinianka przyuszna. Gęste nacieki eozynofiliów tworzące „mikroropnie”.



Fig. 2. Kimura disease. Hypertrophic follicle with germinal center in an enlarged lymph node.  
Ryc. 2. Choroba Kimury. Przerośnięte pęcherzyki z centrami namnażania w powiększonych węzłach chłonnych.

### Differential diagnosis

The differential diagnosis of Kimura's disease, while including obvious lesions such as dermatofibrosar-

coma protuberans and cylindroma, will ultimately be determined by both the clinical picture and the histopathology. Clinically, malignant lymphoma, non-lymphocytic leukaemia, parotid tumours, haemangioma, pyogenic granuloma, scrofula, Mikulicz's disease and Kikuchi's disease are all conditions for which this disease has been mistaken in the past. Other conditions to consider and rule out include Kaposi's sarcoma, angiosarcoma, eosinophilic lymphoma and angioimmunoblastic lymphadenopathy, such as tissue-invasive helminth infections, cysticercosis, sparangiosis, toxocarosis and several forms of invasive miasis [1,2,3, 5,6,7,22,23,24,25,26,27,28,29].

### Therapy

Three major therapeutic options exist for Kimura's disease. Resection of the tumour mass may be effective and permanently eradicate the mass if the entire lesion can be removed, but re-growth is common. Local irradiation has also shown to be effective in shrinking lesions, but it is generally not advocated in younger patients. Systemic corticosteroids and immunosuppressive agents such as cyclosporine A, cyclophosphamide have been used for the treatment of Kimura's disease as well as for the accompanying nephrotic syndrome [2,3,21,22,23,24,25,26,27,28,29].

Recent case reports have reported azathioprine, leflunomide, pentoxifyline and Imatinib (tyrosine kinase inhibitor) to be effective in the treatment of KD. Finally, intralesional corticosteroids have shown to reduce the size of the lesion, but the tumour tends to recur when these drugs are discontinued. In selected patients, it may be advisable to take a conservative approach, treating only if the mass continues to grow or causes significant deformity [3,4,21,22,23,24,25, 26,27,28,29,30,31].

### CONCLUSIONS

Kimura disease is a rare but an important case of lymphadenopathy. KD should be considered in the differential diagnosis of any patient presenting unexplained lymphadenopathy associated with non-specific symptoms. Consideration of the diagnosis is particularly important before prescribing potentially inappropriate drug therapy.

Knowledge of Kimura's disease, its clinical appearance, course and histopathology puts the practitioner in a better position to answer questions from concerned patients and primary caregivers, and to optimize management strategies.

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