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Kimura Disease: A Rare Eosinophilic Inflammatory Disorder – Pathogenesis, Diagnosis, and Emerging Therapies

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ABSTRACT

Kimura disease is a rare, chronic eosinophilic inflammatory disorder, predominantly affecting young Asian males, and typically presents with painless masses in the head and neck region. Its exact etiology remains unclear, but immune dysregulation, including heightened IgE levels and eosinophilic infiltration, is central to its pathogenesis. Although the disease is benign, it can cause significant morbidity through recurrent lesions and potential systemic complications, such as renal involvement and hypercoagulability. Diagnosis relies on clinical presentation, laboratory findings (eosinophilia and elevated serum IgE), imaging studies (such as MRI and ultrasound), and histopathology, with characteristic features including eosinophilic infiltration, follicular hyperplasia, and vascular proliferation. Treatment primarily involves immunosuppressive therapies such as corticosteroids, leflunomide, and cyclosporine, with surgical excision serving as the main approach for localized disease. Recurrence is common, and adjunctive treatments like radiotherapy, IV immunoglobulin, and novel strategies such as 3D printing in radiation delivery offer potential for managing persistent cases. Despite the rarity of Kimura disease, understanding its pathophysiology and treatment options is crucial for improving patient outcomes and minimizing complications.

1. INTRODUCTION

Kimura disease is a rare, chronic inflammatory condition of indeterminate etiology involving the head and neck area predominantly. It is a benign but recurrent and persistent condition that is characterized by painless subcutaneous nodules or lymphadenopathy, usually unilateral but sometimes bilateral. The condition is typically accompanied by regional lymphadenopathy and rarely salivary gland involvement. The condition is benign but is recurrent and persistent and poses diagnostic difficulty due to its mimicry of other neoplastic and lymphoproliferative conditions [1].

The condition was first reported in 1937 in China. In the original series, the condition was reported as "eosinophilic hyperplastic lymphogranuloma," a description used by Kim and Szeto, who reported seven cases in Chinese literature. The condition was named in 1948 when Kimura et al. reported its characteristic vascular features and termed it an "unusual granulation combined with hyperplastic changes in lymphoma tissue." Kimura disease has since been characterized as a distinct clinical entity, reported primarily in East Asian populations but reported in other populations around the globe [2].

After decades of investigation, the pathogenesis and exact etiology of Kimura disease remain unknown. It is a chronic inflammatory condition with a prominent eosinophilic component and a paraneoplastic association with increased serum immunoglobulin E (IgE) levels. The condition shares overlapping histopathological characteristics with other eosinophilic conditions, including angiolymphoid hyperplasia with eosinophilia (ALHE), and may lead to diagnostic uncertainty. Although not malignant, Kimura disease may significantly affect the quality of life of a patient due to recurrence and

complications, including nephrotic syndrome secondary to renal involvement [3].

Because of its rarity, lack of well-defined etiology, and vulnerability to misdiagnosis, Kimura disease remains a significant area of interest for research. Progress in diagnostic imaging, histopathological, and immunological studies has advanced the understanding of the disease, and new therapies offer new prospects for treatment. This review aims to provide a critical summary of the pathogenesis, diagnostic characteristics, and established and new therapeutic strategies for Kimura disease, emphasizing its clinical significance and problems of its treatment in the clinical setting.

2. PATHOPHYSIOLOGY

The pathophysiology of Kimura disease is obscure, and to date, etiology has been established only inadequately; however, one can outline at least several putative hypotheses under which Kimura disease might manifest as a possible consequence of some form of immunodysregulation, apparently triggered by constant antigenic challenge, such as arthropods' bites or viral infections; neoplastic processes are one more potential challenge. Environmental aspects, including various infections or toxin exposure, contribute to the incitement of an autoimmune or type 1 (IgE-mediated) hypersensitivity response.

The main feature of Kimura disease is the association with an elevated serum immunoglobulin E (IgE) level, suggesting an atopic mechanism. Immune response in Kimura disease is characterized by a hyperactive T-helper cell response, and in particular, it is dominated by CD4+ Th2 cells. This imbalance in cell subpopulations leads to an overproduction of cytokines and other signaling molecules, which contribute to the characteristic inflammatory and lymphoid tissue changes seen in the disease. Among the key cytokines implicated are granulocyte-monocyte colony-stimulating factor (GM-CSF), tumor necrosis factor alpha (TNF-α), soluble interleukin 2 receptor (sIL-2R), and interleukins (IL-4, IL-5, IL-10, IL-13). Other chemokines, such as eotaxin and RANTES (regulated on activation, normal T cell expressed and secreted), have also been found to play critical roles in mediating the inflammatory process. These cytokines stimulate the activation and recruitment of eosinophils, mast cells, and other immune cells into the site of inflammation, thus perpetuating the cycle of tissue damage and repair[5].

Further studies demonstrated that CD4+ T cell proliferation is in close association with disease development and recurrence in Kimura disease. Specifically, a higher number of Th2 activity plays a critical role in perpetuating the inflammation that characterizes the disease process. The resultant inflammation contributes to the formation of follicular lymphoma-like structure within the diseased tissues which can be concomitant with tissue fibrosis.

Other studies have also emphasized the role of the IL-21/pERK ½ signaling pathway in the immunopathogenesis of Kimura disease. This pathway is activated during the disease process and pERK ½ might be used as a marker of disease progression. Activation of this pathway indicates that IL-21 may play a key role in regulating the Th2 immune response and promoting chronic inflammation seen in Kimura disease. Some studies have even proposed that monitoring pERK ½ levels could serve as a prognostic indicator for disease severity and recurrence, though this is still under investigation.

In summary, though the exact mechanisms responsible for Kimura disease are unknown, it is apparent that immune dysregulation, especially an imbalance in the Th2 response, is crucial to its pathogenesis. Enhanced IgE levels, overproduction of pro-inflammatory cytokines, and activation of specific signaling pathways contribute to the tissue changes and clinical manifestations of this disorder. The future directions for the continued research of immunological underpinnings of Kimura disease include further exploration into diagnostic markers and therapeutic targets.

3. EPIDEMIOLOGY

Prevalence

The prevalence of Kimura disease is unknown because the disease is rare, and very little data exist regarding its incidence. Most reported cases come from East and Southeast Asia, where the disease is endemic. Outside these regions, Kimura disease is much less commonly encountered, though cases have been sporadically documented in Europe, the United States, and the Middle East. Although it is relatively rare with low incidence globally, the disease carried interest in regions with higher case involvement rates, especially in some Asian people groups.

Race

Kimura disease mainly affects people with Asian heritage, particularly East and Southeast Asians. The disease has more frequently been noted in the population groups described by this heritage. Most case histories have originated from regions like China, Japan, and India. It is rarely seen in non-Asian populations, including those from Europe, the United States, and the Middle East. This racial predilection suggests that genetic, environmental, or immune-related factors specific to Asian populations may play a role in the development of the disease.

Age

While Kimura disease can occur at any age, it is most commonly observed in young adults, typically between the second and

third decades of life. The reported median age of onset has been between 28 and 32 years of age. In addition to these more common manifestations, the disease has also occasionally been noted to occur in a pediatric population with cases reported up to 15 months of age. These latter cases are indeed rare, but the disease that occurs in the pediatric population manifests similarly to adults. The occurrence of Kimura disease in older adults is unusual, and it is primarily seen in younger individuals.

Sex

Kimura disease has been established to demonstrate a clear male predominance where men are more affected than women. The male-to-female ratio varies from study to study but generally is from 3.5:1 to 9:1. This predisposition in men suggests that sex-based factors, possibly hormonal or immunological, might influence the increased male susceptibility to the disease. Nevertheless, the reasons behind this sex disparity have not been understood well and need further investigation [11].

In summary, Kimura disease is a very rare condition which affects predominantly males from Asia. Most cases of this disease have been reported to affect people aged in their second and third decades. It has no specific age limits but appears in most patients who are adults. The East and Southeast Asian countries are where it is predominantly reported, although other parts of the world show fewer cases. The understanding of the epidemiological characteristics of Kimura disease is crucial in identifying at-risk populations and guiding future research into its pathogenesis and treatment.

4. CLINICAL PRESENTATION

History

Kimura disease classically presents as gradual development of painless masses or swelling in the head and neck region, being the most common site. Such masses are mostly subcutaneous and of varying sizes; therefore, it is possible that the deformity could be quite apparent. In addition to the masses, patients may experience pruritus (itching) of the overlying skin, which is thought to be related to the allergic and immune reactions associated with the disease. Many patients with Kimura disease also have a history of allergic conditions, which may include asthma, chronic urticaria (hives), pruritus, and rhinitis. This link between Kimura disease and allergic disorders hints at an immune dysregulation as the underpinning pathophysiology in the development and progression of the disease [7].

Another key feature of Kimura disease is renal involvement, which is observed in as many as 10–60% of the patients. The renal manifestations of the disease may range from conditions such as membranous glomerulonephritis and nephritic syndrome to impaired renal function. Proteinuria, or the presence of excess protein in the urine, is also a common finding in these patients, occurring in 12–16% of individuals. Although less commonly observed, some reports even suggested that Kimura disease may be associated with a hypercoagulable state, even in the absence of nephrotic syndrome. This hypercoagulability may contribute to thrombosis or other complications, making it an important consideration in the management of these patients [8] [9].

Physical Examination

Kimura disease is characterized by non-tender subcutaneous nodules or masses; most of its cases are recognized on physical examination, mainly localized in the head and neck area. It also frequently affects the parotid and submandibular glands, which come with regional lymphadenopathy - enlargement of adjacent lymph nodes. The lesions often vary in size and consistency, but usually are soft and moveable upon palpation [1][10][11].

Although the head and neck are the most common sites, Kimura disease can also affect other parts of the body. Involvement of the orbit, including the eyelids, conjunctiva, and lacrimal glands, has been reported, as well as involvement of structures such as the palate, pharynx, parapharyngeal space, parotid gland, paranasal sinuses, epiglottis, tympanic membrane, axilla, groin, and even the breast. There are also reports of Kimura disease affecting the extremities and inguinal lymph nodes, although less common.

Some patients may present with unusual manifestations, such as a pulmonary hilar mass. The presence of a hilar mass, although rare, suggests that Kimura disease may involve the lungs or mediastinal structures. Visible ischemia of the extremities may also be seen in patients with hypercoagulability, leading to complications like Raynaud's phenomenon (a condition in which spasms of the small blood vessels of the extremities occur) and acute limb ischemia (ALI). If these complications are left untreated, it may lead to more serious consequences, and therefore, early diagnosis and management become essential.

In summary, the clinical presentation of Kimura disease is that of a gradually developing painless subcutaneous mass, more frequently associated with allergic diseases and with renal involvement. Physical examination usually discloses non-tender masses in the head and neck region, possibly involving other areas. Renal complications, hypercoagulability, and rare presentations such as pulmonary hilar masses indeed underscore the complexity of this rare disorder, requiring thorough assessment in affected patients.

5. CASE REPORT

Diagnostic Work-Up

An 18-year-old college student from Patnagarh, Balangir, Odisha, complained of swelling on both sides of the neck that had been progressively enlarging over the past eight months. Initially, the patient noticed small swellings of the size of berries, which gradually increased to the current size of tennis balls. The swelling was not associated with any pain, fever, vomiting, night sweats, throat pain, respiratory symptoms, dysphagia, or weight loss.

On examination, the swelling was found to be non-tender, located in the subcutaneous tissue of the head and neck region, particularly in the parotid and submandibular areas. The patient did not exhibit any other significant symptoms, and there were no signs of systemic involvement. Additionally, there was no history of any systemic conditions such as respiratory distress or gastrointestinal complaints.

The diagnostic work-up included fine needle aspiration cytology (FNAC) and biopsy. Both tests were suggestive of Kimura disease, thus confirming the diagnosis. The exact cause and pathophysiology of the disease are still unknown, although several hypotheses point to immune dysregulation and atopic reactions, with possible triggers being environmental factors or infections.

To support the diagnosis, clinical images of the patient's neck were taken that showed characteristic bilateral swelling (Figure 1). MRI imaging further confirmed the involvement of the parotid and submandibular regions (Figure 2). These findings were consistent with the diagnosis of Kimura disease, as supported by FNAC and biopsy results.

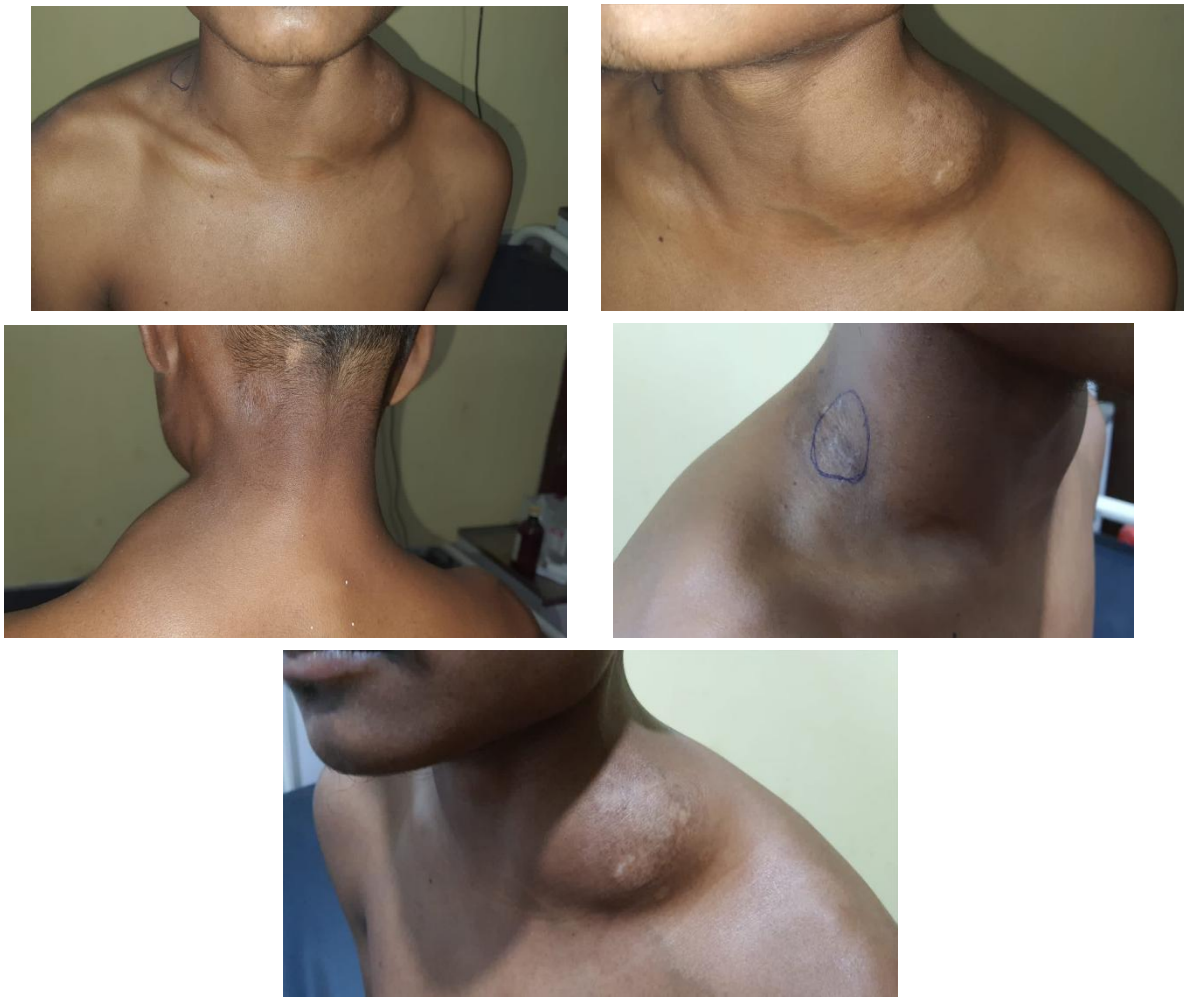

Figure 1: Clinical image of the neck of the patient showing bilateral, non-tender subcutaneous nodules in the parotid and submandibular regions. These nodules have gradually increased in size over the past 8 months and correlate with the clinical presentation of Kimura disease.

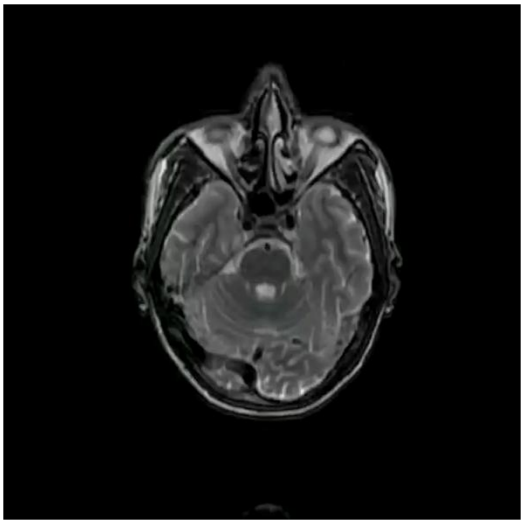

Figure 2: MRI image showing the full extent of the swelling in the head and neck region. These MRI results coincide with the clinical presentation of Kimura disease: involvement of parotid and submandibular glands is confirmed.

Treatment & Outcome

The treatment for Kimura disease is largely symptomatic and involves the management of swelling and related complications. For this patient, standard therapeutic strategies were employed in managing the disease, but no information was available on the actual treatment regimen implemented. Treatment typically involves corticosteroids that reduce inflammation and control the immune response, particularly in cases involving significant swelling or complications such as renal involvement.

Kimura disease is a rare condition and typically responds well to treatment, although relapses may occur. The prognosis is usually good, with most patients having resolution of the swellings and symptoms with proper management. However, given the possibility of recurrence and associated complications such as hypercoagulability and limb ischemia, regular follow-up is important.

This case highlights the typical presentation of Kimura disease with neck swelling and non-tender subcutaneous nodules, predominantly associated in young males. Although this condition is mostly reported in East and Southeast Asia, it can present among other population groups, and this is confirmed through FNAC and biopsy.

6. COMPLICATIONS

Though it characteristically appears to be benign and self-limiting, Kimura disease may trigger several complications when left untreated or not adequately managed. In general, the response of patients to treatment has been good with remission of the symptoms. Still, recurrence and other significant complications have been noted in a small number of cases that would pose a challenge to the patient's health and quality of life.

Recurrence

One of the complications of Kimura disease is that it can easily recur after its initial treatment. Even though therapeutic interventions such as corticosteroids and surgical excision were applied appropriately, some patients relapse, where nodules or swelling appear. Recurrence occurs at any stage of the disease and can even occur months or years after initial treatment. This cyclical character of the illness requires long-term follow-up and monitoring to establish early detection and management of relapses.

Nodules or Masses can Ulcerate

Ulceration of the large nodules or masses may occur in very rare cases among patients with Kimura disease. This is an infrequent complication that can be alarming when it happens. The ulceration can cause pain, possible infection, or secondary complications due to tissue destruction. Not a common feature, ulceration in Kimura disease requires immediate medical attention and may necessitate more aggressive treatments to prevent further tissue destruction and control any symptoms that may accompany it.

Hypercoagulable State and Thromboembolic Events

Another severe complication linked with Kimura disease is the hypercoagulable state, which may be associated with

thromboembolic events. There have been studies that prove patients with Kimura disease are at a higher risk for any thromboembolic events like DVT and PE. For a few rare instances, the induced hypercoagulability may lead to thrombosis formation and cause brain embolisms by this process. These thromboembolic events can be life-threatening and require prompt intervention to avoid long-term neurological damage or other organ complications. The risk of thromboembolism also underscores the need for careful monitoring and management of patients with Kimura disease, especially if they show signs of abnormal clotting or vascular complications.

Other Possible Complications

Apart from these, patients with Kimura disease may exhibit other systemic complications, including renal involvement (such as nephrotic syndrome or glomerulonephritis) and allergic manifestations, such as asthma, rhinitis, and chronic urticaria. These conditions are less common than recurrence or thromboembolic events but can complicate the clinical course of Kimura disease and hence require treatment at various levels.

In summary, though mostly benign, complications of Kimura disease may be present. Of notable concern are the complications of recurrence, ulceration of nodules, and thromboembolic events, among them being brain embolisms. Therefore, careful monitoring, early intervention, and long-term follow-up become important in managing said complications and ensuring the best possible outcome for patients suffering from this rare eosinophilic inflammatory disorder.

7. DIFFERENTIAL DIAGNOSIS

Kimura disease is a rare eosinophilic inflammatory disease that has a characteristic clinical profile, including the presence of painless subcutaneous nodules in the head and neck area. However, because of overlapping symptoms with so many other conditions, it is important to exclude Kimura disease from other conditions that may share similar signs and symptoms. Conditions that should be included in differential diagnosis of Kimura disease include the following:

1. Angioimmunoblastic T-cell lymphoma (AITL)

Angioimmunoblastic T-cell lymphoma is a type of peripheral T-cell lymphoma that may present with lymphadenopathy, eosinophilia, and systemic symptoms like fever and weight loss, similar to Kimura disease. However, AITL is typically associated with a more aggressive clinical course and features such as B-symptoms (fever, night sweats, and weight loss), which are absent in Kimura disease.

2. Angiolymphoid hyperplasia with eosinophilia (ALHE)

This is also sometimes referred to as Kimura-like disease. The condition often considered the closest differential diagnosis for Kimura disease is ALHE. It mainly presents with subcutaneous nodules, usually in the head and neck, but it is characterized by eosinophilia and vascular proliferation. This condition differs from Kimura disease in that involvement is often more localized and less systemic.

3. Castleman Disease

Castleman disease, especially the hyaline-vascular variant, can resemble Kimura disease because it may present with lymphadenopathy and systemic symptoms. However, Castleman disease typically includes large, hyperplastic lymph nodes, and even vascular proliferation, in contrast to localized subcutaneous involvement in Kimura disease.

4. Cylindroma

It presents as nodules, sometimes as seen in Kimura disease, and is one of the benign skin tumors very rarely found in the body. Cylindromas may be confined within the skin since they grow quite slowly and superficially. Nevertheless, the features of cylindroma can appear similar to subcutaneous nodules of Kimura disease because of its characteristic "tubular" structure, which appears under histopathology.

5. Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans is a rare soft tissue tumor that presents like an indolent, firm nodular mass in the skin or subcutaneous tissue, mimicking the nodules of Kimura disease. But the lesion of dermatofibrosarcoma protuberans is usually firmer and has the tendency to infiltrate the deeper tissues, whereas the nodules of Kimura disease are soft and mobile.

6. Dermatologic Manifestations of Kaposi Sarcoma

Kaposi sarcoma, especially in immunocompromised patients, can have skin lesions that may be similar to the nodules seen in Kimura disease. However, Kaposi sarcoma is typically accompanied by a history of HIV or immunosuppressive therapy, and its lesions are often more violaceous in color, whereas Kimura disease nodules are generally not associated with such color changes.

7. Pyogenic Granuloma (Lobular Capillary Hemangioma)

Pyogenic granuloma is a rapidly growing, red friable nodule, which can mimick the nodules in Kimura disease. However, drug-related lymphadenopathy is characterised by various presentations with different histopathological features, predominantly by capillary proliferation without significant eosinophilic infiltration.

8. Drug-Related Lymphadenopathy

Certain drugs like phenytoin, allopurinol, and sulfonamides cause drug-induced lymphadenopathy. This can be taken as a mimic of Kimura disease. The key feature is the lack of eosinophilia and complete resolution of lymphadenopathy after the offending drug is discontinued.

9. Hodgkin's Lymphoma

Hodgkin's lymphoma may present with painless lymphadenopathy, similar to Kimura disease. However, Hodgkin's lymphoma typically presents with systemic symptoms like fever, weight loss, and night sweats (B-symptoms), which are not seen in Kimura disease. Furthermore, Hodgkin's lymphoma usually shows Reed-Sternberg cells on histopathology, which are absent in Kimura disease.

10. IgA-Related Disease

IgA-related disease, including IgA nephropathy or IgA vasculitis, can present with eosinophilia and subcutaneous nodules. However, such conditions are commonly associated with renal involvement, which is not characteristic of Kimura disease.

11. Inflammatory Disease of the Orbit

Inflammatory orbital diseases, including orbital pseudotumor, may present with swelling around the eyes and may be confused with the orbital involvement seen in Kimura disease. However, orbital pseudotumors typically cause pain and vision changes, which are absent in Kimura disease.

12. Langerhans Cell Histiocytosis

Other disease processes, which can also create similar subcutaneous nodules and lymphadenopathy, are Langerhans cell histiocytosis, which has the proliferation of Langerhans cells as its characteristic but often has wide systemic effects through lesions in bone, diabetes insipidus, and organs.

13. Primary Malignant Lymphoma of Bone

Primary malignant lymphoma of bone can present as painless swelling or masses that may occur within the head and neck region similar to Kimura disease. Nevertheless, malignant lymphoma is typically associated with much more aggressive features, including systemic symptoms and a malignant histopathological profile.

14. Malignant Tumors of Head and Neck

Malignant tumors, both squamous cell carcinoma and metastatic cancer in the head and neck region present with swelling, lymphadenopathy, but present with a course of disease significantly more rapid clinically, painful; and often it is associated either with smoking, alcohol use where it is excluded in Kimura disease.

15. Parasitic Lymphadenitis

These are parasitic infections, as with Toxoplasma gondii or lymphatic filariasis. They could be associated with lymphadenopathy and eosinophilia. They often have exposure to the causative parasite; hence, a more acute presentation occurs, contrary to the indolent character of Kimura disease.

16. Epithelioid Hemangioma

Epithelioid hemangiomas are rare vascular lesions, which can appear as nodules in the head and neck region and may simulate the masses of Kimura disease. However, these lesions are generally less mobile and more vascular and have different histopathological features, which include epithelioid cell infiltration.

17. Tuberculosis

Tuberculosis, particularly in its extrapulmonary form, can present with lymphadenopathy and eosinophilia. However, tuberculosis is usually associated with a history of exposure to Mycobacterium tuberculosis, and the lymph nodes may exhibit caseous necrosis upon histopathological examination, which is not a feature of Kimura disease.

18. Eosinophilic Granuloma

Subcutaneous nodules, especially on the head and neck, have been reported to be associated with eosinophilic granuloma, one of the presentations of Langerhans cell histiocytosis. In contrast, bone and skin lesions are more likely to be part of this disorder, and this diagnosis is mostly made by identification of Langerhans cells and Birbeck granules in histopathology.

It thus encompasses a long list of conditions that, together with Kimura disease, might present with clinical features such as

subcutaneous nodules, lymphadenopathy, and eosinophilia. The only method of differentiating Kimura disease from the conditions listed above, thus allowing the accurate diagnosis of the condition for proper management, is through an extensive clinical assessment, histopathological examination, and imaging studies.

Table 1: Clinical and Pathological Differences Between Kimura Disease and ALHE [13]

Feature	**Kimura Disease**	**ALHE (Angiolymphoid Hyperplasia with Eosinophilia)**
Prevalence	Predominantly in Asians, with a male predilection	All racial groups with a slight female predominance
Eosinophilia and Raised Serum IgE	Common	Rare
Gross Lesions	Solitary lesions, mostly in deep subcutaneous tissues, frequently associated with regional lymphadenopathy and salivary gland involvement	Small, superficial dermal papulonodular, frequently erythematous, accompanied by bleeding and pruritus
Histological Features	Three components: 1. Cellular (inflammatory infiltrate including increased eosinophils and follicular hyperplasia) 2. Fibrocollagenous 3. Vascular (arborizing vascular proliferation of the postcapillary venule, endothelial cells are flat and lack cytologic atypia or vacuolization)	Vascular proliferation is most significant, forming aggregates or lobules comprising of plump endothelial cells with epithelioid or histiocytoid changes demonstrating cytologic atypia and vacuolization

Table 2: Cytological and Histological Features of Other Differential Diagnoses [4]

Condition	**Features**	**Other Features**

Angiolymphoid hyperplasia with eosinophilia (ALHE)	Spindle-shaped, polygonal cells with vesicular nuclei and deeply eosinophilic cytoplasm containing well-defined vacuoles and plenty of immunoblasts	Vascular proliferation is most significant, forming aggregates or lobules composed of plump endothelial cells with epithelioid or histiocytoid changes, frequently demonstrating cytologic atypia and vacuolization.
Hodgkin lymphoma	Eosinophils, plasma cells, and atypical cells - presence of Reed-Sternberg cells	Presence of Reed-Sternberg cells determines a positive diagnosis. Eosinophils, plasma cells, and sclerosis seen; but lacks the hyperplastic germinal centers and deposits of IgE.
Castleman disease	Prominent vascularity with hyalinized capillaries and eosinophilic granular material	Vascular hyperplasia but lacks eosinophilia and has atrophic rather than hyperplastic germinal centers.
Dermatopathic lymphadenopathy	Pigment-containing histiocytes	Follicular hyperplasia, sclerosis, and deposits of hemosiderin, melanin, and lipids.
Drug reactions	Eosinophils	Comprising eosinophils, but drug history is important.
Parasitic infection	Granuloma and/or eosinophilia	Granuloma and/or eosinophilia. Detection of parasite remnants may lead to the diagnosis.
Kaposi sarcoma	Overlapping spindle cells with nuclear distortion and ill-defined cytoplasmic borders	Fascicles of atypical spindle cells.

8. DIAGNOSTIC WORK UP

Laboratory Investigation

The laboratory investigations are the primary means by which to diagnose Kimura disease and observe its progress. Peripherally, nearly all patients with Kimura disease will show peripheral eosinophilia, where there is a count above the normal threshold of eosinophils circulating in the blood. Additionally, serum IgE is elevated in most cases, thereby aiding the diagnosis. The eosinophil count is proportional to the neck mass size, meaning that larger lesions usually have higher eosinophil counts. Evaluation of renal involvement can be done by testing BUN, serum creatinine levels, and urinary protein since the disease at times leads to conditions such as glomerulonephritis or nephrotic syndrome. Serum eosinophilic cationic protein is another useful marker that closely follows the course of the disease and provides an indication of disease activity. These laboratory findings are fundamental in the entire diagnostic process and guide the management of the disease.

Imaging Studies

The imaging studies reveal information on the nature and severity of the disease. The nature of Kimura disease as imaged on different modalities like CT scans and MRI is quite variable and relies heavily on the degree of vascular proliferation and fibrosis that might be present in the lesions. The lesions are hypointense or isointense relative to the salivary gland tissue on T1-weighted images, while T2-weighted images reveal hyperintensity, which suggests the inflammatory and fibrotic changes. In post-contrast imaging with gadolinium, T1 C+ typically reveals homogeneous enhancement of the lesions. These imaging features help differentiate Kimura disease from other lymphoproliferative disorders [14].

Ultrasound (USG) is a valuable adjunct for the assessment of neck lesions and can guide biopsy procedures. In Kimura disease, there are usually solid and enlarged lymph nodes. These may be preserved in their normal hilar architecture. The lesions are typically hypoechoic and homogeneous. Around 15% of them contain necrotic foci. It shows increased vascularity, mostly in the hilar region, occurring in up to 90% of cases. The salivary glands are hypoechoic when involved and tend to have more heterogeneity than lymph nodes. CT scanning reveals grossly enlarged cervical nodes, with or without parotid and submandibular gland involvement. These nodes demonstrate intense enhancement, in addition to heterogeneous enhancement of the salivary glands, that aids in distinguishing Kimura disease from other diseases with similar presentations.

Histopathology

Histopathological examination remains the gold standard in the confirmation of the diagnosis of Kimura disease. Though there is no single diagnostic feature that is unique to Kimura disease, FNAC is particularly helpful in preoperative diagnosis. Histologically, the disease has characteristic features that can be classified into constant, frequent, and rare findings. The constant features of Kimura disease include preserved nodal architecture, florid germinal center hyperplasia, eosinophilic infiltration, and the formation of post-capillary venules. These venules are an important vascular feature in Kimura disease and are typically present in the affected lymph nodes [12].

The frequent features of the disease include sclerosis, Warthin-Finkeldey polykaryocytes (which are multinucleated giant cells), vascularization of the germinal centers, and proteinaceous deposits and necrosis within the germinal centers. In addition, eosinophilic abscesses and reticular IgE deposition may be seen. These findings help further distinguish Kimura disease from other similar conditions. In rare cases, progressive transformation of the germinal centers can take place, where the lymphoid nodules fill areas extending from the reticular dermis to the fascia and muscle.

Immunohistochemical assessment of the lesions usually demonstrates a polymorphous infiltrate, which shows that the disease is not clonal. Other reports have even identified plasmacytoid dendritic cells in lesions of Kimura disease, further helping to confirm the diagnosis. Such a combination of laboratory findings, imaging studies, and histopathological features will be essential for confirming the diagnosis and facilitating proper treatment for patients with Kimura disease.

9. TREATMENT

Pharmacotherapy

This treatment of Kimura disease tends to be majorly aimed at reducing morbidity, managing symptomatology, and preventing potential complications associated with this condition. Major pharmacotherapy works in this light by targeting and reducing the background immune dysfunction accompanied by inflammation [5][8][9].

Immunosuppressors are the typical drugs used when managing Kimura disease. Drugs that suppress or reduce the system's response would include corticosteroids- triamcinolone or prednisone. These drugs reduce inflammation through the inhibition of polymorphonuclear leukocyte migration and the reversal of capillary permeability. Intralesional corticosteroids are more effective for localized diseases, while oral corticosteroids are applied for more extensive cases. Nonetheless, the disease often recurs after oral corticosteroid therapy is stopped.

Leflunomide, an immunosuppressant that exerts an anti-proliferative effect on eosinophils, is administered in combination with oral corticosteroids to patients who have failed to show a response to corticosteroids alone. Leflunomide might be useful

when renal involvement exists.

Another is cyclosporine, which, in a few reports, had been shown to induce remission when used at a dose of 5 mg/kg/day. Although this was effective, lesions could recur with the discontinuation of therapy.

Second-generation antihistamines are cetirizine, an inhibitor of the activity and differentiation of eosinophils that could help reduce the symptoms caused by Kimura disease. Its use with oral corticosteroids as alternative treatment could easily reduce nodular masses, serving as a potential non-surgical option.

Oral pentoxifylline has also proven effective in certain cases, however, relapses are frequent as soon as therapy is withdrawn. In a very few cases, all-trans retinoic acid, when associated with prednisone, had resulted in some patients going into remission, and one had remained disease-free for up to 12 months after treatment discontinuation.

IVIG has also been tested as a steroid-sparing agent in a few cases. A patient remained disease-free for more than six years after IVIG therapy, demonstrating the possibility of long-term management with this modality.

Surgery

Surgery is used in cases where pharmacological therapies are not sufficient or when localized masses cause marked discomfort or functional impairment. The surgical excision has been considered conservative and the treatment of choice in Kimura disease. It includes removal of lesions and reduction of the size of nodules especially in the most commonly affected parts, that is, head and neck. Yet, recurrence post-surgery occurs frequently, therefore, long-term follow-up may be required in order to determine the return of disease activity. Although surgery can bring some relief, there is no promise of cure; the patient might need other interventions if the disease recurs.

Radiotherapy

Radiotherapy may also be considered as a mode of treatment in cases of recurrent or persistent lesions of Kimura disease, particularly if pharmacotherapy and surgery are not fully successful. Radiotherapy is considered secondary, as the nature of the disease is benign. It may, however, provide symptomatic relief and reduce the size of chronic lesions. The latest developments in three-dimensional printing technology are now being researched for the enhancement of radiotherapy techniques to minimize the damage caused to the surrounding tissue during bolus delivery to the radiosensitive head and neck areas. This approach ensures more accurate treatment while not exposing healthy tissues to unnecessary radiation, which might improve the prognosis of patients needing radiotherapy.

In summary, management of Kimura disease is multi-dimensional, with pharmacotherapy, surgical options, and radiotherapy. The treatment choice depends on the severity of the disease, response to initial therapies, and the patient's general health. A combination of therapies is usually required to effectively manage the disease and prevent recurrence.

10. CONCLUSION

In conclusion, Kimura disease is a rare and difficult eosinophilic inflammatory disorder that typically affects young Asian males, with manifestations as painless masses in the head and neck region. Although benign, the disease is associated with considerable morbidity because of its propensity for recurrence and association with systemic complications such as renal dysfunction and hypercoagulability. Early and accurate diagnosis, along with support from laboratory studies, imaging, and histopathological evaluation, are well-related to the management of the disease. Pharmacotherapy with drugs like immunosuppressants, including corticosteroids, leflunomide, and cyclosporine, will be useful for controlling the disease. However, it often relapses after treatment cessation. Surgical excision should be the mainstay of therapy in localized lesions, though surgical recurrence is common after excision. Radiotherapy and advanced techniques, for example, through 3-D printing for accurately delivering radiation doses, are researched for the case of persistent individuals. In this regard, therefore, a synthesis of pharmacological and surgical therapeutic interventions, that is, staged according to responses in individual cases, is all-important for optimized outcomes and effective prevention of disease recurrence

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