

# Comparative Imaging Analysis of Kimura's Disease Using $^{18}\text{F}$ -FDG PET/CT and [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT

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**Abstract:** Kimura's disease is a rare, chronic inflammatory disorder characterized by subcutaneous nodules, eosinophilia, and elevated serum IgE levels. It commonly affects young Asian males and typically presents in the head and neck region. Diagnosis is confirmed via histopathological examination, while treatment options include corticosteroids, surgery, and radiotherapy. [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT demonstrated superior imaging, with clearer background and higher target-to-background ratio, highlighting lesions with higher SUV values and greater specificity for fibroblast activity. Compared to  $^{18}\text{F}$ -FDG PET/CT, which is limited by nonspecific uptake in inflammatory tissues, [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT offers superior sensitivity and specificity in visualizing fibroblast activation. These advantages not only improve diagnostic accuracy in Kimura's disease but may also have broader implications for other eosinophilic or inflammatory disorders sharing similar clinical features. This technique improves diagnostic accuracy, facilitates treatment planning, and may guide the development of future treatment.

**Keywords:** kimura's disease, FAPI, PET

## Introduction

Kimura's disease is a rare, chronic inflammatory disorder of unknown etiology, which typically affects young Asian males and is classically marked by three key features: painless subcutaneous nodules in the head and neck region, peripheral eosinophilia, and elevated serum IgE levels.<sup>1–3</sup> Currently, fewer than one thousand cases have been reported worldwide, with most publications consisting of individual case reports or small case series. Kimura's disease is primarily manifested as long-standing and recurrent painless soft tissue masses in the head and neck, most commonly in the parotid region.<sup>4</sup> Other frequent sites include the orbit, axilla, and groin, though it can also involve areas like the skull, lungs, and gastrointestinal tract, often accompanied by regional lymphadenopathy.<sup>5</sup>

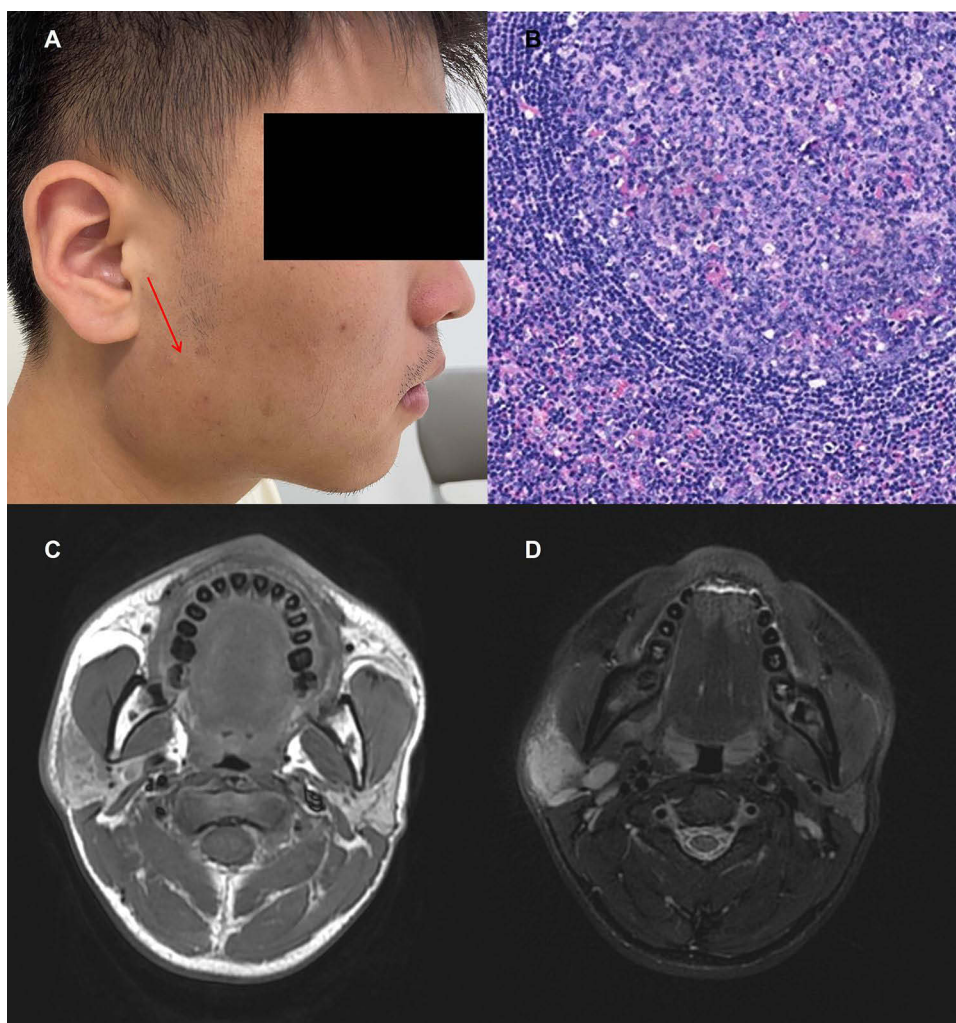
Approximately 20% of patients may experience renal involvement, such as nephrotic syndrome or membranous nephropathy.<sup>6</sup> Additionally, Kimura's disease may be associated with other conditions, such as asthma, urticaria, and allergic rhinitis.

The gold standard for diagnosing Kimura's disease is histopathological examination, which reveals lymphoid follicular hyperplasia with inflammatory cell infiltration, eosinophilic infiltration in the lymphoid cell areas, eosinophilic microabscesses, capillary proliferation, and fibrosis.<sup>7</sup> However, current imaging modalities like  $^{18}\text{F}$ -FDG PET/CT often suffer from nonspecific inflammatory uptake that may obscure lesion delineation. This limitation underscores the need for novel imaging techniques. In this context, [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT emerges as a promising tool due to its ability to target fibroblast activation, offering a cleaner background and improved visualization of fibrotic lesions.

Currently, there is no consensus on the optimal treatment strategy for Kimura's disease. Available treatment options include surgical excision, local radiotherapy, and either local or systemic corticosteroid therapy.<sup>8</sup>

## Case Presentation

A 20-year-old male presented with a mass in the right parotid gland, accompanied by swelling of the right eyelid, first noticed five years earlier. Physical examination found a localized swelling in the right parotid region. A mass measuring approximately 3.5 cm×2.0 cm×2.0 cm was palpable, with well-defined borders, poor mobility, a smooth surface, and a firm texture, without tenderness. He sought treatment at our hospital three years ago, and blood tests revealed a significant eosinophilia (29.7%) and elevated serum IgE levels (>5000 IU/mL). Serum IgG4 levels, erythrocyte sedimentation rate (ESR), highly sensitive C-reactive protein (CRP), and serum immunoglobulin levels are within the normal range, and antinuclear antibodies (ANA) are negative. Magnetic resonance imaging (MRI) of the oropharyngeal region revealed a mass in the right parotid area accompanied by multiple enlarged lymph nodes on both sides of the neck, with a primary consideration of a tumor (Figure 1). Histopathological analysis of a right parotid gland biopsy confirmed Kimura's disease, revealing lymphoid proliferation within fibroadipose tissue, dense infiltration of lymphocytes and eosinophils, and the formation of lymphoid follicles. The tissue also exhibited eosinophilic microabscesses and evident

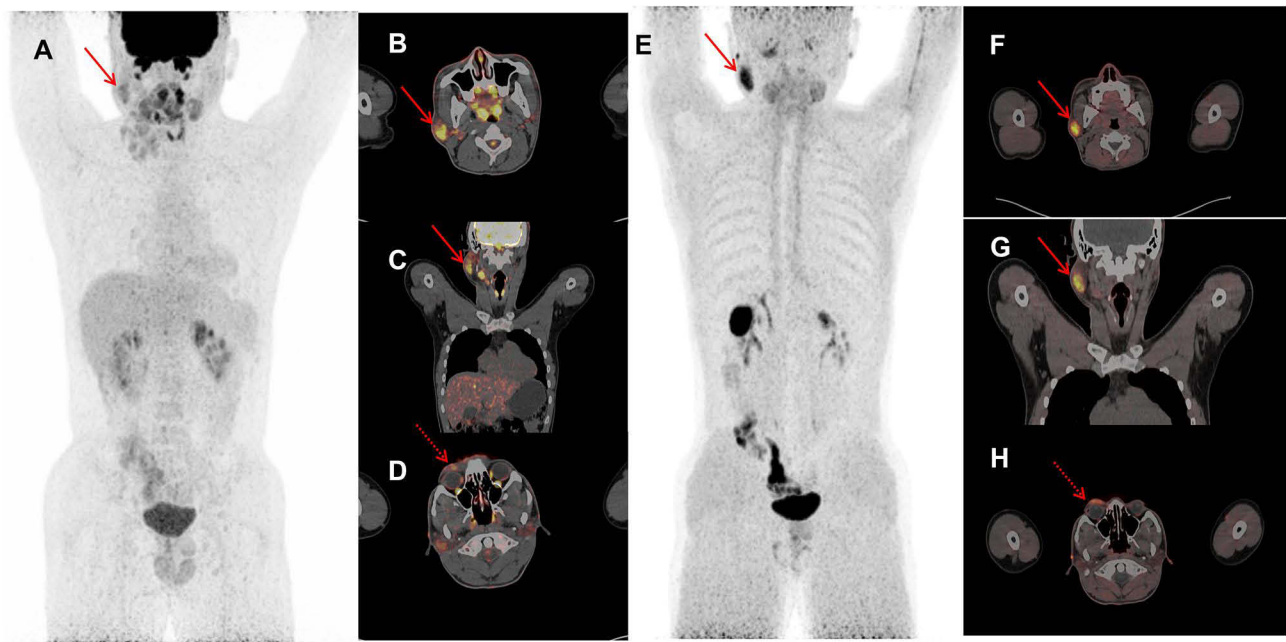


**Figure 1** (A) Enlargement of the right parotid gland (solid arrow); (B) Histopathological image (HE ×20) showing lymphoid proliferation within fibroadipose tissue of the right parotid gland mass, with dense infiltration of lymphocytes and eosinophils, formation of lymphoid follicles, presence of eosinophilic microabscesses, and capillary proliferation. MRI of the oropharynx shows on T1-weighted imaging (C) and T2-weighted imaging (D), an enlarged right parotid gland with patchy areas of high signal intensity on both sequences, measuring approximately 3.0×2.6 cm.



**Figure 2** The scan identified a soft tissue nodule in the right parotid gland, measuring  $1.8 \times 1.1$  cm with increased tracer uptake (solid arrows; **(A)** whole-body MIP image; **(B)** axial fused PET/CT image; **(C)** coronal fused PET/CT image; SUVmax = 3.6). There was also eyelid thickening (1.1 cm) with significant uptake (dotted arrow; **(D)** axial fused PET/CT image; SUVmax = 2.8), consistent with Kimura's disease infiltration. Additionally, multiple lymph nodes were detected in the neck and clavicular region, with the largest measuring 1.6 cm (SUVmax = 4.1), suggesting a chronic inflammatory process.

capillary proliferation, features that further solidified the diagnosis of Kimura's disease. Due to the non-invasive characteristic of positron emission computed tomography (PET), which allows for simultaneous assessment of both anatomical and metabolic abnormalities throughout the body, an initial  $^{18}\text{F}$ -FDG PET/CT scan was performed. The scan identified a soft tissue nodule in the right parotid gland ( $1.8 \times 1.1$  cm) with increased radioactivity uptake (SUVmax=3.6), along with thickening of the eyelid (1.1 cm), both indicative of Kimura's disease infiltration (Figure 2). The patient underwent a year-long treatment with corticosteroids (1 mg/kg) and mycophenolate mofetil (MMF), which resulted in a gradual reduction of the mass size. However, symptoms recurred when the medications were tapered by himself and eventually discontinued. Upon recurrence, a second  $^{18}\text{F}$ -FDG PET/CT scan was conducted, identifying a soft tissue nodule in the right parotid gland measuring  $2.0 \times 2.7$  cm with increased  $^{18}\text{F}$ -FDG uptake (SUVmax=4.5). The eyelid exhibited mild thickening (0.8 cm) with tracer uptake, and enlarged lymph nodes in the right neck and clavicular region (SUVmax = 3.9) were also observed (Figure 3). Meanwhile, the patient participated in a clinical trial evaluating [ $^{18}\text{F}$ ] AIF-NOTA-FAPI-04 PET/CT imaging, approved by the First Affiliated Hospital, College of Medicine, Zhejiang University institutional review board. This scan revealed a nodule in the right parotid gland and thickening of the eyelid, both exhibiting increased [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 uptake, consistent with Kimura's disease. However, the enlarged lymph nodes identified on the  $^{18}\text{F}$ -FDG PET/CT scan were not visible on the [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT. Compared to  $^{18}\text{F}$ -FDG PET/CT, [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT offered superior visualization of fibroblast activation, which is closely associated with the disease process, highlighting its diagnostic advantage. Surgical excision of the mass is planned as the next step in treatment.



**Figure 3**  $^{18}\text{F}$ -FDG PET/CT demonstrated a soft tissue nodule in the right parotid gland ( $2.0 \times 2.7$  cm; solid arrows; (A) whole-body MIP image; (B) axial fused PET/CT image; (C) coronal fused PET/CT image) showed increased  $^{18}\text{F}$ -FDG uptake ( $\text{SUV}_{\text{max}} = 4.5$ ). Mild eyelid thickening (0.8 cm; dotted arrow, (D) demonstrated tracer uptake ( $\text{SUV}_{\text{max}} = 2.8$ ), with enlarged lymph nodes in the right neck and clavicular region ( $\text{SUV}_{\text{max}} = 3.9$ ). Tonsils showed nonspecific inflammatory uptake ( $\text{SUV}_{\text{max}} = 9.4$ ), and scattered lymph nodes in the left paracrotid sheath, submental region, and right axilla exhibited mild uptake, indicative of chronic inflammation. [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT revealed a nodule in the right parotid gland ( $2.0 \times 2.8$  cm; solid arrows; (E) whole-body MIP image; (F) axial fused PET/CT image; (G) coronal fused PET/CT image;  $\text{SUV}_{\text{max}} = 7.8$ ) and eyelid thickening (dotted arrow, H;  $\text{SUV}_{\text{max}} = 7.0$ ), consistent with Kimura's disease. Additional findings included a right preauricular nodule ( $\text{SUV}_{\text{max}} = 6.8$ ) and nodules in the left pinna and posterior neck ( $\text{SUV}_{\text{max}} = 3.9$ ). Enlarged lymph nodes in the right cervical root and clavicular region showed mild uptake ( $\text{SUV}_{\text{max}} = 2.7$ ), considering as chronic inflammation. Physiological FAPI uptake was noted in the gallbladder cavity.

## Discussion

The application of [ $^{18}\text{F}$ ]AIF-NOTA-FAPI-04 PET/CT in diagnosing Kimura's disease may demonstrate clear advantages by providing superior visualization of lesions in the eyelid and parotid gland compared to  $^{18}\text{F}$ -FDG PET/CT. This imaging modality highlights affected tissues and lymphatic structures while minimizing nonspecific inflammatory uptake, as evidenced by its lack of significant uptake in pharyngeal inflammatory lymph nodes, resulting in a cleaner background and enhanced lesion imaging. Fibroblast activation protein (FAP), overexpressed in activated fibroblasts within the tumor microenvironment and at sites of inflammation, is minimally expressed in normal tissues and rapidly cleared from circulation. A careful differential diagnosis is essential in managing suspicious cases of Kimura's disease. Differential considerations include ALHE, lymphoma, and other benign or malignant soft tissue lesions. Indeed, Kimura's disease and angiolymphoid hyperplasia with eosinophilia (ALHE) share significant clinical and histopathological similarities, making differentiation challenging. They used to be considered as different stages of the same disease. However, the key distinction lies in the presence or absence of fibrosis in the stroma.<sup>9</sup> Since FAPI imaging targets fibroblast activation protein (FAP), which is overexpressed in fibrotic tissue, it holds the potential to clearly distinguish between these two conditions by highlighting fibrotic involvement. This specificity could make FAPI PET an invaluable tool for differential diagnosis in such cases. The improved delineation of fibrotic lesions may directly impact treatment decisions by guiding the extent of surgical excision and helping to monitor therapeutic outcomes.

The current clinical use of FAPI-PET extends beyond Kimura's disease. Recent studies have demonstrated its diagnostic utility in various inflammatory and fibrotic disorders, such as idiopathic pulmonary fibrosis and certain rheumatologic conditions, suggesting that its application may be beneficial in a broader clinical context. Its broader application could improve the differentiation between inflammatory and neoplastic lesions, potentially altering clinical management and improving patient outcomes. Among these,  $^{68}\text{Ga}$ -FAPI-04 has shown potential in pre-treatment staging and post-treatment evaluation of various tumors. However, its clinical utility is constrained by its short half-life and the limited preparation volume available for broader application. In contrast,  $^{18}\text{F}$ -labeled FAPI

probes address these limitations with several advantages. Their longer half-life, higher radioactivity yields, and greater radiochemical purity make them more practical for widespread clinical use.<sup>10</sup> Additionally, these probes exhibit favorable pharmacokinetics and efficient uptake in both tumor and normal tissue models, further enhancing their diagnostic value.

[<sup>18</sup>F]AIF-NOTA-FAPI-04 PET/CT holds a higher target-to-background ratio, cleaner imaging and greater sensitivity compared to <sup>18</sup>F-FDG PET/CT. This case marks the first reported application of [<sup>18</sup>F]AIF-NOTA-FAPI-04 PET/CT in Kimura's disease, showcasing its diagnostic potential. In this case, <sup>18</sup>F-FDG PET/CT revealed nonspecific uptake in the tonsils (SUVmax = 9.4), likely due to inflammatory activity, while [<sup>18</sup>F]AIF-NOTA-FAPI-04 PET/CT avoided such uptake, instead clearly delineating lesions in the parotid gland and eyelid. This precision reflects the modality's ability to target fibroblasts and activated stromal cells involved in fibrosis, one of the hallmarks of Kimura's disease.<sup>11</sup> By effectively distinguishing fibrotic from non-specific uptake, [<sup>18</sup>F]AIF-NOTA-FAPI-04 PET/CT facilitates a more precise assessment of disease extent. Its key advantages—high specificity for fibroblast activity, reduced background uptake, and improved differentiation of pathological components—provide critical insights for treatment planning and monitoring therapeutic outcomes. For example, it can guide the extent of surgical excision, minimizing unnecessary tissue damage, while also evaluating residual or progressive lesions following medical therapy.

Treatment of Kimura's disease poses significant challenges, with therapeutic options encompassing pharmacological therapy, surgical intervention, and radiotherapy, as highlighted in current literature. Pharmacological treatment is the most commonly employed strategy. Corticosteroids, such as methylprednisolone, have proven effective in alleviating symptoms and reducing the size of masses in Kimura's disease patients.<sup>12</sup> Biological therapies are gaining attention as potential alternatives for Kimura's disease management. Case reports indicate that treatment with Dupilumab or Omalizumab has led to reduced subcutaneous nodule size, decreased eosinophil counts, and lower total serum IgE levels, highlighting their therapeutic potential.<sup>13,14</sup> Surgical excision is often indicated in cases involving significant mass effects, such as compression symptoms or cosmetic concerns. Surgery provides both diagnostic confirmation and therapeutic benefit.<sup>11</sup> Despite a high local recurrence rate, recurrent masses can typically be resected again without major complications. Radiotherapy offers effective local control for Kimura's disease, particularly in cases where other treatments are not feasible.<sup>15</sup> However, caution is warranted due to potential late side effects, which limit its routine application.

The management of Kimura's disease requires an individualized approach tailored to each patient's specific circumstances. Combining pharmacological therapy with surgical intervention, when appropriate, offers the best potential for optimal outcomes. Continued research is essential to refine treatment strategies and explore emerging therapies. As a new imaging modality, [<sup>18</sup>F]AIF-NOTA-FAPI-04 PET/CT offers a novel perspective on understanding the pathophysiological mechanisms of Kimura's disease. By dynamically visualizing fibroblast activation in the disease process, this technique may contribute to the development of future targeted therapies, further enhancing diagnostic and therapeutic precision. Further research is needed to validate its clinical utility, but this case highlights its potential to improve diagnostic accuracy and treatment planning.

## Conclusion

The case presented here illustrates the diagnostic advantages of [<sup>18</sup>F]AIF-NOTA-FAPI-04 PET/CT in Kimura's disease, particularly its high specificity for fibroblast activity and superior imaging quality compared to <sup>18</sup>F-FDG PET/CT. These benefits may not only refine the diagnostic process and treatment planning for Kimura's disease but also hold promise for other eosinophilic and inflammatory conditions. However, this report is limited by its single-case nature. Future studies involving larger cohorts and multi-center trials are essential to validate these findings and to establish the broader clinical role of FAPI-PET in managing inflammatory and fibrotic diseases.

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## Consent for Publication

The patient has personally signed the informed consent form, which includes consent for both participation in the study and publication of their case details, including any identifiable information. The details published in this article have been approved by the First Affiliated Hospital, College of Medicine, Zhejiang University.

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## Disclosure

The authors declare that they have no competing interest for this work.

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