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Novel Therapeutic Approaches in Kimura Disease: The Role of Omalizumab

Case Report

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Abstract

Kimura disease is a rare, chronic inflammatory disorder characterized by eosinophilic granulomas in soft tissues, primarily involving the head and neck region. We report the case of a 29-year-old male who presented with marked eosinophilia (2.6×10^9/L; reference range: $0.5–1.5 \times 10^9$/L) and significantly elevated IgE levels (3804 IU/mL; reference range: 1.53–114 IU/mL), along with multiple subcutaneous masses over the parotid glands and cervical lymphadenopathy. Following diagnosis, the patient was treated with 16 doses of omalizumab (300 mg each), targeting IgE-mediated pathways. This treatment led to substantial regression of lesions and lymphadenopathy, as confirmed by MRI, and resulted in a marked improvement in the patient's quality of life. The softening of lesions, cessation of mass enlargement, and symptomatic relief demonstrated the potential efficacy of omalizumab in managing Kimura disease.

Keywords: Kimura Disease, Omalizumab

Case Presentation

A 29-year-old male of Asian descent presented to Allergy and Clinical Immunology and Rheumatology clinic with a history of painless, mobile periauricular, submandibular, and parotid masses. His medical history dated back to 2016, characterized by high IgE levels and high eosinophil count and renal involvement. Over time, he developed multiple cervical lymphadenopathy and masses, his initial MRI revealed several masses and nodes, the largest one being left Parotid gland mass measuring 4.6*1.7*8.8, his Initial serum IgE levels were measured at 3804, with eosinophil count at 2.6 (normal range: 0.5-1.5) and abnormal Creatinine (124) (62-115). Rest of his physical exam was unremarkable.

Biopsy of the mass was performed revealing follicular hyperplasia with reactive germinal centers. Additionally, eosinophilic infiltrates were observed within the inner follicular areas, sinusoidal areas, perinodal soft tissues, and subcutaneous tissues. Proliferation of postcapillary venules was noted, leading to a diagnosis of Kimura disease. He was initially given course of Prednisone and other medications like Rituximab and mycophenolate Mofetil were tried but showed no improvement.

Given the diagnosis of Kimura disease and the patient's symptomatic presentation, a treatment plan was initiated. The patient underwent a total of 8 courses of Omalizumab therapy in 2019, followed by an additional 8 courses of 300 mg Omalizumab in 2023.

Following Omalizumab therapy, the patient experienced significant improvement in his condition. The lesions exhibited decreased firmness, size of the lesions was also followed up by MRI, his last imaging result showed regression in most nodes and his largest mass got 20% smaller, showing 3.5*1.5*7.7, and the patient reported a notably improved quality of life, patient mentions much less firmness in masses enabling him to have remarkable better quality of life. Follow-up MRI scans indicated a 20% regression in the size of the lesions, reflecting the therapeutic efficacy of Omalizumab in managing Kimura disease.

Discussion

Kimura's disease is a chronic disease that is characterized by subcutaneous granuloma of soft tissues in the head and neck region, increased eosinophil counts and high serum IgE levels [1-4]. KD was first described by Kim in 1937 [5] as an "eosinophilic hyperplastic lymphogranuloma". A decade later, a systemic description that included the clinical entity of unusual granulation combined with hyperplastic changes of lymphatic tissues in a self-limited allergic or autoimmune process was established by Kimura [6], for whom the disease was named. Although the condition is prevalent in East Asia in an endemic form, relatively few cases have been reported in the Western literature, in African Americans and Caucasians as well as

individuals of Arab ancestry [7,8].

The histologic features of KD include follicular hyperplasia with reactive germinal centers; eosinophilic infiltrates involving the inner follicular areas, sinusoidal areas, perinodal soft tissues, and subcutaneous tissues; and the proliferation of postcapillary venules while preserving the nodal architecture [9–15]. Chen et al. [9] reviewed 21 cases of KD and observed the following histologic features; eosinophils, necrosis, proteinaceous deposits and vascularization of germinal centers, polykaryocytes, eosinophilic folliculolysis, eosinophilic micro-abscesses, stromal sclerosis, perivenular sclerosis, rare giant cells, or small eosinophilic granulomas [5,9,14]. Various degrees of sclerosis are found in KD, and immunohistochemical staining for IgE reveals a reticular pattern of germinal centers [9].

The etiology and pathogenesis of KD are still unknown despite numerous studies. Although increased levels of IgE, tumor necrosis factor α, interleukin (IL)-4, IL-5, IL-13 and mast cells in peripheral blood, as well as in the affected lesions with eosinophilia, have been observed in most patients, no specific antigens have been identified [15–17].

Since there is no definite single specific diagnostic tool for KD, biopsy or excision of the involved mass or lymph node is frequently required for a pathological diagnosis. The histopathological findings of KD are similar, regardless of the anatomical site of involvement, and are characterized by a marked reactive follicular hyperplasia surrounded by a large number of eosinophils, lymphocytes and mast cells, sometimes forming micro-abscesses with vascular proliferation [14,18].

The radiologic findings of masses may aid in diagnosis of KD and differentiate them from other soft tissue tumors. On computed tomography with contrast enhancement, ill-defined enlarged subcutaneous masses with homogeneous, hyper attenuated lymph nodes and swollen salivary glands appear, reflecting the vascular nature of the lesions [19-21]. On magnetic resonance imaging, the lesions show heterogeneity, with both hypointense and mixed or high signal intensity on T1-weighted images and hyperintense signals on T2-weighted images. The degree of enhancement is variable and relates to the degree of fibrosis and vascular hyperplasia [21,22].

Several interventions have been reported in the previous literature; however, there is a lack of evidence on the optimal treatment for KD. Furthermore, owing to the rarity of KD, most clinical studies have been case reports or series reports; therefore, debate continues regarding the optimal treatment of KD.

In this paper we focus on using Omalizumab for treatment of Kimura disease.

Previous studies have reported the efficacy of systemic steroid therapy. Steroids are used to control local lesions, lymphadenopathy, and nephrotic syndrome. In particular, a patient with nephrotic syndrome was responsive to high-dose systemic steroids, with disappearance of proteinuria 7 months after treatment [23]. Another case report from China also revealed that most patients included in the study responded well to treatment with corticosteroids alone [24] However, Nakahara et al [25] reported that local recurrence was frequently observed during steroid dose tapering or drug withdrawal and stated that long-term steroid use may cause digestive ulcers, osteoporosis, and acquired diabetes mellitus [25-27]. Therefore, it is reasonable to use a steroid as a second-line treatment in KD while considering the risk of recurrence and side effects. According to a few recent studies, cyclosporine A is effective for recurrent KD patients [15,25 ,28-32].

cyclosporine A has also been used for combined therapy with steroids to induce re-remission after KD relapse [33]. Cyclosporine A inhibits calcineurin, which signals IL-2 gene transcription in lymphocytes. The reduction of IL-2 inhibits T cell proliferation and suppresses T cell-mediated immune responses [15,34,35] Moreover, Katagiri et al. [15] reported that cyclosporine A also decreased mRNA levels of IL-4, IL-5, and IL-13, resulting in the presence of fewer peripheral eosinophils and lower serum levels of IgE, however, 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 [36].

Omalizumab is an anti-IgE monoclonal antibody that binds to free IgE in the blood, which in turn, inhibits the activation of inflammatory mechanisms. As KD is suspected to be an IgE-mediated allergic disorder, a single pilot study reported evidence of omalizumab for treating KD. According to that study, the size of the masses and eosinophil counts of peripheral blood all decreased after omalizumab administration [37]. Moreover, omalizumab was also reported to be available for patients whose total serum IgE levels were below <1,500 kU/L in another case report. Therefore, omalizumab, as well as anti-IgE therapy, might have the potential to become definite treatment option for KD [38].

Mepolizumab, an anti–IL-5 antibody, has been determined to be effective for the treatment of a patient with Kimura disease by reducing the number of eosinophils, and IgG- and IgG4-producing plasma cells in situ [39]. Benralizumab , another Biologics medication which is Anti-IL5 has also been used in treatment of KD but data showing efficacy is very limited by it [40].

Dupilumab has also been used alone or in combination with corticosteroids for treatment of KD. One study shows markedly decreased in size and serum IgE levels, eosinophil, and basophil counts. [41,42] one study suggests initial use of omalizumab followed by Dupilumab has showed significant improvement in size and Eosinophil count regardless of IgE levels [43].

Radiotherapy is considered an appropriate option for recurrent cases or poor surgical candidates. Hareyama et al. [44] reported that a 90% local control rate was achieved by using 26–30 Gy for irradiation and stated that the radiation field should be confined to the lesion and regional lymph nodes [44,45]. However, other reports showed that surgical excision combined with postoperative radiotherapy achieved a much lower local recurrence rate than surgery or radiotherapy alone [46]. Therefore, postoperative radiotherapy may be effective in controlling the residual lesion, reducing the recurrence rate without notable side effects.

Surgery may allow the greatest diagnostic accuracy and has been the mainstay of treatment. However, as KD tends to be ill-defined on pathological examinations, it is difficult to achieve negative margins during surgical excision, which leads to a relatively high (25%) reported recurrence rate; furthermore, it was revealed that positive margins were a risk factor for disease recurrence [26,47,48].

In addition to conventional therapies, many other treatment options have been suggested. Suplatast tosilate, an anti-allergy drug, attenuated hyper-IgE and eosinophilia, suggesting that other mechanisms than the T cell-mediated immune response are related to the pathogenesis of KD. Cetirizine, which is another antiallergic agent, also showed beneficial effects in KD patients [49,50].

Boulanger et al. [51] reported that all-trans retinoic acids in combination with steroid therapy led to a rapid disappearance of clinical symptoms of KD. It was postulated that all-trans retinoic acids might exert immunomodulatory effects on Th2 cytokines and inhibit IL-4-mediated IgE production, causing the symptoms to disappear. A pediatric patient who had poor adherence to oral medications was treated with intravenous vincristine, resulting in remission of nephrotic syndrome complicated by KD and submandibular swelling [52].

However, these unconventional treatment options should be supported by large-scale clinical evidence, which requires further research.

Conclusion

This case highlights possible management of Kimura disease with Omalizumab therapy. Reduction in lesion size and improvement in symptoms underscore the potential of Omalizumab as a promising treatment option for this rare condition. Further research and larger clinical trials are warranted to establish the long-term efficacy and safety of Omalizumab in the management of Kimura disease.

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