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Case Report

Radiation therapy treats recalcitrant Kimura's disease: a case report

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Abstract: Objective: Treatment of a recalcitrant case of Kimura's disease (KD) is described. Lesions recurred after injection of betamethasone, but responded well to radiation therapy using a Varian 21EX linear accelerator. A literature review and discussion of efficiency and safety issues is included. Method: A 53-year-old female with KD of the right cheek was treated with intramuscular injection of betamethasone (1 mL) and repeated after 21 days, which was followed by recurrence after significant remission. The patient was then given radiation therapy using a Varian 21EX linear accelerator, with a total dosage of 28.16 Gy in 17 fractions (5 d/wk, 1 fraction/d). Result: Radiation therapy led to complete remission of the KD lesions and improvement in the local skin, with no recurrence during 5 months of weekly follow-ups. Conclusion: Radiotherapy with the Varian 21EX was effective for KD involving the cheek area even after failure of betamethasone.

Keywords: Kimura's disease, eosinophilic lymphoid granuloma, angiolymphoid hyperplasia with eosinophilia, histopathology, radiotherapy treatment, therapeutic radiology

Introduction

Kimura's disease (KD), also known as eosinophilic lymphoid granuloma, is a rare chronic inflammatory disorder. The primary presentation is subdermal lesion. The first case was reported in China in 1937, when Kimm Xianzhai described it as eosinophilic hyperplastic lymphogranuloma [1]. It became known as Kimura's disease in 1948 when Kimura and others detailed its histopathological characteristics, and suggested that nephritic syndrome may be associated with KD [2].

The cause of Kimura's disease remains unclear. Generally, it involves painless soft tissue mass, usually with chronic inflammatory changes of the subcutaneous lymph nodes. Pathophysiologically, Kimura's disease manifests as abnormal proliferation of the lymphoid follicles and vascular endothelium [3]. We herein report a female patient with Kimura's disease of the right cheek that was successfully treated with radiotherapy after failure of betamethasone injection. No sign of recurrence of the mass has been observed, as of the last follow-up at 5 months after completion of radiotherapy.

In addition to the clinical study, the relevant literature was reviewed to discuss the appropriate therapeutic approach for such cases. These findings should provide a novel insight for treatment of Kimura's disease involving the cheek.

Case report

A 53-year-old woman visited the Department of Dermatology in December 2014 and presented a 5-year history of swelling of the right facial soft tissue without additional symptoms. The patient complained of toothache in the right mandibular area with no obvious cause, accompanied by mild swelling in the same area. Beginning in May 2014, the swelling aggravated and gradually invaded the right eyelid and forehead, with pink scattered erythema (**Figure 1A**).

The patient was admitted in December 2014. Cardiac, pulmonary, and abdominal examinations revealed no apparent abnormalities. The routine blood test showed an elevated eosinophil ratio (9.3%; normal 2.0-5.0%). The peripheral blood infection test detected increased interleukin-6 (8.8 pg/mL; normal 0-7 pg/mL).

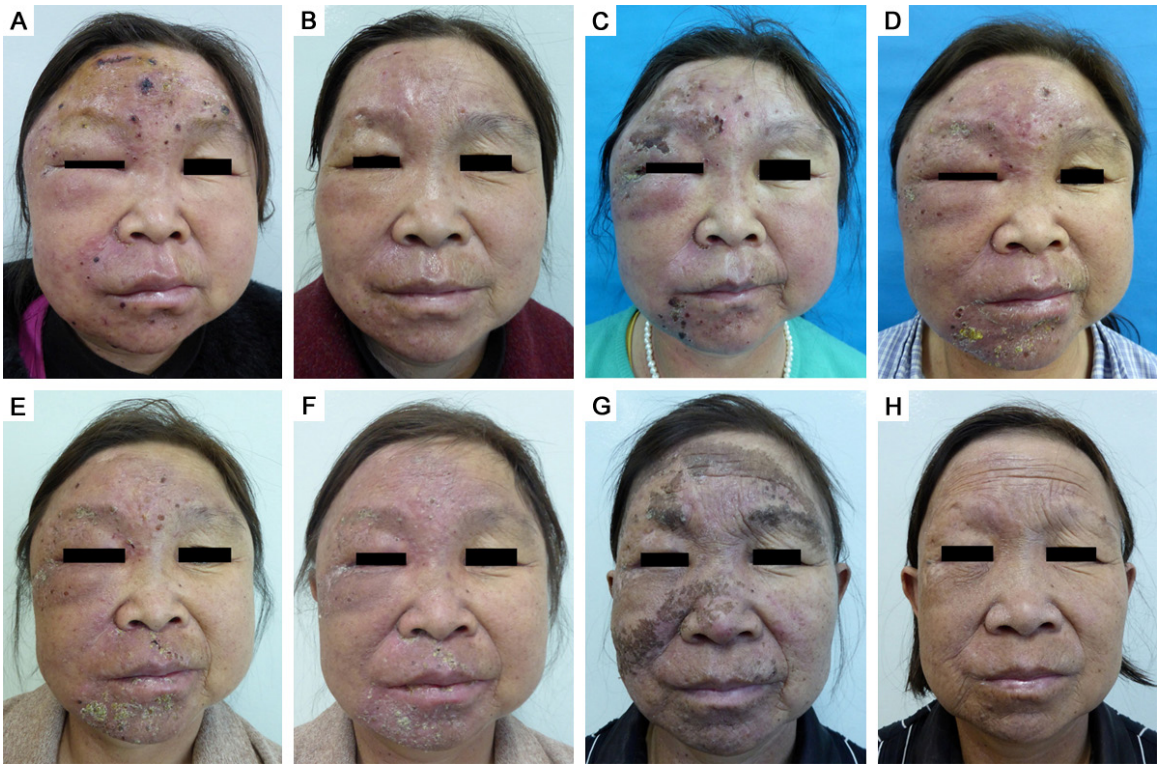

Figure 1. A. Facial skin lesions of a 53-year-old female with Kimura's disease. B. Improvement of skin lesion after 2 intramuscular injections of betamethasone. C. Recurrence of skin lesion 3 weeks after first injection of betamethasone. D. Partial regression after one week of radical radiotherapy. E. Most of skin lesions were relieved after 2 weeks of radical radiotherapy. F. Significant improvement of skin lesion after 17 fractions of radiotherapy. G. Skin lesion recovery and crust formation 1 week after completion of radiotherapy. H. Complete remission of skin lesion without recurrence at 5-month follow-up. The patient provided signed informed consent for use of the image.

A skin biopsy was performed to obtain a tissue sample. The biopsy tissue was fixed in 10% formalin for 12 h, dehydrated, embedded in paraffin, and then blocked and sliced (4 μm). The sections were then dewaxed and stained with hematoxylin and eosin (H&E) [4].

The histopathological examination revealed diffused or focal lymphocytic infiltration involving the dermis, skin appendages, and subcutaneous adipose tissue, and scattered eosinophil infiltration. There was no evidence of malignancy. A pathological diagnosis of Kimura's disease was made after considering the blood test results (elevated eosinophil count in peripheral blood and up-regulated immunoglobulin IgE level) and histopathological examination finding. Specifically, the clinical diagnosis of Kimura's disease mainly depends on the pathological examination of the involved skin, featured by the following histopathological characteristics: (1) lesion affecting dermis and subcutaneous layer with unclear boundary, salivary gland and skeletal muscle are usually affected, with involving lymph nodes observed; (2) widely distributed lymphoid follicle-like structure in affected subcutaneous tissue containing eosinophils, lymphocytes, plasma cells and mast cells in the interfollicular space, forming eosinophilic microabscess; (3) small vessel proliferation in interfollicular space with flat or low cuboidal endothelial cells with large nucleus in basal part observed under microscope, combined with lightly stained cytoplasm; and (4) fibrous hyperplasia, with varying degree of fibrosis that is commonly seen in severe cases (**Figure 2**).

The patient was treated conservatively, including tooth extraction, anti-infective treatment, and removal of the partial masseter muscle, but failed to see any lasting improvement. In January 2016, the patient was treated with a single intramuscular injection of betamethasone (Merck Sharp & Dohme, AG; specification, 1 mL/injection) for the first time. Significant

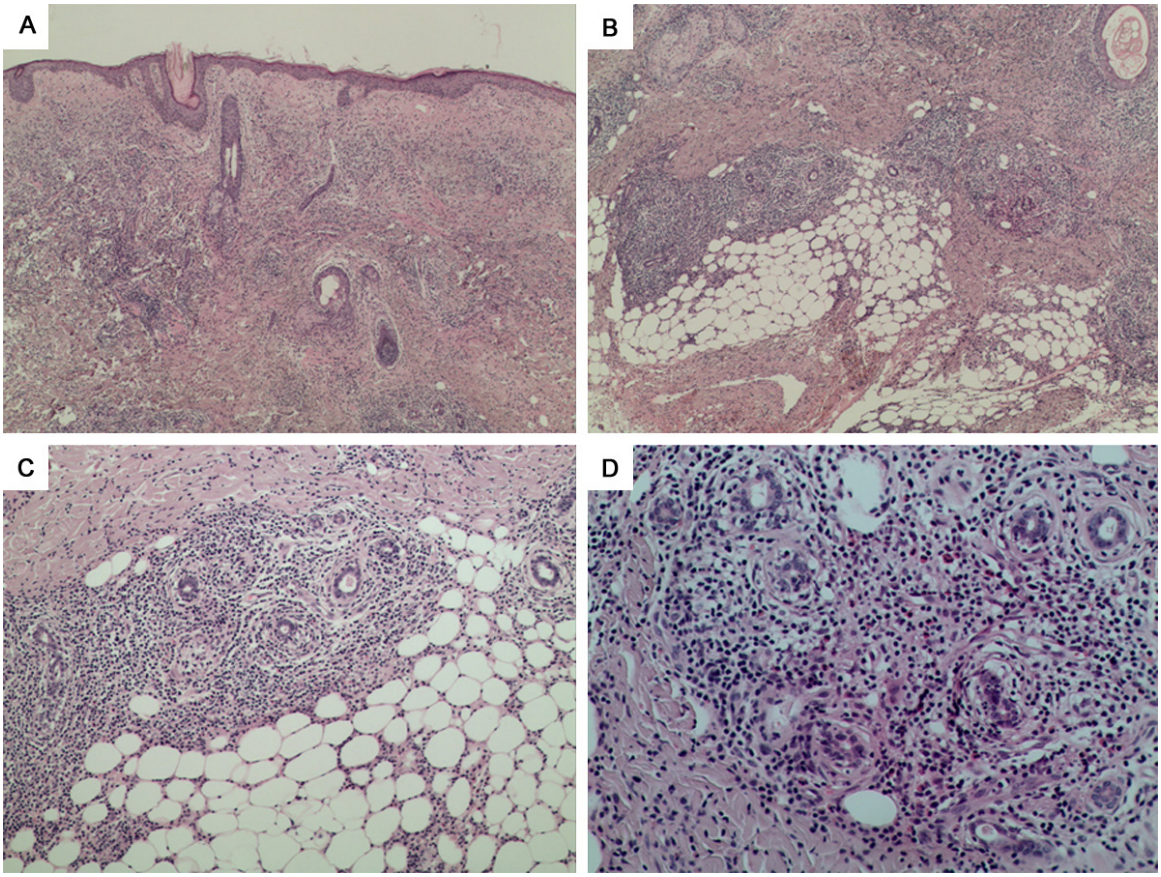

Figure 2. Pathologic examination with skin lesion harvested during biopsy. Photomicrograph stained with H&E. A. No significant abnormal finding in epidermis; extensive infiltration of inflammatory cells found in dermis and subcutaneous tissue (40 ×). B. Subcutaneous fat layer with extensively distributed inflammatory cells (40 ×). C. Extensive lymphoid follicle-like structures containing eosinophils, lymphocytes, plasmocytes and mast cells within the interfollicular space, forming eosinophilic microabscess (100 ×). D. Interfollicular proliferation of small vascular, seen as flat or low-cubic structures with an enlarged, oval-shaped nucleus on the bottom of the medium, surrounded by infiltration of eosinophilic granulocytes and lymphocytes (200 ×).

remission occurred (**Figure 1B**) before subsequent recurrence, and the patient was given a second 1-mL injection of betamethasone, 21 days after the first. However, the symptoms recurred after drug withdrawal (**Figure 1C**).

Magnetic resonance imaging (MRI) examination in March 2016 showed abnormal signals, correlating with swelling of the bilateral masseter and temporal muscles, with exudation from the surrounding muscles indicative of inflammation. Significant subcutaneous soft tissue swelling was observed covering the bilateral frontal, maxillofacial, and nosal dorsum, and exudation from the surrounding fat space, especially on the right side. Inflammatory exudation was suspected. Bilateral maxillary sinusitis and ethmoid sinusitis were reported, and multiple moderately enlarged lymph nodes were noted in the bilateral carotid sheath (**Figure 3**).

Subsequently, radiotherapy was recommended and started in May 2016, using a Varian 21EX linear accelerator (Clinac 21EX, Varian Medical Systems, USA) for intensity-modulated radiation therapy (IMRT). Irradiation with a total dosage of 28.16 Gy was administrated as single doses of 1.656 Gy each in a total of 17 fractions, 5 days per week, 1 fraction per day. Patient reported tongue numbness on the right side and decreased visual acuity of the right eye during the radiotherapy. The visual acuity had recovered to baseline at the 3-month follow-up examination. Swelling and desquamation were observed as well, but reversibly recovered after discontinuation of treatment. Improvement of the skin lesion was observed

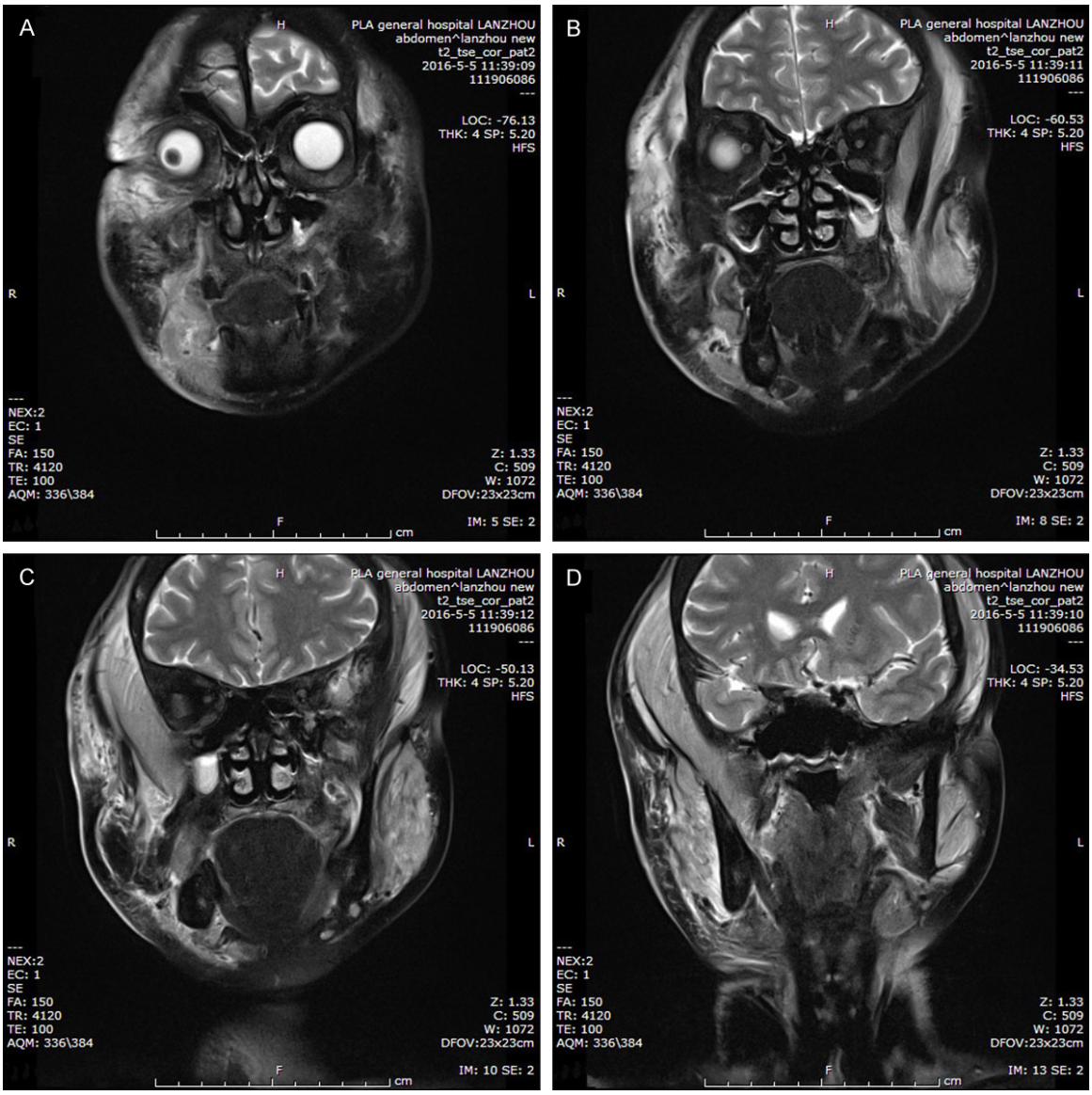

Figure 3. MRI before treatment, with abnormal signals around the musculus temporalis and masseter muscle on the right side, suggesting inflammatory exudation. A. Swelling subcutaneous soft tissue of the maxillofacial region with fat exudates, mainly on the right side. B and C. Bilateral abnormal signals around the swelling masseter and temporal muscles, with the change on the right more significant than the left. D. Moderately enhanced multiple lymphonodus in the bilateral carotid sheath.

during the course of the radiotherapy, as well as recovery of visual acuity (**Figure 1D-F**). Five months after the completion of radiotherapy, there was significant shrinking of the mass on the right-side cheek and almost complete diminishment of swelling on the right-side forehead and eyelid. Facial papules and crusts have faded without relapse. Improvement of right-side vision was also achieved. The patient reported no regrowth of the facial mass or subjective symptoms. A follow-up routine blood test showed that eosinophil counts decreased from 0.51 × 10^9/L (pre-treatment) to 0.27 × 10^9/L (**Figure 1G**, **1H**).

Ethics approval and consent to participate

The experimental protocol was established, according to the ethics guidelines of the Helsinki Declaration, and was approved by the Human Ethics Committee of the Department of Dermatology, Lanzhou General Hospital, China. Written informed consent was obtained from individual participants.

Discussion

Kimura's disease most commonly involves the superficial cervical lymph nodes and soft tissues, primarily around the parotid and submandibular regions, and then the elbow, lacrimal gland and periauricular area. Kimura's disease of the groin, limbs, and trunk have also been reported [5, 6]. Laboratory tests showed elevated peripheral eosinophil counts and serum immunoglobulin E levels. It has been suggested that peripheral eosinophilia was associated with severity of the lesion and should be considered as indicators for severity of KD [7].

Clinical diagnosis of Kimura's disease depends on a pathologic examination of the affected skin tissue. The most common histopathological features are: lesion with no clear boundary involving the dermis or subcutaneous tissue; possible involvement of the salivary gland, skeletal muscle, or lymphonodus is possible; and widely distributed lymph follicle-like structures in the subcutaneous lesion containing eosinophils, lymphocytes, and phagocytes and mast cells in the interfollicular space.

MRI is an established method showing the morphological changes of head lesions. It is reported that radiological characteristics, including diffusion-weighted imaging MRI and magnetic resonance spectroscopic imaging, provided useful evidence by relating pathological features to imaging findings [8, 9]. In our study, MRI depicted abnormalities at sites covering abundant soft tissue of the cheek region. Diffuse intensity of subcutaneous fat was observed around the site of the masses.

Kimura's disease should be differentially diagnosed from angiolymphoid hyperplasia with eosinophilia, lymphoma, benign reactive lymphadenopathy, metastatic lesion, salivary gland tumor, and Mikulicz's syndrome. In the present case, Kimura's disease was diagnosed based on the following indications: typical painless enlargement of the right-sided cheek area; significant elevations of the peripheral blood eosinophil ratio and interleukin levels; pathological section indicating the extensive infiltration of lymphocytes, eosinophils and scattered angiogenesis; and MRI suggesting an intensified signal of the affected region. Especially, examination revealed vigorous proliferation of the vasculature and lymphocytic infiltration enriched with eosinophils, which are considered the gold standard for Kimura's disease diagnosis [10].

Common treatments for Kimura's disease include systemic steroids, radiotherapy, surgical excision, and photodynamic therapy [11, 12]. Immunosuppressive agents (such as cyclosporine A) [13] and hormone treatment can be effective. However, these require long-term follow-up, due to the high risk of recurrence. Thalidomide, cyclosporine, and interferon-α have been reported to achieve amazingly high response rates of up to 100%, while the relapse rates were 100%, 20%, and 50%, respectively [14]. Intravenous immunoglobulin has also been applied to an 8-year-old boy with Kimura's disease, who was successfully treated with 1 dose of intravenous immunoglobulin as a steroid-sparing agent [15].

In the present case, the patient was first treated conservatively, including tooth extraction, anti-infective treatment, and removal of the partial masseter muscle. However, none of these resulted in improved symptoms. After 2nd injection of betamethasone, the patient still suffered from repeated swelling and skin lesion, despite a one-time significant improvement of the skin lesion between two injections (**Figure 1C**). Follow-up radiotherapy was decided, using IMRT. A similar method has not been reported for the treatment of Kimura's disease until recently [16].

The patient received 17 fractions of radical radiotherapy, with a total dosage of 28.16 Gy. Reduced swelling was observed after 5 fractions (1 week of radiotherapy; **Figure 1D**), with continuous improvement during the second week of radiotherapy (**Figure 1E**). No sign of recurrent skin lesion has yet been observed, by weekly follow-up, with the last follow-up 5 months after completion of radiotherapy (**Figure 1H**).

Kimura's disease is usually seen in teenagers or young adults, from age 10 to 40 years [17]. A literature search of PubMed (i.e., the most recent 5 years; http://www.ncbi.nlm.nih.gov/pubmed) in December 2016 using the keywords "Kimura's disease" AND "case report" AND "female" found no reports of Kimura's disease in a middle-aged woman; the oldest patient age was 44 years [18].

In conclusion, herein we described a case of Kimura's disease in a 53-year-old patient successfully treated with IMRT, after failure of betamethasone treatment. Follow-up visits confirmed that the mass has been and continues to be effectively inhibited 5 months after radiotherapy. Although a longer follow-up is essential, radiotherapy appears to be an effective treatment for Kimura's disease of the cheek area.

Disclosure of conflict of interest

None.

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