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CASE REPORT

Kimura's disease in the parotid and submandibular regions: two case reports

Parotis ve submandibüler bölgede Kimura hastalığı: İki olgu sunumu

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Two male patients (aged 13 and 50 years) who presented with a complaint of painless mass in the parotid and submandibular regions, respectively, were found to have eosinophilia and increased blood immunoglobulin E (IgE) levels. Following ultrasonographic examination of the masses, surgical excision was performed. Histopathologic evaluation revealed massive lymphocytic and eosinophilic infiltration. Histopathologic findings and the presence of peripheral eosinophilia and high IgE levels led to a diagnosis of Kimura's disease. Postoperatively, no recurrences were detected within a year follow-up.

Key Words: Angiolymphoid hyperplasia with eosinophilia/pathology/surgery; parotid gland/pathology; submandibular gland; ultrasonography.

Biri parotis bölgesinde diğeri submandibüler bölgede olmak üzere ağrısız kitle şikayetiyle başvuran 13 ve 50 yaşlarındaki iki erkek hastanın kanında eozinofili ve yüksek immünglobulin E (IgE) düzeyi saptandı. Kitle varlığı ultrasonografi ile de belirlendikten sonra lezyonlar cerrahi eksizyonla çıkarıldı. Histopatolojik incelemede örneklerde yoğun lenfositik ve eozinofilik infiltrasyon görüldü. Periferal eozinofili, yüksek IgE düzeyi ve histopatolojik bulgular ışığında olgulara Kimura hastalığı tanısı kondu. Cerrahi tedaviden sonra iki hasta da birer yıl izlendi ve nüks görülmedi.

Anahtar Sözcükler: Ezonofili ve anjiyolenfoid hiperplazi/patoloji/cerrahi; parotis bezi/patoloji; submandibüler bez; ultrasonografi.

Kimura's disease (KD) is a chronic benign disease presenting as a soft tissue mass, peripheral blood and tissue eosinophilia, and elevated serum IgE levels. Although several cases have been reported in Chinese and Japanese literature[1] under the headings of "eosinophilic granuloma of soft tissue," "eosinophilic granuloma," and "eosinophilic lymphofollicular granuloma;" this entity became widely known as KD after Kaneko et al.[2] Although many theories have been suggested, the cause of KD remains unknown. The differential diagnosis and proper management of KD may be challenging.

CASE REPORTS

Case 1– A thirteen-year-old boy was referred to our clinic for a painless mass in the left parotid area, which had a history of five months, during which it enlarged and subsided two times, but never disap-

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peared despite treatment with antibiotics. Physical examination showed a soft, mobile, non-tender mass (3x2 cm) in the left parotid area. No other significant findings were noted. He had eosinophilia (10%) and a high IgE level (175 IU/ml). Ultrasonography showed a well-defined solid mass, 3 cm in diameter, in the superficial parotid lobe. The lesion was surgically removed. Macroscopically, it was a well-defined smooth mass measuring 3x2x2 cm. Histologically, the mass was not encapsulated and there were massive lymphocytic and eosinophilic infiltrates with germinal center formation (Fig. 1a, b). Warthin-Finkeldey-like giant cells were noted near the active germinal centers. There was also prominent postcapillary venule proliferation.

Case 2– A fifty-year-old male patient presented with a non-tender mass of six-month history in the left submandibular region. He had no systemic illness. On physical examination, a mobile, soft, non-tender mass was identified in the left submandibular area, measuring 1.5x1.5 cm. He had mild eosinophilia (7%) and a high IgE level (180 IU/ml).

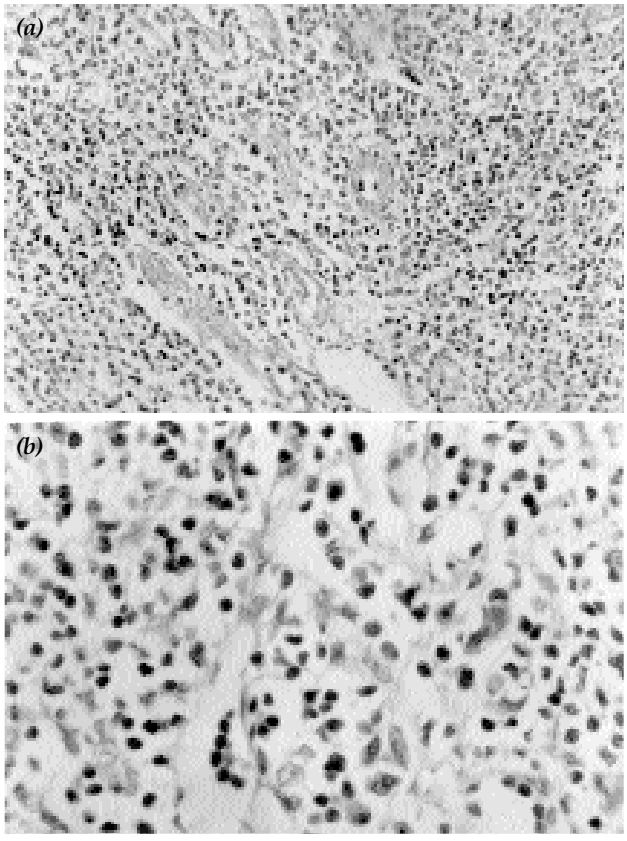

Fig. 1 - *Numerous lymphocytes and eosinophils are seen in the infiltrates* ***(a)*** *(H-E 20 x 0.40).* ***(b)*** *(H-E 100 x 1.30).*

Ultrasonography showed a well-defined solid mass, 13x15 mm in size. Surgical excision was performed. Macroscopically, the surgical specimen was a soft mass, measuring 1.5x1.5x1.5 cm.

On histologic examination, the mass appeared unencapsulated, containing highly lymphocytic infiltrates with germinal centers along the proliferated vascular channels. A large number of eosinophils were interspersed throughout the specimen.

Depending on the histopathologic examination and clinical findings of peripheral eosinophilia and elevated IgE levels, both patients were diagnosed as having KD. The postoperative period was uneventful in both cases. During a year follow-up, neither of the patients had any symptoms or recurrence.

DISCUSSION

Kimura's disease is an uncommon condition seen in young Asians in the second and third decades, with a male predominance.[1] Although many theories have been suggested to explain the etiology and pathogenesis, the cause of KD is still unknown. These include immune system abnormalities, atopic reaction to a continuous antigenic stimulus, parasitic infections, trauma, and neoplasm occurrence. A general consensus exists on the view that KD is a chronic inflammatory condition.[3] Terada et al.[4] proposed that, via triggering interleukin-5 production, *Candida albicans* might be responsible for blood eosinophilia and eosinophilic infiltrates in the tissue mass. However, despite demonstration of *C. albicans*-associated eosinophilic infiltration in laboratory studies,[3] *C. albicans* has not been isolated in any of the KD lesions. Moreover, histologic findings of mast cell hyperplasia, polymorphic lymphoplasmocytic infiltrates and reactive germinal centers, together with peripheral eosinophilia and increased IgE levels,[1] are suggestive of an atopic reaction; yet, no etiologic agent such as bacteria, parasite, or fungus has been demonstrated in KD lesions.[5] On the other hand, in contradiction to the general consensus of inflammation, immunohistochemical studies performed in the skin and lymph nodes of a patient with KD demonstrated abundant CD_4 cells, suggesting the role of a neoplastic or T-cell proliferative disorder.[6] Trauma has also been suggested as a possible etiology, but less than 5% of patients with KD presented with a history of trauma.[7]

The clinical triad of subcutaneous mass in the head and neck region, prominent peripheral

eosinophilia, and increased IgE concentrations is highly suggestive of KD in an Asian male patient.[8] Subcutaneous masses can present as discrete nodules or localized swellings with diffuse margins. Lesions can be single or multiple (bilateral or in multiple regions).[1] The lesions usually appear in the preauricular and submandibular areas in the head and neck region;[3] yet, the parotid and minor salivary glands may also be involved.[9] Most of the time the lesions remain asymptomatic, but may cause local pain or pruritus.[10] Infrequently, axillary, inguinal, popliteal, or epitrochlear nodes may be affected.[8] Involvement of the scalp, eyelids,[11] skeletal muscles, and prostate[12] is rare.

Kimura's disease has a benign and indolent course. If left untreated, subcutaneous masses slowly enlarge and may become disfiguring. They rarely show spontaneous regression; no malignant transformation has been reported. The only known systemic manifestation is renal involvement leading to nephrotic syndrome in up to 60% of the patients.[3]

Granulomatous diseases, metastatic lymphadenopathy, lymphoma, epithelioid hemangioma, and salivary gland tumors should be considered in the differential diagnosis.[3,8] Kimura's disease may be confused both clinically and histologically with angiolymphoid hyperplasia with eosinophilia (ALHE). Although it was previously thought to be the same disease , KD and ALHE are now known to be separate entities.[10] It is difficult to differentiate KD and ALHE histologically, since both diseases cause abundant eosinophilic infiltrates. Vessel changes are more prominent and characteristic in the latter. In ALHE, blood vessels contain hypertrophied endothelial cells with eosinophilic cytoplasm, some of which are characteristically vacuolated. Neither these histiocytoid type blood vessels, nor the vacuolization are seen in KD. Moreover, narrow lumina of the venules seen in KD can easily be differentiated from the uncanalized endothelial cell cords in ALHE. Heavy infiltration in germinal centers causes lysis of follicles, which is typical for KD. Immunohistochemical staining of KD lesions shows IgE in the germinal centers, which is never seen in ALHE.[13]

The management of a patient with KD varies depending on the clinical manifestations. Since KD is a benign disorder, treatment should be cosmetically sparing, preserving function while preventing recurrence and long-term sequela.[10]

Surgical excision of the tumor mass is the common approach. Once the diagnosis is made, the patient should be screened for renal involvement by checking urinary protein levels. If renal dysfunction is excluded and surgical excision is adequate, the patient can then be monitored for future symptoms. Although tumor resection is considered effective in permanent eradication, recurrence up to 25% has been reported following surgical excision alone.[3] Systemic and/or intralesional corticosteroids have been shown to reduce the size of the lesion, but recurrence is likely when these drugs are discontinued.[8] Tumor recurrence after surgical excision can be dealt with by a subsequent resection, but can also be treated by corticosteroids.[3] If there are multiple recurrences or if nephrotic syndrome develops, high dose steroid administration followed by tapering off the dose can be effective. It should also be realized that long-term use of steroids may be limited due to side effects.

In case of unresponsive masses to steroids or tumor relapse after treatment, radiation therapy may be considered.[3] Irradiation may also compensate the need for long-term steroid use. Local irradiation with 25-30 Gy has been shown to be successful in 80% of patients, but due to the risk for secondary malignancies, it is generally not advocated in young patients.[3,8]

Other treatment modalities include cryotherapy, electrodessication, and laser fulguration, with varying outcomes.[10] Kaneko et al[2] reported a patient whose nodular lesions almost disappeared within seven days following cyclosporin 5 mg/kg daily. The cyclosporine dose was gradually reduced to be discontinued after six months. The authors attributed this successful outcome to the effect of cyclosporin on T-helper cells.

To preserve renal function in a patient with severe renal disease and podocyte detachment, aggressive treatment with steroids, cyclophosphamide, and anti-platelet drugs are recommended. However, complete remission may not be possible even with this treatment.[3]

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