Letter to the Editor

A case of refractory Kimura disease with a buccal bulky mass successfully treated with low-dose cyclosporine A: Report and review of the literature

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Dear Editor,

Kimura disease (KD) is a chronic inflammatory disorder that presents as painless lymphadenopathy or subcutaneous masses, most predominantly in the head and neck region. Peripheral eosinophilia and elevated serum IgE levels are the characteristics of the disease. Promoted helper type 2 (Th2) responses are suggested to be the mechanism underlying KD. Although the disease has a benign course, relapse often occurs after the first-line therapy, which includes surgical excision, radiotherapy, and topical steroids. Recently, cyclosporine A (CsA) for the treatment of recurrent KD has been reported. Here, we describe a patient with recurrent KD after surgical and medium-dose steroid therapy who was successfully treated with low-dose (2 mg/kg/d) CsA. We also review the literature related to CsA treatment for KD.

A 25-year-old Japanese man with a childhood history of atopic dermatitis presented with a left buccal soft tumor (Fig. 1A). At the age of 11 years, he had been diagnosed as having KD on the basis of biopsy findings for a left buccal tumor. At the age of 16 years, he had undergone surgical excision of the tumor, followed by oral steroid therapy. Although he had remained in remission for 1 year, after discontinuation of the oral steroid, the tumor had again grown in size, to that of a goose egg. He was referred to the otorhinolaryngology department for surgical excision of the tumor again; this time, however, the tumor could not be excised owing to an ambiguous margin between the tumor and the normal tissue that was due to the progression of fibrosis. He was prescribed 50 mg/d (0.7 mg/kg/d) of oral prednisolone (PSL) after the surgical biopsy, followed by tapering by 10% every 4 days. After the dose of PSL was tapered to 30 mg/d, the tumor reduction ceased, and he was subsequently referred to our internal medicine department. The laboratory findings revealed an increased leukocyte count of 15,200/mm^3 with hypereosinophilia (eosinophils: 10,792/mm^3 [71%]); hemoglobin: 17.4 g/dl; and platelets: 241,000/mm^3. C-reactive protein was negative and the erythrocyte sedimentation rate was normal. The urinalysis and kidney function were also normal. He had extremely elevated serum IgE levels (6519 mg/dl) when taking 30 mg/d of oral PSL. Soluble IL-2 receptor was elevated to 952 U/ml and IgG4 was within normal range. In this case, the serum levels of Th2 cytokines such as IL-4, IL-5, and IL-13 were below detection limits. Magnetic resonance imaging revealed a 75 × 135 × 145-mm tumor in the left buccal region from the

left infraorbital border to the submandibular region (Fig. 1B) with multiple swollen lymph nodes around the left cervical region. Histologic examination of a biopsy sample from the tumor showed a proliferation of lymphoid follicles with germinal center formation. Eosinophils infiltrated the interfollicular spaces with some eosinophilic granulomas (Fig. 1E). Immunohistochemical staining showed c-kit+ mast cells around the follicles and abundant IgE deposition in the lymphoid follicles (Fig. 1E). KD relapse was diagnosed, and the oral PSL dose was subsequently increased from 30 mg/d to 50 mg/d, again followed by slow tapering by 10% every 2 weeks. The eosinophilia, hyper IgE and the left buccal tumor improved soon after oral PSL was increased (Fig. 1F); however, the mass re-grew after PSL was tapered to 30 mg/d. Therefore, PSL was increased from 30 mg/d to 40 mg/d again and 150 mg/d (2 mg/kg/d) of oral CsA was added for the refractory tumor. After the start of oral CsA, the total serum IgE levels continually decreased from 1026 mg/dl to 400 mg/dl (Fig. 1F). The serum trough concentration of CsA was around 80 ng/ml. During the 11 months in which the PSL dose was tapered to 10 mg/d, he experienced no recurrence of the tumor (Fig. 1C, D). For the use of CsA for the treatment to KD, informed consent from the patient and approval from the local ethics committee were obtained (H27-173, University of Tsukuba Hospital).

KD is a chronic inflammatory disorder that presents as painless lymphadenopathy or subcutaneous masses with pathologic characteristics of eosinophilic infiltration of the interfollicular spaces. It most commonly occurs in young or middle-aged men in Asian countries.[1] Normally the effects of the disease are local and the overall prognosis is good; however it is sometimes accompanied by systemic complications such as nephrotic syndrome.[1] Although the etiology of KD is still unknown, it has been suggested that an allergic mechanism may contribute to its pathogenesis.[2] The levels of IgE, Th2 cytokines such as IL-4, IL-5, and IL-13, thymic stromal lymphopoietin (TSLP) are elevated in the peripheral blood or parotid grand tissues of KD patients.[2,3] Recurrence of the disease frequently occurs after surgical, radiation, or steroid therapy and even during steroid therapy after the dose has been reduced, which is known to occur in about 25%–40% of cases.[4] Chen *et al.* reported that younger onset age and a high peripheral blood eosinophil count were significantly associated with disease recurrence, and also that the eosinophil count was related to the size of the mass and the therapeutic response.[4] Recently, immunosuppressant therapy including CsA or anti-IgE antibody (omalizumab) has been reported to be effective for recurrent KD patients.[5–12] CsA inhibits calcineurin, which leads signaling of the transcription of the IL-2
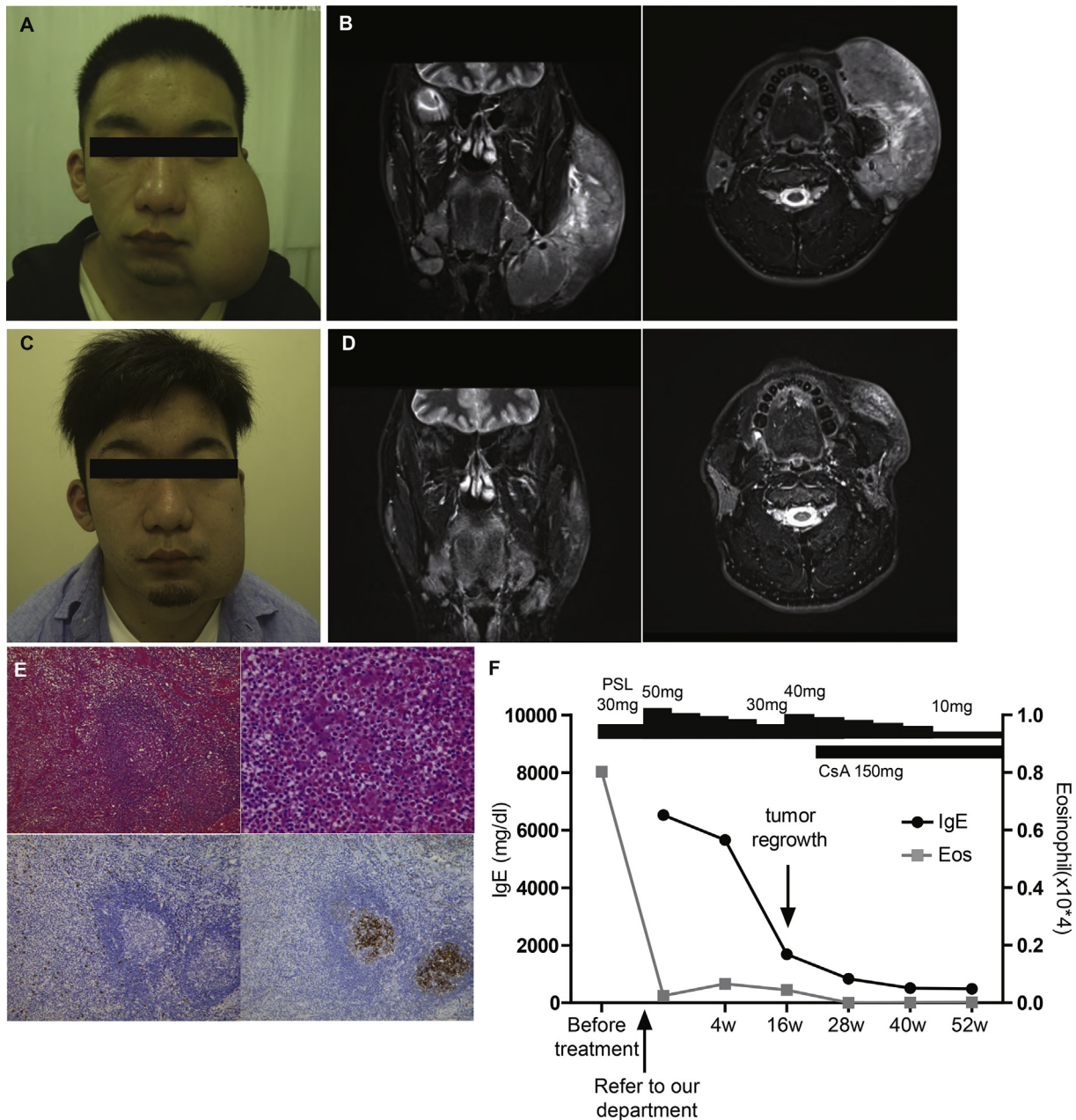
Fig. 1. A. Subcutaneous mass in the left buccal area. **B**. Magnetic resonance imaging (MRI) showing a 75 × 135 × 145 mm mass with partial high signal intensity accompanied with low signal intensity septum in the left buccal area (T2 Short TI inversion Recovery, Axial view (right panel) and Coronal view (left panel)). **C, D**. Subcutaneous mass dramatically reduced after addition of cyclosporine A. **E**. The mass biopsy shows follicular hyperplasia (hematoxylin and eosin, ×100, left upper panel), eosinophilic abscess in the interfollicles (hematoxylin and eosin, ×400, right upper panel). Immunohistochemical staining shows c-kit positive mast cell infiltration around follicles (c-kit staining, ×100, left lower panel), and strong IgE deposition in germinal center of the lymphoid follicles (IgE staining, ×100, right lower panel). **F**. The time course of eosinophil count and total serum IgE levels before and after cyclosporine A treatment. Eos, eosinophil; CsA, cyclosporine A; PSL, prednisolone.

gene in lymphocytes, especially in T cells. Decreased production of IL-2 inhibits T cell proliferation and suppresses T cell-mediated immune responses.[8,9] Indeed, CsA suppresses the levels of IL-4, IL-5, IL-13, and ECP in the lymph nodes and serum of KD patients.[2,8]

Our search of the PubMed database revealed 8 cases of KD treated with CsA (7 reports) published to date (Table 1). In 5 of the 8 cases, CsA was used for combined therapy with steroids to induce re-remission after relapse of the disease. Kaneko *et al.* and Nakahara *et al.* reported that they successfully treated patients with CsA monotherapy for induction or for relapse.[5,6] The initial dose of CsA was usually 3–5 mg/kg/d.[5,8] Notably, Katagiri *et al.*

reported that mRNA levels of Th2 cytokines and eosinophils were fully suppressed when the concentration of CsA in blood was 75 ng/ml in their patient.[2] Monitoring of the serum concentration of CsA is recommended during induction therapy. In our patient, 2 mg/kg/d of low-dose CsA (trough concentration of 80 ng/ml) was effective for the tumor, which was refractory to 30 mg/d of PSL, and we could taper the PSL dose while concomitantly using CsA. For the maintenance of remission, a reduced dose of CsA (to 2 mg/kg/d) could maintain remission without corticosteroids.[10,11] On the other hand, discontinuation of CsA often leads to relapse of the disease.[9–11] Interestingly, Kaneko *et al.* reported a case in

Table 1
Case of KD treated with CsA.

Author (Year)	Age/Sex complications		For induction		For relapse		For maintenance		Recurrence (during maintenance)
			PSL	CsA	PSL	CsA	PSL	CsA	
Kaneko et al, (1999)	29/F	–	–	5 mg/kg	–	–	–	Off	None for 18M
Nakahara et al, (2000)	11/M	Nephrotic synd.	2 mg/kg	–	–	5 mg/kg	–	5 mg/kg	None
Dede et al, (2005)	21/M	Nephrotic synd.	1 mg/kg	5 mg/kg	–	–	10 mg/qod	4 mg/kg	None
Sato et al, (2006)	11/M	–	+	–	40 mg/d	4 mg/kg	5 mg/qod	4 mg/kg	None
Maleki et al, (2010)	25/M	Asthma	1 mg/kg	–	+	400 mg/d	ND	25 mg/d	None for 6M
Soeria et al, (2011)	17/M	Nephrotic synd.	1 mg/kg	–	+	4 mg/kg	Off	2 mg/kg	None for 4Y
	9/M	–	2 mg/kg	–	1 mg/kg	+	Off	+	None
Beccastrini et al, (2013)	40/M	–	25 mg/d	3 mg/kg	25 mg/d	3 mg/kg	Off	2 mg/kg	None for 5Y
Present case (2015)	25/M	–	50 mg/d	–	40 mg/d	2 mg/kg	10 mg/d	2 mg/kg	None for 11M

–, None; +, Yes; Y, Year; M, Month; d, day.
PSL, Prednisolone; CsA, Cyclosporine A; qod, every other day; ND, not described.

which drug-free remission was achieved without any relapse of the disease for 18 months after the initial CsA monotherapy.[5]

We have here described a patient with recurrent, massive, and inoperable KD, who was resistant to medium-dose PSL but successfully treated with low-dose (2 mg/kg/d) CsA. Early low-dose CsA combined with a corticosteroid might be a promising therapeutic option for recurrent and refractory KD.

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