

SHORT COMMUNICATION

Elevated Serum Levels of TARC/CCL17, Eotaxin-3/CCL26 and VEGF in a Patient with Kimura's Disease and Prurigo-like Eruption

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Kimura's disease (KD) is a chronic inflammatory disease characterized by subcutaneous nodular lesions in the head and neck area, eosinophilia, an elevated serum level of IgE and, histologically, the formation of lymphoid follicles with massive eosinophilic infiltration (1). There are several case reports of patients with KD with prurigo-like skin lesions (2, 3). We report here a case of KD that presented with subcutaneous nodules of the eyelids and prurigo-like eruption on the trunk and extremities. Serum concentrations of thymus and activation-regulated chemokine (TARC/CCL17), eotaxin-3/CCL26 and vascular endothelial growth factor (VEGF) were measured before and after treatment.

CASE REPORT

A 61-year-old Japanese woman was referred to our department in January 2012 with a 10-year-history of gradually enlarging subcutaneous nodules on her bilateral eyelids. Multiple brown-reddish papules and nodules had begun to appear on her trunk and extremities 21 years previously. Her family and past histories were not contributory. Physical examination revealed firm subcutaneous nodules on her bilateral eyelids. The overlying skin exhibited dark-reddish and oedematous swelling (Fig. 1A). In addition, multiple dome-shaped red papules and flat-elevated brown-reddish nodules

were found scattered over her whole body (Fig. 1D). Abnormal laboratory results included eosinophilia (4,430/ml: normal 30–500/ml), slightly elevated serum lactate dehydrogenase level, and elevated serum IgE level (4,770.1 IU/ml: normal 0–295 IU/ml). Histopathological examination of subcutaneous nodules in the upper eyelid showed numerous small- to medium-sized mononuclear infiltrates with lymphoid follicles throughout the dermis (Fig. 1B). Numerous eosinophils infiltrated around lymphoid follicles with germinal centres (Fig. 1C). In addition, histopathological examination of prurigo-like eruption in the thigh showed hyperkeratosis and acanthosis of the epidermis, and perivascular infiltration of lymphocytes and eosinophils without lymphoid follicles in the dermis (Fig. 1E, F). Based on the clinico-pathological findings, a diagnosis of KD associated with prurigo-like eruption was established. Topical steroids, oral prednisolone, 30 mg/day, and suplatast tosilate (IPD®) was given. IPD® is an immunomodulator that suppresses eosinophil infiltration, IgE production and allergic inflammation by suppressing production of interleukin (IL)-4 and IL-5 (4). After the treatment started, the subcutaneous nodules in the patient's eyelids and multiple nodules on her whole body improved gradually, along with a decrease in levels of eosinophils and IgE (Fig. S1¹).

CD23 is a low-affinity receptor for IgE (Fcε Receptor II (FcεRII)) and is expressed by follicular dendritic cells (FDCs), B cells, macrophages and eosinophils (5). CD23⁺ FDCs are closely

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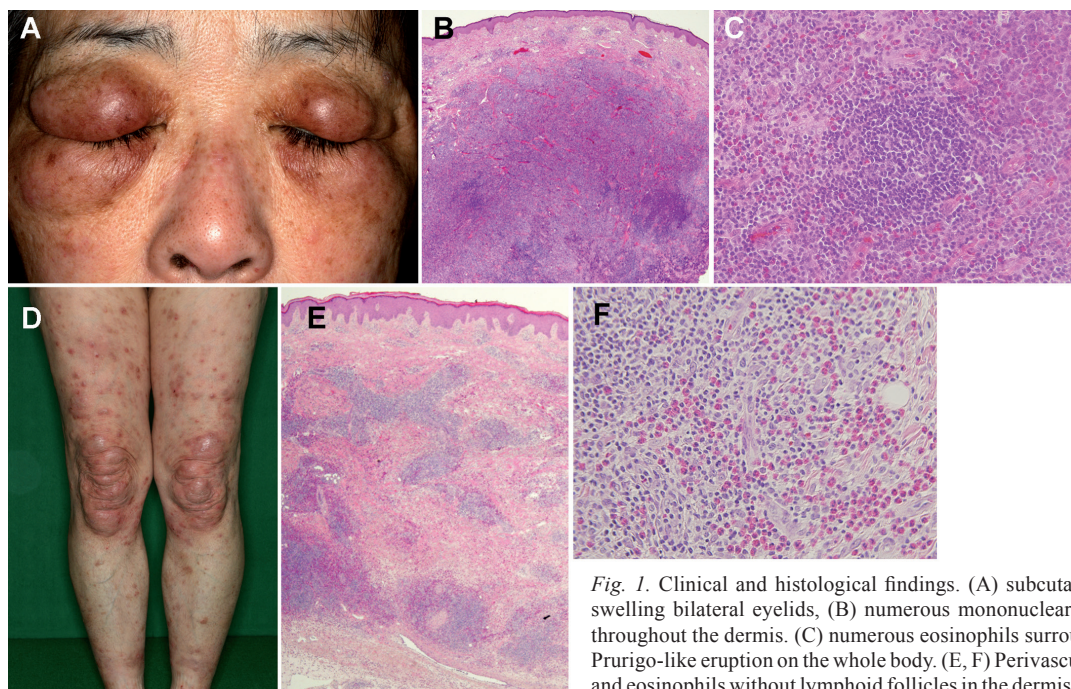


Fig. 1. Clinical and histological findings. (A) subcutaneous nodules in oedematous swelling bilateral eyelids, (B) numerous mononuclear cells with lymphoid follicles throughout the dermis. (C) numerous eosinophils surrounding lymphoid follicles. (D) Prurigo-like eruption on the whole body. (E, F) Perivascular infiltration of lymphocytes and eosinophils without lymphoid follicles in the dermis (H&E, B, E: $\times 40$, C, F: $\times 400$).

related to the IgE immune response and play a key role in the production of IgE. Over-expression of CD23 has been observed in FDCs within the germinal centre of KD (5, 6). In our patient, IgE and CD23 were stained in cells within the germinal centres of lymphoid follicles (rabbit anti-IgE antibody: Abcam, Cambridge, UK, ab75673, mouse anti-CD23 antibody: Nichirei Biosciences, Tokyo, Japan, 1B12) (Fig. S2A and B¹). In prurigo-like lesions, IgE was strongly stained in perivascular infiltrating cells (Fig. S1C¹), but few CD23⁺ cells were observed (Fig. S1D¹). These results suggest that CD23 on FDCs might play a role in the regulation of IgE production and the pathogenesis of KD, and that IgE may be involved in the pathogenesis of prurigo-like eruption.

Th2 cytokines, such as IL-5, IL-4, and IL-13, play a part in the development of KD (7). Chemokine CCL17 and CCL26 are known to promote the growth and migration of eosinophils (8, 9). In addition, IL-5 regulates the release of VEGF from eosinophils (10). However, serum levels of CCL17, CCL26 and VEGF in KD have not been investigated. Therefore, we sequentially measured serum levels of IL-5, CCL17, CCL26 and VEGF by enzyme-linked immunoassay (ELISA) (R&D Systems, USA). We found that serum levels of IL-5 (59.0 pg/ml: normal <3.9), TARC/CCL17 (17,773 pg/ml: normal 71–848), eotaxin-3/CCL26 (28.65 pg/ml: normal <10.3), and VEGF (404.6 pg/ml <220), were elevated before treatment, and decreased to within normal ranges, along with the improvement in subcutaneous nodules and prurigo-like eruption with oral prednisolone and IPD[®] treatment (Fig. 2). In addition, when the relapse occurred, these chemokines and VEGF increased temporarily.

DISCUSSION

Several authors have reported cases of KD preceded by eczematoid lesions, such as pruritic papules, in patients with past histories of atopy (2, 3), and lichen amyloidosis (11). Our patient also had widespread prurigo-like eruption, which preceded the development of KD by several years.

The pathogenesis of KD has not been elucidated. Akatsuka et al. (6) reported that over-expression of CD23 was observed in FDCs within the germinal centre of KD, and suggested that CD23 on FDCs might play a role in the regulation of IgE production and the pathogenesis of KD. In our patient, IgE and CD23 were positive in germinal centre cells. Interestingly, numerous IgE⁺ cells, such as mast cells, eosinophils, and basophils, were observed in the perivascular area in prurigo-like lesions, and this histopathological finding was similar to that in the subcutaneous nodules of the eyelids, except for the formation of lymphoid follicles. These findings indicate that the pathogenesis of subcutaneous lesions of the eyelid may be similar to that of prurigo-like lesions.

In our patient, cytokines and chemokines associated with Th2-type skin diseases, including IL-5, CCL17 and CCL26, returned to the normal ranges, along with the improvement in KD and prurigo-like eruption. IL-5 mRNA is elevated in peripheral blood mononuclear cells and lymph nodes in patients with KD (7). TARC/CCL17, a high-affinity ligand for CCR4, is a chemokine receptor predominantly expressed by Th2 cells (9). There has been no report of changes in serum CCL17 level in patients with KD. Eotaxin-3/CCL26 promotes the growth

and recruitment of eosinophils and skin inflammation (8). Only one case has been reported in which eotaxin-positive cells were seen to be increased in the lesions of KD, using immunofluorescence staining (12). VEGF is a potent multifunctional cytokine, and induces capillary hyperpermeability. IL-5 regulates the release of VEGF from eosinophils (10). However, the relationship between KD and VEGF has not been evaluated.

It has been reported recently that eosinophil cationic protein may be a parameter of disease activity (13). Our study indicates that IL-5, CCL17, CCL26 and VEGF may be useful as serological biomarkers to assess disease activity in KD.

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