

Kimura's Disease Associated with Ulcerative Colitis: Detection of IL-5 mRNA Expression of Peripheral Blood Mononuclear Cells and Colon Lesion

MAKOTO SUGAYA¹, TAKEHISA SUZUKI², AKIHIKO ASAHINA¹, KOICHIRO NAKAMURA¹, MAMITARO OHTSUKI¹ and KUNIHICO TAMAKI¹

¹Department of Dermatology and ²First Department of Internal Medicine, University of Tokyo, Tokyo, Japan

Kimura's disease is considered to be a Th2 type allergic reaction based on the presence of eosinophilia and IgE hyperimmunoglobulinemia. We report a 26-year-old Japanese male with this disorder associated with ulcerative colitis. IL-5 is a selective stimulator for the production of eosinophilia and is considered to play an important role in Kimura's disease. IL-5 mRNA from peripheral blood mononuclear cells and the colon lesion were detected by the reverse-transcriptase polymerase chain reaction method, indicating that IL-5 can also be of importance in ulcerative colitis.

(Accepted March 27, 1998.)

Acta Derm Venereol (Stockh) 1998; 78: 375–377.

Makoto Sugaya, Department of Dermatology, University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan.

Kimura's disease is an uncommon chronic inflammatory disease reported almost exclusively in Asian literature. The disease presents usually as painless subcutaneous swellings in the head and neck region with eosinophilia and IgE hyperimmunoglobulinemia. Although the pathogenesis of the disease is not clear, it is considered to be of allergic origin and may be a manifestation of a systemic immunologic disturbance. We report a patient with Kimura's disease associated with ulcerative colitis (UC), the second case in the literature where these disorders occurred in the same patient (1).

IL-5, which is known as a selective stimulator for the production of eosinophilia, is considered to play an important role in Kimura's disease (2, 3). In addition, some recent experiments indicated that IL-5 secretion was increased in lamina propria T-cells in UC (4). Therefore we have investigated IL-5 mRNA expression by RT-PCR method in peripheral blood mononuclear cells (PBMCs) and the colon lesion of UC from the same patient with Kimura's disease.

CASE REPORT

The patient was a 26-year-old Japanese male. He was admitted to our hospital in 1996 because of a subcutaneous painless tumor in the right periauricular region. The tumor was first noticed 11 years before and enlarged gradually. He had had an operation for torticollis in his infancy. The diagnosis of gout was made three months before the admission for pain around his right hallux and a high blood urinary acid level. He had otherwise been in good health. He had no history of allergic disease such as asthma or atopic dermatitis.

Clinical examination revealed an elastic soft non-tender subcutaneous tumor measuring 5 cm in diameter involving the right periauricular region. Swellings of the upper eyelids and cervical lymph nodes were also detected (Fig. 1). Laboratory tests showed a leukocyte count of 11,000, with 26% eosinophils. The serum IgE level was 3200 mg/dl (normal range: <170), but a *Candida* IgE RAST score was negative.

Blood urinary acid level was 11.0 mg/dl. A tuberculin test was negative. Normal values were obtained for liver and renal function tests, peripheral T-cell, B-cell, CD4, CD8 and serum complements.

He had not been suffering from diarrhoea or bloody stools, but a stool specimen yielded a positive test for occult blood. A stool culture for pathogenic bacteria was negative. Colonoscopy revealed shallow ulcers and edematous mucosa with haemorrhage. A biopsy of the colon lesion revealed a distortion of crypt architecture, a decrease in goblet cells, crypt abscess and lymphocytic infiltration of the lamina propria. There were also many infiltrating eosinophils. There were few, if any, granulomas. These findings were suggestive of UC.

Histopathological findings

A histological examination of a biopsy specimen of the periauricular lesion revealed many lymphoid follicles in the lower dermis and subcutaneous tissue. Around the lymphoid follicles were dense connective tissue and small sized vessels. The centers of the lymphoid follicles were mainly composed of large non-cleaved cells with clear cytoplasm, and the parafollicular areas were composed of dark basophilic lymphocytes. Numerous eosinophils and some monocytes had infiltrated the



Fig. 1. Elastic soft non-tender subcutaneous tumor of the right periauricular region. Swellings of upper eyelids and cervical lymph nodes were also detected.

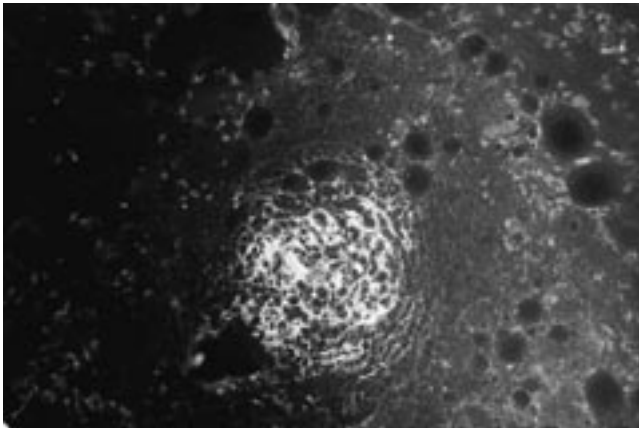


Fig. 2. IgE was stained in a reticular pattern within germinal centers of the lymphoid follicles ($\times 100$).

centers of the follicles as well as around them. IgE was stained by FITC-labelled anti-human IgE (goat IgG) in a reticular pattern within the germinal centers of the lymphoid follicles (Fig. 2).

Immunohistochemical staining by the ABC (avidin-biotin complex) method also revealed that the germinal centers were mainly positive for CD19 and the parafollicular areas were positive for CD4 (Table I). These findings were suggestive of Kimura's disease.

The diagnosis of Kimura's disease was made according to the clinical examination, histological findings, eosinophilia and high serum IgE level, as described above.

IL-5 mRNA detection

Cytoplasmic mRNA was isolated using the QuickPrep Micro mRNA Purification Kit (Pharmacia Biotech, USA) from a biopsy specimen of the colon lesion and peripheral blood mononuclear cells (PBMCs) from the patient, a healthy volunteer and a patient suffering from allergic rhinitis. cDNA was synthesized from mRNA using a First-Strand cDNA Synthesis Kit (Pharmacia Biotech, USA). The oligonucleotide primers that specifically amplify IL-5 and β -actin transcripts were synthesized by Sawady Technology Co., Japan (ref. 5 for IL-5 and ref. 6 for β -actin). One-microliter aliquots from the cDNA reaction products were PCR amplified in 50 μ l reaction as follows: 5 μ l of $10\times$ PCR buffer, 0.2 mM each of dNTPs, 2 μ l of each primer, 1.5 mM $MgCl_2$ and 0.5 μ l of recombinant *Taq* DNA polymerase enzyme (TOYOBO Co., Japan). The reaction consisted of 35 cycles of denaturation at 94°C for 1 min, annealing at 48°C (IL-5) or 57°C (β -actin) for 1 min and extension at 72°C for 2 min. PCR products were analysed by electrophoresis on 1.5% agarose gels and visualized by ethidium bromide staining. The RNA preparations from both PBMCs and the colon lesion from the patient contained IL-5 mRNA. PBMCs from the patient with allergic rhinitis also contained IL-5 mRNA, but PBMCs from the normal volunteer did not (Fig. 3 (1)). All the RNA preparations were positive for the expression of β -actin transcript (Fig. 3 (2)).

Table I. Immunohistochemical staining

	Germinal centers	Parafollicular areas
CD3	+	++
CD4	+	++
CD8	-	-
CD19	++	-
CD45RO	-	-
HLA-DR	++	++

++ positive; + partially positive; - negative.

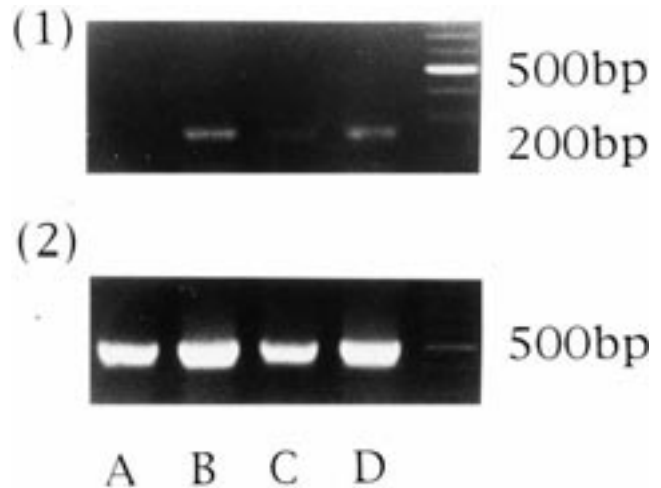


Fig. 3. (1) IL-5 mRNA was detected in lanes B, C and D. (2) β -actin mRNA was detected in all lanes. Lane A: peripheral blood mononuclear cells from a normal volunteer. Lane B: the colon lesion from the patient. Lane C: peripheral blood mononuclear cells from the patient. Lane D: peripheral blood mononuclear cells from a patient suffering from allergic rhinitis.

The periauricular subcutaneous tumor was irradiated with electron beams totalling 30 gray, and indomethacin 75 mg/day was administered. The UC was not so severe as to require him to receive any medication or diet therapy. The tumor disappeared about three months after the radiation, and blood eosinophils and serum IgE level decreased in about two months, but were still higher than normal levels.

DISCUSSION

The clinical course of Kimura's disease is benign, and there have been no reported fatalities. However, complications with immune disorders such as nephrotic syndrome, asthma, atopic dermatitis, urticaria and lichen amyloidosis have been reported (7-10). The previous reported patient with ulcerative colitis suffered from watery diarrhoea and bloody stools (1). It is possible that subclinical colon lesion is present in Kimura's disease, because our patient had not been suffering from diarrhoea or bloody stools. If colonoscopy is performed in every case of this disorder, colon lesion may be detected at a certain rate, suggesting that skin and intestine have important relationships in the immunological system.

Shimamoto *et al.* (1) suspected that the development of the two disorders may involve a systemic immune disorder, although the pathogenesis is as yet unknown. We tried to associate these disorders with each other in terms of IL-5 expression. IL-5 is considered to play an important role in Kimura's disease, as it is a selective stimulator for the production of eosinophilia (2). IL-5 mRNA was already detected by RT-PCR method in PBMCs from patients with Kimura's disease (2). We also tried to detect IL-5 mRNA from the skin lesion of the patient, but we were unable to detect the mRNA. In the skin lesion, the number of infiltrating mononuclear cells might not be large enough. Inoue *et al.* (3) showed IL-5 mRNA expression of lymph node tissue resected from a patient with Kimura's disease by Northern blot analysis.

In inflammatory bowel disease, UC and Crohn's disease,

mononuclear cells in inflamed mucosa synthesize and secrete large numbers of cytokines. In UC, it is as yet unclear whether Th1 type or Th2 type reaction is dominant. Some recent experiments indicated that IL-5 secretion was increased in lamina propria T-cells of patients with UC (4). Our case is the first report of IL-5 mRNA expression in UC associated with Kimura's disease. Although the pathogenesis is not currently evident, these findings and our results reported here suggest that IL-5 may also be important in the development of UC.

REFERENCES

1. Shimamoto C, Takao Y, Hirata I, Ohshiba S. Kimura's disease (angiolymploid hyperplasia with eosinophilia) associated with ulcerative colitis. *Gastroenterol Jpn* 1993; 28: 298–303.
2. Enokihara H, Koike T, Arimura H, Aoyagi M, Watanabe K, Nakamura Y, et al. IL-5 mRNA expression in blood lymphocytes from patients with Kimura's disease and parasite infection. *Am J Hematol* 1994; 47: 69–73.
3. Inoue C, Ichikawa A, Hotta T, Saito H. Constitutive gene expression of interleukin-5 in Kimura's disease. *Brit J Haematol* 1990; 76: 554–555.
4. Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, et al. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. *J Immunol* 1996; 157: 1261–1270.
5. Okayama Y, Petit-Frere C, Kassel O, Semper A, Quint D, Tunon-del-Lara MJ, et al. IgE-dependent expression of mRNA for IL-4 and IL-5 in human lung mast cells. *J Immunol* 1995; 155: 1796–1808.
6. Yamamura M, Uyemura K, Deans RJ, Weinberg K, Rea T, Bloom BR, et al. Defining protective responses to pathogens: cytokine profiles in leprosy lesions. *Science* 1991; 254: 277–279.
7. Qunibi WY, Al-Sibai MB, Akhtar M. Mesangio-proliferative glomerulonephritis associated with Kimura's disease. *Clin Nephrol* 1988; 30: 111–114.
8. Moesner J, Pallesen R, Sorensen B. Angiolymphomatoid hyperplasia with eosinophilia (Kimura's disease): a case with dermal lesions in the knee region and a popliteal arteriovenous fistula. *Arch Dermatol* 1981; 117: 650–653.
9. Nisiyama C, Ochiai T. Kimura's disease associated with atopic dermatitis. *Rinsho Derma* 1977; 19: 1079–1087.
10. Danno K, Horio T, Miyachi Y, Hayakawa M, Takatsuki K. Coexistence of Kimura's disease and lichen amyloidosis in three patients. *Arch Dermatol* 1982; 118: 976–980.