Dermatopathic Lymphadenopathy With Increased IgG4-Positive Plasma Cells

Shoko Nakayama, MD, PhD, Taiji Yokote, MD, PhD, Toshikazu Akioka, MD, Takuji Miyoshi, MD, PhD, Yuji Hirata, MD, PhD, Nobuya Hiraoka, MD, PhD, Kazuki Iwaki, MD, Ayami Takayama, MD, Uta Nishiwaki, MD, Yuki Masuda, MD, Toshiaki Hanafusa, MD, PhD, Yasuichiro Nishimura, PhD, and Motomu Tsuji, MD, PhD

Abstract: Both dermatopathic lymphadenopathy (DL) and immunoglobulin G4-related disease (IgG4-RD) are frequently complicated with allergic diseases. However, the relationship between DL and IgG4-RD is not well known. To clarify this relationship on the basis of clinical and pathological findings, including IgG4-positive (IgG4+) plasma cell infiltration in lymph nodes (LNs) of DL patients, we analyzed LNs of 11 DL patients using immunostaining of IgG, IgG4, forkhead box P3 (FOXP3), transforming growth factor (TGF)-β, interferon (IFN)-γ, and matrix metalloproteinase (MMP)-1, MMP-8, and MMP-13. Toluidine blue staining was also performed to identify mast cells. Of 3 patients of DL patients with a high ratio of IgG4+/IgG+ cells (>40%) and elevated serum IgG4 levels, 2 developed IgG4-RD, whereas the other patient did not. Of 8 patients with a low ratio of IgG4+/IgG+ cells (<40%) or no infiltration of IgG4+ cells, 5 who could be followed did not develop IgG4-RD. The numbers of mast cells were similar to those of TGF-β-positive cells, and serial sections showed that mast cells possibly produce TGF-β. LNs of DL patients with a high ratio of IgG4+/IgG+ cells had significantly more mast cells and TGF-β-positive cells than those of patients with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells. However, no fibrosis was observed in LNs of both groups. IFN-γ was positive in interdigitating dendritic cells, Langerhans cells, and macrophages. MMP-1, MMP-8, or MMP-13 was expressed in macrophages. The lack of fibrosis in LNs may have been due to the production of IFN-γ, MMP-1, MMP-8, or MMP-13. Thus, DL with increased IgG4+ cells seems to be a phenotype of IgG4-RD in LNs.

(Observational Study)

INTRODUCTION

Dermatopathic lymphadenitis (DL) is a rare type of benign reactive lymphatic hyperplasia associated with skin lesions of the exfoliative or eczematoid type, including pemphigus, psoriasis, eczema, atopic dermatitis, and allergic skin diseases. DL is often observed in inguinal and axially lymph nodes (LNs) but may be found in LNs anywhere in the body. These LNs are moderately enlarged, firm, movable, and rather painless. A diagnosis of DL ultimately depends on histological findings; these include interfollicular and paracortical hyperplasia of LNs by infiltration of interdigitating dendritic cells (IDCs), Langerhans cells, macrophages, and T cells. Melanin granule-laden macrophages are often scattered in these LNs. These findings are associated with LNs that drain the sites of skin irritation, inflammation, or infection. The time interval between the appearance of skin manifestations and LNs of DL varies; however, DL has been occasionally reported in patients without active dermatopathies.

Kamisawa et al proposed a new disease entity in 2006 that was characterized by elevated serum IgG4 levels, tumefactive inflammation of organs, infiltration of IgG4-positive (IgG4+) plasma cells, and fibrosis in the affected tissue and with a favorable response to steroid therapy. This disease has become known as IgG4-related disease (IgG4-RD). Although IgG4-RD mainly affects extranodal sites, particularly glandular organs/tissues such as the pancreas, salivary glands, lacrimal glands, and soft tissues, lymphadenopathy is one of the common findings. In fact, up to 80% of patients with IgG4-RD are found to have localized or systemic lymphadenopathy on imaging. Moreover, lymphadenopathy occasionally appears as the first manifestation of IgG4-RD.

Thus, it is thought that there are 4 clinical scenarios for which lymphadenopathy occurs in IgG4-RD (IgG4-related lymphadenopathy): regional LNs are serendipitously found in excision specimens of organs affected by IgG4-RD; lymphadenopathy is found as a part of the presentation of IgG4-RD by clinical examination or imaging studies; lymphadenopathy appears within weeks to years after the onset of preceding IgG4-RD; and lymphadenopathy is found as the initial manifestation without preceding extranodal IgG4-RD, and these patients develop extranodal involvement after varying time...
intervals. Therefore, lymphadenopathy of this type is considered as a primary lesion of IgG4-RD.6,9

Histologically, IgG4-related lymphadenopathy can exhibit a broad morphological spectrum and is currently classified into 5 types: type I, multicentric Castleman disease-like; type II, follicular hyperplasia; type III, interfollicular expansion; type IV, progressive transformation of germinal centers; and type V, inflammatory pseudotumor-like. However, typing can be complicated by the possible overlap of patterns in individual cases.9,10

IgG4-RD is also known to be frequently complicated with allergic diseases and sometimes shows elevated serum IgE levels. In contrast, allergic diseases such as atop dermatitis, asthma, some parasitic diseases, and bullous skin diseases sometimes manifest with elevated serum IgG levels.11–13

\[ \text{Statistical Analysis} \]

Results for continuous variables are given as means ± standard deviations (SDs) or medians. Patients’ ages, the numbers of mast cells/mm², and the numbers of TGF-β-positive cells/mm² in LNs were compared between the 2 groups of patients using \( \chi^2 \) tests. \( P \) values <0.05 were considered significant. Statistical analyses were performed using JMP Pro 11 (SAS Institute, Inc, Cary, NC).

\[ \text{RESULTS} \]

\[ \text{Patients’ Clinical Characteristics} \]

Table 1 summarizes the patients’ clinical characteristics, laboratory results, pathological findings, and clinical outcomes. The average age of the 11 DL patients was 61 years (range: 13–72 years). There was no significant difference in age between the 2 groups of patients: 64 ± 13 years for DL patients with a high ratio of IgG4+/IgG+ cells and 69 ± 7 years for DL patients with a low ratio of IgG4+/IgG+ cells or no IgG4+ cell infiltration (\( P = 0.7709 \)). Of these 11 patients, 8 had a skin disease such as psoriasis vulgaris, atop dermatitis, erythema multiforme, or allergic dermatitis. Three had no skin disease. Serum IgG4 levels for the patients with a high ratio of IgG4+/IgG+ cells was elevated to 176, 173, and 156 mg/dL for patients 1, 2, and 3, respectively (normal: 4.8–105 mg/dL). IgG4 levels were not measured for the other patients.

\[ \text{Patients’ Clinical Courses} \]

For case 1, a patient without any conspicuous skin disease, swelling of the right inguinal LN was found, and the biopsied specimen was diagnosed as DL. At 1 month after this biopsy, retroperitoneal fibrosis was identified by a computed tomography (CT) scan. The tissue was biopsied and histologically showed fibrosis, a large number of IgG4+ cells, and a high ratio (51.4%) of IgG4+/IgG+ cells (Figure 1A and B). A diagnosis of IgG4-related retroperitoneal fibrosis was made. He was treated with steroid therapy for 3 years and has been well without any clinical symptoms.

For case 2, a patient with psoriasis vulgaris, swelling of the right inguinal LN was found and was histologically diagnosed as having DL. After 5 months, swelling of the para-aortic LNs newly appeared on a follow-up CT scan. The biopsied specimen from the paraaortic LN obtained by laparoscopy showed fibrosis and a high ratio (48.2%) of IgG4+/IgG+ cells (Figure 2A and B). No gene rearrangements were found for T-cell receptors or the immunoglobulin heavy chain J region. A diagnosis of IgG4-related lymphadenopathy, type V, was made.9,10 He was followed for 8 months, and his paraaortic LNs decreased in size with steroid therapy.

For case 3, a patient who had been treated with steroid therapy for severe atop dermatitis and asthma for 5 years, swelling of bilateral axillary and inguinal LNs was found. The right inguinal LN was biopsied and diagnosed as DL. A whole-body positron emission tomography (PET)-CT scan showed no extranodal involvement. He was treated with steroid therapy for atop dermatitis and asthma for another 10 months, and he has been well.

For case 4, a patient who had been treated with steroid and methotrexate (MTX) therapy for rheumatoid arthritis for 18 years, swelling of bilateral axillary and left inguinal LNs was found. The left inguinal LN was biopsied and diagnosed as DL.
| Case | Sex | Age | Biopsied Lymph Node | Skin Disease | Systemic Disease | IgG4/ IgG (%) | Serum IgG4 Level, mg/dL | No. of Mast Cells/mm² | No. of TGF-β-positive Cells/mm² | Other Laboratory Findings | Clinical outcome After Diagnosis of DL | Follow-up Period |
|------|-----|-----|---------------------|--------------|------------------|---------------|-------------------------|----------------------|------------------------------|-----------------------------|----------------------------------------|-----------------|
| 1    | M   | 66  | Inguinal lymph node | None         | None             | 62.8          | 176 (4.8–105)          | 4.4                  | 6.1                          | IgG 1807 (870–1700) mg/dL, IgA 419 (110–410) mg/dL, IgM 30 (35–220) mg/dL, IgE 484 (<340) mg/dL, IL-2 receptor 1360 (220–530) U/mL | One month later, retroperitoneal fibrosis was found. He has been treated with steroid therapy and has been well. | 3 years          |
| 2    | M   | 66  | Inguinal lymph node | Psoriasis vulgaris | None             | 65.3          | 173                    | 15.6                 | 16.7                         | IgG 2071 mg/dL, IgA 346 mg/dL, IgM 178 mg/dL, IL-2 receptor 1520 U/mL | Five months later, IgG4-related lymphadenopathy of paraaortic lymph node was found. He has been treated with steroid therapy. The lymph node decreased in size. | 8 months         |
| 3    | M   | 60  | Inguinal lymph node | Atopic dermatitis treated with steroid therapy for 5 years | Asthma          | 52.7          | 156                    | 11.0                 | 13.3                         | IgG 1817 mg/dL, IgA 287 mg/dL, IgM 54 mg/dL, IgE 49709 mg/dL | He has been treated with steroid therapy for severe atopic dermatitis and asthma, and he has been well. | 10 months        |
| 4    | M   | 71  | Inguinal lymph node | None         | Rheumatoid arthritis treated with steroid and MTX therapy for 18 years | 1.5           | ND                     | 4.3                  | 5.4                          | MMP-3 377 mg/mL (36.9–121) mg/dL, IgG 1128 mg/dL, IgA 174 mg/dL, IgM 335 mg/dL | He has been treated with steroid therapy for RA and has been well. | 3 years          |

TABLE 1. Clinical Findings For 11 DL patients
| Case | Sex | Age | Biopsied Lymph Node | Skin Disease | Systemic Disease | IgG4/IgG (%) | Serum IgG4 Level, mg/dL | No. of Mast Cells/mm² | No. of TGF-β-positive Cells/mm² | Other Laboratory Findings | Clinical outcome After Diagnosis of DL | Follow-up Period |
|------|-----|-----|---------------------|--------------|------------------|--------------|------------------------|----------------------|---------------------------------|-------------------------------|------------------------------------------|------------------|
| 5    | M   | 27  | Inguinal lymph node | Atopic dermatitis | None.           | 0            | ND                     | 1.0                  | 0.7                             | IgE 12432 mg/dL IL-2 receptor 1890 U/mL | He had been well for 5 years without medication; however, after that, the follow-up was discontinued. | 5 years          |
| 6    | F   | 13  | Inguinal lymph node | Allergic dermatitis | None            | 0            | ND                     | 0.5                  | 0.9                             | IL-2 receptor 4070 U/mL | Well without medication. | 9 years          |
| 7    | M   | 71  | Inguinal lymph node | Erythema multifome | None            | 0            | ND                     | 3.5                  | 3.9                             | ANA antibody 1:80 titer (1:20) IgG 836 mg/dL IgA 249 mg/dL IgM 89 mg/dL | Fourteen months later, the swelling of the right brachium lymph node appeared. It was biopsied and diagnosed as ATLL. He was treated with CHOP therapy and lymph node swelling disappeared. He has been well. | 4 years          |
| 8    | M   | 70  | Cervical lymph node | None.           | None            | 2.3          | ND                     | 1.9                  | 1.9                             | None | No follow-up. | None          |
| 9    | M   | 83  | Inguinal lymph node | Allergic dermatitis treated with steroid therapy for a month | None            | 1.7          | ND                     | 2.5                  | 2.4                             | WBC 4740 (3300–8190)/µL Eos 36.3% IL2 receptor 2360 U/mL ANA antibody positive | He had been treated with steroid therapy and was well. After 3 months, the follow-up was discontinued. | 3 months          |
### Histological and Immunohistochemical Results for LNs of DL

Nodular expansion of the interfollicular spaces and paracortex by confluent pale-staining areas composed of numerous Langerhans cells that were both S100 protein- and CD1a-positive and IDCs that were S100 protein-positive but CD1a-negative were seen. CD68-positive macrophages were mixed among IDCs and Langerhans cells and accumulated around the pale-staining areas (Figure 3A). Some melanin granule-containing macrophages were scattered in all LNs. Many reactive small lymphocytes, particularly CD4-positive T cells that outnumbered CD8-positive T cells, had infiltrated the interfollicular spaces and paracortex (Figure 3B). FOXP3/CD25 double-positive Treg cells were also observed in these areas (Figure 3C). In some LNs, IgG4+ or IgG4+/IgG- plasma cells had infiltrated the interfollicular spaces and paracortex.

The 11 DL patients were divided into 2 groups on the basis of the grade of infiltration of IgG4+ cells: 3 with a high ratio (>40%) of IgG4+/IgG- cells and 8 with a low ratio (<40%) of IgG4+/IgG- cells or no infiltration of IgG4+ cells. LNs of cases 1, 2, and 3 had high ratios of IgG4+/IgG- cells at 62.8%, 65.3%, and 52.7%, respectively (Figure 3D and E). LNs of cases 4 to 11 had 0% to 2.9% (mean 1.4%) of IgG4+/IgG- cells.

He was treated with steroid therapy for rheumatoid arthritis for another 3 years, and he has been well.

For case 5, a patient with atopic dermatitis, swelling of bilateral cervical, inguinal, and left axillary LNs was found. The biopsied right inguinal LN was diagnosed as DL. He was followed without medication for 5 years, and he was well, although subsequent follow-up was discontinued.

For case 6, a patient with allergic dermatitis, swelling of bilateral inguinal LNs was found. The left inguinal LN was biopsied and diagnosed as DL. She was followed without medication for 9 years, and she has been well.

For case 7, a patient with psoriasis vulgaris, swelling of bilateral inguinal LNs was found. Histological examination of the right inguinal LN showed DL. After 14 months, swelling of the right brachium LN newly appeared. This was biopsied and diagnosed as adult T-cell leukemia/lymphoma on the basis of monoclonal integration of human T-cell lymphotropic virus 1 proviral DNA by Southern blot analysis. He was treated with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisolone (CHOP therapy). Swelling of LN disappeared, and he has been well for 4 years.

For case 8, a patient with no skin disease, swelling of the left cervical LN was found. The histological diagnosis was DL. He did not receive any medications and was no longer followed.

For case 9, a patient with allergic dermatitis with focal skin Langerhans cell histiocytosis who had been treated with steroid therapy for a month, swelling of the right inguinal LN was found. The biopsied right inguinal LN was DL. He was followed and had been well for another 3 months with steroid therapy, although subsequent follow-up was discontinued.

For case 10, a patient with psoriasis vulgaris, swelling of bilateral inguinal LNs was found. The right inguinal LN was biopsied and diagnosed as DL. He was followed for 8 years without medication, and he has been well.

For case 11, a patient with allergic dermatitis, swelling of the left cervical LN was found. This was biopsied and diagnosed as DL. He did not receive any medications and was no longer followed.

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### Table: Clinical Outcome of DL

| Case | Sex | Age | Skin Disease | Other Laboratory Findings | No. of TGF-β-positive Cells/mm² | No. of Mast Cells/mm² | IgG4/IgG Serum Level, mg/dL | ANA antibody | IL-2 receptor, U/mL | TGF-β, pg/mL | Follow-up Period | Clinical outcome of DL |
|------|-----|-----|--------------|---------------------------|-------------------------------|-----------------------|--------------------------|---------------|---------------------|--------------|----------------------|----------------------|
| 10   | M   | 72  | Inguinal lymph nodal nodule | None | 2.6 | 1.7 | ND | None | None | None | None | 8 years | He has been treated with etretinate and mequitazine for psoriasis vulgaris and has been well. |
| 11   | M   | 69  | Cervical lymph node | None | 3.8 | 2.5 | 2.5 | None | None | None | None | None | No follow-up |
| 5    | F   | 45  | Atopic dermatitis | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | She was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and she has been well for 4 years. |
| 6    | M   | 32  | Allergic dermatitis | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | He was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and he has been well for 4 years. |
| 7    | M   | 67  | Erythema multiforme | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | He was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and he has been well for 4 years. |
| 8    | M   | 52  | No skin disease | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | He was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and he has been well for 4 years. |
| 9    | F   | 32  | Allergic dermatitis with focal skin Langerhans cell histiocytosis | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | He was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and he has been well for 4 years. |
| 10   | M   | 45  | Atopic dermatitis | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | He was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and he has been well for 4 years. |
| 11   | F   | 32  | Allergic dermatitis with focal skin Langerhans cell histiocytosis | None | 9.1 | 5.2 | 4.3 | None | None | None | None | 12 years | He was treated with prednisolone (CHOP therapy). Swelling of LN disappeared, and she has been well for 4 years. |

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The 11 DL patients were divided into 2 groups on the basis of the grade of infiltration of IgG4+ cells: 3 with a high ratio (>40%) of IgG4+/IgG- cells and 8 with a low ratio (<40%) of IgG4+/IgG- cells or no infiltration of IgG4+ cells. LNs of cases 1, 2, and 3 had high ratios of IgG4+/IgG- cells at 62.8%, 65.3%, and 52.7%, respectively (Figure 3D and E). LNs of cases 4 to 11 had 0% to 2.9% (mean 1.4%) of IgG4+/IgG- cells.
Sclerosis and phlebitis were not observed in any LNs, regardless of a high or low ratio of IgG4+/IgG+ cells. Some mast cells were scattered within the interfollicular spaces and paracortex of LNs (for all 11 LNs, mean of 4.46 ± 4.65/mm2), and the mean number of mast cells/mm2 was significantly higher in the group with a high ratio of IgG4+/IgG+ cells (10.31 ± 1.66/mm2; Figure 3F) than in the group with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells (2.26 ± 1.02/mm2; P = 0.0025; Table 1 and Figure 4A).

Some TGF-β-positive cells were scattered in LNs of both groups (for all 11 LNs, mean of 5.22 ± 5.16/mm2), and there was a significantly higher infiltration of TGF-β-positive cells in the group with a high ratio of IgG4+/IgG+ cells (12.00 ± 1.68/mm2; Figure 3G) than in the group with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells (2.68 ± 1.03/mm2; P = 0.0011; Table 1 and Figure 4B). The number of TGF-β-positive cells was much lesser than that of FOXP3/CD25 double-positive regulatory T cells (Treg cells). Moreover, FOXP3/TGF-β3 double staining revealed that TGF-β-positive cells were different from FOXP3-positive cells and there were no FOXP3/TGF-β double-positive cells (Figure 3H). The distribution and population of TGF-β-positive cells were similar to those of mast cells, and in serial sections, mast cells appeared to be positive for TGF-β (Figure 3I). IFN-γ expression was positive for IDCs, Langerhans cells, and macrophages in addition to a small number of lymphocytes (Figure 3J). MMP-1, MMP-8-, or MMP-13-positive macrophages were also observed in LNs (Figure 3K, L, M).

**DISCUSSION**

DL is a benign histopathological disease associated with skin diseases. Although a patient’s history and clinical examination could raise a suspicion, histological examination of biopsied LNs is mandatory for the diagnosis of DL. Dermatopathic LNs are characterized by infiltrations of IDCs, Langerhans cells, macrophages, melanin granule-laden macrophages, and T cells. After Langerhans cells are exposed to antigens in the skin, they migrate to regional LNs where they interact with...
FIGURE 3. Histological analysis of representative LN specimens from DL patients. (A) CD68/S100 protein double immunohistochemical staining. Many S100 protein-positive IDCs and Langerhans cells (red cytoplasm) are observed in the pale-staining areas within the interfollicular areas and paracortex. Macrophages (brown cytoplasm) are mixed among S100 protein-positive cells and have infiltrated the areas surrounding these cells. (b) CD4/CD8 double immunohistochemical staining. Many CD4-positive cells (red cells) and CD8-positive cells (brown cytoplasm) have mainly infiltrated the interfollicular spaces and the areas around the pale-staining areas. (C) FOXP3/CD25 double immunohistochemical staining. Many both FOXP3- (brown nucleus) and CD25-positive (red cytoplasm) Treg cells are also observed. Immunohistochemical staining for (D) IgG and (E) IgG4 in LN with a high ratio of IgG4+/IgG+ cells (case 1). (F) Toluidine blue staining. Some mast cells showing metachromasy (arrow) are scattered within the interfollicular spaces and paracortex in LN (case 2). (G) Immunohistochemical staining for TGF-β in LN with a high ratio of IgG4+/IgG+ cells (case 2). Some TGF-β-positive cells are scattered within the interfollicular spaces and paracortex. (H) FOXP3/TGF-β double immunohistochemical staining. FOXP3-positive (brown nucleus) and TGF-β-positive cells (red cytoplasm) are found separately, and double-positive cells are not observed. (I) Toluidine blue staining and immunohistochemical staining for TGF-β in serial sections. A mast cell (left: arrow) positive for TGF-β (right: arrow). (J) Immunohistochemical staining for IFN-γ. IFN-γ expression is positive in cells in pale-staining areas, including IDCs, Langerhans cells, and macrophages. (K, L, and M) Immunohistochemical staining for MMP-1, MMP-8, and MMP-13. Macrophages are positive for (K) MMP-1, (L) MMP-8, and (M) MMP-13. Note that many cells in the pale-staining areas are negative for these MMPs. (A, objective magnification, 4×; B, objective magnification, 10×; C, F, G, J, K, L, M, objective magnification, 40×; D, E, objective magnification, 20×; H, I, objective magnification, 100×). DL = dermatopathic lymphadenopathy, IFN = interferon, LN = lymph node, MMP = matrix metalloproteinase, TGF = transforming growth factor.
CD4-positive helper T cells to present antigen and initiate an immune response in conjunction with IDCs and macrophages. This series of immune reactions can be induced by destruction of the epidermis, inflammatory cytokines, and other agents, including bacterial components.14

On the contrary, IgG4-RD is likely autoimmune in nature and a fibroinflammatory disorder that involves various organs and tissues. The proposed diagnostic criteria are as follows: clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; elevated serum IgG4 levels (>135 mg/dL); and histological findings of marked infiltration of lymphocytes and plasma cells, >10 IgG4+ cells/HPF; a ratio of IgG4+/IgG+ plasma cells of >40%, and fibrosis.15,16 The pathogenesis of this disease, including IgG4 involvement, has not been elucidated.

Fibrosis is an important histological finding for the diagnosis of IgG4-RD. Although the mechanism underlying fibrosis development also remains unclear, the growth factor TGF-β is known to play an important role in fibrosis via its effects on the proliferation of fibroblasts in IgG4-RD.17 Infiltration of FOXP3/CD25 double-positive Treg cells that release TGF-β has been thought to be related to fibrosis in affected sites.6 However, it has been recently reported that mast cells but not Treg cells at the affected sites produce TGF-β and play a role in fibrosis in IgG4-RD.18

In the present study, three of 11 cases (27%) showed infiltration by a large number of IgG4-positive cells and a high ratio of IgG4+/IgG+ cells of >40%. Except for no fibrosis, these 3 cases met the criteria for IgG4-RD: swelling of organs (LNs), elevated serum IgG4 levels (>135 mg/dL), a ratio of IgG4+/IgG+ cells of >40%, and >10 IgG4+ cells/HPF. Our findings also suggested that mast cells and not Treg cells produced TGF-β on the basis of the following histological findings: FOXP3-positive cells were negative for TGF-β with FOXP3/TGF-β double staining; the population and location of mast cells were similar to those of TGF-β-positive cells; and mast cells appeared to be identical to TGF-β-positive cells in serial sections. The number of mast cells and TGF-β-positive cells was significantly increased in the group of DL patients with a high ratio of IgG4+/IgG+ cells than that in the group of patients with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells. However, despite these findings, fibrosis characteristic of extra-nodal IgG4-RD was not observed in both these groups.

Fibrogenesis is known to be inhibited by IFN-γ and MMPs. IFN-γ can inhibit fibroblast proliferation and reduce extracellular matrix deposition.19 IFN-γ is produced by T(H)1 cells, a subgroup of CD4-positive helper T cells, and antigen-presenting cells such as monocytes/macrophages and dendritic cells, the main cellular components of LNs of DL.20,21 Among MMPs, a family of zinc-dependent proteases, MMP-1, MMP-8, and MMP-13 are classified as collagenases that play essential roles in breaking down components of the extracellular matrix and participate in collagen degradation.22 Macrophages have been known to produce these MMPs.23–25 Therefore, we performed immunostaining of IFN-γ and MMPs 1, 8, and 13 on LNs of DL patients. As a result, in addition to a small number of lymphocytes, many IDCs, Langerhans cells, and macrophages were positive for IFN-γ, and macrophages were positive for MMP-1, MMP-8, or MMP-13 in LNs of DL. Thus, these findings indicate that the lack of fibrosis in LNs of DL with a high ratio of IgG4+/IgG+ cells might be a result of IFN-γ and MMPs produced by IDCs, Langerhans cells, and macrophages.

DL is considered as benign and requires no intervention. In the present study, of 8 patients with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells, 5 who could be followed did not develop IgG4-RD within the follow-up periods. In contrast, of 3 cases of DL with a high ratio of IgG4+/IgG+ cells, one became complicated with retroperitoneal fibrosis at a month after the diagnosis of DL, whereas another developed IgG4-lymphadenopathy at 5 months after the diagnosis of DL.

Because IgG4-RD is systemic and progressive, a timely diagnosis is necessary. Without appropriate treatment, this disease will progress and result in a loss of function of potentially any exocrine gland as well as local destruction because of mass-forming lesions and fibrosis. Therefore, in cases without clinical and characteristic morphological features at the time of diagnosis, the presence of excess of IgG4-positive plasma cells in LNs of DL may be non-specific and this finding should not prompt treatment initiation in these patients.26 The findings of the present study suggest that pathologists, hematologists, and

**FIGURE 4.** Numbers of (A) mast cells and (B) TGF-β-positive cells/mm² in DL patients with a high ratio of infiltrating IgG4+ plasma cells to IgG+ cells (IgG4+/IgG+ cells) and in DL patients with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells. The numbers of both cell types are greater in DL with a high ratio of IgG4+/IgG+ cells than in DL with a low ratio of IgG4+/IgG+ cells or no infiltration of IgG4+ cells. *P < 0.05. DL = dermatopathic lymphadenopathy, TGF = transforming growth factor.
dermatologists need to recognize DL with increased IgG4-positive plasma cells and carefully conduct follow-up of these DL patients to ensure timely treatment initiation in the event of future development of IgG4-RD. For further characterization, additional studies with larger sample sizes are required.

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