Immunoblastic Lymphadenopathy-Like T-Cell Lymphoma Displaying Rearrangement of Both IgH and TCR/β Genes after 4-Year Follow-Up of Idiopathic Eosinophilia

Mitsuaki Takeda, Kyuhei Kohda, Yoshifumi Fujisaki, Akiko Tsuji, Norihiro Takayanagi, Osamu Nakazawa, Masakatsu Andoh* and Osamu Yanai**

Immunoblastic lymphadenopathy (IBL)-like T-cell lymphoma (IBL-T) occurred in a 60-year-old female after a 4-year follow-up of idiopathic eosinophilia and upper pharyngeal inflammatory tumor with infiltration of mature eosinophils. Gene analysis of tumor cells revealed rearrangement of both IgH and TCR/β genes. The patient died of lymphoma seven months after the onset of the illness, in spite of chemotherapy against lymphoma. The relationship between eosinophilia and the pathogenesis of IBL-T, as well as the significance of the rearrangement of both IgH and TCR/β genes are discussed.

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Introduction

Immunoblastic lymphadenopathy (IBL)-like T-cell lymphoma (IBL-T) was first reported by Shimoyama et al (1) in 1979 as a subtype of T-cell lymphoma which is relatively rare. Here, we report a case of IBL-T displaying rearrangement of both IgH and TCR/β genes after follow-up of idiopathic eosinophilia.

Case Report

A 60-year-old female visited the department of otolaryngology of our hospital in January 1988 with the chief finding of bilateral upper pharyngeal tumor. She was found to have marked eosinophilia (about 70% of peripheral leukocytes); histological diagnosis of the tumor was inflammatory tumor with infiltration of mature eosinophils (Fig. 1). Collagen disease, parasitic disease, allergic disease and neoplastic disease which can be associated with eosinophilia were excluded on the basis of the results of clinical and laboratory examination. She was followed up for inflammatory pharyngeal tumor with idiopathic eosinophilia in the out-patient clinic of otolaryngology for about 4 years, and biopsy specimens taken from the pharyngeal tumor several times during this period did not show any neoplastic findings. The upper pharyngeal tumor showed marked regression and the eosinophilia was partially improved by administration of prednisolone and azathioprine (Fig. 2).

Tonsillectomy was performed in December 1990 due to regrowth of the pharyngeal tumor, however the histology of the resected tissue was similar to the previous diagnosis. Because the pharyngeal tumor had re-grown after tonsillectomy and generalized lymphadenopathy appeared from September 1991, she was referred to our department in October 1991. On admission to our department, elastic soft, smooth-surfaced, 1–2 cm-sized lymph nodes were palpable bilaterally in the neck, axillary and inguinal regions without any tenderness. A 3–4 cm tumor was observed on the right upper pharyngeal region. Skin eruption was observed. Slight crepitant rales were audible throughout both lungs. Liver and spleen were not palpable.

Laboratory test results (Table 1) showed normochromic normocytic anemia, eosinophilia (27% of peripheral leukocytes), polyclonal hypergammaglobulinemia (especially high IgE levels), and elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels. Coombs tests were negative. Bone marrow was morphologically normal except for slight increase of mature eosinophils. Serum cytokine analysis showed elevated of interleukin (IL)-2 and IL-6 levels.

Histological findings of the cervical lymph node

A cervical lymph node biopsy demonstrated diffuse oblit-
IBL-T with Double Gene Rearrangement

**Fig. 1.** Histology of the upper pharyngeal tumor in January 1988. Biopsy specimens taken from pharyngeal tumor show marked infiltration of the mature eosinophils (HE, ×2,000). Arrows indicate the infiltrated mature eosinophils.

![Histology of the upper pharyngeal tumor](image)

**Gene rearrangement in cervical lymph node tissue (Fig. 5)**

DNA, extracted from a cervical lymph node was digested with restriction enzymes, separated by electrophoresis in 0.8% agarose gel, and then transferred to activated nylon membranes according to the method of Southern (3). The DNA fragments on the membranes were hybridized with nick-translated 32P-labeled probes, and examined by autoradiography. The probes used in this study were Cβ1 probe (from human T-cell line, Oncogene Science, Inc., NY) and JH probe (from human, Oncor, Inc., Gaithersburg, MD). The restriction enzymes used were BamHI (from Bacillus amyloliquefaciens H; Boehringer

**Fig. 2.** Clinical Course in the department of otolaryngology. AZP: azathioprine, PDN: prednisolone, WBC: white blood cell count, EOS: eosinophil count.

![Clinical Course in the department of otolaryngology](image)

eration of normal lymph node architecture with vascular proliferation, disappearance of germinal centers, and diffuse proliferation of immunoblast-like cells and lymphoid cells with pale cytoplasm (Fig. 3). These cells were demonstrated to be positive for UCHL-1 (anti CD45-RO) (DAKO, Glostrup, Denmark) (Fig. 4-a), but negative for L-26 (anti CD20) (Kyowa, Tokyo, Japan) (Fig. 4-b) by immunostaining using peroxidase anti-peroxidase method (2). In addition to these main findings, non-neoplastic infiltration of plasma cells and eosinophils was observed.
Mannheim Biochemica) and EcoRV (from Escherichia coli J6 pLG74; Boehringer Mannheim Biochemica) for C/31 probe, and BamHI, HindIII (from Haemophilus influenza Rd com-10; Boehringer Mannheim Biochemica) and EcoRI (from Escherichia coli BS5; Boehringer Mannheim Biochemica) for JH probe.

Southern blot analysis of extracted DNA from the cervical lymph node digested with BamHI or EcoRV using C/31 probe demonstrated clonal rearrangement of β chain of the T cell antigen receptor (TCRβ) gene. Southern blot analysis of the same DNA which was digested with BamHI and HindIII using JH probe also demonstrated clonal rearrangement of IgH gene.

Clinical course (Fig. 6)

She was diagnosed as having IBL-like T-cell lymphoma (IBL-T) which developed from idiopathic eosinophilia, and given cyclophosphamide, doxorubicin, vincristine, prednisolone, and etoposide (E-CHOP therapy) from October 1991. After one month of chemotherapy, the swelling of lymph nodes was reduced and the eosinophil count was decreased. Because lymph nodes became regrown after 3 courses of E-CHOP and modified E-CHOP (administration of vindesine in place of vincristine. MACOP; cyclophosphamide, doxorubicin, methotrexate and prednisolone) therapy (4) was started from January 1992. She partially responded to NEO-MACOP therapy, however she died of progressed lymphoma accompanied with eosinophilia seven months after the onset of IBL-T, complicated by disseminated intravascular coagulation and adult respiratory distress.
IBL-T with Double Gene Rearrangement

Fig. 3. Histology of the cervical lymph node. Diffuse obliteration of normal lymph node architecture with vascular proliferation, disappearance of germinal centers, and diffuse proliferation of immunoblast-like cells and lymphoid cells with pale cytoplasm were seen (HE, x500).

Discussion

IBL, first proposed by Lukes and Tindle (5), had been considered to be an abnormal proliferation of B cell lineage. However, cases of T cell lymphoma having the characteristics of IBL, have recently been detected histologically and clinically. Shimoyama et al (1) proposed to define them as IBL-T.

We could diagnose this case as typical IBL-T at the time of admission to our department in October 1991, because the histology of the lymph node showed morphological similarity to that of IBL and proliferation of immunoblast-like cells and pale cells, as reported by Shimoyama et al (1) and Watanabe et al (6), which showed T cell phenotype, presenting clinical manifestation of systemic lymph node swelling, polyclonal hypergammaglobulinemia, fever and skin eruption.

At present, the pathogenesis of IBL-T is unknown, and the relationship between IBL and IBL-T is unclear, although it is reported that IBL might be a state of T cell dysplasia which has high potential to develop into IBL-T (7). However, in IBL-T, pale cell and clonal proliferation of T cells are recognized by clinicopathologic, immunophenotypic, immunogenotypic and karyotypic analyses (8, 9).

This case developed IBL-T after follow-up of idiopathic eosinophilia with inflammatory pharyngeal tumor for 4 years. Both the pharyngeal tumor and eosinophilia before development of IBL-T responded well to the treatment with prednisolone and azathioprine in out-patient clinic of otorlaryngology. Frequent histological examination of pharyngeal tumor revealed the findings of neither IBL nor malignant lymphoma. After she was diagnosed as IBL-T in our department, the absolute number of eosinophils correlated with the degree of lymphadenopathy during the treatment period.

A variety of malignant disorders, especially lymphoma, also may be accompanied by eosinophilia. Murata et al (10) reported that 21% of adult T cell leukemia lymphoma (ATLL), 11.1% of T cell lymphoma and 10.5% of B cell lymphoma showed eosinophilia (>570/µl), studying the incidence of eosinophilia in 62 patients with lymphoproliferative disorders. It is also reported that eosinophilia was observed in 100% of 5 cases with IBL-T (11), however precise incidence of eosinophilia in IBL-T has not been studied in detail. Although the exact mechanism for the development of eosinophilia associated with lymphoma remains unclear, it is considered that some lymphokines such as granulocyte/macrophage colony-stimulating factor, IL-3 and IL-5 secreted by the lymphoma cells or T-lymphocytes stimulated by tumor antigen might cause eosinophilia (10). However, in this case, serum cytokine analysis showed elevated IL-2 and IL-6 levels. It is possible that these cytokines are associated with eosinophilia. Although there are few case reports of

Fig. 4. Immunostaining findings of the cervical lymph node. a) Diffuse proliferation of positive cells for UCHL-1 were revealed by immunostaining (PAP, x1,000). b) These cells were demonstrated to be negative for L-26 (PAP, x600).
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**Fig. 5.** Southern blot analysis of extracted DNA from cervical lymph node tissue. Lane 1: DNA digested with BamHI using Cβ1 probe, Lane 2: DNA digested with EcoRV using Cβ1 probe, Lane 3: DNA digested with BamHI and HindIII using JH probe, Lane 4: DNA digested with HindIII using JH probe, Lane 5: DNA digested with EcoRI using JH probe. R: rearranged band, G: germ line.

**Fig. 6.** Clinical course in our department. CY: cyclophosphamide, ADM: doxorubicin, VCR: vincristine, VP16: etoposide, VDS: vindesine, PDN: prednisolone, G-CSF: granulocyte colony-stimulating factor, MTX: methotrexate, MIT: mitoxantrone, Radi.: irradiation, Gy: gray unit, WBC: white blood cell count, EOS: eosinophil count.
malignant lymphoma developing from eosinophilia followed up for several years (12, 13), no case of IBL-T to date developed from idiopathic eosinophilia such as the present case. In this case, we can consider two possibilities for the mechanism for development of IBL-T. One is that immunological abnormality or pre-lymphomatous abnormal T cells which caused the preceding eosinophilia were related to the development of IBL-T, and another possibility is that a very small amount of malignant lymphoma cell which is not detectable by histological examination was present during the period of idiopathic eosinophilia.

Another interesting point in the present case is the rearrangement of both TCRβ and IgH genes found in the DNA from the lymph node. Although the accumulation of reports for IBL-T cases examined for rearrangement of T cell antigen receptor (TCR) and Ig genes may not be necessarily satisfactory, Kaneko (14) reviewed that the rearrangement of only TCRβ was found in 44 cases (62%), and the rearrangement of both TCRβ and IgH genes was found in 7 cases (10%) of 71 cases of IBL, however the rearrangement of only TCRβ was found in 24 cases (69%); the rearrangement of IgH was not found in any of the 35 cases of IBL-T. Thus the rearrangement of both TCRβ and IgH genes in IBL-T seem to be considerably uncommon.

The rearrangement of both TCR and Ig genes are reported to be observed in 4–10% of leukemia and lymphoma (15). It is possible that rearrangement of both genes may occur in the development into malignant tumor of hematopoietic stem cell due to interruption of some gene rearrangement followed by occurrence of another gene rearrangement. It is speculated that such cross-lineage gene rearrangement may occur in undifferentiated hematopoietic tumor cells (16).

Although the rearrangement of both genes in this case may indicate whether this case is genetically closer to IBL or this case is a more undifferentiated IBL-T, the aggressive clinical course of the present case resembled malignant lymphoma with a high grade malignancy might support the latter implication. The relationship between gene rearrangements and prognosis of IBL-T should be studied in detail, in future.

References