CASE REPORT

CD20-Positive T-Cell Large Granular Lymphocyte Leukemia: Case Report and Review of the Literature

Koji Miyazaki, Manabu Ohsaka, Yuhko Suzuki, Mikio Danbara, Ryouichi Horie and Masaaki Higashihara

Abstract

CD20-positive T-cell malignancy is a rare disease. We report a case of CD20-positive T-cell large granular lymphocyte leukemia (T-LGLL). The leukemic cells were positive for CD20 and T cell markers, such as CD3, CD4, CD5, CD8 and CD57. A monoclonal rearrangement of the T-cell receptor (TCR) β chain gene was detected. Twenty-three cases of well-documented CD20-positive T-cell malignancies were reviewed. Most cases were mature T-cell malignancies, especially exhibiting a cytotoxic T-cell phenotype, despite a diversity of the pathological diagnoses. Additional cases must be evaluated to clarify the implications of CD20 expression on T-cell malignancies and to elucidate whether such cases constitute a distinct biologic and clinical disease entity. The accumulation of cases will help to facilitate provision of a proper treatment for CD20-positive T-cell malignancies in the future.

Key words: hematopoietic differentiation antigens, immunophenotyping, flow cytometry, cytotoxic T-cell

Introduction

T-cell large granular lymphocyte leukemia (T-LGLL), a subtype of chronic lymphocytic leukemia, is a clonal proliferation of cytotoxic T lymphocytes, characterized by the CD3+, CD57+, CD56- immunophenotype and the clonal rearrangement of the T-cell receptor genes (1). It presents clinically with a rather indolent course of disease, complicated by frequent infections secondary to neutropenia, anemia, splenomegaly and autoimmune disorders especially rheumatoid arthritis.

CD20 is a transmembrane protein, which has been thought to be a B-cell specific marker. Hultin et al, however, identified a distinct subpopulation of T cells expressing CD20 molecule in peripheral blood and bone marrow from normal individuals (2). Meanwhile more than twenty cases of T-cell malignancies expressing CD20 have been reported over the past two decades (3-21). Although the significance of CD20 expression in these cases is unclarified, there might be some relevance to the normal CD20-positive T-cells. As the number of reported cases is still small, the accumulation of cases is necessary to address this issue. Here, we report a rare case of CD20-positive T-LGLL and review the literature.

Case Report

A 74-year-old Japanese man was referred to the hospital for evaluation of bicytopenia. He had at least a 20-month history of bicytopenia without any significant symptoms. He had had sero-positive rheumatoid arthritis for a few decades, although he did not require any medications for it. A physical examination showed neither hepatosplenomegaly nor peripheral lymphadenopathy, which was confirmed with a computerized tomographic scan. The blood count showed a hemoglobin level of 13.4 g/dL, a platelet count of 62 × 10^9/L and a white blood cell count of 1.3 × 10^9/L with 23% neutrophils, 32% monocytes and 42% lymphocytes, with a normal morphology. No significant increase in the number of large granular lymphocytes was observed.

Serum lactate dehydrogenase and C-reactive protein levels (128 IU/L, 0.248 mg/dL, respectively) were within normal ranges, whereas the serum level of soluble interleukin 2 re-
ceptor (sIL-2R) was moderately increased (856 IU/mL; normal range, 220-530 IU/mL). The serum vitamin B12 and folate levels (581 pg/mL, 5.1 ng/mL, respectively) were still within normal ranges, even though he had undergone a partial gastrectomy about 30 years previously.

A bone marrow aspiration revealed suppression of normal hematopoiesis and infiltration of the leukemic cells as shown in Fig. 1A (23.5% of nucleated cells), presenting a specific immunophenotype described below. A cytogenetic analysis detected the abnormal karyotype of 46,XY,t(3;17)(q26;p13) in only one out of 20 dividing cells, which could not be proven to be the leukemic karyotype by repeated analyses. The patient has been free of disease progression without any treatment for more than 20 months after diagnosis.

Flow cytometric analysis

The immunophenotypes of the leukemic cells in the bone marrow were analyzed by direct immunofluorescence using a flow cytometer. The proportion of CD2+ cells was 100%, CD3+ 100%, CD4+ 92.1%, CD5 99.6%, CD7+ 51.5%, CD8 99.7%, CD11c 56.0%, CD20 85.7%, CD57 90.4%, HLA-DR 91.4% and TCRαβ 99.4%. In contrast, CD1, CD10, CD11b, CD13, CD14, CD16, CD19, CD21, CD22, CD23, CD25, CD30, CD33, CD34, CD41, CD56 and terminal deoxynucleotydyl transferase (TdT) were all negative. We could not identify a significant population of leukemic cells showing a similar immunophenotype in the peripheral blood. The positivity for CD20 was confirmed using two different monoclonal antibodies (mAb), B-Ly1 (Dako Corporation, Santa Barbara, CA) and H299 (Beckman Coulter, Inc., Fullerton, CA). The expression of CD20 on leukemic cells was also demonstrated by two-color analysis using phycoerythrin (PE)-conjugated anti CD20 mAb and fluorescein isothiocyanate (FITC)-conjugated anti-CD5 mAb (Dako Corporation; Fig. 1B).

Southern blot analysis

A Southern blot analysis was performed to detect the rearrangement of the T-cell receptor (TCR) β chain and immunoglobulin (Ig) heavy chain genes using a 32P-labeled TCR-β chain gene probe (Cβ fragment) and an IgH chain gene probe (JH), respectively. Rearranged bands were detected in the TCR-β gene (Fig. 1C).

Discussion

T-LGLL, a subtype of chronic lymphocytic leukemia, is a clonal proliferation of CD3+ large granular lymphocytes (i.e. cytotoxic T lymphocytes), which are usually identified by a size greater than normal lymphocytes, abundant pale cytoplasm and prominent azurophilic granules. However, these features may vary, and occasionally clonally expanded lymphocytes with characteristic immunophenotype may not have LGL morphology on peripheral blood smear. It is also recognized that some patients may not have an absolute lymphocytosis. Because of this, the diagnosis may be overlooked unless the blood smear is examined carefully (1). T-LGLL should be included in the differential diagnoses in patients with unexplained cytopenias.

The present case had neither absolute lymphocytosis, massive infiltration of the leukemic cells in the bone marrow, splenomegaly, nor lymphadenopathies. These features might have misled the diagnosis to aplastic anemia or myelodysplastic syndrome. Careful examination and immunophenotyping with flow cytometry was necessary to reach the correct diagnosis.

The leukemic cells of this patient presented with a characteristic immunophenotypes, CD3+, CD8+, CD57+, CD56-
and the clonal rearrangement of TCR β which indicate a diagnosis of T-cell type LGLL. Specifically in this case, they co-expressed CD20 molecule, a pan-B cell marker. The CD20 expression was confirmed using two different monoclonal antibodies to determine whether the antigen is identical to the real CD20 molecule or to a CD20-like moiety.

Table 1. Clinical Features of Patients with CD20-positive T-cell Malignancies

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Table 2. Immunophenotypic Features of CD20-positive T-cell Malignancies

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Among the twenty cases of mature T-cell malignancies expressing CD20, patients ranged in age from 11-84 years with the median age being 67 years, and the man-to-woman ratio was 17 : 2. About half of the cases were CD8-positive,
and some of them expressed a cytotoxic T cell phenotype, exhibiting CD8, TIA-1, granzymes, or perforin. As CD8-positive lymphomas account for only about 10% of the total peripheral T cell lymphomas reported, the incidence of CD8-positivity among CD20-positive T cell lymphomas was significantly high. A cytotoxic T cell immunophenotype seems to be dominant for CD20-positive T cell leukemia and lymphoma. Interestingly the present case expressed CD4 in addition to CD8. Coexpression of CD4 and CD8 is observed in immature T cells of normal individuals. However, the leukemic cells expressed CD3 and the rearrangement of TCRβ chain gene was detected, suggesting that the leukemic cells exhibit a mature T cell phenotype, specifically a cytotoxic T cell phenotype. Several previous reports described CD4+CD8− T-LGL lymphocytosis (monoclonal lymphocytosis), which demonstrated unique clinical features compared with CD8− T-LGL leukemia, such as low incidence of cytopenia and autoimmune phenomena, and increased association with neoplasia (22). The present case did not exhibit these clinical characteristics, or rather typical features of conventional CD8− T-LGLL. It would be more probable that CD4 expression is an aberrant expression of the leukemic cells. CD4 expression of the leukemic cells might be relevant to suppressed expression of CD16, which is typically expressed in a cytotoxic T cell (23).

There are two possible hypotheses that might explain the CD20 expression of T cell malignancies. First, malignant T cells showed an aberrant expression of CD20 that is lineage infidelity. As a second possibility, they may originate from CD20-positive mature T cells, which were identified in peripheral blood or bone marrow from normal individuals. This distinct subpopulation of T cells exhibits a predominant memory cytotoxic phenotype and increases in number with age (24). Therefore, the latter is more plausible at least in some cases including the present case, although additional cases must be reviewed.

CD20 has been one of the most successful molecular targets for antibody therapy with rituximab or ibritumomab. While the present case had an indolent clinical course without any treatment, most previous cases required some combined chemotherapies, and could not attain a favorable prognosis. Two cases of CD20-positive T-cell lymphoma, who received the rituximab therapy, have been reported (18, 19). Although the effects could not be evaluated in these cases, rituximab may have therapeutic implications for CD20-positive T-cell malignancies.

In conclusion, this report describes a rare case of CD20-positive T-LGLL. Our literature review of CD20-positive T-cell malignancies revealed that most cases were mature T-cell malignancies, predominantly exhibiting a cytotoxic T-cell phenotype. As the number of reported cases is still small, additional cases must be evaluated to clarify the implications of CD20 expression on T-cell malignancies and also to elucidate whether such cases constitute a distinct biologic and clinical disease entity. Recognition of CD20-positive T-cell malignancies is important to provide adequate therapy for these patients, hopefully thereby improving the prognosis.

Acknowledgement

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References

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