

Case Report

A case study of t(14;22)(q32;q11) involving immunoglobulin heavy and light chain in follicular lymphoma

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Abstract: Chromosome 14 is the most frequently rearranged chromosome in non-Hodgkin lymphoma (NHL), with aberrations particularly involving the heavy-chain immunoglobulin gene (*IGH*) in the chromosome band 14q32. Several translocation partners have been described: t(14;18)(q32;21)/*IGH-BCL2* in follicular lymphoma (FL), t(11;14)(q13;q32)/*CCND1-IGH* in mantle cell lymphoma, and t(8;14)(q24;q32)/*MYC-IGH* in Burkitt lymphoma. The chromosomal locus 22q11 contains two important genes associated with leukemia and lymphoma; one is *BCR*, which fuses with *ABL* from 9q34 in chronic myeloid leukemia, and the other is the immunoglobulin lambda gene (*IGL*), which is rarely involved in the translocations observed in B-cell NHL. The t(14;22)(q32;q11) translocation has been previously reported in 8 cases of B-cell NHL; however, the translocation between *IGH* and *IGL* has been experimentally confirmed using fluorescence in situ hybridization (FISH) for only 4 cases. Here, we describe the first case of FL with a t(14;22)(q32;q11)/*IGH-IGL* translocation confirmed using FISH analysis. The patient in our case report was immunocompromised and was treated for aplastic anemia with cyclosporine A (CsA). The patient was diagnosed with follicular lymphoma, most likely caused by CsA.

Keywords: Follicular lymphoma, translocation t(14;22)(q32;q11), aplastic anemia, cyclosporine A

Introduction

Chromosome translocations that involve the heavy-chain immunoglobulin gene (*IGH*) in chromosome band 14q32 are associated with mature B-cell lymphoid malignancies [1-4]. These translocations include t(14;18)(q32;21)/*IGH-BCL2* in follicular lymphoma (FL), t(11;14)(q13;q32)/*CCND1-IGH* in mantle cell lymphoma, and t(8;14)(q24;q32)/*MYC-IGH* in Burkitt lymphoma [5].

There are two important genes on the chromosomal locus 22q11, associated with leukemia and lymphoma: *BCR*, which fuses with *ABL* from 9q34 in chronic myeloid leukemia, and the immunoglobulin lambda gene (*IGL*), which is rarely involved in B-cell non-Hodgkin lymphoma (NHL) translocations [6].

Chromosomal translocations between 14q32 and 22q11 have been reported in only 8 cases of B-cell NHL; 4 cases of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), 1 case of hairy cell leukemia (HCL), 1 case of HCL variant (HCL-v), 1 case of diffuse large B cell lymphoma (DLBCL), and 1 case of marginal zone B-cell lymphoma (MZBCL) [2, 6-11]. To the best of our knowledge, there has been no previous reported case of FL with t(14;22)(q32;q11).

FL constitutes approximately 10-20% of all newly diagnosed lymphoma cases, making it the second or third most common subtype of B-cell lymphoma [12-14]. It is characterized by an indolent clinical course, typical histopathological morphology, and the presence of a specific chromosomal translocation, t(14;18)

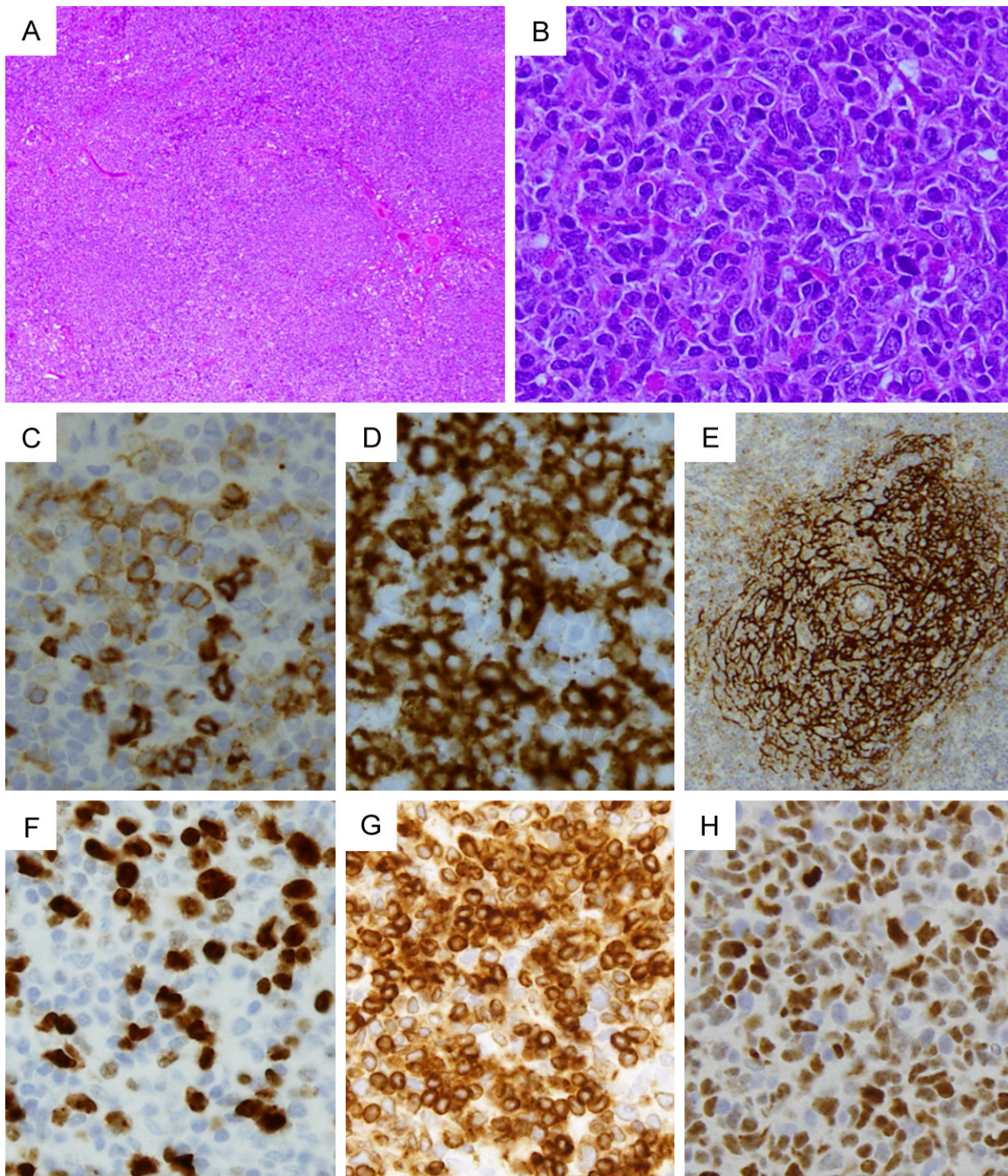


Figure 1. Specimen of the biopsy from a lymph node. (A, B) The specimen was stained with hematoxylin and eosin (HE) and revealed the replacement of the normal architecture of the lymph nodes by follicular proliferation of atypical lymphoid cells, consisting of small-to-medium-sized cleaved cells. There was a small number of centroblasts per high-power field. (A: $\times 40$, B: $\times 400$). (C, D) The atypical lymphoid cells positive for CD10 (C) and CD20 (D). ($\times 400$). (E) The aggregate includes follicular dendritic cells with CD21 positivity. ($\times 100$). (F) The MIB-1 index of the cells was approximately 70%. ($\times 400$). (G, H) The atypical lymphoid cells positive for BCL2 (G) and BCL6 (H). ($\times 400$).

(q32;q21)/IGH-BCL2, in more than 80% of patients [5, 15].

Cyclosporine A (CsA) is used to prevent rejection after transplantation and to treat autoim-

mune and hematological diseases. According to the World Health Organization (WHO) classification [5], the category of other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPD) and post-transplant

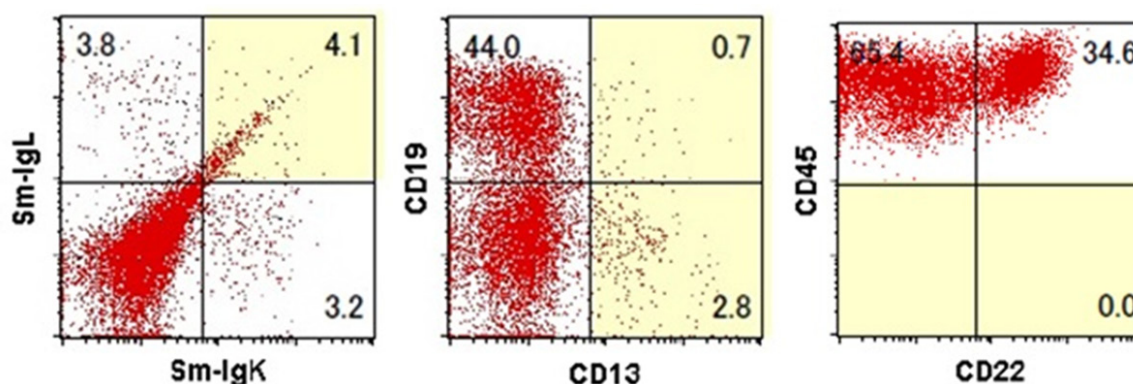


Figure 2. Flow cytometry analysis. Flow cytometry analysis of the lymph node showed that tumor cells (about 35% of total counted large cells) with CD19 and CD22 positivity were expressing neither immunoglobulin lambda nor kappa light chains.

lymphoproliferative disorders (PTLD) may have been related to the use of CsA.

In this report, we describe a case of a patient, who developed follicular lymphoma with the t(14;22)(q32;q21)/IGH-IGL translocation after CsA treatment for aplastic anemia for three years and three months.

Case report

Clinical history

A 65-year-old man undergoing hemodialysis due to diabetic nephropathy was admitted to our hospital with pancytopenia in May 2013. Peripheral blood cell count showed the following: red blood cell (RBC) count, 2.99 million/ μ L; hemoglobin (Hb), 9.6 g/dL; reticulocytes, 0.7%; white blood cell (WBC) count, 1230/ μ L (24% neutrophils, 50% lymphocytes, 14% monocytes, 12% eosinophils); and platelet count (Plt), 11,000/ μ L. A bone marrow biopsy from the posterior superior iliac spine revealed a severely hypocellular fatty bone marrow, with a nucleated cell count of 6000/ μ L, and a megakaryocyte count of 30/ μ L. The erythrocyte series was 32% and myeloid series was 38% with an M/E ratio of 1.2. There were no morphological abnormalities in erythroid, myeloid, and megakaryocytic lineages and there was no elevation of myeloblast levels. Chromosome analysis revealed the karyotype of 46XY. The erythropoietin level was 368 mU/mL. Consequently, the patient was diagnosed with aplastic anemia. The patient received a monotherapy of CsA (150 mg/day) starting on August 10.

His hematologic profile improved slowly and in February 2014, six months after the start of the treatment, the peripheral blood cell count was: RBC, 3.53 million/ μ L; Hb, 11.8 g/dL; WBC, 3500/ μ L (38% neutrophils, 42% lymphocytes, 8% monocytes, 12% eosinophils); and Plt, 58,000/ μ L. Three years and two months after the initial treatment, the patient presented with left cervical and supraclavicular lymphadenopathy. A computed tomography scan showed left cervical, left supraclavicular, left axillary and upper mediastinal lymphadenopathy. Bone marrow biopsy revealed no infiltration of abnormal cells. The patient denied any B symptoms such as weight loss, fever, or night sweats. The patient underwent excisional biopsy of the left supraclavicular lymph node, and the tumor was diagnosed as follicular lymphoma grade 1-2. The patient has not been treated because the tumor did not become larger; he had no tumor symptoms, no organ dysfunction, and refused chemotherapy.

Results

Pathological findings

The specimen mostly revealed replacement of the normal architecture of the lymph nodes with follicular proliferation of atypical lymphoid cells consisting of small-to-medium-sized cleaved cells. There was a small number of centroblasts per high-power field (**Figure 1A, 1B**). Flow cytometry (FCM) analysis of the lymph nodes showed an abnormal cell population expressing CD45, CD19, CD20, and CD22, with a loss of immunoglobulin lambda and kappa

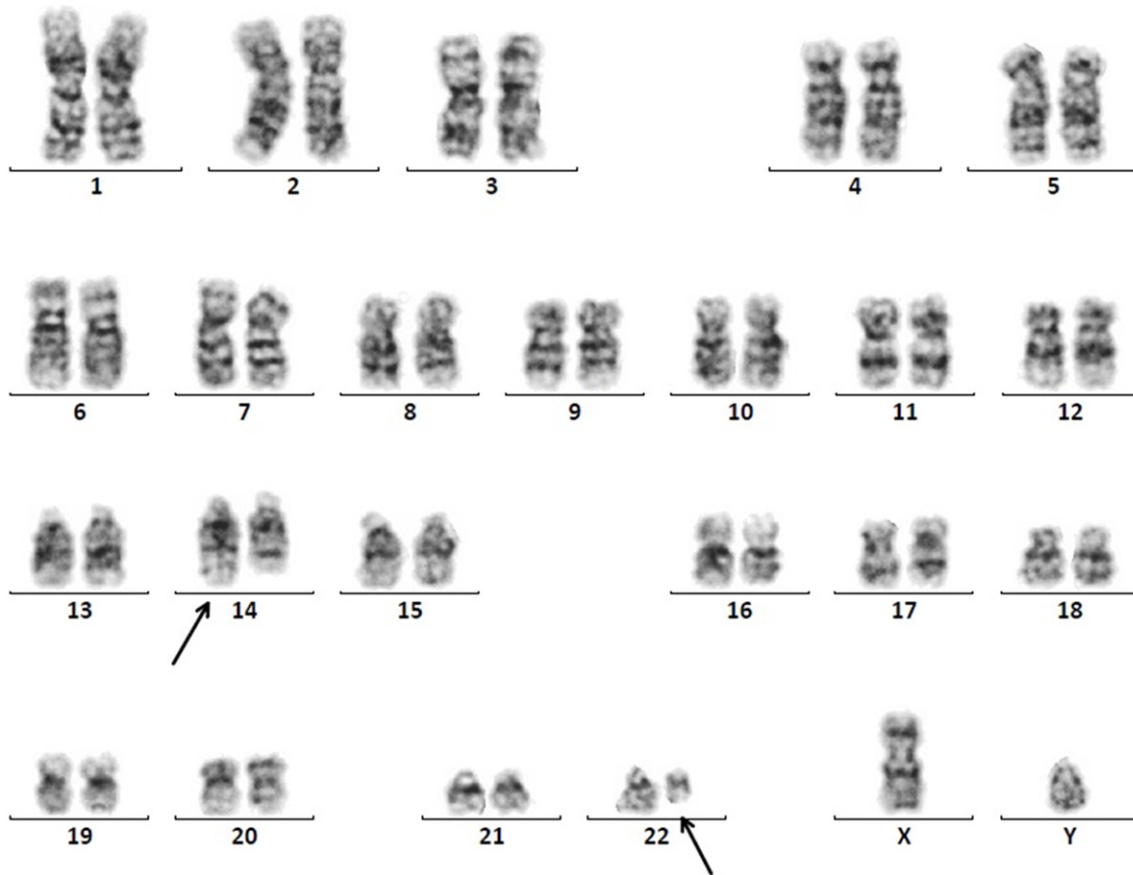


Figure 3. G-band analysis. G-banding revealed the following karyotype: 46,XY,t(14;22)(q32;q11.2).

light chains (**Figure 2**), CD5, and CD10. Immunohistochemistry showed that the atypical lymphoid cells were positive for CD45, CD10, CD79a, CD20, BCL2, BCL6, and MUM1, but negative for CD3, CD5, cyclin D1, and c-myc (**Figure 1C, 1D, 1G, 1H**). A population of follicular dendritic cells positive for CD21 was also detected (**Figure 1E**). Tumor cells were negative for Epstein-Barr virus (EBV), as assessed using in situ hybridization for EBV-encoded RNA (EBER), whereas a few non-tumor cells were EBV positive. The MIB-1 proliferation index of the cells was 50% (**Figure 1F**). The examination of chromosomes using G-banding revealed the following karyotype (**Figure 3**): 46,XY,t(14;22)(q32;q11.2) in 18 of 20 cells/47,X,+X,t(1;16)(q25;q12-13),+8 in one of 20 cells/46,XY in one of 20 cells. Fluorescence in situ hybridization (FISH) analysis was performed on 4 μ m paraffin-embedded sections, using dual color break-apart probes for the *IGH* locus at 14q32, the *IGL* locus at 22q11, and the *BCL2* locus at 18q21. FISH analysis showed split signals for

14q32/*IGH* in 9.1% of the examined cells (**Figure 4A**) and split signals for 22q11/*IGL* in 10.2% of the examined cells (**Figure 4B**), suggesting the presence of translocations involving 14q32/*IGH* and 22q11/*IGL*. No translocation involving 18q21/*BCL2* was observed. Based on these results, the patient was eventually diagnosed with grade 1-2 FL with a t(14;22)(q32;q11)/*IGH-IGL* translocation.

Discussion

FL constitutes approximately 10-20% of all newly diagnosed lymphoma cases, making it the second or third most common subtype of B-cell lymphoma [12-14]. About 80-90% of FL harbor the reciprocal chromosomal translocations t(14;18)(q32;q21) for the fusion gene between *BCL2* and *IGH* that result in constitutive *BCL2* protein overexpression. The translocations t(18;22)(q21;q11) for the fusion gene between *BCL2* and *IGL* may rarely cause *BCL2* overexpression [16]. In the present case of

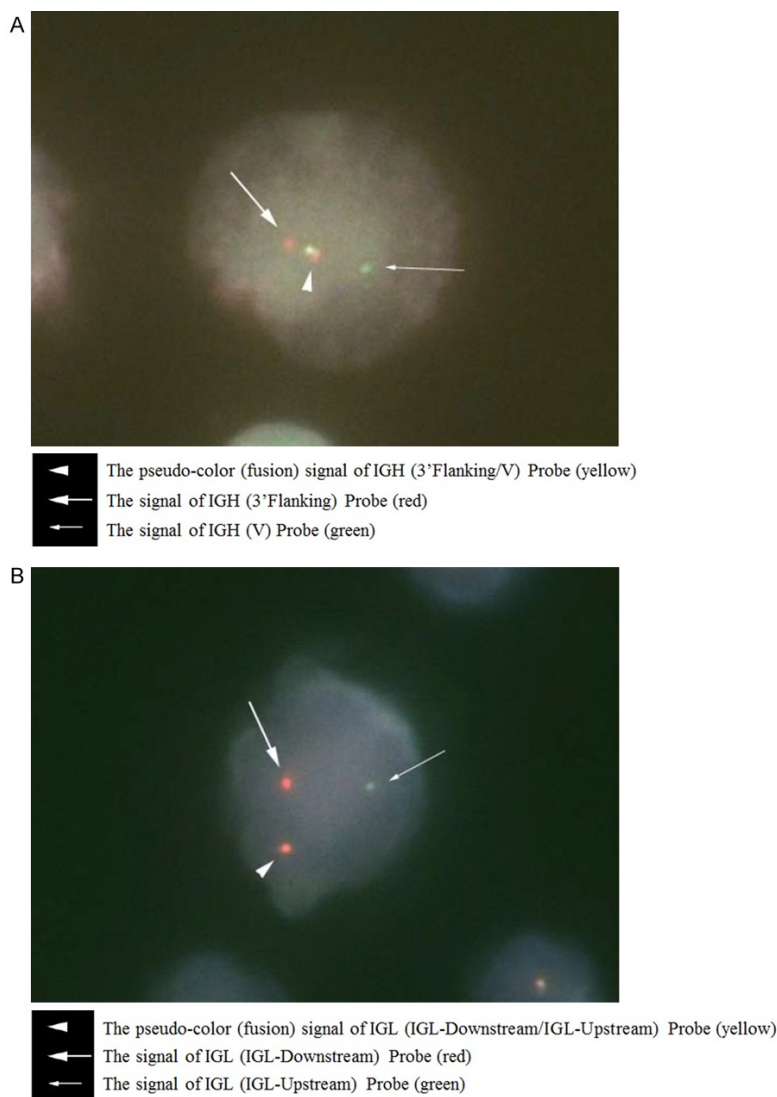


Figure 4. Fluorescence in situ hybridization (FISH) analysis. A: FISH using IGH (3'Flanking/V) Probe shows the split signals (red and green), indicating the presence of *IGH* translocation. B: FISH using IGL (IGL-Downstream/IGL-Upstream) Probe shows the split signals (green and red), indicating the presence of *IGL* translocation.

grade 1-2 FL, immunohistochemistry of the resected specimen was positive for BCL2, but the common t(14;18)(q32;q21)/*IGH-BCL2* translocation was not observed using G-banding and FISH analysis. Interestingly, we detected the presence of the t(14;22)(q32;q11)/*IGH-IGL* translocation for the first time in a grade 1-2 FL.

In addition to the 15 cases of lymphoma/leukemia with t(14;22)(q32;q11) reported in 2005, Aemot et al. reported another 5 cases [2]. However, these 20 cases included myeloid tumors, lymphoid tumors, and tumors with

“three-way variant translocations”. Excluding myeloid tumors and tumors with “three-way variant translocations”. Li et al. reported only 8 cases of t(14;22)(q32;q11) in 2014 [2, 6-11]; however, this translocation has not yet been reported in follicular lymphoma.

Details for the above-mentioned 8 cases and our case are shown in **Table 1**. To the best of our knowledge, only 9 cases of lymphoid neoplasms with a translocation of t(14;22)(q32;q11) have been reported [2, 6-11]. Although the translocations of 14q32 and 22q11 have been confirmed using G-banding analysis in all cases, it is known that *BCR* and *IGL* are very close to each other in 22q11. Therefore, we decided to confirm the translocation involving 22q11/*IGL*, using FISH analysis. FISH analysis showed that only 4 out of 9 cases, including our case, are lymphoid neoplasms with a translocation of t(14;22)(q32;q11)/*IGH-IGL*. Herein, we describe the first case of FL with the t(14;22)(q32;q11)/*IGH-IGL* translocation.

Translocations involving the chromosomal locus 22q11

have been reported in 20 cases of lymphoid neoplasms, including 12 cases of CLL/SLL and 5 cases of FL [16]. The translocation t(14;22)(q32;q11) was confirmed using G-banding analysis for 9 of the above mentioned cases, and 4 cases of CLL/SLL were included. Interestingly, 12 out of 20 cases and 4 out of 9 cases were CLL/SLL, which renders the 22q11 gene abnormality more frequent in CLL/SLL cases. According to Lin et al., *IGL* rearrangement occurs at a later stage of B-cell development; therefore, the translocation involving the chromosomal locus 22q11 may arise in relatively

Table 1. Details of B-cell lymphoma/leukemia with t(14;22)(q32;q11) by G-banding

Diagnosis	Karyotype	FISH	Authors/Reference [No]
CLL	46,XX,t(14;22)(q24-32;q11)	ND	Nowell et al./[7]
HCL	46,XY,del(1)(q32.1q42.3),t(14;22)(q32;q11.2)	ND	Nishida et al./[8]
CLL	46,XX,t(14;22)(q32;q11)	ND	Nowell et al./[9]
HCL-v	46,XY,t(14;22)(q32;q11)[8]/46,XY,del(12)(p13)x2,t(14;22)(q32;q11)[2]/46,XY[2].	ND	Brit-Babapulle et al./[10]
CLL	46,XX[16]/47,XX,+12[2]/47,idem,t(14;22)(q32;q11)[2]	ND	Gozzetti et al./[11]
DLBCL	52,XY,+Y,+der(3)t(3;9)(p11;p21),del(3)(q21),+7,+9,der(9)t(3;9)(q21;p21)x2,t(14;22)(q32;q11),der(15)t(1;15)(q21;p11),del(16)(p13).	t(14;22)(q32;q11)/IGH-IGL	Aamot et al./[2]
CLL/SLL	46,XX,t(14;22)(q32;q11)[3]/46,XX[12].	t(14;22)(q32;q11)/IGH-IGL	Aamot et al./[2]
MZBCL	46,XX,t(14;22)(q32;q11.2)[13]/46,XX[7].	t(14;22)(q32;q11)/IGH-IGL	Li et al./[6]
FL	46,XY,t(14;22)(q32;q11.2)[18]/47,X,X,?t(1;16)(q25;q12-13),+8[1]/46,XY[1].	t(14;22)(q32;q11)/IGH-IGL	Ours

The data were retrieved from the Table in the report by Li et al. [6] and were modified by us. FISH: fluorescence in situ hybridization; CLL/SLL: chronic lymphocytic leukemia/small lymphocytic lymphoma; HCL: hairy cell leukemia; HCL-v: hairy cell leukemia variant; DLBCL: diffuse large B-cell lymphoma; MZBCL: marginal zone B-cell lymphoma; FL: follicular lymphoma; IGH: immunoglobulin heavy chain; IGL: immunoglobulin light chain lambda; ND: Not done.

mature B-cells corresponding to the cell origin of typical CLL/SLL [16]. However, in our case, cells were negative for both surface and cytoplasmic expression of immunoglobulin kappa and lambda light chain by FCM. Although the reason for this negative expression is not clear, this result is consistent with a previous report [6].

Li et al. described in detail the clinical course of one patient with a systemic lupus erythematosus history, who was treated only with hydroxychloroquine, an immunosuppressive agent [6]. Patients with autoimmune diseases receiving immunosuppressive therapy are at a greater risk of developing lymphoproliferative diseases [17]. Despite the fact that our patient suffered from a hematological disease, he was also treated with the immunosuppressive agent CsA. Lymphoid neoplasms caused by the use of an immunosuppressive agent correspond to the subtype of OIIA-LPD, according to the WHO classification [5]. Methotrexate (MTX) is a common immunosuppressive agent used for the treatment of rheumatoid arthritis, and its use is often associated with the development of DLBCL and Hodgkin lymphoma, but rarely with FL. The rate of EBV positivity is about 40% [5]. In addition, immunosuppressed patients after transplantation are at high risk of developing PTLT for variable pathological subtypes; EBV positivity is frequent but variable. According to the population-based study of lymphoid neoplasms in Japan, only 2 out of 2098 were confirmed as new cases of LPD (annual incidence, 0.17 per 1 million people), and only 3 out of 2098 were confirmed as new cases of PTLT

(annual incidence, 0.25 per 1 million people) [14]. Even though the onset of lymphoid neoplasms in immunocompromised patients is rare, we hypothesized that the development of FL in our case was associated with the CsA treatment. Regarding the treatment of LPD and PTLT, we plan to decrease or stop the immunosuppressant, and follow up with rituximab alone (in case of CD20 positivity) or proceed to chemotherapy. Because our patient currently has no B symptoms, tumor growth, or organ disorders, we decided to observe the clinical course following the treatment policy for grade 1-2 FL.

Here, we report the first case of FL with the t(14;32)(q32;q11)/IGH-IGL translocation. However, because this is a case without precedence, it is necessary to carefully observe the clinical course of the disease until similar cases are described.

Disclosure of conflict of interest

None.

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