Immune Pancytopenia Associated with a Leukemic B-Cell Tumor Carrying t(14;18)(q32;q21) Translocation

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Abstract

We report a 75-year-old man who was initially suggested to have acute leukemia. The hemoglobin level was 3.8 g/dL, white cell count was 7,700/μL, with an absence of mature neutrophils and 69.0% leukemic cells, and platelet was 0.4×10⁴/μL. Coombs’ antiglobulin test was positive. Leukemic cells were CD5-, CD10+, CD20+, CD23- , and IgG/λdim+. The bone marrow consisted of normal hematopoietic precursors, whereas fluorescence in situ hybridization detected the BCL2/IgH fusion gene. He was treated with rituximab-containing chemotherapy, resulting in the resolution of pancytopenia. The underlying disease was a leukemic B-cell tumor with t(14;18)(q32;q21), and the pancytopenia was mainly caused by autoimmune mechanisms.

Key words: immune pancytopenia, leukemic B-cell tumor, t(14;18)(q32;q21) translocation, rituximab


Introduction

Autoimmune hemolytic anemia (AIHA), immune thrombocytopenia, and/or immune neutropenia can develop simultaneously in the absence of any underlying cause or in association with other diseases such as autoimmune diseases, lymphoproliferative disorders, or primary immunodeficiencies (1, 2). Rituximab, a monoclonal antibody for the CD20 antigen, has been introduced into the treatment of immune cytopenia with the aim to eliminate antibody-producing B cells (2-4). In one retrospective series of Evans syndrome, the long-term response rate to rituximab was reported to be 64%, and the use of rituximab for corticosteroid-resistant cases was warranted (1).

We herein describe a patient who presented with anemia, thrombocytopenia, and neutropenia. Although the peripheral blood picture initially suggested acute lymphocytic leukemia, an autoimmune condition in the setting of a B-cell tumor in the leukemic phase was revealed to be responsible for the critical level of pancytopenia. The clinical course and response to treatment including rituximab are presented.

Case Report

The patient was a 75-year-old man who first presented to the emergency department of our hospital with tarry stools and exertional dyspnea. On examination, he was pale and had many skin petechiae. No superficial lymph nodes were palpable. Computed tomography and ultrasonography of the body revealed equivocal lymphadenopathy within the axillary and paratracheal regions as well as mild splenomegaly; no abdominal lymphadenopathy was identified. Endoscopic examination of the upper gastrointestinal tract disclosed bleeding vessels at the lesser curvature of the mid-body of the stomach, where endo-clips were successfully placed. The hemoglobin level was 3.8 g/dL, white blood cell count was 7,700/μL, and platelet count was 0.4×10⁴/μL. The white cell differential was 1.5% basophils, 1.0% eosinophils, 0% mature neutrophils, 16.5% lymphocytes, 11.5% monocytes, 0.5% myelocytes, and 69.0% leukemic cells (Fig. 1A); erythroblasts appeared at a rate of 4 per 200 white cells. Reticulocytes comprised 7.3% of red cells. Biochemical data included: lactate dehydrogenase value was 161 IU/L; total
bilirubin value was 1.3 mg/dL; haptoglobin level was 174 mg/dL. Immunological data included the following: Coombs’ direct antiglobulin test was positive; the platelet-associated IgG value was 313.0 ng/10^7 cells (normal range, 5.0 to 25.0); the anti-nuclear antibody level was ×160; the CH50 value was below the level of detection (<15.0 U/mL); and the plasma C3 and C4 levels were 77 mg/dL (normal, 86 to 160) and 10 mg/dL (normal, 17 to 45), respectively. Soluble interleukin-2 receptor was 2,003 U/mL. Hepatitis B and C serologies were negative.

The bone marrow was composed of normal hematopoietic precursors: the erythroid series showed relative hyperplasia with mild megaloblastic change; myeloid lineage cells showed a normal differentiation to the metamyelocyte stage, whereas mature neutrophils were not found; and megakaryocytes were normal in number and morphology, with minimal platelet release at the periphery (Fig. 1B to D). Histological sections prepared from the bone marrow aspirates confirmed hypercellularity with proliferation of the three-lineage precursor cells. There was no region that had been occupied by neoplastic infiltration accounting for cytopenia at least in bone marrow clot section. Bone marrow biopsy was not performed due to severe bleeding tendency. Flow cytometry revealed that leukemic cells were CD5-, CD10+, CD19+, CD20-, CD23-, CD25-, HLA-DR+, Bcl-2-, and surface membrane IgG/κdim+ (Fig. 2A). The bone marrow included the B-cell population with an identical immunophenotype, comprising 12% nucleated cells. Although conventional cytogenetic analysis failed to identify a neoplastic clone, fluorescence in situ hybridization (FISH) using a kit for t(14;18)(q32;q21) chromosomal translocation detected fusion signals of the BCL2 and immunoglobulin heavy chain (IgH) genes in 18% of interphase nuclei prepared from the bone marrow aspirates (Fig. 2B). The discrepancy between the percentage of leukemic cells identified on the smear slide of the bone marrow (Fig. 1B) and those of monoclonal cells determined by flow cytometry/FISH may have been caused by contamination of the peripheral blood in the latter materials.

The laboratory data indicated that the underlying disease was a B-cell tumor predominantly involving the peripheral blood and pancytopenia was caused by the destruction of mature blood cells through autoimmune mechanisms. We initially started prednisone followed by weekly doses of rituximab. After the first dose of rituximab, leukemic cells quickly disappeared and transfusion-refractory anemia as well as thrombocytopenia were resolved (Fig. 3). By combining vincristine and cyclophosphamide with the support of granulocyte-colony stimulating factor, mature neutrophils appeared in the peripheral blood (Fig. 3). Coombs’ test turned to be negative. Additional cycles of R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) chemotherapy and maintenance treatment with weekly infusion of rituximab for 4 consecutive weeks every 6 months (5) led to the complete resolution of both hematological and immu-
B-cell chronic lymphocytic leukemia, there is evidence that cases of AIHA and cold agglutinin disease associated with tic B-cells themselves (10). On the other hand, in some mor (8, 9). The autoantibodies may be produced by neoplastic association with or following many types of lymphoid tu-

Figure 2. Flow cytometry and FISH data indicative of a B-cell tumor carrying t(14; 18)(q32; q21). (A) Flow cytometry of the peripheral blood white cells. The FSC-SSC scattergram showed a marked decrease of the granulocyte population. The cells of interest were CD5-, CD10+, CD19+, CD20+, CD23-; and Bcl-2+, and weakly expressed the surface membrane light chain; the associated heavy chain was γ (not shown). (B) FISH of t(14; 18)(q32; q21). The FISH probe was a mixture of the BCL2 (red) and IgH (green) gene probes. The interphase cell contains two yellow signals (arrows), indicating that the cell carries t(14;18).

Clinical laboratories (6, 7), these are less reliable than the di-

Figure 3. Clinical course and response to treatment. The treatment consisted of rituximab (R, 375mg/m²), vincristine (V, 1mg/m²), cyclophosphamide (C, 500mg/m²), and predni-
sone (maximum 1mg/kg/day, tapered appropriately). The values of hemoglobin (Hb, g/dL), white blood cell count (WBC, x10^3/μL), absolute neutrophil count (ANC, x10^3/μL), and platelet count (PLT, x10^3/μL) are shown. Endoscopic clipping treatment was performed on the first day. Abbreviations: RCC: red cell concentrate, PC: platelet concentrate, G-CSF: granulocyte-colony stimulating factor

Discussion

We described here an unusual case of B-cell tumor, which initially presented with pancytopenia mainly caused by auto-

immunity mechanisms and then responded well to rituximab and R-CVP chemotherapy. Although tests for anti-platelet and anti-neutrophil antibodies are performed in specialized clinical laboratories (6, 7), these are less reliable than the di-

rect antiglobulin test employed for the detection of IgG and/ or complement on circulating red cells. In the current case, the presence of normal hematopoietic precursors in the bone marrow strongly indicated that pancytopenia was caused by the increased destruction of mature blood cells. Although se-

vere anemia on admission was in part due to bleeding, we considered hemolysis was the major cause of anemia, as the anemia progressed even after the placement of endo-clips (Fig. 3).

Autoimmune cytopenia has been described to develop in association with or following many types of lymphoid tu-

mors (8, 9). The autoantibodies may be produced by neoplastic B-cells themselves (10). On the other hand, in some cases of AIHA and cold agglutinin disease associated with B-cell chronic lymphocytic leukemia, there is evidence that

the autoantibodies are produced by reactive polyclonal B cells that have undergone somatic hypermutation (3, 11, 12). In the present case, it seems unlikely that the neoplastic B cells carrying t(14;18) were capable of producing antibodies directed against three-lineage blood cells. Instead, it seems reasonable to suppose that polyclonal B-cells stimulated by the underlying B-cell tumor secreted a variety of autoanti-

bodies, thereby leading to immune pancytopenia.

The CD5/CD10+/CD23 immunophenotype and BCL2/IgH fusion gene suggest that the underlying B-cell tumor was follicular lymphoma (FL) (13); however, imaging studies in-

cluding positron emission tomography performed after the initiation of therapy failed to demonstrate unequivocal lymphoma lesions within the body. Although FL is primarily a nodal lymphoma showing indolent clinical behavior, the disease can manifest a leukemic picture at presentation; circu-

lating FL cells have notches or clefts, and correspond to centrocytes (14). On the other hand, the association of FL and immune cytopenia has been reported in the literature, and AIHA is the predominant type of cytopenia in FL (8).

In the present case, leukemic cells showed an immature morphology and the associated immune cytopenia affected
the three lineages to the critical level; nevertheless, achieving long-term remission with rituximab and R-CVP may indicate the low-grade nature of the underlying B-cell tumor.

The authors state that they have no Conflict of Interest (COI).

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References