Gamma Heavy Chain Disease with T-cell Large Granular Lymphocytic Leukemia: A Case Report and Review of the Literature

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Abstract

Gamma heavy chain disease (gHCD) is a rare lymphoproliferative disorder characterized by the production of a truncated immunoglobulin heavy chain. Although some cases of gHCD are concurrent with other lymphoid neoplasms, few have been reported. We herein present the case of a 73-year-old woman with gHCD and T-cell large granular lymphocytic leukemia. A multiparameter flow cytometry analysis revealed neoplastic cells that were positive for CD28, a marker of T-cell activation, the anti-apoptotic antigen of neoplastic plasma cells, CD38 and CD45. The results of this multiparameter flow cytometry analysis may contribute to furthering the understanding of the clinicopathological features of gHCD.

Key words: gamma heavy chain disease, T-cell large granular lymphocytic leukemia, composite lymphoid malignancy, multiparameter flow cytometry analysis


Introduction

Gamma heavy chain disease (gHCD) is defined, based on the 2008 World Health Organization (WHO) classification, as an indolent B-cell malignancy. gHCD is characterized by the production of an abnormal incomplete gamma immunoglobulin heavy chain, which lacks a light chain (1). Since Franklin first described gHCD in 1964, fewer than 150 cases have been reported in the literature (1-4). Due to the rarity of gHCD, the mechanisms underlying its carcinogenesis have not yet been elucidated in detail. However, gHCD has been associated with a wide variety of underlying disorders. Approximately one third of gHCD cases have a history of an autoimmune disorder, with the most frequent being rheumatoid arthritis (5, 6). Furthermore, in some cases gHCD occurs with other lymphoid neoplasms, frequently Hodgkin or non-Hodgkin lymphoma (2, 3). The mechanism responsible for composite cases currently remains unknown.

T-cell large granular lymphocytic leukemia (T-LGLL) is also a rare lymphoid malignancy. The majority of cases occur in elderly patients (7). The main sites of involvement are the peripheral blood and bone marrow, while lymphadenopathy is uncommon. Morphologically, neoplastic lymphocytes have moderate to rich cytoplasm with granules. Immunophenotypically, most cases are positive for CD3 and CD8, while rare cases are positive for CD3 and CD4. Over 80% of T-LGLL cases are positive for CD16 and CD57. The clinical course is typically indolent with a median survival of 13 years (8).

We herein present a case of gHCD accompanied by T-LGLL and also conduct a literature review.

Case Report

A 73-year-old woman was admitted to our hospital with anemia, fatigue, and lymphocytosis. She had no medical history of an autoimmune disorder. A physical examination revealed no lymphadenopathy or hepatosplenomegaly and computed tomography scans also showed no evidence of...
lymphadenopathy or hepatosplenomegaly. The laboratory data on admission were as follows: white blood cell=104×10^9/L, lymphocytes=81.0% (almost all were atypical lymphocytes), hemoglobin=8.6 g/dL, platelet count=15.2×10^9/L, lactate dehydrogenase=223 IU/L, immunoglobulin G (IgG)=2,710 mg/dL, IgA=132 mg/dL, IgM=68 mg/dL, serum free kappa-light chain=34.5 mg/dL, serum free lambda light chain=48.6 mg/dL, and kappa/lambda ratio=0.71 (usual range: 0.26-1.65) (Table 1). Bone marrow aspirates showed two types of lymphocytes: atypical lymphoplasmacytic cells and/or plasma cells (Fig. 1A), and large granular lymphocytes (Fig. 1B). A bone marrow biopsy specimen also revealed the diffuse invasion of two types of atypical lymphoid cells (data not shown): lymphoplasmacytic cells that were positive for CD138 and IgG and negative for kappa and lambda, and small to mediumsized atypical lymphocytes with moderate to abundant cytoplasm, which were positive for CD3 and CD8, and negative for CD4. Serum protein electrophoresis revealed an M-spike in the β fraction (Fig. 2A). Serum immunofixation electrophoresis showed a monoclonal band in the IgG and Fc fragment bands (arrows), but not in the kappa or lambda light chain band. A multiparameter flow cytometry analysis was performed to clarify the immunophenotypic features of the neoplastic cells of gHCD. The neoplastic cells detected by CD38 gating were positive for CD45 and CD28 (Fig. 3), and negative for CD19, 20, and 56. CD45 gating was then conducted to determine the immunophenotypic features of the large granule lymphocytes. The results showed that the neoplastic cells were positive for CD3, CD8, CD16, and CD57, and negative for CD4 (data not shown). A conventional cytogenetic analysis revealed a normal karyotype, while a Southern blot analysis for the T-cell receptor Cβ1
gene rearrangement was positive. Therefore, the patient was diagnosed with a composite lymphoid neoplasm with both gHCD and T-LGL leukemia based on the 2008 WHO classification at the time of her first diagnosis (1, 7). Her clinical course was indolent for 6 years and specific chemotherapy was not required, although red blood cell transfusions were occasionally performed.

**Discussion**

gHCD has a wide variety of clinical features, with most patients exhibiting systemic symptoms. The Mayo Clinic has conducted large scale retrospective studies in recent years. Their findings indicated that the incidence of gHCD was higher in females, and that the median age at the time of diagnosis was 68 years. The disease was complicated by autoimmune diseases (26%), lymphadenopathy (34%), hepatomegaly (4%), splenomegaly (30%), or bone marrow involvement (30%). The median survival time was 7.4 years (2). In the present case, the patient was 73 years old and without a history of an autoimmune disorder. Her clinical course was indolent for 6 years.

The concurrence of gHCD and other lymphoid neoplasms has previously been reported (2, 3, 9-12), with composite cases of gHCD accounting for approximately one third of the total number of gHCD cases (2, 3). However, at the time of writing, there have been no detailed descriptions of the clinical background of composite cases. Furthermore, most cases in the literature were classified by old criteria and lacked sufficient histopathological and cytogenetic information. Table 2 summarizes the composite cases based on the literature since 2000. Six studies were available on composite cases. Although Hodgkin lymphoma has been previously reported in composite cases, a wide range of disorders have been described in recent years. Bieliauskas et al. separated gHCD patients into 2 groups (3): group 1 consisted of typical cases (according to the WHO classification), while group 2 included composite cases. The frequency of autoimmune disorders in groups 1 and 2 was 100% and 20%, respectively, while the frequency of adenopathy was 87% and 20%. The present case was therefore classified as group 2.

The mechanisms responsible for the carcinogenesis of gHCD currently remain unclear, and the mechanisms in composite cases are unknown. Küppers et al. attributed the pathogenesis of composite lymphoproliferative disorders to 1) a chance occurrence or an underlying genetic predisposition, or 2) an environmental risk factor such as an immunological effect, including autoimmune disease (13). Zhang et al. hypothesized that the etiology of their case of gHCD with T-LGLL was related to the relationship between T-LGLL proliferation and gHCD as a result of strong antigen stimulation or immune dysregulation; in other words, a putative antigen triggered the activation and proliferation of B cells and T cells (12).

Few studies have conducted a flow cytometry analysis in patients with gHCD (3). In the present case, the neoplastic
cells were found by flow cytometry to be positive for CD28, 38, and 45, but negative for CD19 and 20. Flow cytometry also indicated that the neoplastic cells had the immunophenotypical features of plasma cells. CD28 is a well-known antigen that is widely expressed on T cells. It is also an essential co-stimulatory signal for T-cell activation, proliferation, effector function, and enhanced survival following the binding to its ligands of CD80 and/or CD86. CD28 was recently shown to be expressed on neoplastic plasma cells, and this expression was found to be upregulated with disease progression. CD28-positive plasma cells have been shown to account for 26% of all plasma cells in multiple myeloma at diagnosis, 59% at medullary relapse, 93% at extramedullary relapse, and 100% in secondary plasma cell leukemia (14). The PETHEMA/GEM Cooperative Study Groups identified CD28 positivity as being a poor prognostic factor in myeloma patients (15). Bahlis et al. reported that the in vitro activation of CD28 in myeloma cells triggered downstream NF-kB signaling and protected against apoptosis (16). Although these findings suggest that CD28 may be crucially involved in the activation of neoplastic plasma cells, there is currently no evidence to support the role of CD28 in gHCD. The results of multiparameter flow cytometry may contribute to a deeper understanding of the clinicopathological features of gHCD.

In conclusion, gHCD may develop as a composite lymphoid neoplasm. The pathogenesis of gHCD currently remains unclear; however, the multiparameter flow cytometry analysis may contribute to a clearer understanding of its clinicopathological features. Further studies are warranted.

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

References


