Gamma heavy chain disease associated with large granular lymphocytic leukemia: A report of two cases and review of the literature

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Objective and importance: Gamma heavy chain diseases (γHCD) and large granular lymphocyte (LGL) leukemia are two rare lymphoproliferative diseases, respectively with B and T phenotype. Both γHCD and LGL leukemia share some similar clinical features, such as cytopenias, splenomegaly, and recurrent infections. Association of these two diseases is exceptional and suggest pathogenic link. We report two cases of γHCD associated with T-LGL leukemia.

Clinical presentation: Patient 1 was a 70-year-old woman, with lymphoplasmacytic lymphoma, refractory to chlorambucil-rituximab treatment. She developed during the follow up a γHCD with T-LGL leukemia, unresponsive to melphalan, thalidomide, and steroids, requiring supportive care. Patient 2 was a 40-year-old man with chronic severe asymptomatic neutropenia, revealing both γHCD and T-LGL leukemia. He is still well without any treatment nor complications, with 7 years follow up.

Conclusion: Several types of B lymphoproliferative disease are associated with LGL leukemia. Although exceptional, this association of two rare lymphoproliferative disorders, with a different phenotype, does not seem fortuitous.

Keywords: Gamma heavy chain disease, Franklin disease, Large granular lymphocyte leukemia

Introduction

Gamma heavy chain disease (γHCD) is a rare B-cell lymphoproliferative disease characterized by the production of a truncated gamma heavy chains devoid of light chains. Less than 200 cases have been reported in the literature.2,3

Large granular lymphocyte (LGL) leukemia is another rare lymphoproliferative disorder usually associated with autoimmune disease. LGL leukemia is of T phenotype or less often NK. The diagnosis of LGL leukemia is based on the presence of chronic (>6 months) and expanded circulating LGL (>0.5 × 10⁹/l).4,5

T-LGL leukemia has a CD3+/TCRaβ+/CD4−/CD8+/CD5dim phenotype as NK LGL leukemia is CD2+CD3−CD16+CD56+. While LGL leukemia is usually described as an indolent disease, about half of the patients require treatment because of cytopenias, such as anemia, and life-threatening infections associated with neutropenia.6 There is no standard treatment for patient with LGL leukemia. Immunosuppressive therapy remains the foundation of treatment, including single agents methotrexate, oral cyclophosphamide, and cyclosporin A.

We report two cases of γHCD associated with LGL leukemia. Although exceptional, this association of two rare lymphoproliferative disorders, with a different phenotype, does not seem fortuitous.

Case 1

A 70-year-old woman, without significant medical history, presented with a pancytopenia. Hemoglobin was 8.7 g/dl, platelets count 99 × 10⁹/l, and neutrophils 0.99 × 10⁹/l. Physical examination disclosed a splenomegaly. Serum protein electrophoresis showed polyclonal hypergammaglobulinemia at 23.2 g/l, with a small monoclonal IgM component. Blood test identified a type 2 cryoglobulinemia (without clinical symptoms). Serologic tests for HIV, hepatitis B and C virus were all negative. Antinuclear antibodies and rheumatoid factor were also negative. Bone marrow aspirate revealed lymphoplasmacytic infiltrate, with
final diagnosis of lymphoplasmacytic lymphoma. Chlorambucil and rituximab were ineffective, and she required repeated blood transfusions.

Few years later, pancytopenia and splenomegaly worsened. Bone marrow examination still showed a lymphoplasmacytic infiltrate, with 15% of abnormal clonal plasma cells population and 35% of lymphocytes (3% of CD3+ cells). T lymphocytes had phenotypic characteristics of LGL cells (CD3+/CD8+/TCRαβ+/CD5−) with clonal T-cell receptor gene rearrangement (polymerase chain reaction, PCR). Serum protein electrophoresis disclosed a single IgG peak devoid kappa or lambda light chain. Serum IgG level was 35.1 g/l, IgA 0.18 g/l, and IgM 0.37 g/l, with serum beta-2 macroglobulin level at 14.1 mg/l. Antinuclear antibodies, rheumatoid factor, antineutrophilic cytoplasm antibodies, and cryoglobulinemia were negative. Treatment with melphalan–prednisone–thalidomide was ineffective and poorly tolerated. Then, she required supportive care with blood transfusions.

Case 2
A 40-year-old man, without significant medical history, presented with hepatosplenomegaly and bicytopenia, discovered on a routine blood test. Hemoglobin was 12 g/dl, platelets count 170 × 10^9/l, and neutrophils 0.56 × 10^9/l. Peripheral blood smear analysis disclosed LGLs expansion, which represented 70% of lymphocytes (1.295 × 10^9/l). Blood lymphocytes immunophenotyping confirmed clonal expansion of T-LGL with a CD3+, CD8+, CD57+ phenotype, with clonal T-cell receptor gene rearrangement (PCR). Serum protein electrophoresis showed a gamma heavy chain without light chains, with a peak of 19.4 g/l. Serum IgG level was 25.8 g/l, IgA was 0.49 g/l, and beta-2 macroglobulin was 6.2 mg/l. Blood tests for cryoglobulinemia and antinuclear antibodies were negative, as serological tests for HIV, hepatitis B and C virus, and HTLV1 virus. Thoracic, abdominal, and pelvic computed tomography showed hepatosplenomegaly and multiple small lymph nodes. FDG-PET scan was normal. Bone marrow aspirate revealed 15% of lymphocytes and 5% of plasma cells. Bone marrow biopsy disclosed moderate polyclonal plasma cell expansion and excess of little mature T-lymphocytes CD8+ CD57+.

With 7-year follow-up, the patient remained asymptomatic. Despite neutropenia about 0.5 × 10^9/l, he did not develop infectious or autoimmune complications.

Discussion
Association of γHCD and LGL leukemia is exceptional. In the review of literature, we found only five cases of this association, four of them without clinical and biological description.2,3,7 Clinical characteristics of our two patients and the single case report are shown in Table 1.

Both γHCD and LGL leukemia share some similar clinical features, such as cytopenias, splenomegaly, and recurrent infections. It could result in a diagnostic dilemma that could influence treatment decision.

γHCD is often associated with low-grade lymphoproliferative disease, mainly lymphoplasmacytic lymphoma, and less often, other B lymphoproliferative diseases, like marginal-zone lymphoma, plasmacytoma, Hodgkin disease, etc. It could also be associated with autoimmune disease. However, the coexistence of γHCD with T lymphoproliferative disease is exceptional. In the review of literature, we found only five cases of this association, four of them without clinical and biological description.2,3,7 Clinical characteristics of our two patients and the single case report are shown in Table 1.

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Table 1 Clinical characteristics of three patients with γHCD disease and LGL leukemia

| Age | 70 | 40 | 69 |
|---|---|---|---|
| Sex | F | M | F |
| Splenomegaly | ++ | + | + |
| Hepatomegaly | + | + | + |
| Lymphadenopathy | – | – | – |
| Infections | – | – | – |
| Hb (g/dl) | 8.7 | 12 | ND |
| PNN (per mm³) | 999 | 560 | 500 |
| Platelets (per mm³) | 99 000 | 170 000 | 89 000 |
| Monoclonal peak (g/l) | ND | 16 | ND |
| IgG (g/l) | 35.1 | 37.3 | 34.5 |
| IgA (g/l) | 0.18 | 0.49 | ND |
| IgM (g/l) | 0.37 | 0.82 | ND |
| Light chains | – | – | – |
| β2 microglobulin (mg/l) | 14.1 | 6.2 | 13.9 |
| Autoimmune disease | – | – | – |
| Other hematologic malignancies | Indeterminate lymphoproliferative disease | – | – |
| Treatment | Melphalan–prednisone–thalidomide | No treatment | Splenectomy cyclophosphamide–prednisone |
| Response | No response | Partial response | |
Several types of B lymphoproliferative disease are associated with LGL leukemia. The most common is monoclonal gammopathy of undetermined significance. Association with chronic lymphocytic leukemia, hairy cell leukemia, Hodgkin disease, multiple myeloma, lymphomatoid granulomatosis, and myelodysplasia has also been described. Some authors speculated that LGL leukemia may represent anti-tumor surveillance reflecting an exaggerated clonal expansion in the context of polyclonal anti-tumor response.

Association of this both lymphoproliferative disease, one with B phenotype, and the other with T phenotype, could be the result of strong common antigen stimulation, mediated by an infectious agent or autoantigen.

Polyclonal hyperggammaglobulinemia and multiple autoantibodies present in 37% of patients with LGL leukemia suggest a defect in B-cell immunoregulation. It has been demonstrated that LGL cells from healthy patients are able to inhibit immunoglobulins production, but defective or immature LGL cells may fail to suppress B-cells and thus permit the formation of multiple autoantibodies or the overproduction of immunoglobulins. Development of clonal B-cell disorders could be the fact of LGL cells immunological dysregulation.

Another hypothesis suggests that B-cell dysregulation could be responsible of LGL cells clonal expansion. Several cases of LGL leukemia appeared after rituximab treatment have been reported. In our case no. 1, rituximab was ineffective and LGL leukemia appeared secondarily.

In conclusion, we report a rare association of two lymphoproliferative diseases with different phenotypes, but with similar clinical presentation. In our cases, evolution was quite different with aggressive and refractory disease in the first patient, and spontaneously indolent course without complications for the other one. Both diseases are rare, and a fortuitous association would be quite exceptional. γHCD has to be added to B lymphoproliferative disease associated with LGL leukemia spectrum.

Disclaimer statements
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