



Letter to the Editor

Gamma Heavy Chain Disease Associated with T-Cell Large Granular Lymphocyte Lymphoproliferative Disorder: Case Report and Literature Review

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To the editor.

Heavy chain diseases (HCDs) are rare B-cell neoplasms characterized by the production of a monoclonal immunoglobulin composed of the only heavy chain without corresponding light chains.

These alterations are caused by the loss of a large portion of the constant region C1 domain of the heavy chain, which prevents the normal link to the light chain.¹ Monoclonal heavy chains do not result in a monoclonal peak at routine serum protein electrophoresis and are detectable only by immunofixation. The 2017 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues includes three variants of HCD: gamma-HCD (with IgG production), mu-HCD (with IgM production), and alfa-HCD (with IgA production). Gamma-HCD (γ HCD), also known as Franklin's disease, is a mature B-cell neoplasm, usually with plasmacytic differentiation, first described by Franklin in 1964. It is a rare adult disease that may involve the most common lymph nodes, bone marrow, and spleen. Histologically γ HCD has a broad morphologic spectrum and may resemble various lymphoproliferative disorders. Some cases are difficult to classify and do not fall into a distinct WHO-defined entity. Most patients show systemic symptoms such as anorexia, weakness, fever, weight loss, recurrent bacterial infections, organomegaly, and increasing circulating lymphocytes and plasma cells. Autoimmune manifestations are also common (25-70% of cases), frequently preceding the diagnosis of gamma-HCD, and they are maybe due to an autoimmune response stimulating the capability of the abnormal gamma heavy chain. The clinical course is highly variable, from indolent to rapidly progressive, depending on the extension of the disease (localized or disseminated). For this reason, treatment was reserved for symptomatic patients in the largest series of HCD.² We present the case of a patient with γ HCD and concomitant T-cell large granular lymphocyte (T-LGL) disorder. Other six

similar cases were described in the literature before.³⁻⁵ A 65-year-old woman came to our observation because of pancytopenia at routine blood tests, with hemoglobin 9.6 g/dL, white blood cells $4.78 \times 10^9/L$, neutrophils $1.6 \times 10^9/L$, lymphocytes $2.47 \times 10^9/L$ and platelets $47 \times 10^9/L$. She complained of mild widespread joint pain, especially in the upper limbs and pelvis. LDH levels and liver and kidney function were normal and physical examination was negative for superficial adenopathy or splenomegaly. A blood smear showed an increase in LGL, equal to 42% of total lymphocytes, while PB flow cytometry revealed 9% B-lymphocytes CD19+, CD20+, CD22+, CD200+, CD38+, and CD5- with a small aberrant population lacking expression of light chains (5% of total lymphocytes). Natural killer (NK) and T-NK cells were 1% and 3%, respectively. T4/T8 ratio was about 1.64%. Bone marrow (BM) aspirate showed an increase in lymphocytes (34%) and plasma cells (8%), along with preserved hemopoietic maturation and absence of blasts. The cytogenetic study displayed a normal female karyotype. BM biopsy identified 20% interstitial infiltrate of small B-lymphocytes CD20+/CD5-/CD23-/CyclinD1-/DBA.44-/IgM-/IgD along with mature plasma cells CD138 and IgG positive and negative for IgM, IgD and both kappa and lambda light chains, similarly as observed with flow cytometry (**Figure 1a**). Moreover, an additional 10% interstitial and intrasinusoidal T-cell infiltrate CD3+, CD8+, CD57+/-, and CD4- consistent with T-LGL expansion was found (**Figure 1b**). Molecular analysis on PB and BM showed a monoclonal rearrangement of the T-cell receptor gamma chain gene (TCR), confirming the clonal nature of the T-LGL component and, accordingly to PB morphologic and immunophenotypic data, the diagnosis of T-LGL lymphoproliferative disorder. Serum electrophoresis showed hypogammaglobulinemia at 0.35 g/dL with increased alfa-2-region at 1.6 g/dL but no clear monoclonal component (**Figure 3a**). IgA and IgM levels were reduced, while

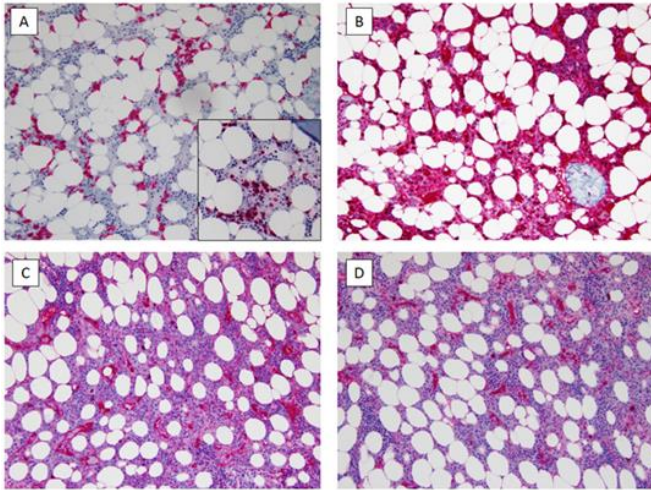


Figure 1. Histologic features of the B-cell and plasma cell component, consistent with gamma-heavy chain disease. CD138 (A) and CD20 (A, inset) show a mild, interstitial infiltrate made up of mature plasma cells and small B-lymphocytes. The plasma cell component is positive for IgG (B) but does not express light chains (C: kappa; D: lambda).

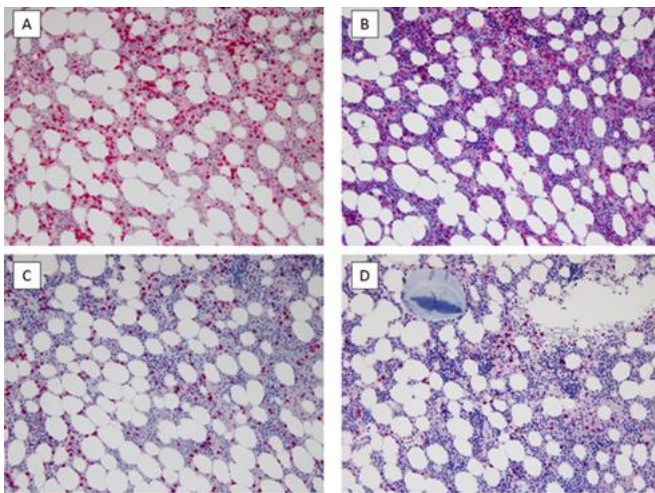


Figure 2. Histologic features of the T-cell component, consistent with T-cell large granular lymphocyte lymphoproliferative disorder. CD3 (A) highlights a discrete interstitial and intrasinusoidal T-cell component, made up by small cells with prevailing cytotoxic CD8+ phenotype (B: CD4; C: CD8) and partial expression of CD57 (D).

about IgG, the subclasses IgG1, IgG2, and IgG3 were increased, with a normal level of IgG4. Nevertheless, serum immunofixation identified a monoclonal IgG heavy chain without corresponding light chains (Figure 3b), also present in the urine, according to flow cytometric analysis. A total body CT scan resulted negative for lymphadenopathy and hepatosplenomegaly. Due to the clinical history of arthralgia, the patient was tested for autoantibodies: only a low titer of IgM cryoglobulin was found, while ANA, ENA, C3, C4, anti-ccp, and anti-DNA native resulted negative. The final diagnosis was gamma-HCD with concomitant T-LGL disorder. For the lack of symptoms, the patient was kept under watchful control without any specific treatment. In February 2022, our patient developed a COVID-19 infection but remained

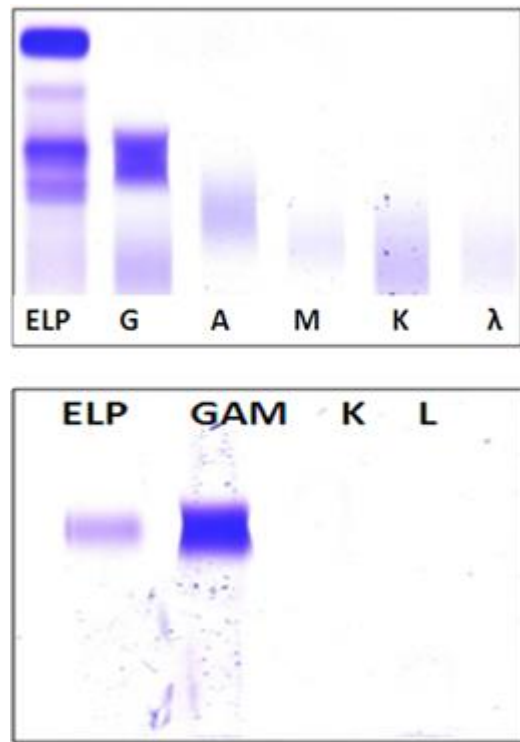


Figure 3. Serum electrophoresis (A) and serum immunofixation (B).

asymptomatic despite the immunosuppression linked to his disease. At 36 months after diagnosis, she only suffers mild widespread joint pain. We observed spontaneous improvement of PB cells count (hemoglobin 10.3 g/dL, white blood cells $5.46 \times 10^9/L$, neutrophils $2 \times 10^9/L$, lymphocytes $2.91 \times 10^9/L$, platelets $198 \times 10^9/L$), normal renal function, increased 24-hour proteinuria and quite stable IgG values at 3 g/dL. The occurrence of γ HCD and, even more, the association with T-LGL is rare. Our literature review identified only six patients with γ HCD and concomitant T-LGL disorder, one of which was without clinical and biological description.³⁻⁵ T-LGL is a persistent (more than six months) clonal expansion of cytotoxic T-cells that can arise as a primitive disease or associate with autoimmune disorders and/or B cell lymphoproliferative diseases.⁶⁻⁹ As shown in Table 1, they were middle-aged adults investigated to study cytopenia, splenomegaly, or lymphadenopathy. Clinically, patients have either claimed few or several systemic symptoms, and histologically, there was a broad morphologic spectrum. The therapeutic approach used in the cases reported depends on clinical and histological findings with a favorable outcome. Cytopenia, more precisely neutropenia, is the most common clinical finding, but up to 60% of cases are asymptomatic. Moderate splenomegaly is frequent, while lymphadenopathy is very rare. The clinical course is usually indolent and non-progressive; since the association of γ HCD and T-LGL disorder is exceptional, currently, there are no defined therapeutic strategies; “watch and wait” could be a valid attitude with accurate clinical observation,

Table 1. Clinicopathological features of gamma-HCD associated with T-LGL LPD reported in the literature.

Case [ref]	Age/Sex	Clinical features	Serum Electrophoresis	PB	MFC	PCR	Further investigations	Diagnosis	Therapy	Follow-up
1 [3]	73/W	lymphadenopathy	monoclonal pattern of gamma heavy chain in the absence of corresponding light chains	/	malignant lymphoma	/	Lymph node biopsy	lymphoplasmacytic lymphoma and γ HCD	CP CVP FND R	42 months
2 [4]	59/W	neutropenia	monoclonal pattern of gamma heavy chain in the absence of corresponding light chains	LGLs increasing	T-cells phenotype	Clonal T-cell population	Spleen biopsy	splenic diffuse red pulp small B-cell lymphoma and T-LGL	splenectomy	13 months
3 [4]	45/W	anemia and neutropenia	monoclonal pattern of gamma heavy chain in the absence of corresponding light chains	LGLs increasing	NK-cells phenotype	Clonal T-cell population	Bone marrow biopsy and aspirate	MGUS and chronic NK-cell lymphocytosis	MTX + CTX	37 months
4 [5]	70/W	pancytopenia splenomegaly	small monoclonal IgM component and single IgG peak devoid kappa or lambda light chain	LGLs increasing	T-cells phenotype	Clonal T-cell population	Bone marrow aspirate	lymphoplasmacytic lymphoma + T-LGLs clonal infiltrate	RC MPT	Death
5 [5]	40/M	hepato-splenomegaly and neutropenia	monoclonal pattern of gamma heavy chain in the absence of corresponding light chains	LGLs expansion	clonal expansion of T-LGL	Clonal T-cell population	Bone marrow aspirate	moderate polyclonal plasma cell expansion and excess of little mature T-lymphocytes	No treatment	7 years
6 [6]	69/W	neutropenia and splenomegaly	IgG peak without accompanying light chain	LGLs expansion	clonal expansion of T-LGL	Clonal T-cell population	Bone marrow aspirate	T-cell large granular lymphocytic leukemia and γ HCD	Splenectomy, prednisone, CTX	4 months

RC, Chlorambucil and rituximab; MPT, melphalan– prednisone–thalidomide, HCD gamma heavy chain disease; CTX cyclophosphamide; CVP cyclophosphamide, vincristine, and prednisone; FND fludarabine, mitoxantrone, and dexamethasone, R rituximab.

especially for asymptomatic patients. Currently, the prognosis of these patients remains unclear. However, the somatic mutations on genes involved in the pathogenesis of these entities (i.e., STAT3) may play a role in the course of the disease.¹⁰ In conclusion, we report a rare association of two lymphoproliferative diseases, one with B phenotype and the other with T phenotype. As postulated in previous reports, it may be a non-casual coexistence since it could result from strong common antigen stimulation mediated by an infectious agent or autoantigen. However, the exact etiopathogenetic substratum is still to be clarified.

Further investigations of the pathogenesis of γ HCD with or without T-LGL disorders in a larger study cohort could be of value.

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Competing interests: The authors declare no conflict of Interest.

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