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# Leukaemia Section
## Short Communication

# Gamma heavy chain disease

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## Abstract

Gamma heavy chain disease (HCD) is a rare variant of HCD, a family of syndromes associated with or representing a B cell malignancy variant. The hallmark characteristic and the pathogenic mechanism of HCD is the synthesis of a mutant, misfolded immunoglobulin heavy chain (IgH) incapable of either reaching a quaternary conformation with the immunoglobulin light chain (IgL) and/or being degraded by the proteasome. The isotype of mutated IgH (α,γ or μ) determines the nomenclature of HCD subtypes. Less than 200 cases of gamma HCD have been published. Gamma HCD predominantly affects women in their 5$^{th}$-6$^{th}$ decade of life, and a pre-existing autoimmune disease is present in about a quarter of patients. Rheumatoid arthritis (RA) is the most commonly associated autoimmune disorder, but association with systemic lupus erythematosus (SLE), Sjögren syndrome, myasthenia gravis, vasculitis and idiopathic thrombocytopenic purpura (ITP) has been reported. The vast majority of patients with gamma HCD have a localized or systemic lymphoplasmacytic lymphoma. Gamma HCD patients can present with disseminated lymphomatous involvement, localized (medullary or extramedullary) lymphomatous disease or with no apparent lymphomatous involvement. Disseminated lymphoma is the most common form, being diagnosed in 57-66% of patients with gamma HCD. These patients typically present with B symptoms such as fever, fatigue, and unintentional weight loss. Circa half of the patients have generalized lymphadenopathy, splenomegaly, and more rarely hepatomegaly. Twenty-five percent of patients with gamma HCD present with either localized medullary disease or localized extramedullary disease. Lymphomatous infiltration is present only in the bone marrow in the former, and in extranodal sites in the latter. The most common site of extranodal involvement is the skin, although involvement of thyroid and parotid, oropharynx, and gastrointestinal tract has been reported. Gamma HCD patients with no identifiable lymphoma at diagnosis (~9-17%) typically have a pre-existing autoimmune condition, with associated symptoms and signs. Definitive diagnosis is based on the identification of a gamma immunoglobulin heavy chain (IgH) without associated Ig light chain (IgL) assessed using serum or urine protein electrophoresis (SPEP or UPEP, respectively) and immunofixation (IF).

Treatment ranges from expectant management for patients with no detectable lymphoma, to local surgical or radiation therapy for localized extramedullary disease, and combination therapies for systemic and localized medullary disease. Prognosis is very good in patients with no detectable lymphoma or completely treated, limited extramedullary lymphoma; patients with systemic disease can have a rapidly aggressive or more indolent course with highly variable median survival (1 month to over 20 years).

**Keywords**

gamma heavy chain disease; B cell malignancy; Franklin disease; immunoglobulin heavy chain

## Identity

**Other names**

Franklin disease; γ HCD

**Note**

Gamma heavy chain disease (HCD) is the second most common form of HCD, a rare family of syndromes associated with or representing a B cell malignancy variant.(Franklin et al., 1964; Fermand et al., 1989) The hallmark characteristic and the pathogenic mechanism of HCD is the synthesis of a mutant, misfolded immunoglobulin heavy chain (IgH), which is incapable of forming a quaternary conformation with the immunoglobulin light chain (IgL) and/or of being degraded by the proteasome. The isotype of mutated IgH (α,γ or μ) determines the nomenclature of HCD subtypes.(Munshi et al., 2008; Bianchi et al., 2014)

# Clinics and pathology

The clinical presentation of gamma HCD varies according to disease subtype.(Wahner-Roedler et al., 2003; Bieliauskas et al., 2012) Patients with systemic disease typically present with constitutional symptoms such as fever, unintentional weight loss, and malaise. Generalized lymphadenopathy, splenomegaly and hepatomegaly are present in about half of the patients. Patients with localized medullary disease typically present with cytopenia, most commonly a normocytic, normochromic anemia. Lymphomatous infiltration of the skin is the most common presentation in patients with extramedullary, localized gamma HCD, but thyroid or parotid gland infiltration, as well as oropharyngeal, gastrointestinal or conjunctival involvement, have been reported.(Witzig and Wahner-Roedler, 2002) Autoimmune, Coombs-positive, hemolytic anemia or thrombocytopenia can be present. Occasionally, circulating monoclonal plasma cells or plasmacytoid lymphocytes can be detected, but features of chronic lymphocytic leukaemia (CLL) or plasma cell leukemia are rarely present. Recently, an association between gamma HCD and large granular lymphocytic leukemia and extranodal marginal zone lymphoma has been reported.(Mittal et al., 2015; Wahbi et al., 2016) The clinical presentation of patients with the gamma HCD variant without lymphoma at diagnosis is due to the underlying autoimmune diathesis.(Bieliauskas et al., 2012). The abnormal Ig gamma heavy chain can be detected by IF of SPEP or UPEP; however, the pathologic IgH typically migrates in the -β region of the protein electrophoresis, making detection often difficult. In contrast to alpha and mu HCD, the mutant gamma IgH is often detected in the urine, due to its low molecular weight as a monomer relative to dimeric or pentameric form of IgA and IgM heavy chain, respectively.

To further aid in diagnosis, treatment of serum/urine with 2-mercapto-ethanol can be used to elicit detection of free light chain by dissociating Ig polymers. Elevation of total serum IgG in the setting of normal serum free light chains (FLC) further supports this diagnosis.

Typically, histopathologic analysis of gamma HCD-associated lymphoma shows a mixed population of small lymphocytes, plasmacytoid lymphocytes, and plasma cells, resembling plasmacytic lymphoma.(Presti et al., 1990; Ho et al., 2014) Occasionally, a more polymorphic infiltrate of immunoblasts, eosinophils, histiocytes and atypical Reed-Sternberg cells can be present; or alternatively, the infiltrate can be mostly composed of small B lymphocytes resembling mucosa-associated lymphoid tissue lymphoma (MALT) or splenic marginal zone lymphoma. Immunohistochemistry (IHC), in situ hybridization (ISH) or flow cytometry analysis reveals IgG positive, CD19+, CD20+, CD5-, CD10- B cells that lack IgL chain.

Neoplastic plasmacytoid cells express post germinal center Mum/IRF4, while plasma cells are positive for CD38 and CD138. Molecular analysis shows that gamma HCD lymphoma lack MYD88 L265P mutation, a pathognomonic mutation observed in over 90% cases of lymphoplasmacytic lymphoma.

## Disease

Topography (ICD-O3): Disseminated form: C77.8, C42.2, C22.0; Lymph nodes of multiple regions, spleen, liver. localized medullary disease: C42.1; Bone marrow.

Localized extramedullary disease: C44.9, C07.9, C10.9, C69.0, C73.9, C26.9; Skin nos, parotid gland, oropharynx, conjunctiva, thyroid gland, gastrointestinal tract nos.

## Phenotype/cell stem origin

Most typical pathologic variant is lymphoplasmacytic lymphoma.

## Etiology

Deletions, insertions or point mutations in the constant 1 (CH1) domain of the IgH are acquired during the process of somatic hypermutation.

These mutations typically result in: 1- inability to bind and reach a stable quaternary structure with IgL chain; 2- inability to bind to the chaperone heat shock protein 78 (HSP 78), which mediates proteasomal degradation of free IgH.(Goossens et al., 1998) As a result, free IgH can be detected in both serum and urine.

Pathogenesis is unknown. Autoimmune disease is present in ~25% of patients and typically precedes by many years the onset of gamma HCD.(Wahner-Roedler et al., 2003)

## Epidemiology

Predominantly women with median age at diagnosis 51-68 years.

## Clinics

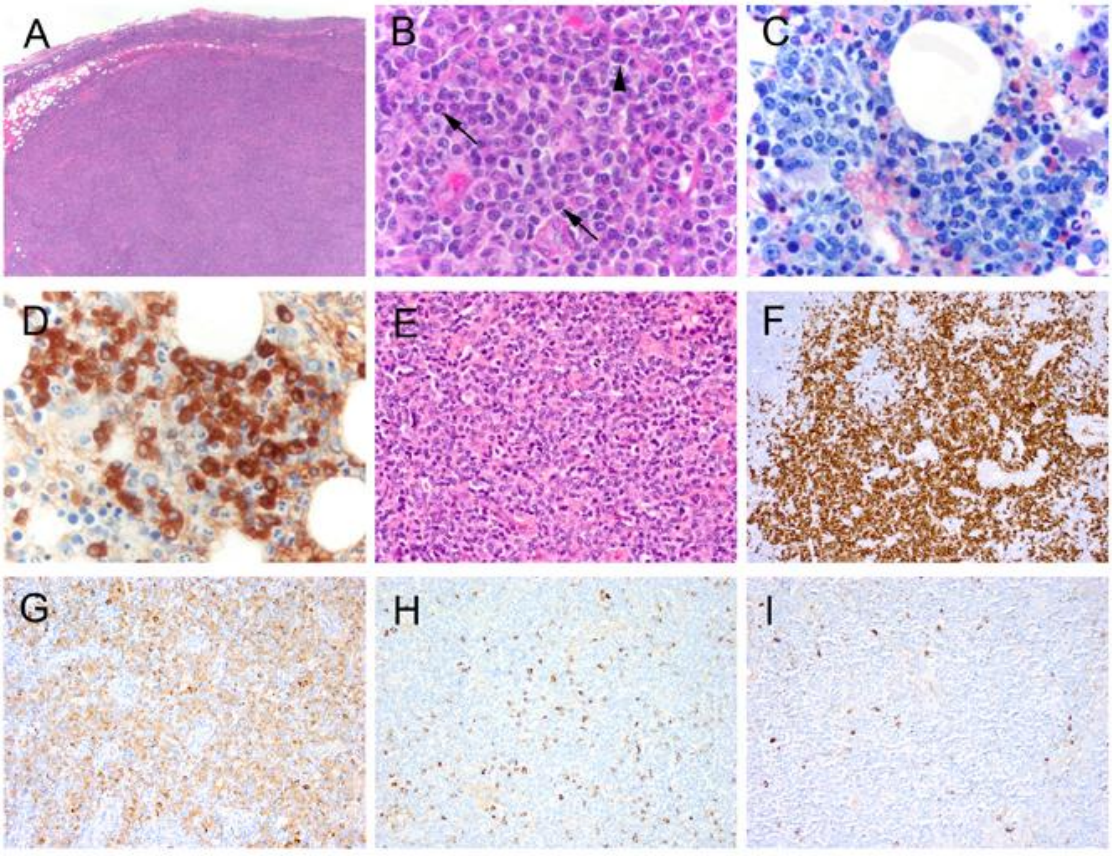
The clinical presentation of gamma HCD varies according to disease subtype.(Wahner-Roedler et al., 2003) Patients with systemic disease typically present with constitutional symptoms such as fever, unintentional weight loss, and malaise. Generalized lymphadenopathy, splenomegaly and hepatomegaly are present in about half of the patients. Patients with localized medullary disease typically present with cytopenia, most commonly a normocytic normochromic anemia. Lymphomatous infiltration of the skin is the most common presentation in patients with extramedullary, limited gamma HCD, but thyroid or parotid gland infiltration, as well as oropharyngeal, gastrointestinal or conjunctival involvement, have been reported.(Bianchi et al., 2014) Autoimmune, Coombs-positive, hemolytic anemia or thrombocytopenia can be present. Occasionally, circulating monoclonal plasma cells or plasmacytoid lymphocytes can be detected upon flow cytometry analysis of peripheral blood; however, features of CLL or plasma cell leukemia are rarely present.

The clinical presentation of patients with the gamma HCD variant without lymphoma at diagnosis is associated with the underlying autoimmune diathesis.(Fermand et al., 1989)

## Pathology

The lymphoproliferative infiltrate associated with gamma HCD is heterogeneous.

A mixed population of small lymphocytes, plasmacytoid lymphocytes, and plasma cells, resembling plasmacytic lymphoma is the predominantly observed histologic subtype. Occasionally, a more polymorphic infiltrate of immunoblasts, eosinophils, histiocytes, and atypical Reed-Sternberg cells can be present; or alternatively, the infiltrate can be mostly composed of small B lymphocytes resembling MALT or splenic marginal zone lymphoma.




**Panel A:** Low magnification H&E staining of lymph node biopsy of a patient with gamma HCD characterized by a polymorphous infiltrate of small, mature appearing and plasmacytoid lymphocytes, as well as plasma cells. **Panel B:** Higher magnification H&E stain of pathologic specimen in A outlining a medium-to-large size cell with prominent eosinophilic nuclei, consistent with an immunoblast (arrow head), and two mature plasma cells (arrows). **Panel C-D:** Wright's-Giemsa stain of a bone marrow biopsy of a patient with gamma HCD highlights a lymphoplasmacytic infiltrate (panel C), IHC staining positive for IgG (panel D). **Panel E-I.** Low magnification H&E staining of a lymph node biopsy of a patient with gamma HCD showing a lymphoplasmacytic infiltrate (panel E), which stains positive for CD138 (panel F) and IgG (panel G), but negative for κ (panel H) and λ (panel I) on iHC. Reproduced with permission from Bianchi et al. Oncology, 2014;28(1):45-53.

Immunohistochemistry (IHC), in situ hybridization (ISH) or flow cytometry analysis of identifies IgG positive, CD19+, CD20+, CD5-, CD10- B cells that lack IgL chain.(Harris NL, 2008) Neoplastic plasmacytoid cells express post germinal center Mum/IRF4, while plasma cells are positive for CD38 and CD138.(Ho et al., 2014) Molecular analysis shows that gamma HCD lymphoma lacks MYD88 L265P mutation, a pathognomonic mutation observed in over 90% cases of lymphoplasmacytic lymphoma.(Treon et al., 2012; Hamadeh et al., 2014)

## Treatment

Treatment is not standardized and depends on the disease subtype. In all cases, if an underlying autoimmune disease is present, it should be treated accordingly. Expectant management with clinical and laboratory surveillance is indicated in patients with no overt lymphoma. Patients with localized, extramedullary disease can be successfully treated surgically or via radiation therapy, with curative intent. Systemic chemotherapy is recommended for patients presenting with localized medullary and disseminated disease. A variety of regimens used in DLBCL, lymphoplasmacytic lymphoma, and multiple myeloma are efficacious in gamma HCD including: CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) plus/minus rituximab depending on CD20 expression; fludarabine and rituximab; chlorambucil; rituximab; melphalan and prednisone; as well as bortezomib and prednisone.(Inoue et al., 2012) The predominant lymphocytic subtype and IHC staining can inform treatment.

Infectious prophylaxis and early treatment are key in this immunosuppressed population. Prognosis is excellent in patients with no detectable lymphoma or completely treated, limited extramedullary lymphoma; patients with systemic disease can have either a rapidly aggressive or more indolent course, with median survival varying from 1 month to over 20 years.(median 7.4 years ).

## Evolution

Variable.

## Prognosis

The clinical course is variable, depending on subtype. Outcome is very good in patients without lymphoma, in whom prognosis is related to underlying autoimmune disease. Similarly, patients with completely treated, localized extramedullary lymphoma have a very good prognosis. Patients with systemic disease can have either a rapidly aggressive or more indolent course, with median survival varying from 1 month to over 20 years (median 7.4 years).

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