

# Rare Case of a Patient Presenting with Parathyroid Hormone-Related Peptide Mediated Hypercalcemia and IgG Heavy Chain Disease: Case Report and Review of Literature

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## Abstract

**IgG Heavy Chain Disease ( $\gamma$ HCD) is a rare plasma cell disorder. Hypercalcemia related to plasma cell dyscrasias is related to non-PTHrP related mechanisms. Here we describe the first case of a patient with  $\gamma$ HCD and PTHrP related hypercalcemia. Methods: Patient case derived from chart review from 2011 to 2015. Literature review performed searching PubMed 1968-current. Results: The patient was diagnosed with hypercalcemia with elevated PTHrP and exclusion of other etiologies of hypercalcemia. She was diagnosed with ( $\gamma$ HCD) by M-spike 0.64 g/dL, IFE showing a broad band of IgG heavy chain, without associated light chains and severe depression of the non-monoclonal IgG. Serum immunoglobulins demonstrated elevated IgG (2110 mg/dL), normal IgA (46 mg/dL) and decreased IgM (<21 mg/dL). Bone marrow biopsy showed 5% PCs, non-clonal by kappa/lambda, but exclusive for IgG by IHC, without any staining for IgA or IgM. The patient was started on therapy with improved hypercalcemia and PTHrP levels. Conclusions: This is the first reported case of  $\gamma$ HCD presenting with PTHrP related hypercalcemia. Given that skeletal involvement is uncommon in  $\gamma$ HCD, hypercalcemia secondary to  $\gamma$ HCD may at times be a PTHrP driven phenomenon and we recommend that this test be ordered in such cases.**

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## Keywords

**Hypercalcemia, Parathyroid Hormone-Related Peptide (PTHrP), Franklin Disease, Heavy Chain Myeloma**

### 1. Background

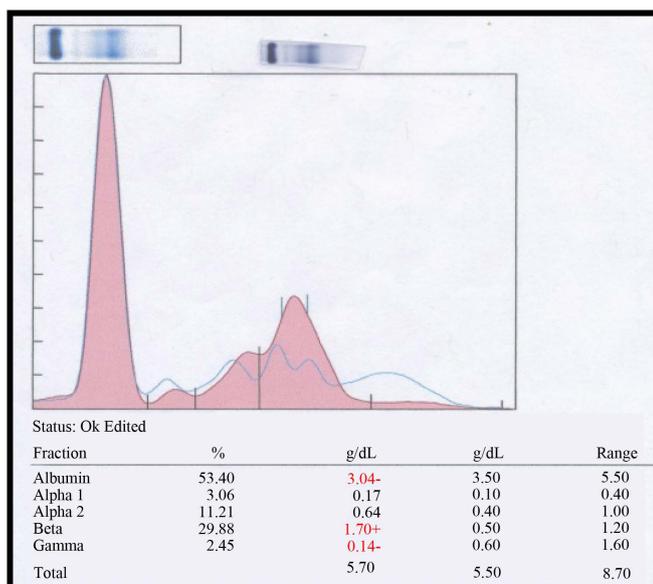
IgG Heavy Chain Disease ( $\gamma$ HCD) is a rare and often lymphoplasmacytic neoplasm that produces an abnormally truncated gamma heavy chain protein that lacks associated light chains [1]. It is a heterogeneous entity that occurs within a wide spectrum of lymphoproliferative disorders. Consequently,  $\gamma$ HCD displays a wide range of clinicopathologic characteristics. Here we describe a unique case of a patient diagnosed with Hodgkin’s lymphoma and diagnosed several years later with  $\gamma$ HCD who presents with PTHrP related hypercalcemia.

### 2. Methods

A retrospective chart review of one patient from 2011 to 2015 including detailed clinical history, laboratory data, imaging, pathology and treatment response was performed. PubMed, EMBASE and the Cochrane Library databases were searched for English language abstracts that included mesh terms “IgG Heavy Chain Disease” or “franklin disease” from 1968-current. 79 abstracts were retrieved. 38/79 abstracts were available for review of clinicopathologic information.

### 3. Results

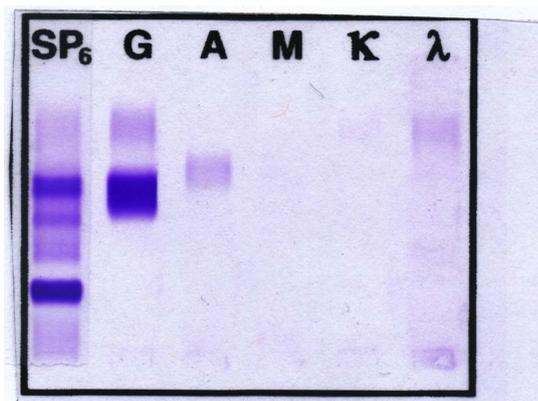
This is a case of a 60-year-old woman diagnosed in 1992 with stage IIA Hodgkin’s lymphoma, treated with total nodal radiation with recurrence in 1997 then treated with 6 cycles of ABVD achieving complete remission. On March 2011 the patient was then found to have hypercalcemia (11.0 mg/dL) and renal failure (1.29 mg/dL). Workup for the hypercalcemia revealed suppressed PTH (<3 pg/ml), elevated ionized calcium (6.1 mg/dL) elevated parathyroid related peptide (38 pg/ml), normal vitamin D and ACE levels. Complete blood count was normal. Serum protein electrophoresis (SPEP) showed M-spike of 0.9 g/dL. Immunofixation electrophoresis (IFE) demonstrated an IgG monoclonal immunoglobulin without a corresponding light chain (Figure 1). Free serum kappa and lamda light chains were within normal limits. Serum IgG was elevated (4678 mg/dL) with



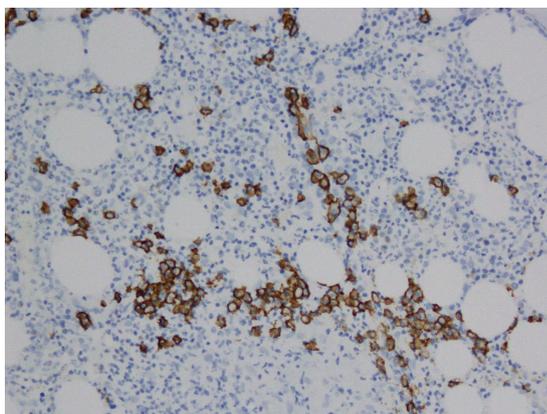
**Figure 1.** SPEP demonstrating M-spike. The blue trace shows a normal SPEP pattern.

normal IgA (127 mg/dL), and low IgM (39 mg/dL). Beta-2 microglobulin was elevated (14.3 mg/L) also. The patient was seen by hematology for monoclonal gammopathy and hypercalcemia. Since the most common mechanism of hypercalcemia for multiple myeloma is bone turnover driven and not PTHrP related a solid tumor work up was done including CT chest/abdomen/pelvis, bone scan, bone survey, mammography, pelvis ultrasound which were all negative. Bone marrow biopsy was performed in November 2011 showing 10% plasma cells (PC) by CD138, non-clonal by kappa/lambda staining. Despite zoledronic acid therapy and IV fluids for hypercalcemia, her renal function and hypercalcemia continued to worsen for the next couple of months. A kidney biopsy was performed in April, 2012 and revealed acute and chronic tubulointerstitial nephritis with secondary glomerulosclerosis, mild interstitial fibrosis and tubular atrophy suggestive of sarcoidosis so the patient was placed on a course of prednisone with transient improvement in calcium and renal function but patient lost to follow up.

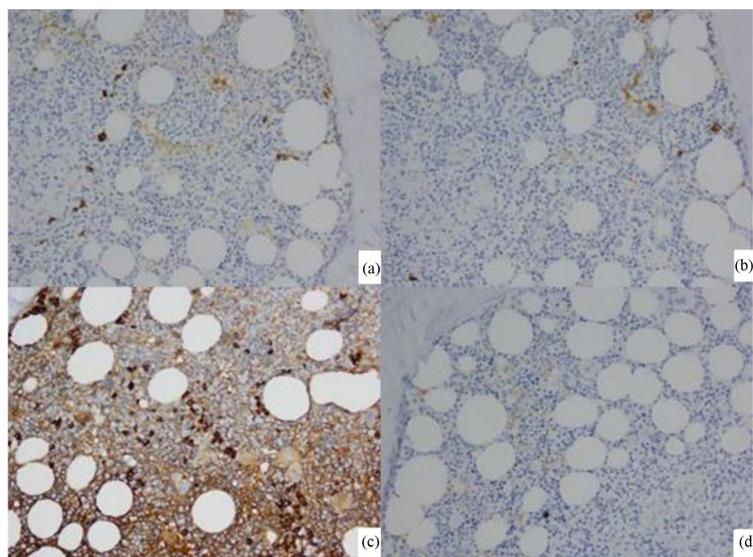
She presented in emergency room in April 2013 with altered mental status. She was found to have hypercalcemia (12.0 mg/dL), renal failure (1.55 mg/dL). SPEP revealed M-spike 0.64 g/dl. IFE displayed a broad band of IgG heavy chain, without associated light chains and severe depression of the non-monoclonal IgG. Serum immunoglobulins demonstrated similar results with elevated IgG (2110 mg/dL), normal IgA (46 mg/dL) and decreased IgM (<21 mg/dL). Bone marrow biopsy showed 5% PCs (**Figure 2**), CD 138 positive by IHC (**Figure 3**), non-clonal by kappa/lambda-but exclusive for IgG by IHC, without any staining for IgA or IgM (**Figure 4**). Cytogenetics were normal. Based on the constellation of findings and similarity to prior workup the patient was diagnosed with IgG heavy chain disease. She received 5 cycles of cytoxan, dexamethasone, bortezomib. PTHrP declined along with her IgG level and M-spike. Due to compliance issues, therapy was changed in multiple occasions receiving Revlimid, Carfilzomib, Bendmustine with different responses as showed in **Table 1**.



**Figure 2.** IFE demonstrating monoclonal IgG without corresponding light chain.



**Figure 3.** Bone marrow biopsy 200×, CD138+ plasma cells arranged in an interstitial and perivascular pattern.



**Figure 4.** (a) 200 $\times$ , few plasma cells positive for kappa light chain by immunohistochemistry. (b) 200 $\times$ , few plasma cells positive for lambda light chain by immunohistochemistry. (c) 200 $\times$ , majority of the plasma cells show positive staining for IgG by immunohistochemistry. (d) 200 $\times$ , plasma cells are negative for IgM by immunohistochemistry.

**Table 1.** Treatments and responses.

Day	6/27/11	5/14/13	6/12/13	12/04/13	1/29/14	2/24/14	3/5/14	7/23/14	1/28/15	2/15/2015	3/18/15	7/1/15
Treatment	Observation	Observation Worsening renal function.	After 1 <sup>st</sup> cycle cyBORd	After last 5 <sup>th</sup> cycle of cyBORd <sup>1</sup>	Started on Revlimid	On Revlimid <sup>2</sup>	Started on Carfilzomib	On Carfilzomib <sup>3</sup>	Not on therapy	Started on Bendamustine due to increasing IgG	On Bendamustine <sup>4</sup>	Not on treatment since march 2015.
IgG levels	4678	2470	1650	1570	1930	1900	1080	1040	2180	N/A	1760	2360

<sup>1</sup>CyBORd: velcade-cytoxan-dexametason. Discontinued due to noncompliance. <sup>2</sup>Revlimid discontinued due to patient noncompliance. <sup>3</sup>Received 6 months of Carfilzomib and then discontinued on 12/2014 due to side effects. <sup>4</sup>Bendamustine stopped per patient request on March 2015. Not further treatment.

## 4. Discussion

The clonal disease underlying Gamma heavy-chain disease ( $\gamma$ HCD) is heterogeneous mix, including a wide spectrum of lymphoproliferative disorders. Most cases are described as a neoplasm of lymphocytes and plasma cells similar to lymphoplasmacytic lymphoma (LPL) [1] [2] however  $\gamma$ HCD has been reported in association with marginal zone lymphoma [1], T cell LGL, [3], monoclonal gammopathy of unknown significance [1] [4] [5], plasmacytoma [1] [4] [6] [7], Waldenström's macroglobulinemia [4] [8], Hodgkin lymphoma [1] [4] [9], chronic lymphocytic leukemia (CLL) [4] [9]. In addition to arising in the setting of a lymphoproliferative neoplasm, patients frequently have a pre-existing autoimmune disorder such as rheumatoid arthritis [1] [4] [9] [10] [11], Sjögren's syndrome [4] [12], systemic lupus erythematosus [1] [4] [9]. Patients with  $\gamma$ HCD can present with various clinical and pathologic features, which usually precede the diagnosis of  $\gamma$ HCD.

### 4.1. Clinical Presentation

$\gamma$ HCD occurs equally in males in females. One case series by Femand *et al.* reported 8/16 (50%) of patient to be female and they cite in literature review 47% female predominance. Two more recent series, however, report female predominance. In one series 11/13 (85%) were female [1] and 15/23 (65%) were female in another series [9]. Patients with  $\gamma$ HCD are predominantly middle aged. Median age at diagnosis reported in largest case series ranges 59 [1] to 68 [9] and  $\gamma$ HCD can occur in younger patients as there are 6 reports in children and adults less than 20 years old [4]. At diagnosis lymphadenopathy is present 34% to 61% of patient [1] [4] [9]. Splenomegaly is also common feature with 30% to 75% patient affected [1] [4] [9]. There is a variety of different extranodal sites with reported involvement including thyroid [2] [4] [6] [7] [9], renal [2] [13]-[17] skin [14] [18], skeletal

muscle [16], stomach [19], submaxillary gland [20], tongue [9], vocal cord [9], lung and pleura [9], and parotid gland involvement [21].

## 4.2. Associated Disorders

Autoimmune disorders are common in  $\gamma$ HCD with one literature review reporting 26% of patients with  $\gamma$ HCD having autoimmune disorder [4]. Rheumatoid arthritis is the most commonly reported [4] [10] [11]. Other autoimmune diseases reported include Sjögren's syndrome [12], systemic lupus erythematosus [1], vasculitis [4], livedo reticularis [1], thyroiditis [4] myasthenia gravis [22], idiopathic thrombocytopenic purpura [4]. Numerous reports exist of  $\gamma$ HCD occurring in the setting of infection such as progressive multifocal leukoencephalopathy [23], pachymeningitis [24], herpes zoster [9] disseminated herpes simplex [9], cryptococcal meningitis [9], orbital cellulitis [29]. Infections were not exclusive to patients treated with immunosuppressive agents for autoimmune disorders. Last,  $\gamma$ HCD patients have been described in the setting of neurosensory dysfunction including polyneuropathy and peripheral neuropathy [4].

## 4.3. Laboratory Findings

Anemia is a common finding with one series reporting 9/16 (56%) patients being anemic [4] and a literature review showed 48% of patients reported to be anemic [4]. Coombs positive autoimmune hemolytic anemia [9] [25] has been reported with one series demonstrating 2/23 (9%) patients with a positive coombs [9]. Leukocyte count is frequently normal [4] [9] but leukocytosis and leukopenia can occur as well [4] [9]. Eosinophilia was present in 8/16 (50%) in one series [4] and 4/23 (17%) in another [9]. Thrombocytopenia is present in 4/23 (17%) in one series [9], and 4/16 (25%) in another series [9]. Hypocomplementemia was noted in one case [14]. Hypercalcemia has been reported in several cases [4] [9] [26]. In a literature review, hypercalcemia was reported in 5 cases with osteolytic lesions diagnosed in 2 [4]. Hypercalcemia was noted in 2/23 (9%) of cases in one series [9] and there were no mention of osseous lesions in the individual reports. Of note the incidence of osseous lesions is low  $\gamma$ HCD with one series reporting 0/5 (0%) and another 2/12 (17%) with bony involvement [4] [9]. Based on these observations, hypercalcemia in  $\gamma$ HCD may less often be osteoclast driven as in multiple myeloma, and perhaps other mechanisms are in play

## 4.4. Pathologic Characteristics

Pathologic diagnosis of  $\gamma$ HCD represents a challenge for many reasons. First  $\gamma$ HCD may be underdiagnosed and classified elsewhere since it arises in the setting of many lymphoproliferative disorders with specific WHO criteria. Also,  $\gamma$ HCD is a rare entity with less than 200 reports in the literature and the majority of cases was diagnosed and classified using outdated classification schemes [1]. Last, the WHO 2008 classification is conflicted as  $\gamma$ HCD is classified as both a variant of LPL and as a distinct disorder [27].

## 4.5. Protein Findings

Monoclonal spike on serum protein electrophoresis was present in 19/23 (83%) in one series [9] and 12/28 (40%) in one literature review [4]. The presence of  $\gamma$ -heavy chain is documented in the serum of all 23/23 (100%) patients in one series [9] in 16/16 (100%) of cases in another [4] and 13/13 (100%) in another [1] by immunofixation. Median serum IgG level was reported as 1940 mg/dL (range 462 - 5280 mg/dL) in one series [9] and less than 1g/dL (range <0.5 g - 20 g/dL) in another [4]. M-spike in the urine was present in 19/23 (83%) of patients in one series [9].

## 4.6. Bone Marrow Findings

Marrow involvement is common and morphologically described as a lymphoplasmacytoid proliferative process [4] [9]. Some reports of increased plasma cells [4], CLL [4], mast cells [28]. One series reported having 7/23 (32%) patients having marrow involvement [9] another 10/16 (63%) [4]. In previous series, bone marrow involvement was reported in 58% - 63% of cases [4].

## 4.7. Histopathology Findings

$\gamma$ HCD has no specific histological pattern [4] and there is a great diversity with lymphoplasmacytoid proliferation

being most common [4]. However,  $\gamma$ HCD has been described in association with a plasmacytic process (as in our patient), CLL [4]. Furthermore  $\gamma$ HCD has been reported to arise in the setting of non-Hodgkin lymphoma of various morphologic types, Hodgkin lymphoma, amyloidosis, myelodysplastic syndrome [4] [29] [30].

#### 4.8. Chromosomal Findings

Chromosomal abnormalities are uncommon in  $\gamma$ HCD with no frequent abnormality identified [1] [4] [9]. There are isolated reports of trisomy 7 [31], trisomy 3q [1], trisomy 21 [32], complex karyotype [4] and aneuploidy in two cases [33] [34].

#### 4.9. Immunophenotypic Findings

Immunophenotypic findings are reported inconsistently in the literature. One recent study by Bieliausjas *et al.* reported complete Immunophenotypic and molecular cytogenetic analysis on 13 patients [1]. In this series 13/13 (100%) of patients were CD 20 positive, and 13/13 (100%) were CD5, CD 10 negative. In this series 6/8 (75%) tested positive for CD 138 [1]. 9/13 patients were negative for Immunohistochemistry for  $\kappa/\lambda$  (1). Clonality by polymerase chain reaction (PCR) performed for IGH was negative in 13/13 (100%) of cases and PCR for IGK was positive in (5/10) 50% of cases [1]. Fluorescence in situ hybridization (FISH) for t(IGH), t(MALT), +18q, t(BCL6) in 10/10 (100%) of cases were negative [1]. FISH for +3q was positive in 1/10 (10%) of cases. It is interesting to note the high degree of CD 20 positivity in this series and there are many cases reported in the literature [1] [4] [9] [10] [35]. This is important since CD 20 positive patients may benefit from immunotherapy with rituximab.

#### 4.10. Clinical Outcomes

Given  $\gamma$ HCD is a heterogeneous entity and its clinical course is expected to be quite variable as well. The clinical course can vary from an asymptomatic stable process to an aggressive rapidly progressive malignancy [4]. In some cases  $\gamma$ HCD protein is the only abnormality and no treatment is necessary [4]. In fact, spontaneous disappearance of the  $\gamma$ HCD protein has been documented in several instances [28] [36]. For example, one patient with  $\gamma$ HCD was observed and had stable disease after 134 months follow up [1]. When an underlying malignancy exists, therapy should be directed at the underlying hematologic malignancy and pathologic findings. A wide variety of chemotherapies with or without rituximab have been used successfully including rituximab monotherapy with resolution of adenopathy at 22 month follow up [1], fludarabine and rituximab resulting in partial response (PR) with one cycle [35], second line fludarabine with complete remission (CR) [37], fludarabine, mitoxantrone, dexamethasone (FND) with PR [9], melphalan and prednisone resulting in PR [14], rituximab, etoposide, cyclophosphamide, prednisone, procarbazine resulting in PR [10], sustained CR 20 years with chlorambucil prednisone [9], cyclophosphamide, vincristine, prednisone with PR [9], bortezomib and prednisone with CR [1]. Even autologous stem cell transplant with high dose melphalan has been reported where the patient achieved stable disease after 26 months [38]. In one series where 16/23 patients were treated (14 chemotherapy, 1 splenectomy, 1 thyroidectomy) 6 had CR, 10 had SD. Of the 7 untreated patients 4 had SD, 3 patients died of disease within 15 months. The median survival in this series was 7.4 years [9].

### 5. Conclusion

This case highlights the challenge of correctly recognizing and diagnosing  $\gamma$ HCD which is due to its highly heterogeneous clinicopathologic presentation most common being a lymphoproliferative disorder, autoimmune disease or both. It represents a diagnostic challenge since it arises in the setting of many lymphoproliferative disorders, and the WHO 2008 classification is conflicted as  $\gamma$ HCD is classified as both a variant of LPL and a distinct disorder [27]. Another critical point related to this case is that kappa/lambda staining, the primary mechanism of determining plasma cell clonality, is not useful in exclusively heavy chain disease and can, in such cases, obscure the diagnosis of this malignancy. This is the first reported case of IgG heavy chain disease presenting with PTHrP related hypercalcemia further added to the diagnostic challenge because PTHrP related hypercalcemia is more common in solid tumors and uncommon in hematologic malignancies. Given that skeletal involvement is uncommon in  $\gamma$ HCD, hypercalcemia secondary to  $\gamma$ HCD may at times be a PTHrP driven phenomenon; we will recommend that this test be ordered in such cases. Because  $\gamma$ HCD is a heterogeneous entity, the

choice of therapy should target the underlying entity and pathologic findings. In our case, the etiology of the  $\gamma$ HCD is a plasma cell clone and this is what we target with therapy, with good clinical effect.

## Disclaimer

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