Conditions associated with polyclonal hypergammaglobulinemia in the IgG4-related disease era: a retrospective study from a hematology tertiary care center

Hypergammaglobulinemia, the overproduction of immunoglobulins by plasma cells, is broadly divided into monoclonal and polyclonal subtypes. Monoclonal paraproteins are typically associated with plasma cell neoplasms and B-cell lymphomas such as monoclonal gammopathy of undetermined significance (MGUS), plasma cell myeloma, primary amyloidosis, chronic lymphocytic leukemia and lymphoplasmacytic lymphoma. Some rare conditions such as Schnitzler syndrome (IgM), TEMPI syndrome (IgG), and Clarkson/capillary leak syndrome (IgG) can also demonstrate a monoclonal paraprotein in the absence of a known clonal lymphocyte or plasma cell population.

Polyclonal hypergammaglobulinemia (PHGG) has historically been associated with a variety of conditions including liver disease,[1] infections such as that by human immunodeficiency virus,[2] hematologic disorders such as idiopathic neutropenia,[3] nonhematologic malignancies, and autoimmune conditions such as Sjögren syndrome.[4] To date, the largest study of PHGG examined 148 patients seen at the Mayo Clinic with PHGG ≥30 g/L as determined by serum protein electrophoresis.[5] In that retrospective study, liver disease was the most common associated condition at 61%, followed by autoimmune conditions (22%), chronic infections (6%), hematologic disorders (5%), and nonhematologic malignancies (3%). Since that study was published in 2001, a new and important cause of PHGG has emerged, namely IgG4-related disease (IgG4-RD).[6] IgG4-RD is associated with elevated serum total IgG and a disproportionate elevation in IgG4 compared to other subclasses, often with beta-gamma bridging.[6] We sought to characterize the causes of PHGG in the IgG4-RD era by examining consecutive patients referred to a hematology tertiary care center with PHGG.

We reviewed the medical records of all patients seen by the Vancouver General Hospital Hematology group between October 1, 2016 and November 1, 2017 who had polyclonal hypergammagloublinemia ≥20 g/L. We abstracted the patients' demographics, medical history, and laboratory values. This retrospective case series was conducted under ethical approval from the University of British Columbia Clinical Research Ethics Board.

The patients' confirmed diagnoses were organized into one of the following categories: (i) liver disease (including viral hepatitis); (ii) autoimmune conditions; (iii) hematologic disorders, including hematologic malignancies; (iv) nonhematologic malignancies; (v) infectious disease (excluding viral hepatitis); (vi) IgG4-RD; and (vii) other.

We identified 66 patients with PHGG, as defined by a polyclonal increase in gamma globulins >20 g/L on serum protein electrophoresis (normal 7-14 g/L) or IgG >20 g/L determined by immunonephelometry (normal 7-16 g/L), of whom 50 had IgG subclass data. Fifty-three of these 66 patients had a single diagnosis in one of the predetermined categories and seven had a diagnosis categorized as "other." The demographic and clinical characteristics of these 66 patients are summarized in Table 1.

Autoimmune diseases were the most commonly diagnosed conditions in our cohort, with 21 such diagnoses. There were four cases of Sjögren syndrome, one case of Sjögren syndrome with connective tissue disease overlap, one case each of autoimmune vasculitis, systemic lupus erythematosus, polymyalgia rheumatica, rheumatoid arthritis, inflammatory arthritis, orbital inflammatory syndrome, adult onset Still disease, and eosinophilic granulomatosis with polyangiitis. The remaining eight cases consisted of undifferentiated connective tissue disease.

Fourteen of the 66 patients had a hematologic condition as the most likely cause of their PHGG. There was one case of T-cell large granular lymphocytic leukemia, two cases of MonoMAC syndrome (GATA2 deficiency), and one case each of Rosai-Dorfman-Destombes disease, polycythemia vera, cutaneous plasmacytosis, suspected Ras-associated autoimmune leukoproliferative disorder (RALD), chronic lymphocytic leukemia, valvular hemolysis, iron-deficiency anemia, autoimmune neutropenia, chronic myelogenous leukemia, anemia secondary to occult gastrointestinal bleeding, and hepatosplenic T-cell lymphoma.

IgG4-RD was the third most common diagnostic category in this cohort. There were 11 histologically confirmed cases of IgG4-RD with an additional two cases for which clinical suspicion was strong, but there was not a definite histopathological diagnosis. Lymphadenopathy was the most common clinical presentation, affecting eight of these 13 patients. Four patients had renal involvement with IgG4-related tubulointerstitial nephritis, four patients had biliary involvement, three had type 1 autoimmune pancreatitis, three had chronic sinusitis, three had ocular involvement, one patient had lymphoplasmacytic interstitial lung disease, and one patient had IgG4-prostatitis.

Liver disease was diagnosed in seven of the patients in our cohort. Of these, three had steatosis, two had an active hepatitis B infection, one had autoimmune hepati-

Table 1. Characteristics of the 66 patients with polyclonal hypergammaglobulinemia, grouped by class of diagnosis.

Characteristic	Total (n=66)	Liver disease (n=7)	Autoimmune (n=21)	Hematologic disorder (n=14)	Malignancy (n=1)	Infection (n=3)	IgG4-RD (n=13)	Other (n=7)
Median age (years)	64	56	54	66	73	60	65	66
Age range (years)	20-92	52-92	20-80	22-87	(73)	58-73	39-85	39-82
Female sex (%)	61	57	95	71	0	33	31	14
Hepatomegaly (%)	7.6	0	4.8	21	0	0	0	14
Splenomegaly (%)	14	29	9.5	29	0	0	0	14
Lymphadenopathy (%)	33	14	29	29	0	33	62	29

IgG4-RD: IgG4-related disease.

tis, and one had cirrhosis likely secondary to nonalcoholic steatohepatitis.

Malignancy was diagnosed in only one patient, who had an invasive squamous cell carcinoma of the lung. Infection was determined to be the primary associated condition in three patients, two of whom had human immunodeficiency virus infection and one had culture-negative endocarditis. Seven of the patients had uncertain diagnoses and were classified in the "other" group.

All 13 of the patients with IgG4-RD had elevated

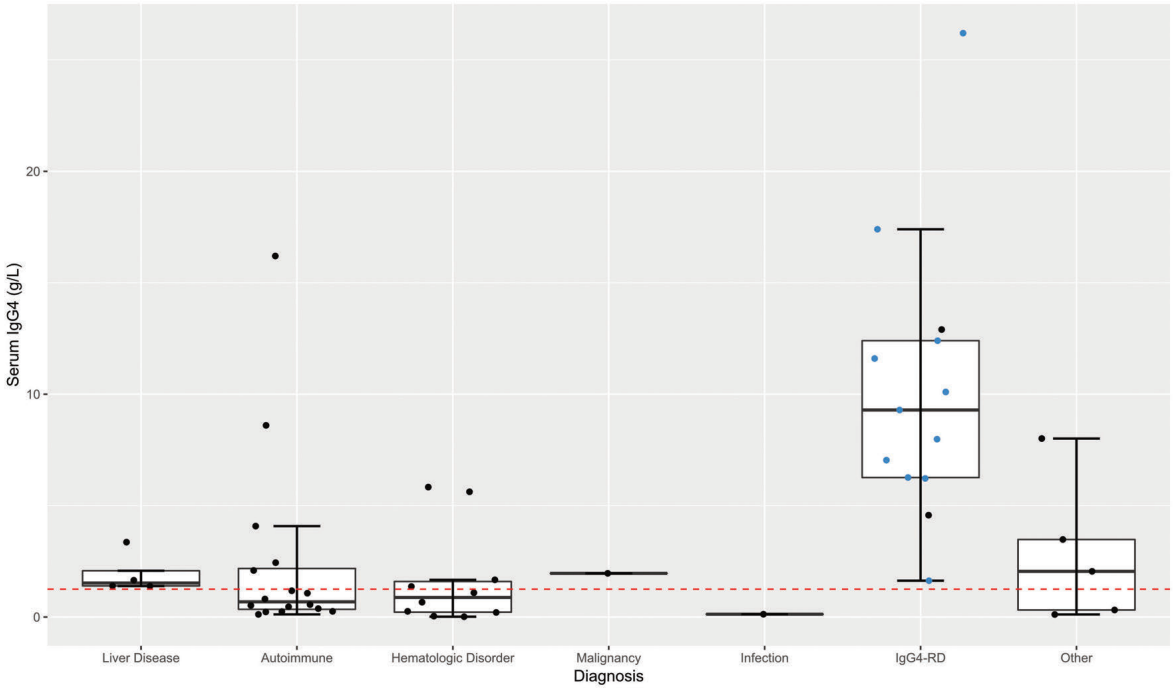

Figure 1. Serum IgG4 level according to diagnosis. IgG subclass information was available for 50 of the 66 patients. Each boxplot has a median line, with the hinges marking the 25th and 75th percentiles, and whiskers extending at most to values 1.5 times the interquartile range. Exact values are overlaid as dot plots. Blue dots represent values for patients with histologically confirmed IgG4-RD. Dashed line: 1.25 g/L, upper limit of normal serum IgG4 level in our laboratory.[7]

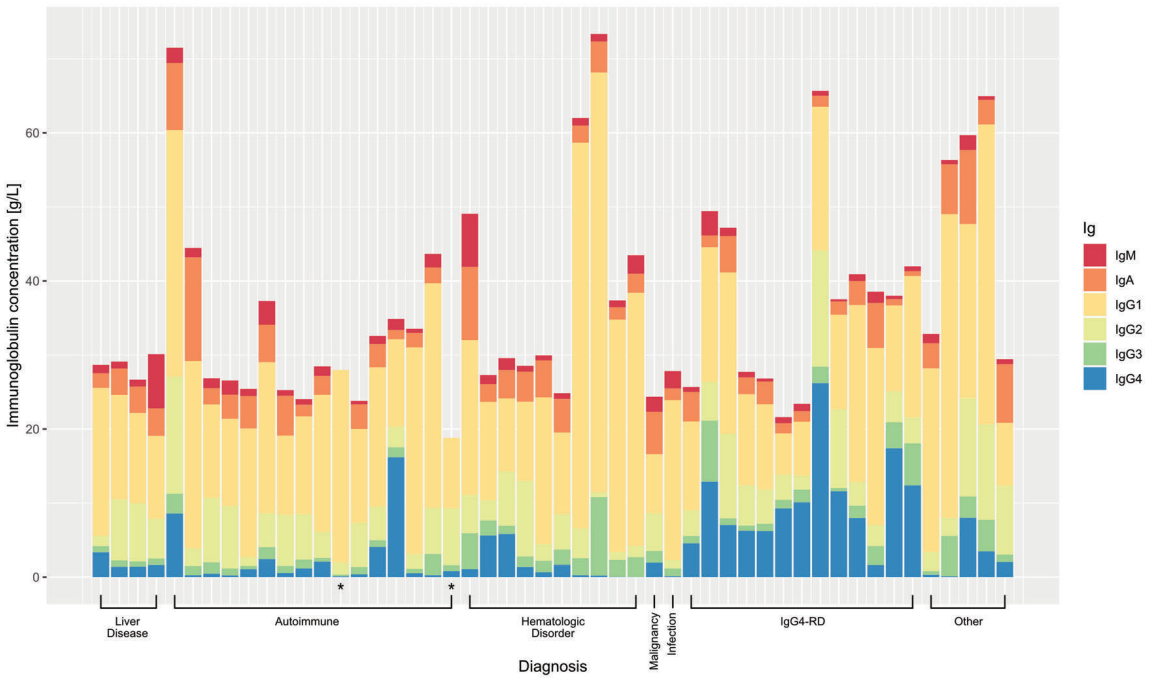

Figure 2. Concentrations of immunoglobulin subclasses according to diagnosis. IgM, IgA, and IgG subclasses for each of the 50 patients with IgG subclass data, grouped by diagnosis. Two patients with autoimmune conditions did not have IgM or IgA results and are marked by *.

serum IgG4, with values ranging from 1.63-26.2 g/L (normal <1.25 g/L). IgG subclasses were measured by immunonephelometry in two of the 13 cases and by mass spectrometry in the remaining 11.[7] Of the 37 patients with non-Ig4-RD PHGG who underwent IgG subclass testing, 17 had elevated serum IgG4, ranging from 1.37-16.2 g/L. Five of these patients had serum IgG4 >5 g/L, including one patient with Sjögren syndrome (bone marrow and minor salivary gland biopsies negative for IgG4-RD), one with eosinophilic granulomatosis with polyangiitis, one with Rosai-Dorfman-Destombes disease, one with hepatosplenic T-cell lymphoma, and one classified in the "other" group with an overall clinical picture suspicious for multicentric Castleman disease. Figure 1 shows the distribution of serum IgG4 level by class of diagnosis via boxplots, with precise values overlaid as dot plots. Figure 2 shows the composition of immunoglobulins (IgM, IgA and IgG subclasses) by disease category.

In a large study of 380 subjects, including 72 patients with probable or definite IgG4-RD, serum IgG4 >1.35 g/L had a sensitivity of 90% and a specificity of 60% in diagnosing IgG4-RD.[8] Our data demonstrate a sensitivity of 100% [with a 95% confidence interval (95% CI): of 75%-100%] and specificity of 54% (95% CI: 37%-71%) for a serum IgG4 >1.25 g/L in diagnosing IgG4-RD.. Increasing the serum IgG4 cutoff to >5 g/L decreased the sensitivity to 85% and increased specificity to 86%. Twenty-one patients had a serum IgG4/IgG ratio ≥10%, including 12 of the 13 patients with IgG4-RD. One patient with IgG4-RD had an IgG4/IgG ratio of 5%. This gives a sensitivity of 92% (95% CI:64%-99.8%) and specificity of 76% (95% CI:59%-88%) for an Ig4/IgG ratio ≥10%.

This study has a number of limitations. The sample size is relatively small, and the proportion of patients with IgG4-RD is likely much higher than in other hematology centers. Approximately 20% of the patients in this study had histologically confirmed (n=11) or likely (n=2) IgG4-RD, which reflects a referral pattern to our IgG4-RD specialists rather than the population prevalence of this rare disease. The true prevalence is unknown, but is likely to be somewhat higher than 4.6/100 000, which is the estimated prevalence of IgG4-autoimmune pancreatitis in Japan (autoimmune pancreatitis affects approximately 25% of patients with IgG4-RD). The proportion of patients with PHGG who have IgG4-RD will likely be quite variable in different centers depending on referral patterns, ethnicity[9] and the cutoff value used for degree of hypergammaglobulinemia. Furthermore, our center provides tertiary care for rare and emerging hematologic disorders in the province of British Columbia and thus some patients with rare conditions such as a GATA2 deficiency were included in this study, which may not reflect causes of PHGG in the general population. The cutoff for IgG of ≥20 g/L is lower than the ≥30 g/L used in the 2001 Mayo clinic study, and the much higher prevalence of liver disease in the Mayo clinic study likely reflects PHGG in the general population better.[5]

Despite these limitations, this study demonstrates that IgG4-RD is an important cause of PHGG. Moreover, PHGG can also be a useful diagnostic clue in many patients, given that only 7/66 (11%) of patients were classified as "other". The majority of underlying causes can be divided into one of six classes: liver disease, autoimmune conditions, hematologic disorders, non-hematologic malignancies, infectious diseases, and IgG4-RD. While the proportion of patients with IgG4-RD will likely be lower in other centers, the main point of this study is to show that it should be included in the differential diagnosis of PHGG and that IgG subclasses are a useful diagnostic test in these patients.[6] Mildly elevated serum IgG4 is non-specific, but markedly elevated serum IgG4 (>5 g/L) is highly suggestive of IgG4-RD and warrants further investigation, including histological confirmation in most cases. Of special importance for hematologists, a very dense serum IgG4 band can be mistaken as a "monoclonal" band, typically running in the fast gamma or beta-gamma region, and some patients with IgG4-RD may initially be thought to have plasma cell myeloma, or MGUS.[6,10] Other important investigations in these patients include autoantibodies, C-reactive protein, and screening for infection, malignancy and other inflammatory disorders. Hematologists should be aware of the myriad clinical manifestations of IgG4-RD, which are reviewed in detail elsewhere.[6]

Eric J. Zhao,[1] Mollie N. Carruthers,[2] Charles H. Li,[1] Andre Mattman[3] and Luke Y. C. Chen[1]

[1]Division of Hematology, University of British Columbia; [2]Division of Rheumatology, University of British Columbia and [3]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada

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Correspondence: LUKE Y. C. CHEN
lchen2@bccancer.bc.ca

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References

1. Massonnet B, Delwail A, Ayrault JM, Chagneau-Derrode C, Lecron JC, Silvain C. Increased immunoglobulin A in alcoholic liver cirrhosis: Exploring the response of B cells to Toll-like receptor 9 activation. Clin Exp Immunol. 2009;158(1):115-124.
2. Zemlin AE, Ipp H, Maleka S, Erasmus RT. Serum protein electrophoresis patterns in human immunodeficiency virus-infected individuals not on antiretroviral treatment. Ann Clin Biochem. 2015; 52(Pt 3):346-351.
3. Watanabe N, Kobayashi M, Shigeta Y, Hara H. Chronic idiopathic neutropenia with hypergammaglobulinemia. Jpn J Med. 1987; 26(1):65-68.
4. Nocturne G, Mariette X. B cells in the pathogenesis of primary Sjogren syndrome. Nat Rev Rheumatol. 2018;14(3):133–145.
5. Dispenzieri A, Gertz MA, Therneau TM, Kyle RA. Retrospective cohort study of 148 patients with polyclonal gammopathy. Mayo Clin Proc. 2001;76(5):476-487.
6. Chen LYC, Mattman A, Seidman MA, Carruthers MN. IgG4-related disease: what a hematologist needs to know. Haematologica. 2019; 104(3):1-13.
7. van der Gugten G, DeMarco ML, Chen LYC, et al. Resolution of spurious immunonephelometric IgG subclass measurement discrepancies by LC-MS/MS. Clin Chem. 2018;64(4):735-742.
8. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis. 2015;74(1):14-18.
9. Qi R, Chen LYC, Park S, et al. Utility of Serum IgG4 Levels in a Multiethnic Population. Am J Med Sci. 2018;355(1):61-66.
10. Jacobs JFM, van der Molen RG, Keren DF. Relatively restricted migration of polyclonal IgG4 may mimic a monoclonal gammopathy in IgG4-related disease. Am J Clin Pathol. 2014;142(1):76-81.