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Secondary Hypogammaglobulinemia

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Introduction

Secondary hypogammaglobulinemia (SHG) is characterized by reduced immunoglobulin levels due to extrinsic causes, such as a medication or an acquired disease process, resulting in decreased immunoglobulin production or increased immunoglobulin loss. Most published reports of SHG refer to IgG hypogammaglobulinemia and data on isolated IgA or IgM hypogammaglobulinemia is limited. The common causes of SHG include medications, hematological malignancies, and conditions associated with protein loss. Hypogammaglobulinemia can increase the risk of infection, morbidity and mortality, particularly in patients who may already be immunocompromised due to their associated condition or use of immunosuppressive therapies.[1,2] With growing use of immunosuppressive or immunomodulatory treatments that affect B-cells, it is increasingly important to assess and monitor for SHG. Treatment of the underlying condition or removal of the extrinsic factor often results in resolution of the SHG. A subset of patients presenting with autoimmune or malignant conditions can have a primary immunodeficiency (PID) or primary immune regulatory disorder. It is therefore important to consider both primary and secondary causes when assessing hypogammaglobulinemia. This article will review these common causes and discuss an approach to assessment and management of SHG.

Medications

Many classes of medications can cause hypogammaglobulinemia. The most commonly implicated therapies include immunosuppressive or immunomodulatory medications, such as B-cell targeted therapies (BCTT), corticosteroids, and antiepileptic drugs.

BCTT are increasingly used for treatment of malignant, autoimmune and inflammatory conditions. Most literature regarding BCTT-associated SHG exists for rituximab, a chimeric anti-CD20 monoclonal antibody. Rituximab results in B-cell depletion within 72 hours with persistence of B-cell lymphopenia for 2–6 months after treatment. B-cell levels usually return to those of pre-treatment within 12 months.[3] B-cell impairment is limited primarily to depletion of pre-plasma B cells, halted differentiation from naïve to memory B-cell, increased B-cell apoptosis, and altered T-cell homeostasis. Hypogammaglobulinemia has been identified in up to 40–50% of patients who received rituximab.[4,5] Significantly delayed B-cell recovery is associated with persistent

hypogammaglobulinemia. A low IgG level prior to or at the time of rituximab use is a risk factor for development of hypogammaglobulinemia after rituximab use.[4] Low IgG levels at any time after rituximab use has been associated with a higher risk of serious infections.[5] Risk factors for moderate persistent hypogammaglobulinemia post-rituximab use include prior cyclophosphamide use, lower nadir IgG in the first 12 months, corticosteroid use at 12 months and female sex.[6] Anti-CD19 chimeric antigen receptor (CD19 CAR)-T-cell therapy causes B-cell aplasia and SHG as its "on target" "off tumor" effect. SHG occurs frequently and can persist for months or years.[7] The association between hypogammaglobulinemia and risk of infection in CD19 CAR-T-cell therapy is variable and complicated by additional risk factors including corticosteroid or other immunosuppressive medication use, cytokine release storm, underlying malignancy, neutropenia, and prior infection history.

Corticosteroid use primarily affects IgG levels and has less impact on IgA and IgM, which can be helpful in distinguishing between primary hypogammaglobulinemia and hypogammaglobulinemia secondary to corticosteroids.[8,9] Prolonged or high-dose use of oral corticosteroids has a greater effect on IgG levels than short-term use. Specific antibody responses are usually preserved and therefore corticosteroid-induced SHG is not associated with significant increased frequency or severity of infectious complications. The infections associated with corticosteroid use are usually due to its associated CD4 T-cell lymphopenia. However, use of corticosteroids in combination with other immunosuppressive therapies can result in more significant hypogammaglobulinemia. High-dose inhaled corticosteroid use has not been associated with SHG.[9]

Antiepileptic drugs (AEDs) can carry an increased risk of hypogammaglobulinemia. Although panhypogammaglobulinemia has been associated with AEDs, IgG is the most commonly reported immunoglobulin class involved[10] Phenytoin, carbamazepine, and lamotrigine have been associated with low IgA. Topiramate has not been associated with a significant risk of SHG. AEDs are thought to have an effect on B-cell maturation or regulatory T-cells, which can affect immunoglobulin isotype production. There is an exposure-response relationship with a trend of increased odds of hypogammaglobulinemia with increasing duration of AED exposure. Hypogammaglobulinemia tends to normalize after AEDs cessation. Most patients have not had significant demonstrated antibody deficiency and it is unclear what the infection risk is for these patients.

Malignancies

Hematological malignancies, such as chronic lymphocytic leukemia (CLL) and multiple myeloma (MM) are common causes of SHG. Hypogammaglobulinemia is present in up to 85% of patients with CLL and up to 83% of patients with MM.[11] SHG in CLL is thought to be due to the underlying disease process, such as defective B-cell maturation and dysfunction of nonclonal CD5-negative B-cells, as well as immunomodulatory treatments. The frequency of infection correlates with hypogammaglobulinemia and contributes significantly to morbidity and mortality. SHG is more pronounced with advanced disease stage or longer disease duration in CLL.

Transplantation

Hypogammaglobulinemia occurs commonly in solid organ transplantation (SOT) and hematopoietic stem cell transplantation (HSCT). It has been observed in approximately 60% of lung transplant recipients, 50% of heart transplant recipients, 40% of renal transplant recipients, 16% of liver transplant recipients,[2] and 50–77% of allogeneic HSCT recipients[12,13] at 1 year. Severe hypogammaglobulinemia (IgG level less than 4 g/L) in the first year post-SOT is associated with increased risk of infections, particularly cytomegalovirus and fungal and respiratory infections, as well as mortality.[14] B-cell recovery after HSCT takes 3–6 months but can be delayed by the presence of graft-versus-host disease (GVHD), conditioning and immunosuppressive medications, and type of donor cells. Risk factors for SHG post-HSCT include younger age, lower pre-transplant IgG level, diagnosis of malignant disease, development of acute GVHD, and receiving an unrelated HSCT.[13]

Conditions Associated with Protein Loss

Protein-losing states can be due to renal (e.g., nephrotic syndrome), gastrointestinal (e.g., protein-losing enteropathy) or cutaneous (e.g., severe burn) loss. Patients with loss of IgG often have retained specific antibody production

and may have a lower risk of infection compared to those with a failure to produce antibodies. However, the use of immunosuppressive therapies and urinary loss of complement (in nephrotic syndrome) can contribute to an immunocompromised state and risk of infection. One study of pediatric patients who received rituximab for complicated nephrotic syndrome did not find a significant association between severity of hypogammaglobulinemia and infection rate.[15] Management is usually targeted at the underlying condition and there is limited data on the efficacy of immunoglobulin replacement therapy.

Assessment and Management Considerations

When assessing patents with hypogammaglobulinemia, it is important to consider primary immunodeficiency (PID) as many conditions that require immunosuppressive or immunomodulatory treatments may also be presentations of PID. For example, patients with PID can present with immune dysregulation and autoimmunity, such as autoimmune cytopenias and rheumatologic presentations and malignancies, which frequently require treatment with immunosuppressive medications. Often, baseline immunoglobulin levels are not routinely established at the time of diagnosis of the initial condition or before treatment with immunosuppressive medications. When the concern for hypogammaglobulinemia arises, the immune evaluation may be affected by the current immunosuppressive therapy, thus hampering the assessment of primary versus secondary immunodeficiency. Two studies demonstrated that a significant subset of children who received rituximab for autoimmune cytopenia and experienced persistent hypogammaglobulinemia were subsequently diagnosed with PID.[5,16] Another study identified variants in PID genes in approximately half of adult patients with rheumatic diseases who had persistent hypogammaglobulinemia after immunomodulatory therapy.[17] Red flags for PID in the context of hypogammaglobulinemia after immunosuppressive or immunomodulatory therapy are listed in **Table 1**.

Ideally, a clinical immunologist should be involved as part of the multidisciplinary team and patients would have baseline immune testing done. Patients who present with red flags or additional features concerning for PID should undergo more extensive immune evaluation by a clinical immunologist, which often includes genetic testing.

There is significant variation in practice regarding screening and management of SHG.[18-20] Society guidelines and expert recommendations have been published for specific populations or conditions, such as CLL and SOT.[21,22] Patients with secondary antibody deficiency have been shown to experience delays in diagnosis similar to those with PID.[23] Therefore, increased awareness, screening and monitoring are essential for timely diagnosis and management. Most recommendations suggest that baseline immunoglobulin levels be measured either at diagnosis or prior to initiation of treatment for at-risk patients. The frequency of immunoglobulin monitoring ranges from 3 to 12 months, depending on the treatment, underlying condition and frequency or severity of infections. For patients in whom hypogammaglobulinemia is identified or with a history of frequent infections, further evaluation of humoral immune function includes IgG, IgA and IgM levels, lymphocyte subsets and B-cell immunophenotyping, and measurement of specific antibody responses to vaccines. Interpretation of specific antibody titres may be complicated by the effect of immunosuppression on vaccine responses.

Management of SHG is complex. While removal of the treatment or condition causing SHG is preferred, it is often not easily accomplished or possible. Many patients with hypogammaglobulinemia may not develop infections and there is limited evidence regarding what is clinically meaningful SHG or when immunologic intervention should be initiated, particularly in the absence of symptoms. Supportive treatment options for SHG include immunization, antimicrobial prophylaxis and immunoglobulin replacement therapy (IGRT).

Immunizations with non-live vaccines are recommended according to routine immunization schedules, including influenza and pneumococcal vaccines, although the response may be suboptimal.[24] When possible, immunizations should be completed before immunosuppression. Live vaccines are generally not recommended for patients with malignant disorders, post-transplantation, or in those receiving immunosuppressive medications. In addition to providing protection against infection, immunizations can help assess humoral function through the measurement of antibody responses post-vaccination.

- Previous history of infections, autoimmunity, or lymphoproliferation
- Immune abnormalities prior to immune suppression: low immunoglobulin levels, low antibody responses to vaccines, low memory B cells
- Positive family history for immunodeficiency
- Young age (<10 years)
- Persistent hypogammaglobulinemia
- Abnormal B-cell subsets

Table 1. Red flags for PID in patients with hypogammaglobulinemia after immunosuppressive or immunomodulatory therapy; *courtesy of Vy H.D. Kim, MD.*

Evidence supporting the use of prophylactic antibiotics or IGRT for SHG is limited. The choice of antibiotics for prophylaxis should be based on the history of infections, allergies, spectrum of infection risk, and local resistance patterns. Most guidelines recommend a trial of IGRT when IgG levels are less than 4 g/L or when IgG levels are less than 7 g/L and there are suboptimal responses to vaccination, a history of recurrent or severe infections and/or failure of antibiotic prophylaxis.[21] The dosing used for IGRT is usually similar to that used for patients with primary antibody deficiency, starting at 400–600 mg/kg/month. IGRT use has been associated with significant reduction in rates of serious bacterial infections and antimicrobial use.[1] As the SHG may be transient, periodic assessments to evaluate if IGRT should be paused or discontinued should be completed every 6 to 12 months; if immunosuppression has been discontinued; or when the SHG-associated condition has been successfully treated. Re-evaluation of immune function after IGRT has been discontinued is often done following a period of 4–6 months, to allow for exogenous IgG to be cleared.

Summary

Many conditions and treatments can cause SHG. Increasing use of novel immunomodulatory or BCTT therapies contribute to increasing incidence of SHG. As hypogammaglobulinemia may be an indicator for PID and is associated with increased risk of infection, it is important to assess and monitor for hypogammaglobulinemia and antibody deficiency in at-risk patients. Baseline immune evaluation can be helpful to stratify the risk of recurrent or severe infections in patients who may have PID. Patients with SHG should have periodic assessments for infection and immune function. Shared decision-making is important for the initiation of supportive therapy in SHG, such as IGRT. More research is needed to identify optimal laboratory evaluations for screening and monitoring, what is clinically significant SHG, and which patients would benefit from IGRT.

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References

1. Monleón Bonet C, Waser N, Cheng K, et al. A systematic literature review of the effects of immunoglobulin replacement therapy on the burden of secondary immunodeficiency diseases associated with hematological malignancies and stem cell transplants. Expert Rev Clin Immunol. 2020;16(9):911-21.
2. Lichvar AB, Ensor CR, Zeevi A, et al. Detrimental association of hypogammaglobulinemia with chronic lung allograft dysfunction and death is not mitigated by on-demand immunoglobulin G replacement after lung transplantation. Prog Transplant. 2019;29(1):18-25.
3. Kimby E. Tolerability and safety of rituximab (MabThera®). Cancer Treat Rev. 2005;31(6):456-73.
4. Roberts DM, Jones RB, Smith RM, et al. Rituximab-associated hypogammaglobulinemia: Incidence, predictors and outcomes in patients with multi-system autoimmune disease. J Autoimmun. 2015;57:60-5.
5. Labrosse R, Barmettler S, Derfalvi B, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. J Allergy Clin Immunol. 2021;148(2):523-32.e8.
6. Tieu J, Smith RM, Gopaluni S, et al. Rituximab associated hypogammaglobulinemia in autoimmune disease. Front Immunol. 2021;12:671503.
7. Kampouri E, Walti CS, Gauthier J, et al. Managing hypogammaglobulinemia in patients treated with CAR-T-cell therapy: key points for clinicians. Expert Rev Hematol. 2022;15(4):305-20.
8. Wirsum C, Glaser C, Gutenberger S, et al. Secondary antibody deficiency in glucocorticoid therapy clearly differs from primary antibody deficiency. J Clin Immunol. 2016;36(4):406-12.
9. Kawano T, Matsuse H, Obase Y, et al. Hypogammaglobulinemia in steroid-dependent asthmatics correlates with the daily dose of oral prednisolone. Int Arch Allergy Immunol. 2002;128(3):240-3.
10. Perrott S, Macleod A. Associations between antiepileptic use and hypogammaglobulinaemia: findings from a population-based case-control study using data linkage. J Neurol Neurosurg Psychiatry. 2022;93(9):e2.
11. Na I, Buckland M, Agostini C, et al. Current clinical practice and challenges in the management of secondary immunodeficiency in hematological malignancies. Eur J Haematol. 2019;102(6):447-56.
12. Karakulska-Prystupiuk E, Dwilewicz-Trojaczek J, Drozd-Sokołowska J, et al. Prevalence of hypogammaglobulinemia and its management with subcutaneous immunoglobulin supplementation in patients after allogeneic hematopoietic stem cell transplantation—a single-center analysis. Ann Hematol. 2021;100(12):3007-16.
13. Frangoul H, M, Frangoul H, Min E, et al. Incidence and risk factors for hypogammaglobulinemia in pediatric patients following allo-SCT. Neoplasia. 2013;48(11):1456-59.
14. Florescu DF, Kalil AC, Qiu F, et al. What Is the impact of hypogammaglobulinemia on the rate of infections and survival in solid organ transplantation? A meta-analysis. Am J Transplant. 2013;13(10):2601-10.
15. Inoki Y, Nishi K, Sato M, et al. The association between hypogammaglobulinemia severity and infection risk in rituximab-treated patients with childhood-onset idiopathic nephrotic syndrome. Pediatr Nephrol. 2023;38(2):451-60.
16. Ottaviano G, Marinoni M, Graziani S, et al. Rituximab unveils hypogammaglobulinemia and immunodeficiency in children with autoimmune cytopenia. JACI (Cambridge, MA) 2020;8(1):273-82.
17. Sogkas G, Dubrowinskaja N, Adriawan IR, et al. High frequency of variants in genes associated with primary immunodeficiencies in patients with rheumatic diseases with secondary hypogammaglobulinaemia. Ann Rheum Dis. 2021;80(3):392-9.
18. Ar MC, El Fakih R, Gabbassova S, et al. Management of humoral secondary immunodeficiency in hematological malignancies and following hematopoietic stem cell transplantation: Regional perspectives. Leuk Res. 2023;133:107365.
19. Patel SY, Carbone J, Jolles S. The expanding field of secondary antibody deficiency: causes, diagnosis, and management. Front Immunol. 2019;10:33.
20. Bourassa-Blanchette S, Knoll G, Tay J, et al. A national survey of screening and management of hypogammaglobulinemia in Canadian transplantation centers. Transpl Infect Disease. 2017;19(4).
21. Otani IM, Lehman HK, Jongco AM, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. J Allergy Clin Immunol. 2022;149(5):1525-1560.
22. Jolles S, Michallet M, Agostini C, et al. Treating secondary antibody deficiency in patients with haematological malignancy: European expert consensus. Eur J Haematol. 2021;106(4):439-49.
23. Duraisingham SS, Buckland M, Dempster J, et al. Primary vs. secondary antibody deficiency: clinical features and infection outcomes of immunoglobulin replacement. PloS one 2014;9(6):e100324.
24. Public Health Agency of Canada. Immunization of immunocompromised persons: Canadian Immunization Guide. 2018; Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-8-immunization-immunocompromised-persons.html#a13. Accessed June 15, 2024.