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INVITED COMMENTARY

Secondary Hypogammaglobulinemia: An Under-Recognized Clinical Entity in Children

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Secondary hypogammaglobulinemia (SHG) is a clinical entity that is now increasingly being recognized in diverse clinical situations. It is characterized by low serum immunoglobulin levels (i.e. IgG, IgM, and IgA) and can result from either an increased loss or a decreased production of immunoglobulins. The latter can be secondary to drugs or other forms of therapies [1]. Majority of the publications on SHG pertain to low IgG levels, and the most well-characterized form of SHG is the one that follows administration of B cell targeted therapy such as rituximab. Other drugs that have also been implicated in the causation of SHG include phenytoin, carbamazepine, clozapine, azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil. Serial monitoring of serum immunoglobulins and B cell counts after administration of immunosuppressive medications, and especially after B cell depleting therapies, is now the standard of care [1–3]. Chemotherapy can impair B cell function, leading to decreased antibody production and a weakened immune response. SHG has also been well documented in patients with chronic lymphocytic leukemia and in those following CD19 CAR-T cell therapy [4, 5].

However, there is paucity of literature on SHG following chemotherapy for childhood leukemias and lymphomas. A retrospective study from Italy reported that rates of SHG are high following administration of fludarabine-based chemotherapies in children with non-Hodgkin lymphoma, and presence of SHG is associated with an increased frequency of pulmonary infections [6].

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Management of SHG typically involves a close clinical follow-up for infections and serial monitoring of immunoglobulin levels. Immunoglobulin replacement therapy (IGRT) is often necessary to reduce infection rates and improve the quality of life. However, the decision to initiate IGRT depends on factors such as the severity of hypogammaglobulinemia, the frequency of infections, and the overall clinical assessment [1]. Recent studies emphasize the importance of individualized treatment plans, as SHG can vary widely in severity and clinical impact. Early identification and proactive management of SHG are crucial to minimizing complications and ensuring better outcomes [1].

In this issue of *Indian Pediatrics*, the authors from a tertiary care pediatric oncology referral center in Thiruvananthapuram, Kerala, have analyzed the serum immunoglobulin levels of 199 children (112 boys, 87 girls) with acute lymphoblastic leukemia (ALL) during the maintenance phase of chemotherapy [7]. These included 166 children with B-ALL, 32 with T-ALL, and 1 with mixed phenotype acute leukemia. Serum immunoglobulins were assayed (by immunoturbidimetry) at varying follow-up periods during the maintenance phase of chemotherapy: at 0–6 months ($n=58$), 7–12 months ($n=52$), 13–18 months ($n=47$), and 19–24 months ($n=42$), respectively. The median follow-up duration at the time of assay was 9 months after start of chemotherapy. Stratification included 110 children (55.3%) in high-risk (HR), and 89 (44.7%) in standard risk (SR) groups; 93 children in HR group had also received cranial irradiation [7]. The study has a prospective observational design, and this is appropriate for analyzing the outcomes of children receiving chemotherapy and identifying the putative risk factors for complications.

The authors documented low levels of IgG, IgM, and IgA in 57%, 86%, and 86% of children on maintenance chemotherapy, respectively. Though the prevalence of low immunoglobulins is high, the distribution and comparison across chemotherapy periods showed no significant differences. Older children (>5 years) and girls had lower risks of

hypo-IgG and hypo-IgA. A univariate analysis linked older age to reduced odds of hypo-IgM and hypogammaglobulinemia of one or all classes [7].

It is important to note that baseline immunoglobulin levels were not assayed before initiation of chemotherapy. Similarly, serial IgG levels have not been assayed on follow-up. Therefore, the association between these two variables, and the quantum of fall in immunoglobulin levels cannot be clearly established. The authors also report that they did not find a significant association between hypogammaglobulinemia and occurrence of infections. Stratification of groups between different ranges of IgG levels would have given the impact of both profoundly low IgG levels (< 300 mg/dL) and mildly low IgG levels (300–600 mg/dL) on the presence of infections. Additionally, the presence of neutropenia influences the development of infections. Consequently, it will be important to compare infections in neutropenic and non-neutropenic patients with hypogammaglobulinemia. Analyzing the functional antibody responses (as for instance, by an assay of pre- and post-vaccination titres) may be crucial to show whether the low antibody levels have clinical relevance. It will also be essential to monitor B cell counts, as an increase in these counts may lead to the restoration of immunoglobulin levels. As the authors themselves allude to in the manuscript, the chemotherapy regimens are shown to impact both cellular and humoral immunity. Therefore, detailed immunophenotyping of the T lymphocyte subsets during follow-up after chemotherapy will also be of relevance. While the calculated sample size of 197 is adequate, a single-center study usually limits generalizability and extrapolation of results. A larger, more diverse cohort could enhance external validity. Moreover, this study only captures the outcomes over a relatively short follow-up period, i.e., up to 6 months, or until treatment completion. The potential long-term effects of persistent hypogammaglobulinemia on occurrence of febrile illnesses during follow-up would remain conjectural.

Nevertheless, the authors need to be complimented for carrying out this important clinical study and venturing into the domain of SHG in the context of common childhood leukemias. This is a landmark study in as much as it is probably the first of its kind from a resource constrained setting. The findings are clinically relevant as they highlight the potential risk factors for hypogammaglobulinemia and severe febrile illness in children with ALL undergoing chemotherapy. These results underscore the need for monitoring and possible interventions to mitigate the risks. Future research should explore the role of immunoglobulin replacement therapy (IgRT) in reducing the morbidity in children with SHG. A multicenter approach could validate findings across diverse populations and treatment regimens.

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