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Perspective

The Role of Hemophagocytic Lymphohistiocytosis in Lymphoma

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DESCRIPTION

If left untreated, Hemophagocytic Lymphohistiocytosis (HLH) is a severe hyper inflammatory condition characterized by the pathologic activation of cytotoxic T-lymphocytes and macrophages, which can cause organ damage and cytokine storm. Originally identified as histiocytic medullary reticulosis in 1939 by Bodley Scott and Robb-Smith, HLH is currently categorized by the Histiocyte Society as one of the "H"-group of histiocytoses. Another name for HLH in the context of autoimmune/auto inflammatory illnesses is Macrophage Activation Syndrome (MAS or MAS-HLH). Given pathophysiology, there are two forms of HLH: A primary form that is dictated by genetics and a secondary form that is acquired. Mutations in genes regulating lymphocyte toxicity or immunological regulation cause improper death of antigen-presenting cells in primary HLH (also known as familial HLH, or FHL), which leads to chronic immune stimulation and an excessive immune response. The complex pathophysiology leading to the clinical picture of hyper inflammation in secondary HLH is reflected in the interplay between pre-existing immunosuppression, inflammation (i.e., auto inflammatory or rheumatic disorders), cytokine release within infections or malignant diseases, and potential genetic predisposition.

Secondary or acquired HLH is more common in adults as opposed to primary HLH, which usually manifests in infancy. While viral infections are the primary cause of FHL, a wide range of underlying illnesses can cause secondary HLH, with infections and cancers being the most prevalent. Notably, Malignancy-Associated HLH (M-HLH) might manifest as infection-triggered HLH during treatment, over the course of the disease in case of progression or relapse, or in the setting of the original diagnosis indicating para neoplasia. Furthermore, in the setting of innovative therapeutics, M-HLH may manifest after T-cell activation and cytokine release in both hematological and solid malignancies, making the distinction between treatment toxicity and inflammation associated with malignancy particularly difficult. As with other cancers, immune-stimulating and cellular therapies (e.g., checkpoint inhibitors, T-cell engaging bispecific antibodies, chimeric antigen receptor modified T-cells) are increasingly used in the treatment of lymphomas. One well-known side effect of these therapies is cytokine release, which in severe cases can result in a potentially fatal HLH-like clinical picture (also known as HLH-like toxicity). Conversely, a pilot study using the programmed cell death protein-1 antibody Nivolumab proved to be good in treating refractory or relapsed Epstein-Barr Virus (EBV)-HLH. This is probably because the antibody expanded PD-1 positive T-cells and corrected the compromised anti-EBV response.

The most frequent cause and usually the one with the worst prognosis in the M-HLH group is lymphoma. This may be caused by the frequently aggressive disease courses of specific lymphoma subtypes that are more prevalent in M-HLH patients, as well as by unique and uncommon clinical characteristics that make lymphoma diagnosis more difficult. Specifically, the similarity between HLH and other inflammatory illnesses like sepsis may cause a delay in the first diagnosis. Furthermore, tissue infiltration with activated lymphocytes and macrophages that permit tumor cells to conceal them behind inflammatory infiltrates may impede histological diagnosis. Clinically, depending on the underlying illness, HLH patients may exhibit a range of symptoms; a triad of fever, splenomegaly, and cytopenia is frequently seen. The Histiocyte Society's HLH-2004 criteria, which require the fulfilment of five of the eight criteria in order to diagnose HLH, are now used for this purpose. Given the non-specificity of several of the HLH-2004 criteria, such as using higher ferritin or soluble CD25 (sCD25; synonym: soluble interleukin-2 receptor chain alpha, sIL-2Rα) cut-off values to best identify patients with HLH and distinguish from other inflammatory states like sepsis, adaptation of these criteria has been proposed in the past few years, particularly for adult patients with secondary HLH.

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