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Haemophagocytic lymphohistiocytosis: Are we sailing an unchartered sea?

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EDITORIAL

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Haemophagocytic lymphohistiocytosis (HLH), a potentially fatal disorder, may occur as a primary genetic abnormality or secondary to a number of diseases, including malignancies, infections, and connective tissue disorders. The clinical course and outcome of underlying disease is often dramatically altered in the presence of secondary HLH. Although data on incidence in adults are inadequate, paediatric HLH is estimated to occur in 1–225 per 300,000 live births.[1–3] There is growing evidence that HLH is probably an underdiagnosed condition, primarily due to lack of awareness. Consequently, apart from haematologists and physicians practicing at tertiary care hospitals, this entity seldom crosses the minds of general practitioners. This leads to considerable delay in diagnosing HLH, especially in patients presenting with fever of unknown origin or cytopenias. Such patients get referred to specialists usually after a battery of infectious and inflammatory disorder workups, and at times after a course of empiric antibiotic therapy.

The currently used diagnostic criteria that include clinical and laboratory parameters were derived from the HLH-2004 criteria based almost entirely on data from studies on primary HLH in the paediatric population.[4] Fever, cytopenias (in at least two cell lines), splenomegaly, elevated serum ferritin (more than 500µg/L), hypertriglyceridemia (more than 265mg/dL), presence of hemophagocytosis in the marrow, spleen or lymph nodes, absent or diminished NK T cell activity and elevated soluble CD 25 (more than 2400U/mL) form part of the clinico-laboratory criteria. The presence of any five of these is compatible with a diagnosis of HLH. A molecular diagnosis consistent with HLH is sufficient to diagnose primary HLH, even in the absence of the other criteria.

One major diagnostic issue in adult HLH relates to the relative non-specificity of the criteria. Although markers such as reduced NK T cell activity and increased CD 25 are reliable markers of the condition,[5] their utility is compromised by limited availability and high cost. The other parameters like ferritin and triglyceride levels are non-specific even at the cut-off levels suggested by the HLH-2004 criteria. In one center, ferritin cut-offs as high as 50,000µg/L were found to be non-specific for HLH.[6] Further, reliance on demonstration of hemophagocytosis in tissues for diagnosis may not be rewarding as this is absent in a significant proportion of cases and not a requisite for diagnosis. Generalisability of these diagnostic criteria based on paediatric HLH trials to adults (especially with presumed secondary HLH) is also questionable. Although newer diagnostic approaches have been developed and validated such as the HScore and Delphi scores, they have not come into popular use.[7,8]

Therapy of HLH, again based on extrapolations of results from paediatric population, is primarily aimed at reducing hyper-inflammation and destroying defective immune cells by immunosuppressive chemotherapy. The HLH-94, HLH-2004 and various modifications of these protocols are being practiced worldwide. The original protocol (HLH-94) consisted of an eight-week intensive phase using dexamethasone and etoposide followed by continuation with cyclosporine.[9] Subsequently, the HLH–2004 protocol added cyclosporine to the intensive phase with a resultant increase in neurotoxicity. Therefore, haematologists in several centers now use cyclosporine during maintenance. Definitive cure is haematopoetic stem cell transplantation (HSCT), particularly for primary HLH and treatment refractory secondary HLH. HSCT and chemotherapy have dramatically improved the long-term survival of HLH patients from 4 per cent about three decades ago to 54 per cent at present.[10, 11]

There exist several challenges, however, in the management of secondary HLH. First, one of the common etiologies for secondary HLH is an Epstein-Barr Virus (EBV) infection,[12] the detection of which remains a challenge in many middle- and low-income countries. This is significant because HLH associated with EBV carries the worst prognosis among infection-associated HLH, particularly if treatment is started later than four weeks.[13]

Second, the most widely practiced treatment for secondary HLH that includes a glucocorticoid with etoposide is again based on data from trials on primary HLH. Although etoposide has become standard of care, its use is not based on prospective trial data. These potent immunosuppressive agents, apart from reducing the cytokine storm in HLH, may have adverse consequences on the course of the underlying disorder like viral or bacterial infections. An example is the HLH associated with tuberculosis wherein the administration of etoposide and steroids may have significant implications on the tuberculous process. While drugs like rifampicin used in tuberculosis can induce metabolism of etoposide and blunt its therapeutic benefit, etoposide itself may lead to hepatic dysfunction that may preclude the administration of many of the first-line anti-tubercular drugs.

Third, whether potentially toxic treatment protocols such as the HLH-2004 is warranted in secondary HLH-complicating infections like scrub typhus is not clear.[14] If diagnosed sufficiently early and treated with tetracyclines, this infection carries an excellent prognosis and the immune dysregulation associated with HLH may subside in due course. However, what is lacking at present is robust data to strongly suggest or discourage treatments in these situations. Finally, there is a large group of secondary HLH that occurs in association with malignancies primarily of the haematopoetic system where there exist no consensus regarding priorities of treatment—the tumor or HLH.

While many clinicians are bold enough to initiate steroids in suspected or proven HLH, albeit as a desperate attempt in a sinking patient, not many would venture to administer etoposide or cyclosporine A for reasons obvious from previous discussion. No data are available as to the outcomes of these patients treated with steroids alone. While the results of the first prospective trial of adult HLH are likely to inspire more research on adult HLH, the variability in etiologies of secondary HLH in different parts of the world would be another challenge to keep in mind. A large Chinese trial explored the role of doxorubicin, etoposide, and methyl prednisolone to salvage HLH patients refractory to conventional treatment, and found a 76 per cent overall response rate.[15] More than one-half of the patients who achieved remission survived to receive some form of definitive treatment, including allogenic bone marrow transplantation. Another promising result is the good response of EBV-associated HLH observed in this trial in contrast to the dismal outcome of this subgroup to the existing etoposide-based regimen.

Experience with secondary HLH in adults is limited worldwide and there exists no uniform treatment guidelines other than the HLH-2004 protocol. Accordingly, what is needed are large, multicenter trials involving adults with secondary HLH due to various infectious, malignant, and rheumatologic disorders addressing the optimum therapy and exploring additional avenues for intervention. Diagnosis of this fatal disorder must be made as early as possible and spreading awareness among practicing clinicians would be the most important step. Until then, we are probably sailing an unchartered sea of dysregulated immune response.

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