Additional considerations related to the elusive boundaries of EBV-associated T/NK-cell lymphoproliferative disorders

We appreciate the comments made by Chen and Guan and entirely agree that the diagnoses of the entities in the spectrum of EBV+ T/NK-cell lymphoproliferative disorders (LPD) is a difficult one even for experts. They propose using the terminology of systemic acute Epstein-Barr virus infection (SAEBV) to define non-neoplastic lesions with systemic symptoms of EBV infection within a three-month time interval. This proposal has clinical utility, in particular, if the cellular lineage affected is included in the diagnosis: T cell, NK cell or B cell. We also agree with Chen and Guan that it is currently not possible to prospectively determine if cases of SAEBV will progress to CAEBV, a more aggressive LPD, or represent a brief illness in the form of infectious mononucleosis. Thus, having a diagnosis of SAEBV may alert treating physicians to the fact that acute EBV infection may have various clinical consequences.

Chen and Guan also suggest that EBV-associated hemophagocytic lymphohistiocytosis (HLH) should be considered acute EBV infection accompanied by HLH. We agree with the point that typically the diagnosis of HLH cannot be made at the time of histopathologic evaluation, which contributes only one of eight criteria that can be used to support a diagnosis of HLH. Therefore, frequently the pathologist can only make the diagnosis of an EBV+ LPD, document that hemophagocytosis is seen, and alert the treating physician to the possibility of HLH and the need for additional studies. Thus, from a practical consideration, we agree with Chen and Guan that EBV+ HLH will typically not be a pathologic diagnosis, but

rather a diagnosis made by treating physicians once all relevant data are available. This practical consideration, however, does not warrant referring to EBV infection and concomitant HLH as separate entities when discussing distinct disease categories. There is a well-established association between EBV and HLH clinically. Furthermore, EBV is pathogenically related to HLH as there is evidence demonstrating that EBV directly contributes to the cytokine storm that results in histocyte and macrophage activation and hemophagocytosis. By deconstructing EBV-HLH into AEBV and HLH, the explicit pathophysiologic relationship between EBV and HLH may not be fully appreciated.

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