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● ● ● CLINICAL TRIALS AND OBSERVATIONS

Comment on Yu et al, page 1658

Unraveling Castleman: progress in a complex process

Kieron Dunleavy NATIONAL CANCER INSTITUTE

In this issue of *Blood*, Yu et al report on the clinical and pathologic features, as well as the treatment outcomes of a large patient population with Castleman disease (CD), negative for HIV and human herpesvirus 8 (HHV-8).[1]

CD was very first described by Benjamin Castleman more than 60 years ago.[2] It is a rarely encountered, poorly understood, lymphoproliferative disorder that really comprises a broad spectrum of clinicopathologic entities and has widely variable therapeutic outcomes.[3] Unicentric and multicentric variants have been described. Unicentric CD (UCD) is confined to one lymph node region and is usually treated by lymph node excision; inflammatory symptoms are mild and typically abate with lymph node removal. Multicentric CD (MCD) on the other hand, is clinically aggressive and is characterized by very significant cytokine over-activity that may lead to systemic organ dysfunction and failure. A high proportion of multicentric cases are driven by HHV-8, which drives cytokine hyperactivity and may cause lymphoid proliferations and lymphoma; these cases usually occur in HIV-infected individuals.[4] HHV-8 and HIV-negative MCD cases (the so called idiopathic MCD [iMCD] because there is no known viral etiology) are also encountered.[5] Interleukin-6 (IL-6) is the most commonly elevated cytokine in MCD, and although the release of cytokines is thought to be HHV-8 driven in HHV-8–positive cases, the cause of cytokine release in iMCD is poorly understood and may result from etiologic mechanisms such as somatic mutations or other viruses.[6] iMCD cases may in particular present a clinicopathologic diagnostic challenge and to that end, recently published international consensus diagnostic criteria are welcomed.[7]

Considering the paucity of data and prospective studies to inform on how to approach the diagnosis and treatment of patients with this complex and heterogeneous disease, this study by Yu et al is helpful, particularly with regards to iMCD. There is little consensus on how iMCD should be managed and most published experience on this is in the form of case reports or mini series. Approaches such as rituximab and chemotherapy have been somewhat useful and recently, antibodies that target the IL-6 signaling cascade, such as siltuximab, have demonstrated good efficacy but require long-term administration.[8] Herein, the authors analyzed clinicopathologic features and therapeutic outcome in a large series of HIV/HHV-8–negative CD (UCD and iMCD). There were several interesting findings. Lymph node immunophenotyping demonstrated significant differences in T- and B-cell populations between UCD and iMCD cases, suggesting distinct pathophysiologies and likely disparate mechanisms of cytokine deregulation. In addition, more than one-third of cases of iMCD had a history of an autoimmune disease, suggesting either a role of or strong association with autoimmunity. This raises the question of whether or not these cases occurring in a milieu of autoimmunity are biologically and pathogenetically distinct, and prognostically different from cases not associated with autoimmune disease? In this series, the authors observed a very high response rate with siltuximab, and in iMCD this was significantly more effective than rituximab and chemotherapy approaches.

CD, particularly iMCD, remains a challenge on several levels due to its rarity, heterogeneity, and thus far, poorly understood pathogenesis. Moving forward, the most expedient ways to make progress will likely come from international collaborations that focus on developing optimal shared tissue repositories and other clinicopathologic data, to better understand the biology of iMCD in order to pave the way for novel clinical trial development and ultimately improved outcomes.

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