Nearly 70 years later: the continued unraveling of Castleman disease

Frits van Rhee

Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Correspondence: F. van Rhee
vanrheefrits@uams.edu

Received: April 12, 2022.
Accepted: April 19, 2022.
Prepublished: April 28, 2022.

https://doi.org/10.3324/haematol.2022.280902

Much progress has been made in our understanding of Castleman disease over the past 60-70 years since it was first described in 1954.[1] Castleman disease is a heterogeneous group of lymph node disorders with shared pathological findings. The histopathology of the disease spans a spectrum from, at one end, lymph nodes showing regressed or atretic follicles with prominent follicular dendritic cell networks, expanded mantle zones consisting of small B-lymphocytes and prominent interfollicular hyalinized vessels referred to as the hyaline vascular type. At the other end is the plasmacytic pathology characterized by increased numbers of hyperplastic follicles and marked interfollicular plasmacytosis, also with increased vascularity. Clinically, a unicentric form of Castleman disease (UCD) affecting one lymph node station and a multicentric form (MCD) involving multiple lymph node areas have now been recognized. Patients with MCD often have inflammatory symptomatology driven by hyper-cytokinemia. There is a predilection for hyaline vascular pathology in UCD and plasmacytic findings in MCD, but there is considerable overlap. Cytokines and chemokines such as interleukin (IL)-6 and vascular endothelial growth factor (VEGF) play an important role in driving the phenotype of the idiopathic form of MCD (iMCD), but the cellular origins of these factors have not been identified. UCD is treated with surgery and iMCD with antibodies that target IL6 with 33-50% of patients responding.[2,3] These response rates underscore the notion that a better understanding of iMCD is sorely needed to improve the therapeutic options for all.

UCD and iMCD have remained poorly understood disorders in terms of molecular pathogenesis, cellular etiology and signaling pathways. In this issue of *Haematologica*, Horna *et al.* report the first lymph node transcriptome analysis of UCD and iMCD supplemented by immunohistochemistry for CXCL13 and C4d, a marker of the classical complement pathway.[4] Similar to the histopathology, the transcriptomes of UCD and iMCD have both common and distinct features. For instance, there was over-representation of genes involved in collagenous fibrosis in UCD and increased expression of proteasome genes reflective of the increased plasmacytosis often seen in iMCD. iMCD lymph nodes showed upregulation of genes in the mammalian target of rapamycin (m-TOR) complex, consistent with recent findings that m-TOR is activated in multiple cell types in the interfollicular space in iMCD and the presence of a serum m-TOR proteomic signature.[5]

An unexpected shared feature of UCD and iMCD was the upregulation of the complement effector *C3* and components of the classical component pathway (UCD: *C1S* and *C1R*; iMCD *C4* and *C4B*) suggesting that complement activation plays a role in the B-cell activation/plasma cell differentiation as well as the inflammatory response seen in Castleman disease. Immunohistochemistry showed that C4d was often, but not exclusively, located within or near follicular dendritic cells in regressed germinal centers as well as in mantle zones.

Expression of the CXCL13 chemokine was also increased in both UCD and iMCD, and CXCL13 was mostly localized to follicular dendritic cells. CXCL13 is one of the most upregulated chemo/cytokines in iMCD according to proteomic studies.[6] CXCL13 plays a role in the attraction and differentiation of B-lymphocytes, and helps to orchestrate the organization of the germinal center architecture and B-cell response. It seems likely that excess CXCL13 produced by follicular dendritic cells plays a critical role in abnormal B-cell follicle formation observed in Castleman disease.

A further common feature of UCD and iMCD histopathology was the increased vascularity. Many patients with iMCD have elevated serum VEGF. Interestingly, the expression of the *FL1* gene, which encodes for the vascular endothelial growth factor receptor 1 (VEGFR-1) was upregulated in both UCD and iMCD. Transcripts for the proangiogenic factor placental growth factor (PGF), which is a ligand for VEGFR-1, were also increased in both forms of Castleman disease. A not previously described feature in Castleman disease was upregulation of the apelin receptor (in UCD and MCD) as well as apelin (in UCD), which also serve to promote angiogenesis.

A recent study by Wing *et al.* examined the expression of immune-related genes in UCD and MCD lymph nodes.[7] In common with the findings reported by Horna *et al.*, there was overexpression of *CXCL13* in both UCD and MCD. There was again increased representation of genes involved in the complement cascade, angiogenesis and VEGF signaling. Increased expression of genes for extracellular matrix modification, suggesting stromal remodeling, was unique to UCD, whereas plasma-cell-related genes, genes involved in cytokine signaling and inflammation (IL-1, IL-13 and IL-4) as well as enrichment for IL-6 pathway genes were specific to MCD.

Common themes emerge from both datasets, including the importance of angiogenesis in Castleman disease, which is consistent with the vascular histopathology. The involvement of the complement pathway in Castleman disease raises the question of whether this could be a therapeutic target, especially in iMCD patients suffering from thrombotic micro-angiopathy and renal failure. Clearly, follicular dendritic cells play an important role in the pathogenesis of both UCD and MCD. A recent Japanese study in a mouse model of iMCD showed that anti-CXCL13 antibody was able to mitigate the inflammatory syndrome underscoring the notion that CXCL13 may be a novel therapeutic target (Kikushige, presented at the International Symposium on Castleman Disease, 2021).

The cellular origin of IL-6 production has been challenged, with some suggesting that this cytokine is produced outside the lymph node compartment, consistent with the findings of Horna *et al.*, while others have implicated lymph node B-lymphocytes, macrophages and follicular dendritic cells. The data from Wing *et al.* suggest that IL-6 was present in CD31-positive endothelial cells, while VEGF was found in follicular dendritic cells and interfollicular M2 macrophages.

Overall, the present findings suggest potential alternative pathways, which can be targeted in non-responders to therapy against IL-6 by using anti-complement agents, anti-CXC13 monoclonal antibodies and molecules that bind VEGF and PGF. Other research has identified m-TOR and the JAK-STAT pathway as potential therapeutic targets. A clinical trial with the m-TOR inhibitor sirolimus is in progress (NCT03933904).[8,9] It is encouraging to see that the veil over the enigma of Castleman disease is slowly lifting and that a more thorough understanding of this disease will likely result in better therapies in the near future.

Disclosures

FVR sits on an advisory board for EUSA Pharmaceuticals.

References

1. Castleman B, Towne VW. Case records of the Massachusetts General Hospital; weekly clinicopathological exercises; founded by Richard C. Cabot. N Engl J Med. 1954;251(10):396-400.
2. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. Blood. 2005;106(8):2627-2632.
3. van Rhee F, Wong RS, Munshi N, et al. Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2014;15(9):966-974.
4. Horna P, King RL, Jevremovic D, Fajgenbaum DC, Dispenzieri A. The lymph node transcriptome of idiopathic multicentric Castleman disease. Haematologica. 2023;108(1):207-218.
5 Pai RL, Japp AS, Gonzalez M, et al. Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathic multicentric Castleman disease. JCI Insight. 2020;5(9):e135031.
6. Pierson SK, Stonestrom AJ, Shilling D, et al. Plasma proteomics identifies a 'chemokine storm' in idiopathic multicentric Castleman disease. Am J Hematol. 2018;93(7):902-912.
7. Wing A, Xu J, Meng W, et al. Transcriptome and unique cytokine microenvironment of Castleman disease. Mod Pathol. 2022;35(4):451-461.
8. Fajgenbaum DC, Langan RA, Japp AS, et al. Identifying and targeting pathogenic PI3K/AKT/mTOR signaling in IL-6-blockade-refractory idiopathic multicentric Castleman disease. J Clin Invest. 2019;129(10):4451-4463.
9. Arenas DJ, Floess K, Kobrin D, et al. Increased mTOR activation in idiopathic multicentric Castleman disease. Blood. 2020;135(19):1673-1684.