haematologica
Journal of the Ferrata Storti Foundation

Interleukin-6 in Castleman disease subtypes: look to tissues, not just blood

by Mariam Goubran and Luke Y.C. Chen

Received: October 20, 2025.
Accepted: October 30, 2025.

Citation: Mariam Goubran and Luke Y.C. Chen. Interleukin-6 in Castleman disease subtypes: look to tissues, not just blood.
Haematologica. 2025 Nov 6. doi: 10.3324/haematol.2025.289031 [Epub ahead of print]

Interleukin-6 in Castleman disease subtypes: look to tissues, not just blood

Mariam Goubran [1,3]

Luke Y.C. Chen [1,2,3]

[1] Division of Hematology, University of British Columbia, Vancouver, British Columbia, Canada

[2] Division of Hematology, Dalhousie University, Halifax, Nova Scotia, Canada

[3] Coastal Program for Rare Inflammatory Diseases, Nova Scotia Health Research Innovation Hub, Halifax, Nova Scotia, Canada

Correspondence to: Luke Y.C. Chen, lchen2@bccancer.bc.ca

Key words: cytokine storm; IL-6; endothelialitis

In this issue of *Haematologica,* Nishikori *et al* examine the differential interleukin 6 (IL-6) production pathways in two subtypes of idiopathic multicentric Castleman disease (iMCD): iMCD-idiopathic plasmacytic lymphadenopathy (iMCD-IPL) and iMCD-thrombocytopenia, anasarca, fever/reticulin fibrosis, renal dysfunction and organomegaly (iMCD-TAFRO).[1] Using immunohistochemistry (IHC) and in-situ hybridization (ISH) on lymph nodes, they demonstrated that IL-6 is highly expressed in plasma cells in iMCD-IPL, whereas in iMCD-TAFRO, IL-6 expression is found mainly in vascular endothelial cells [Figure]

This study addresses one of the most pressing questions in Castleman Disease (CD): namely, what pathophysiological mechanism(s) account for the major phenotypic differences between iMCD-IPL and iMCD-TAFRO? While IL-6 has long been known to play a central role in all subtypes of iMCD, and IL-6 inhibition is very effective in a subset of all iMCD patients, IPL and TAFRO have very different clinical presentations. Patients with iMCD-IPL have thrombocytosis, profound polyclonal hypergammaglobulinemia, plasmacytic lymph node histology, and a surprisingly indolent clinical course despite severe systemic inflammation, whereas those with iMCD-TAFRO have an acute, rapidly progressive cytokine storm syndrome characterized by thrombocytopenia, low-to-normal serum IgG and hypervascular lymph node histology (Table).

While clinicians tend to focus on cytokines levels in peripheral blood, tissues are in fact where immune cells and their associated signals function.[2] In rheumatoid arthritis (RA), synovial tissues are a significant source of IL-6,[3] as are temporal arteries in giant cell arteritis (GCA).[4] An historical, landmark study in Castleman disease reported IL-6 production from lymph nodes in a 14 year old woman with unicentric CD and a 52 year old woman with multicentric CD, both of whom had an “IPL” like picture of systemic inflammation with indolent, 5-6 year history, anemia, and IgG > 40 g/L .[5] Thus, the tissue(s) where IL-6 is expressed clearly plays a role in the clinical presentation of patients with CD and other IL-6 driven diseases. However, the IL-6 causing systemic inflammation cannot come solely from lymph nodes, as many patients with unicentric CD and a very large lymph node mass have no systemic inflammation, whereas patients with iMCD-TAFRO typically have very minor lymphadenopathy associated with severe inflammation and end organ damage.[6] The study by Nishikori *et al.* begins to unlock one of the mysteries of CD by demonstrating the importance of IL-6 expression in lymph node in IPL and vascular endothelial cells in TAFRO.

Lessons learned from coronavirus disease (COVID-19) cytokine storm provide added context. In the early days of the COVID-19 pandemic, there was robust debate about whether severe COVID-19 was due to vasculopathy or cytokine storm.[7] Ultimately the

was answer was “yes” – to both. Vascular endothelialopathy characterized by high levels of thrombomodulin and soluble P-selectin was a major component of severe COVID-19,[8] and IL-6 inhibition with tocilizumab decreases mortality in patients with COVID-19 cytokine storm.[9] In this light, finding high endothelial expression of IL-6 in the cytokine storm of iMCD-TAFRO is not surprising, as blood and blood vessels are not mutually exclusive tissue compartments, but interact substantially with each other. Further, the modest elevations of median serum IL-6 levels in both iMCD-IPL and iMCD-TAFRO in the present study, 37.5 pg/mL and 15.6 pg/mL (reference range < 8 pg/mL in most laboratories), are also not surprising. At first glance, the markedly elevated serum IL-6 levels (often over 1000 pg/mL) in other inflammatory conditions such as sepsis, acute respiratory distress syndrome and chimeric antigen receptor T-cell cytokine release syndrome, not all of which benefit from IL-6 inhibition, may seem to contradict the concept of iMCD and COVID-19 as cytokine storm syndromes.[10] However, the apparent paradox of relatively low serum IL-6 levels in conditions such as iMCD, RA, GCA and COVID-19 cytokine storm, all of which are driven by IL-6, and respond to IL-6 inhibition, is explained both by the role of IL-6 production in tissue, and the fact that most tissues rely on trans-signaling of IL-6, which is turn dependent on soluble IL-6 receptor (cleaved from dendritic cells) and its buffer, sgp130.[9] Thus, serum levels of IL-6 are only one piece of the “puzzle” of IL-6 induced inflammation. Further, Nishikori *et al*. highlight that the cytokine storm of TAFRO involves multiple inflammatory pathways including upregulation of genes such as TNF, IL-1R, mTOR, and VEGFA. In contrast, iMCD-IPL demonstrates constitutive *XBP1*-driven IL-6 production suggesting that chronic autocrine IL-6 signalling could be sustaining ongoing plasma cell proliferation and related symptoms in iMCD-IPL (Figure).

Castleman disease is currently a broad umbrella concept encompassing diverse entities ranging from unicentric CD to HHV-8 associated multicentric CD to the three subtypes of iMCD. The unifying feature of all CD subtypes is lymph node histology findings such as regressed germinal centers, polyclonal plasmacytosis, and hypervascularity. However, such features can also be seen in reactive conditions such as viral infection and autoimmune disease, and up to one quarter of patients with the cytokine storm TAFRO have no lymphadenopathy (and thus no CD),[6] which begs the question of whether all of the entities currently classified as CD are truly part of one disease spectrum, or whether distinct genetic, infectious, or other drivers of disease will be uncovered over time. Regardless of the final answer to this enigma, Nishikori *et al*. have made significant strides toward removing the troubling term “idiopathic” from iMCD.

References

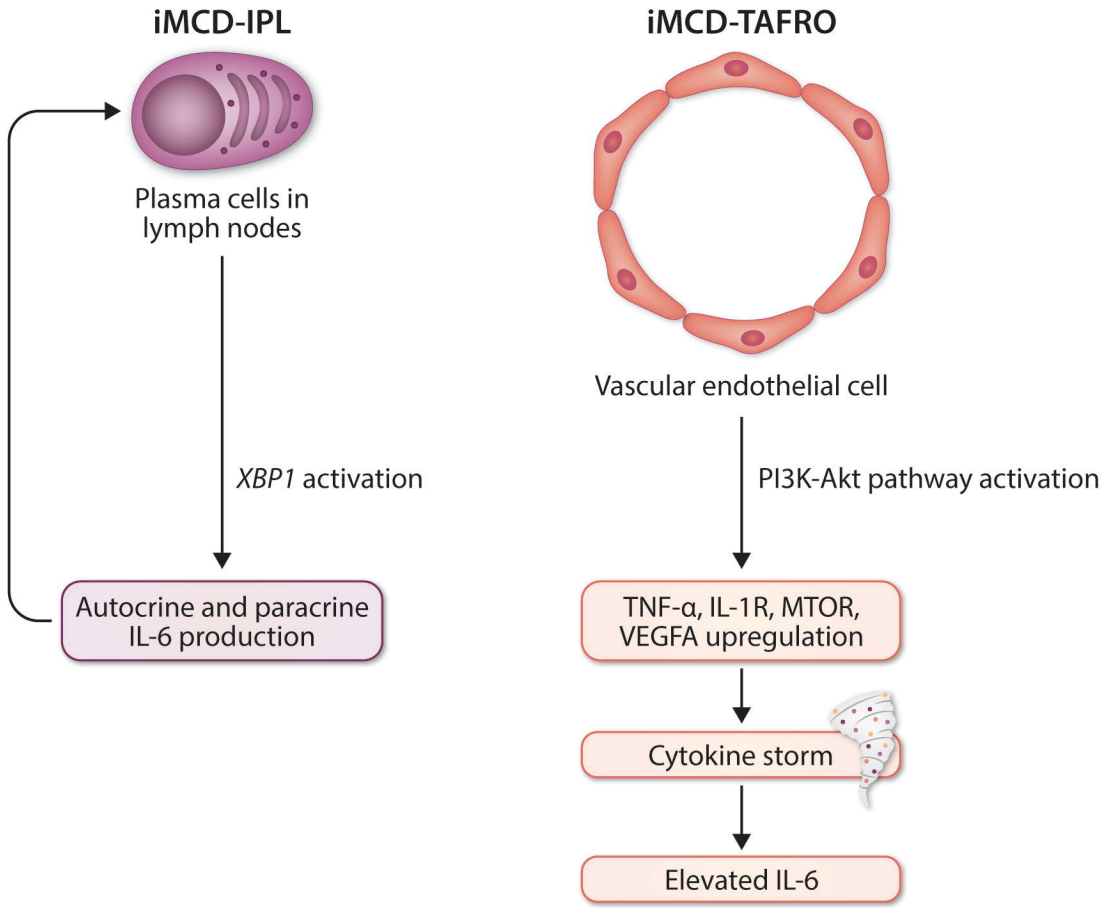
1. Nishikori A, Nishimura MF, Nishimura Y, et al. Distinct interleukin-6 production in IPL and TAFRO subtypes of idiopathic multicentric Castleman disease. Haematologica. xxx
2. Farber DL. Tissues, not blood, are where immune cells function. Nature. 2021;593(7860):506-509.
3. Hirano T, Matsuda T, Turner M, et al. Excessive production of interleukin 6/B cell stimulatory factor-2 in rheumatoid arthritis. Eur J Immunol. 1988;18(11):1797-1801.
4. Hernández-Rodríguez J, Segarra M, Vilardell C, et al. Tissue production of pro-inflammatory cytokines (IL-1β, TNFα and IL-6) correlates with the intensity of the systemic inflammatory response and with corticosteroid requirements in giant-cell arteritis. Rheumatology. 2003;43(3):294-301.
5. Yoshizaki K, Murayama S, Ito H, Koga T. The Role of Interleukin-6 in Castleman Disease. Hematol Oncol Clin North Am. 2018;32(1):23-36.
6. Chen LYC, Zhang L, Fajgenbaum DC. Expert Perspective: Diagnosis and Treatment of Castleman Disease. Arthritis Rheumatol. 2025.
7. Chen LYC, Hoiland RL, Stukas S, Wellington CL, Sekhon MS. Confronting the controversy: interleukin-6 and the COVID-19 cytokine storm syndrome. Eur Respir J. 2020;56(4):2003006.
8. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet. 2020;7(8):e575-e582.
9. Chen LYC, Biggs CM, Jamal S, Stukas S, Wellington CL, Sekhon MS. Soluble interleukin-6 receptor in the COVID-19 cytokine storm syndrome. Cell Rep Med. 2021;2(5):100269.
10. Leisman DE, Ronner L, Pinotti R, et al. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020;8(12):1233-1244.

Table: Comparison of idiopathic Multicentric Castleman subtypes

	iMCD-TAFRO	**iMCD-NOS**	**iMCD-IPL**
Clinical presentation	Acute cytokine storm	Chronic lymphadenopathy	Chronic indolent lymphadenopathy, inflammation
Lymph node volume	Small (often < 2 cm short axis)	Medium-large	Medium (often 2-4 cm short axis)
C-reactive protein	>100 mg/L (may be lower early in course but often rises to >> 100 mg/L)	10-100 mg/L	> 100 mg/L (chronically 50-200 mg/L in many patients)
Platelets	Low	normal	Often elevated
Gamma globulins	Low or normal	Mild PHGG	Severe PHGG typically > 35 g/L
IL-6 mRNA	Vascular endothelial cells	--	Plasma cells [XBP-1 mediated autocrine production]
Typical histology	Hypervascular	Plasmacytic or mixed	Plasmacytic

IPL: idiopathic plasmacytic lymphadenopathy; NOS: not otherwise specified; PHGG: polyclonal hypergammaglobulinemia; TAFRO: thrombocytopenia, anasarca, fever/[reticulin] fibrosis, renal dysfunction, organomegaly; UCD: unicentric Castleman Disease

Figure: Proposed mechanisms of IL-6 mediated inflammation in idiopathic Multicentric Castleman Disease Idiopathic Plasmacytic Lymphadenopathy (iMCD-IPL) vs idiopathic Multicentric Castleman Disease, thrombocytopenia, anasarca, fever/[reticulin] fibrosis, renal dysfunction, organomegaly (iMCD-TAFRO) subtypes. Nishikori et al demonstrate that IL-6 is highly expressed in plasma cells in iMCD-IPL where autocrine and paracrine signalling, driven in part by *XBP1* gene expression, is the favoured mechanism for sustained cytokine production. In contrast, IL-6 expression is more prominent in vascular endothelial cells in patients with iMCD-TAFRO where the authors also identified upregulation of cytokine storm-related genes such as *TNF, IL-1R, mTOR*, and *VEGFA*. This suggests that IL-6 elevation in iMCD-TAFRO is secondary to the cytokine storm and not the primary disease driver


iMCD-IPL
Plasma cells in lymph nodes
XBP1 activation
Autocrine and paracrine IL-6 production
iMCD-TAFRO
Vascular endothelial cell
PI3K-Akt pathway activation
TNF-α, IL-1R, MTOR, VEGFA upregulation
Cytokine storm
Elevated IL-6