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

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In this issue of *Haematologica*, Nishikori *et al*. examine the different pathways of interleukin 6 (IL-6) production 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 and *in-situ* hybridization 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 1).

This study addresses one of the most pressing questions in Castleman disease: 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, iMCD-IPL and iMCD-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 1).

While clinicians tend to focus on cytokine levels in peripheral blood, tissues are in fact where immune cells and their associated signals function.[2] In rheumatoid arthritis, synovial tissues are a significant source of IL-6,[3] as are temporal arteries in giant cell arteritis.[4] A historical, landmark study in Castleman disease reported IL-6 production from lymph nodes in a 14-year-old woman with unicentric Castleman disease and a 52-year-old woman with multicentric Castleman disease, both of whom had an "IPL"-like picture of systemic inflammation with an indolent, 5- to 6-year history, anemia, and IgG >40 g/L.[5] Thus, the tissues in which IL-6 is expressed clearly play a

Table 1. Comparison of idiopathic multicentric Castleman subtypes

Characteristics	iMCD-TAFRO	iMCD-NOS	iMCD-IPL
Clinical presentation	Acute cytokine storm	Chronic lymphadenopathy	Chronic indolent lymphadenopathy, inflammation
Lymph node volume	Small (short axis often <2 cm)	Medium-large	Medium (short axis often 2-4 cm)
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)
Platelet count	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

iMCD: idiopathic multicentric Castleman disease; IPL: idiopathic plasmacytic lymphadenopathy; NOS: not otherwise specified; TAFRO: thrombocytopenia, anasarca, fever/(reticulin) fibrosis, renal dysfunction, organomegaly; PHGG: polyclonal hypergammaglobulinemia; IL-6: interleukin-6.

role in the clinical presentation of patients with Castleman disease and other IL-6-driven diseases. However, the IL-6 causing systemic inflammation cannot come solely from lymph nodes, as many patients with unicentric Castleman disease 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 Castleman disease by demonstrating the importance of IL-6 expression in lymph nodes in iMCD-IPL and vascular endothelial cells in iMCD-TAFRO.

Lessons learned from the cytokine storm that occurs in coronavirus disease 2019 (COVID-19) 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 a 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. Furthermore, the modest elevations of median serum IL-6 levels in both iMCD-IPL and iMCD-TAFRO in the study by Nishikori *et al*., 37.5 pg/mL and 15.6 pg/mL (reference range <8 pg/mL in most laboratories), are also not surprising. At a first glance, the markedly elevated serum IL-6 levels (often over 1,000 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, rheumatoid arthritis, giant cell arteritis 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

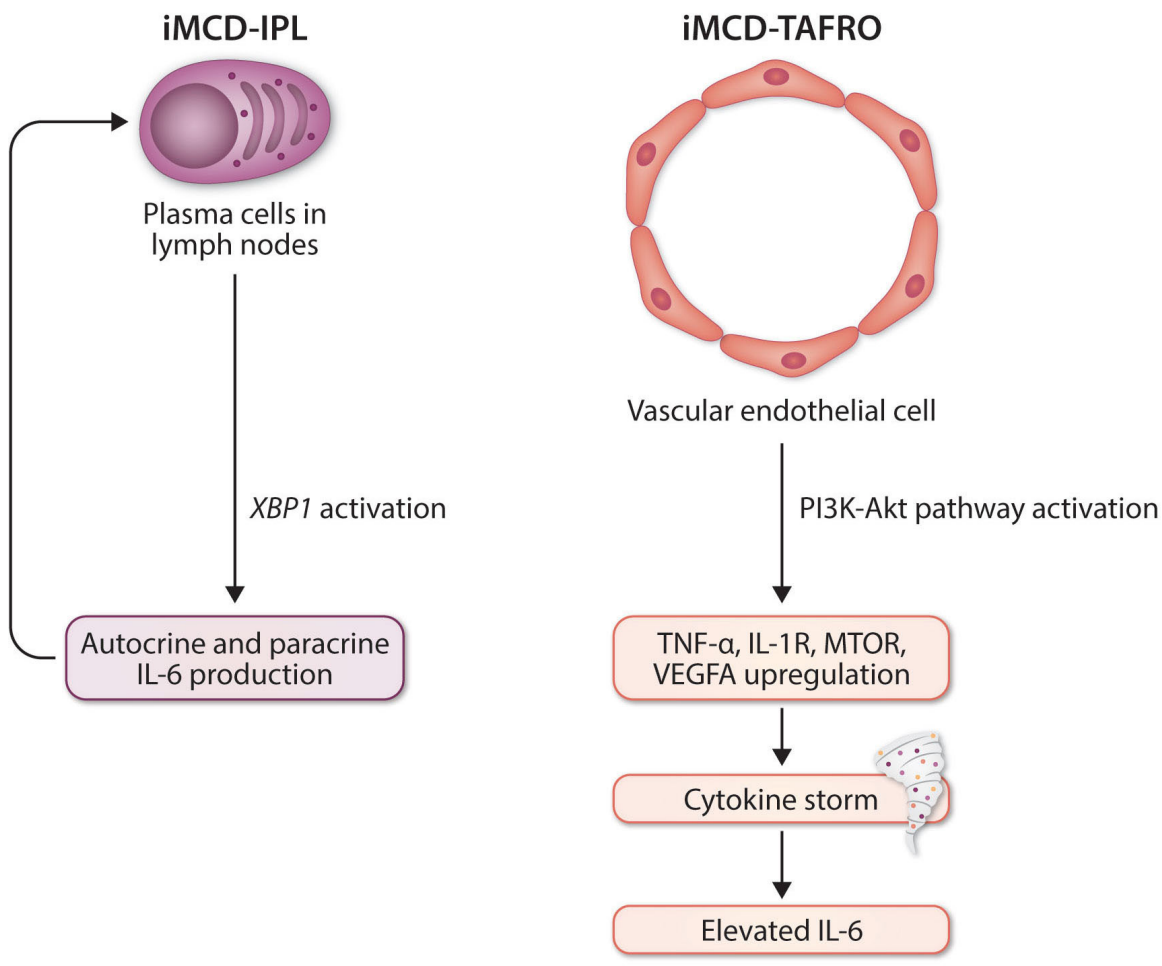

Figure 1. Proposed mechanisms of interleukin-6-mediated inflammation in different subtypes of idiopathic multicentric Castleman disease. Nishikori *et al*. demonstrate that interleukin-6 (IL-6) is highly expressed in plasma cells in idiopathic multicentric Castleman disease (iMCD)- idiopathic plasmacytic lymphadenopathy (IPL) in which autocrine and paracrine signaling, driven in part by *XBP1* gene expression, is the favored mechanism for sustained cytokine production. In contrast, IL-6 expression is more prominent in vascular endothelial cells in patients with iMCD-thrombocytopenia, anasarca, fever/[reticulin] fibrosis, renal dysfunction, organomegaly (TAFRO), in which the authors also identified upregulation of cytokine storm-related genes such as *TNF*, *IL1R*, *MTOR*, and *VEGFA*. This suggests that IL-6 elevation in iMCD-TAFRO is secondary to the cytokine storm and not the primary disease driver.

IL-6-induced inflammation. Furthermore, Nishikori *et al*. highlight that the cytokine storm of iMCD-TAFRO involves multiple inflammatory pathways including upregulation of genes such as *TNF*, *IL1R*, *MTOR*, and *VEGFA*. In contrast, iMCD-IPL demonstrates constitutive *XBP1*-driven IL-6 production suggesting that chronic autocrine IL-6 signaling could be sustaining ongoing plasma cell proliferation and related symptoms in iMCD-IPL (Figure 1).

Castleman disease is currently a broad umbrella concept encompassing diverse entities ranging from unicentric Castleman disease to human herpesvirus-8-associated multicentric Castleman disease to the three subtypes of iMCD. The unifying feature of all Castleman disease 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 Castleman disease),[6] which begs the question of whether all of the entities currently classified as Castleman disease 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.

Disclosures

LYCC has received speaker’s fees from Recordati Rare Diseases. MG has no conflicts of interest to disclose.

Contributions

MG and LYCC both wrote and edited the mansucript and approved the final version.

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