Editorial

The American Journal of Hematology

New perspectives on the origins of Castleman illness.

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Received Date : June 04, 2024
Accepted Date : June 06, 2024
Published Date : July 06, 2024

Two germ line mutations that may contribute to the development of iMCD are described by Chan et al. Each twin had heterozygous mutations in the tumor necrosis factor receptor-associated factor (TRAF) gene and homozygous mutations in the nuclear receptor cooperator 4 (NCOA4) gene. You et al. previously reported variants in NCOA4 in 5 out of 22 patients (23%) with iMCD.2. Even though You et al. classified those variants as probably somatic, their unique approach of using external patient controls for somatic variant calling and the variant allele frequency of roughly 50% in each case imply that those variants in that study are most likely germ line heterozygous variants. This route can also be triggered by interleukin-6 (IL-6), and it has been proposed that the interaction between androgen receptor-associated proteins such NCOA4 and MAPK may improve it.Two TRAF mutations have been connected to aberrant immunity, higher risk for B-cell malignancies, enhanced inflammatory response, and B-cell dysregulation and hyperactivity. The fact that the two twins' clinical phenotype and the development of iMCD did not occur at the same time raises interesting possibilities about the interaction of unknown environmental triggers with a genetic background.

Many hematologic conditions with comparable lymph node histological characteristics are together referred to as Castleman disease (CD). In general, CD can be classified as either unicentric or multicentric based on the degree of lymphadenopathy. Human herpes virus type 8 (HHV8) is the primary cause of many multicentric CD cases; it usually occurs in the context of immunosuppression (HHV8-associated multicentric CD); nevertheless, in some cases, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin abnormalities) syndrome (POEMS syndrome–associated multicentric CD) coexists with immunosuppression. Nevertheless, no cause is found in about 50% of instances; these patients are now classified as having iMCD. The cytokine-driven inflammatory syndrome linked to iMCD, which frequently involves IL-6, is responsible for fevers, sweats at night, and other constitutional symptoms. It also causes abnormalities in laboratory tests, including high levels of C-reactive protein, erythrocyte sedimentation rate, and hypergammaglobulinemia. Organ dysfunction, including renal failure, or even death, may occur in extreme circumstances. Lately, Under the direction of the Castleman Disease Collaborative Network (CDCN), an expert group has made progress in developing international consensus criteria for the diagnosis of Castleman.3. Similar to this, the CDCN has developed worldwide consensus treatment guidelines, according to which siltuximab monoclonal antibody therapy is advised as the first line of treatment for neutralizing the cytokine IL-6.

International consensus criteria for the diagnosis of Castleman disease have been developed by an expert committee working under the guidance of the Castleman Disease Collaborative Network (CDCN).3. In a similar vein, the CDCN has produced global consensus treatment guidelines, the first of which recommends treating the cytokine IL-6 with siltuximab monoclonal antibody therapy iMCD. About one-third of patients may have low-level autoantibodies, but they are almost usually nonspecific. In reality, the existence of a well-defined autoimmune disease precludes an iMCD diagnosis according to the revised diagnostic criteria. According to Chan et al.'s findings in this study, germ line mutations in genes implicated in the inflammatory cascade are one of the other theories for the genesis of iMCD. On the other hand, somatic mutations in lymph node cells could possibly play a role. Activating mutations in the platelet-derived growth factor receptor-β have been detected in 17% of patients with CD45−stromal cells who have unicentric CD (UCD).

The significance of IL-6 in iMCD has long been recognized.

There has been inconclusive research on the cellular source of IL-6 production, and plasma cells were once assumed to be the source of IL-6. RNA in situ hybridization was used in conjunction with a recent transcriptome analysis of paraffin-embedded lymph node tissues to discover IL-6 overexpression in CD31+ endothelium or lymphatic structures.7. Chan et al. also discovered upregulation of genes related to the IL-6 pathway in nodal fibroblastic cells and endothelial cells, indicating a potential function for the stroma in iMCD, similar to what is seen in UCD.

Proteomic analysis has led to novel therapy opportunities and offered intriguing new insights into the pathophysiology of

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iMCD when combined with immunohistochemistry and other studies. It is crucial to keep in mind that between 35 and 50 percent of patients with iMCD respond to IL-6 pathway blocking, indicating the significance of additional drivers and signaling pathways.

It has recently been discovered that the JAK-STAT pathway is active even in patients who do not react to siltuximab, an anti-IL-6 monoclonal antibody.8 Incident reports of patients responding to treatment with JAK-STAT inhibitors have been made. It's feasible that some people signal through JAK-STAT because of ligands or other cytokines. Furthermore, mTOR (mammalian target of rapamycin)/Akt/phosphatidylinositol 3-kinase signaling is observed in anti-IL-6 resistant individuals. This heightened mTOR activation prompted a treatment trial with the mTOR inhibitor sirolimus, to which certain patients showed response.All things considered, it appears that the picture of iMCD is complicated but getting clearer. Numerous clinically distinct iMCD phenotypes, such as organomegaly, reticulin fibrosis, thrombocytopenia, anasarca, fever, and idiopathicplasmacytic lymphadenopathy, have been reported. According to proteomic analysis, there could be five different groups, one of which is enriched for siltuximab responders.

The goal of deep sequencing research has been to identify the iMCD counterpart of the Hodgkin disease Reed-Sternberg cell. Nevertheless, given the clinical and biochemical variability of iMCD, it is perhaps not surprising that no common mutational profile has emerged from the few investigations conducted to date (reviewed by Butzmann et al).10 The larger picture of the Chan et al. study highlights the critical necessity for a thorough search in lymph node tissue for germ line mutations as well as somatic abnormalities, as they could reveal a range of alterations impacting inflammatory pathways. The notoriously challenging diagnosis of iMCD is made more difficult by the lack of certain biomarkers in lymph nodes and blood. In addition to aiding in diagnosis, a focused sequencing panel in the future might provide pathologists and doctors new treatment ideas.

REFERENCES

1. Chan JY, Loh JW, Lim JQ, et al. Single-cell landscape of idiopathic multicentric Castleman disease in identical twins. Blood.

2. 024;143(18):1837-1844. 2. You L, Lin Q, Zhao J, Shi F, Young KH, Qian W. Whole-exome sequencing identifies novel somatic alterations associated with outcomes in idiopathic multicentric Castleman disease. Br J Haematol. 2020; 188(5):e64-e67.

3. Fajgenbaum DC, Uldrick TS, Bagg A, et al. International, evidence-based consensus diagnostic criteria for HHV-8-negative/ idiopathic multicentric Castleman disease. Blood. 2017;129(12):1646-1657.

4. van Rhee F, Voorhees P, Dispenzieri A, et al. International, evidence-based consensus treatment guidelines for idiopathicmulticentric Castleman disease. Blood. 2018; 132(20):2115-2124.

5. Nabel CS, Sameroff S, Shilling D, et al. Virome capture sequencing does not identify active viral infection in unicentric and idiopathic multicentric Castleman disease. PLoS One. 2019;14(6):e0218660.

6. Li Z, Lan X, Li C, et al. Recurrent PDGFRB mutations in unicentric Castleman disease. Leukemia. 2019;33(4):1035-1038.

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. Pai RAL, Japp AS, Gonzalez M, et al. Type I IFN response associated with mTOR activation in the TAFRO subtype of idiopathicmulticentric Castleman disease. JCI Insight. 2020;5(9):e135031.

9. Pierson SK, Shenoy S, Oromendia AB, et al. Discovery and validation of a novel subgroup and therapeutic target in idiopathic multicentric Castleman disease. Blood Adv. 2021;5(17):3445-3456.

10. Butzmann A, Kumar J, Sridhar K, Gollapudi S, Ohgami RS. A review of genetic abnormalities in unicentric and multicentric Castleman disease. Biology (Basel). 2021; 10(4):251.