The Development of Diagnostic Criteria and Utilization of Excisional Lymph Node Biopsies Shorten Time to Diagnosis for Idiopathic Multicentric Castleman Disease

Mateo Sarmiento Bustamante[1]*, Criswell L. M. Lavery[1]*, Adam Bagg[3], Mary Jo Lechowicz[4], Daisy Alapat[5], Amy Chadburn[6], Megan S. Lim[7], Gordan Srkalovic[8], Frits van Rhee[9], Joshua D. Brandstadter[1,2], and David C. Fajgenbaum[1]

[1]Center for Cytokine Storm Treatment & Laboratory, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [2]Division of Hematology/Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [3]Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA; [4]Department of Hematology & Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA; [5]Department of Pathology, College of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; [6]Division of Hematopathology, Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY; [7]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY; [8]University of Michigan Health-Sparrow Herbert-Herman Cancer Center, Lansing, MI; [9]Myeloma Center, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR

Introduction

- Idiopathic multicentric Castleman Disease (iMCD) is a rare lymphoproliferative disorder defined by multifocal lymphadenopathy and systemic inflammation potentially causing end-stage organ failure and death.
- iMCD presents as distinct clinical subtypes:
  - **N**ot **O**therwise **S**pecified (NOS) patients experience moderate, chronic constitutional symptoms.
  - **T**hrombocytopenia, **A**nasarca, **F**ever, **R**enal Dysfunction, **O**rganomegaly (TAFRO) patients present more severely, frequently requiring hospitalization and life-saving interventions.
- iMCD patients endure a lengthy path to diagnosis, requiring imaging, a lymph node biopsy, and blood work in addition to the exclusion of more common disorders.
- Consensus diagnostic criteria for iMCD were not published until 2017.[1]
- We investigated differences in diagnosis times between subtypes, the impact of the 2017 diagnostic criteria on diagnosis times, the morbidity of delayed diagnosis, and the impact of different lymph node biopsies on diagnosis.

Methods

- 110 patients enrolled in the ACCELERATE Natural History registry had their iMCD diagnosis confirmed by an expert panel of CD physicians and pathologists.
- Time to diagnosis was defined as days elapsed between the date of the first day of a patient's first iMCD flare to the date of pathological diagnosis.
- Patients were divided into "Pre-Criteria" and "Post-Criteria" groups based on symptom onset +/- 5.1 years from 2018 (5.1 years chosen to allow equal time frames of comparison based on most recently diagnosed patient in cohort, 2018 chosen to allow one year for dissemination of diagnostic criteria).
- Proportion of time spent hospitalized from disease onset to diagnosis was calculated for each patient.
- Number and types of biopsies received leading to diagnosis were documented for each patient.

Results

Table 1. Demographic characteristics of 110 iMCD patients

Age at Diagnosis, Years	
Median (IQR)	37 (22, 48)
Range	2, 75
Sex, n (%)	
Male	61 (55)
Female	49 (45)
Race, n (%)	
White	71 (65)
Black/African American	13 (12)
Asian	16 (15)
Native Hawaiian/Pacific Islander	1 (1)
American Indian/Alaska Native	0
Other/Refused to Answer	9 (8)
Clinical Subtype, n (%)	
TAFRO	67 (61)
NOS	43 (39)

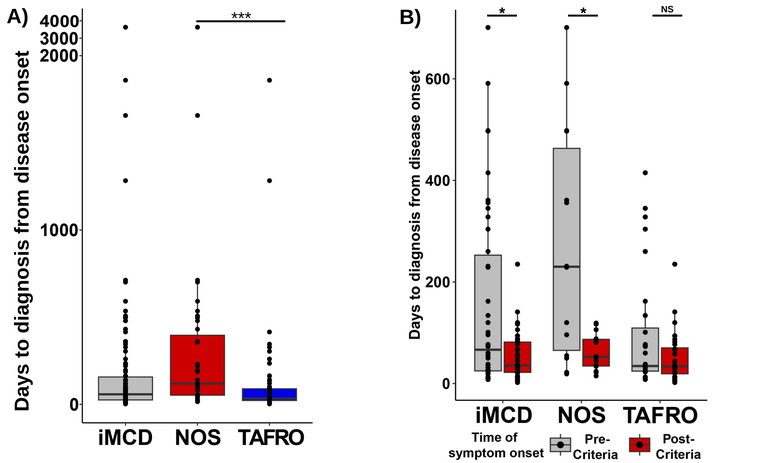

Figure 1. Diagnosis times for iMCD patients both historically and pre/post diagnostic criteria. A) iMCD patients had a median (IQR) diagnosis time of 58 (25, 157) days. Stratified by subtype, NOS patients had significantly longer diagnosis times than TAFRO patients (median [IQR]: 119 [53, 396] vs. 35 [22, 89] days, p= 1.8 x 10^{-5}). B) Patients diagnosed pre-criteria had a median (IQR) diagnosis time of 67 (25, 253) days, significantly longer than the 36 (22, 82) days it took for patients to be diagnosed post-criteria (p= 0.04). Reduction in diagnosis time was driven entirely by a reduction in median diagnosis times for NOS patients (pre: 218 days vs. post: 53 days, p=0.01).

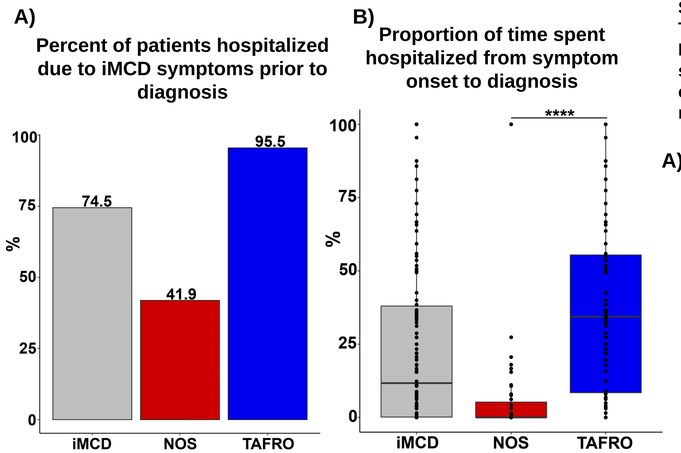

Figure 2. iMCD patients require hospitalization pending diagnosis
A) Of the 110 iMCD patients, 82 (74.5%) were hospitalized due to disease flare prior to diagnosis. When stratified by subtype, 18/43 (41.9%) NOS patients and 64/67 (95.5%) TAFRO patients were hospitalized prior to diagnosis. B) iMCD patients spent a median (IQR) 11.7% (0.1, 38.0) of time from disease onset to diagnosis hospitalized. TAFRO patients spent a significantly greater portion of time hospitalized prior to diagnosis than NOS patients (median [IQR]: 34.4% [8.5, 55.4] vs 0% [0, 5.3], p= 3.4 x 10^{-8}).

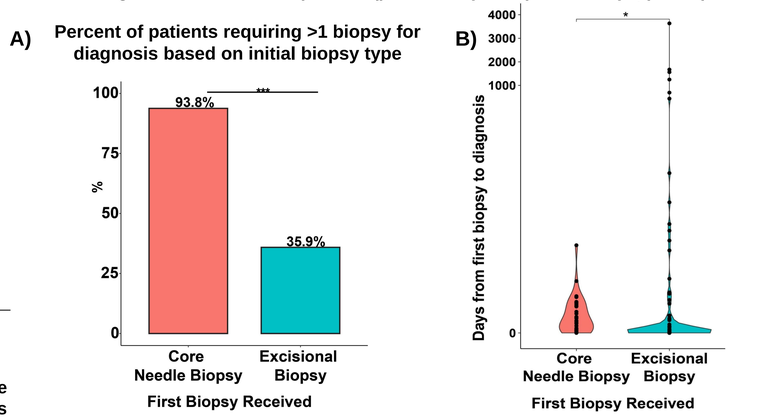

Figure 3. Core needle biopsies are insufficient for iMCD Diagnosis. A) 30/32 (93.8%) patients receiving a core needle biopsy as their initial biopsy required an additional excisional biopsy for diagnosis, compared to 28/78 (35.9%) patients who initially received an excisional biopsy (p=0.001). B) Time from first biopsy to diagnosis was significantly longer for patients who initially received a core needle biopsy, with median (IQR) time from first biopsy to diagnosis of 26 (7, 59) days compared to 5 (1, 28) days for patients who began with an excisional biopsy (p=0.017).

Summary and Discussion

- iMCD patients frequently encounter diagnostic delays, which can lead to increased morbidity.
- NOS patients have historically faced longer diagnosis times than TAFRO patients, likely due to their more indolent presentation.
- The creation of diagnostic guidelines in 2017 has led to a significant reduction in diagnosis times for NOS patients, bringing them more inline with TAFRO times.
- iMCD patients require hospitalization due to their iMCD symptoms prior to diagnosis, with TAFRO patients spending a large proportion of time from disease onset to diagnosis hospitalized.
- Core needle biopsies are almost always insufficient for an iMCD diagnosis and add time to an iMCD patient's diagnostic journey.
- Over 1/3 of patients initially receiving an excisional biopsy, however, required an additional biopsy for diagnosis, highlighting the difficulty of diagnosis.
- Our findings highlight the morbidity of diagnostic delay and emphasize the importance of diagnostic guidelines and excisional biopsies in reducing time to diagnosis.
- Our findings also emphasize the need for a serum biomarker or alternative diagnostic approach to further reduce time to diagnosis.

Future Directions

- Further investigate outcomes associated with longer diagnosis times in iMCD patients.
- Examine role of PET/CT imaging in diagnosis time and accuracy.
- Examine characteristics of patients misdiagnosed with iMCD.

References

1. Fajgenbaum, D.C., Uldrick, T.S., Bagg, A., Frank, D., Wu, D., Srkalovic, G., Simpson, D., Liu, A.Y., Menke, D., Chandrakasan, S. and Lechowicz, M.J., 2017. International, evidence-based consensus diagnostic criteria for HHV-8–negative/idiopathic multicentric Castleman disease. *Blood, The Journal of the American Society of Hematology*, *129*(12), pp.1646-1657. Contact: Mateo Sarmiento Bustamante: mateo@castlemannetwork.org