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Characterizing the heterogeneity of Castleman disease and oligocentric subtype: Findings from the ACCELERATE registry

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Abstract:
Castleman disease (CD) describes a group of rare lymphoproliferative disorders that exhibit a wide range of symptomatology and degree of lymphadenopathy, particularly across the two forms of CD with unknown etiology, unicentric CD (UCD) and HHV-8-negative/idiopathic multicentric CD (iMCD). Whereas UCD cases typically present with localized lymphadenopathy and mild symptoms, iMCD involves multicentric lymphadenopathy and cytokine-storm driven symptoms with three recognized clinical phenotypes. Increasingly, there are anecdotal reports of cases that do not fit into this framework, but these cases have not been systematically described. Herein, we utilize the ACCELERATE natural history registry to characterize the spectrum of CD based on disease features, symptomatology, and severity. Our results characterize a cohort of 179 CD cases, which were reviewed and confirmed by an expert panel of clinicians and hematopathologists. We show that CD patients present on a continuous spectrum of clinical phenotypes, and we describe oligocentric CD (OligoCD), an intermediate phenotype that does not fit the criteria for UCD or iMCD. These cases tend to have “oligocentric” lymphadenopathy (median [interquartile range] regions of lymphadenopathy: 3.0 [2.0,4.0]) in a regional pattern and exhibit a mild clinical phenotype that is more similar to UCD than iMCD. We also show that OligoCD patients are inconsistently categorized as UCD versus iMCD, highlighting the need for this characterization. Future data collected through ACCELERATE may further elucidate the natural history and risk profile of these patients.

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Abstract

Castleman disease (CD) describes a group of rare lymphoproliferative disorders that exhibit a wide range of symptomatology and degree of lymphadenopathy, particularly across the two forms of CD with unknown etiology, unicentric CD (UCD) and HHV-8-negative/idiopathic multicentric CD (iMCD). Whereas UCD cases typically present with localized lymphadenopathy and mild symptoms, iMCD involves multicentric lymphadenopathy and cytokine-storm driven symptoms with three recognized clinical phenotypes. Increasingly, there are anecdotal reports of cases that do not fit into this framework, but these cases have not been systematically described. Herein, we utilize the ACCELERATE natural history registry to characterize the spectrum of CD based on disease features, symptomatology, and severity. Our results characterize a cohort of 179 CD cases, which were reviewed and confirmed by an expert panel of clinicians and hematopathologists. We show that CD patients present on a continuous spectrum of clinical phenotypes, and we describe oligocentric CD (OligoCD), an intermediate phenotype that does not fit the criteria for UCD or iMCD. These cases tend to have "oligocentric" lymphadenopathy (median [interquartile range] regions of lymphadenopathy: 3.0 [2.0,4.0]) in a regional pattern and exhibit a mild clinical phenotype that is more similar to UCD than iMCD. We also show that OligoCD patients are inconsistently categorized as UCD versus iMCD, highlighting the need for this characterization. Future data collected through ACCELERATE may further elucidate the natural history and risk profile of these patients.

Key points

- Oligocentric Castleman disease (CD) is an intermediate phenotype distinctly characterized from unicentric and idiopathic multicentric CD
- Oligocentric Castleman disease cases demonstrate a pattern of oligocentric or regional lymphadenopathy and few inflammatory symptoms

Introduction

Castleman disease (CD) comprises a group of lymphoproliferative disorders with a spectrum of shared lymph node histopathological features and highly variable clinical symptomatology. CD was first reported in 1956 by Dr. Benjamin Castleman, who characterized hyaline vascular histopathologic findings in two localized cases – subsequently termed unicentric CD (UCD).[1] The histopathologic definition of CD has since broadened to include cases with characteristic plasmacytic and mixed histopathologic findings and, in addition to UCD, now includes a set of disorders with multicentric lymphadenopathy – termed multicentric CD (MCD). A subset of MCD cases is caused by uncontrolled human herpesvirus-8 (HHV8) infection (HHV8-associated MCD), most often seen among individuals infected with HIV or who are otherwise immunocompromised.[2] Among the MCD cases negative for HHV8, a small proportion are associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS-associated MCD).[2] The remaining HHV8-negative MCD cases have an unknown etiology and are termed idiopathic MCD (iMCD).[2]

Diagnosis of iMCD requires ≥2 enlarged lymph nodes (≥1 centimeter in short-axis diameter), lymph node histopathological features consistent with CD, and at least 2 of 11 minor diagnostic criteria, with at least one being a laboratory abnormality.[3] Histopathologic features consistent with CD are observed across a spectrum and include regressed or hypertrophic germinal centers, follicular dendritic cell prominence, vascularity, and plasmacytosis. Clinico-pathologic findings are non-specific to iMCD, and without a definitive diagnostic biomarker, iMCD remains a diagnosis of exclusion. This results in a substantial risk of misdiagnosing patients with closely overlapping disorders and heightens the need for clinico-pathological recognition.

Among patients meeting iMCD criteria, several distinct clinical phenotypes have been reported and recognized. The most severe phenotype of iMCD includes patients who have

thrombocytopenia, anasarca, fever/inflammation, renal failure/reticulin fibrosis of bone marrow, and organomegaly (TAFRO).[4,5] These patients tend to experience the most intense periods of active disease, characterized by prolonged hospitalizations and invasive health care interventions due to multi-organ failure; separated by periods of disease remission after effective treatment.[6] A second phenotype of patients present with thrombocytosis and hypergammaglobulinemia. These patients were described as early as 1980 and have been labeled as having the idiopathic plasmacytic lymphadenopathy (IPL) subtype.[7–9] iMCD patients who do not meet the criteria of either of these phenotypes have a phenotype that is not otherwise specified (NOS).[10,11] IPL and NOS patients tend to have fewer hospitalizations and interventions than those with TAFRO, but often experience a longer lower-grade disease flare.[6]

The etiology of iMCD is currently unknown, and it is not clear if etiology differs between the three clinical phenotypes. Several causes for iMCD have been proposed including autoimmune/ autoinflammatory, infectious, and neoplastic origins.[11–13] Current research suggests the cause is unlikely to be infectious and ongoing investigations into alternative hypotheses are underway; however, no single cause has yet been proven.[13,14] Regardless of the trigger, the systemic symptoms, generalized lymphadenopathy, and multi-organ dysfunction of iMCD are driven by a cytokine storm that often includes interleukin 6 (IL-6). Indeed inhibition of IL-6 with the monoclonal antibody siltuximab is the only approved therapy for iMCD.[15–17] All patients with iMCD are recommended to receive siltuximab, or, when siltuximab is unavailable, tocilizumab, which targets the IL-6 receptor.[18] Severity of disease and response to anti-IL-6 therapy dictate subsequent treatment recommendations.[18]

As with iMCD, the etiology of UCD is not well understood, though a clonal expansion of lymph node non-hematopoietic stromal cells has been implicated.[2,19] Diagnosis requires a solitary enlarged lymph node region with CD histopathology and exclusion of overlapping disorders; no laboratory or clinical abnormalities are required to diagnose UCD. Surgical

resection is recommended and highly effective when feasible.[20] For cases where resection is not feasible, treatment recommendations are based on the site of involvement, the degree of compression of adjacent structures, and the presence of systemic inflammation. Patients with UCD typically experience fewer and less severe symptoms than iMCD. However, some UCD patients can have an inflammatory syndrome. A recent report highlighted that a subset of UCD patients experience inflammatory symptoms at presentation, and ongoing symptoms can persist in some patients, even following complete lymph node excision.[21,22]

CD has historically been thought of as either occurring with a single region of lymphadenopathy and mild symptoms (UCD) or many regions of lymphadenopathy and severe symptoms (iMCD). However, anecdotally, some patients do not fit into this framework and rather show CD histopathology and a clinical phenotype that falls between that of UCD and iMCD.[20] Case reports and anecdotal accounts describe these patients as having >1 region of lymphadenopathy, which is often adjacent or regionally limited and milder systemic symptoms than iMCD patients.[20,23–26] Given the differences in natural history, recommended treatment approaches for iMCD may not be appropriate for these patients. As such, an international consensus group defining diagnostic and treatment guidelines for UCD provided similar recommendations for treating this intermediate phenotype with surgical debulking and removal, when possible, over systemic therapies like IL-6 blocking antibodies or cytotoxic chemotherapies.[20] These intermediate CD cases have not been comprehensively characterized and are currently not included as a recognized CD subtype, which may lead to misdiagnosis and patients who feel unrecognized.

Previous studies of CD have described the bifurcation of CD into UCD and MCD and have subtyped MCD based on presence or absence of HHV8 and POEMS syndrome.[2,7,10,27,28] These classifications have helped to better inform treatment decisions – especially for clear cases of UCD, iMCD, HHV8-associated MCD, and POEMS-associated MCD. However, there

remain large knowledge gaps among borderline cases of CD subtypes with unknown etiology, and filling these gaps remains crucial to improving treatment and outcomes. Herein, we draw on the ACCELERATE natural history registry of CD[29] to report the phenotypic continuum of CD among cases with no clearly identifiable etiology – namely UCD, iMCD, and undefined CD cases. We describe cases with an undefined phenotype as oligocentric (OligoCD) and provide data on disease characteristics and treatment patterns.

Methods

Human Subjects

Patients of all ages from the United States and globally and who have ever received a pathologic diagnosis of CD were invited to self-enroll into the ACCELERATE research study online. All patients consented to the research and provided Health Insurance Portability and Accountability Act waivers for collection of complete medical data. This research protocol was approved by the University of Pennsylvania Institutional Review Board.

Procedures and Definitions

Patients enrolled into ACCELERATE between October 2016 and April 2023. After enrollment, complete medical records were collected and abstracted by trained research analysts; hematoxylin and eosin (H&E) stained lymph node slides were also collected and made available for review. A panel of four clinicians and three hematopathologists with expertise in the CD field reviewed and adjudicated each case for the likelihood of accurate CD diagnosis. At the time of analysis, 343 cases had been enrolled, extracted into the study database and were available for inclusion in analysis. Cases of confirmed HHV-8-associated MCD (N=12) and POEMS-associated MCD (N=10) were excluded from the analysis. Seventeen cases missing diagnostic radiologic data were also excluded.

To describe the spectrum of CD, we categorized all cases as either probable UCD, probable iMCD, or probable CD of undefined subtype prior to panel review. Probable UCD was defined as patients with a solitary enlarged LN region and a pathology report compatible with CD.[20] Probable iMCD was defined as patients with ≥2 enlarged LN regions, 2 of 11 minor diagnostic criteria with at least one abnormal laboratory parameter, and a pathology report compatible with CD.[30] Probable CD of undefined subtype (CD-undefined) was defined as all patients with a pathology report compatible with CD and neither met the probable UCD nor or probable iMCD categories. Panel review confirmed or rejected diagnosis with CD and identified the respective histopathological subtype. For nine cases, an H&E stained slide was not available for review, but the panel was able to confirm a diagnosis by review of the initial diagnostic pathology report and histopathologic subtype was imputed from the diagnostic pathology report. iMCD patients were also subcategorized according to phenotypic subtypes TAFRO, IPL, and NOS. Criteria and categorizations for CD subtypes and phenotypes can be found in Table S1, and the number of cases that met each criteria for TAFRO and IPL can be found in Table S2.

Inflammatory syndrome was defined as at least two of three occurring simultaneously within at least 90 days of diagnosis: anemia, hypoalbuminemia, and inflammation, defined as hemoglobin < 11.5 g/dL (males) or <10.5 g/dl (females), albumin <3.5 g/dL, and either C-reactive protein (CRP) > 20 mg/dL or erythrocyte sedimentation rate (ESR) > 30 mm/hr, respectively. Regimens were defined according to treatment start dates. Response assessment was determined according to the change in the proportion of symptoms present before and after a given regimen was initiated. A durable response was recorded if there was at least 50% improvement in the proportion of symptoms present after a regimen initiation compared to before or at the time of initiation and that response lasted at least one year. For a patient who received a given regimen more than once, the best response ever achieved was documented.

Lymph node response was defined as at least 50% decrease in the short axis measurement of the enlarged lymph node or 50% reduction in the number of enlarged lymph nodes.

A blinded radiological review was undertaken to investigate differences in the distribution and size of enlarged lymph nodes between patients who were panel-confirmed and patients who were not panel confirmed. Among the ACCELERATE cohort, there were 108 patients with available radiological images (including computed tomography or positron emission tomography with or without contrast) for review by a blinded radiologist. For each image, the radiologist reviewed and extracted the number of enlarged lymph nodes (short axis >1 cm) per location (according to the Ann Arbor lymph node staging system[31]) and recorded the size of the largest lymph node. From these data, we compared those of patients who were probable iMCD and panel-confirmed (N=53) and those who were probable iMCD and not panel-confirmed (N=22).

Quantification and Statistical Analysis

Data are primarily presented descriptively. Comparisons between groups were performed by Chi-Square or Fisher's exact test for categorical data and by Wilcoxon Rank Sum for quantitative data. Bonferroni adjustment was made for multiple comparisons. Three way group testing was done by Kruskal-Wallis with post hoc Dunn's test. Data analysis was performed by S.K.P. using R version 4.0.5. For original data used to produce this manuscript, please contact davidfa@pennmedicine.upenn.edu.

Results

Richly characterized cohort of CD patients reveals a continuous spectrum of clinical phenotypes

To assemble a cohort of clinically annotated CD cases, we accessed the ACCELERATE natural history registry of CD,[29] where patients with a pathology report suggestive of CD self-enrolled into ACCELERATE. At the time of analysis, 304 cases met criteria and underwent study team preliminary review and assessment of radiological and medical data for categorization by

probable subtype (as defined in the methods) based on meeting diagnostic criteria for UCD, iMCD, or neither (Figure 1). Forty-one cases had insufficient documentation to determine a probable subtype, 63 cases were probable UCD, 168 probable iMCD, and 32 probable CD-undefined (Figure 1). Forty-six of the 63 probable UCD cases (73%), 119 of the 168 probable iMCD cases (70.8%), and 14 of the 32 probable CD-undefined (43.8%) were confirmed by the expert panel. Cases whose CD diagnosis was panel-confirmed were significantly more likely to be classified as UCD or iMCD than as CD-undefined (p=0.007). Of note, all 14 of these CD-undefined cases have received care at an academic-affiliated hospital at least once in their follow-up.

For both probable UCD and probable iMCD, the most frequent reason for not meeting panel confirmation was pathologic inconsistency (52.9% and 40.8%, respectively). However, for probable CD of undefined subtype, the most frequent reason for not meeting panel confirmation was lack of overall consistency with CD (defined as being clinically and pathologically inconsistent with CD) in 50%. When feasible, the panel identified suspected alternative diagnoses for patients not confirmed (Figure 1). In-depth radiological review performed on a subset of probable iMCD patients for whom imaging was available (N=75) failed to reveal any clear differences in the distribution and size of enlarged lymph nodes between 53 iMCD patients that were panel-confirmed and 22 that were not confirmed (Figure S1). Demographic and diagnostics characteristics of the unconfirmed patients can be found in Table S3, and treatment patterns can be found in Table S4. Interestingly, the unconfirmed iMCD group was significantly older than the confirmed iMCD group (mean 47.7 years vs. 36.0 years, p=8.9 x10-5) and had a significantly shorter follow-up time (median 1.2 years vs 2.9 years, p=0.007). Three deaths occurred, all of which were in the unconfirmed iMCD group (3/49, 6.1%). Among unconfirmed iMCD cases, 11 had been suspected TAFRO, 14 suspected IPL, and 24 suspected NOS. Of

note, 5/7(71.4%) unconfirmed iMCD patients who were suspected IPL responded to siltuximab (Table S4).

Heterogeneous characteristics observed between CD subtypes and among iMCD phenotypes

After identifying a cohort of panel-confirmed cases for each subtype, we investigated characteristics and relationships between the confirmed subtypes. Mean (standard deviation [SD]) age at diagnosis of UCD patients was 41.4 (12.5) years, 34.0 (16.1) years for CD-undefined, and 36.0 (15.8) years for iMCD cases (Table 1). Continuous distribution in age between iMCD, UCD, and CD-undefined was not different (p=0.084). Exploratory post hoc pairwise testing was performed given the small sample and showed no difference between iMCD and CD-undefined (p=0.46) or between UCD and CD-undefined (p=0.09), but there was a difference between iMCD and UCD (p=0.01) (Figure S2A). Nine (7.6%) iMCD patients had died at the time of analysis – five of which occurred in the first year after diagnosis, compared to one (2.2%) UCD and zero CD-undefined patients. Median survival time could not be determined due to the small number of deaths. iMCD cases were evenly distributed between males (n=58, 49.6%) and females (n=60, 50.4%), while both CD-undefined and UCD cases were approximately two-thirds female (71.4% and 67.4%, respectively). Hypervascular/hyaline vascular histopathology predominated among all three subtypes. Mixed (n=31, 26.1%) and plasmacytic (n=8, 6.7%) were more prevalent in iMCD compared to the other categories, but still relatively uncommon. According to our definition and among those with sufficient data, inflammatory syndrome was noted among a minority of UCD patients (n=7, 25.9% among those with sufficient data) and not noted among CD-undefined patients (n=0, 0%). Eighteen (17.6%) iMCD patients did not meet these criteria for an inflammatory syndrome, which is a more stringent definition than the iMCD minor diagnostic criteria, and 17 did not have sufficient information to confirm inflammation.

As part of our investigation into the CD spectrum, we further characterized the three clinical phenotypes of patients meeting iMCD criteria: TAFRO, IPL, and NOS (Table 2, Table S5). Sixty-five (54.6%) patients met TAFRO and 12 (10.1%) met IPL criteria, with 42 (35.3%) defined as NOS. Interestingly, the mean age of IPL patients was 44 years, compared to 33.5 years for TAFRO and 37.6 years for NOS, and the majority of iMCD diagnosed <18 years had the TAFRO subtype (17/21, 81%). The age distribution (Figure S2B) between TAFRO, IPL, and NOS was not significantly different (p=0.051). However, since evidence for a difference was weak but marginally non-significant, we performed a post hoc pairwise comparison to examine possible differences between groups. There was no difference between IPL and NOS (p=0.10) or between TAFRO and NOS (p=0.07), but comparison between TAFRO and IPL showed a difference (p=0.01). These results demonstrate a trend towards TAFRO being diagnosed in younger patients; a larger sample may have achieved significance. Of the nine iMCD patients who died, six (66.7%) were TAFRO and three (33.3%) were NOS. No IPL patients in this cohort had died at the time of analysis. TAFRO patients were predominantly male (n=40, 61.5%), while IPL and NOS were predominantly female (n=8, 66.7% and n=27, 64.3% female, respectively). All histopathologic variants were found among IPL patients, but the plasmacytic variant was the most common (n=8, 66.7%). While evaluation of the IPL group was limited by small numbers, TAFRO and IPL patients tended to demonstrate more laboratory abnormalities and more clinical symptomatology. As expected, there were differences in the proportion of patients within each subgroup demonstrating abnormal clinical and laboratory tests (Table S5), such as thrombocytopenia ($p=1.6x10^{-14}$), thrombocytosis ($p=1.1x10^{-5}$), elevated CRP (p=0.002), low hemoglobin ($p=2.1x10^{-6}$), elevated creatinine ($p=3.05x10^{-5}$), low eGFR (p=0.001), elevated gammaglobulin ($p=5.4x10^{-4}$), and elevated IgG ($p=9.0x10^{-7}$). Notably, a higher proportion of TAFRO and IPL patients exhibited elevated CRP and low hemoglobin compared to NOS, while TAFRO patients had higher creatinine and lower eGFR values compared to both NOS and IPL, and IPL patients showed elevated gammaglobulins compared to both NOS and TAFRO.

CD-undefined patients tend to demonstrate oligocentric lymphadenopathy

To characterize the range of lymphadenopathy and clinical symptoms across CD, we plotted the number of documented minor diagnostic criteria against the number of enlarged lymph node stations and visualized patterns by subtype (Figure 2A). As per definition, UCD patients had one station of enlarged lymph nodes, and the number of minor diagnostic criteria ranged from zero to seven. iMCD patients demonstrated a range between two and 16 enlarged lymph node stations (median (interquartile range [IQR]): 8.0 (5.0, 10.5)) and between two and 10 minor diagnostic criterion. The 14 CD-undefined cases demonstrated between two and five enlarged lymph node stations (median (IQR): 3.0 (2.0, 4.0)) and 13 had only one minor diagnostic criteria. The apparent difference between CD-undefined and UCD is expected given the cohort definitions, but the apparent difference between CD-undefined and iMCD is noteworthy. One CD-undefined case had two minor clinical criteria but did not meet the iMCD criteria because the patient did not have at least one laboratory abnormality.

The 'oligocentric' pattern with a few enlarged lymph nodes observed in these CD-undefined cases was consistent with anecdotal clinical descriptions.[23–25] These cases have also been described as 'regional' because they tend to have adjacent lymphadenopathy. When we examined the location of enlarged lymph nodes for each of the 14 CD-undefined cases (Figure 2B), we found the enlarged nodes tended to fall within adjacent or nearby lymph node stations. Notably, in every case, the enlarged lymph node stations occurred on the same side of the diaphragm. Twelve cases involved enlarged lymph nodes that were located superiorly to the diaphragm, and two cases involved enlarged lymph nodes that were located inferiorly to the diaphragm.

We also examined which subtype had been assigned to the CD-undefined patients by their treating physicians according to documentation in patient medical records. Among the 119 panel-confirmed iMCD patients, 91.6% (n=109) had been diagnosed with iMCD by their treating

physician and 8.4% (n=10) diagnosed with UCD. Among the 46 panel-confirmed UCD patients, 89.1% (n=41) had been diagnosed with UCD by their treating physician and 10.9% (n=5) with iMCD. Among the 14 CD-undefined patients, 64.3% (n=9) had been diagnosed with UCD by their treating physician and 35.7% (n=5) diagnosed with iMCD. These data suggest greater discordance among patients with an undefined subtype (Figure 2C) and occasional ambiguity among UCD and iMCD despite diagnostic criteria. Given the oligocentric lymphadenopathy observed, we suggest the term 'oligocentric' CD (OligoCD) to describe this undefined subtype that does not meet UCD or iMCD criteria, and we will henceforth refer to the previously undefined cases as having OligoCD.

Oligocentric CD shares clinical resemblance to UCD

We next sought to determine whether OligoCD shares a greater clinical resemblance to UCD or iMCD. We compared diagnostic clinical, histopathological, and laboratory features between iMCD, UCD, and OligoCD cases and found OligoCD cases exhibited a clinical phenotype more similar to UCD than to iMCD (Figure 3A-C). iMCD and OligoCD had significantly different albumin, creatinine, CRP, and hemoglobin values ($p < 0.05$), but UCD and OligoCD showed no significant differences with respect to these laboratory values (Figure 3B). We investigated whether OligoCD patients had elevated IL-6 levels, but only two patients had IL-6 measured outside of a siltuximab treatment interval. One showed IL-6 within normal range, and one showed IL-6 at a level exceeding the reference interval of 5 pg/mL by nearly 8 times. OligoCD patients demonstrated relatively few clinical abnormalities, which was more similar to UCD. Conclusions from histopathology are difficult given that all three subtypes were predominantly hypervascular/hyaline vascular. Altogether, we note comparable laboratory and clinical findings between UCD and OligoCD, suggesting that OligoCD belongs on a spectrum of CD that includes UCD, OligoCD, and the three iMCD clinical phenotypes: TAFRO, IPL, and NOS (Figure 4).

Next, we compared clinical outcomes between groups, so we investigated the incidence of flares as well as the incidence of new nodal involvement beyond the diagnostic window (Table S6). We identified patients who experienced a flare or a resurgence of symptoms after having achieved at least a 50% reduction in symptoms from the initial diagnostic flare. Forty-eight (40.3%) iMCD patients experienced a subsequent flare, compared to 5 (35.7%) OligoCD and 9 (19.6%) UCD (p=0.04). Further, we reviewed radiology reports to identify patients who subsequently developed emergent nodal involvement at sites not previously affected during the year following their diagnosis. Of 119 iMCD patients, 35 (29.4%) had lymphadenopathy at newly involved nodal sites at least one year after diagnosis, compared to 5 (35.7%) of 14 OligoCD patients and 5 (10.9%) of 46 UCD patients (p=0.03). These findings suggest that while OligoCD patients are more clinically comparable to UCD patients at presentation, they may behave more like iMCD with regards to flares of disease over time.

Data on differential treatment approaches for individual clinical phenotypes is limited

Lastly, we investigated treatment patterns of patients across the spectrum from UCD through iMCD. It is important to note that some patients may not receive treatment at any time despite waxing and waning disease, whereas others may need multiple rounds of different treatments for refractory or relapsing disease. Among UCD, OligoCD, and the three clinical phenotypes of iMCD (TAFRO, IPL, and NOS), we categorized best durable response (lasting at least one year, Table 3) and lymph node response (Table S7) to treatment for regimens that are either consensus recommended or commonly administered. Response is more likely to be unknown in patients with few or no clinical symptoms other than lymphadenopathy. UCD patients received a median (IQR) of 1 (1.0, 2.0) treatment regimens, OligoCD received 2 (2.0, 3.0), NOS received 3 (2.0, 4.0), IPL received 4 (2.8, 5.0), and TAFRO received 3 (2.0, 4.0).

We found a 63.2% (12/19 evaluable) durable clinical response and an 85.7% (30/35 evaluable) lymph node response to surgical lymph node excision among UCD patients, a 16.7%

(1/6 evaluable) durable clinical response and a 40% (4/10 evaluable) lymph node response to surgical lymph node excision among OligoCD patients, and a 0% (0/10 evaluable) durable clinical response and 0% (0/4 evaluable) lymph node response among iMCD patients. A closer examination into the eight OligoCD patients who were categorized as not having an evaluable durable clinical response to surgical excision revealed that four had too few clinical symptoms at the start of treatment to assess a response, two achieved a response but there was not enough follow up data to determine the durability of that response, and two did not have enough data for a determination. These results suggest that OligoCD and UCD patients may have too few clinical/laboratory abnormalities prior to initiating a regimen to be able to reliably assess response to therapy. In fact, we found that across all regimen types (including any reason for which a patient may have started a new treatment), OligoCD (8/14; 57.1%) patients had a higher proportion of regimens where a response could not be determined due to lack of symptoms at the initiation of the regimen than UCD (17/46; 37.0%) or iMCD, (29/119; 24.4%; p=0.03). Limited data on treatments and response precluded definitive statistical comparison of treatment patterns across CD subtypes and among OligoCD patients.

Discussion

The data presented herein underscore the variability of CD and highlight that CD occurs across a spectrum rather than the previously described binary model of CD into UCD and MCD. Considering the degree of lymphadenopathy, laboratory abnormalities, symptomatology, and overall severity, we propose CD cases of unknown etiology be considered along a spectrum of symptoms and that these factors should be considered when determining treatment approaches for the various subtypes. Importantly, it is not yet known if the etiology of the different subtypes on this spectrum is related or unrelated, and there is no evidence to suggest that patients can progress from one subtype to another along this spectrum of clinical subtypes. While this study was not able to fully evaluate survival and prognostic factors due to limitations in study design

and sample sizes, we report that nine of the ten deaths in this cohort occurred in iMCD patients, and six of these were TAFRO. A recent multi-center study in China, which included 580 iMCD cases, found 3-year overall survival across the iMCD subtypes of 65.7% for TAFRO, 87.2% for NOS, and 98.5% for IPL.[10] The TAFRO subtype likely represents the most severe subtype on the multicentric end of the CD spectrum.

Characterization of the full spectrum of CD has been challenging to date due to its rarity, heterogeneity, and the fact that it remains a diagnosis of exclusion. The ACCELERATE natural history registry of CD serves as an ideal source of information due to the annotated set of data and independent diagnosis adjudication by a panel of disease experts. Diagnosis requires careful pathologic inspection to assess features of CD histopathology but high variability among pathologist interpretations can complicate diagnosis.[32] In fact, depending on subtype, between one-third and two-thirds of patients in our study who received a CD diagnosis at an outside institution did not have their diagnosis confirmed when their lymph node tissue and medical records were reviewed by CD experts. Interestingly we observed a 71.4% (5/7) response to siltuximab with or without steroids among patients who were probable iMCD-IPL but whose diagnosis was not confirmed by the panel. This raises the possibility that some patients who were not panel confirmed were misclassified or that siltuximab is effective for inflammatory diseases that overlap clinicopathologically with iMCD. Given the difficulty of diagnosing CD based on clinicopathologic features, the clinicopathologic spectrum of CD must be understood to facilitate its recognition and a diagnostic biomarker is needed.

We found a subset of patients who did not meet the diagnostic criteria for iMCD but who had enlarged lymph nodes in at least two regions and therefore did not have UCD. We have characterized these patients with oligocentric lymphadenopathy, often in a regional pattern, as OligoCD. These patients were clinically more similar to UCD than iMCD. While treatment data were limited, the milder clinical and laboratory abnormalities support the recommendation to

approach treatment with surgical debulking and removal when feasible and to limit systemic therapies, similar to the diagnostic and treatment guidelines for UCD.[20] However, extensive surgical procedures should also be avoided, and patients with inflammatory symptoms may benefit from systemic therapies. Among the small number of OligoCD cases that all exhibited mild disease severity in this study, few OligoCD patients received drug treatment regimens, and a large proportion (8/14, 57.1%) initiated treatment with few clinical symptoms. The incidence of future lymphadenopathy and subsequent flares being more similar to iMCD suggest monitoring may be needed. Further research and expert consensus are needed to advise on appropriate treatment approaches as OligoCD may have a different natural history and risk profile than UCD and iMCD. ACCELERATE and other population-based cohorts may provide additional data on the natural course of OligoCD.[10,33]

Patients with OligoCD were less likely to be panel-confirmed in this study, which may be because OligoCD has never been formally described by diagnostic criteria. Patients with an OligoCD-like profile may also be more likely to have an alternative disease process. Other published studies have described the presence of patients with an OligoCD phenotype,[20,23,25,34] but our study provides a large and richly annotated cohort of CD patients allowing for characterization of cases with OligoCD along the CD spectrum.[27,28,35,36] Interestingly, a larger proportion of patients in the UCD subtype had an inflammatory-like syndrome than in the OligoCD subtype, but this is in part driven by the definitions used. Likewise, a notable proportion of patients in the iMCD group did not have an inflammatory-like syndrome (18%). These patients with ≥2 enlarged lymph node stations and few minor criteria may be more similar to the OligoCD group. It remains to be known if the underlying disease pathogenesis is the same across these subtypes.

There are several limitations to this study. Patients are invited to self-enroll, which may lead to a self-selection sample bias. Our study does have a high proportion of individuals with

iMCD, and particularly with TAFRO, who tend to be the most severely affected patients. It is possible that these patients are more motivated to enroll in a research study due to the severity of their disease. Our rigorous confirmation process, however, helps to exclude patients who may be less likely to have an accurate CD diagnosis and who might not be excluded in large claims database research where clinico-pathological adjudication is not performed. Furthermore, real-world data presents challenges for analysis compared to clinical trials. Data are collected at non-standard intervals. To address this, subtypes were defined using criteria collected within 90 days of diagnosis, which may not reflect a real-world diagnosis timeframe. Our finding that the majority of cases with a probable intermediate/OligoCD subtype are not panel-confirmed may reflect the lack of diagnostic criteria for OligoCD, which could bias selection against these patients. The unequal and small number of patients in some subtypes limits our statistical power to make comparisons; however, most of our findings are descriptive in nature and generally support previous anecdotal reports related to OligoCD.

Herein, we have described the full spectrum of CD among subtypes with no clear etiology, which has allowed us to characterize the OligoCD subtype. Careful consideration should be given to alternative diagnoses for patients who do not meet UCD or iMCD diagnostic criteria. Investigations into a larger cohort of OligoCD patients will enable the development of diagnostic and treatment guidance.

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Disclosure of Conflicts of Interests

J.D.B. is supported by a Doris Duke Foundation's Physician Scientist Fellowship and American Society of Transplantation and Cellular Therapy New Investigator Award; has consulted for Recordati Rare Diseases and EUSA Pharma. D.A.T is a Co-founder of Quantitative Radiology Solutions LLC. M.J.L reports consulting fees from Secura Bio, EUSA Pharma, and Kyowa Kirin, as well as travel support from Secura Bio. C.C. is a paid consultant and speaker for Recordati Rare Diseases and receives research funding from Johnson & Johnson and Immunity Bio. A.D. has served on the advisory board and independent review committees for Janssen Pharmaceuticals, has received research dollars from Alynlam, Pfizer, Takeda, and BMS, and is on the scientific advisory board for AbbVie HemalogiX. R.K. has received research funding from Boehringer Ingelheim, Debiopharm, Foundation Medicine, Genentech, Grifols, Guardant,

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Tables with titles and legends

Table 1. Demographics and baseline characteristics of confirmed CD cases

	iMCD N=119	CD-undefined N=14	UCD N=46
Age, years, mean (SD)	36.0 (15.8)	34.0 (16.1)	41.4 (12.5)
<18 ye**ars, N (%)**	21 (18.1)	2 (14.3)	2 (4.3)
Deceased, N (%)	9 (7.6)	0	1 (2.2)
Sex, N (%)			
Female	60 (50.4)	10 (71.4)	31 (67.4)
Male	59 (49.6)	4 (28.6)	15 (32.6)
Race, N (%)			
American Indian/Alaska Native	1 (0.8)	0	0
Asian	14 (11.8)	0	2 (4.3)
Black	12 (10.1)	0	1 (2.2)
Native Hawaiian/ Pacific Islander	1 (0.8)	0	0
White	80 (67.2)	14 (100)	42 (91.3)
Not provided	11 (9.2)	0	1 (2.2)
Histopathological subtype, N (%)			
Hyaline vascular/ Hypervascular	80 (67.2)	11 (78.6)	40 (87)
Mixed	31 (26.1)	3 (21.4)	6 (13)
Plasmacytic	8 (6.7)	0	0
Assessed number of minor criteria, median (IQR)	11 (10, 11)	9 (8, 10)	7 (6.3, 10)
Abnormal number of minor criteria, median (IQR)	7 (5, 8)	2 (1, 3)	1 (0, 1)
Inflammatory syndrome*, N (%)			
Present	84 (82.3)	0	7 (25.9)
Absent	18 (17.6)	7 (100)	20 (74.1)
Insufficient information	17	7	19
N enlarged node stations, median (IQR)	8.0 (5.0, 10.5)	3.0 (2.0, 4.0)	1.0 (1.0, 1.0)
Follow-up time, years, median (IQR)	2.9 (1.2, 5.2)	1.3 (0.4, 4.3)	2.7 (1.1, 5.7)

*Inflammatory syndrome was defined as at least two of three parameters occurring simultaneously within at least 90 days of diagnosis: anemia, hypoalbuminemia, and inflammation, defined as hemoglobin < 11.5 g/dL (males) or <10.5 g/dl (females), albumin <3.5 g/dL, and either CRP > 20 mg/dL or ESR > 30 mm/hr, respectively. Insufficient information reflects cases for which hemoglobin, albumin, and CRP/ESR were not measured or were not measured concurrently and therefore there was not sufficient information to assign inflammatory syndrome. Abbreviations: SD: standard deviation; IQR: interquartile range

Table 2. Demographic, clinical, and laboratory features of iMCD phenotypes

	TAFRO N=65	**NOS N=42**	**IPL N=12**
Age, years, mean (SD)	33.5 (17.8)	37.6 (12.8)	44.0 (10.4)
<18 years, N (%)	17 (26.2)	4 (9.5)	0
Deceased, N (%)	6 (9.2)	3 (7.1)	0
Sex, N (%)			
Female	25 (38.5)	27 (64.3)	8 (66.7)
Male	40 (61.5)	15 (35.7)	4 (33.3)
Race, N (%)			
American Indian/Alaska Native	0	0	1 (8.3)
Asian	7 (10.8)	1 (2.4)	6 (50)
Black	6 (9.2)	6 (14.3)	0
Native Hawaiian/ Pacific Islander	1 (1.5)	0	0
White	47 (72.3)	29 (69)	4 (33.3)
Not provided	4 (6.2)	6 (14.3)	1 (8.3)
Histopathological subtype, N (%)			
Hyaline vascular/ Hypervascular	46 (70.8)	33 (78.6)	1 (8.3)
Mixed	19 (29.2)	9 (21.4)	3 (25)
Plasmacytic	0	0	8 (66.7)
Inflammatory disease, N (%)			
Present	63 (100)	13 (44.8)	8 (80)
Absent	0	16 (55.1)	2 (20)
Insufficient information	2	13	2
Follow-up time, years, median (IQR)	3.3 (1.3, 5.0)	2.0 (1.0, 4.6)	5.7 (1.9, 13.6)
Clinical symptoms, N/assessed (%)			
Constitutional symptoms	63/65 (96.9)	37/41 (88.1)	11/12 (91.7)
Organomegaly	59/65 (90.8)	16/40 (38.1)	5/12 (41.7)
Cherry hemangioma/violaceous papules	4/56 (7.1)	0	0
Lymphocytic interstitial pneumonitis	0	0	0
Fluid retention	64/65 (98.5)	23/40 (54.8)	6/11 (54.5)
Platelets, k/uL (Median, IQR)	83 (51, 136)	283 (219, 348)	451 (373, 489)
CRP, mg/L (Median, IQR)	80.5 (22.7, 185.0)	14.0 (5.0, 55.0)	114.0 (73.0, 165.1)
ESR, mm/hr (Median, IQR)	78 (47.5, 109.3)	43 (22, 72.0)	73 (32.5, 113.5)
Hemoglobin, g/dL (Median, IQR)	9.2 (8.0, 10.9)	11.9 (10.8, 13.4)	9.9 (8.0, 11.3)
Albumin, g/dL (Median, IQR)	2.5 (2.1, 2.9)	3.9 (3.3, 4.3)	2.8 (2.5, 3.6)
Creatinine, mg/dL (Median, IQR)	1.3 (1.0, 1.8)	0.8 (0.6, 1.0)	0.8 (0.7, 1.0)
eGFR, ml/min/1.73m^2			
≤60, N (%)	32 (31.9)	18 (56.3)	5 (6.3)
>60, N (%)	15 (68.1)	14 (43.8)	3 (3.8)
Not documented, N (%)	18	10	4
IgG, mg/dL (Median, IQR)	985 (736, 1528)	1137 (988, 1264)	4270 (3190, 6178)
Gammaglobulin, g/dL, (Median, IQR)	1.1 (0.8, 1.7)	1.2 (0.9, 1.5)	4.4 (4.1, 5.9)

Acronyms: TAFRO: Thrombocytopenia, anasarca, fever, reticulin fibrosis/renal insufficiency, organomegaly; NOS: not otherwise specified; IPL: idiopathic plasmacytic lymphadenopathy; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate; IgG: immunoglobulin G

Table 3. Treatment patterns and durable response* among OligoCD and iMCD subtypes

	TAFRO N=65	IPL N=12	NOS N=42	OligoCD N=14	UCD N=46
Number of regimens administered, Median (IQR)	3 (2, 4)	4 (2.75, 5)	3 (2, 4)	2 (2, 3)	1 (1, 2)
LN excision (partial or complete)					
Ever received, N	11	10	31	14	43
Response evaluable, n	10	9	25	6	19
Response ratio (%)	0/10 (0)	0/9	2/25 (8.0)	1/6 (16.7)	12/19 (63.2)
Response unknown, n	1	1	6	8	24
Steroid monotherapy					
Ever received, N	27	6	14	2	6
Response evaluable, n	24	5	10	1	1
Response ratio (%)	0/24 (0)	0/5 (0)	2/10 (20)	0/1 (0)	0/1 (0)
Response unknown, n	3	1	4	1	5
AntiIL-6 ± steroids*					
Ever received, N	39	10	21	2	3
Response evaluable, n	36	10	16	2	3
Response ratio (%)	16/36 (44.4)	6/10 (60)	7/16 (43.8)	1/2 (50)	1/3 (33.3)
Response unknown, n	3	0	5	0	0
Siltuximab ± steroids					
Ever received, N	28	8	20	2	3
Response evaluable, n	24	8	15	2	3
Response ratio (%)	11/24 (45.8)	5/8 (62.5)	6/15 (40)	1/2 (50)	1/3 (33.3)
Response unknown, n	4	0	5	0	0
Tocilizumab ± steroids					
Ever received, N	15	4	1	1	0
Response evaluable, n	14	3	1	1	0
Response ratio (%)	5/14 (35.7)	2/3 (66.7)	1/1 (100)	0/1 (0)	0
Response unknown, n	1	1	0	0	0
Rituximab ± steroids					
Ever received, N	12	6	21	4	5
Response evaluable, n	11	6	12	3	4
Response ratio (%)	3/11 (27.3)	0/6 (0)	3/12 (25.0)	0/3 (0)	1/4 (25)
Response unknown, n	1	0	9	1	1
Chemotherapy +/- other agents					
Ever received, N	29	0	3	2	2
Response evaluable, n	23	0	2	2	2
Response ratio (%)	11/23 (47.8)	0	1/2 (50)	0/2 (0)	0/2 (0)
Response unknown, n	6	0	1	0	0
Other					
Ever received, N	37	4	10	2	7
Response evaluable, n	33	4	9	2	4
Response ratio (%)	14/33 (42.4)	0/4 (0)	3/9 (33.3)	1/2 (50.0)	2/4 (50)
Response unknown, n	4	0	1	0	3

*Response assessment was determined according to the change in the proportion of symptoms present before and after a given regimen was initiated. A response was recorded if there was at least 50%

improvement in the proportion of symptoms present after a regimen initiation compared to before or at the time of initiation.

Figure legends

Figure 1. A large and richly-annotated cohort of CD patients reveals a small subset of cases with a form of CD that does not meet UCD or iMCD criteria.

A total of 304 cases with sufficient diagnostic radiologic data underwent preliminary review for categorization by probable subtype. Forty-one cases had insufficient documentation to undergo panel review. The remaining cases were categorized probable UCD (N=63), probable iMCD (N=168), and probable CD with an undefined subtype (N=32). Following expert panel review for diagnosis adjudication, 46 UCD, 119 iMCD, and 14 CD-undefined were panel-confirmed. Cases whose CD diagnosis was panel-confirmed were significantly more likely to be classified as UCD or iMCD than as CD-undefined (p=0.007).

Figure 2. Investigation of involved lymph node stations reveals that patients with an undefined subtype demonstrate oligocentricity.

Patients with an undefined subtype demonstrate oligocentricity. (A) The relationship between the number of enlarged lymph node stations and the number of minor diagnostic criteria. Patients with a CD-undefined can be visualized separately from both UCD and iMCD. (B) The majority of CD-undefined cases had four or fewer enlarged lymph nodes in the same general region. These patients demonstrate oligocentric lymphadenopathy and henceforth will be referred to as 'OligoCD'. (C) Cases that were panel-confirmed iMCD were typically diagnosed iMCD by their treating physician (n=109, 91.6%), and cases that were panel-confirmed UCD were typically diagnosed UCD by their treating physician (n=41, 89.1%). CD-undefined patients were diagnosed UCD in 64.3% of cases (n=9), and iMCD in the remaining 35.7% (n=5).

Figure 3. Disease features of OligoCD more closely resemble UCD than iMCD.

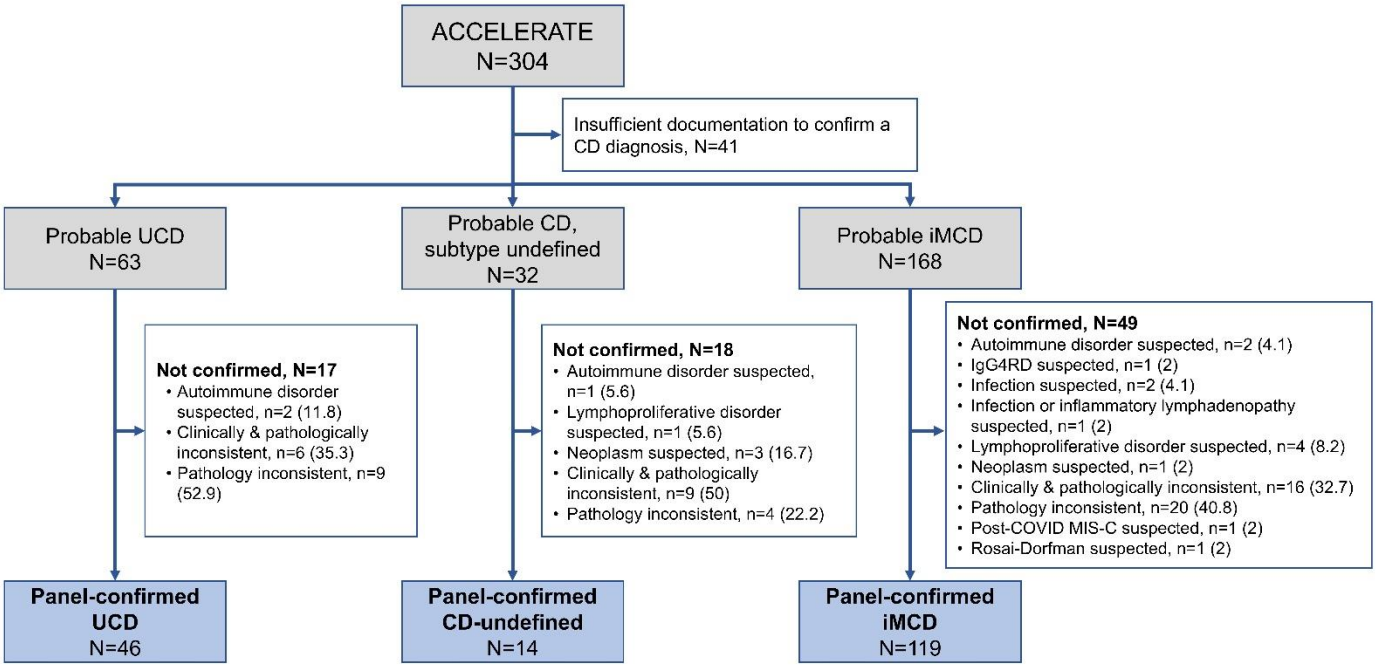
OligoCD demonstrates features that are more similar to UCD than to iMCD. (A) Clinical (B) laboratory and (C) histopathologic features of UCD, iMCD, and OligoCD cases demonstrate

stronger similarities between UCD and OligoCD. Significance: ns, p>0.05; *, p≤0.05; **, p≤0.01; ***, p≤0.001; **, p≤0.0001.

Figure 4. A summary of common clinical, laboratory and histopathological features on the spectrum of UCD to OligoCD to iMCD patients.

Patients demonstrate differences in lymphadenopathy, histopathology, laboratory and clinical abnormalities, and degree of inflammation. The least severe patients are typically UCD, and the most severe are typically iMCD-TAFRO. Severity of symptoms along this spectrum should be considered when making a diagnosis.

Figure 1.



	UCD N=63	CD-undefined N=32	iMCD N=168
Panel-confirmed	46 (73.0)	14 (43.8)	119 (70.8)
NOT Panel-confirmed	17 (36.0)	18 (56.3)	49 (29.2)

p-value = 0.007

Figure 2.

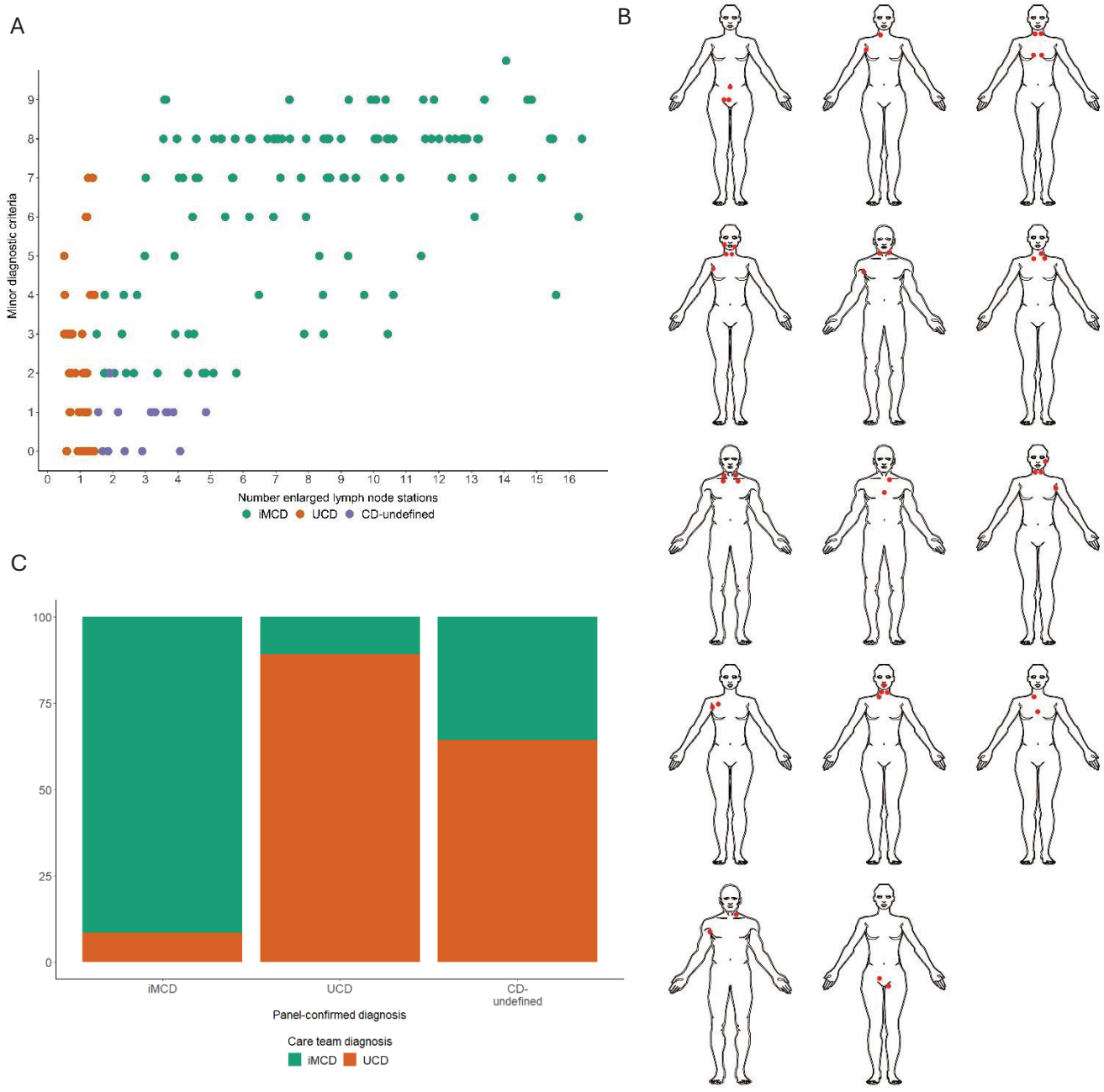


Figure 3.

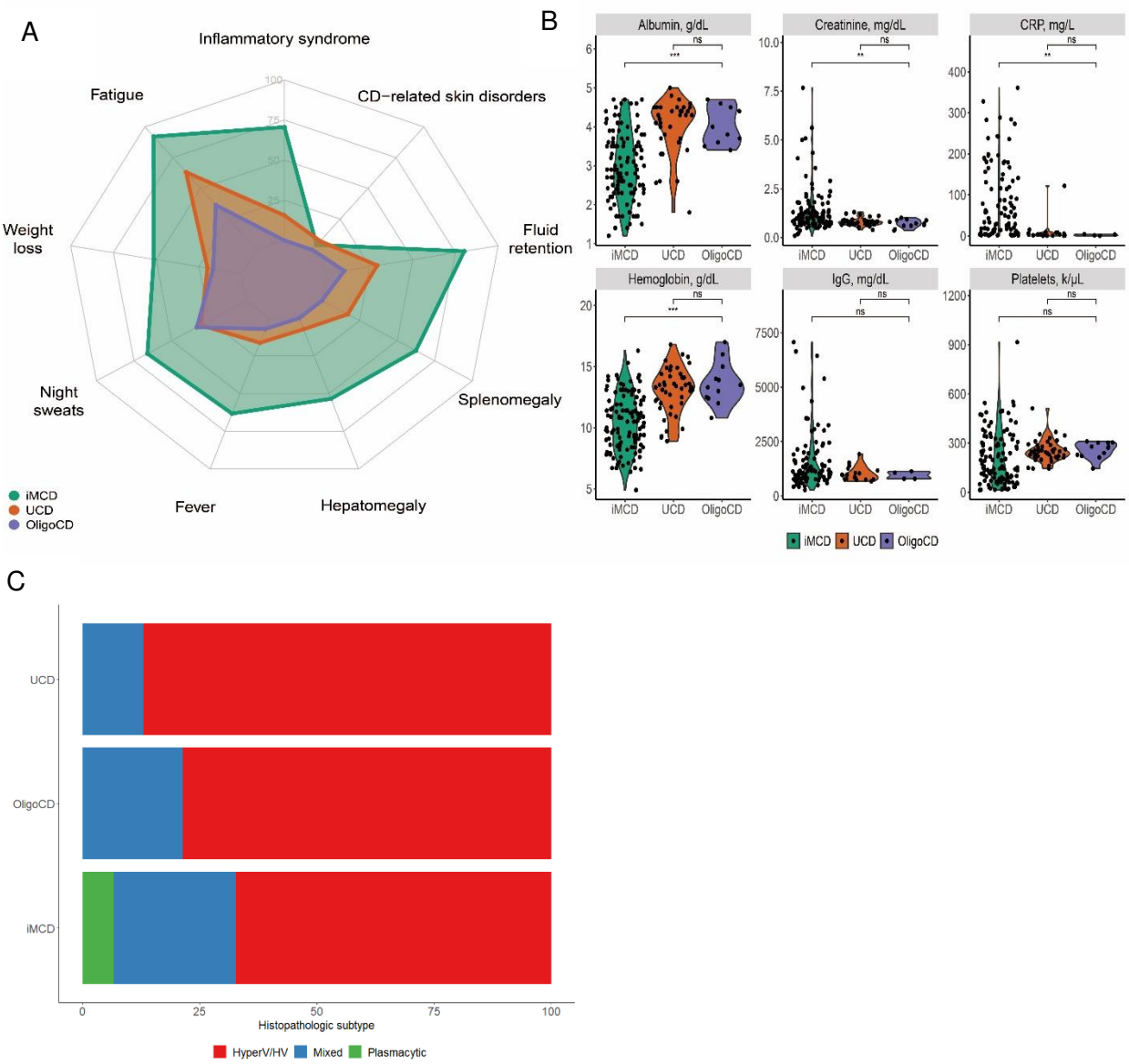


Figure 4.