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Novel somatic alterations in unicentric and idiopathic multicentric Castleman disease

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Abstract

Objectives: Castleman disease (CD) is a heterogeneous group of disorders involving systemic inflammation and lymphoproliferation. Recently, clonal mutations have been identified in unicentric CD (UCD) and idiopathic multicentric CD (iMCD), suggesting a potential underlying neoplastic process.

Methods: Patients with UCD or iMCD with next generation sequencing (NGS) data on tissue DNA and/or circulating tumor DNA (ctDNA) were included.

Results: Five patients were included, 4 with iMCD and 1 with UCD. Four patients (80%) were women; median age was 40 years. Three of five patients (60%) had ≥1 clonal mutation detected on biopsy among the genes included in the panel. One patient with iMCD had a 14q32-1p35 rearrangement and a der(1)dup(1)(q42q21)del(1)(q42) (1q21 being IL-6R locus) on karyotype. This patient also had a *NF1* K2459fs alteration on ctDNA (0.3%). Another patient with iMCD had a *KDM5C* Q836* mutation, and one patient with UCD had a *TNS3-ALK* fusion but no ALK expression by immunohistochemistry.

Conclusions: We report 4 novel somatic alterations found in patients with UCD or iMCD. The 1q21 locus contains IL-6R, and duplication of this locus may increase IL-6 expression. These findings suggest that a clonal process may be responsible for the inflammatory phenotype in some patients with UCD and iMCD.

Aaron M. Goodman and Ah-Reum Jeong: Co first-authors.

Novelty Statement: 4 novel somatic alterations were found in patients with UCSD and iMCD.

KEYWORDS

Castleman disease, genomics, next generation sequencing

1 | INTRODUCTION

Castleman disease (CD) represents a heterogeneous group of lymphoplasmacytic proliferative disorders with a wide range of clinical presentations. Patients can exhibit asymptomatic single station lymphadenopathy [unicentric Castleman disease (UCD)] or a life-threatening inflammatory syndrome with multi-system organ failure [multicentric Castleman disease (MCD)]. CD is anatomically classified based on the number of lymph nodes regions involved into UCD and MCD. MCD is further sub-classified by etiology into human herpesvirus-8 (HHV-8) associated MCD (HHV-8-MCD), idiopathic MCD (iMCD), and polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS) syndrome associated MCD (POEMS-MCD).[1,2]

The etiologies of HHV-8 and POEMS syndrome associated MCD are well-established. HHV-8-MCD often presents in immunocompromised individuals, most commonly in patients with human immunodeficiency virus (HIV) infection, resulting in uncontrolled HHV-8 replication and production of virally encoded interleukin-6 (vIL-6). Overproduction of vIL-6 initiates a cascade of events resulting in severe systemic inflammation and ultimately organ failure.[3] Treatment of HHV-8-MCD with rituximab-based regimens has resulted in improved outcomes.[4] In POEMS-MCD, an underlying clonal plasma cell population leads to excessive vascular endothelial growth factor (VEGF) and interleukin-12 (IL-12) production resulting in organomegaly, peripheral neuropathy, and skin disease.[5] Treatment is directed toward the underlying plasma cell clone.

In contrast to HHV-8-MCD and POEMS-MCD, the etiology of UCD and the trigger for excess interleukein-6 (IL-6) and subsequent inflammatory syndrome in iMCD remains unknown. UCD was thought to be a benign reactive proliferation; however, recent data suggest a clonal component originating from the stromal cells within the lymph node.[6] Removal of the affected lymph node is typically curative, consistent with a localized etiology. Three processes have been proposed as potential disease drivers in iMCD: infection with a virus other than HHV-8, systemic inflammatory disease mechanisms via autoantibodies or inflammatory germline gene mutations or paraneoplastic process from a population of clonal cells.[7] An underlying virus other than HHV-8 seems unlikely based on the results of recent data,[8] and the role of autoantibodies is currently under investigation. Regardless of the trigger, inflammation, often mediated by IL-6, is directly implicated in all cases of iMCD.[9] The anti-IL-6 monoclonal antibody siltuximab has revolutionized the treatment of iMCD.[10-16] However, approximately 50% of patients will fail or lose their response to siltuximab. Therefore, it is important to elucidate the underlying pathogenesis of iMCD to help develop novel therapies.

What is the NEW aspect of your work?

This manuscript describes novel somatic mutations found in Castleman disease, suggesting potential clonal and neoplastic etiology.

What is the CENTRAL finding of your work?

Three of the five patients with iMCD or UCD, who had next generation sequencing and cytogenetics demonstrated clonal mutations (14q32-1p35 rearrangement and a der(1)dup(1)(q42q21)del(1)(q42), *KDM5C* Q836* mutation, and *TNS3-ALK* fusion).

What is (or could be) the SPECIFIC clinical relevance of your work?

As the etiology and pathogenesis of unicentric and idiopathic multicentric Castleman disease remains unclear, these findings advance our understanding in this subject that potentially a clonal and neoplastic process triggers the development of Castleman disease.

Recently, somatic clonal mutations of UCD and iMCD have been reported.[17-30] Here, we describe two cases of iMCD and one case of UCD with novel chromosomal structural abnormalities and somatic point mutations.

2 | METHODS

2.1 | Patients

All patients who were diagnosed with UCD and iMCD at University of California San Diego (UCSD) were retrospectively reviewed with censor date of 6/30/2021. The pathology slides or pathology reports (if pathology slides were not available) were re-reviewed by a hematopathologist (HYW) and the diagnostic criteria of UCD and iMCD were re-reviewed (AMG and HYW) to confirm the diagnosis according to the Castleman Disease Collaborative Network (CDCN) criteria outlined by Fajgenbaum et al.[31] Patients who had comprehensive genomic profiling were included in the final analysis. The study was carried out under the PREDICT study (NCT02478931) approved by the institutional review board and any investigational studies administered for which the patients gave consent.

2.2 | Immunohistochemistry

Immunohistochemistry (IHC) using formalin-fixed paraffin-embedded (FFPE) tissue blocks was carried out using Ventana BenchMark Special Satins platform (Roche). The monoclonal mouse anti-human anaplastic lymphoma kinase [ALK, (Clone ALK1)] antibody was purchased from Dako (Carpinteria, CA, USA). According to the Manufacturer's datasheet, the ALK monoclonal antibody recognizes amino acids 1359-1460 of the full length human ALK protein.

2.3 | Cytogenetics

Fresh tissue, if available at the time of excisional biopsy, was used for karyotyping using Giemsa banding method. Twenty metaphase cells were analyzed according to standard protocol.

2.4 | Genomic sequencing

Genomic sequencing by next generation sequencing (NGS) was performed either on the FoundationOne Heme panel (Foundation Medicine)[32] or UCSD comprehensive panel of genes. Briefly, the FoundationOne Heme platform uses extracted deoxyribonucleic acid (DNA) from FFPE specimens to interrogate the coding sequence of 406 genes and select introns of 31 genes involved in rearrangements. The platform also utilizes ribonucleic acid (RNA) sequencing to interrogate 265 genes known to be altered in human hematologic malignancies; all classes of alterations are assessed, including single nucleotide variants (SNVs), short insertions and deletions (indels), copy number alterations (CNAs), gene fusions, and rearrangements.[32] For UCSD hematolymphoid panel of genes, solution-based hybrid capture was used on extracted DNA from FFPE specimens to select mutational hotspot regions for a selected panel of 397 genes. The DNA library was then sequenced using sequencing-by-synthesis technology. Gene fusions, rearrangements, SNV, indels, and CNAs were identified and if necessary, clinically significant variants were re-sequenced using Sanger technique.

Cell free DNA (cfDNA) analysis from peripheral blood was performed using Guardant360 assay (Guardant Health).[33] Briefly, at least 5.0 ng of DNA was extracted from peripheral blood and oligonucleotide barcoding of each DNA strand was performed. Selected exons from 68 or 73 cancer-related genes were sequenced with HiSeq2500 (Illumina, USA), evaluating for SNVs, fusions, indels, and CNAs.

3 | RESULTS

3.1 | Demographic and clinical data

A total of 8 patients with UCD and 6 patients with iMCD were identified. On further review, 1 patient considered to have iMCD did not meet the formal diagnostic criteria and was excluded. Among the 13 patients, 1 patient with UCD and 4 patients with iMCD had NGS performed on biopsy sample and were included for further analysis (Figure S1).

Characteristics of the five patients are summarized in Table 1. Diagnostic studies performed are summarized in Table S1. Four of five patients (80%) were women; median age at diagnosis was 40 years. The patient with UCD had resection of the lymph node and has no evidence of recurrent disease at 4.6 years of follow-up. Three of the four patients with iMCD received siltuximab: one patient is maintained on siltuximab at 3.2 years of follow-up with partial response, one patient discontinued siltuximab after 8 cycles due to unknown reasons, maintained on sirolimus for 3 years, but now deceased after a massive aspiration event from an unknown underlying etiology, and one patient had progression of disease after 3 cycles of siltuximab and is currently in remission for 1 year after rituximab-based therapy. One patient with iMCD is on active surveillance for 5 years without any therapy.

3.2 | Genomic alterations

Three of the 5 patients (60%) demonstrated chromosomal and/or genomic clonal alterations at levels of either karyotype and/or point mutations by NGS (Table 1). Patient #3 had duplication of 1q at 1q42q21 and deletion of 1q42 locus on karyotype (Figure 1), a locus, which contains IL-6 receptor (IL-6R). By NGS, there was 14q32-1p35 reciprocal rearrangement (59 supporting reads). Of note, immunoglobulin heavy (IgH) chain gene resides on 14q32 locus; however, there is no monoclonal rearrangement of IgH by polymerase chain reaction (PCR) in this patient. Patient #3 also had neurofibromin 1 (*NF1*) K2459fs identified in 0.3% of cfDNA but not in lymph node tissue. Patient #4 had lysine-specific demethylase 5C (*KDM5C)* Q836* mutation (VAF 5.1%, tumor purity 20%) and patient #5 with UCD had tensin 3 (*TNS3*)-*ALK* fusion (109 supporting reads) identified on NGS (Figure 1). There was no ALK expression by IHC with appropriate positive control, and there were no aberrant T-cells by flow cytometry. In addition, there was no monoclonal rearrangement of T-cell receptor gamma gene (*TRG*).

3.3 | Case presentation

Patient #3 had particularly notable clinical and genomic findings. She is a 58-year-old Asian woman with history of bronchiectasis, violaceous skin lesions, polyclonal hypergammaglobulinemia, and thrombocytosis who was referred to our center for evaluation of iMCD. On physical examination, she had diffuse, 1-2 cm violaceous patches over her torso and extremities (Figure 2). Patient's physical examination, laboratory studies, imaging findings, and pathology examinations confirmed diagnosis of iMCD. Genomic alterations were discovered as described above. She was started on siltuximab 11 mg/kg every three weeks with improvement of her cough and resolution

TABLE 1 Patient characteristics

Patient	Age (years)[a]/ Sex	Diagnosis[b]	Histology	Monotypia by flow cytometry/ monoclonality of B-cells	Treatment	OS (years)	Tissue[c]	Genomics[d]	TMB (mut/mb)	cfDNA[e]	Comment
1	29/F	iMCD	Hyaline vascular	Polytypic/ND	Siltuximab, Sirolimus, Anakinra	3.5	LN	No alterations	3	No alterations	
2	30/F	iMCD	Plasma cell	ND	Siltuximab, Rituximab + chemotherapy, Rituximab monotherapy	4.9	LN	No alterations	N/A	No alterations	
3[f]	58/F	iMCD	Plasma cell	Polytypic/ Polyclonal	Siltuximab	3.2	LN	NGS: 14q32-1p35 rearrangement (59 supporting reads) Karyotype: der(1) dup(1)(q42q21)del(1)(q42) [2/14]	N/A	*NF1* K2459fs (VAF 0.3%)	*IL-6 R* resides on 1q21
4	40/M	iMCD	Plasma cell	ND	Observation	6.5	Skin	NGS: *KDM5C* Q836* (VAF 5.1%, tumor purity 20%)	N/A	No alterations	
5	40/F	UCD	Hyaline vascular	Polytypic/ND	Resection	4.6	LN	NGS: *TNS3-ALK* fusion (109 supporting reads)	1	ND	No ALK protein detected by IHC

Abbreviations: ALK, Anaplastic lymphoma kinase; cfDNA, cell free DNA; F, female; fs, frame shift; iMCD, idiopathic multicentric Castleman disease; ND, not done; LN, lymph node; M, male; mb, megabase pair; mut, mutation; N/A, not available; ND, not done; NF1, neurofibromin 1; NGS, next generation sequencing; OS, overall survival; TNS3, Tensin3; TMB, tumor mutation burden; UCD, unicentric Castleman disease.

[a]At diagnosis.

[b]Cases of iMCD had to meet the diagnostic criteria outlined by D. Fajgenbaum et al.[31]

[c]Tissue used for next generation sequencing.

[d]Patients 1, 2, 4, and 5 underwent sequencing using the Foundation One Heme panel. Patient 3 underwent sequencing using the University of California San Diego Comprehensive NGS mutation panel analysis. Excludes variant of unknown significance.

[e]Patients 1, 2, 3, and 4 underwent cfDNA analysis using the Guardant360 assay.

[f]Details of afebrile pneumonia in this patient while receiving siltuximab has been previously reported.[34]

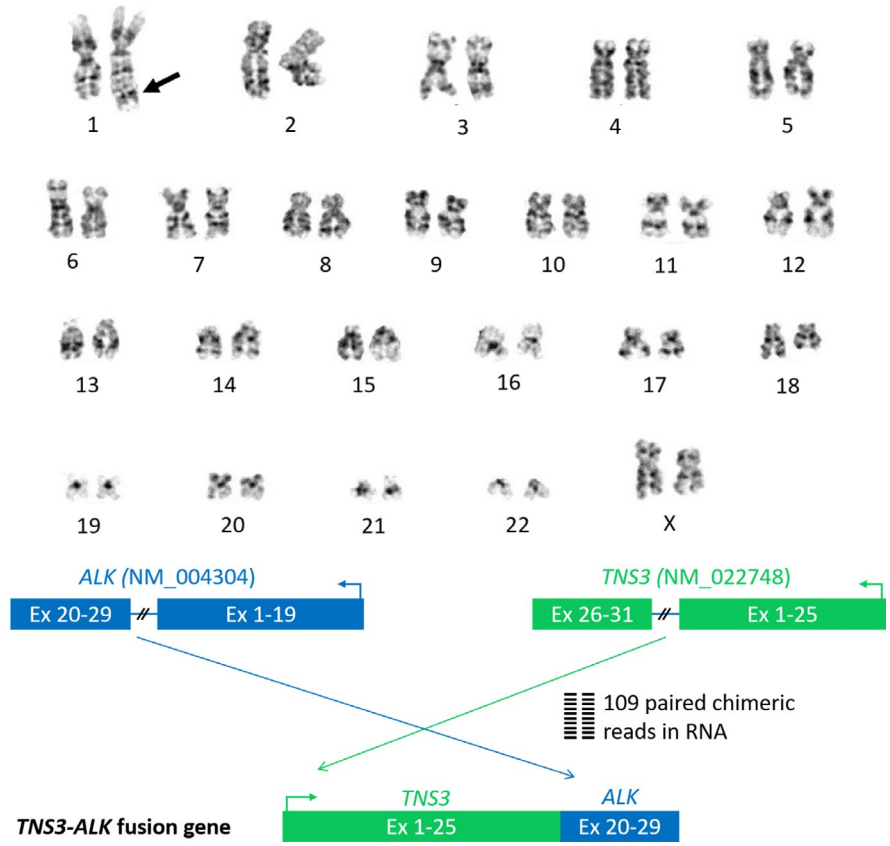

FIGURE 1 Chromosomal alterations by karyotype for patient #3 and predicted TNS3-ALK fusion gene for patient #5. (Top panel) Chromosomal alterations from patient #3 by karyotype. Among 14 metaphase cells from unstimulated cell culture by G-banding, two cells showed a derivative chromosome 1 with inverted duplication of segment 1q21-q42 and suspected deletion 1q42 (arrow). (Bottom panel) Chromosomal rearrangement identified in patient #5 resulting in a TNS3-ALK fusion (TNS3 exons 1-25; ALK exons 20-29)

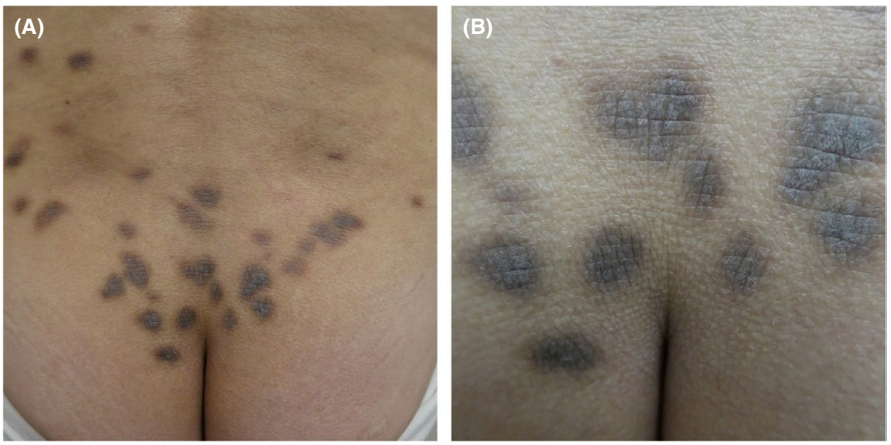

FIGURE 2 Skin lesions of patient #3. A distant (A) and close (B) view of the gluteal cutaneous lesions of Castleman disease presenting as infiltrative hyperpigmented dermal plaques[34]

of thrombocytosis and lymphadenopathy. The details when this patient developed an afebrile pneumonia while being treated with siltuximab have previously been described.[34] She continues to receive siltuximab with excellent disease control at 2.5-year follow-up.

4 | DISCUSSION

MCD includes a group of diseases with systemic inflammatory phenotypes, ranging from mild symptoms to life-threatening multiorgan failure. Some subtypes of MCD have defined etiologies such as HHV-8 infection in HHV-8-MCD or a neoplastic plasma cell clone in POEMS-MCD. However, the driver of increased IL-6 production and subsequent cytokine storm in iMCD has not been defined. Similarly, the inciting event for UCD and its relationship to MCD is unknown. Recently, an association between a germline mutation of Mediterranean fever (*MEFV*) gene, a gene implicated in familial Mediterranean fever, and iMCD was reported.[21] However, it is unclear if this case truly represents iMCD or familial Mediterranean fever due to the clinical overlap between these diseases. Similarly, a germline mutation in FAS, a gene implicated in autoimmune lymphoproliferative syndrome (ALPS), was recently reported in an iMCD patient and his father with UCD, but these patients may be more appropriately considered to have ALPS.[17] Thus far, a clear genomic alteration causing iMCD has not been found. In addition, the pathogen hypothesis other than HHV-8 has proven to be unlikely.[8]

The paraneoplastic hypothesis is gaining attention as increasing numbers of clonal alterations have been reported in patients with UCD and iMCD, where the underlying clonal neoplastic process could potentially lead to lymph node findings characteristic of CD and increased IL-6 in iMCD (Table S2). Notably, Li et al[6] reported platelet-derived growth factor receptor β (*PDGFRB*) Asn666Ser mutations in 17% (7/41) patients with UCD using whole exome sequencing (WES). These authors further demonstrated that the PDFGRB Asn666Ser mutations were localized to non-hematopoietic stromal cells. It is hypothesized that a clonal population of stromal cells may lead to increased cytokine production at least locally; however, this hypothesis has yet to be proven. In our UCD patient (#5) who underwent NGS, a *PDGFRB* alteration was not detected, but a novel ALK gene fusion was found.

In our cohort, two somatic alterations in iMCD were identified that have not been previously reported. Immunophenotyping studies using flow cytometry found that there were no monotypic B-cells or aberrant T-cell populations. Molecular studies using PCR have shown that there were no monoclonal rearrangements for IgH/immunoglobulin kappa (IgK) and TRG thus the findings are not attributable to the bystander B-cells or T-cells.

Patient #3 demonstrated very interesting findings. She was found to have dup(1q42q21), a locus, which contains IL-6R. Copy number variations of this locus have been shown to increase expression of IL-6 and IL-6R,[35] which may explain the increased IL-6 seen in our patient and her excellent response to siltuximab. Similarly, a report by Nakamura et al[24] demonstrated a somatic mutation in the IL-6 locus in a patient with iMCD. In their report, the affected lymph node was found to have t(7;14)(p22;q22) by karyotype. The patient also had an elevated IL-6 level. The locus 7p21-22 contains *IL-6*, thus the translocation could potentially lead to increased production of IL-6. Yoshimi et al[29] also reported a mutation in mitogen-activated protein kinase 2 (*MEK2*) P128L, which has been shown to be associated with hyperactivated mitogen-activated protein kinase (MAPK) signaling and increased proliferation. These data suggest that some cases of iMCD may be the result of a clonal process resulting in increased cytokine production including IL-6 or overexpression of IL-6R. However, this remains to be proven. Besides dup(1q42q21) and del(1q42), patient #3 also harbored 14q32-1p35 rearrangement. The 14q32 locus contains many genes other than IgH, and the genes from 1p35 is unknown. The significance of this rearrangement is unclear because there was no monoclonal rearrangement of IgH, thus the gene involved from 14q32 locus is unlikely to be IgH. This patient was also found to have *NF1* K2459fs mutation on cfDNA assay but not in tissue. *NF1* is a tumor suppressor gene involved in the rat sarcoma (RAS)/MAPK pathway.[36] Somatic mutations of *NF1* are found in various cancers such as melanoma, lung adenocarcinoma, and leukemia.[36] It is unclear how the frame shift mutation affects protein function. Since the *NF1* mutation was not detected in NGS of the lymph node, its association with CD remains unclear.

Patient #4 was found to have a somatic mutation in *KDM5C* (Q836*), a gene encoding histone lysine demethylase that controls gene expression by histone modification.[37] Somatic mutations are linked to clear cell renal cell carcinoma and prostate adenocarcinoma.[38,39] The significance of this mutation in iMCD is unclear, as currently the *KDM5C* gene does not have any known association with inflammatory conditions.

Patient #5 harbored a novel chromosomal translocation t(2;7)(p23;p12) involving *ALK* from 2p23, and *TNS3* from 7p12, which on RNA sequencing is predicted to result in a fusion of 5′-TNS3(ex1-25 NM_022748)-ALK(ex20-29 NM_004304). *TNS3*, one of the 4 members of TNS family involved in regulation of Rho GTPase signaling and cell adhesion,[40] was reported as a thyroid-specific gene.[41] While deregulation of TNS3 has not been reported in lymphoid disorders, fusions and less frequently mutations of *ALK* have long been known to be oncogenic and are seen in an increasing number of hematolymphoid and solid malignancies including lymphoma of T- and B-cell lineages, carcinoma, sarcoma, and neuroblastoma.[42] While the role of the *ALK* gene rearrangement in the pathogenesis of the UCD case remains to be elucidated, it is clear that the ALK was not expressed in this case by IHC. This contrasts with the genomic structure of the TNS3-ALK fusion transcript, which is identified with high read support (109 supporting reads), is in-frame and retains the *ALK* kinase domain. Since the ALK monoclonal antibody used in the IHC should have recognized the epitopes present in the C-terminus of ALK portion from TNS3-ALK fusion, the lack of ALK protein by IHC is suggestive of defects in post-transcriptional and/or translational steps.

There are several other reports that have described clonal alterations in patients with UCD and iMCD (Table S2). Patel et al[25] reported a mutation in janus kinase 1 (*JAK1*) V310I in a patient with a condition demonstrating CD-like features in skin lesions only and no lymphadenopathy, which can sometimes be referred to as cutaneous CD. Treatment with siltuximab resulted in a complete response ongoing at seven years.[16] Interestingly, the patient's pretreatment serum IL-6 level was normal. *JAK1* is a crucial signaling component of the IL-6/IL-6R/gp130 machinery. *JAK1* V310I may induce a conformation change with functional activation effect leading to enhanced sensitivity to the IL-6 ligand.

There are limitations in our study including small number of cases and lack-of-functional studies of genomic alternations. Furthermore, the panel only evaluated a selected number of genes, so genes, which are not included in the panel may have mutations. Conversely, mutations present in genes included in the panel may not have been detected due to mutation abundance below the sensitivity of the assay. Additional NGS and functional studies will be needed to validate whether or not our findings have pathogenic significance.

5 | CONCLUSIONS

In summary, we describe several novel gene mutations and chromosomal abnormalities from 2 iMCD and 1 UCD cases by karyotyping and NGS. Our new findings, in addition to the previously reported gene mutations, will advance the understanding of the pathogenesis of CD. As first-line treatment with siltuximab is only effective in

approximately half of iMCD patients,[10,11] further genomic interrogation is warranted as a basis of identifying new therapeutic targets.

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CONFLICT OF INTEREST

AMG receives speaking and consulting fees from Seattle Genetics and consulting fees from EUSA Pharma. ESS is an employee of Foundation Medicine and a shareholder of Roche. PRC is a consultant for ParaPRO. DCF receives research funding from EUSA Pharma and has a provisional patent pending related to JAK1/2 inhibition in iMCD. RK receives research funding from Genentech, Merck Serono, Pfizer, Boehringer Ingelheim, TopAlliance, Takeda, Incyte, Debiopharm, Medimmune, Sequenom, Foundation Medicine, Konica Minolta, Grifols, Omniseq, and Guardant, as well as consultant and/or speaker fees and/or advisory board for X-Biotech, Neomed, Pfizer, Actuate Therapeutics, and Roche, has an equity interest in IDbyDNA and CureMatch Inc, serves on the Board of CureMatch and CureMetrix, and is a co-founder of CureMatch.

AUTHOR CONTRIBUTIONS

AMG designed the work, acquired and analyzed the patient data, and was a major contributor in writing the manuscript. ARJ acquired and analyzed the patient data, performed the literature review, and was a major contributor in writing the manuscript. HYW performed histologic examination of the lymph node and skin, interpreted sequencing data, and substantially revised the manuscript. ESS interpreted sequencing data and substantially revised the manuscript. PRC provided photographs of the patient's skin lesions and substantially revised the manuscript. AP, JS, DCF, and RK substantially revised the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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