Novel Somatic Alterations in Unicentric and Idiopathic Multicentric Castleman Disease

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Introduction

- Castleman disease (CD) represents a heterogeneous group of lymphoplasmacytic proliferative disorders with a wide range of clinical presentations.
- The etiology of unicentric CD (UCD) and idiopathic MCD (iMCD) remains unknown.
- Recent data suggest there may be a clonal component originating from the stromal cells within the lymph node(1).
- 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(2).
- It is important to elucidate the underlying pathogenesis of iMCD to help develop novel therapies.
- Recently, somatic clonal mutations of UCD and iMCD have been reported.
- We describe two cases of iMCD and one case of UCD with novel chromosomal structural abnormalities and somatic point mutations.

Materials and Methods

- 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. Patients who had comprehensive genomic profiling were included in the final analysis (Figure 1).
- 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.

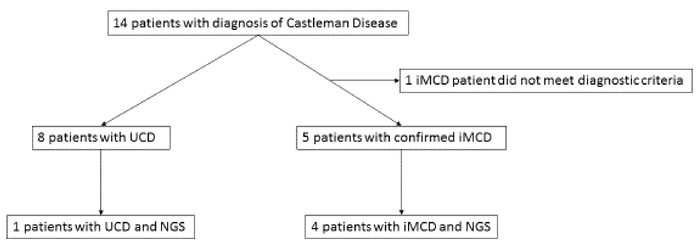

Figure 1. Consort diagram

- Genomic sequencing by next generation sequencing (NGS) was performed either on the FoundationOne-Heme panel (FoundationMedicine) or UCSD comprehensive panel of genes.
- Cell free DNA (cfDNA) analysis from peripheral blood was performed using Guardant360 assay (Guardant Health).

Results

- A total of 8 patients with UCD and 6 patients with iMCD were identified. Four patients with iMCD and 1 patient with UCD had NGS performed.
- Characteristics of the five patients are summarized in Table 1.
- Three of the 5 patients (60%) demonstrated chromosomal and/or genomic clonal alterations at levels of either karyotype and/or point mutations by NGS.
- Patient #3 had duplication of 1q at 1q42q21 and deletion of 1q42 locus on karyotype (Figure 2), 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%)
- 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).

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

Table 1. Patient characteristics †At diagnosis ‡Cases of iMCD had to meet the diagnostic criteria outlined by D. Fajgenbaum et al.(3) § Tissue used for next generation sequencing. ¶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. ^Patients 1,2,3, and 4 underwent cfDNA analysis using the Guardant360 assay. ※Details of afebrile pneumonia in this patient while receiving siltuximab has been previously reported(4).

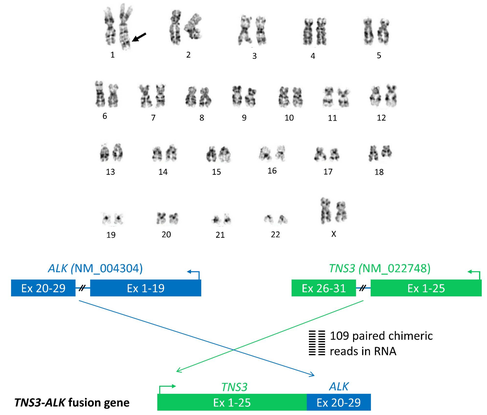

Figure 2. Chromosomal alterations by karyotype for patient #3 and predicted TNS3-ALK fusion gene for patient #5

Conclusion

- The paraneoplastic hypothesis as etiology of UCD and iMCD is gaining attention as increasing numbers of clonal alterations have been reported, where the underlying clonal neoplastic process could potentially lead to lymph node findings characteristic of CD and increased IL-6 in iMCD.
- In our cohort, two somatic alterations in iMCD were identified that have not been previously reported.
- 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(5), further genomic interrogation is warranted as a basis of identifying new therapeutic targets.

References

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