Novel Somatic Alterations in Unicentric and Idiopathic Multicentric Castleman Disease

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Introduction

• Castleman disease (CD) represents a heterogeneous group of lymphoplasmytic proliferative disorders with a wide range of clinical presentations.
• The etiology of unicentric CD (UCD) and idiopathic multicentric CD (iMCD) remains unknown.
• Recent data suggest there may be a clonal component originating from the stromal cells within the lymph node(s).
• 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 cell(s).
• It is important to elucidate the underlying pathogenesis of iMCD to help develop novel therapies.
• Recently, somatic clonal cases 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.

Genomic sequencing by next generation sequencing (NGS) was performed on peripheral blood cfDNA for 5 patients with UCD and iMCD using the Guardant360 assay (Guardant Health).

Table 1. Patient characteristics and 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, and 5 underwent sequencing using the Foundation One Heme panel. Patient 3 underwent sequencing using the University of California San Diego Comprehensive NGS panel. Excludes variant of unknown significance. *Patients 1, 2, 3, and 4 underwent cfDNA analysis using the Guardant360 assay. Figures 1 and 5 show details of allele-specific fusion on NGS.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Race</th>
<th>iMCD/MCD Diagnosis</th>
<th>Histology</th>
<th>Multiples by flow cytometry and genomics</th>
<th>Treatment</th>
<th>OS (months)</th>
<th>Cause of death</th>
<th>NGS (whole exome)</th>
<th>FFPE (whole exome)</th>
<th>Comments</th>
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<tr>
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<td>M</td>
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<td>iMCD</td>
<td>PLB</td>
<td>2, 3, 4</td>
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<td>15</td>
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<td>N/A</td>
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<tr>
<td>2</td>
<td>57</td>
<td>F</td>
<td>CA</td>
<td>iMCD</td>
<td>PMB</td>
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</tbody>
</table>

Figure 1. Consort diagram

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

<table>
<thead>
<tr>
<th>Chromosomal alteration</th>
<th>Karyotype</th>
<th>TNS3-ALK fusion gene</th>
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<tbody>
<tr>
<td>1p36.32 deletion</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td>14q32.13 deletion</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td>8q24.13 deletion</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td>14q32.13 duplication</td>
<td>46,XX</td>
<td></td>
</tr>
<tr>
<td>8q24.13 duplication</td>
<td>46,XX</td>
<td></td>
</tr>
</tbody>
</table>

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 14q32-1p32 reciprocal rearrangement (99 supporting reads). Of note, immunoglobulin heavy (IgH) chain gene resides on 14q32 locus; however, there is no monochromosomal 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 translocation (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 monochromosomal rearrangement of T-cell receptor gamma gene (TRG).

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