An Anemic Patient with CCUS

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DISCLOSURE

I have no financial relationships to disclose.
Case Presentation

- **CC:** 73 y.o. M, persistent anemia for 6 months
- **CBC:** Hb: 11.9 (L), MCV: 92.5(N), RDW: 13.5 (N), WBC: 6.7 (N), platelet: 168 (N)
- **Workup for anemia:** ruled out other etiologies for anemia
- **Bone Marrow Biopsy:** Slightly hypercellular bone marrow with trilineage hyperplasia, no atypia; No morphologic features of myeloid neoplasm.
- **Cytogenetics:** 46, XY [20]
- **Next Generation Sequencing:** TET2 mutation with VAF 36% and ZRSR2 mutation with VAF 38%
- **Final Diagnosis:** Clonal Cytopenia of Undetermined Significance (CCUS)
Learning Objectives

- Comprehend definitions, prevalence, and phenotypic data of Clonal Hematopoiesis (CH), Clonal Hematopoiesis of Indeterminate Potential (CHIP), and Clonal Cytopenia(s) of Undetermined Significance (CCUS)

- Decipher stratification strategies used in CCUS to estimate risk for progression

- Learn about clinical trial opportunities that exist for patients with CCUS.
The Prevalence of Anemia in Older Adults

ACI, anemia of chronic inflammation; CKD, chronic kidney disease; Heme malig, hematologic malignancy; IDA, iron deficiency anemia; thal, thalassemia trait.

Other includes hemolysis = 4, alcohol = 3, hypothyroidism = 1, vitamin B12 deficiency = 1, medication = 1.

Stauder, et al. Blood, 2018
Artz, et al. J Gerontology 2017
The Prevalence of CHIP

CH: age-associated phenomenon

Jaiswal S et al. NEJM, 2014
Watson et al. Science, 2020
The Number, Type, and VAF of the mutation in CHIP

Jaiswal S et al. NEJM, 2014
The Consequences of CHIP

- Hematologic malignancies (HR 11-13)
- Increased all-cause mortality (HR 1.4; 95% CI 1.1-1.8)
- Cardiovascular disease (HR 2.0; 95% CI 1.1-1.8)
- Stroke (HR 2.6; 95% CI 1.4 - 4.8)

Jaiswal S et al., NEJM 2014
Jaiswal S et al., Blood, 2020
Clonal Evolution

Background mutations unrelated to hematopoietic expansion

Early mutations that initiate clonal expansion
eg, TET2, DNMT3A, GNAS, ASXL1, JAK2, SF3B1, PPM1D

Cooperating mutations that contribute to disease features
eg, RUNX1, IDH1/2, U2AF1, KRAS, NRAS, STAG2, CEBPA, NPM1, FLT3

Steensma D et al., Blood. 2015
Jaiswal S et al., NEJM. 2014
Genovese G et al., NEJM. 2014
Challen et al., Blood. 2020
The Prevalence of CCUS

Kowk et al., Blood, 2015
van Zeventer et al., Blood, 2020
# Definition of CH vs. CHIP vs. CCUS

<table>
<thead>
<tr>
<th>CH</th>
<th>CHIP</th>
<th>CCUS</th>
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<tbody>
<tr>
<td>• Somatic mutations</td>
<td>• Leukemia-associated somatic driver mutations</td>
<td>• Leukemia-associated somatic driver mutations, or clonal cytogenetic abnormalities</td>
</tr>
<tr>
<td>• VAF&lt;2%</td>
<td>• VAF≥2%</td>
<td>• VAF≥2%</td>
</tr>
<tr>
<td>• Without an underlying hematological neoplasms</td>
<td>• Without an underlying hematological neoplasm</td>
<td>• Without evidence of dysplasia or associated with very mild dysplasia</td>
</tr>
<tr>
<td>• With the potential to expand over time</td>
<td>• Without persistent cytopenias</td>
<td>• Unexplained and persistent cytopenia(s)&gt;4 months</td>
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The Mutational Patterns in CCUS

Malcovati et al., Blood, 2017
van Zeventer et al., Blood, 2020
Galli et al., Blood, 2021
The Variant Allele Fraction in CCUS

Kwok et al., Blood, 2015
Li et al., Blood Advance, 2021
Learning Objectives

Decipher stratification strategies used in CCUS to estimate risk for progression
What is the true prognosis of CCUS?

Malcovati et al., Blood, 2017

High risk group:
Spliceosome gene;
Co-mutation with DAT

Low risk

≥ 1 mutation

No mutation

What matters?

The number of the mutations

The VAF of the mutations

The pattern of the mutations

Malcovati et al., Blood, 2017
The Impact of Number of Mutations

Risk of Progression

- ≥1 mutation, PPV 0.81
- ≥2 mutations, PPV 0.88

Overall Survival

HR: 2.29

Malcovati et al., Blood, 2017;
van Zeventer et al., Blood, 2020
Desai et al. Nature medicine, 2018
The Impact of VAF of the Mutations

van Zeventer et al., Blood, 2020
Galli et al., Blood, 2021
Watson et al. Science, 2020
Fabre et al, preprint, 2021

CH growth rate varies and is associated with leukemogenesis
The Impact of the Mutation Hotspots

Feusier et al., Blood Cancer Discovery, 2021
The Type of Mutations: CH-like vs. MN-like Clusters

- CH-like cluster: Isolated *DNMT3A* Mutation
- MN-like cluster: splicing factors, *TP53*, or DTA genes in combination with additional mutated genes

### Overall survival

- **No mutations**
- **CH-like cluster** HR: 1.8, p<.001
- **MN-like cluster** HR: 2.73, p<.001

### Incidence of Progression

- **CH-like cluster**
The Type of Mutations: Myeloid-CHIP vs. Lymphoid CHIP

Niroula et al. Nature Medicine, 2021
Learn about clinical trial opportunities that exist for CCUS patients.
Current Available Clinical Trials

• **NCT03418038**: Intravenous Ascorbic Acid in TET2 mutated CCUS
• Phase 2 interventional study

Huang et al. Blood 2021
Bensberg et al, Blood, 2021
Current Available Clinical Trials

- Using Canakinumab in CCUS
  - CANTOS study: Canakinumab: a human monoclonal antibody targeting IL-1β
  - TET2 mutant patients within the CANTOS trial response to Canakinumab (HR:0.36, p=0.034)

Ridker et al. NEJM, 2017
Yura et al. JACC, 2020;
Svensson et al. Circulation, 2018
CCUS Consortium Collaboration [30+ Cancer Centers]

Primary Aims:
- Clinical characteristics
- Progression outcome
- Identify risk factors for progression

Secondary Aims:
- To describe the clonal evolution/dynamics-VAF changes
- To describe the survival outcome
Total number of patients: 258 by July 1, 2021

The median follow up duration: 15.6 months

Median Age: 71

Most Common Mutation: TET2

Risk Factors, PFS, OS
CCUS Consortium

ASH Poster Session Name:
503. Clonal Hematopoiesis, Aging and Inflammation: Poster II

TITLE: Characteristics and Clinical Outcome of Patients with Clonal Cytopenias of Undetermined Significance: A Large Retrospective Multi-Center International Study

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