Myeloid neoplasms with germline predisposition including MDS

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Disclosure of speaker’s interests

Dr. Geyer

• Potential conflict of interest
  None
Introduction

• The updated WHO classification introduces a new provisional diagnostic category of “myeloid neoplasms with germline predisposition”

• Cases associated with inherited or de novo germline mutations that significantly increase the incidence of myeloid neoplasms (MDS and AML)

• These syndromes are very rare

• They are likely under-recognized and under-reported
Introduction

• Recognition of these patients is critical
• Patients may require specialized approaches to therapy
  – Traditional scoring systems such as IPSS are not applicable
  – Immunosuppressive therapy is not effective in patients with bone marrow failure syndromes
  – Receive reduced intensity conditioning regimens prior to allogeneic stem cell transplant
  – Family members should be carefully screened if matched related allogeneic stem cell transplant is considered
• Frequent nonhematologic manifestations
• Families may benefit from genetic counseling, including preimplantation genetic diagnosis for future pregnancies
Updated WHO classification of Myeloid Neoplasms with Germline Predisposition

• Myeloid neoplasms with germline predisposition without a pre-existing disorder or organ dysfunction
  – CEBPA mutation
  – DDX41 mutation

• Myeloid neoplasms with germline predisposition and pre-existing platelet disorders
  – RUNX1 mutation
  – ANKRD26 mutation
  – ETV6 mutation

• Myeloid neoplasms with germline predisposition and other organ dysfunction
  – GATA2 mutation
  – Myeloid neoplasms associated with bone marrow failure syndromes
  – Myeloid neoplasms associated with telomere biology disorders

Adapted from Czuchlewski DR, Peterson LC. Surg Pathol 2016
Genetic testing

- Routine cytogenetic testing may be normal
- Many of involved genes are acquired events in MDS/AML (*CEBPA*, *RUNX1*, *GATA2*, *ETV6*, etc)
  - Critical to confirm with germline testing on constitutional DNA
- Skin fibroblasts is a gold standard for obtaining germline DNA
  - Hair and nails can be used
  - Blood and bone marrow should be used with caution in cases of myeloid neoplasms (T cell sorting)
  - Saliva and buccal mucosa are often contaminated and should be used with caution
- Many families have unique mutations, reported as “variants of unknown significance” → functional testing is needed to determine if they are pathogenic
- Very frequently targeted testing for known mutations is negative
  - Whole exome sequencing is recommended to look for novel mutations
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AML with germline *CEBPA* mutation

- Described in 2004 in one UK family
- *CEBPA* encodes a granulocyte differentiation factor on chromosome 19q13
- Inheritance of a single copy of mutated *CEBPA*
  - germline mutation usually found in the N-terminal end of the gene
- AML associated with biallelic (double) *CEBPA* mutation
  - an acquired, somatic mutation in the C-terminal region at the time of progression to AML
- Penetrance is close to 100%

Pabst T, et al. JCO 2008
AML with germline *CEBPA* mutation
AML with germline *CEBPA* mutation

- Patients typically develop AML as children and young adults (median age 25 years, range 2-46 years)
- Patients present with AML without preceding hematologic abnormalities
- Morphologic and immunophenotypic features are similar to sporadic *CEBPA*+ AML

AML with germline \textit{CEBPA} mutation

• Standard testing for AML includes \textit{CEBPA}

• \textit{CEBPA} mutations are detected by PCR amplification, fragment analysis and targeted DNA sequencing of the \textit{CEBPA} coding and junctional regions

• \(~10\%\) of cases with biallelic mutations represent a germline and a somatic mutation
  \(\Rightarrow\) Identification of biallelic \textit{CEBPA} mutations in AML should prompt evaluation of possible germline inheritance

• Somatic \textit{CEBPA} mutations appear unstable throughout the disease course
  – novel independent clones identified at recurrence

AML with germline *CEBPA* mutation

Overall survival in all patients

- Patients appear to have a favorable prognosis compared to both single *CEBPA* and double nonfamilial *CEBPA*
- Familial *CEBPA*: 67% overall survival at 10 years, but with multiple relapses

Survival after relapse

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Myeloid neoplasms with germline *DDX41* mutation

- Autosomal dominant MDS/AML syndrome described in 2015
  - ~20 families described
- Inherited mutations in *DDX41* gene (DEAD/H-box helicase gene) on chromosome 5q35.3
  - The gene encodes an RNA helicase protein with a function in RNA splicing
- Similar to *CEBPA*, many patients have biallelic mutations
- *DDX41* mutations found in ~1.5% of myeloid neoplasms; 50% of these patients have germline mutations

Myeloid neoplasms with germline *DDX41* mutation

- Mean presentation similar to de novo disease
  - 62 years old (range, 40-85)
- Most patients have normal blood counts until malignancy develops
- Clinical presentation:
  - Mostly MDS/AML
  - CML
  - CMML
  - Lymphoid malignancy (early onset follicular lymphoma, Hodgkin lymphoma, myeloma)
- 3 families also had predisposition to immune disorders (SLE, eczema, asthma, vasculitis)
- Penetrance has not been well established

Myeloid neoplasms with germline \textit{DDX41} mutation

• Patients with MDS/AML usually present with cytopenias or macrocytosis
• Bone marrow examination of carriers showed hypocellularity, prominent dyserythropoiesis and normal karyotype
  – AML is frequently of pure erythroid type (M6)
• Diagnosis: whole exome sequencing, PCR, Sanger sequencing
• Prognosis is uncertain
  – Possible response to lenalidomide
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Myeloid neoplasms with germline *RUNX1* mutation

- Familial platelet disorder with propensity to AML, initially described in 1999
- Approximately 60 families have been described
- An autosomal dominant transmission
- *RUNX1* is a transcription factor that plays a key role in megakaryocyte maturation, differentiation, ploidization and proplatelet formation
- The clinical presentation is variable, even within the same family
  - Usually mild to moderate thrombocytopenia (>50 x 10^9/L)
  - Normal platelet morphology, but abnormalities of platelet function
- Distinct families have varying risks of progression to myeloid neoplasms (range: 11-100%; median 40%) of family members
- Age at thrombocytopenia diagnosis has a wide range (2-67 years)
- The median age of onset of MDS/AML is 39 years

Myeloid neoplasms with germline \textit{RUNX1} mutation

- \textit{RUNX1} mutations are distributed throughout the gene
- Numerous mutations have been identified
  - Frequently each mutation is unique to a given family
- Acquisition of a mutation of the second \textit{RUNX1} allele appears to be a common second hit, but it is not required
- Diagnostic molecular testing: Sanger sequencing or NGS +/- comparative gene hybridization/single nucleotide polymorphism arrays
  - Include tests sensitive to deletions, duplications, and rearrangements, which may go undetected by standard PCR or sequencing

Jongmans MC, et al. Leukemia 2010
Genetic abnormalities comprise complete deletions of \textit{RUNX1}, splice-site mutations, missense, nonsense and frameshift mutations. Some of the mutations appear to act by haploinsufficiency and have dominant negative effects.
Myeloid neoplasms with germline \textit{RUNX1} mutation

- MDS and AML are the most common hematologic neoplasms
  - CMML and T-ALL also noted
  - rarely, B-cell neoplasms including hairy cell leukemia
- Bone marrow morphology has not been systematically evaluated
  - Marrow tends to be hypocellular for age
  - Abnormal megakaryopoiesis described in both carriers and patients with MDS/AML: micromegakaryocytes, bare megakaryocytic nuclei, asynchronous nuclear cytoplasmic maturation
  - Frequent eosinophilia
- Patients with progression to MDS/AML typically develop acquired cytogenetic abnormalities and/or somatic mutations
- Prognosis is uncertain due to limited long-term outcome data

Tsang H, et al. Mod Pathol 2017
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Myeloid neoplasms with germline ANKRD26 mutation

- Familial congenital thrombocytopenia with ANKRD26 mutation was initially described in 2011
- It is one of the more common forms of congenital thrombocytopenia
- Approximately 45 families have been identified
- Autosomal-dominant transmission
- Due to germline mutations within ANKRD26 located on chromosome band 10p12.1
  - increased gene transcription and signaling through the MPL pathway
  - impaired pro-platelet formation by megakaryocytes
- It is characterized by normal platelet size, moderate thrombocytopenia, and absent or mild bleeding tendency

Myeloid neoplasms with germline ANKRD26 mutation

• Most of the reported cases are AML or MDS
  – Rare cases of CML, CMML or CLL
• Results of bone marrow examination have been described in six patients
  – all showed megakaryocytic atypia with an increased number of small hypolobated megakaryocytes
• Diagnosis is based on targeted PCR of 5'-untranslated region of ANKRD26
  – Thus far, 12 variant mutations have been described

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Myeloid neoplasms with germline \textit{ETV6} mutation

- In 2015, 4 publications identified 7 families with germline mutation in \textit{ETV6}
  - Thrombocytopenia
  - Hematologic malignancies (usually B-ALL)
  - Occasionally high MCV
- Autosomal-dominant transmission
- Missense mutations identified to date have a dominant negative effect
  - result in disrupted nuclear localization of the \textit{ETV6} transcription factor
  - reduced expression of platelet-associated genes
- Affected patients have variable thrombocytopenia with normal sized platelets, and a mild to moderate bleeding tendency

Topka S, et al. PLOS Genetics 2015
Myeloid neoplasms with germline *ETV6* mutation

- The hematologic malignancies include:
  - B lymphoblastic leukemia (usually in children with high hyperdiploid karyotype)
  - MDS/AML (age 17)
  - MPAL (age 50)
  - CMML (age 82)
  - plasma cell myeloma (age 51)
- Colorectal, kidney and skin cancer cases have been also reported in these families
- Limited number of bone marrow biopsies from carriers without leukemia
  - small hypolobulated megakaryocytes
  - mild dyserythropoiesis
- Diagnostic testing: Sanger sequencing

Topka S, et al. PLOS Genetics 2015
Filled symbols represent individuals with thrombocytopenia and high MCV
* Asterisks indicate individuals who developed B-ALL
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Myeloid neoplasms with germline $GATA2$ mutation

• Germline $GATA2$ gene mutations were originally identified in 2011 as four separate syndromes:
  – MonoMac syndrome, characterized by monocytopenia and non-tuberculous mycobacterial infection
  – dendritic cell, monocyte, B, and NK lymphoid deficiency (DCML) with vulnerability to viral infections
  – familial MDS/AML
  – Emberger syndrome, characterized by primary lymphedema, warts and a predisposition to MDS/AML

• $GATA2$ mutations were also recognized in a minority of cases of congenital neutropenia and aplastic anemia

• Autosomal dominant transmission

• Considerable overlapping features were present in these disorders

• → Subsequently recognized as a single genetic disorder with protean manifestations

Vihn DC, et al. Blood 2010
Myeloid neoplasms with germline \textit{GATA2} mutation

- \textit{GATA2} is a zinc-finger transcription factor regulating hematopoiesis, autoimmunity, inflammatory and developmental processes
  - \textit{GATA2} knockout mice die \textit{in utero} due to lack of hematopoiesis
- Germline \textit{GATA2} mutations result in loss of function of the mutated allele, resulting in haploinsufficiency
  - Causes loss of hematopoietic stem cells and leads to depletion of dendritic cells, monocytes, B cells and NK cells
- No significant association between genotype and clinical manifestations

• At least 44 distinct mutations have been identified
• Mutations identified in both coding and non-coding regions
• Monoallelic mutations
• Classified as missense, null and regulatory
Myeloid neoplasms with germline GATA2 mutation

• The clinical presentation is very heterogeneous
• The largest study of 57 patients
  – the median age at presentation was 20 years (range: 5 months to 78 years)
  – 64% presented with infection, 21% with MDS/AML and 9% with lymphedema
• Most patients are diagnosed with MDS, but a subset presented with AML or CMML
• MDS/AML develops in approximately 70% of affected individuals at a median age of 29 years
• Many patients who develop MDS/AML have a concurrent ASXL1 mutation, which is likely a collaborating event in the development of overt malignancy

Micol GB, Abdel-Wahab O. Haematologica 2014
Schematic diagram summarizing the evolution of cellular deficiency in GATA2 mutation

Protean manifestations of germ-line, heterozygous mutations of GATA2

- Sensorineural hearing loss
- Pulmonary alveolar proteinosis
- Disseminated nontuberculous mycobacteria infection
- Cytopenias MDS/AML
- Warts
- Lymphedema

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Marshall S. Horwitz Blood 2014;123:799-800
Myeloid neoplasms with germline GATA2 mutation

• In a pediatric cohort with MDS, germline GATA2 mutation was present in 7% of all MDS cases and 15% of advanced MDS
• In the vast majority of children with GATA2 mutation (71%), MDS appears to be sporadic without pre-existing family history of myeloid leukemia or other GATA2-related symptoms
• in adolescent MDS patients, GATA2 germline mutations are significantly correlated with monosomy 7 (70% vs 11% in GATAwt MDS)

Myeloid neoplasms with germline GATA2 mutation

- MDS is suspected when patients develop cytopenias
- Bone marrow examination shows hypocellularity and multilineage dysplasia
  - Dysmegakaryopoiesis is the most prominent and consistent feature seen in 82% of studied cases (micromegakaryocytes and megakaryocytes with separated and peripheralized nuclear lobes)
- Many cases have increased reticulin fibrosis ($\geq$ MF-2)
- In adults the majority of the cases were diagnosed as MDS-RCMD
  - some cases of MDS-EB and rare cases called CMML and aCML
- In children an almost equal number of RCC and RAEB
- Bone marrow examination of asymptomatic carriers appeared normal including normal number of B/NK/dendritic cells and monocytes

Bone marrow features
Dysplastic myeloid precursors

Dysplastic neutrophils (25%)

Dysplastic erythroid precursors (39%)

Atypical plasma cells
Myeloid neoplasms with germline GATA2 mutation

• Flow cytometry shows characteristic findings:
  – abnormal granulocytic maturation
  – monocytopenia
    • however disease progression may correlate with monocytosis
  – reduced numbers of NK cells and B cells
  – nearly absent hematogones
  – plasma cells are often abnormal (e.g. CD56+, CD19-)
  – T-cell large granular lymphocytes are expanded

• These features may help in identifying patients with GATA2 mutation among patients with “idiopathic” aplastic anemia

Bone marrow flow cytometric analysis in GATA2 and AA patients

Karthik A. Ganapathi et al. Blood 2015;125:56-70

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Myeloid neoplasms with germline GATA2 mutation

- Cytogenetics: abnormal in ~60%; monosomy 7 and trisomy 8 are the most frequent abnormalities
- Molecular diagnosis: full gene sequencing
- Prognosis in MDS/AML appears similar to matched sporadic cases
  - MDS subtype was more prognostically significant than GATA mutation status
- Improved outcomes have been reported with hematopoietic stem cell transplantation
  - The only curative option
  - Ideal time window appears to be in the hypocellular MDS phase preceding severe complications

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Myeloid neoplasms with germline predisposition associated with inherited bone marrow failure syndromes and with telomere biology disorders

- Fanconi anemia
- Severe congenital neutropenia
- Shwachman-Diamond syndrome
- Diamond-Blackfan anemia
- Dyskeratosis congenita and related short telomere syndromes
Diagnostic challenges in disease progression

- Patients have to be closely monitored due to increased risk of myeloid neoplasm
- The morphologic distinction between baseline marrow morphology and disease progression can be difficult
  - Relevant clinical history is frequently absent
  - Data on expected bone marrow findings in disease carriers is very limited
- Studies report that patients with congenital thrombocytopenia and germline GATA2 mutations have abnormal megakaryopoiesis ("dysmegakaryopoiesis", "megakaryocytic dysplasia")
  → What are the minimal criteria for the diagnosis of myelodysplastic syndrome?
Table 2. Summary of patient and bone marrow biopsy characteristics

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Tsang HC, et al. Mod Pathol 2017
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<td>1</td>
<td>TAR</td>
<td>M</td>
<td>27</td>
<td>21</td>
<td>14</td>
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<td>MDS/MPN-like</td>
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<tr>
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<td>ANKRD26-RT</td>
<td>M</td>
<td>47</td>
<td>7</td>
<td>10</td>
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<td>MDS/MPN-like</td>
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<tr>
<td>3</td>
<td>STS</td>
<td>M</td>
<td>40</td>
<td>1</td>
<td>3</td>
<td>TERT</td>
<td>MDS/MPN-like</td>
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<tr>
<td>4</td>
<td>MYH9-RD</td>
<td>F</td>
<td>38</td>
<td>&lt;1</td>
<td>1</td>
<td>MYH9, inv(9)(p12q13)</td>
<td>MDS/MPN-like</td>
</tr>
<tr>
<td>5</td>
<td>CTRUS</td>
<td>M</td>
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<td>16</td>
<td>6</td>
<td>-</td>
<td>Bone marrow failure-like</td>
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<tr>
<td>6</td>
<td>FTP</td>
<td>F</td>
<td>34</td>
<td>&lt;1</td>
<td>1</td>
<td>-</td>
<td>Bone marrow failure-like</td>
</tr>
<tr>
<td>7</td>
<td>CTP with giant platelets</td>
<td>M</td>
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<td>2</td>
<td>2</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>WAS</td>
<td>M</td>
<td>27</td>
<td>25</td>
<td>1</td>
<td>WAS</td>
<td>Normal</td>
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Tsang HC, et al. Mod Pathol 2017
Figure 2 Bone marrow cellularity. Hematoxylin and eosin of bone marrow biopsies demonstrating hypercellularity in (a) Case 1: thrombocytopenia-absent radius syndrome, (b) Case 2: ANKR2D26-related thrombocytopenia, (c) Case 3: shortened telomere syndrome, (d) Case 4: MYH9-related disorder. Hypocellular marrow was observed in (e) Case 5: familial platelet disorder with predisposition to acute myeloid leukemia and (f) Case 6: congenital thrombocytopenia with radial-ulnar synostosis. Normocellular marrow was observed in (g) Case 7: unspecified congenital thrombocytopenia with giant platelets and (h) Case 8: Wiskott-Aldrich syndrome.
Figure 4 Presence of micromegakaryocytes was a notable feature in six patients. CD42b immunohistochemical stain highlights megakaryocytes (a) Case 1: thrombocytopenia-absent radius syndrome, (b) Case 2: ANKRD26-related thrombocytopenia, (c) Case 3: shortened telomere syndrome, (d) Case 4: MYH9-related disorder, (e) Case 5: familial platelet disorder with predisposition to acute myeloid leukemia, (f) Case 6: congenital thrombocytopenia with radial–ulnar synostosis, (g) Case 7: unspecified congenital thrombocytopenia with giant platelets, and (h) Case 8: Wiskott–Aldrich syndrome.
### Table 3. Bone marrow changes in patients with disease progression

<table>
<thead>
<tr>
<th>Entity</th>
<th>Cellularity</th>
<th>M:E ratio</th>
<th>Blasts</th>
<th>Myeloid dysplasia</th>
<th>Erythroid dysplasia</th>
<th>Fibrosis</th>
<th>Cytogenetic progression</th>
<th>Molecular progression</th>
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<tr>
<td>1 TAR</td>
<td>~100% all biopsies</td>
<td>&gt;10:1 all biopsies</td>
<td>1%, steady increase to 23%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>+(3)(p13), +(12)(q13)</td>
<td>CALR mutation</td>
</tr>
<tr>
<td>2 ANKRD26-RT</td>
<td>&gt;90% all biopsies</td>
<td>4:1-5:1 all biopsies</td>
<td>1%, steady increase to 7%</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>CBL mutation</td>
</tr>
<tr>
<td>3 STS</td>
<td>80%</td>
<td>4:1</td>
<td>3%, then 5%</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>47,XY,+i(1)(q10)[20]</td>
<td>RUNX1 and ETV6 mutation</td>
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TAR: thrombocytopenia-absent radius syndrome; ANKRD26-RT: ANRKD26-related thrombocytopenia; STS: shortened telomere syndrome
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Take home messages

• Myeloid neoplasms with germline predisposition are relatively obscure and remain under-diagnosed by pathologists and clinicians
• Pathologists have a critical role: to help suggest the diagnostic possibilities, describe the baseline bone marrow morphology and to rule out disease progression
• Children and adolescents with MDS need to be screened for germline GATA2 mutation
  – Most patients don’t have relevant family history
• Patients with inherited thrombocytopenia are frequently misdiagnosed as immune thrombocytopenia (ITP)
  → bone marrow biopsy with small abnormal megakaryocytes suggests CTP
Take home messages

• Finding a pathogenic mutation is not sufficient for diagnosis
  → Need to confirm that the abnormality is germline and not somatic, preferably with skin biopsy testing

• >50% of patients with hereditary myeloid neoplasms have unique mutations that are as yet undiscovered
  → Even sophisticated targeted sequencing testing will have negative results
Take home messages

• Need to develop criteria for diagnosis of disease progression (MDS or MDS/MPN)
  – Development of anemia and/or neutropenia
  – Dysplasia in erythroid and/or myeloid precursors
  – Acquired cytogenetic or molecular abnormality
  – Exclusion of non-neoplastic causes

• 40, 47, 52 years= age of patients with congenital thrombocytopenia when they were diagnosed with myeloid neoplasm
  → Long and indolent clinical course
  → can be seen in children and adults

• Studies on expected morphologic bone marrow findings are very limited
  → Conservative approach is recommended to avoid over-diagnosis of disease progression
THANK YOU!