Systemic inflammatory manifestations in a young adult (1987 ♂)

MDS Foundation Meeting, Tel Aviv, 6.3.2020
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Dermatological emergency (11/18)

Psoriasiform skin lesions

Nodulocystic acne

Focal bone lesions
Histology

**Skin**
- Dense and diffuse neutrophilic infiltrate in the dermis
- No pathogens by culture and PCR including atypical mycobacteria

**Right distal femur**
- Vital lamellar bone with signs of remodeling
- Medullary fibrosis
- No signs of active inflammation
- No sign of malignancy (sarcoma, myeloma)
- Serologies, cultures and PCR negative for bacterial or mycotic pathogens
Diagnoses 1

Neutrophilic dermatosis with granulomatous and sclerosing skin changes

Erythema nodosum, panniculitis since 2/2017: MTX, dapsone, plaquenil and systemic steroid therapy

Acne papulopustulosa grade IV (erythrosis faciei, keratosis pilaris atrophicans faciei): Isotretinoid

Hidradenitis suppurativa Hurley stage I: Triclosan soap

Multiple warts (verruca planae): Tretinoin Creme
Diagnoses 2

Relapsing systemic inflammatory manifestations

- **Unclear focal marrow fibrosis DD aseptic osteomyelitis**: no evidence of infection or malignancy (sarcoma or myeloma)

- **Aseptic meningitis (02 and 08/2017)**: corticosteroids, antibiotics, antiviral therapy
Personal history 1

Unclassifiable immunodeficiency DD CVID since 10/17

- Monocytopenia
- Severe NK cell depletion, CD4 lymphopenia (CD4/CD8 ratio (0.34))
- Mildly reduced B cells, IgG/IgA decreased under treatment 2017, IgG normal in 2011/17/19
- ANA borderline, ANCA and RF IgM: negative
- IL-1/TNF-alpha: normal
Personal history 2

Fluctuating mild macrocytic anemia, thrombocytopenia and leukopenia

1. BM assessment 2003
   - hypo- to normocellular
   - moderately active megakaryopoiesis, increased erythropoiesis, normal myelopoiesis, no dysplasia, no blasts.
   - Cytogenetics, FISH, PNH: normal findings

=> non-diagnostic bone-marrow
BM assessment 4/2013

PB: Hb 132 g/l, MCV 103 fl, Lc 2.7 G/l, Tc 121 G/l, Nc 1.24 G/l, Mono 0.09 G/l, Ly 1.32 G/l
2. **BM assessment 4/2013:**
   - Hypocellular BM
   - No increase of blasts, no clear signs of dysplasia
   - Cytogenetics:
     - C1: 46,XY,der(4)t(1;4)q21;q31),del(13)(q?22q?34)[5]
     - C2: 46,XY,+1,der(1;22)(q10;q10)[4]
     - 46,XY[1]
   - No signs of Fanconi Anemia in PB
   - Telomer lenghts < 10. percentile in all investigated cells
   - Mutation analysis telomerase complex (CTC1, DKC1, TERC, TINF2, TCAB1, TERT, NOP10, NHP2 all normal):
     - **SNP TERC n.514A>G** (reported as benign in ClinVar)
What are your next steps?

A. What is your hematological diagnosis?
B. What additional analysis do you need?
C. What is your initial treatment?
D. What is your long term goal?
Discussion
BM assessment 2/2019

PB: Hb 120 g/l, MCV 101 fl, Lc 4.71 G/l, Tc 249 G/l, Nc 3.4 G/L, Mono 0.04 G/L, Ly 0.9 G/L

H&E 1.5x

CD34, 20x

BMH

BMC

Clone 2

CG
Follow-up 1

3. BM-assessment 2/2019:
   - Hypocellular
   - Increased, dysplastic megakaryopoiesis and erythropoiesis with normal myelopoiesis
   - Blast equivalents (CD34) 2-3%. MF 0
   - Cytogenetics. 46, XY, +1, der(1;22)(q10;q10)[19]/46,XY[1]
   - Special diagnostics: Fibroblast cultures with MMC slightly increased (G2 17.5%), not diagnostic for FA
   - NGS (somatic panel, BM): ETV6 p.Arg399Cys (VAF 42%, germline mutation); ZRSR2 p.Phe247Ser (VAF 49%; unknown, deleterary)
   - No GATA2 mutations
   - NGS (somatic panel, saliva): ETV6 p.Arg399Cys (VAF 31%, germline mutation); ZRSR2 p.Phe247Ser (VAF 30%; unknown, deleterary).

=) MDS-MLD with ETV6 germ-line predisposition
Follow-up 2

4. BM assessment 9/2019:
PB: Hb 119 g/l, MCV 111 fl, Lc 4.93 G/l, Nc 3.21 G/L, Mono 0.05 G/L, Ly 1.03 G/L, Tc 289 G/l, blasts 0.5 %
- Unchanged

**Actual state:**
**Repeated hyperinflammatory systemic manifestations**
- Atypical right lower lobe pneumonia, DD auto-inflammatory:
  Doxycycline, Cefepime, Co-Amoxicillin 11/19
- PFO Grad III, TEE: LVEF/RVEF normal, RA dilat. 19.06.2019
- 2 HLA compatible siblings without ETV6 mutation
- On viral, PCP and fungal prophylaxis
Risk stratification

- IPSS (0.5-1 points): int-1
- IPSS-R (4 points): int
- HCT-CI (2-3 points; rheumatic, infectiological): intermediate-high
## WHO 2016 Classification: Myeloid Neoplasms with Germ Line Predisposition

<table>
<thead>
<tr>
<th>Myeloid Neoplasm Classification</th>
<th>Year of Description</th>
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<tbody>
<tr>
<td><strong>Myeloid Neoplasms with Germ Line Predisposition without a Preexisting Disorder or Organ Dysfunction</strong></td>
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<tr>
<td>AML with germ line <em>CEBPA</em> mutation</td>
<td>2004</td>
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<td>Myeloid Neoplasms with germ line <em>DDX41</em> mutation</td>
<td>2015</td>
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<td><strong>Myeloid Neoplasms with Germ Line Predisposition and Preexisting Platelet Disorders</strong></td>
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<td>Myeloid Neoplasms with germ line <em>RUNX1</em> mutation</td>
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<td>Myeloid Neoplasms with germ line <em>ANKRD26</em> mutation</td>
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<tr>
<td>Myeloid Neoplasms with germ line <em>ETV6</em> mutation</td>
<td>2015</td>
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<tr>
<td><strong>Myeloid Neoplasms with Germ Line Predisposition and Other Organ Dysfunction</strong></td>
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<tr>
<td>Myeloid Neoplasms with germ line <em>GATA2</em> mutation</td>
<td>2011</td>
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<tr>
<td>Myeloid Neoplasms associated with BM failure syndromes (i.e. Fanconi Anemia)</td>
<td>1927ff</td>
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<td>Myeloid Neoplasms associated with telomere biology disorders</td>
<td>1964ff</td>
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<td>JMML associated with neurofibromatosis, Noonan syndrome or Noonan syndrome-like disorders</td>
<td>1963ff</td>
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<td>Myeloid Neoplasms associated with Down syndrome</td>
<td>1866ff</td>
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**MDS/BMF with SRP72, SAMD9L, SAMD9, PPM1D, others will follow**

Arber et al, Blood 2016
Figure 1. Physical manifestations of the known HMMs. It is vital that the persona and family history include details regarding nonhematopoietic processes as HMMs can present in a syndromic manner with multiple organ systems involved. Adapted from Churpek and 3odley26 with permission.

Adapted from UC-HMCRT, Blood 2016
THANK YOU