Unusual cutaneous presentation of a T-cell lymphoproliferation

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History

• Male 78 yo
• 9 month history
• Multiple cutaneous, aggressive looking, ulcerated nodules on lower legs, chest and arms
• Some nodules appear to spontaneously regress
• No B symptoms
• No evidence of systemic lymphadenopathy or hepatosplenomegaly
• Laboratory investigations: mild anaemia and elevated LDH (270 U/L)
• Excision skin biopsy of one of the nodules
Molecular testing

(Torrent PGM- Life Technology) (AIL panel: RHOA, IDH2, TET2, DNMT3A)

• Monoclonal PCR

• RHOA+ (codon 17) VAF 15%
• TET2+ (x3) VAF 55% (exon 3)
  VAF 10% (exon 7)
  VAF 37% (exon 10)

Courtesy to
Prof. Leticia Quintanilla de Fend
Prof. Falko Fend
Diagnosis

Cutaneous presentation of angioimmunoblastic T-cell lymphoma
Discussion points

• Extranodal (cutaneous) presentation of AIL
  • Important differential diagnoses

• Utility of phenotypic and molecular testing for diagnosis
Angioimmunoblastic T-cell lymphoma (AIL) Definition and Classification

- Peripheral T-cell lymphoma of specialised CD4+ follicular T-helper cell ($T_{FH}$)
- Elderly patients
- Systemic disease
  - Slow insidious start
  - Skin rash, hyperglobulinemia, autoantibodies
  - Progressive disease with generalised lymphadenopathy
- Pathologically one of the most misdiagnosed lymphomas
AITL Morphological Patterns

Pattern 1

Pattern 2

Pattern 3

Attygalle A, Blood 2002;99:627-633
Molecular and GEP classification of AIL
14% of PTCL NOS are AIL by GEP

<table>
<thead>
<tr>
<th>AITL</th>
<th>ALK-</th>
<th>ALK+</th>
<th>ATL</th>
<th>NK</th>
<th>γδT</th>
<th>PTCL-NOS</th>
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Relative Level of Expression (x)

0.25  0.5  1   2   4

TFH lymphomas - Common mutations
RHOA, TET2, IDH2, DNMT3A (40-80%)

Gene fusions
CTLA4-CD28 (>50%)
ITK-SYK (FTCL)

Yoo et al. at Genet. 2014 Apr;46(4):371-5
Lemonnier et al. Blood. 2012 Aug 16;120(7)
Gene expression profiling and mutational analysis – Greater understanding of PTCL of follicular T-helper origin
AIL – Skin manifestations

• Clinical skin manifestations in 50-90% of cases
  • Maculopapular rash
  • Also purpuric, petechial, nodular, plaque-like, urticarial, bullous
  • Widespread, different parts of the body

• Minority present with clinical picture which suggests skin infiltration by lymphoma
AIL – Skin manifestations
Histological and molecular features

- Variable histological appearance when biopsied
  - Perivascular infiltrate 47%
  - Vascular hyperplasia or proliferation 44%
  - Vasculitis 27%
  - Combined patterns

- Molecular evidence of lymphoma more common than usually expected
  - Clonal TCR 87%
  - Cytologically atypical T-cell population 40%

Differential diagnosis of AIL in the skin – Tfh phenotype

- 2 (3) of 5 Tfh markers (PD-1, CXCL-13, ICOS, BCL-6, and CD10):
  - Peripheral T-cell lymphoma, not otherwise specified
  - Mycosis fungoides
  - Cutaneous CD30+ LPD
  - Cutaneous CD4+ small/medium T-cell LP (CD4+ SMTCLP)
  - Sézary syndrome
  - Subcutaneous panniculitis-like TCL

Primary cutaneous CD4+ small/medium T-cell LPD

- Solitary nodules on face, neck or upper trunk
- Patients otherwise asymptomatic
- Excellent prognosis with no treatment – LPD rather than lymphoma

Swerdlow et al. 2018
PTCL NOS, Cutaneous presentation

- CD3
- CD4
- CD8
- CD30
- CD10
- PD1

Markers:
- PCRT monoclonal
- TCRbeta+
- ICOS-
- CXCL13-
- BCL6-
- CD21 FDC-
- RHOA-
- IDH2-
- TET2-
- DNMT3A-
Clinical follow up

• Chemotherapy: CEOP (1 cycle) in May 2018
• Septic shock
• August 2018: alive, no visible skin lesions, no palpable lymphadenopathy or organomegaly
Concluding remarks
Diagnosis of AIL in skin

• AIL rarely involves skin at initial presentation

• Cornerstone of diagnosis remains critical compilation of
  – Clinical
  – Morphological
  – Immunophenotypic
  – Molecular features

• But crucial novel tests, including mutational analysis, must be performed

• Specific mutations serve as indicators for ctDNA – useful for non invasive monitoring of minimal residual disease in AIL

Sakata-Yanagimoto M et al, Ann Hematol 2017