A CD30+ LYMPHOPROLIFERATION PRESENTING IN SKIN

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University of Glasgow
CLINICAL HISTORY

- 64-year-old male
- Developed a red nodule on his right forearm
- Was referred for excision but lump had spontaneously resolved when he attended clinic
- Five months later developed a further lump on the right forearm; had grown slowly over one month and developed overlying erythema
- On examination the lesion measured 15 x 10 mm
- The lump was excised.
Dense nodular dermal infiltrate
• Ill-defined nodular lymphoid aggregates in dermis

• Linear basal epidermotropism in overlying and adjacent epidermis
• Ill-defined nodular lymphoid aggregates in dermis

• Linear basal epidermotropism in overlying and adjacent dermis
• Epidermotropic lymphocytes generally small with irregular nuclei
  • Nodules of larger more blast-like lymphoid cells in dermis
Anti-CD3: infiltrate consists of T-cells
Biphasic pattern of staining for CD30
- Large cells in dermal nodules strongly positive
- Smaller cells in dermis and epidermis weakly positive
CD30
Pan-T-cell antigens

- Loss of CD7
T-cells express CD8; CD4 negative
PATHOLOGICAL SUMMARY

CD30 positive T-cell LPD with predominant dermal component but also prominent epidermotropism

**Phenotype:**
- Positive: CD2, CD3, CD5, CD8, CD30, TIA1, TCRBF1
- Negative: CD4, CD7, CD56, CD57, Granzyme B, ALK1

DIFFERENTIAL DIAGNOSIS

- Primary cutaneous CD30+ lymphoproliferative disorder
  - Lymphomatoid papulosis (LyP)
  - Primary cutaneous anaplastic large cell lymphoma (pcALCL)
- Transformed mycosis fungoides (T-MF)
- Systemic T-cell lymphoma disseminating to skin
PATHOLOGICAL CLUES / CONUNDRUMS

Epidermotropism suggests primary cutaneous disease more likely

Appearances not typical for classic LyP (e.g. type A and C) or pcALCL:

- Epidermotropism may be seen in some cases (e.g. LyP types B & D)
- Not usually associated with pronounced dermal infiltrate

Appearances not entirely typical for MF

- Dermal component of large cells would suggest classification as large cell transformation of MF
- During transformation epidermotropic component of MF is frequently lost
FURTHER INVESTIGATIONS: CLINICAL CORRELATION ESSENTIAL

Further questioning of patient
  • No history to suggest previous mycosis fungoides

Physical examination
  • No other skin lesions, e.g. patches and plaques
  • No lymphadenopathy or hepatosplenomegaly

CT scan of neck, chest, abdomen and pelvis
  • No lymphadenopathy or hepatosplenomegaly
CAN MOLECULAR TESTS HELP CONFIRM A DIAGNOSIS?

FISH performed by Dr Leticia Quintanilla-Fend, Tübingen

FISH reveals *DUSP22* rearrangement

*DUSP22/IRF4* break apart probe
Around 50% the cells show a clear break
WHAT IS THE SIGNIFICANCE OF A DUSP22 REARRANGEMENT?

Historical FISH studies find DUSP22 rearrangements predominantly in pcALCL

<table>
<thead>
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<th>Wada et al</th>
<th>Pham-Ledard et al</th>
<th>Total</th>
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<tbody>
<tr>
<td>pcALCL</td>
<td>9/45</td>
<td>6/23</td>
<td>15/68</td>
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<tr>
<td>LyP</td>
<td>1/32</td>
<td>0/7</td>
<td>1/39</td>
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<tr>
<td>Mycosis fungoides /</td>
<td>0/31</td>
<td>0/13</td>
<td>0/44</td>
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<td>Sezary syndrome</td>
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<td>Transformed mycosis</td>
<td>0/13</td>
<td>2/11*</td>
<td>2/24</td>
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<td>fungoides</td>
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Also found in ALK- ALCL

ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes


Implies relatively favourable prognosis

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<th>Translocation</th>
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<tr>
<td>ALK</td>
<td>85%</td>
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<td>DUSP22</td>
<td>90%</td>
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<td>None</td>
<td>42%</td>
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<td>TP63</td>
<td>17%</td>
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Transformed MF and *DUSP22* rearrangement: are these cases really LyP/pcALCL?

Approx. 10% of LyP cases and occasional cases of pcALCL also have MF (Bekkenk et al 2000)

Large genomic study of cutaneous T-cell LPDs: solitary case of T-MF harbouring a *DUSP22* translocation
- Had a particularly good prognosis
- Shared other genetic features with cases of pcALCL

It could be that, in patients with MF, the development of a CD30+ lymphoproliferative disorder with *DUSP22* rearrangement represents concurrent LyP/pcALCL rather than large cell transformation, i.e. in primary cutaneous disease, *DUSP22* translocation is relatively specific for LyP/pcALCL.

WHAT ABOUT THE UNUSUAL MORPHOLOGY?

LyP with *DUSP22* rearrangement: frequently display same distinctive pathology as seen in our case

- Epidermotropic component; small CD30 dim lymphocytes
- Dermal nodules; larger CD30 bright cells
pcALCL with *DUSP22* rearrangement: frequently display same distinct appearances as seen in our case

Primary cutaneous anaplastic large cell lymphomas with 6p25.3 rearrangement exhibit particular histological features

Arantza Onaindia, Santiago Montes-Moreno, Socorro M Rodríguez-Pinilla, Ana Batlle, Sonia González de Villambrosia, Antonio M Rodríguez, Víctor Alegre, Glenda M Bermúdez, Carmen González-Vela & Miguel A Piris

- Epidermotropic component; small CD30 dim lymphocytes
- Dermal nodules; larger CD30 bright cells
However, DUSP22 rearrangements may be present in cases of primary cutaneous CD30+ LPD showing more typical pathology, e.g.

EAHP 2018 Lymphoma Workshop Case Submissions: two cases of pcALCL with DUSP22 rearrangement

EAHP18-LYWS-133; Dr G Penn
Mary Rutan Hospital
Bellefontaine, USA

EAHP18-LYWS-112; Dr P Katoch
Aalborg Universitetshospital, Aalborg, Denmark
PROPOSED DIAGNOSIS

PRIMARY CUTANEOUS CD30+ LYMPHOPROLIFERATIVE DISORDER (WITH DUSP22 REARRANGEMENT)

- The spontaneously resolving lump that had not been biopsied likely to have been a lesion of LyP.

- Second lump was excised, therefore no way of telling whether or not spontaneous resolution would have taken place, or of differentiating between LyP and pcALCL.

FOLLOW-UP

- No further action was taken

- Patient was alive with no evidence of disease when last seen 6 months after the excisional procedure.
CONCLUSIONS

*DUSP22* rearrangements are found principally in primary cutaneous CD30+ LPDs (LyP and pcALCL) and systemic ALK- ALCL.

Cutaneous cases often (but not always) have distinctive “biphasic” pathological features:

- **Prominent epidermotropic component**
  - Small lymphocytes with irregular nuclei
  - CD30 dim
- **Significant dermal component with nodules of**
  - Large blast-like lymphoid cells
  - CD30 bright

Awareness of this relationship (morphology and molecular abnormality) is important:

1. Stimulate FISH studies for *DUSP22* translocation in biopsies showing “biphasic” features and/or
2. Facilitate interpretation of positive *DUSP22* FISH result
3. Reinforce diagnosis of primary cutaneous CD30+ LPD
4. Prevent over diagnosis as more aggressive neoplasm

N.B. whilst molecular-morphological correlation is important, clinical-pathological correlation also remains essential in arriving at correct diagnosis and managing patient appropriately.