Lymphoma Slide Seminar - Case 6

Dr Stefan Dojcino\nUniversity Hospital of Wales
Cardiff, UK
• Male, 53
• History of 2 recent episodes of tonsillitis, fatigue and night sweats. No significant past medical history. Smoker, married with 2 children.
• From onset of symptoms, intermittent NSAID use, no other medication.
• Found to have left tonsil tumour clinically suspected of squamous cell carcinoma with enlarged left neck lymphadenopathy.
• Excision biopsy in October 2014.
B-cell PCR

IGH FR1

TCR B-B

PCR
B: Monoclonal in a polyclonal background
T: Restricted, oligoclonal
Patient also found to be TP+
Diagnosis

EBV positive mucocutaneous ulcer in an immunosuppressed subject with HIV infection
EBV+ Mucocutaneous Ulcer (EBVMCU)

Interface of reactive and neoplastic - Provisional WHO 2016 Entity

Iatrogenic IS
(SLE, Sarcoidosis, RA, IBD, Transplant)
  • Methotrexate
  • Cyclosporin A
  • Azathioprine
  • MMF
  • Steroids (IR ipilimumab colitis)

Immunosenescence (old age)
HIV

Age: childhood to old (median 77)

Localised ulcers with no systemic disease

Oropharynx, tongue, entire GI tube, skin, other mucosal sites

No lymphadenopathy or other clinical evidence of lymphoma

Concomitant other EBV+ B-cell LPD

B-cell clonal (1/3); T-cell clonality (1/3); T-cell restricted (1/3)
EBVMCU - Clinical relevance

Conservative management

Reduction of IS

Rituximab

Jaffe & Dojcinov in WHO Classification of Skin Tumours; IARC 2018

MCU - 10 years on
110 cases; 38 papers

• Expanded clinical and pathological spectrum

• Insights into pathogenesis
• Differential diagnosis
EBVMCU – Not always solitary (17% multiple lesions)

Case 154. EAHP/SH Workshop LA 2011

Patient with folliculotropic MF treated with topical steroids
Lesions regressed and reappeared as ulcers

EBVMCU complicating Ipilimumab associated colitis
Pugh et al. Clin Gastroenterol and Hepatol. 2019 in press
EBVMCU – Develops at sites of tissue damage

Case 154. EAHP/SH Workshop LA 2011
Song et al. Am J Clin Pathol 2013;139:466-490

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Biopsy day 113  Biopsy day 122  Resection day 138
Pathogenesis

- Tissue damage
- Vascular damage (aided by EBV (MIG))
- Localised immune sequestered avascular ulcer slough environment
- EBV driven B-cell LP in the absence of specific T-cells (aided by IS state)
Referred Diagnosis and Management

- 40% diagnosed as cHL, DLBCL
- 25% received aggressive therapy
EBV+ MCU or cHL?

<table>
<thead>
<tr>
<th></th>
<th><strong>EBV+ MCU</strong></th>
<th><strong>cHL</strong></th>
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</thead>
<tbody>
<tr>
<td>Presentation</td>
<td>Mucosa and skin</td>
<td>Nodal – Not in mucosa and skin</td>
</tr>
<tr>
<td>Morphology</td>
<td>Range of cell sizes</td>
<td>HRS cells only</td>
</tr>
<tr>
<td></td>
<td>Histiocytic and lymphocytic background</td>
<td>Mixed infiltrate</td>
</tr>
<tr>
<td></td>
<td>Angioinvasion</td>
<td>No angioinvasion</td>
</tr>
<tr>
<td></td>
<td>Necrosis common</td>
<td>Necrosis not so common</td>
</tr>
<tr>
<td></td>
<td>Numerous EBER+ cells (variable size)</td>
<td>Fewer EBER+ cells (uniform)</td>
</tr>
<tr>
<td></td>
<td>Circumscription (lymphocytic rim)</td>
<td></td>
</tr>
<tr>
<td>Phenotype</td>
<td>CD45+/-</td>
<td>CD45-</td>
</tr>
<tr>
<td></td>
<td>CD20 +/-</td>
<td>CD20-</td>
</tr>
<tr>
<td></td>
<td>PAX5+</td>
<td>PAX5+ (weak)</td>
</tr>
<tr>
<td></td>
<td>OCT2+</td>
<td>OCT2-</td>
</tr>
<tr>
<td></td>
<td>BOB1+</td>
<td>BOB1-</td>
</tr>
<tr>
<td></td>
<td>MUM1+</td>
<td>MUM1-</td>
</tr>
<tr>
<td></td>
<td>CD30+</td>
<td>CD30+</td>
</tr>
<tr>
<td></td>
<td>CD15+/- (68%)</td>
<td>CD15+</td>
</tr>
<tr>
<td></td>
<td>EBNA2+/-</td>
<td><strong>EBNA2</strong>-</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Self limiting disease</td>
<td>Progressive disease not responsive to conservative measures</td>
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<tr>
<td></td>
<td>Response to IS withdrawal</td>
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EBV+ Lymphomas/LPDs
“Host Response” Type Lymphomas

1. NFkB signature

2. Immunoregulatory response signature
   - PDL1/2 – PD1 (9p gains)
   - SLAM IRPR (1q gains)
   - CTLA4/B7

3. Innate antiviral inflammatory response

Montes-Moreno et al. Modern Pathology (2012) 25, 968–982
Ok et al. Clin Cancer Res. 2014 May 1;20(9):2338-49
Menter & Tzankov. Front Oncol. 2018 Mar 7;8:54
Kinch et al. Leuk Lymphoma. 2019 Feb;60(2):376-384
Gebauer et al. Leuk Lymphoma, 2015 Apr;56(4):1100-6

EBV+ Lymphomas/LPDs

Cancer Cell
EBV+ DLBCL

Cytokines

Indirect INF-gamma mediated STAT1 activation in PTLD
### Microenvironment EBVMCU and CHL

<table>
<thead>
<tr>
<th></th>
<th>PDL1</th>
<th>cHL</th>
<th>cHL EBV+</th>
<th>cHL EBV-</th>
<th>EBVMCU</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td>17 (77%)</td>
<td>10 (71%)</td>
<td>7 (88%)</td>
<td>11 (100%)</td>
<td>0.137</td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>5 (23%)</td>
<td>4 (29%)</td>
<td>1 (12%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22</td>
<td>14</td>
<td>8</td>
<td>11</td>
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Pugh et al. EAHP Edinburgh, 2018; LYS-P16
MCU Summary

• Isolated indolent EBV+ LPD in IS, mimicking lymphoma (CHL, DLBCL)
• Clinical features most valuable diagnostic clue

• Morphology wider
  – Small and multiple lesions recognised
  – PC rich – CHL like – DLBCL like

• Pathogenesis involves preceding tissue damage with early vascular lesions

• Microenvironment similar with other EBV LP
Case 6 follow-up

- Antiretroviral therapy
- No further treatment for MCU
- Alive, well, asymptomatic