Case

• In October 2004, a 46 year-old woman came to UT MDACC for a second opinion about and discussion of treatment options for a diffuse large B-cell lymphoma diagnosed and treated at an outside institution.
• She had initially presented in March 2003 with right shoulder pain and swelling in the right upper extremity.
• CT examination showed an 8.4 x 5.3 cm mass in the upper mediastinum.

Case

• An open chest biopsy was performed, and a diffuse large B-cell lymphoma was diagnosed.
• She received chemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), but showed no significant improvement.
• PET scan revealed persistent disease, the regimen was changed to 2 cycles of ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) and rituximab with adjuvant radiation therapy (December 2003).

Case

• In August 2004, the patient began complaining of left hip pain.
• In October 2004, physical examination at the time of admission at MDACC revealed severe left gluteal pain.
• Laboratory tests including a complete blood count and chemical profiles were normal.

Case

• CT scan of the chest and abdomen revealed a 5.3-cm mass at the superior mediastinum, multiple lytic bone lesions in the pelvis bone, and a large 5.0-cm mass on the left sacrum.
• Excisional biopsy of the sacral mass & bilateral BM biopsies were performed.
• H&E stained slide from the previous biopsy of the mediastinal mass was reviewed.
• IHC studies were performed on all 3 specimens.
HEMATOPATHOLOGY EVENING SESSION

Mediastinal mass

CD20, Mediastinal

CD21

CD23
Immunophenotypic findings

• IHC staining revealed that the tumor cells of the mediastinal mass:
  • Positive: CD21, CD23, CD35, EGFR, clusterin
  • Negative: CD45, CD30, CD20, CD5, CD1a, vimentin, S-100, keratin cocktail

• IHC staining of sacral mass revealed tumor cell foci that were:
  • Positive: strongly for CD21, CD23, clusterin, EGFR; weakly positive for CD35, CD45, and CD68
  • Negative: CD20, S-100, keratin cocktail

• IHC tumor cells in the BM: same staining pattern

Genetic studies and follow-up

• Karyotype:
  • Insufficient yield of analyzable metaphases, 46,XX[1] (2004)
• Molecular tests:
  • Not done
• Rx:
  • Gemcitabine plus docetaxel, immediate improvement
  • CR followed by multiple relapses, died in 36 months
  • 45-50,XX.del(6)(q21), +8,inv(9)(p11q12), +5-8mar, 2dim[cp4] (2006)

Diagnosis

Follicular dendritic cell sarcoma
Follicular dendritic cell (FDC) functions and interactions in the germinal center

FDC are key for the recruitment of B and T cells in B follicles, especially by secreting CXCL13 (a) and directly interact with B cells by integrins/integrin receptors.


Follicular dendritic cell sarcoma

• Follicular dendritic cell sarcoma is a mesenchymal tumor
• With morphological & phenotypical features of follicular dendritic cells
• Spindle to ovoid cells forming fascicles, storiform arrays, whorls, diffuse sheets
• Morphologic variants: Spindle/typical, epithelioid (EBER-) & inflammatory pseudotumor-like (EBER+)
• Immunophenotype: variable expression of CD21, CD23, CD35, CXCL13, clusterin, or EGFR
• Electron microscopy: Long cellular processes connected by desmosomes


Sensitivity, specificity, AUC, p-value <0.0001 of FDC markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under the curve (AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCL13</td>
<td>90.9%</td>
<td>100.0%</td>
<td>0.96</td>
</tr>
<tr>
<td>CD21</td>
<td>81.8%</td>
<td>100.0%</td>
<td>0.91</td>
</tr>
<tr>
<td>CD35</td>
<td>72.7%</td>
<td>100.0%</td>
<td>0.86</td>
</tr>
<tr>
<td>FDCSP</td>
<td>72.7%</td>
<td>97.2%</td>
<td>0.85</td>
</tr>
<tr>
<td>SRGN</td>
<td>68.2%</td>
<td>100.0%</td>
<td>0.84</td>
</tr>
<tr>
<td>Clusterin</td>
<td>81.8%</td>
<td>81.9%</td>
<td>0.81</td>
</tr>
<tr>
<td>CD23</td>
<td>63.6%</td>
<td>180.0%</td>
<td>0.80</td>
</tr>
<tr>
<td>Podoplanin</td>
<td>63.6%</td>
<td>83.3%</td>
<td>0.77</td>
</tr>
</tbody>
</table>


Key Points

• Include FDC sarcoma/tumor in the differential diagnosis of extranodal sarcomas and lymphomas
• Proposed marker panel for FDCS diagnosis (positive for at least 2 markers among CXCL13, CD21, CD35, FDC Secreted protein, Serglycin. Clusterin, CD23, podoplanin, claudin 4, if necessary

Characteristics, management, and outcomes of patients with FDCS at UT MDACC

Overall

<table>
<thead>
<tr>
<th>Initial Stage</th>
<th>Localized</th>
<th>Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 (53%)</td>
<td>26 (46%)</td>
<td>6 (11%)</td>
</tr>
</tbody>
</table>

Bulky disease (n, %) 41 (74%) 0 (0%) 41 (68%)
Castleman’s disease (n, %) 3 (6%) 0 (0%) 3 (5%)
Autoimmune disease (n, %) 13 (20%) 1 (17%) 14 (19%)

Survival outcomes is significantly inferior in patients with extranodal disease at initial presentation

**Progression-free survival**

**Overall survival**

*Jain P*, et al. 2017

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Survival outcomes is significantly inferior in patients with bulky disease at initial presentation

**Progression-free survival**

**Overall survival**

*Jain P*, et al. 2017

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Survival outcomes is significantly inferior in patients with bulky, intra-abdominal or extranodal disease at initial presentation

**Progression-free survival**

**Overall survival**

*Bulky Intra-abdominal Extranodal*

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FDCS patients who underwent an upfront gross total resection (GTR) experienced better PFS and OS

- Response to initial therapy:
  - Overall response rate (ORR): 78%
  - Complete response (CR) observed in 45%

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In FDCS patients who underwent a GTR, consolidative RT was associated with improved local control

**Progression-free survival**

**Overall survival**

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MDACC… NGS with a 50-gene panel for 2 patients

- PTEN: Mutation (c.388C>T p.R130, exon 5) in one sample
- BRAF V600E: No mutation
- EGFR: No mutation

Recent NGS in one and 13 cases of FDCS

- TP53: Mutations (missense and non-sense)
- PTEN: Mutation (missense and non-sense)
- NF-kB: Mutations and copy number variations in NFKBIA, CYLD involved in NF-kB pathway regulation (5/13)
- Cell cycle: Mutations and copy number variations in CDKN2A, RB1 involved in cell cycle progression (4/13)
- Immune: Copy number gain on 9p24 containing the genes CD274 (PD-L1) & PDCD1LG2 (PD-L2) (3/13) in keeping with previous observations that FDCS express PD-L1

Epidermal growth factor receptor (EGFR)

- Receptor tyrosine kinase whose overexpression in cancer leads to deregulated proliferation or differentiation.
- Expression of EGFR in FDC sarcomas and the upregulation of EGFR in the FDC of hyaline vascular Castleman’s disease.
- One study on a series of 16 FDCS cases did NOT show activating mutations on EGFR (exons 18, 19, 21).
- EGFR signaling is mediated by locally produced ligands rather than by oncogenic mutations (FDC cell line).

Key Point

- EGFR-inhibitors may have a potential role in the treatment of aggressive FDCS
- Tyrosine kinase inhibitors have been recently used in few FDCS cases, showing durable partial response in one patient and prolonged benefit in other four.

Take home messages

- FDCS are rare tumors with morphologic & phenotypic features of FDCs.
- 54% of patients present with localized disease & 48% with systemic involvement
- Survival outcomes: inferior in patients with extranodal, bulky or intra-abdominal disease at presentation
- Loss of function alterations in NF-kB regulatory pathway & cell cycle
**Case 2 - Panelists Diagnoses**

- Follicular dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Follicular dendritic cell sarcoma

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**Important Information Regarding CME/SAMs**

The Online CME/Evaluations/SAMs claim process will only be available on the USCAP website until September 30, 2017. No claims can be processed after that date.

After September 30, 2017 you will NOT be able to obtain any CME or SAMs credits for attending this meeting.

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**THANK YOU**