Hepatosplenic T-cell Lymphoma: Two cases with different clinicopathological features and therapeutic approaches.

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Fellow meeting
November 7th 2014
Clinical case 1: presentation and diagnosis

- HPI (August 2009)
  - 55yo woman presented to PCP with fatigue and dizziness. She also reported night sweats, easy bruising on her arms, early satiety and pressure in her left upper quadrant.

- Labs
  - PLT 53, WBC 3.7 ANC 2.5, Hct 30

- Radiology
  - Abdomen CT scan: Spleen 17 cm (with 3 wedge-shaped areas suggestive of splenic infarcts). Hepatomegaly with no presence of retroperitoneal lymphadenopathy.

- PMH
  - No significant

- FHx
  - No contributory
• Bone marrow studies:
  - Morphology: Hypercellular BM with 78% cellularity with small lymphoid aggregates approximately 30%. Mild to moderate myelofibrosis with reticulin stain.
  - Flow/Immunochemistry: Infiltrate of neoplastic cells that expressed CD3, CD2, CD7, CD56 and alpha-beta TCR without CD4, CD8, CD10, CD16, CD25, CD30 or CD52 negative T cell population. No abnormal B cell population.
  - Cytogenetic: Normal female karyotype
  - TCR rearrangement study: Clonal alpha-beta TCR rearrangement.
• Liver biopsy:
  - Morphology: Atypical sinusoidal lymphoid infiltrate that had the same immunophenotype as the bone marrow aspirate.
• Splenectomy:
  - Abnormal T-cell population having abnormal expression of CD3 (increased), CD5 (absent), CD45 (increased), CD56 and CD57 (low to absent) with normal expression of CD2, CD4 and CD7 without CD8 or CD34.
Clinical case 1: therapeutic approach and response

- Hyper-CVAD followed by allogeneic transplant
  - Starting from December 2009 she received 6 cycles with good response and reduction to 0.1% abnormal T-cell population pre-transplant
  - Lumbar puncture pre-transplant revealed an abnormal T-cell population.
  - Received multiple intrathecal treatment with Ara-C and methotrexate.

- June 2009: Matched related transplant on protocol 739 (TBI + Cytoxan) + boost of craniospinal radiation during conditioning.
  - PBSC transplant from sister major ABO incompatible. GVHD prophylaxis methotrexate and tacrolimus.
  - Acute gut GVHD treated with prednisone, B&B at day 80 departure had subclinical oral GVHD.
  - Post transplant had 2 doses of IT Methotrexate and 2 doses of Liposmal ARA-C.
  - Low-level of abnormal T-cells in the BM post-transplant that disappeared with immunosuppressive tapering.
Clinical case 1: follow-up

• January 2014: Onset of abdominal pain. Pain persisted until June 2014 when she presented to ER w/severe pain. CT indicated 12cm abdominal abscess that required laparotomy with resection of segment of the small bowel as well as the abscess.

• Histological exam showed sheets of small lymphoid cells that on immunohistochemical staining were neoplastic T-cell population expressing CD2, CD3, CD7, and CD56. There was no expression of CD4, CD8, CD5, CD30, or LKLK-1. Ki-67 was 95%.

• Molecular studies identified a TCR gamma gene rearrangement identical in size to the clonal peak previously characterized on the both marrow and liver biopsy in 2009.

• Staging studies showed no other sites of the lymphoma.

• The patient received one cycle of single-agent pralatrexate therapy in preparation for donor lymphocyte infusion.
• After 1st cycle of pralatrexate therapy she was found to have frank disease progression with large soft tissue mass in the abdomen as well as evidence of lymphomatous meningitis.

• Infiltrative soft tissue extending from the site of the small bowel anastomosis to the lesser sac, extending inferiorly along the transverse mesocolon. Maximum axial dimension is 12.9 x 3.8 cm and craniocaudal dimensions measure 11.4 cm.

• Treatment:
  - EPOCH regimen

• October 2014: Colonic perforation during therapy with dose-adjusted EPOCH. She now is status post ileostomy and plan is to continue treatment hoping for CR and DLI infusion.
Clinical case 2: presentation and diagnosis

• HPI (March 2014)
  - 59 yo man with progressive constitutional symptoms and weight loss. In addition, he experienced vocal cord paralysis and dysphagia.

• Labs
  - PLT 88, WBC 1.5 ANC 0.7, Hgb 9

• PMH
  - No significant

• FHx
  - No contributory

• Bone marrow studies:
  - Left shifted granulocyte maturation with small aberrant T-cell population (1% of total nucleated cells), showing loss of CD5 and CD7.
• Radiology:
  - Neck CT scan: showed 5.7 x 3.0 x 1.7 cm soft tissue mass extending from the skull base to the left carotid bifurcation.
  - Abdomen CT scan: Splenomegaly 17.5 cm; no hepatomegaly.
  - Brain MRI: multiple enhancing masses of the skull which were considered most likely neurogenic in origin; 6.0 x 3.0 cm heterogenous mildly enhancing mass in the carotid space.

• Removal of neck mass: Schwannomma

• Splenectomy:
  - Presence of atypical cells small to intermediate in size.
  - Flow/Immunochemistry: cells positive for CD3, negative for CD56, CD17, CD20, and CD138. CD5 was negative for the majority of cells. Cells were also negative for CD4, CD7, CD8, and T-cell receptor beta F1.
  - T-cell receptor rearrangement studies yielded oligoclonal pattern.
  - FISH analysis for isochromosome 7q was negative.
  - Review of splenectomy at UW confirmed the diagnosis of hepatosplenic T-cell lymphoma, likely gamma delta subtype.
Clinical case 2: follow-up

- After splenectomy, patient’s peripheral blood counts normalized and his constitutional symptoms resolved.

- October 2014:
  - PE: Negative
  - ROS: Appetite improved with weight gaining.
  - Labs: Hct 41, Plt 300, WBC 6500 ANC 3990.

- Therapeutic approach: Close clinical follow-up
Hepatosplenic T-cell lymphoma (HSTL)

• It is a very rare (less than 1% of lymphoid neoplasm) subtype of mature T-cell lymphomas with poor outcomes despite combination chemotherapies. First described by Farcet et al. in 1990 and recognized as independent clinical entity in the revised European-American Lymphoma classification in 1994 and in the subsequent WHO classification.

• It is characterized by frequent involvement of splenic red pulp, liver sinusoids and bone marrow.

• Nodal and other extranodal sites are rarely affected.

• Patients usually present with cytopenias and B-symptoms.

• Although cases with alpha-beta T-cell receptor expression have been described, the hallmark of HSTL is expression of gamma-delta T-cell receptors.

• Hepatosplenic T-cell lymphoma can occur at any age but is most often seen in teenagers or young adults, with a strong male predominance.
Hepatosplenic T-cell lymphoma (HSTL)

• Immunosocompromised patients are overrepresented, with reports of HSTCL developing during long-term immunosuppression after solid-organ transplant (in particular association in patients treated with anti-TNF alpha) and in the setting of other immune dysregulation including malignancy and infection.

• Most frequent chromosomal abnormality are isochromosome 7q and trisomy 8.

• Malignant cells are medium-size mature T-cells.
Hepatosplenic T-cell lymphoma appearing

a) Lymphoid cells with basophilic cytoplasm and multiple nucleoli.

b/c) Small cells presents with scant cytoplasm and condensed chromatin while the large cells with a large cytoplasm and moderately dispersed chromatin.

d) Histological section of the bone marrow stained with anti-CD3 shows dendritic distribution of lymphoid cells suggesting their sinusoidal infiltration.
Hepatosplenic T-cell lymphoma histology

- Spleen: Diffuse involvement of the red pulp with neoplastic lymphocytes
- Bone marrow: Interstitial infiltrate with neoplastic lymphoid cells
- Liver: Infiltration of lymphoid cells in the sinusoids
Hepatosplenic T-cell lymphoma (HSTL)

• The immunophenotype typically is a CD4-/CD8- T-cell with CD2 and CD3 expression.

• Other markers such as CD5, CD25, and granzyme B are usually absent. NK cell markers, such as CD56 and CD16 might be expressed.

• In the literature, the prognosis of HSTCL is almost uniformly poor, and no prospective trials investigating treatment approaches are reported.

• Most of the published data consists of case reports and series, with 2 larger single-institution series focused on treatment outcomes demonstrating exceedingly poor long-term therapeutic results with a CHOP based regimen.
Hepatosplenic gammadelta T-cell lymphoma is a rare clinicopathologic entity with poor outcome: report on a series of 21 patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Induction phase</th>
<th>Consolidation phase</th>
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### Hepatosplenic gammadelta T-cell lymphoma: clinicopathological features and treatment

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<th>Patient number</th>
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25 patients (18 alloHSCT, 7 autoHSCT).

The 18 patients receiving alloHSCT had a median age of 39 years (range 25–67) and most had stage IV disease (83%) with B symptoms (72%).

The median interval from diagnosis to transplant was 5 months (range, 2–51) and patients had received a median of 2 (range 1–4) lines of prior treatment.

Allogeneic donors were HLA-identical siblings (10), unrelated volunteers (6) and one each of mismatched relative and cord blood.

The conditioning was considered myeloablative in 67% patients with alloHSCT and included total body irradiation in 50%.

Of the seven auto HSCT patients, five patients relapsed and subsequently died.

Tanase et al. Leukemia 2014 in press
Forty-two patients 24 male and 18 female, with the median age of 35 (range, 17-79) years.

- Splenomegaly was reported in 39/42 (93%), hepatomegaly in 23/40 (58%), and bone marrow involvement in 32/39 (82%) patients. Lymph nodes were involved in only 12/40 (30%).

- History of immunosuppressive therapy was present in 13/42 (31%) patients.

- Overall response rate to initial therapy was 63%, with 44% achieving complete remission.

- Twenty-three (55%) patients underwent autologous (n=2) or allogeneic (n=19) HSCT, and 2 underwent both.

- With the median follow-up of 56 months (range 15-105) for living patients, the median OS was 15.8 mo
DISCUSSION