Patient Case Studies & Panel Discussion

Panelists: Ranjana H. Advani, MD, Stanford Cancer Institute; Francine Foss, MD, Yale Cancer Center/Smilow Cancer Hospital; Steven M. Horwitz, MD, Memorial Sloan Kettering Cancer Center
CASE 1

Ranjana H. Advani, MD
Stanford Cancer Institute
Patient Case

• 33-year-old male with no past medical history presents with a 4 month history of breathing difficulties/stuffy nose not relieved by nasal sprays or antibiotics
• 1 month ago he noted gum swelling of upper teeth that gradually worsened despite chlorhexidine mouthwash along with fevers to 100.0 F and a 20 pound weight loss
• A dentist biopsied the gingiva of the right maxilla
• Pathology: a dense infiltrate of pleomorphic atypical round cells with high mitotic rates, with angiocentric and angiodestructive growth pattern with fibrinoid changes in blood vessels.
• IHC: Negative for CD20, CD 4, CD 5, CD138, and MUM1. Positive for cytoplasmic CD 2, CD3, CD30, CD56, TIA 1 and EBER.
Patient Case
Q1: What is the most likely diagnosis?
1. Anaplastic large cell lymphoma
2. Angioimmunoblastic T-cell lymphoma
3. Extranodal NK/T-cell lymphoma
4. Plasmablastic lymphoma
5. Peripheral T-cell lymphoma, NOS
Follow-up:

- Pathology review is consistent with extranodal NK/T-cell lymphoma and he is referred to you.
- Labs: WBC 2.1 K/ul (ANC 1240, ALC 770), Hgb 8.6, pltts 222.  AST 102, ALT 111, LDH 644.
- PET-CT: right hard palate hypermetabolic mass (SUV 19.8) and right submandibular nodal conglomerate of 2.8 cm (SUV 9.3).
- Bone marrow biopsy demonstrates extensive involvement with lymphoma (90%) with note of hemophagocytic histiocytes.
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• Bone marrow biopsy demonstrates extensive involvement with lymphoma (90%) with note of hemophagocytic histiocytes.
Q2: What further testing should you order?

1. Plasma EBV DNA PCR
2. Serum ferritin
3. Serum triglycerides
4. Soluble IL-2 receptor
5. All of the above

- 66%
- 30%
- 2%
- 0%
- 2%
WORKUP

ESSENTIAL:
- Physical exam: attention to complete ENT evaluation nasopharynx involvement (including Waldeyer's ring), testicles, and skin
- Performance status
- B symptoms
- CBC, differential platelets
- LDH
- Comprehensive metabolic panel
- Uric acid
- Bone marrow biopsy + aspirate
- Chest/abdominal/pelvic CT with contrast of diagnostic quality and/or PET-CT scan
- Dedicated CT or MRI of the nasal cavity, hard palate, anterior fossa, nasopharynx
- Calculation of NK/T-cell PI
- MUGA scan/echocardiogram if treatment includes regimens containing anthracyclines or anthracenedione

EBV viral load

Concurrent referral to RT for pre-treatment evaluation

USEFUL IN SELECTED CASES:
- Pregnancy testing in women of child-bearing age
- Discussion of fertility and sperm banking
- HIV

NKTL-1
ESSENTIAL:
- Physical exam: attention to complete ENT evaluation nasopharynx involvement

**BM aspirate:**
- Lymphoid aggregates are rare and are considered involved if EBER-1 positive.
- Hemophagocytosis maybe present

**EBV viral load:**
- Important in diagnosis
- Positive result is consistent with NK/T cell, nasal type
- Monitoring of disease
- Lack of normalization of viremia considered indirect evidence of persistent disease.

- Pregnancy testing in women of child-bearing age
- Discussion of fertility and sperm banking
- HIV

**NKTL-1**
Extranodal NK/T-cell lymphoma (ENNK/TCL): EBV

Survival by pre rx EBV-DNA

Change of plasma EBV-DNA during Rx

EBV DNA levels prognostic in Extranodal NK/T-cell Lymphoma

Hemophagocytic Lymphohistiocytosis (HLH) Criteria

Fulfillment of five out of the eight criteria below:

• Fever (>100.4 °F, >38 °C)
• Splenomegaly
• Cytopenias affecting at least two of three lineages in the peripheral blood:
  • Hemoglobin <9 g/100 ml, Platelets <100×10⁹/L, Neutrophils <1×10⁹/L
• Hypertriglyceridemia (fasting, greater than or equal to 265 mg/100 ml) and/or hypofibrinogenemia (≤ 150 mg/100 ml)
• Ferritin ≥ 500 ng/ml
• Hemophagocytosis in the bone marrow, spleen or lymph nodes
• Low or absent NK cell activity
• Soluble CD 25 (soluble IL-2 receptor) >2400 U/ml

Jordan et al Bone Marrow Transplant 2008
Follow-up:

- EBV DNA PCR: positive (59696 IU/mL).
- Ferritin: 25000 (normal 8-282)
- Triglycerides 221 (normal < 150 mg/dL)
- Soluble IL-2 receptor 30,000 units/mL (normal 45-1105)
Audience Polling Results

Q3: What is the most appropriate initial treatment?

1. Etoposide and dexamethasone
2. Modified SMILE
3. CHOEP
4. DeVIC x 3 cycles with concurrent radiation therapy

21%  21%  43%  14%
Extranodal NK/T-Cell Lymphoma, nasal type

STAGE

Nasal

Stage I, II

Performance status

Fit for chemotherapy

Stage IV

Extranodal → Stage I-IV

INDUCTION THERAPY

Unfit for chemotherapy

Clinical trial or RT alone

Clinical trial or Concurrent chemoradiation or Sequential chemoradiation or Sandwich chemoradiation in selected patients

See Post-RT Evaluation (NKTL-3)

Clinical trial or Concurrent chemoradiation or Combination chemotherapy regimen (pegaspargase-based) ± RT


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SUGGESTED TREATMENT REGIMENS
(in alphabetical order)

Combination chemotherapy regimen (pegaspargase-based)
- AspaMetDex (pegaspargase, methotrexate, and dexamethasone) (Reported as a second-line regimen)
- SMILE (steroid [dexamethasone], methotrexate, ifosfamide, pegaspargase, and etoposide) x 4–6 cycles for advanced stage
- GELOX (gemcitabine, pegaspargase, and oxaliplatin)

Concurrent chemoradiation therapy (CCRT)
- CCRT (radiation 50 Gy and 3 courses of DeVIC [dexamethasone, etoposide, ifosfamide, and carboplatin])
- CCRT (radiation 40–52.8 Gy and cisplatin) followed by 3 cycles of VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone)

Sequential chemoradiation
- For Stage I, II, SMILE followed by RT 45–50.4 Gy x 2–4 cycles

Sandwich chemoradiation
- GELOX x 2 cycles followed by RT 56 Gy followed by GELOX x 2–4 cycles

Radiation therapy alone
- Recommended tumor dose is ≥50 Gy
  - Early or up-front RT had an essential role in improved OS and DFS in patients with localized extranodal NK/T-cell lymphoma, nasal-type, in the upper aerodigestive tract.
  - Up-front RT may yield more benefits in survival in patients with stage I disease.
SMILE for Extranodal NK/T-cell Lymphoma

Table 1. SMILE Chemotherapy

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose/d</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>2 g/m²&lt;sup&gt;*&lt;/sup&gt;</td>
<td>IV (8 hours)</td>
<td>1</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>15 mg × 4</td>
<td>IV or PO</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>1,500 mg/m²</td>
<td>IV</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>Mesna</td>
<td>300 mg/m² × 3</td>
<td>IV</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg/d</td>
<td>IV or PO</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²&lt;sup&gt;*&lt;/sup&gt;</td>
<td>IV</td>
<td>2, 3, 4</td>
</tr>
<tr>
<td>L-asparaginase (Escherichia coli)</td>
<td>6,000 U/m²</td>
<td>IV</td>
<td>8, 10, 12, 14, 16, 18, 20</td>
</tr>
<tr>
<td>G-CSF</td>
<td>SC or IV</td>
<td>Day 6 to WBC &gt; 5,000/μL</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Cycles were repeated every 28 days. Two courses were planned as the protocol treatment.

Abbreviations: G-CSF, granulocyte-colony stimulating factor; IV, intravenously; PO, orally; SC, subcutaneous injection; SMILE, steroid (dexamethasone), methotrexate, ifosfamide, L-asparaginase, and etoposide.

*The recommended dose was determined in the preceding phase I study.

Supportive Care Important

92% Grade 4 ANC, 40% grade 4 thrombocytopenia

Yamaguchi et al. JCO 2011;29(33):4410-6.
SMILE for Extranodal NK/T-cell Lymphoma: Safety And Efficacy from The Asia Lymphoma Study Group


N = 87
~ 50% frontline
~ 50% Stage III-IV
Outcomes similar for frontline vs relapsed/refractory

Median f/u:
31 mo (1-84 mo)
5-y OS 50%
4-y DFS 64%.
Follow-up:

- He receives 2 cycles of modified SMILE and achieves a CR on PET/CT.
Q4: Which of the following is the most appropriate next step in management?

1. 30 Gy RT to nasal cavity, hard palate, right maxilla
2. 50 Gy RT to nasal cavity, hard palate, right maxilla
3. 30 Gy RT to nasal cavity, hard palate, right maxilla followed by transplant
4. 50 Gy RT to nasal cavity, hard palate, right maxilla followed by transplant
5. Modified SMILE x 2 additional cycles

- Option 1: 5%
- Option 2: 8%
- Option 3: 32%
- Option 4: 11%
- Option 5: 44%
Extranodal NK/T-Cell Lymphoma, nasal type

POST RT EVALUATION

- Post-RT evaluation
- Repeat initial imaging of CT, MRI, or PET-CT scan
- Endoscopy with visual inspection and repeat biopsies
- EBV viral load

RESPONSE TO THERAPY

- CR
- PR
- Refractory disease

ADDITIONAL THERAPY

- Observe
- Biopsy
- HSCT, if eligible
- Clinical trial or second-line chemotherapy
- Best supportive care

Stage I, II

- Nasal

Stage I-IV

- Extranasal

Stage IV

- CR
- PR
- Refractory disease


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ASCT in Extranodal NK/T-cell Lymphoma
A Multinational, Multicenter, Matched Controlled Study

Lee et al. Biology of Blood and Marrow Transplant 2008; 14(12):1356-64.
Allogenic Transplant in Extranodal NK/T-cell Lymphoma

Tse et al BMT 2014;49(7):902-6.
Follow-up:

- He completes 50 Gy of RT and proceeds to allogeneic transplant with an HLA-matched sibling. He remains with no evidence of disease.
CASE 2

Steven M. Horwitz, MD
Memorial Sloan Kettering Cancer Center
Case:

A 47-year-old woman presents to her PMD with a 2-week history of progressive fatigue, rash, and abdominal pain.

Labs:
- WBC 12.9 K/uL with 75% atypical lymphs
- Hemoglobin 10.8 g/dL, platelet 237 K/uL,
- Normal renal function
- Normal liver function tests,
- Ca++ 11.3, albumin 3.4 and
- LDH 527 U/L (ULN 246)

Physical Exam:
- Rash
- Palpable nodes up to 2 cm left inguinal area.
- Fullness in mid abdomen.
Case:

She is referred to you with a diagnosis of “Lymphoid Leukemia”

Your initial workup includes:

- PET-CT
- Skin biopsy
- Flow cytometry peripheral blood-
  - an abnormal T-cell population
  - abnormal expression of CD2 (bright)
  - sCD3 (dim to absent), CD4 (bright)
  - CD5 (major subset absent), CD7 (absent)
  - CD25 (bright)
- HTLV 1/2 Ab Reactive

Diagnosis: Adult T-cell Leukemia/Lymphoma
Adult T-cell Leukemia-Lymphoma (ATLL)

2 Adapted from Katsuya, Blood. 2015;126(24):2570
## Diagnostic Criteria and Classification of Clinical Subtypes of ATLL

<table>
<thead>
<tr>
<th></th>
<th>Healthy carrier</th>
<th>Smoldering ATL</th>
<th>Chronic ATL</th>
<th>Acute ATL</th>
<th>ATL Lymphoma</th>
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<tbody>
<tr>
<td><strong>Anti-HTLV-1 serology</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Clonal integration of provirus</strong></td>
<td>- (blood)</td>
<td>+ (blood)</td>
<td>+ (blood)</td>
<td>+ (blood)</td>
<td>+ (lymph nodes)</td>
</tr>
<tr>
<td><strong>Lymphocyte count</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td><strong>Abnormal cells (%)</strong></td>
<td>&lt; 5%</td>
<td>&gt; 5%</td>
<td>&gt; 5%</td>
<td>&gt; 5%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td><strong>Hypercalcemia</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>LDH</strong></td>
<td>Normal</td>
<td>≤ 1.5 N</td>
<td>≤ 2 N</td>
<td>&gt; 2 N</td>
<td>&gt; 2 N</td>
</tr>
<tr>
<td><strong>Skin and lung involvement</strong></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Bone marrow or spleen involvement</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Bone, GI or CNS involvement</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

### Audience Polling Results

**Case:** You want to complete your work-up quickly before initiating therapy. Which of the following is not needed?

1. Lumbar puncture
2. Strongyloides Ab
3. MRI Head/Spine
4. Echocardiogram
5. HTLV-1 viral load

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
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<tr>
<td>1.</td>
<td>24%</td>
</tr>
<tr>
<td>2.</td>
<td>33%</td>
</tr>
<tr>
<td>3.</td>
<td>21%</td>
</tr>
<tr>
<td>4.</td>
<td>6%</td>
</tr>
<tr>
<td>5.</td>
<td>16%</td>
</tr>
</tbody>
</table>
T-cell Lymphomas: Time to CNS relapse

Case: What treatment do you recommend?

1. CHOP
2. CHOEP
3. Interferon and zidovudine
4. EPOCH
5. R-Hyper-CVAD
Treatment in ATLL

JCOG 9801 study

Tsukasaki K et al. JCO 2007;25:5458-5464
Survival By First-line Treatment For Patients With Adult T-cell Leukemia/Lymphoma (ATLL) By Subtype: Meta-analysis

Ali Bazarbachi et al. JCO 2010;28:4177-4183

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**Case:** She achieves a CR after 4 cycles of EPOCH and IT methotrexate, you now recommend?

1. Complete 2 more cycles of EPOCH
2. Continue with EPOCH and refer for high dose therapy and autologous stem cell rescue
3. Continue with EPOCH and refer for allogeneic stem cell transplantation
4. Complete 2 more cycles of EPOCH then add interferon and zidovudine maintenance
Treatment in ATLL

AMC Trial
EPOCH-INF/Lamivudine/Zidovudine

Allogeneic Transplantation in ATLL

Hazard ratio = 0.751 (95% CI, 0.50 to 1.13)
One-sided P = .085

MST = 13M
3 year OS (%) = 24

MST = 11M
3 year OS (%) = 13

OS w/Allo

Tsukasaki K et al. JCO 2007;25:5458-5464
# Lenalidomide in ATLL

<table>
<thead>
<tr>
<th>Population</th>
<th>No.</th>
<th>ORR, No. (%)</th>
<th>CR/CRu, No. (%)</th>
<th>PR, No. (%)</th>
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<tr>
<td>All patients</td>
<td>26</td>
<td>11 (42)</td>
<td>5 (19)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>ATL subtype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>15</td>
<td>5 (33)</td>
<td>3 (20)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>7</td>
<td>4 (57)</td>
<td>2 (29)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Unfavorable chronic</td>
<td>4</td>
<td>2 (50)</td>
<td>0</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Disease site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodal and extranodal lesions</td>
<td>16*</td>
<td>5 (31)</td>
<td>5 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>8</td>
<td>6 (75)</td>
<td>4 (50)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>10</td>
<td>6 (60)</td>
<td>4 (40)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Had at least one dose reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>4 (57)</td>
<td>2 (29)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>7 (37)</td>
<td>3 (16)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Prior mogamulizumab treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>2 (18)</td>
<td>1 (9)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>9 (60)</td>
<td>4 (27)</td>
<td>5 (33)</td>
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</tbody>
</table>

![Graph A: Progression-Free Survival](image1.png)

Median PFS, 3.9 months (95% CI, 1.9 to NE)

![Graph B: Overall Survival](image2.png)

Median OS, 20.3 months (95% CI, 9.1 to NE)

Takashi Ishida et al. JCO doi:10.1200/JCO.2016.67.7732

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CASE 3

Francine Foss, MD
Yale Cancer Center/Smilow Cancer Hospital
Case presentation

• 34-year-old African American woman presented with a history of skin nodules. She saw a Dermatologist and had a biopsy which was reported to show lupus profundus. ANA was positive at 1:160 and CBC was normal.

• Several months later she developed several new lesions and CBC showed that her WBC dropped to 2.5.

• She was placed on Hydroxychloroquine and prednisone

• Over the next three months, she developed a non-healing ulceration of her ankle and had debridement and skin grafting performed.
Case presentation

- She continued to have neutropenia. A bone marrow biopsy showed no evidence of hematologic malignancy.
- A new nodule appeared on her lower extremity and was biopsied.
- She subsequently developed multiple new nodules which formed eschars.
- She was referred to our clinic after biopsy results were reviewed.
CYTOTOXIC GAMMA DELTA T-CELLS: CD3+, CD4-, CD8-, TIA-1+, CD56+, CD2+, CD5-, CD7-, CD43+, CD45RO+
TCRd1+, TCRb1-
EBV (EBER) ISH: NEGATIVE
Ki-67: 50%
NEGATIVE FOR: B-CELL ANTIGENS (CD79a-, CD20-); CD30-; ALK-, CD123-; CD21-
Clinical assessment

- WBC 2.0 HCT 40, Plts 242
- Chemistry profile WNL
- LDH elevated at 687
- Flow cytometry and TCRR negative in peripheral blood
- PET scan showed uptake in multiple skin lesions and in bilateral inguinal nodes
- Bone marrow biopsy negative for malignancy
Clinical examination

- Patient thin and ill appearing
- Exam showed multiple cutaneous eschars, multiple subcutaneous nodules could be palpated and were painful
- Palpable adenopathy in bilateral inguinal regions
- No hepatosplenomegaly
Diagnosis and next steps

The patient is a 34-year-old woman who presents with primary cutaneous gamma delta T-cell lymphoma with multiple skin lesions and adenopathy with no hepatosplenomegaly, negative bone marrow biopsy.

What would your initial therapy be for this patient?
**Question 1**
What would your initial therapy be for this patient?
1. CHOP
2. EPOCH or CHOEP (CHOP plus etoposide)
3. Gemcitabine-based chemotherapy regimen
4. Total skin radiotherapy
5. Pentostatin
6. Pralatrexate

<table>
<thead>
<tr>
<th>Option</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>9%</td>
</tr>
<tr>
<td>3</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>3%</td>
</tr>
<tr>
<td>6</td>
<td>10%</td>
</tr>
</tbody>
</table>
Case continued

• The patient is treated with EPOCH and has significant improvement in lesions after two cycles. She delays cycle 3 by 2 weeks due to attempt to harvest eggs with GYN service.

• On the day of admission for cycle 3 she has new lesions in her right shoulder, right breast, and over her knee. Lesions are painful.

• LDH has risen to 772, WBC is 3.2.

What is your treatment recommendation at this point?
Question 2
What is your treatment recommendation at this point?
1. ICE or platinum based chemotherapy
2. Gemcitabine-based regimen
3. Pralatrexate
4. Pentostatin
5. Stain tissue for CD30 expression and consider brentuximab vedotin
6. HLA typing of patient and siblings and initiate chemotherapy

37%
2%
5%
0%
17%
38%
Case continued

• The patient receives 3 cycles of ICE chemotherapy and has a partial response with shrinkage of most of the lesions.
• Prior to cycle 4 she has progression with multiple new nodules. She begins spiking fevers and is admitted.
• Work up is negative for infectious etiology and fevers persist despite broad spectrum antibiotics.
• Viral work up is negative for CMV, EBV and HHV-6.
• CT scan shows splenomegaly and persistent inguinal adenopathy.
• Patient is pancytopenic.

What would you do at this point?
**Question 3**
What would you do at this point?
1. Do a bone marrow biopsy
2. Check ferritin, soluble IL2R
3. Administer high dose steroids
4. Start another chemotherapy regimen
5. 1, 2, and 3
6. 1, 3, and 4
## WHO EORTC Classification of Cutaneous Lymphomas

### Cutaneous T-cell and NK-cell lymphomas

- **Mycosis fungoides**
- **MF variants and subtypes**
  - Folliculotropic MF
  - Pagetoid reticulosis
  - Granulomatous slack skin
- **Sézary syndrome**
- **Adult T-cell leukemia/lymphoma**
- **Primary cutaneous CD30⁺ lymphoproliferative disorders**
  - Primary cutaneous anaplastic large cell lymphoma
  - Lymphomatoid papulosis
- **Subcutaneous panniculitis-like T-cell lymphoma**
- **Extranodal NK/T-cell lymphoma, nasal type**
- **Primary cutaneous peripheral T-cell lymphoma, unspecified**
  - Primary cutaneous aggressive epidermotropic CD8⁺ T-cell lymphoma (provisional)
  - **Cutaneous γ/δ T-cell lymphoma (provisional)**
  - Primary cutaneous CD4⁺ small/medium-sized pleomorphic T-cell lymphoma (provisional)

Primary Cutaneous γδ T-cell lymphoma
Clinical Features

- Mostly multifocal
- B symptoms common
- Poor prognosis
- Not all patients received chemotherapy
- CHOP commonly used
- Small number of patients (5-22% did well)
- Hemophagocytosis in up to 45% of patients

<table>
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<tr>
<th></th>
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<tbody>
<tr>
<td>Patients n</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Median age years (range)</td>
<td>54 (13–82)</td>
<td>59 (13–79)</td>
</tr>
<tr>
<td>Sex ratio male:female</td>
<td>16:7</td>
<td>7:13</td>
</tr>
<tr>
<td>B symptoms n (%)</td>
<td>NR</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Hemophagocytic syndrome n (%)</td>
<td>4 (17)</td>
<td>9 (45)</td>
</tr>
</tbody>
</table>

### Extent of cutaneous involvement

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Localized n (%)</td>
<td>3 (13)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Multifocal n (%)</td>
<td>20 (87)</td>
<td>15 (75)</td>
</tr>
</tbody>
</table>

### Treatment and outcome

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>None n (%)</td>
<td>0</td>
<td>3 (15)</td>
</tr>
<tr>
<td>PUVA n (%)</td>
<td>6 (26)</td>
<td>0</td>
</tr>
<tr>
<td>Radiation therapy n (%)</td>
<td>7 (30)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Immunosuppressive treatment n (%)</td>
<td>2 (8)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>CHOP or CHOP-like treatment n (%)</td>
<td>10 (43)</td>
<td>14 (70)</td>
</tr>
</tbody>
</table>

### Status at last follow-up

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Died of lymphoma n (%)</td>
<td>16 (70)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Alive with disease n (%)</td>
<td>5 (22)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Alive and in complete remission n (%)</td>
<td>2 (8)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>5-year overall survival (%)</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

*These data were calculated from the figures originally reported by the authors. *Single lesion or single site (for example, one limb) involved. Abbreviations: CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone; NR, not reported; PUVA, psoralen-ultraviolet A irradiation.

• Retrospective review of 53 patients median age 60 (30-91) 30M>22F
• Median duration of lesions: 1.25 years (1m-20 y)
• Clinical Features- plaques panniculitis-like (38), ulcerated (27), patches (10)
• B symptoms 25/46
• LDH elevated 22/39 patients
• 20/37 positive PET and/or CT scans (mostly soft tissue, 1 lymph nodes, 1 pleura/lung, 1 testes, 1 GI tract)
• 3 had CNS involvement
• Few cases with lymphadenopathy 8% (3/38) or bone marrow involvement 21% (6/29)

Many were resistant to multiagent chemotherapies (CHOP, ESHAP, CVAD, EPOCH)

Reports of prolonged remissions with high dose cytarabine and platinum-containing regimens

26 deaths including complications of HLH (4) and CNS involvement (3)

Median survival 18 months (3-107m)

MV analysis: age (50+/-), sex, race, distribution, previous therapies: Not significant

Trend for worse prognosis if ulcerated or panniculitis like presentation, HPS, activated phenotype (CD30/GB+)

• 9 cases of PC γδ-TCL reported
• CD30 staining reported in 2
• More favorable outcomes in patients expressing CD4, CD30 or TCR BF1.

• 5 cases identified

  – CR with fludarabine, in remission 7 years
  – 33-year-old female, Rash for several years, CHOP/Allo BMT, in remission x 2 years
  – 36-year-old female, had LEP for years, then developed more aggressive skin nodules and hemophagocytosis, received CHOP and died from lymphoma 2 years later
  – 76-year-old female had axillary mass biopsy proven gamma delta panniculitis, had XRT and in CR
  – 45-year-old female had necrotic panniculitis treated with topical steroids off and on x 5 years, then had multiple new nodules, treated with fludarabine with progression, then CHOP with no response, then DICE (dexamethasone, ifosfamide, cisplatin, and etoposide), with no response, then alemtuzumab with some shrinkage, then she succumbed to EBV pneumonia

New Targets: Stat mutations in Primary Cutaneous Gamma Delta T cell Lymphomas

- Activating Stat mutations identified
- Agents targeting Jak-Stat pathways may have activity
- Phase II trial of ruxolitinib underway

Kucuk et al, Nature Communications 2015
Primary cutaneous gamma delta T-cell Lymphomas (PCGD-TCL): Conclusions

• PCGD-TCL is rare and often have an aggressive clinical course
• Tumor cells express cytotoxic markers
• May be associated with HLH (hemophagocytic lymphohistiocytosis)
• There is no consensus on the best treatment for these neoplasms but long term remissions have been seen with allogeneic stem cell transplant
• A less aggressive subset of PCGD-TCL has been identified that expresses CD30 which can be targeted with brentuximab vedotin as a novel strategy
• Further studies are needed to elucidate targetable pathways in these rare neoplasms. Activating Stat mutations have been identified
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