Rare Dermatologic Condition That Belongs in the Differential of Granulomatous Cutaneous Disorders

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HPI

- 53 y/o female with autoimmune thyroiditis presented with dry cough and weight loss
- Laboratory findings included leukopenia and elevated serum alkaline phosphatase
- Bone marrow biopsy
  - Hypercellularity with trilineage hematopoiesis
  - Multiple, non-caseating granulomas
  - Microorganism stains negative
HPI

• CT abdomen/pelvis showed a complex cystic mass along the right ureter and right common iliac artery
• Bilateral palpable inguinal LAD
  – Non-caseating granulomas
• HR CT chest showed a background of diffuse perilymphatic nodules
• Diagnosed with Sarcoidosis
HPI

• Excellent response to prednisone
• Developed severe constitutional symptoms + dyspnea and a new, enlarged and tender right inguinal lymph node
• Initiated methotrexate (MTX)
  – Received five weekly oral doses
  – Total MTX dose of 75mg
HPI

• Continued enlargement of inguinal lymph node
  – Majority of cells Epstein-Barr virus (EBV) +
  – Serum PCR + for EBV
  – Iatrogenic immunodeficiency associated lymphoproliferative disorder – polymorphic type

• MTX discontinued and prednisone tapered
Additional Workup

• HIV negative
• Quantitative Immunoglobulins
  – Low IgG
  – Low IgM
  – IgA near lower limits of normal
• Common Variable Immune Deficiency
• IVIg initiated
  – Cutaneous lesions appeared one week later
Initial Presentation
Initial Presentation
Four Weeks Later
Four Weeks Later
Left Thigh
Atypical Granulomas
Angiocentricity
Atypical Cellularity
CD3
CD20
Interval Course

• Repeat PET CT imaging showed progression
  – Multi-agent chemotherapy with R-CHOP x 2 cycles

• Sinus congestion with nasal airway obstruction requiring nasal sinus debridement
  – Atypical polymorphous lymphoid infiltrate with necrotizing granulomas
  – ANCA negative x 2

• Lymphocyte analysis
  – Low CD4 and CD8
  – Decreased CD4:CD8
Cutaneous Progression
EBER
Lymphomatoid Granulomatosis

- Infectious work-up negative
- Granulomatosis with polyangiitis (Wegener’s) excluded
- Multiple biopsies showing granulomatosus vasculitis
- Persistent serum PCR for EBV
- Recent biopsies with weakly positive EBER-1
Lymphomatoid Granulomatosis

- Interferon α-2b
- Bexarotene 75mg BID
- Antimicrobial prophylaxis
- Future considerations
Lymphomatoid Granulomatosis

- Mature B-cell neoplasm
- “An angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of Epstein-Barr virus (EBV)-positive B-cells mixed with reactive T cells, which usually predominate”
  - WHO Classification of Tumors of Hematopoietic and Lymphoid Tissue 2008

Pathogenesis

• EBV drives the disease process
  – Abnormal lymphocytes
  – Perpetuated by immune defect
• Infiltrative, nodular lesions
• Angiodestruction
  – Direct invasion of T-cells
  – Chemokines induced by EBV

## Involved Anatomic Sites at Diagnosis

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Constitutional (fever and malaise)</td>
<td>50-60%</td>
</tr>
<tr>
<td>Kidneys</td>
<td>40-50%</td>
</tr>
<tr>
<td>Skin</td>
<td>25-50%</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>25-50%</td>
</tr>
<tr>
<td>Peripheral Nervous System</td>
<td>15-20%</td>
</tr>
<tr>
<td>Liver</td>
<td>10%</td>
</tr>
<tr>
<td>Spleen</td>
<td>10%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>rare</td>
</tr>
</tbody>
</table>

- Most common presenting symptoms are fever, cough and dyspnea
- Lungs most commonly involved as bilateral nodular infiltrates
- Lymph nodes and spleen typically become involved later in disease course


Clinical Features

• Male : Female approximately 2:1
• Between fourth and sixth decades of life
• Underlying immune dysregulation
  – Wiscott Aldrich, CVID
  – Autoimmune disease
  – HIV
  – Iatrogenic/transplant

Cutaneous Features

• Erythematous to violaceous maculopapular eruptions are the most common presenting morphology
• Systematic review of 32 skin biopsies from 20 patients:
  – 55% tan to plum colored dermal and/or subcutaneous nodules
  – 27% ulcerations
  – 20% dermal nodules and multiple erythematous papules
  – 15% well-demarcated indurated plaques only
  – 10% atrophic, white oval plaques with violaceous borders
• Extremities and trunk ± head & neck (40%), extremities only (30%) trunk only (10%), head & neck only (10%)
• EBV demonstrated by ISH in 6 patients

Histologic Features

• Mixed mononuclear cell infiltrate with an abundance of T-cells
• Vascular infiltration
• Areas of necrosis
• CD20-positive, CD15-negative B-cells that are positive for EBER by ISH
• Numerous CD3-positive small lymphocytes

Grading

• Based on proportion of EBV+ B-cells
  – Grade 1: < 5 EBV+ cells per HPF
  – Grade 2: 5-20 EBV+ cells per HPF
  – Grade 3: > 50 EBV+ cells per HPF

• Distinguishing between low and high-grade is important for determining therapeutic approach

Therapeutic Considerations

- Observation may be justified in patients with low-grade disease
- Immediate therapy for high-grade disease
- Discontinue immunosuppression
- Mortality due to pulmonary complications

Therapy

• No standard treatment
  – Corticosteroids
  – Rituximab
  – IFN alpha
  – Bexarotene
  – Combined chemotherapy
  – Autologous stem cell transplantation

Rituximab

- Targets neoplastic B-cells harboring EBV
- Favorable response to therapy has been reported in the medical literature
  - Both as a single agent and in combination with multi-agent chemotherapy
- One report of grade 3 lymphomatoid granulomatosis with progression of disease while receiving R-CHOP therapy
Interferon α-2b

• Anti-viral, anti-proliferative, and immunomodulatory effects

• Three of four patients with low-grade disease in complete remission at median 43 months follow-up

• One report of successful use of interferon α-2a as maintenance therapy after autologous stem cell transplantation


Bexarotene

• Case report of successful treatment of relapsed disease
  – Grade I disease
  – Relapse after 6 cycles of R-CHOP
  – CT chest 3 weeks later showed improvement
  – Remains asymptomatic two years later

Current NCI Trial

- **NCI-94-C-0074** “Treatment and Natural History Study of Lymphomatoid Granulomatosis.”
- Grade 1 and 2 receive interferon α 3 times per week for 1 year beyond best response
- Grade 3 (or grade 1 or 2 progressing on IFN α) receive dose-adjusted EPOCH-R chemotherapy
Current NCI Trial

- First 31 patients:
  - Grade 1 and 2
    - Complete remission 60%
    - Progression-free survival 56% (median 5yr follow-up)
  - Grade 3
    - Complete remission 66%
    - Progression-free survival 40% (median 28mo follow-up)

- Overall survival 68%

- Relapse is common
  - Patients with low-grade disease can relapse with high-grade disease and vice versa
  - Low threshold to re-biopsy patients in order to guide treatment strategy

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References