ARROCase: Ewing Sarcoma

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Case Presentation

• 13 year old boy
• Localized, waxing & waning right leg pain
• 3 weeks duration
  • Gradual onset
  • Increasing in intensity

• ROS
  • Otherwise negative
  • No fever, night sweats, fatigue, weight loss
Case Presentation

• History unrevealing
  • No history of trauma
  • Negative past medical/surgical history
  • Family history non-contributory
  • No medications or known allergies

• Physical examination
  • Afebrile, vital signs within normal range
  • Point tenderness on palpation of mid-lateral side of right leg with mild overlying swelling
  • Normal gait and range of motion; Neuro exam non-focal
Imaging

X-ray of the Right Leg
Imaging

X-ray of the Right Leg
Imaging

X-ray of the Right Leg:
- Codman triangle (Red Arrow)
- Sunburst Appearance (Blue Arrow)
- Onion-Skin Periosteal reaction (Yellow Arrow)
Biopsy*

Sheets of small, uniform cells with scant cytoplasm, round nuclei, and small punctate nucleoli

*Open incisional biopsy is preferred so that the biopsy tract can be removed with definitive surgery.
Diagnosis and Workup

EWING SARCOMA
Epidemiology

- **Aggressive** bone and soft-tissue cancer
- Predominant in children and adolescents
  - Peak incidence at **15 years** of age
  - About 2% of all cancers in children
  - Around **200 new cases/year**
  - **Second** most common bone cancer
  - Male > Female
  - About 25% present with metastatic disease
Presentation

• Localized pain and swelling
  • Most commonly in pelvis and proximal long bones
• Possible palpation of a firm mass
• Pathological fracture in 10-15% of cases
• Constitutional symptoms
  • Fever, night sweats, fatigue, and weight loss
## Diagnosis

<table>
<thead>
<tr>
<th>TEST</th>
<th>RESULT</th>
</tr>
</thead>
</table>
| **Plain radiograph**  | • Multiple confluent lytic lesions, like “Moth eaten” bone  
                         • Periosteal reaction, giving rise to “onion peel” or Codman’s triangle                                                      |
| **Biopsy**            | • Sheets of small, round, blue cells with a prominent nucleus and scant cytoplasm                                                       |
| **Blood tests**       | • May show elevated levels of nonspecific markers of inflammation and bone remodeling (ESR, Alk Phos)  
                         • Elevated serum LDH                                                                                                                |
Differential Diagnosis for **Small Round Blue Cell Tumors**

- Histologic findings shared with:
  - Neuroblastoma
  - Desmoplastic small round-cell tumor
  - Alveolar rhabdomyosarcoma
  - Peripheral neuroectodermal tumor
  - Non-Hodgkin’s lymphoma
  - Acute lymphoblastic leukemia
  - Poorly differentiated synovial sarcoma
  - Other rare “Ewing-like” tumors
Molecular Studies

• **Fusion of:**
  - EWS gene (chr. 22)
  - Gene of the ETS family

• Most common (85%):
  - **EWS & FLI-1 fusion;** t(11;22)(q24;q12)
  - Associated with a **better prognosis**

• Identification of signature chromosomal translocation —> **Definitive diagnosis**
  - Consider fusion panels if initial studies -ve
Prognostic Factors

• **Favorable**
  - Distal lesion
  - Tumor volume < 100 mL
  - Normal LDH level

• **Adverse**
  - Metastatic disease at presentation
  - Poor response to initial chemotherapy
Staging

• **MRI** with or without CT of 1° lesion (with contrast)
• Head-to-toe **PET CT** scan and/or **bone scan**
• In case of **high risk disease or concerning symptoms**, consider:
  • CT Chest with contrast
  • Bone marrow biopsy
  • Scanning MRI of spine and pelvis
Staging System

• **Localized v.s. Metastatic**
  - Metastases can be
    - **Regional** (nearby structures/lymph nodes)
    - **Distant** (distant organs; eg, lung)

• **TNM** staging
  - Less commonly used
# TNM Staging

## Appendicular skeleton, trunk, skull, and facial bones

<table>
<thead>
<tr>
<th>T category</th>
<th>T criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤8 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt;8 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Discontinuous tumors in the primary bone site</td>
</tr>
</tbody>
</table>

## Spine

<table>
<thead>
<tr>
<th>T category</th>
<th>T criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to one vertebral segment or two adjacent vertebral segments</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor confined to three adjacent vertebral segments</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor confined to four or more adjacent vertebral segments, or any nonadjacent vertebral segments</td>
</tr>
<tr>
<td>T4</td>
<td>Extension into the spinal canal or great vessels</td>
</tr>
<tr>
<td>T4a</td>
<td>Extension into the spinal canal</td>
</tr>
<tr>
<td>T4b</td>
<td>Evidence of gross vascular invasion or tumor thrombus in the great vessels</td>
</tr>
</tbody>
</table>
# TNM Staging

<table>
<thead>
<tr>
<th>Pelvis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T category</strong></td>
</tr>
<tr>
<td>TX</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T1a</td>
</tr>
<tr>
<td>T1b</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T2a</td>
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<tr>
<td>T2b</td>
</tr>
<tr>
<td>T3</td>
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<tr>
<td>T3a</td>
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<tr>
<td>T3b</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>T4a</td>
</tr>
<tr>
<td>T4b</td>
</tr>
</tbody>
</table>
# TNM Staging

## Regional lymph nodes (N)

<table>
<thead>
<tr>
<th>N category</th>
<th>N criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed. Because of the rarity of lymph node involvement in bone sarcomas, the designation NX may not be appropriate, and cases should be considered N0 unless clinical node involvement clearly is evident.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

## Distant metastasis (M)

<table>
<thead>
<tr>
<th>M category</th>
<th>M criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Lung</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone or other distant sites</td>
</tr>
</tbody>
</table>
Outcomes

• 5-year relative survival rates
  • Localized: 82%
  • Regional: 70%
  • Distant: 39%

• All stages combined: 62%

Outcomes

• Cure rate in case of metastases in:
  • Lung: 30%
  • Bone/bone marrow: 20%

• Local control rates:
  • Surgery for extremity tumor: >90%
  • Surgery for central tumor: 75%
  • Radiation therapy: 75-90%
GUIDELINES ON MANAGEMENT
LOCALIZED EWING SARCOMA
Treatment of **Localized** Ewing Sarcoma

- **In brief:**
  - Induction Chemotherapy
  - Local Treatment
  - Consolidation Chemotherapy
Treatment of **Localized** Ewing Sarcoma

- **Induction Chemotherapy**
  - Alternating VDC & IE
    - Vincristine, Doxorubicin, Cyclophosphamide
    - Ifosfamide, Etoposide
  - Six Cycles
- **Re-staging**
  - Repeat imaging of initial workup
    - Stable/improved v.s. progressive
Treatment of **Localized** Ewing Sarcoma

• **If stable or improved** —> Local therapy at ~ 15 wks

• **Surgery**
  • **Wide local excision** or **amputation**
  • Followed by
    • Chemo (regardless of surgical margins)
    • + RT (if close or positive margins, consider for pelvic tumors)

• **OR** **Definitive chemoradiation**
Treatment of **Localized** Ewing Sarcoma

- **If progressive** —> Consider **local therapy**
  - **RT or**
  - Surgery
- **For local control or palliation**
Treatment of **Localized** Ewing Sarcoma

- More on **local therapy**
- Prefer **surgery** for:
  - Younger children (to avoid 2\textsuperscript{nd} malignancy)
  - Tumors in proximal fibula, lateral clavicle, ribs, scapular body, iliac wings, small bones of the hands/feet (i.e. “expendable” bones)
- Prefer **definitive chemoRT** for:
  - Prevention of limb amputation
  - Tumors in pelvis/spine (surgery would be debilitating)
Treatment of **Localized** Ewing Sarcoma

- **Consolidation chemotherapy**
  - To be given after local therapy
  - Alternating VDC & IE
  - For 11 cycles
METASTATIC EWING SARCOMA
Treatment of **Metastatic** Ewing Sarcoma

- **Primary Treatment:** *Chemotherapy*
- **Then:**
  - Consider **local therapy**, especially if:
    - Oligometastatic
    - Good response to chemotherapy
  - Otherwise, **if widely metastatic**, consider:
    - Chemo with palliative surgery
    - Palliative RT to symptomatic areas
Treatment of **Metastatic** Ewing Sarcoma

• **Special case:**

  Ewing sarcoma metastatic to lung only

• **Treat definitively:**

  - Induction Chemotherapy
  - Local Treatment
  - Consolidation Chemotherapy
  - Consolidation whole lung RT
More on

RADIATION THERAPY
Radiation Therapy

- **Definitive RT**
  - **GTV1**: pretreatment bone + soft tissue (45 Gy at 1.8 Gy/fx)
    - **CTV1**: 1-1.5 cm
    - **PTV1**: 0.5-1 cm
  - **GTV2**: post-chemotherapy soft tissue (55.8 Gy at 1.8 Gy/fx)
    - **CTV2**: 1-1.5 cm
    - **PTV2**: 0.5-1 cm

- **N.B.**
  - Anatomically modified CTV so as not to cross nearby borders
  - No need to expand into structures which the tumor abutted (but did not invade)
  - **PTV2** of *vertebral body* tumors receives 50.4 Gy instead

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Radiation Therapy

• Preoperative RT
  • For marginally resectable tumors to improve margin status
    • Eg, R1 —> potential R0
    • Goal is not to downstage an un-resectable tumor (Eg, R2 —> potential R1/R0)
  • Initial GTV + 2 cm
  • Dose: 36-45 Gy (1.8 Gy/fx)
Radiation Therapy

• **Postoperative** RT (Within 60 days) all at (1.8 Gy/fx)
  • GTV2 (45 Gy) + CTV1 + PTV1
    • **R0 resection** (No microscopic residual)
      • Esp. if unfavorable histology
    • **R1 resection** (Microscopic residual)
    • **R2 resection** (Gross residual)
      • With cone down to residual
      • Total dose: 55.8 Gy to GTV2 + CTV2 + PTV2
  • **LN +ve areas**
    • Resected: 50.4 Gy
    • Un-resected: 55.8 Gy

NCCN v2.2022
Radiation Therapy

• **Hemithorax** Irradiation
  • **Indication:** Chest wall 1º tumor w/ extensive pleural involvement
  • **Dose:**
    • **15-20 Gy** (1.5 Gy/fx) to ipsilateral whole lung and pleura; THEN
    • **21.6 Gy** (1.8 Gy/fx) to PTV1; AND
    • **14.4 Gy** boost to PTV2
  • Note: same PTV1 & PTV2 as definitive RT expansions

• **Whole Lung** Irradiation
  • **Indication:** pulmonary metastases after chemotherapy (even if complete response) or surgical resection
  • **Dose:** **15 Gy** if <14 y.o. or **18 Gy** if >14 y.o. (1.5 Gy/fx)
Radiation Therapy - Some Constraints

• Keep $V_{40} < 66\%$
  • To avoid pathological fracture
• Avoid circumferential RT & add skin strip
  • To avoid lymphedema
• Keep in mind:
  • Epiphyseal closure at $\sim 20\ Gy$
  • Ovarian failure at $\sim 8\ Gy$
    —> Lead shielding or ovarian transposition out of field
  • Testicular failure at $\sim 2\ Gy$
    —> Lead shielding
Radiation Therapy - Side Effects

- Secondary malignancy
- Growth abnormalities
- Fibrosis/edema
- Hypoplasia of muscles
- Femoral head necrosis
- Pathologic fractures
- Infertility
Chemotherapy - Side Effects

- Regimen: alternating VDC & IE
- Secondary AML (DC & IE)
- Cardiomyopathy (D)
- Infertility (I &C)
- Renal toxicity (I)
- Cystitis (C)

V: Vincristine, D: Doxorubicin, C: Cyclophosphamide, I: Ifosfamide, E: Etoposide
Evidence

STUDIES AND TRIALS
Induction Chemotherapy

- **IESS-I:** *(VACD)* v.s. *(VAC)* v.s. *(VAC +BPR)* (Nesbit et al. 1990)
  - Localized Ewing sarcoma; N=342
  - 5-year RFS: 60% v.s. 24% v.s. 44% (p < 0.001)
  - 5-year OS: 65% v.s. 28% v.s. 53% (p < 0.001)

- **IESS-II:** High-dose intermittent v.s. Moderate-dose continuous of VACD (Burgert et al. 1990)
  - 5-year RFS: 73% v.s. 56% (p=0.03)
  - 5-year OS: 77% v.s. 63% (p=0.05)

V: Vincristine; A: Actinomycin D; C: Cyclophosphamide; D: Doxorubicin; BPR: Bilateral pulmonary radiation
Induction Chemotherapy

- **INT-0091: (VACD + IE) v.s. VACD** (Grier et al. 2003)
  - Ewing, PNET or primitive sarcoma of bone; N=398 with non-metastatic dx
  - 5-year EFS: **69%** v.s. 54% (p=0.005)
  - 5-year OS: **72%** v.s. 61% (p=0.01)

V: Vincristine; A: Actinomycin D; C: Cyclophosphamide; D: Doxorubicin; I: Ifosfamide; E: Etoposide
Induction Chemotherapy

• **INT-0154**: VADC/IE in 30 w (dose intensified) v.s. 48 weeks (Granowetter et al. 2009)
  - Ewing sarcoma family of tumors; N=478
  - 5-year EFS: 70.1% v.s. 72.1% (p=0.57)

• **COG AEWS0031**: VDC-IE q2w v.s. q3w (Womer et al. 2012)
  - Localized, extradural Ewing sarcoma; N=568
  - 5-year EFS: **73%** v.s. 65% (p=0.048)
  - No increase in toxicity

V: Vincristine; A: Actinomycin D; C: Cyclophosphamide; D: Doxorubicin; I: Ifosfamide; E: Etoposide
Local Modality: Surgery v.s. RT

- **COG Meta Analysis** of INT-0091, INT-0154, and AEWS0031 (Ahmed et al. 2017)
  - Ewing sarcoma; N=956
  - Modality: **Surgery** v.s. RT v.s. (Surgery + RT)
  - 5-year LF: **3.9%** v.s. 15.3% (p<0.01) v.s. 6.6% (p=0.12)
  - Stratified by tumor location and age:

<table>
<thead>
<tr>
<th>Location</th>
<th>5-year local failure</th>
<th>5-year local failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Definitive RT</td>
</tr>
<tr>
<td>Extremity</td>
<td>3.7%</td>
<td>14.8% (p≤0.01)</td>
</tr>
<tr>
<td>Pelvic</td>
<td>3.9%</td>
<td>22.4% (p≤0.01)</td>
</tr>
<tr>
<td>Axial non-spine</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td>Extraskeletal</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>

- A statistically greater number of patients who underwent surgery had tumors in more favorable locations (ie. Extremity).
Consolidation Treatment

  - Localized Ewing sarcoma at high risk for relapse; N=240
  - VIDE induction (x6) then *(VAI x1 and BuMel HDT)* v.s. *(VAI x 8)*
  - 8-year EFS: 60.7% v.s. 47.1% (HR of event: 0.64; p=0.026)
  - 8-year OS: 64.5% v.s. 55.6% (HR of death: 0.63; p=0.028)

High risk for relapse:
- Poor histologic response (≥10% viable cells) after induction chemotherapy (VIDE)
- Large tumor volume at diagnosis (≥ 200 mL) for tumors that were unresected, initially resected, or resected after radiotherapy

V: Vincristine; A: Actinomycin D; D: Doxorubicin; I: Ifosfamide; E: Etoposide; BuMel HDT: High dose Busulfan and Mephalan with autologous SCT
Ewing sarcoma + Pulmonary Mets

  - Ewing sarcoma + pulmonary/pleural mets only; N=287
  - VIDE induction (x6) then
    - **(VAI x8 with WLI)** v.s. (VAI x1 with BuMel HDT)
  - 8-year EFS: 43.1% v.s. 52.9% (HR=0.79, p=0.16)
  - No difference in OS (HR=1, p=0.99)
  - Toxicity-related death: No patients v.s. 4 patients

WLI: Whole lung irradiation
V: Vincristine; A: Actinomycin D; D: Doxorubicin; I: Ifosfamide; E: Etoposide; BuMel HDT: High dose Busulfan and Mephalan with autologous SCT
Proton therapy & Ewing Sarcoma

- Retrospective chart review (Rombi et al. 2012)
  - Pediatric Ewing’s sarcoma at different sites; N=30
  - Proton + Chemotherapy
  - Median dose: 54 Gy RBE (range: 45-58 Gy)
  - 3-year LC, EFS, OS: 86%, 60%, 89% respectively
- Adverse effects:
  - Scoliosis/kyphosis (x5)
  - Eye canalicular stenosis (x1) & corneal ulcer (x1)
  - Endocrine deficiency (x2)
  - High frequency hearing loss (x1)
  - Secondary hematologic malignancies (x4)
Risk of Secondary Malignancy

- Retrospective chart review (Fuchs et al. 2003)
  - Ewing’s sarcoma s/p tx; N=397
  - Secondary malignancy (29 tumors) in 26 (6.5%) patients
    - Mean interval: 9.5 years (range: 1-32.5 years)
    - Distribution:
      - Hematologic (x8) - Chemo induced
      - Sarcoma (x12) - RT induced
      - Carcinoma (x9)
    - Worse prognosis in case of sarcoma/hematologic secondary malignancy
Prospective Trial

• NCT00186992: Radiation Therapy to Treat Musculoskeletal Tumors
  • Phase 2 trial, St. Jude Children's Research Hospital
  • Single group assignment, active & not recruiting
  • MSK tumors, including Ewing’s; N=202
  • Intervention: image-guided radiotherapy
  • Outcomes:
    • Local control (1\textdegree)
    • RT-related changes in growth and muscle function
Beyond Treatment

SURVEILLANCE AND RELAPSE
Surveillance

- Physical exam
- CBC
- Imaging
- Intervals
  - Initially q2-3 months for at least 2 years
  - Annually after 5 years
Relapsed Disease

• **30-40%** recurrence
• Very poor prognosis (esp. if within 2 years)
• Management
  • Chemotherapy
  • +/- RT
  • +/- surgery
References


References


Please provide feedback regarding this case or other ARROcases to arrocase@gmail.com