

A Patient with a History of Pulmonary *Mycobacterium avium* Complex Infection and Chronic Fever

CIS 2016 PID Summer School Presentation

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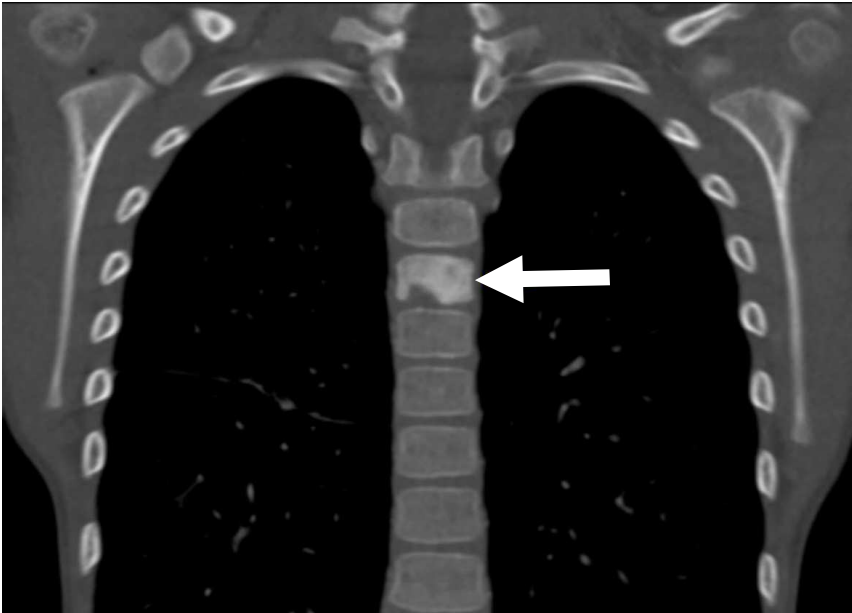
6 year old male presents for immunodeficiency evaluation for 6 weeks of nocturnal fevers, body aches, and fatigue

HPI: Began to have frequent “asthma exacerbations” and otitis media 6 months prior to visit

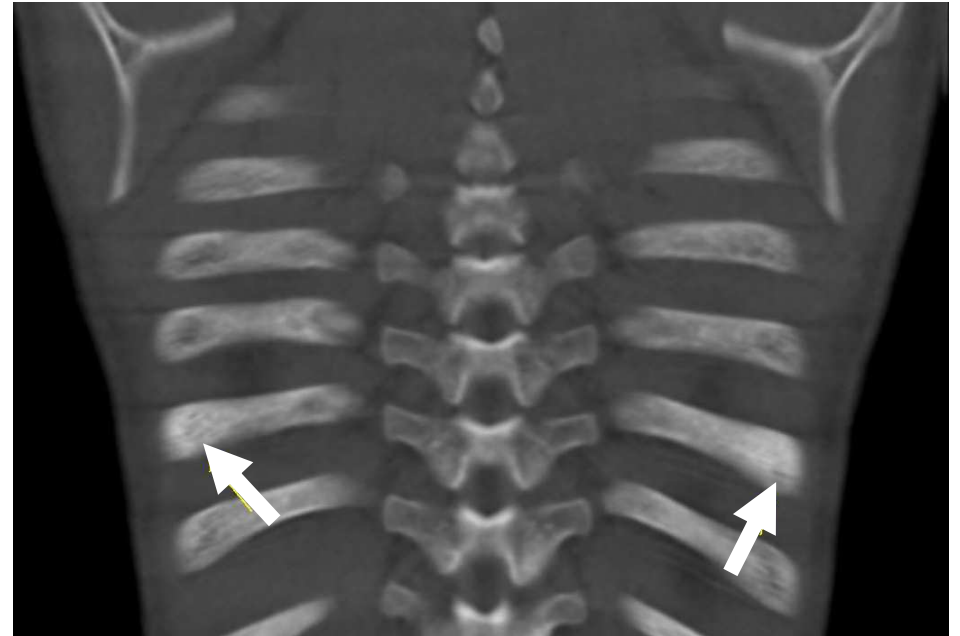
Past Medical History

- Born full-term to non-consanguineous family
- Diagnosed with asthma at the age of 6 months
- Admitted and treated for pulmonary *Mycobacterium avium* complex (MAC) infection at 2 years of age
 - Completed 2 years of treatment--azithromycin, rifampin, ethambutol, and ciprofloxacin
 - CT imaging of his chest 14 months into treatment showed a multi-cystic lesion in the right lung base

HRCT revealed sclerosis of bones



Vertebrae

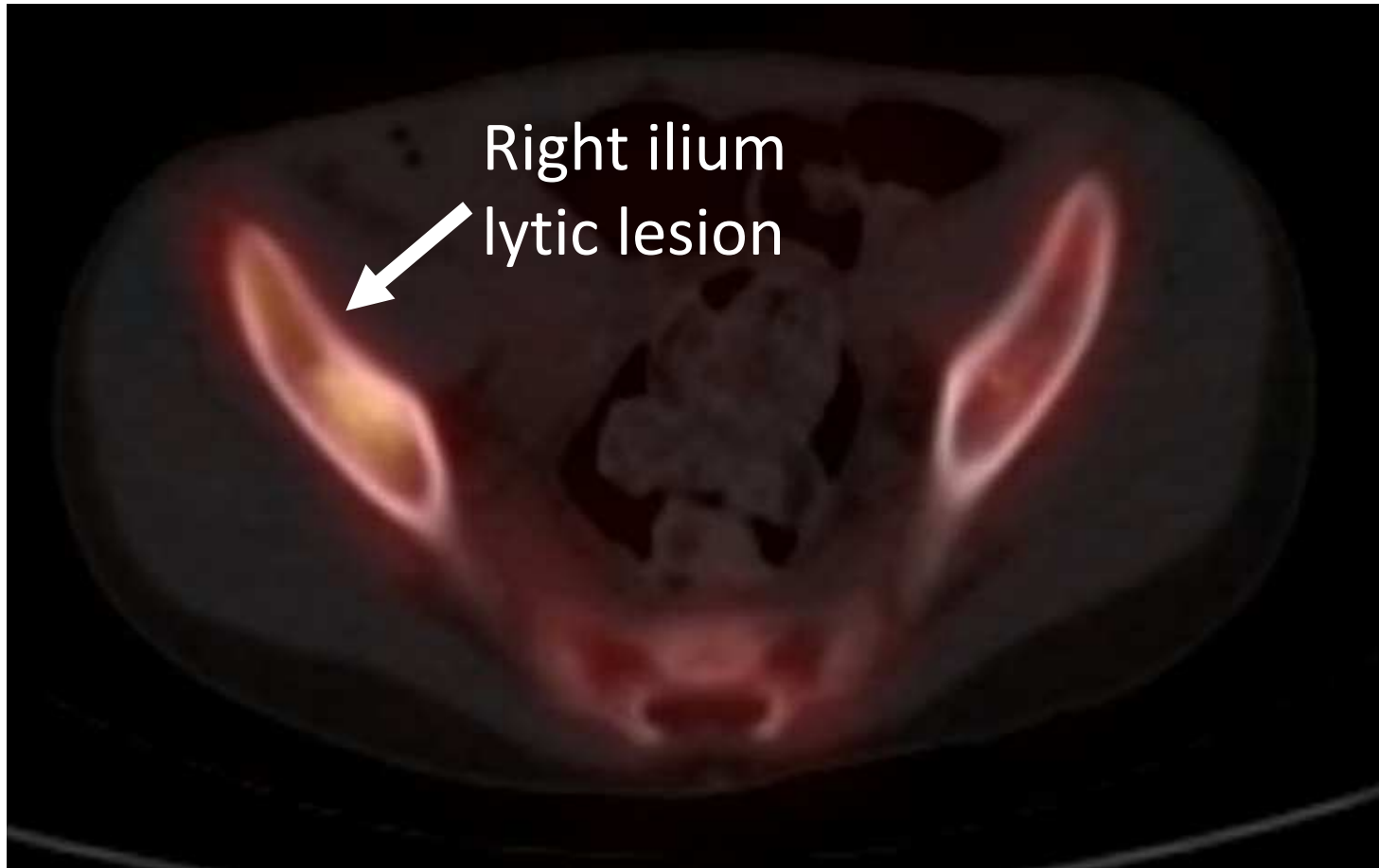


Ribs

Laboratory Results

| Laboratory Test | Pertinent Results |
|-------------------------------|--|
| CBC with Differential | ↓ Hgb/Hct, ↑ platelets, ↑ monocytes |
| Inflammatory Markers | ↑ CRP, ↑ ESR |
| Immunoglobulins | ↑ IgG with ↑ IgG2 and IgG4 |
| Antigenic T-cell Stimulation | ↓ by 75% (spontaneous normal; response to candida and tetanus decreased) |
| Cytotoxic Lymphocyte Function | ↓ cytotoxic lymphocyte function with absent CTL lytic units |
| Plasma cytokines | ↑ IL-6 |
| STAT1 phosphorylation | Normal |
| Other Tests Normal | Lymphocyte subpopulation, B cell number/maturation, vaccine responses, toll-like receptor function |

Bone Scan/PET Scan



Disease Course

- “Back pain and fatigue” somewhat improved
- In vitro STAT1 phosphorylation in response to interferon-gamma and interferon-alpha normal
- Sequencing of the *STAT1* gene revealed a novel, heterozygous missense mutation, c.1378A>G (p.N460D), in the DNA-binding domain
- PET scan at 6 month F/U revealed new lytic lesions, but no changes in previous lesions
 - Biopsy of left acromion lesion grew MAC
 - ID: Ethambutol, Rifampin, and Azithromycin
- HLA typing for donor search for BMT: >50 full matched donors

Acknowledgements

- Zeynep Yesim Kucuk, MD (BMT-PID-CCHMC)
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- Elizabeth Sampaio MD, PhD (NIH-NIAID-LCID)
- Steve Holland MD, (NIH-NIAID-LCID)
- Sergio Rosenzweig, MD, PhD-PID Summer School Mentor

Extras

Next slides are for possible questions/further information

Questions arise:

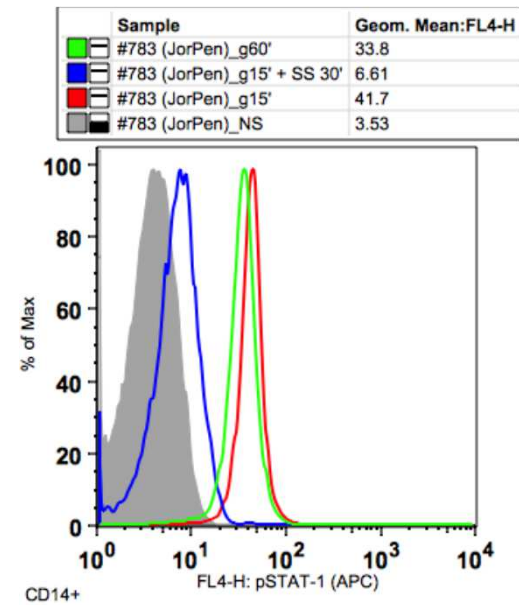
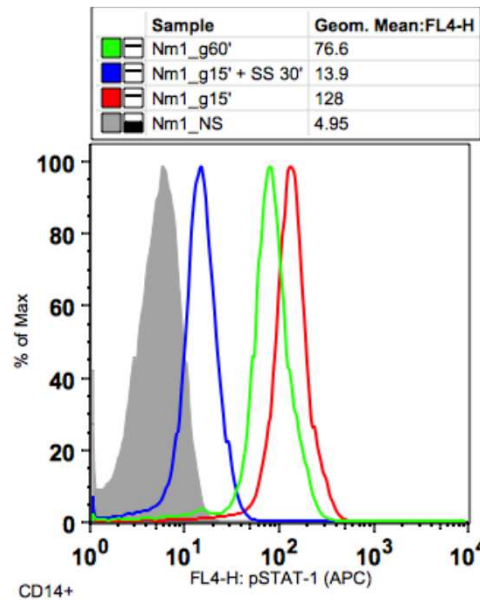
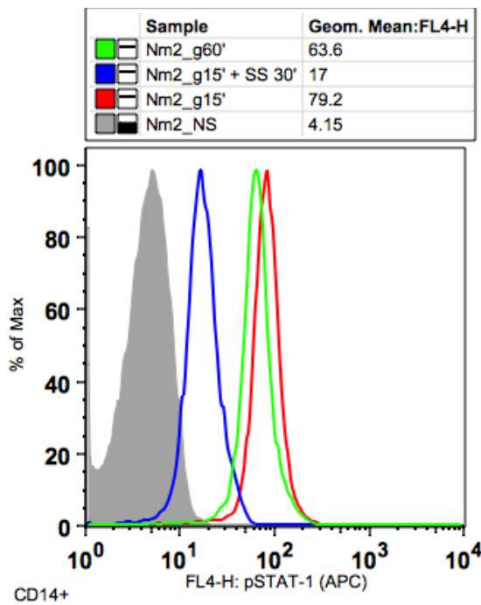
- Would you consider proceeding to HSCT? If so, when?
- Would you consider adding interferon-gamma onto treatment? Why or why not?

STAT1 Phosphorylation: Decreased in patient, but no defect in dephosphorylation

Normal 2

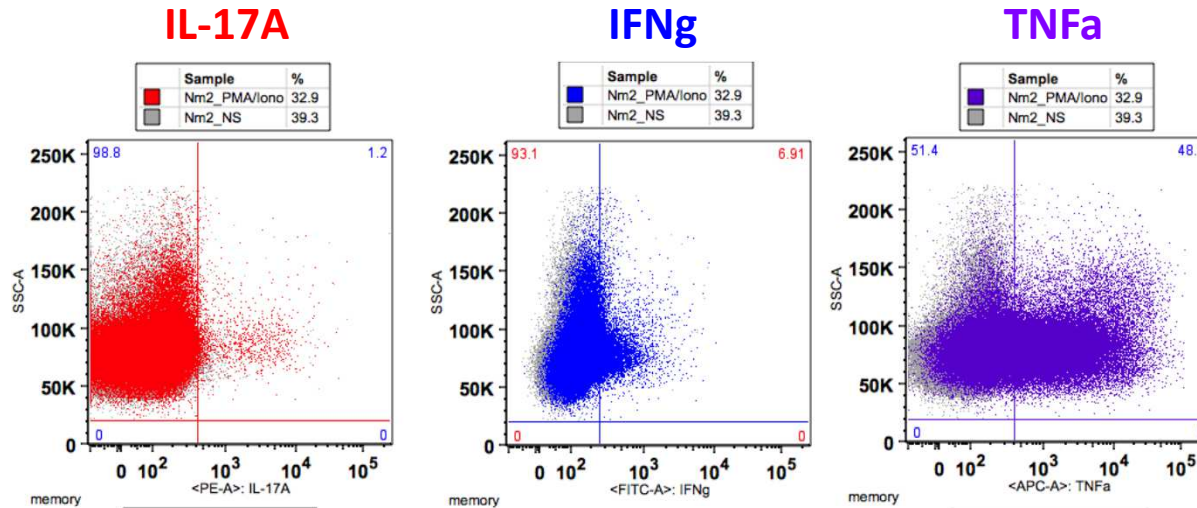
Normal 1

Patient

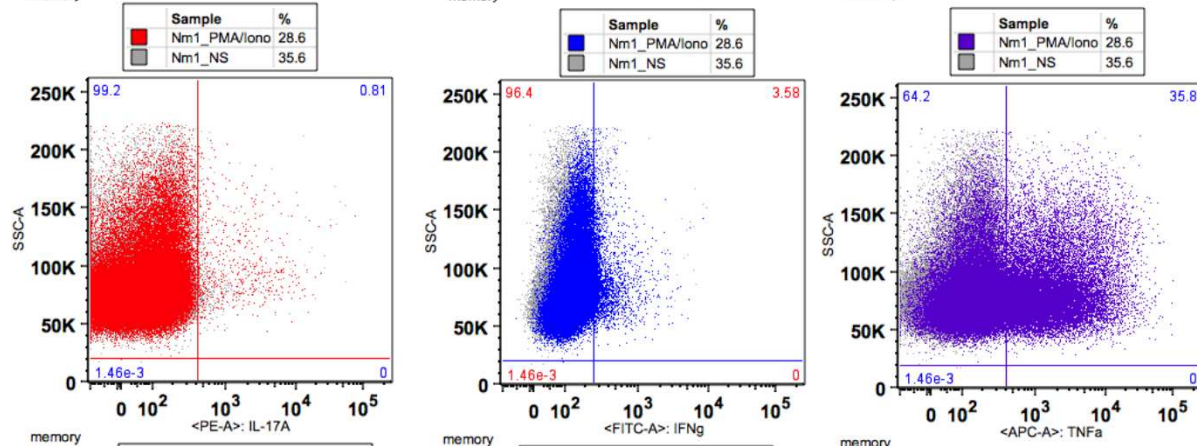


- Unstimulated
 - IFNg-400 for 15 min
 - IFNg-400 for 15 min, then staurosporine* for an additional 30 min
 - IFNg-400 for 60 min
- * (Tyrosine kinase-inhib.)

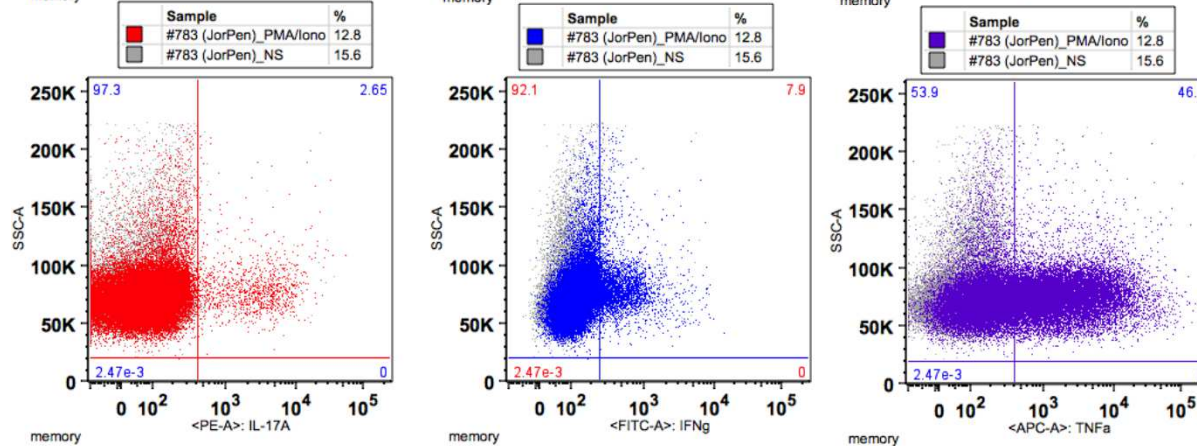
Normal 2



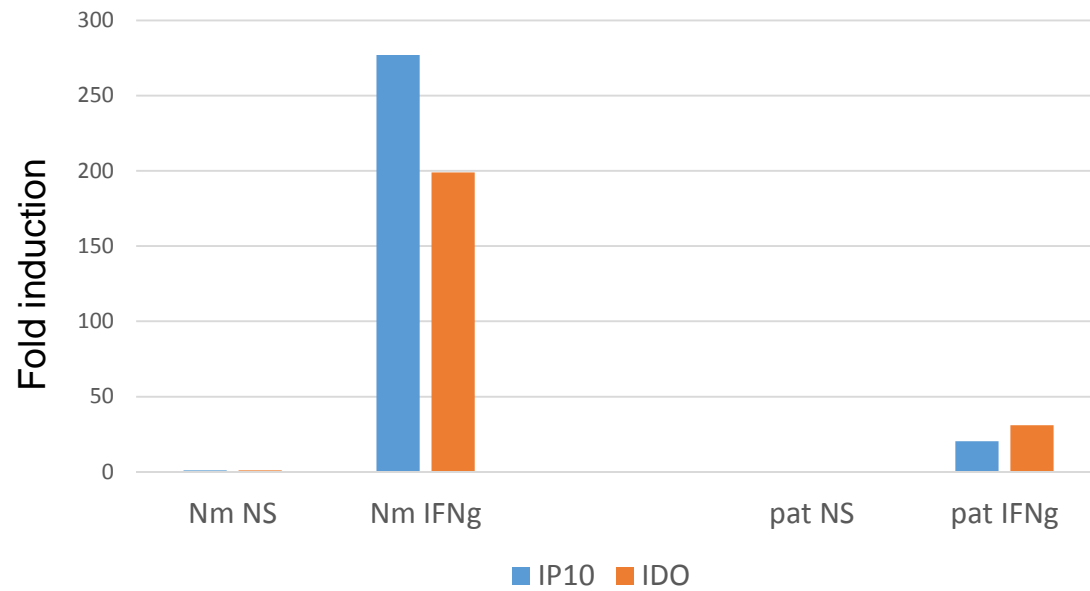
Normal 1



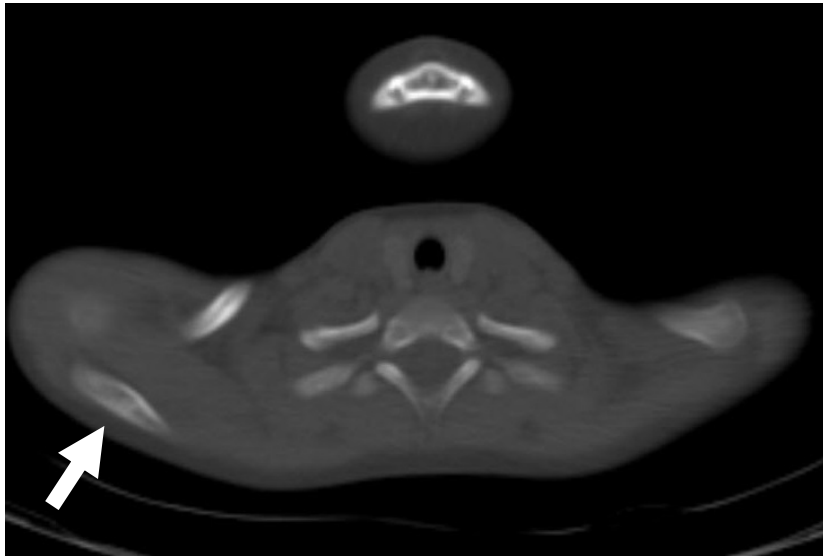
Patient



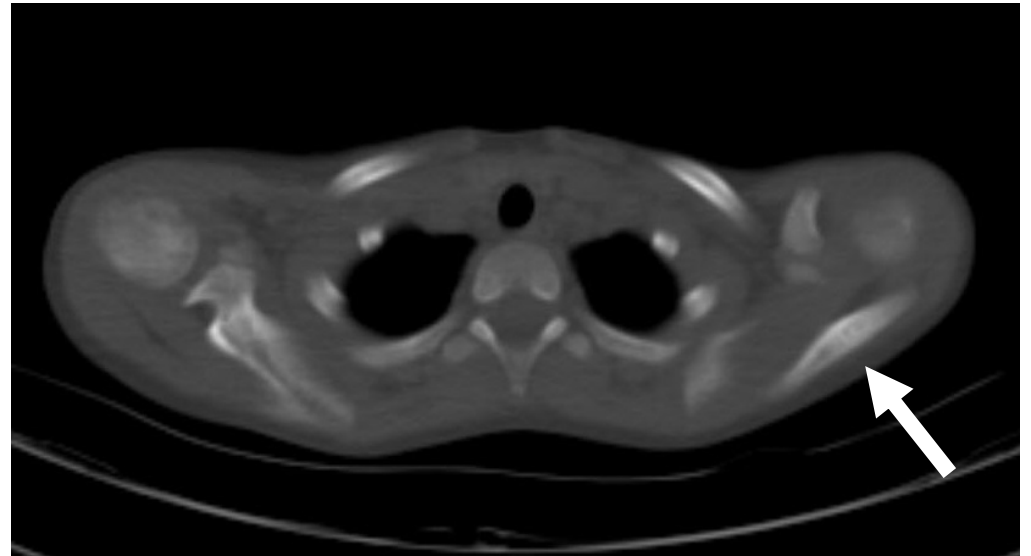
Decreased STAT1 Gene Expression



PET Scan

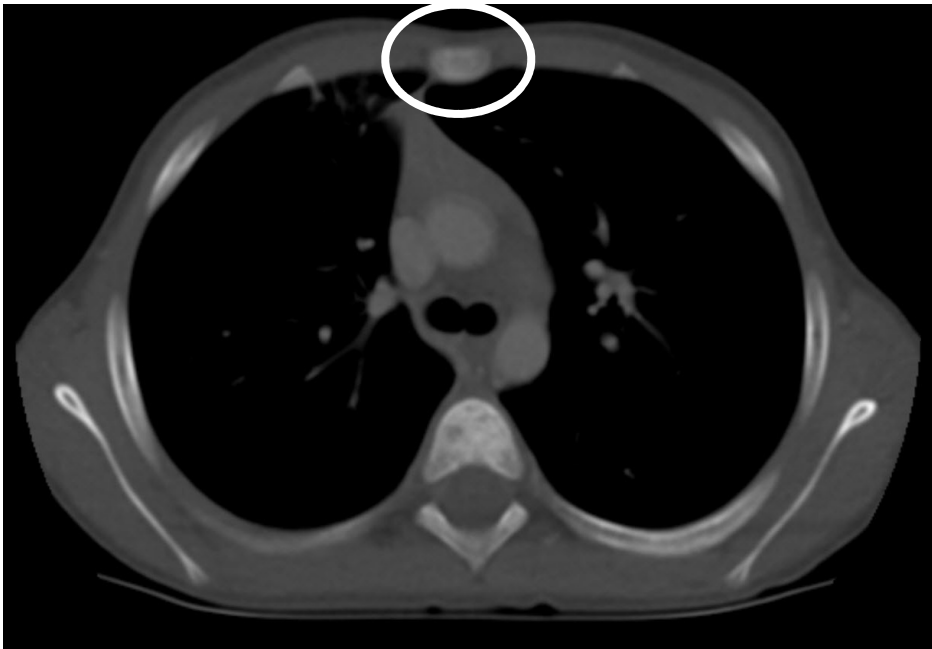


Normal Acromion

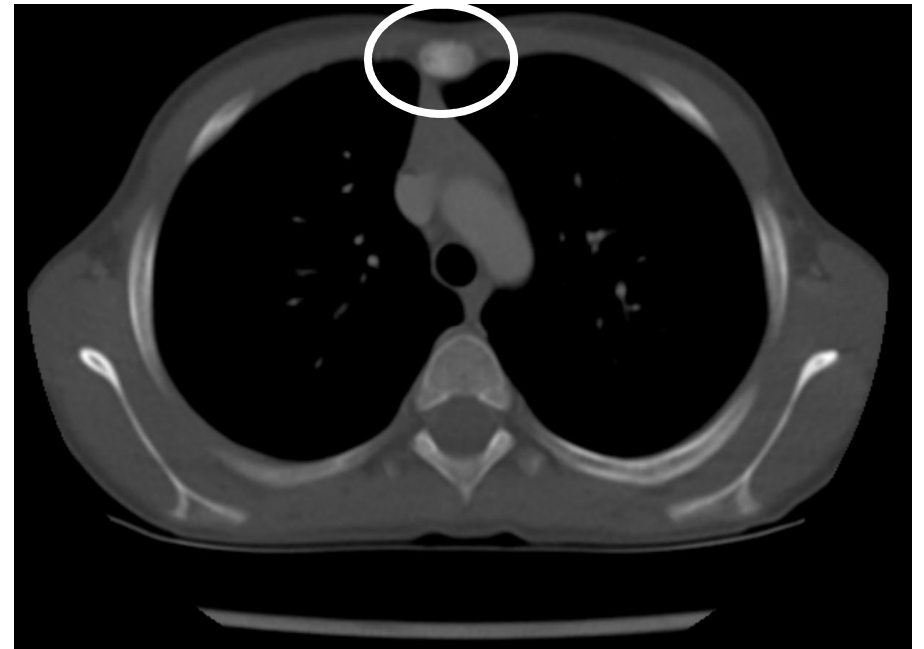


Abnormal Acromion

High Resolution CT Chest

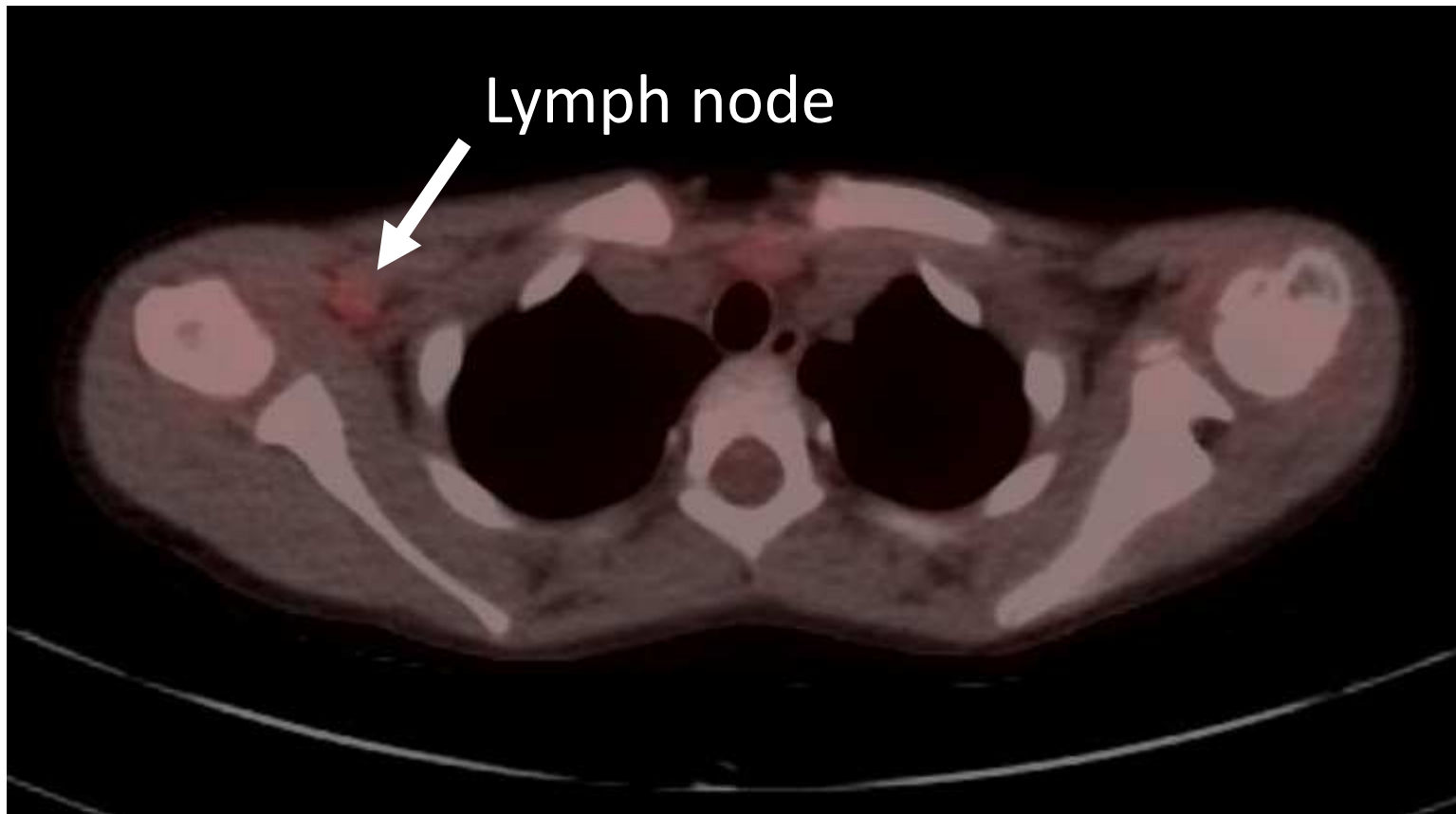


Normal Sternum



Abnormal Sternum

PET Scan



Laboratory Values

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------|------------------|-----------|-------------|
| WBC (K/mcL) | 4.5-13.5K/mcL | 12.8 | 8.7 |
| Hgb (gm/dL) | 12-16 gm/dL | 11.4 | 12.5 |
| PLT (K/mcL) | 135-466K/mcL | 762 | 498 |
| Neutrophils | 40-62% | 53% | 43% |
| Lymphocytes | 15-45% | 35% | 41% |
| Monocytes | 0-8% | 8% | 10% |
| Eosinophils | 0-5% | 2% | 4% |
| Basophils | 0-1% | 1% | 1% |
| ANC | 1.8-8K/mcL | 6.78 | 3.74 |
| ALC | 1.5-6.5K/mcL | 4.61 | 3.57 |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|------------------------|------------------|-----------|-------------|
| Auto Antibodies Screen | | - | - |
| C3 | 71.0-150.0 mg/dL | 209 | 159 |
| C4 | 11.8-39.0 mg/dL | 38.4 | 26.3 |
| CH50 | 101-300 | 292 | |
| C-Reactive Protein | <=0.30 mg/dL | 5.64 | 0.40 |
| Sedimentation Rate | 0-20 mm/hr | 84 | 27 |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------|------------------------------|-------------|-------------|
| CD3 | 52-78% 800-3500 cells/mcL | 71% 2824 | 71% 2757 |
| CD4 | 25-48% 400-2100 cells/mcL | 39% 1555 | 38% 1479 |
| CD8 | 9-35% 200-1200 cells/mcL | 24% 954 | 24% 952 |
| CD19 | (8-24%) 200-600 cells/mcL | 22% 857 | 19% 752 |
| CD16/56 | 6-27% 70-1200 | 6% 229 | 8% 307 |
| CD4/CD8 | 1.0-3.6 | 1.6 | 1.6 |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------|---------------------|------------------|-------------|
| FOXP3+Tregs | 55-81% | 58% | |
| CD4+25+127 low Tregs | 4.2-9.9% of CD4+ | 8.5% | |
| TCRV11/VA24 | >=0.01% | 0.06 | |
| CD4+CCR6+CD45RA-* | 10.7-27% of CD4+ | | 13.3 |
| CCR6+CD45RA-IL-17A+ | 1.2-4.6% of * cells | 5.6 | 4.5 |
| TCR-v-β | | Normal expansion | |
| CD40L | | | |
| CD40L (Resting) | 0-20% | 0% | |
| ICOS (Resting) | 0-29% | 18% | |
| CD40L (Stimulated) | 79-96% | 71% | |
| ICOS (Stimulated) | 74-97% | 87% | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|----------------------------|------------------|--------------|-------------|
| Activation Markers | | | |
| CD69 | 0-3% | 0% | |
| CD25 | 18-34% | 22% | |
| CD71 | 0-25% | 12% | |
| CD40L (CD154) | 0-11% | 1% | |
| CD134 | 0-12% | 3% | |
| HLA-DR | 0-15% | 3% | |
| CD95 | 27-79% | 34% | |
| Neutrophil Oxidative Burst | | Normal Study | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------|------------------|-----------|-------------|
| Plasma Cytokines | | | |
| IL-1B | <= 58 pg/mL | <10 | <10 |
| IL-2 | <= 9 pg/mL | <5 | <5 |
| IL-4 | <= 17 pg/mL | 5 | 6 |
| IL-5 | <= 4 pg/mL | 1 | 1 |
| IL-6 | <=7 pg/mL | 39 | <5 |
| IL-8 | <=47 pg/mL | 4 | 6 |
| IL-10 | <= 7pg/mL | 1 | 2 |
| IL-18 | 89-540 pg/mL | 82 | 94 |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-------------------------|------------------|-----------|---|
| Intracellular Cytokines | | | |
| G-IFN | | | |
| CD4 | 8-24% | 6% | 4% |
| CD8 | 20-48% | 16% | 12% |
| NK Cells | 48-80% | 29% | 5% |
| NKT Cells | 18-64% | 30% | NR (insufficient number of cells in sample) |
| TNF-a | | | |
| CD4 | 39-67% | 18% | 4% |
| CD8 | 17-61% | 14% | 6% |
| NK Cells | 29-61% | 18% | 3% |
| NKT Cells | 23-73% | 30% | NR |
| IL-4 | | | |
| CD4 | <= 3.7% | 0.2% | 0.0% |
| CD8 | <= 3.0% | 0.0% | 0.0% |
| NK Cells | <= 1.6% | 0.1% | 0.1% |
| NKT Cells | <= 3.1% | 0.0% | NR |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------|------------------|-----------|-------------|
| IgG | 560-1307 mg/dL | 1370 | 1080 |
| IgG1 | 400-1080 mg/dL | 823 | |
| IgG2 | 85-410 mg/dL | 519 | |
| IgG3 | 13-142 mg/dL | 66 | |
| IgG4 | <=189 mg/dL | 487 | |
| IgM | 60-263 mg/dL | 153 | 127 |
| IgA | 68-378 mg/dL | 191 | 116 |
| IgE | 2-307 IU/mL | 137 | |
| Mannan Binding Lectin | >= 50ng/mL | >3882 | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------------------|------------------|-----------|-------------|
| Auto Antibodies Screen | | - | - |
| C3 | 71.0-150.0 mg/dL | 209 | 159 |
| C4 | 11.8-39.0 mg/dL | 38.4 | 26.3 |
| CH50 | 101-300 | 292 | |
| C-Reactive Protein | <=0.30 mg/dL | 5.64 | 0.40 |
| Sedimentation Rate | 0-20 mm/hr | 84 | 27 |
| Toll-Like Receptor Function Assay | | Normal | |
| Vaccine Response | | Normal | |
| Toll-Like Receptor Function Assay | | Normal | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|--------------------------|----------------------------------|-----------|-------------|
| B cell panel | | | |
| CD19+ B cells | 10-31 % | 20% | |
| CD19+CD27-CD21- IgM++ | 0.1-5.1 % | 0.7% | |
| CD19+CD27- | 64- 81 % | 73% | |
| CD19+CD27-CD21+ | 60-74 % | 69% | |
| CD19+CD27-IgM+IgD+ | 58-78 % | 67% | |
| CD19+CD27-IgM+IgD+ | 91-98 % of CD27- | 91% | |
| CD19+CD27-CD21- CD38- | 0.5-2.9 % | 1.0% | |
| CD19+CD27+ | 19-37 % | 27% | |
| CD19+CD27+IgM+IgD+ | 8- 22 % | 17% | |
| CD19+CD27+IgM+IgD+ | 42-72 % of CD27+ | 62% | |
| CD19+CD27+IgM+IgD- | 0.7-5.2% | 1.5% | |
| CD19+CD27+IgM+IgD- | 2.8-16.0 % of CD27+ | 5.4% | |
| CD19+CD27+IgM-IgD- | 3.5-14.4 % | 7.9% | |
| CD19+CD27+IgM-IgD- | 17-39 % of CD27+ | 29% | |
| CD38++CD138++ | 0.000- 0.032 % of Lymphocytes | 0.020% | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|-----------------------|------------------|-----------|-------------|
| CD45RA/CD45R0 | | | |
| CD3+ | 62.2-77% | 71.7% | |
| CD4+ (of CD3) | 39.8-69.4% | 54.9% | |
| Naive | 47.4-86.2% | 70.3% | |
| Memory | 13.5-52.0% | 29.7% | |
| Naïve CD31+ | 69.1-95.6% | 73.5% | |
| Naïve CD31- | 4.2-30.7% | 26.2% | |
| Memory Tcm | 10.7-42.6% | 27.0% | |
| Memory Tem | 30.3-72.0 | 42.5% | |
| TEMRA | 0.0-0.2% | 0.0% | |
| CD8+ (of CD3) | 21.6-44.3% | 31.7% | |
| Naive | 46.3-98.6% | 67.8% | |
| Memory | 1.1-42.4% | 30.7% | |
| Memory Tcm | 0.0-27.6% | 3.6% | |
| Memory Tem | 7.6-74.1% | 44.9% | |
| TEMRA | 0.0-12.7% | 1.5% | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|---------------------------------|------------------|-----------|-------------|
| NK Cell Function | | | |
| NK 50:1 | >= 20% | | 12% |
| NK 25:1 | >=10% | | 7% |
| NK 12:1 | >=5% | | 4% |
| NK 6:1 | >=1% | | 3% |
| NK Lytic Units | >=2.6 | | 2.5 |
| CD16/56% Positive | 4-26% | | 10% |
| Cytotoxic T Lymphocyte Function | | | |
| CTL 50:1 | >=35% | 9% | |
| CTL 25:1 | >=25% | 5% | |
| CTL 12:1 | >=15% | 3% | |
| CTL 6:1 | >=10% | 2% | |
| Lytic Units | >=6.0 | 0 | |

| Laboratory Evaluation | Reference Ranges | Fall 2015 | Summer 2016 |
|---|------------------|-----------------------|-------------|
| Lymphocyte Proliferation to Antigen Stimulation | | | |
| Spontaneous Response | 0-280 cpm | 853 cpm | 4361 cpm |
| Phytohemagglutinin | | Mitogen not available | 197465 cpm |
| Candida albicans | >= 15289 cpm | 2598 cpm | 59442 cpm |
| Tetanus | >=4761 cpm | 1085 cpm | 61224 cpm |
| Quantiferon TB Gold | | Negative | - |
| CMV IgG/IgM | | - / - | |
| EBV IgG/IgM/EBNA | | + / - / + | |