RADY 403 Case Presentation

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UNC SCHOOL OF MEDICINE
Radiology

Focused patient history and workup

March 2016

- 9 y.o. male with PMHx of asthma and salt wasting CAH presents to ED with right knee pain following fall 2 weeks ago
- Meds: hydrocortisone 5 mg tablet TID, fludrocortisone 0.1 mg tablet BID
- Physical exam: circumferential knee pain with full range of motion and no swelling. Patient is weight bearing. No bruising, swelling, erythema, signs of infection, or external signs of trauma
- DDx: patellar fracture vs SCFE (given steroids and elevated BMI)
- Imaging: AP radiograph of hip/pelvis and knee
- Treatment: Tylenol or ibuprofen PRN for pain and discharged

Focused patient history and workup continued

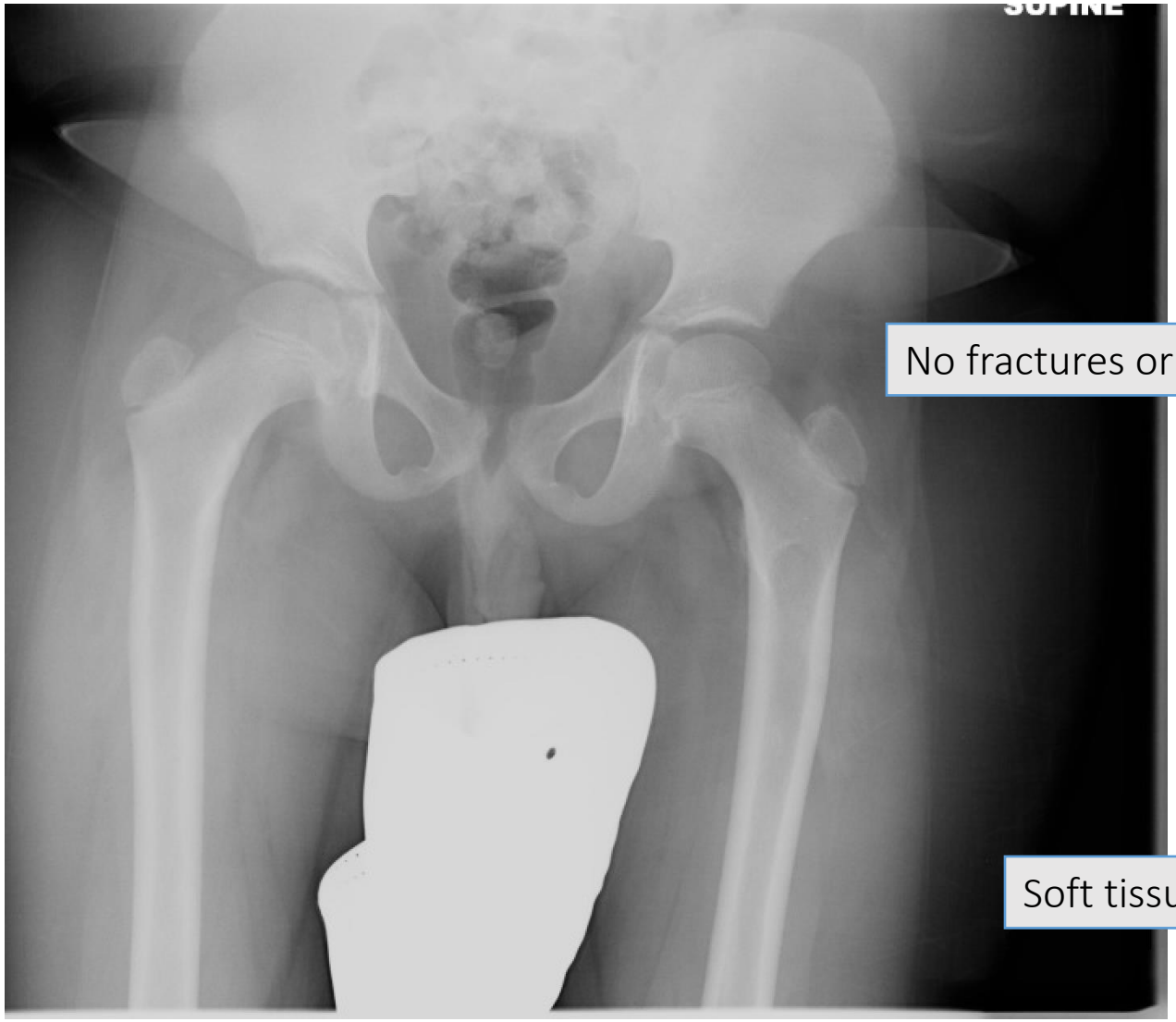
May 2016

- Patient returns to ED with continued right knee pain and unsteady gait/limp for 1 week following fall 2 months ago
- Patient reports the pain awakens him from sleep but denies popping or locking of right knee
- Physical exam: right knee tenderness to palpation over patella and patellar tendon. Negative A/P drawer test and McMurray test. Pain in knee with flexion and extension of right hip joint. No pain on palpation of hip
- Meds: Addition of Motrin PRN for pain
- Imaging: AP radiograph of hip/pelvis and knee
- Plan: consult orthopedic surgery; ordered MR of pelvis, bilateral femurs, and right knee

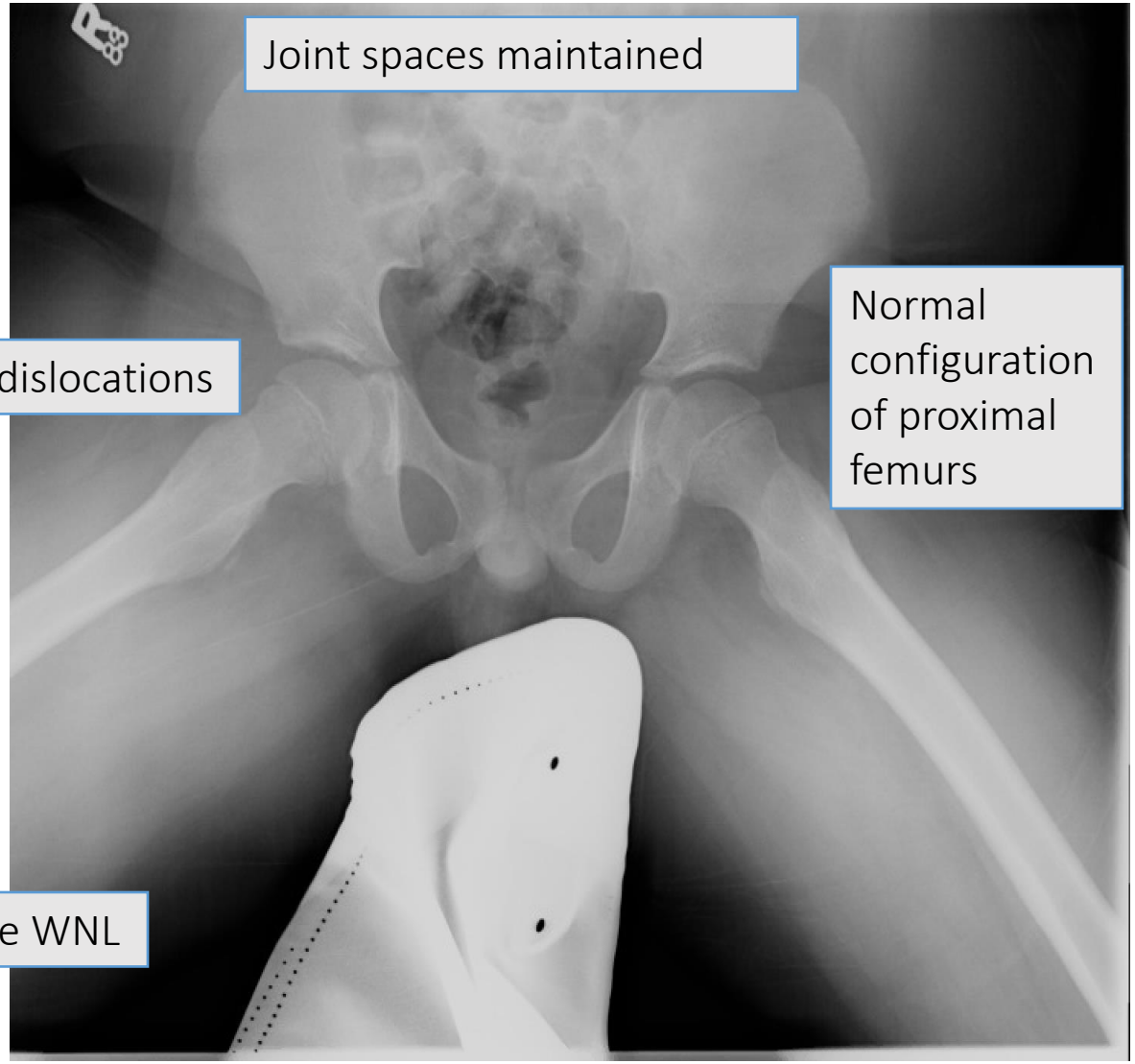
List of imaging studies

- XR of pelvis and right knee upon initial presentation in ED (March)
  - unremarkable
- Repeat XR of pelvis, bilateral femurs, and right knee (May)
  - Lytic bone lesion in right iliac supra-acetabular region
  - Poorly defined distortion of left proximal femur
  - Normal knee radiograph
- MR of pelvis and right knee (May)
  - Hyperenhancing 2.1 x 2 x 3 cm lesion within the right iliac bone that abuts the acetabular surface
  - Edema in the adjacent soft tissues
  - Normal knee MR
- PET CT (July)
  - Osseous lesions in the right acetabulum and left 4th rib
  - Consistent with LCH

March: XR Pelvis



AP pelvis



AP frog leg pelvis

Joint spaces maintained

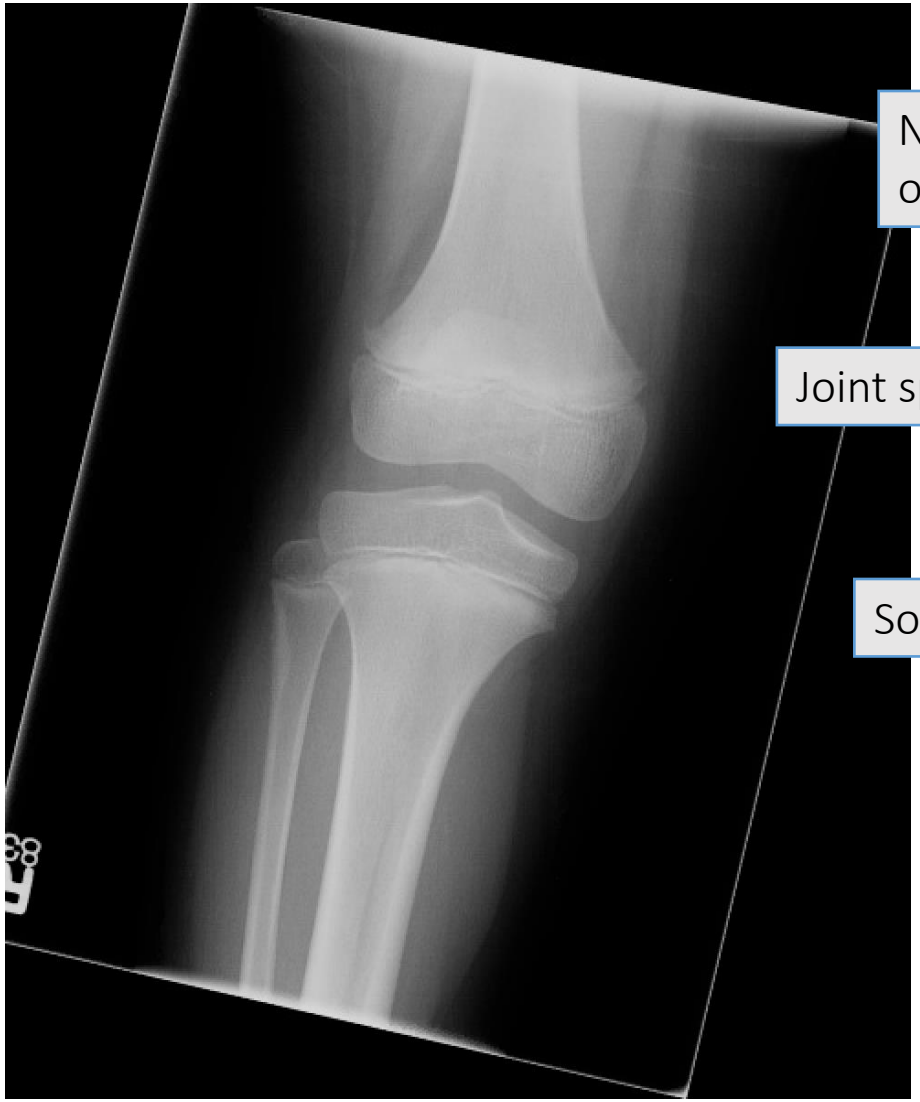
Normal configuration of proximal femurs

No fractures or dislocations

Soft tissue WNL

Normal hip radiograph

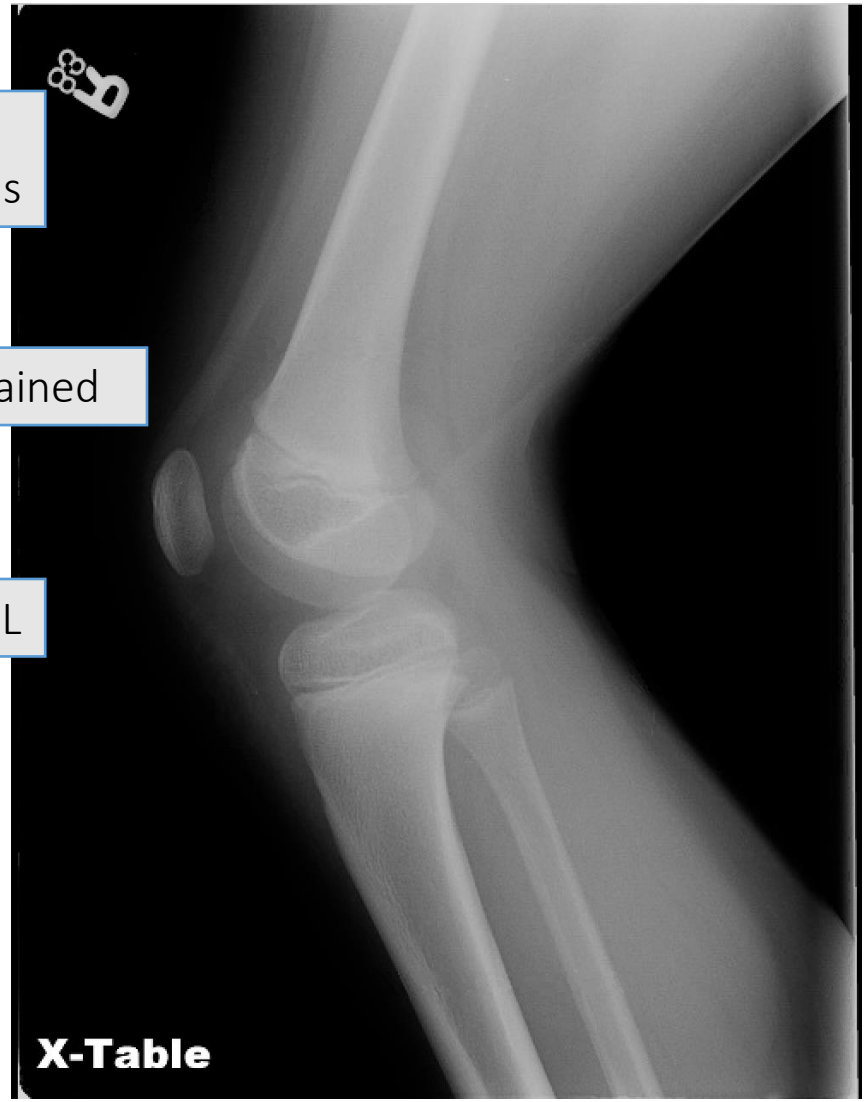
March: XR Knee



No fractures or dislocations

Joint spaces maintained

Soft tissue WNL



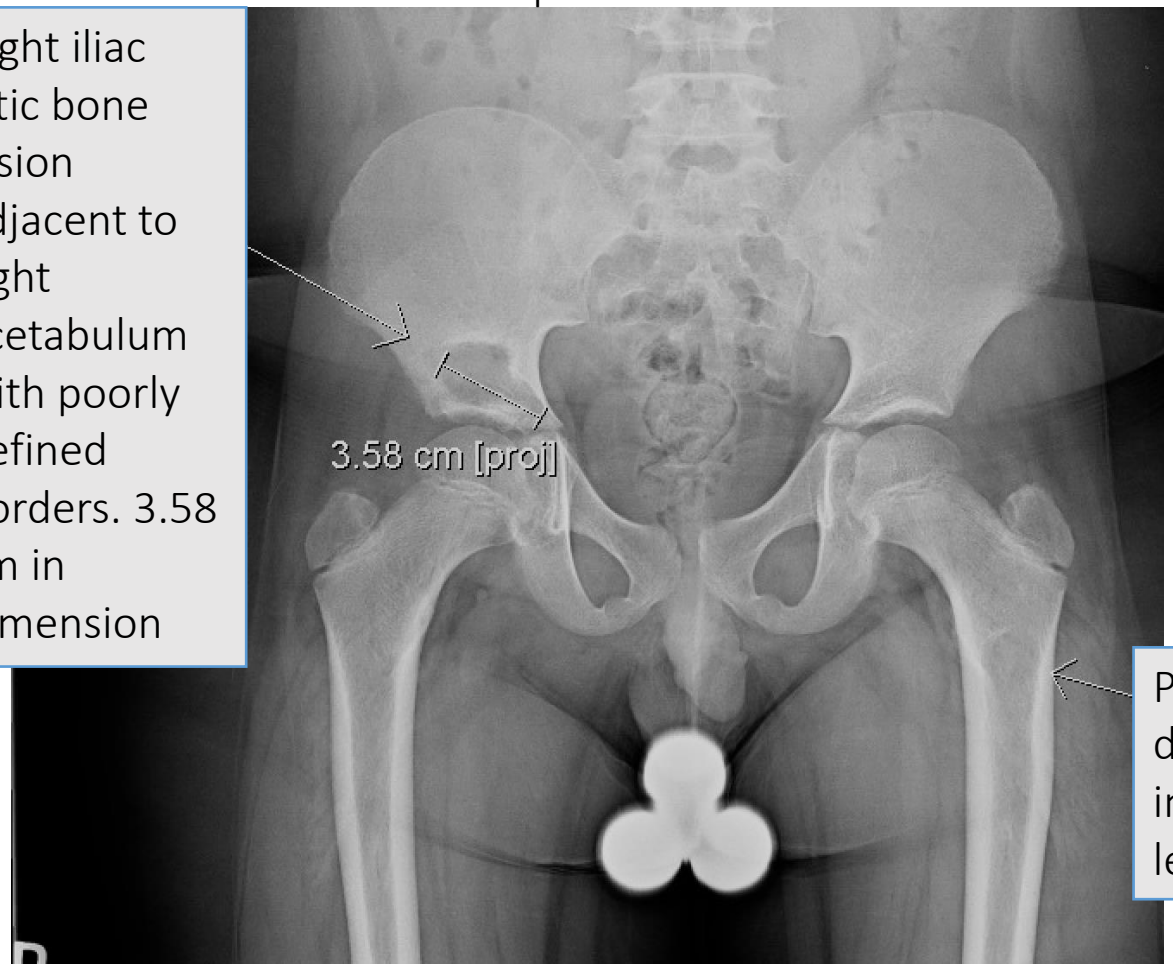
AP knee

Normal knee radiograph

Lateral knee

May: XR Pelvis, Femur, and Knee

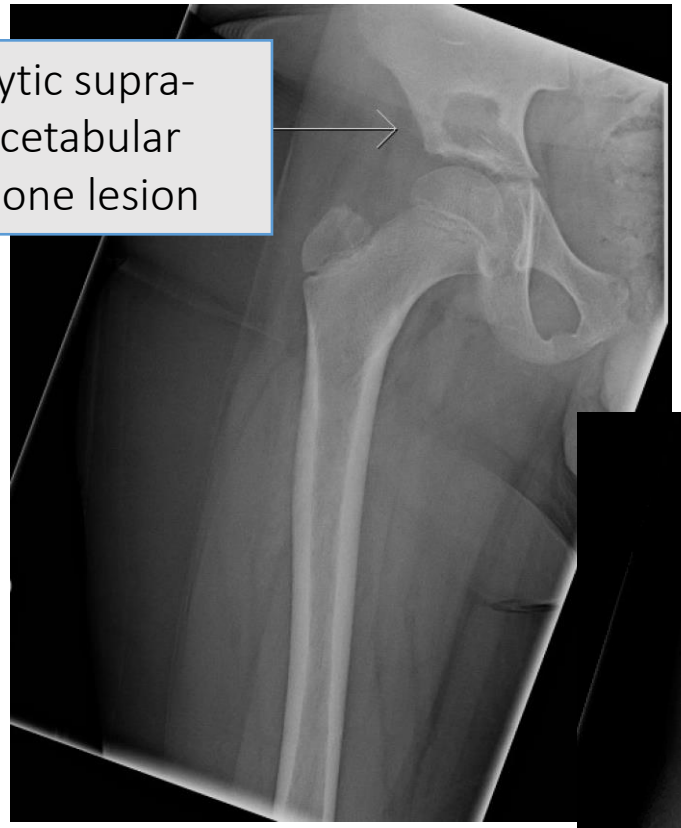
AP pelvis



Right iliac lytic bone lesion adjacent to right acetabulum with poorly defined borders. 3.58 cm in dimension

Poorly defined lesion in proximal left femur

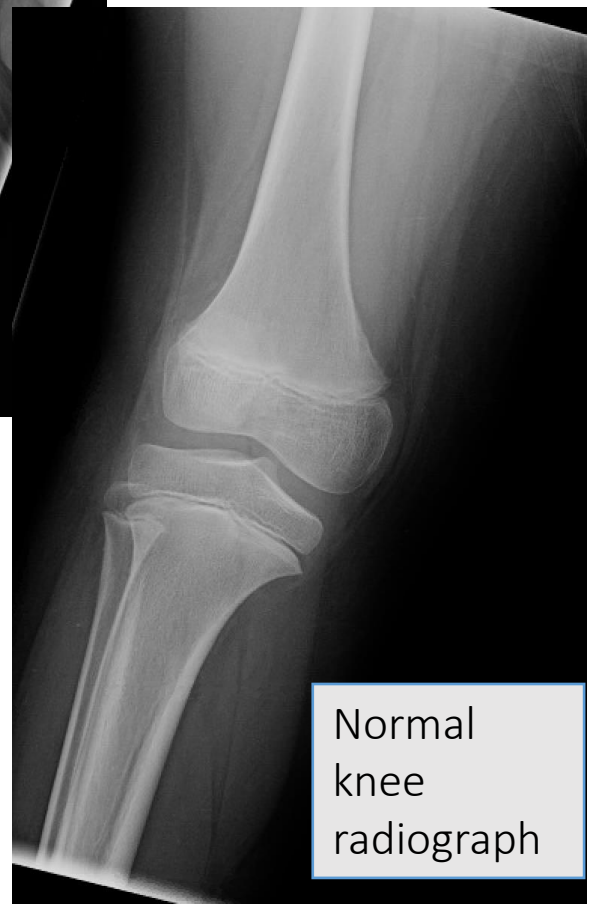
Right proximal femur normal in appearance



Lytic supra-acetabular bone lesion

AP femur

AP knee



Normal knee radiograph

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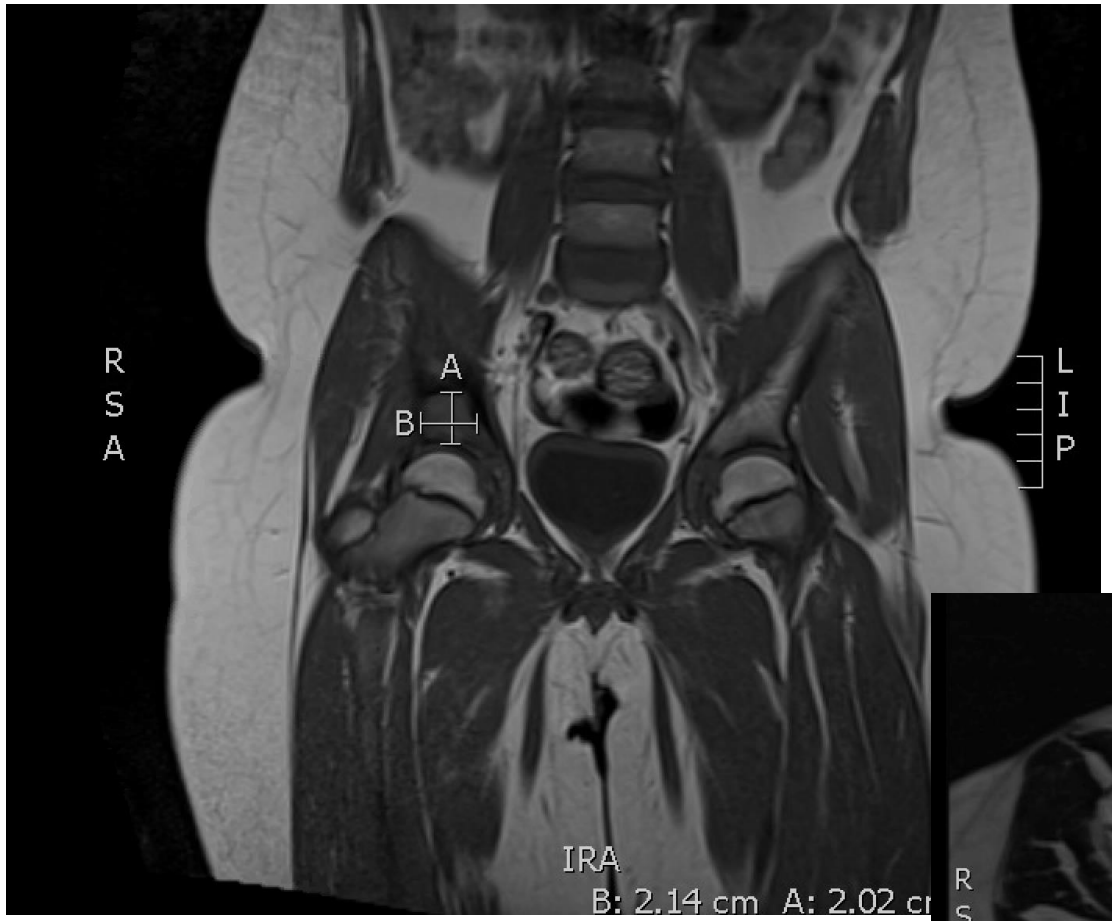
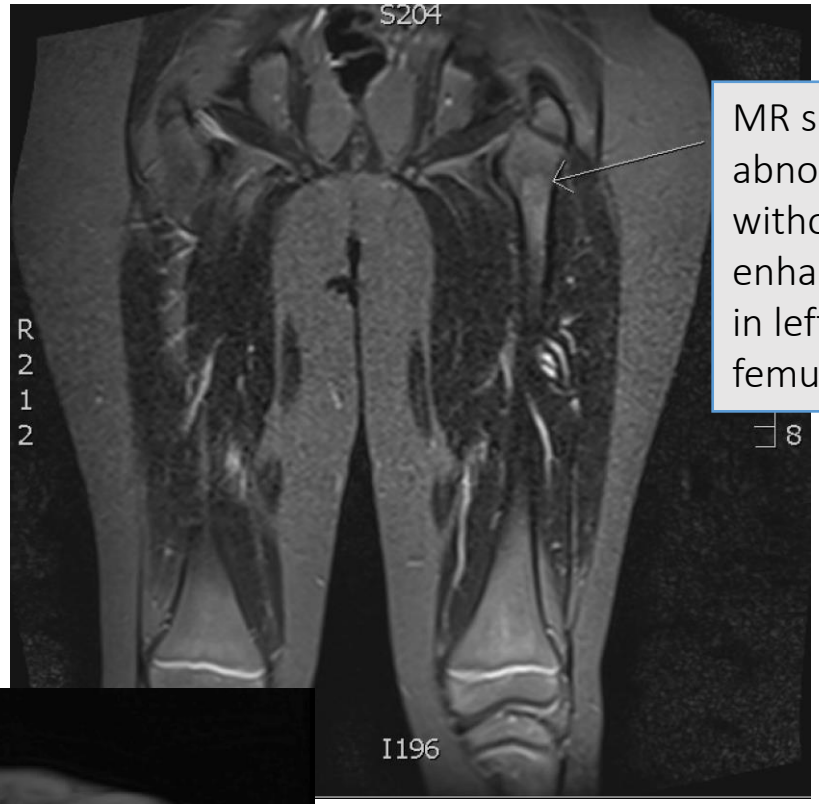
May: MR Pelvis

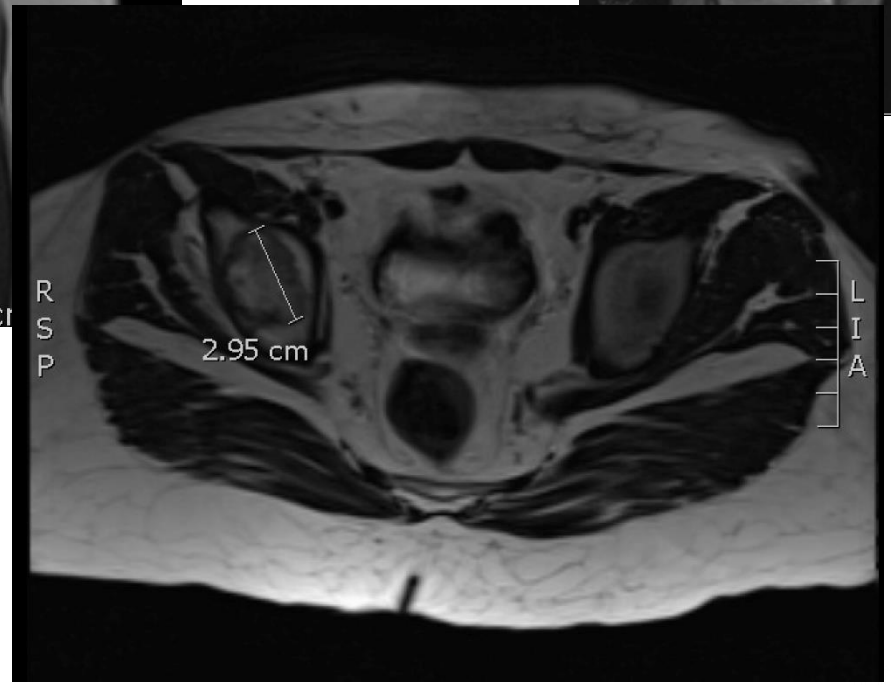


T1 coronal



MR signal abnormality without enhancement in left proximal femur

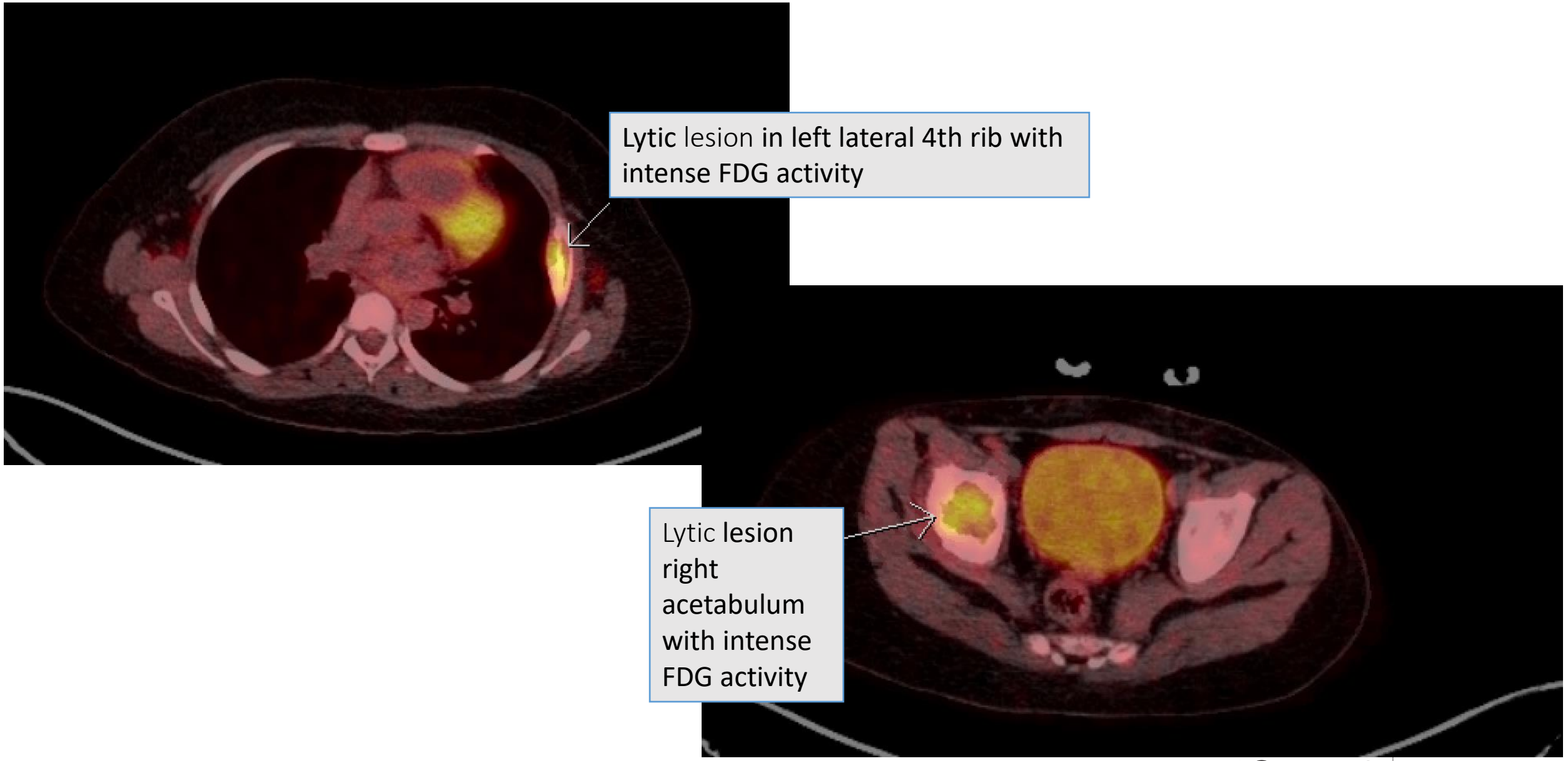
T1 coronal



T2 axial

Hyperenhancing 2.1 x 2 x 3 cm lesion within the right iliac bone, abutting the acetabular surface with edema in the adjacent soft tissues

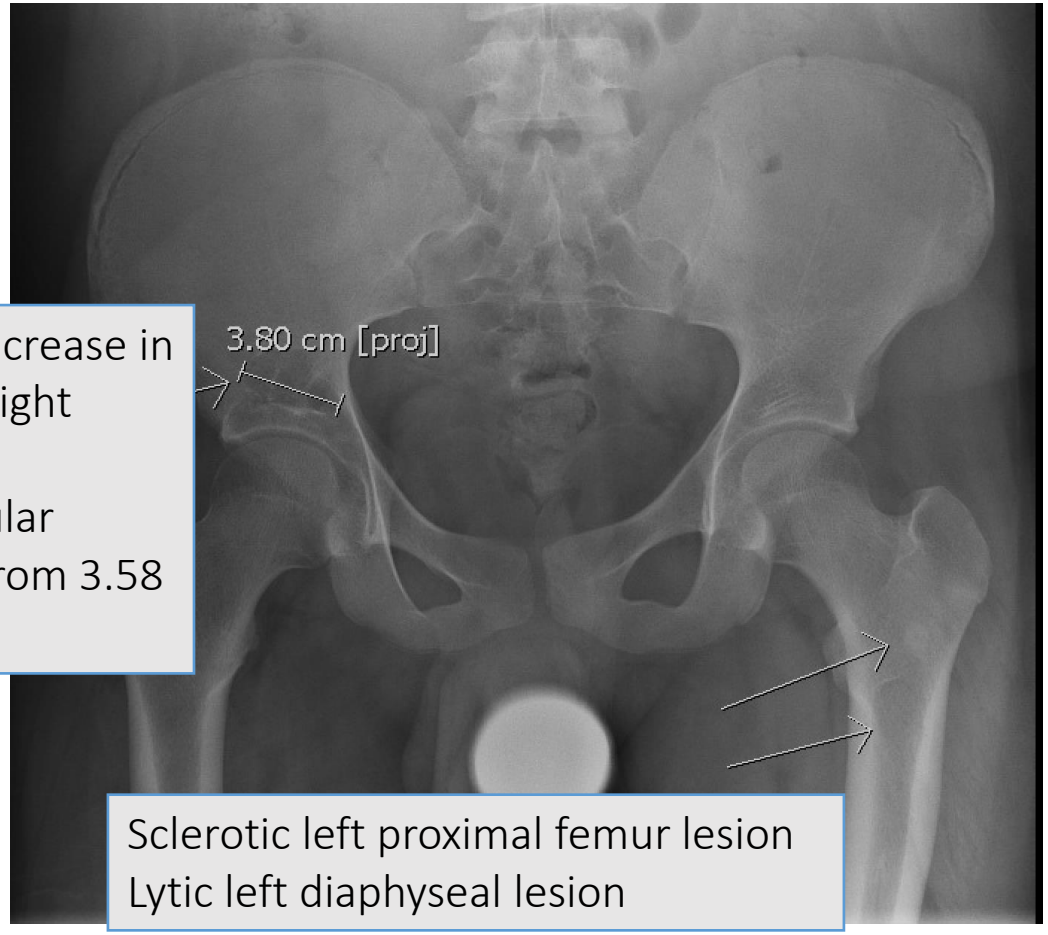
July: PET CT


Lytic lesion in left lateral 4th rib with intense FDG activity
Lytic lesion right acetabulum with intense FDG activity

Patient treatment and outcome

- Patient received CT guided bone biopsy to evaluate the right iliac bone lesion
- Pathology: positive for Langerhans cell histiocytosis
- PET scan showed additional lytic lesion in left 4th rib
- Presented a few days later with low energy, intermittent headaches, and excessive urination
  - Initial concern for pituitary invasion and subsequent diabetes insipidus
- Began treatment with vinblastine and prednisone for 12 months
- PET scan 1 year later was normal, but concern for persistent LCH on radiograph
  - Stable appearance of right supra-acetabular lytic lesion
  - Less defined appearance of proximal left femoral diaphyseal lytic lesion

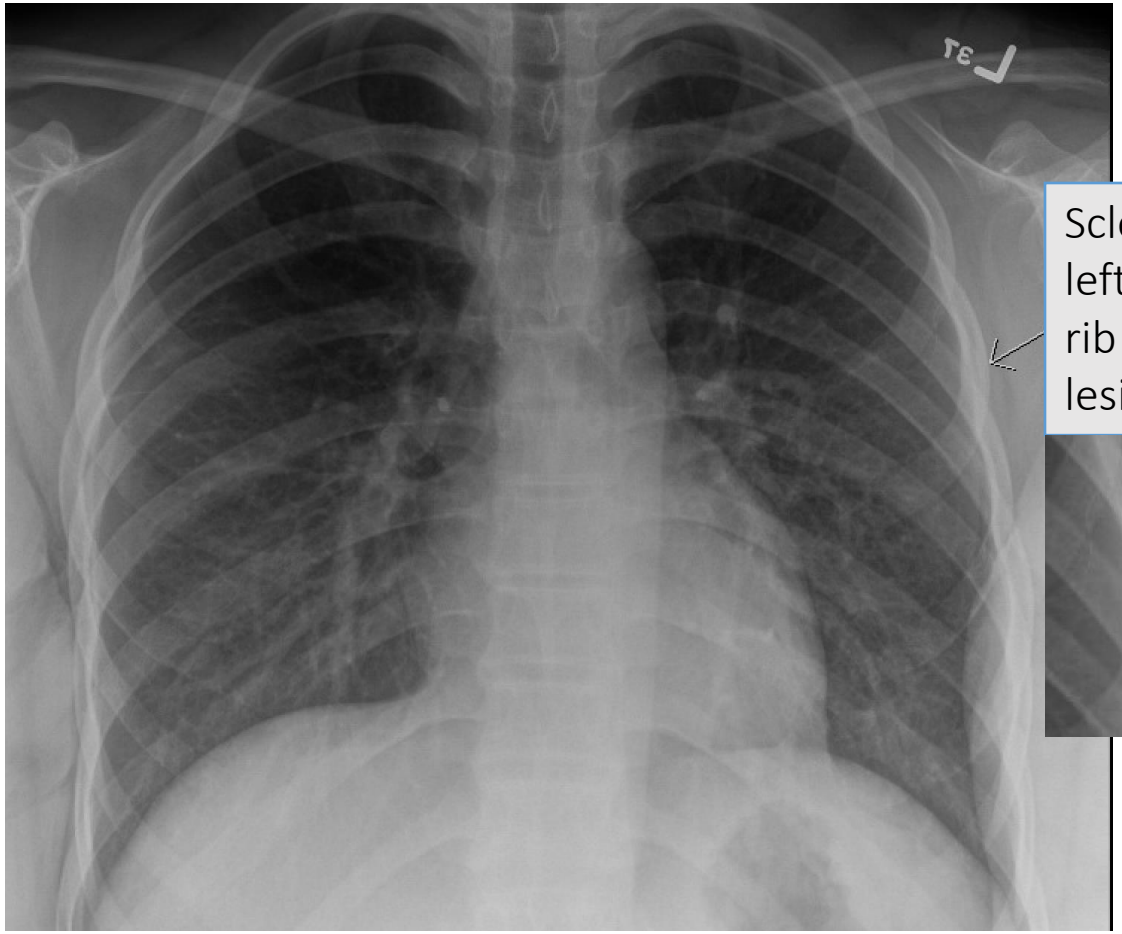
Follow-up Radiographs From Bone Survey (2020)



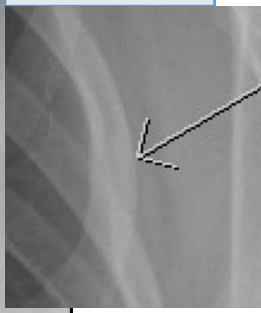
Slight increase in size of right supra-acetabular lesion from 3.58 cm

Sclerotic left proximal femur lesion
Lytic left diaphyseal lesion

AP pelvis



Sclerotic left 4th rib lesion



PA chest

Discussion: Langerhans Cell Histiocytosis

- Also called eosinophilic granuloma
- L group of histiocytic disorders
- A histiocytic disorder most characterized by single (monostotic) or multiple (polyostotic) osteolytic bone lesions demonstrating infiltration with histocytes on biopsy
  - Bean-shaped nuclei
- Histiocytes may infiltrate every organ apart from the heart or kidneys
- No staging system
- Named because the morphology and immunophenotype of the cells resembled Langerhans cells
  - LCH derived from myeloid progenitor cells from the bone marrow
    - CD207+ (langerin) histiocytes

Table 1. The revised classification system of histiocytoses and neoplasms of macrophage-dendritic cell lineages [1]

No.	Group of histiocytic disorders	Histiocytosis
1	L group	LCH ICH: – ECD Mixed LCH/ECD
2	C group	Cutaneous non-LCH: – XG family: JXG, AXG, SRH, BCH, GEH, PNH – Non-XG family: cutaneous RDD, NXG, other not otherwise specified Cutaneous non-LCH with a major systemic component: – XG family – XD – Non-XG family – MRH
3	M group	Primary MH Secondary MH (following or associated with another hematologic neoplasia)
4	R group	Familial RDD Sporadic RDD: – Classical (nodal) – Extra-nodal – RDD with neoplasia or immune disease – Other, non-C, non-L, non-M, non-H histiocytoses
5	H group	Primary HLH: Mendellan inherited conditions leading to HLH Secondary HLH (non-Mendelian HLH) HLH of unknown/uncertain origin

AXG – adult xanthogranuloma, BCH – benign cephalic histiocytosis, ECD – Erdheim-Chester disease, GEH – generalized eruptive histiocytosis, HLH – haemophagocytic lymphohistiocytosis, ICH – indeterminate cell histiocytosis, JXG – juvenile xanthogranuloma, LCH – Langerhans cell histiocytosis, MH – malignant histiocytoses, MRH – multicentric reticulohistiocytosis, NXG – necrobiotic xanthogranuloma, PNH – progressive nodular histiocytosis, RDD – Rosai-Dorfman disease, SRH – solitary reticulohistiocytoma, XD – xanthoma disseminatum, XG – xanthogranuloma.

Figure from Jezierska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M. Langerhans cell histiocytosis in children - a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. *Postepy Dermatol Alergol*. 2018;35(1):6-17. doi:10.5114/pdia.2017.67095

Discussion: LCH Classification

- Divided into 3 groups based on number of lesions and systems involved:
- Unifocal
  - 70% of cases
  - Limited to a single bone or a few bones
  - May involve the lung
  - Presents at 5-15 years of age
- Multifocal unisystem
  - 20% of cases
  - Multiples bones + reticuloendothelial system
  - Diabetes insipidus when pituitary involved
  - Presents at 1-5 years of age
- Multifocal multisystem
  - 10% of cases
  - Disseminated involvement of RES, anemia, and thrombocytopenia = often fatal
  - Diagnosed in first 2 years of life

Table 2. Incidence and symptomatology of systems and organs involvement in Langerhans cell histiocytosis in children [1, 2, 4, 5, 9]

No.	System involved	Organ involved	Symptomatology	Incidence
1	Skeletal	Flat and long bones, spine/skullcap bones, femurs, humeri, spine	Bone pains, lumps	80%
		Orbital cavity	Exophthalmos	
		Temporal bone	Discharge from the middle ear, hearing loss	
2	Integumentary	Skin	Seborrhoeic erythematous rash, haemorrhagic rash	60%
3	Lymphatic	Lymph nodes	Swollen lymph nodes	33%
		Thymus	Widened opacity of the mediastinum	2.6%
		Spleen	Splenomegaly, cytopenias	15%
4	Liver	Liver	Hepatomegaly, liver dysfunction	15%
5	Respiratory	Lungs	Respiratory failure	1–15%
6	Bone marrow cavity	Bone marrow	Neutropenia, anaemia, thrombocytopenia	15–30%
7	CNS	Hypothalamic-pituitary disease	Diabetes insipidus, short stature, secondary hydrocephalus, cranial nerve palsies	25%
		CNS	Neurodegenerative disease of the CNS	
8	Digestive	Gastrointestinal tract	Haemorrhagic diarrhoea, anaemia	< 5%

Figure from Jezierska M, Stefanowicz J, Romanowicz G, Kosiak W, Lange M. Langerhans cell histiocytosis in children - a disease with many faces. Recent advances in pathogenesis, diagnostic examinations and treatment. *Postepy Dermatol Alergol*. 2018;35(1):6-17. doi:10.5114/pdia.2017.67095

Discussion: LCH Imaging

- Conventional radiographs are primary imaging method to identify and follow LCH lesions
  - In long bones: well-defined, lytic lesion +/- sclerotic margins usually present in the diaphysis or metaphysis
  - Associated soft tissue mass may be present
- LCH lesions are “hot” on radionuclide bone scans. This modality can detect some lesions that are poorly visualized by radiography
- MR scans show the lytic lesion with high T2 and low T1-weighted imaging
  - Use of gadolinium contrast enhances the lesion and soft tissue components
- “Activity” of lesions may be judged by MR or PET
  - PET: most accurate for detecting LCH lesions and response to therapy, except for vertebral lesions (MR most helpful)

Discussion: Radiologic Findings in LCH

Table 1: Review of Radiologic Findings in LCH

System	Findings
Skull	"Punched-out" lesion, beveled edge (asymmetric destruction of inner and outer cortices), geographic skull (lesions grow, coalesce, and become maplike)
Spine	Vertebra plana (symmetric flattening of vertebral body)
Long bones	More commonly involved in children; diaphyseal or metaphyseal
Flat bones	"Floating teeth" if enough alveolar destruction; lytic lesion with sclerotic rim and surrounding areas of sclerosis more common in iliac bone
Liver	Hepatomegaly and solid or cystlike lesions
Lymph nodes	Most common in neck
CNS	Diabetes insipidus and neurodegeneration, absent posterior pituitary bright spot, thickening of pituitary stalk
Lung	Centrilobular nodules or cysts of varying sizes, with mid- to upper-lung distribution and sparing of costophrenic angles

Note.—CNS = central nervous system.

Figure from Zaveri J, La Q, Yarmish G, Neuman J. More than just Langerhans cell histiocytosis: a radiologic review of histiocytic disorders. Radiographics. 2014;34(7):2008-2024. doi:10.1148/rg.347130132

Discussion: Comparison of Imaging Modalities

	True-positive lesions	False-negative lesions	False-positive lesions	Sensitivity (95% confidence interval)*	Mean No. of false-positives per patient†
Overall‡					
Skeletal survey	56	43	0	56.6% (46.7–66.0%)	0 (0/38)
Bone scan	38	61	4	38.4% (29.4–48.3%)	0.11 (4/38)
WB-MRI	98	1	2	99.0% (93.2–99.9%)	0.05 (2/38)
Skeletal lesions§					
Skeletal survey	51	30	0	63.0% (52.0–72.7%)	0 (0/33)
Bone scan	38	43	4	46.9% (36.4–57.8%)	0.12 (4/33)
WB-MRI	80	1	1	98.8% (91.8–99.8%)	0.03 (1/33)

WB-MRI = whole-body magnetic resonance imaging.

*For all comparisons, $P < 0.017$.

†For all comparisons, $P > 0.017$.

‡The number of overall lesions: 99 true lesions and 6 false-positive lesions in 38 patients.

§The number of skeletal lesions: 81 true lesions and 5 false-positive lesions in 33 patients.

Figure from Kim, J.R., Yoon, H.M., Jung, A.Y. et al. Comparison of whole-body MRI, bone scan, and radiographic skeletal survey for lesion detection and risk stratification of Langerhans Cell Histiocytosis. Sci Rep 9, 317 (2019). https://doi.org/10.1038/s41598-018-36501-1

Discussion: LCH Diagnosis and Treatment

- Histologic confirmation is necessary for diagnosis
  - Clinical and imaging characteristics of LCH mimic other disease processes
- Fine needle aspiration or core needle biopsy and staining for CD1a and/or anti-langerin (CD207)
- Electron microscopy to identify Birbeck granules performed less frequently
- Testing for the BRAF V600E mutation is utilized if the patient needs targeted therapy
- Treatment – depends upon extent of disease and presence of CNS lesions
  - Solitary – no universally accepted protocol
  - High risk lesions – vinblastine and prednisone for 12 months

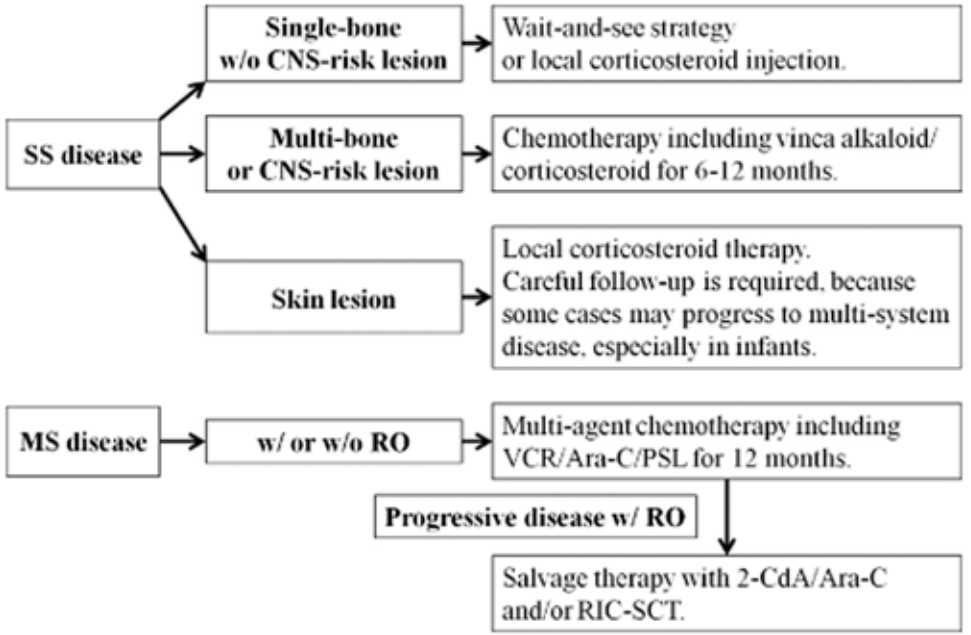


Figure from Morimoto A, Oh Y, Shioda Y, Kudo K, Imamura T. Recent advances in Langerhans cell histiocytosis. *Pediatr Int*. 2014;56(4):451-461. doi:10.1111/ped.12380

Wrap Up

- Langerhans cell histiocytosis is a rare condition that presents more often in children
- Infiltrative cells are not Langerhans cells but are myeloid progenitor CD207+ (langerin) histiocytes
- Radiograph is the initial imaging modality of choice as it can reveal the lytic bone lesions
- Bone biopsy + staining for CD1a/CD207 for confirmation
- Treatment depends on extent of lesions and CNS involvement
  - Vinblastine and prednisone for 12 months for severe cases
- PET scans needed to monitor response to chemotherapy except for vertebral lesions

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