Non-malignant hematologic disorders associated arthropathies: hemoglobinopathy-associated musculoskeletal manifestations, hemophilia

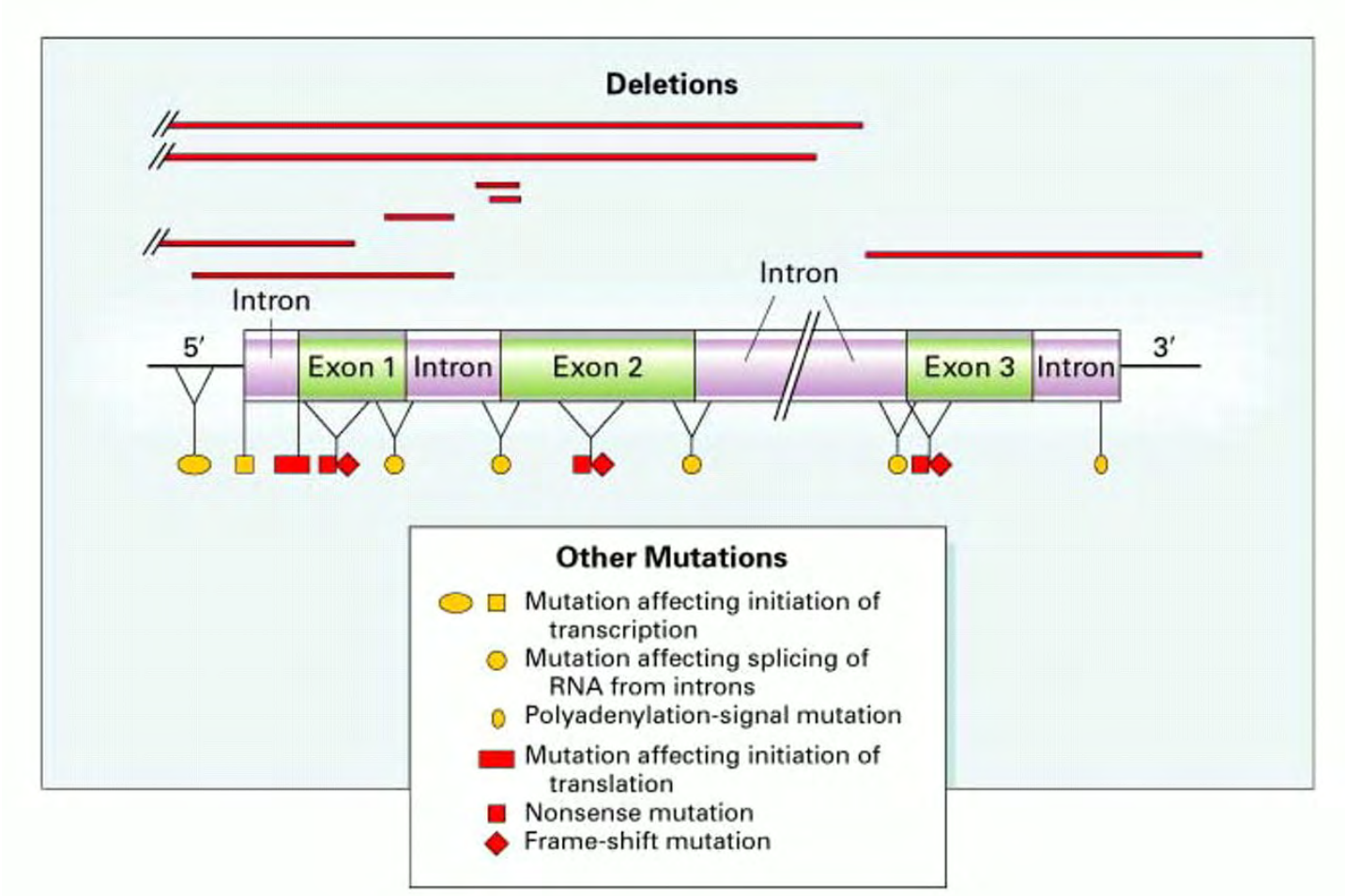
HAEMOGLOBINOPATHIES
= inherited disorders of globin

divided into:

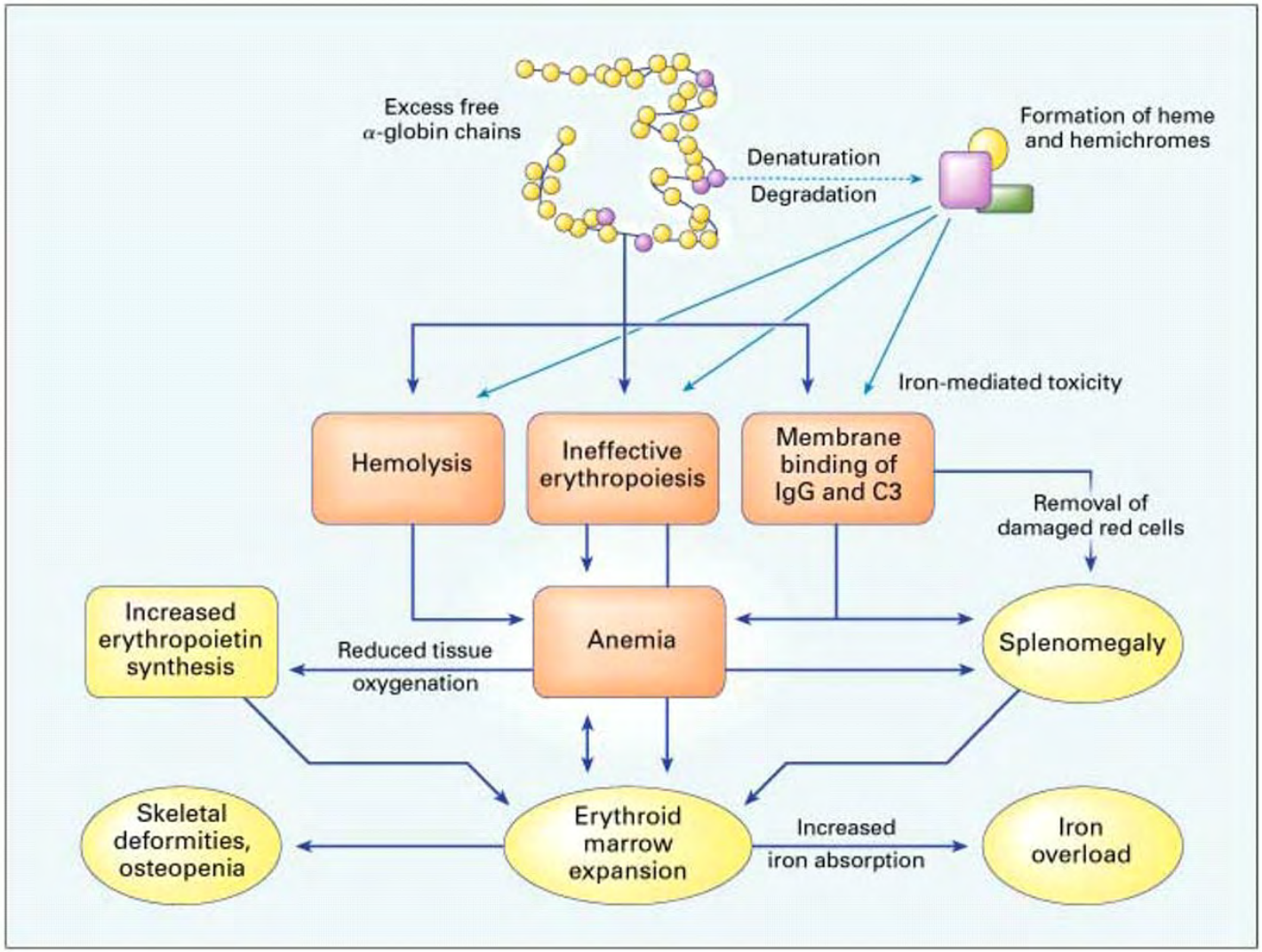
Thalassaemia Syndromes

Variant Haemoglobins

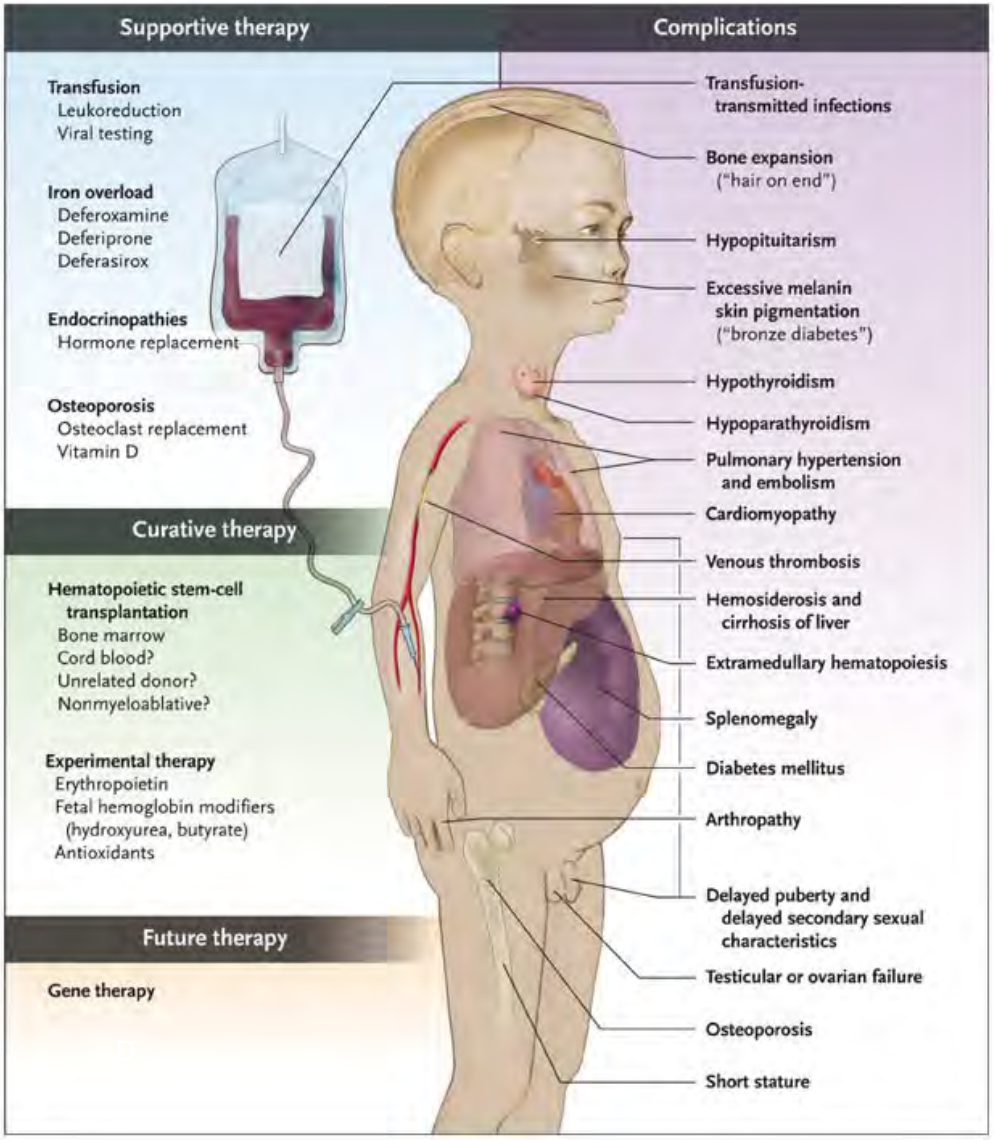
The Normal Structure of the {beta}-Globin Gene and the Locations and Types of Mutations Resulting in {beta}-Thalassemia



Effects of excess production of free α-globin chains



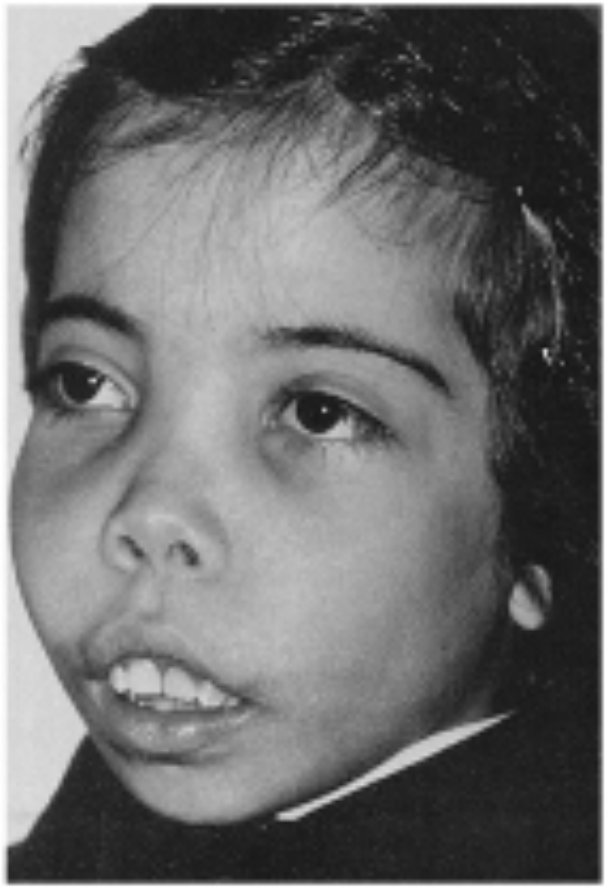
Thalassemia and Treatment-Related Complications



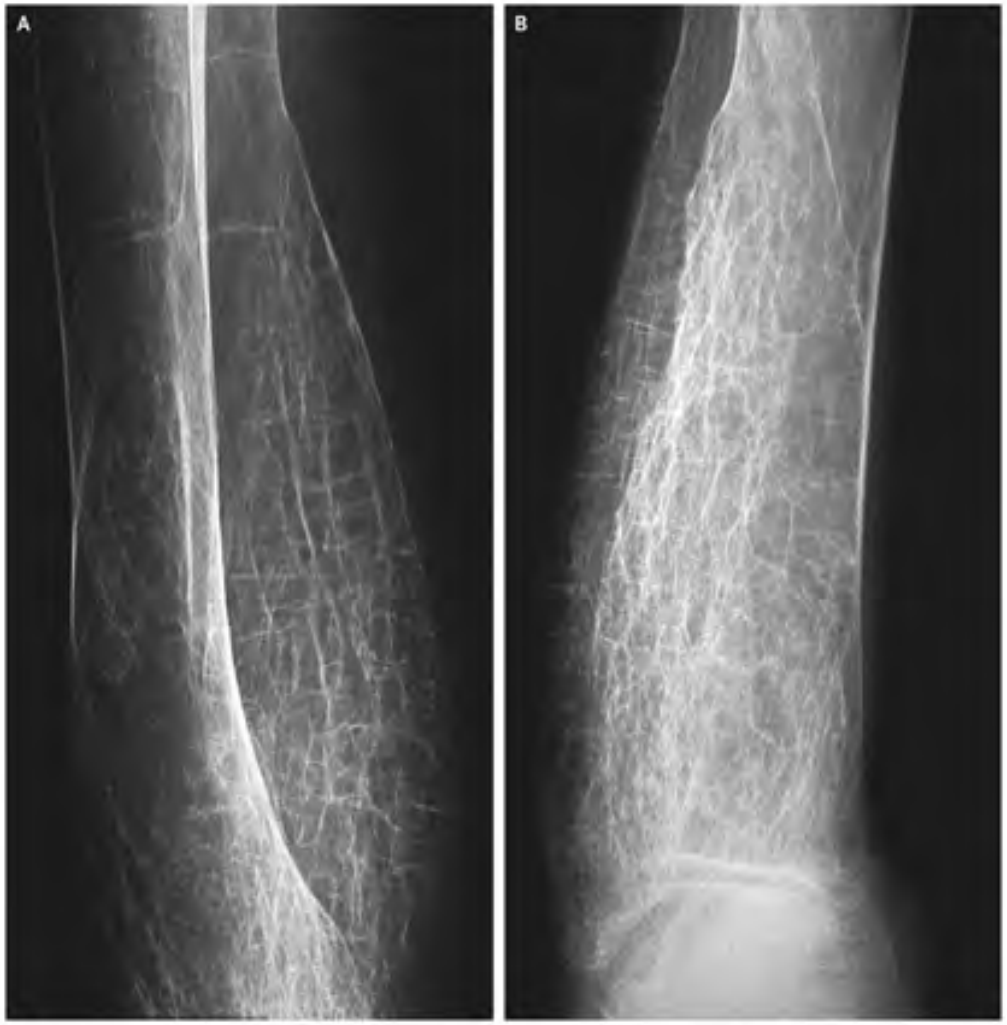
Bone lesions in untransfused or undertransfused β-thalassemia major

Expansion of the bone marrow
Fragility of the bones
Osteoporosis
Growth retardation

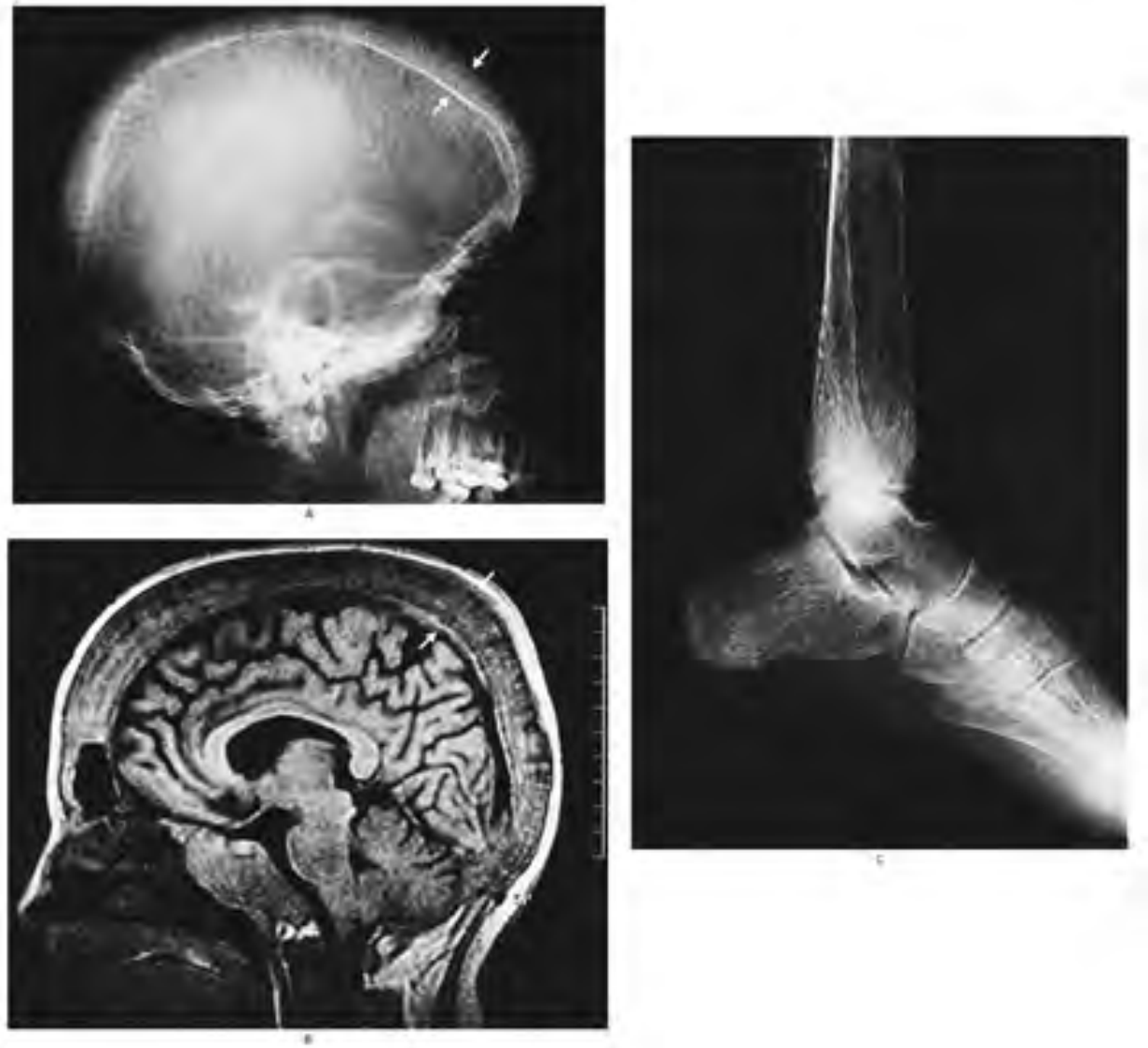
The typical facial appearance of a child with untreated b-thalassemia



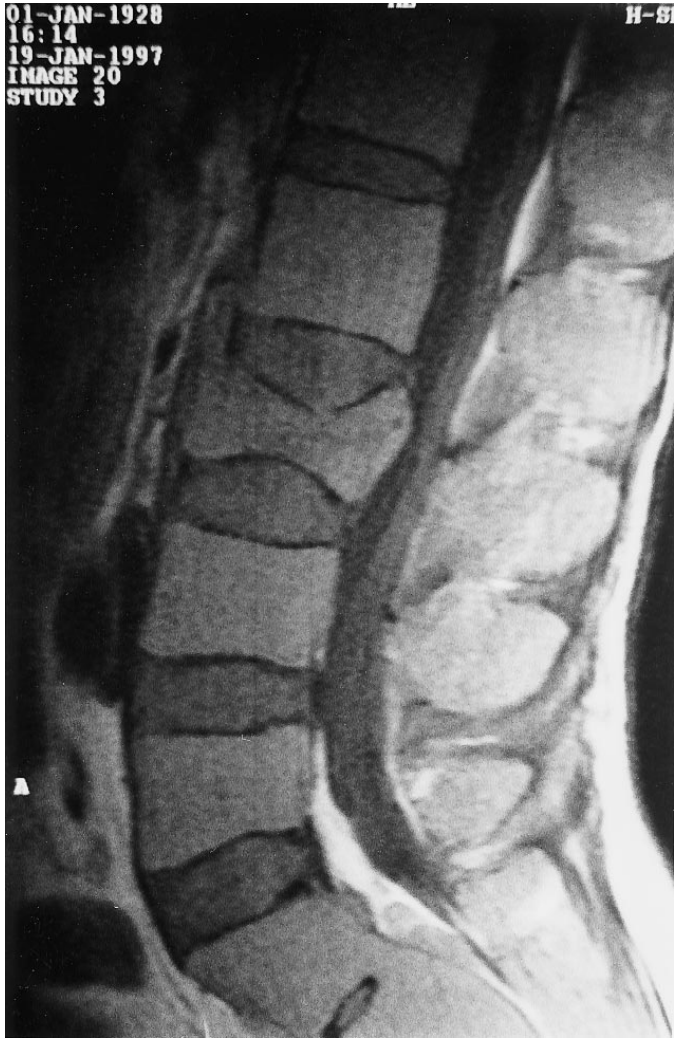
A Cobwebbing Trabecular Pattern



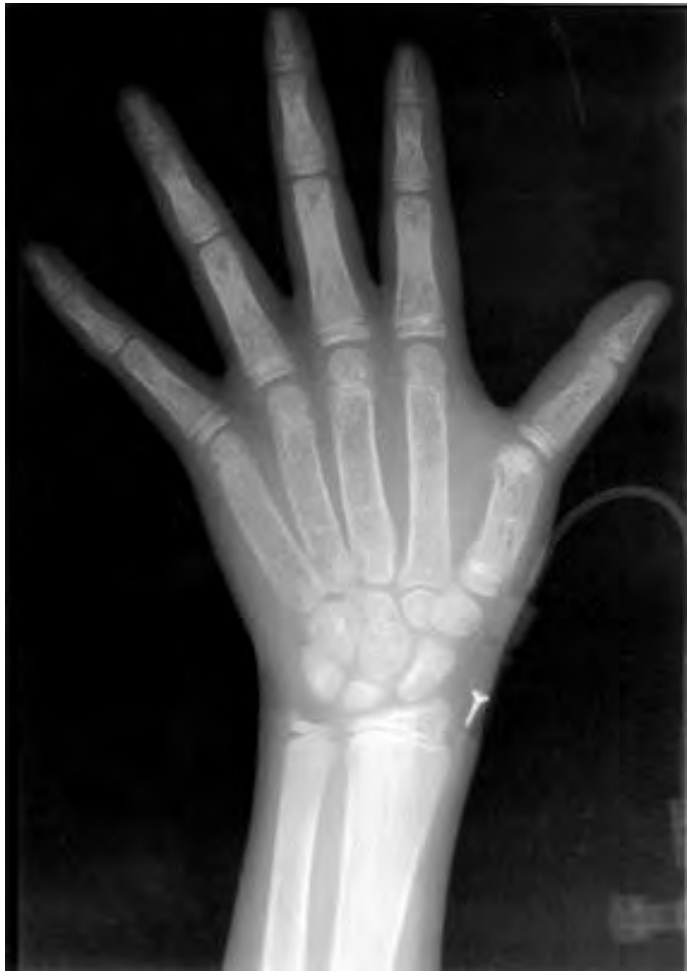
A Hair-on-End Skull



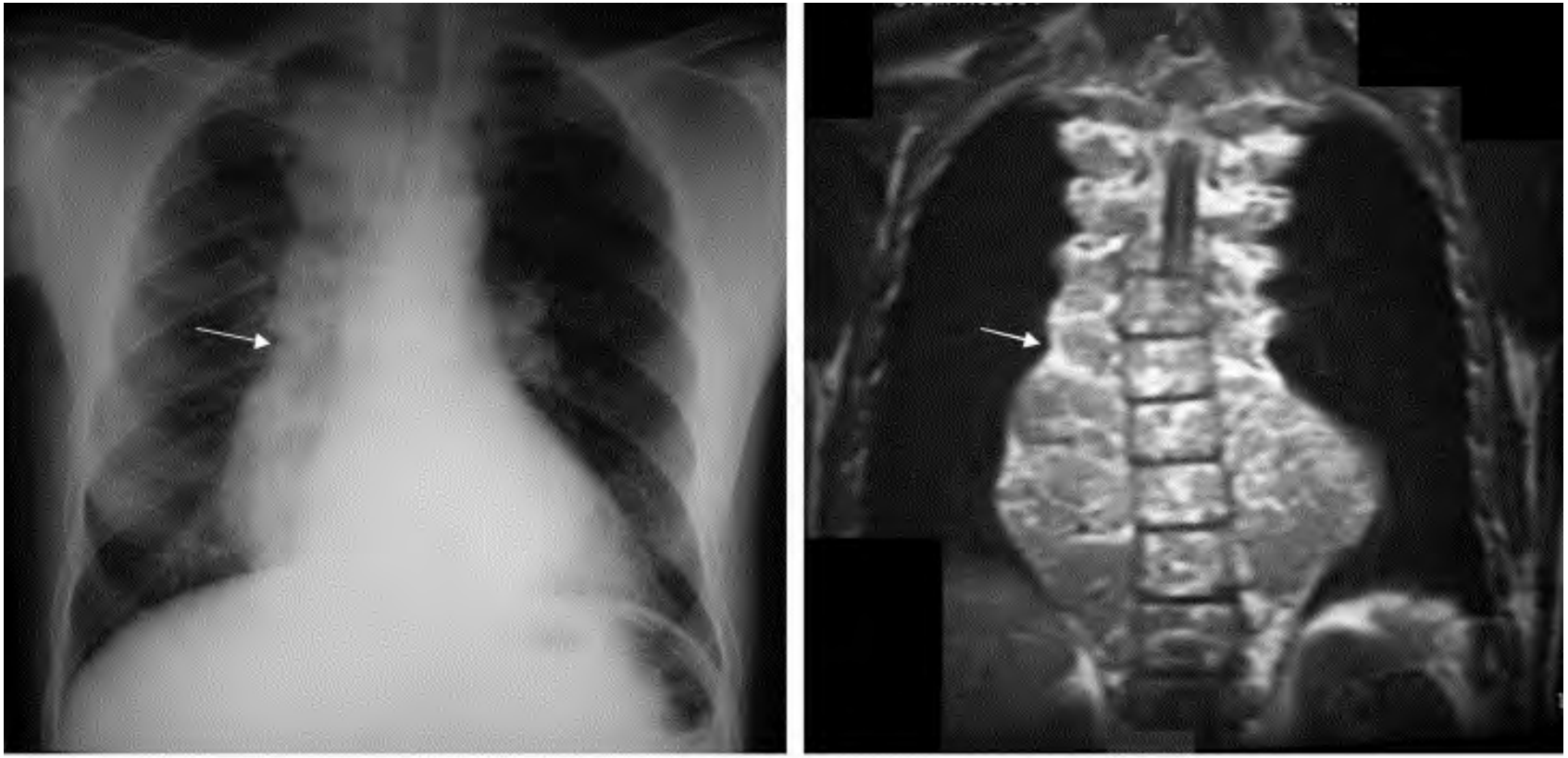
Compression fracturing of the vertebra



Coarse trabeculation and exaggerated biconvexity of the 5th metacarpal

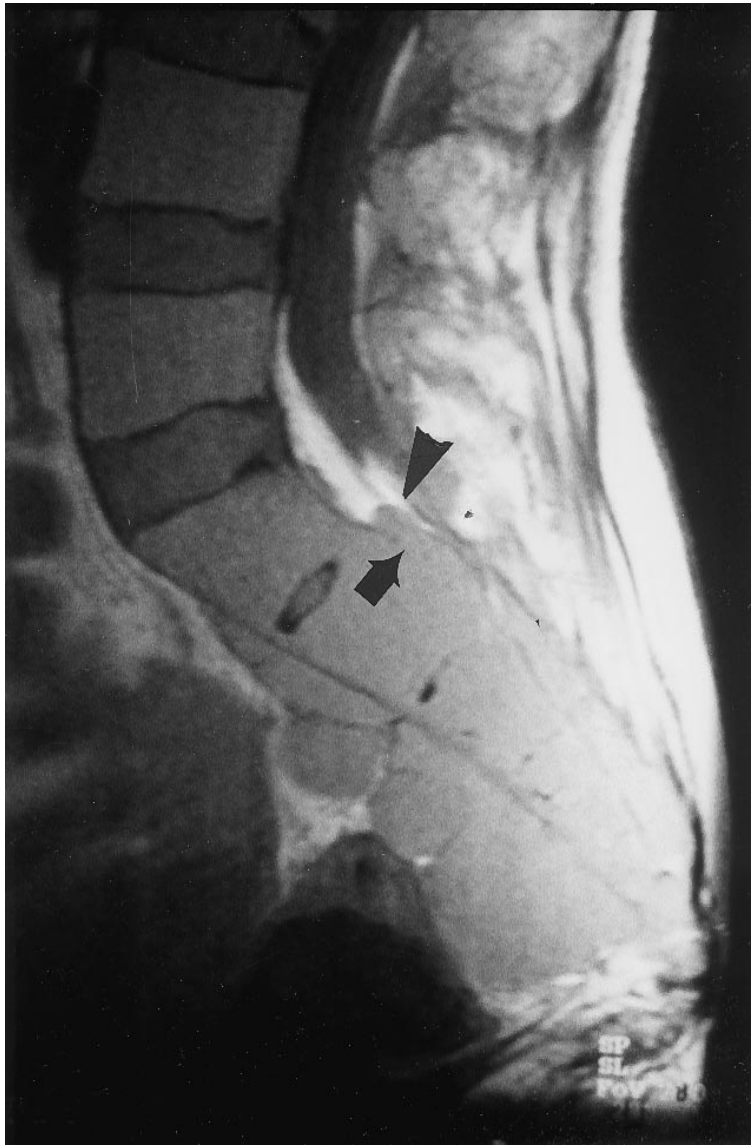


Extramedullary haematopoiesis

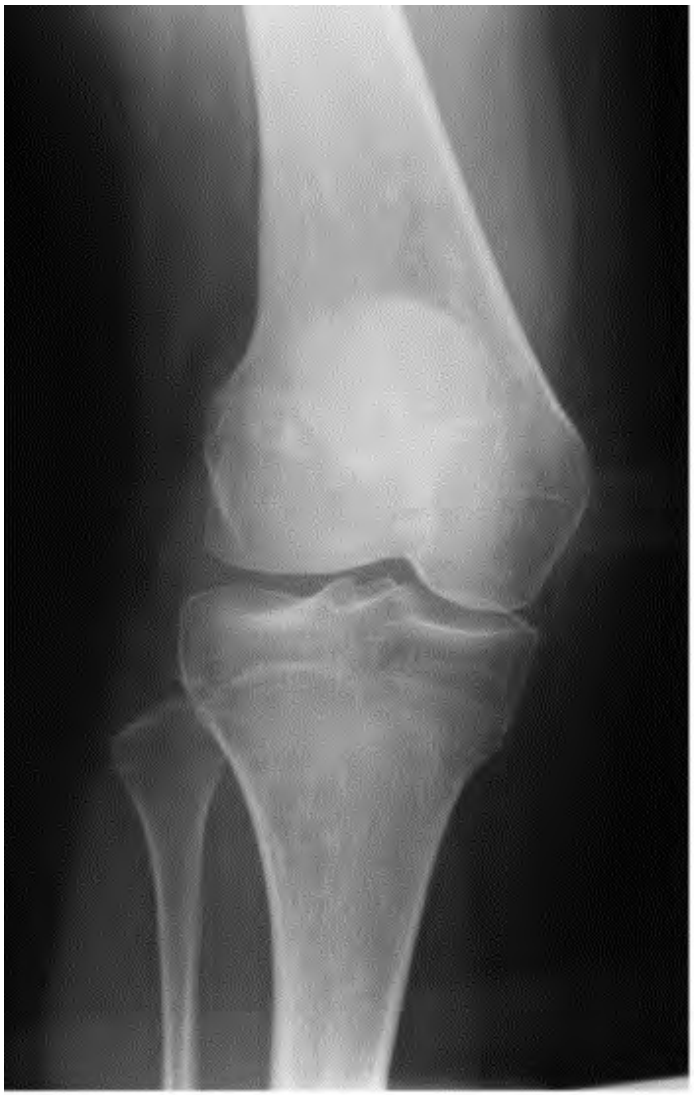


(a) (b)

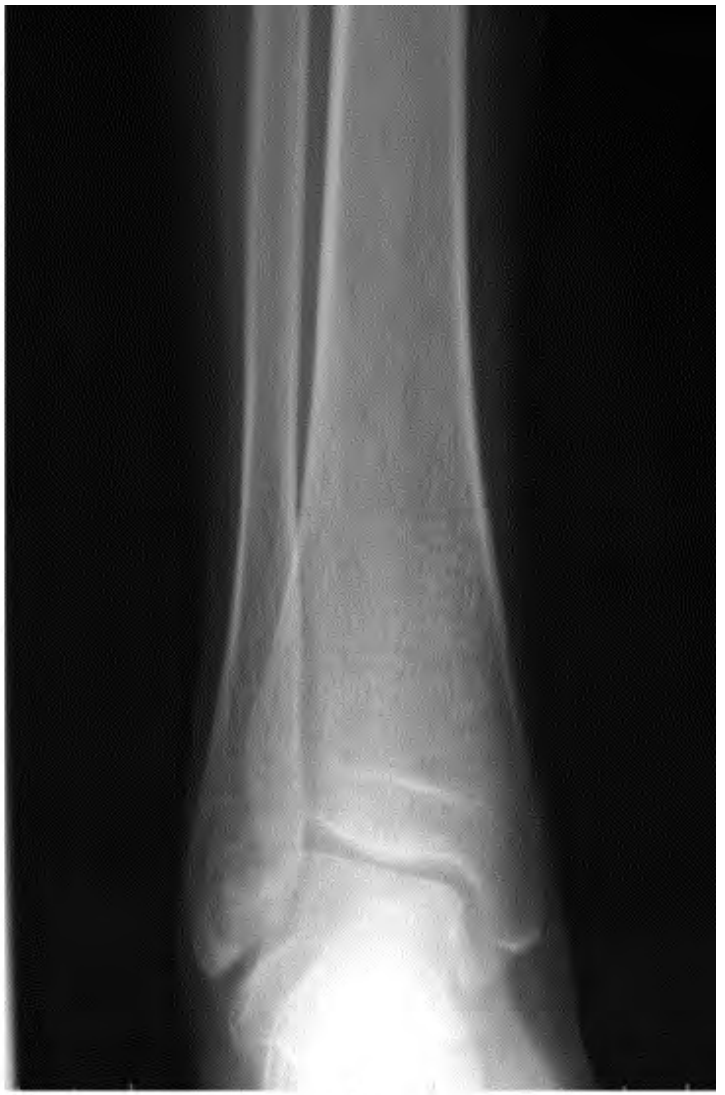
Epidural extension



Premature fusion of the epiphyses



(a)

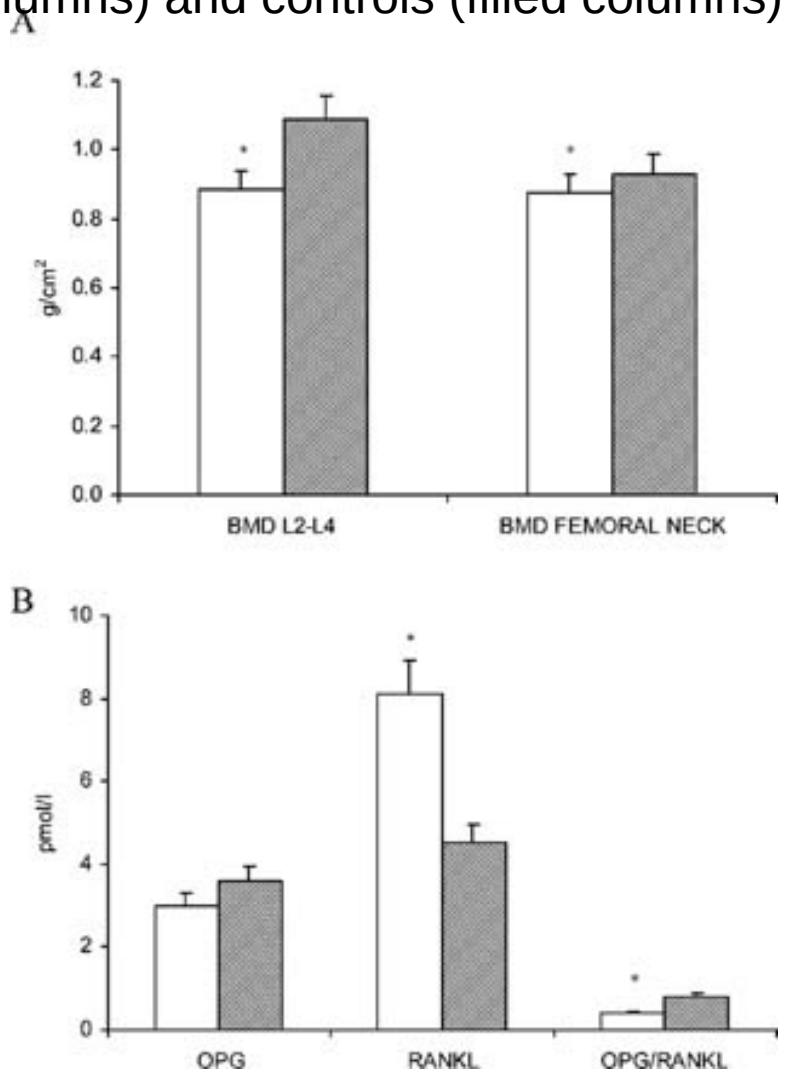


(b)

Osteoporosis in optimally treated thalassemia patients

Bone marrow expansion
Endocrine complications
Iron overload and desferrioxamine
Vitamin and trace mineral deficiencies
Physical activity
Genetic factors

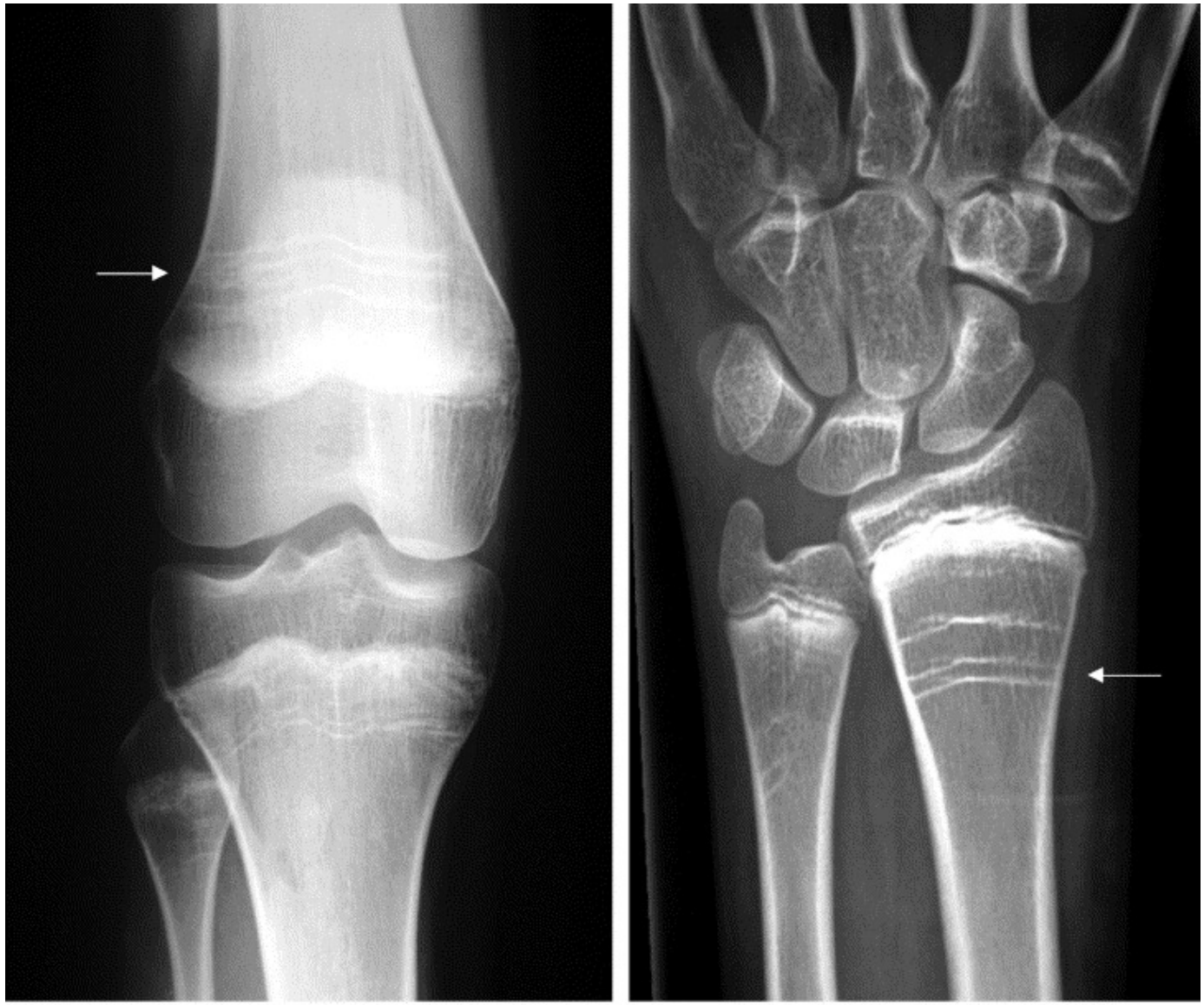
(A) The BMD values at lumbar and femoral level in thalassemics (empty columns) and controls (filled columns).
(B) The OPG, RANKL, and OPG/RANKL ratio values in thalassemics (empty columns) and controls (filled columns). *p < 0.05.



Bone lesions associated with desferrioxamine toxicity in well-transfused and iron-chelated patients

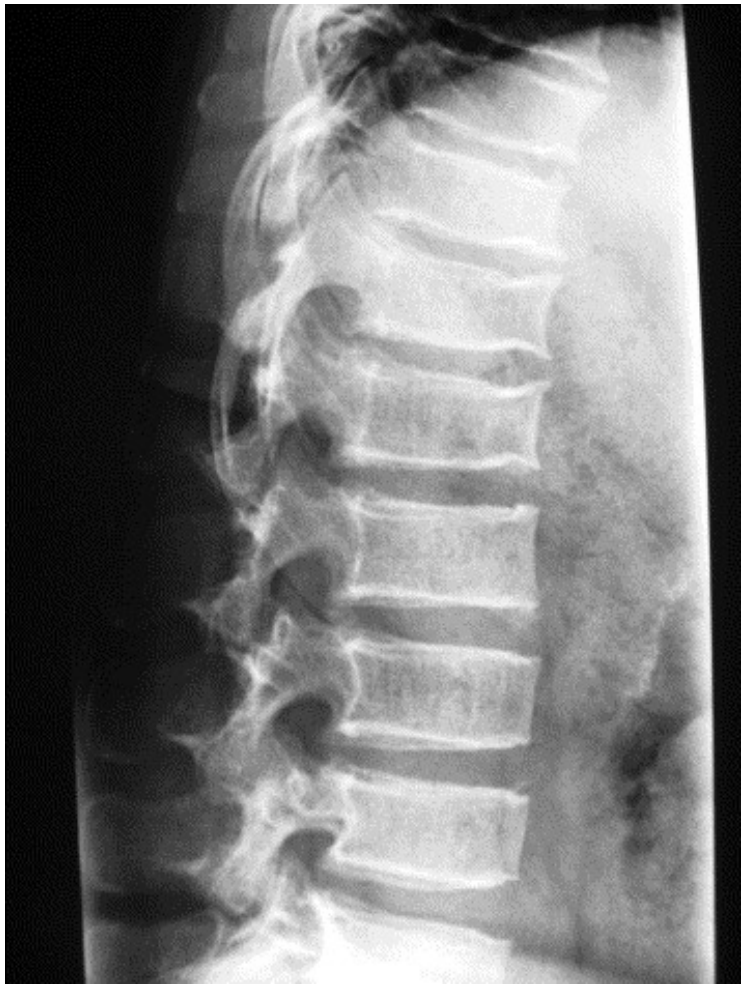
Irregularity of the physeal-metaphyseal junction
Sclerosis of the metaphysis
Sclerosis at the costochondral junction
Platyspondyly
Growth failure

DFX-induced skeletal dysplasia



(a) (b)

DFX-induced skeletal dysplasia

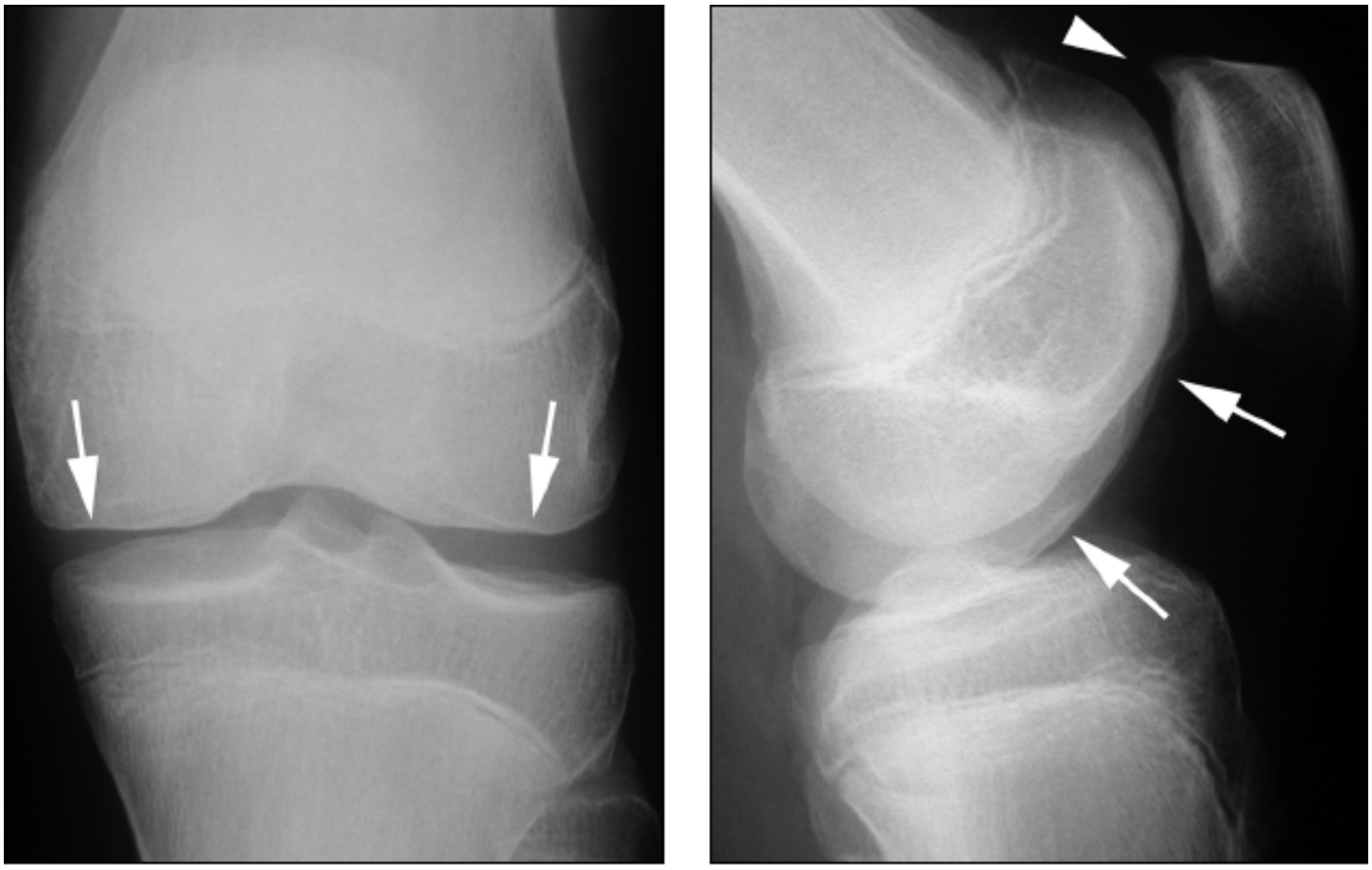


Deferiprone-related arthropathy

TABLE 1 Radiographic Findings of the Knees in 14 Patients with β-Thalassemia Major Treated with Deferiprone

Patient No.	Sex	Age (yr)[a]	Symptoms[b]	Radiographic Findings		
				Joint Effusion	Subchondral Irregularity	Patellar Beak
1	M	11.0	Severe	Mild	Severe	Mild
2	M	12.4	Severe	Mild	Mild	Absent
3	M	15.5	Severe	Moderate	Mild	Mild
4	M	13.4	Severe	Moderate	Moderate	Mild
5	M	17.4	Severe	Mild	Mild	Mild
6	M	9.9	Severe	Moderate	Moderate	Absent
7	F	30.5	Mild	Mild	Absent	Mild
8	F	32.8	Severe	Absent	Absent	Mild
9	M	14.7	Absent	Absent	Mild	Absent
10	F	17.3	Absent	Absent	Absent	Absent
11	F	17.7	Mild	Absent	Mild	Absent
12	F	17.9	Absent	Absent	Absent	Absent
13	M	6.8	Mild[c]	Mild	Absent	Absent
14	F	11.2	Absent	Absent	Mild	Absent

Deferiprone-related arthropathy



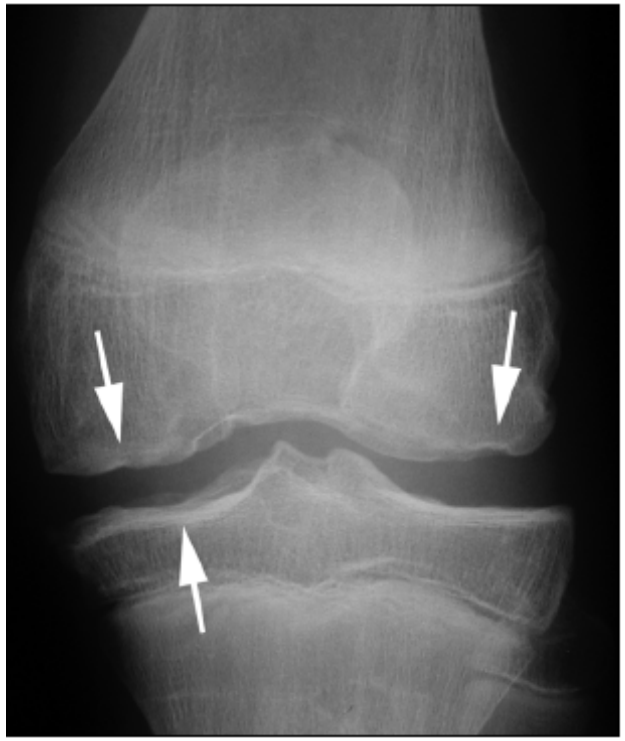
Deferiprone-related arthropathy

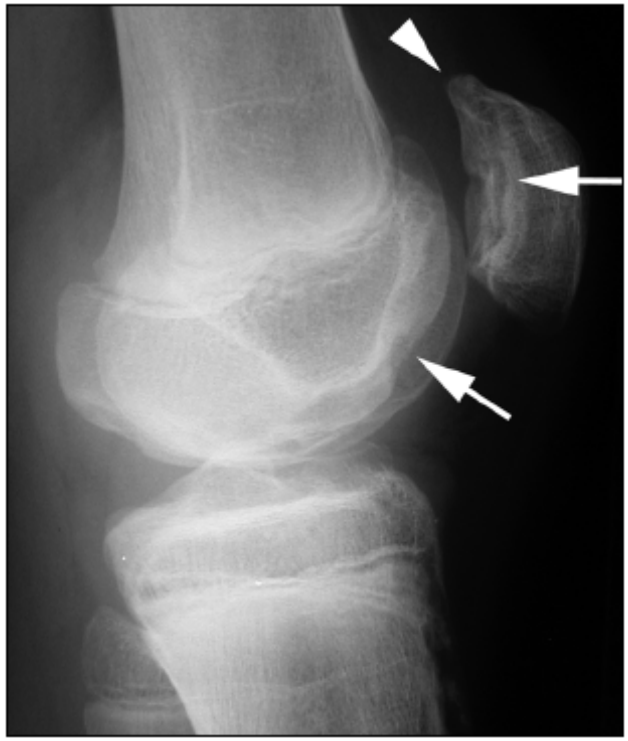
Radiography and MRI of Arthropathy of the Knees

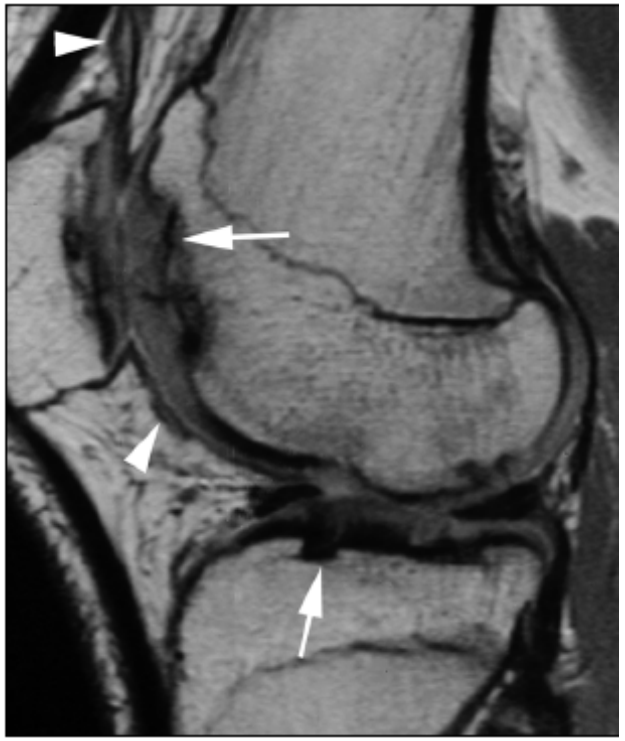
TABLE 2 MRI Findings in Six Patients with Deferiprone-Related Arthropathy Correlated with Knee Symptoms

Finding	Patient 1 (13.7 yr)		Patient 2 (12.4 yr)		Patient 3 (15.5 yr)		Patient 4 (13.4 yr)		Patient 5 (17.8 yr)		Patient 6 (9.9 yr)	
	Initial MRI	26-Mo Follow-Up	Initial MRI	20-Mo Follow-Up	Initial MRI	9-Mo Follow-Up	Initial MRI	13-Mo Follow-Up	Initial MRI	16-Mo Follow-Up	Initial MRI	14-Mo Follow-Up
Symptoms at MRI	Mild	Absent	Moderate	Absent	Severe	Mild	Moderate	Mild	Moderate	Absent	Moderate	Mild
MRI finding												
Joint effusion	Mild	Absent	Mild	Mild	Moderate	Mild	Moderate	Mild	Moderate	Mild	Severe	Moderate
Synovial thickening	Mild	Mild	Absent	Absent	Mild	Mild	Mild	Mild	Mild	Mild	Severe	Severe
Synovial enhancement	NA	NA	Absent	Absent	Mild	Mild	Mild	NA	Mild	Mild	Severe	Severe
Synovial bands	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Mild	Moderate
Articular cartilage signal changes	Moderate	Moderate	Absent	Absent	Absent	Absent	Absent	Absent	Mild	Mild[a]	Moderate	Mild
Thickened cartilage[b]	Moderate	Severe	Absent	Absent	Absent	Absent	Mild	Mild	Mild	Mild	Mild	Mild

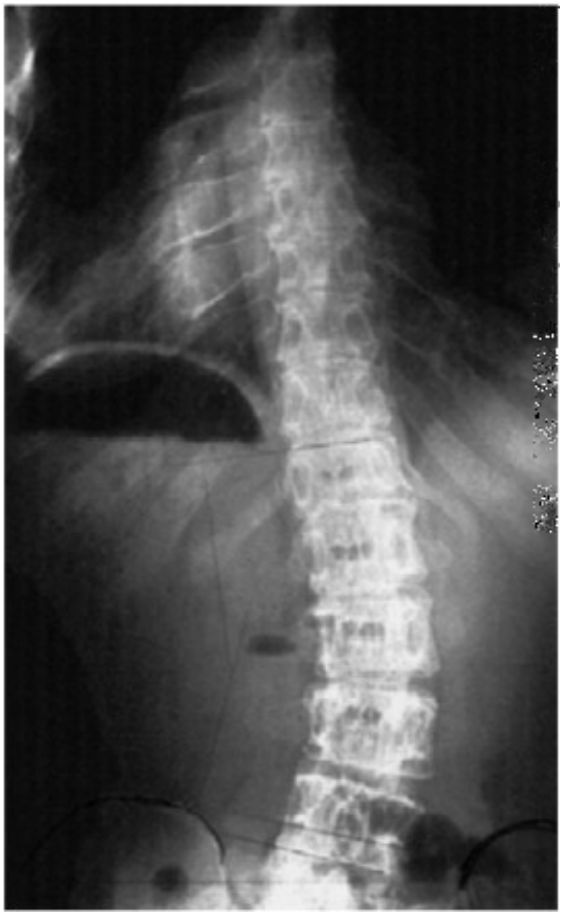
Deferiprone-related arthropathy







Thalassemia with right-sided lumbar scoliosis

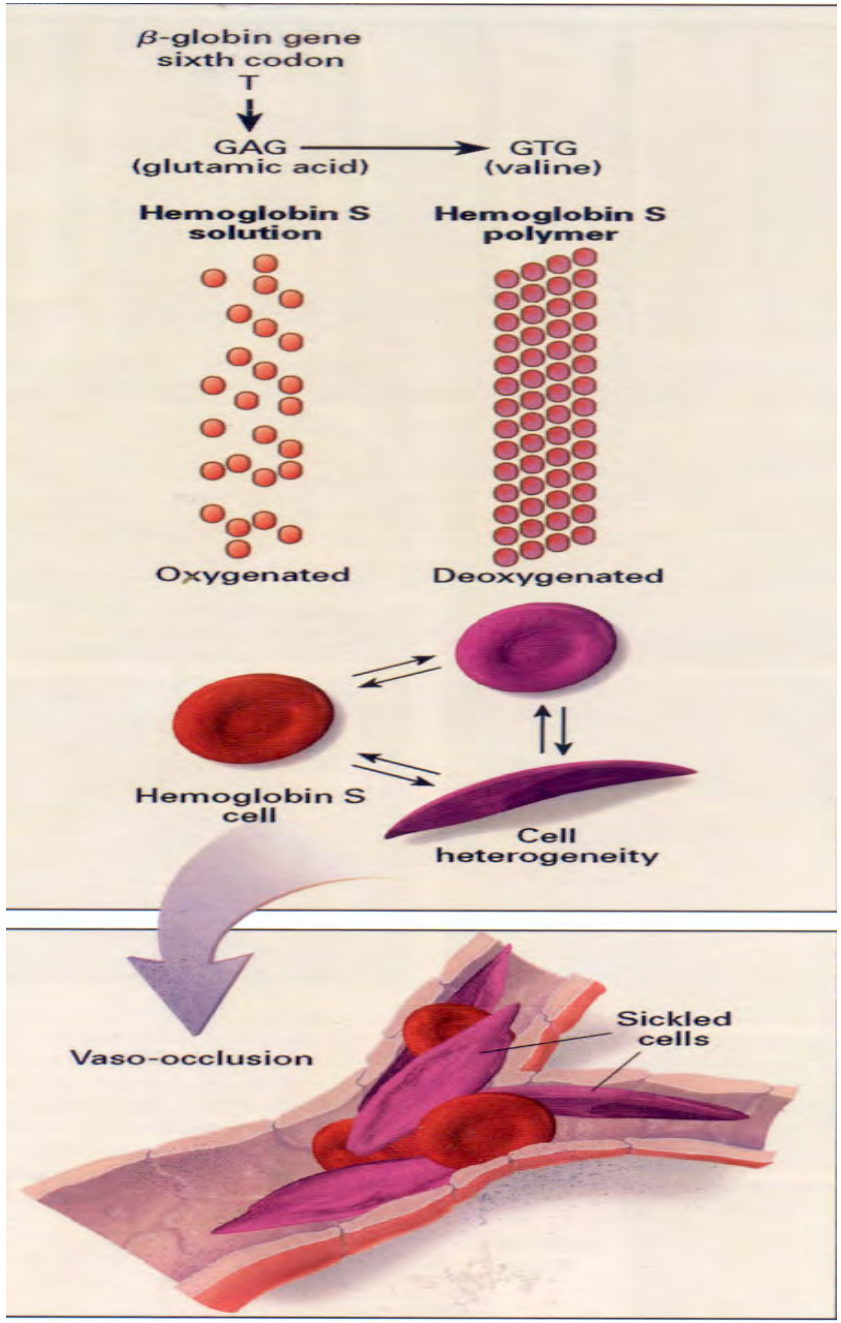


Sickle cell anemia

Normal Red blood cells hemoglobin are round and flexible.

Individuals with sickle cell disease, the abnormal hemoglobin forces the cells to lose their normally round and flexible shape, becoming distorted and rigid.

When viewed under a microscope, these abnormal cells may look like the C-shaped farm tool called a sickle.



Pathophysiology of sickle cell disease

β_6 Glu ⟶ Val

Deoxy Hb S polymer forms with low O_2, depends on Hgb S concentration, low pH, high temperature, high 2,3-DPG

Under a variety of circumstances, different organs are susceptible:

spleen, renal medulla (papillary necrosis), & many other complications

Pathophysiology

- Red cells:
  - Shape change
  - Extracellular exposure of protein and glycolipids
  - Aberrant expression of adhesion molecules on stressed reticulocytes
- Activated endothelial cells
- Adherent leukocytes
- Multiple adhesion pathways involved

Complications from Sickle Cell Disease

- Chronic hemolytic anemia
- Acute splenic sequestration-spleen traps RBCs
- Aplastic crisis-bone marrow stops making RBCs
- Painful crises (bones and chest)
- Bacterial infections (children)
- Acute chest syndrome (children)
- Kidney failure
- Gallbladder stones and inflammation
- Avascular necrosis
- Pulmonary hypertension
- Stroke (children)

Acute bone problems in sickle cell disease

Vaso-occlusive crises
Dactylitis
Stress fracture
Vertebral collapse
Orbital compression syndrome
Bone marrow necrosis
Osteomyelitis

Sickle Cell Anemia Vaso-occlusive Events (Pain Crisis)

- Precipitating factors
  - Hypoxia
  - Acidosis
  - Fever
  - Infection
  - Dehydration
  - Exposure to cold
- Perceived factors
  - Exposure to cold 34%
  - Emotional stress 10%
  - Physical exertion 7%
  - Pregnancy 5%
  - Alcohol consumption 4%
  - Not identified 40%

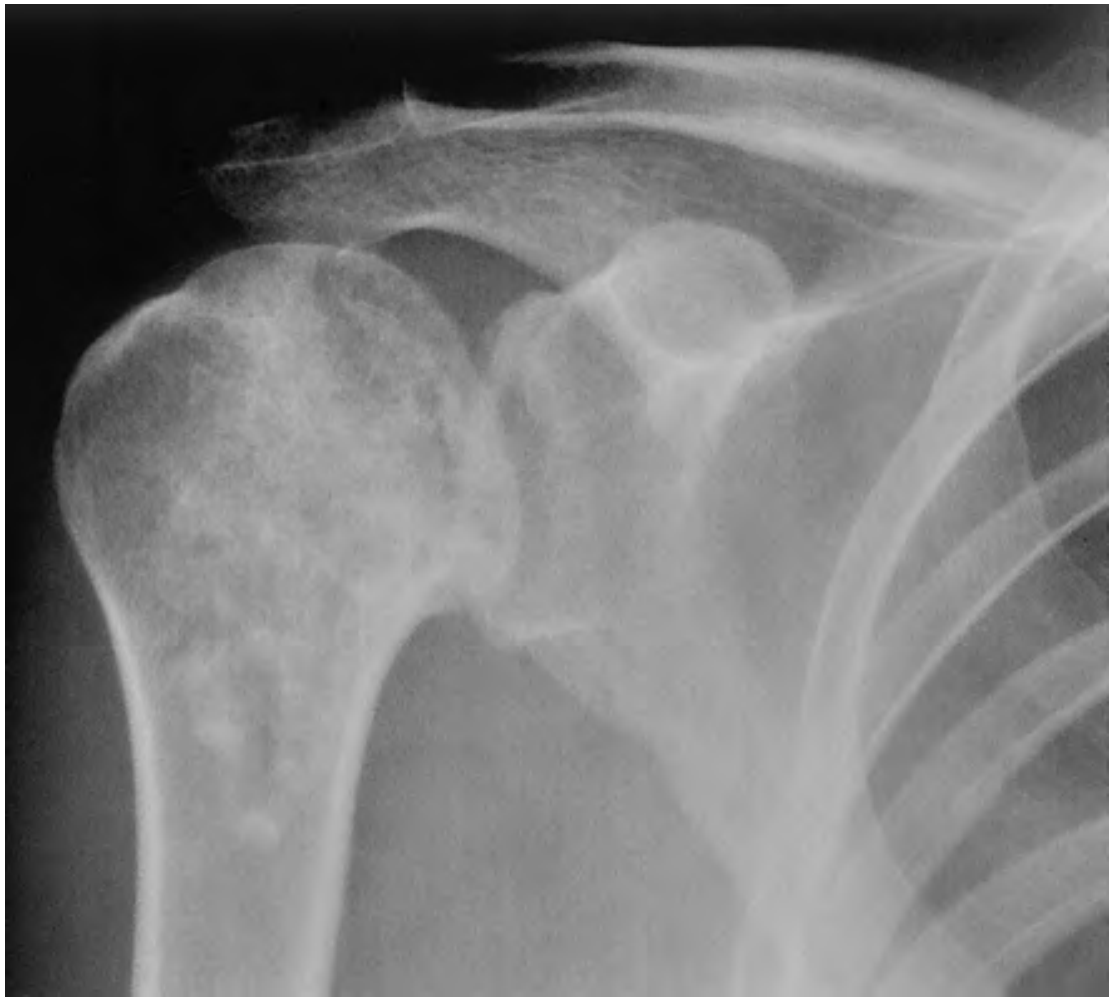
Sergeant, G. et al., Brit J. Haemat 1994: 87;586.

Sites of vaso-occlusive pain

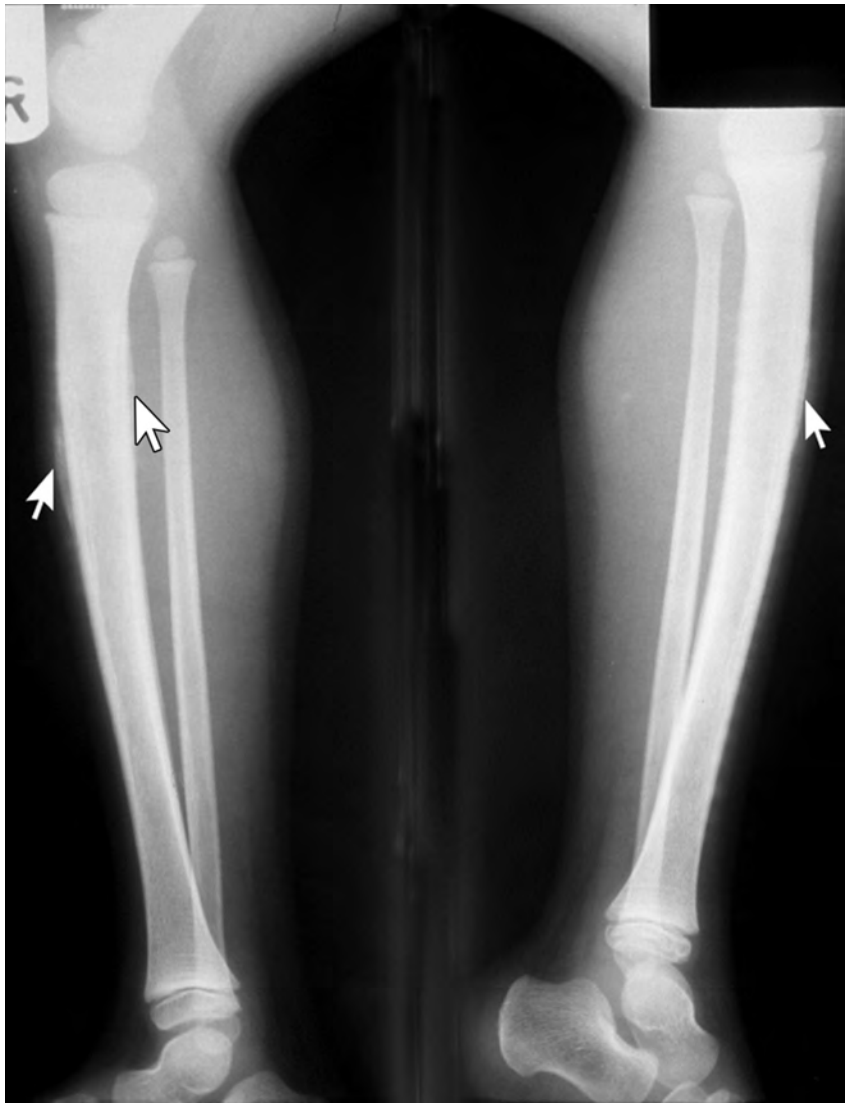
n= 183

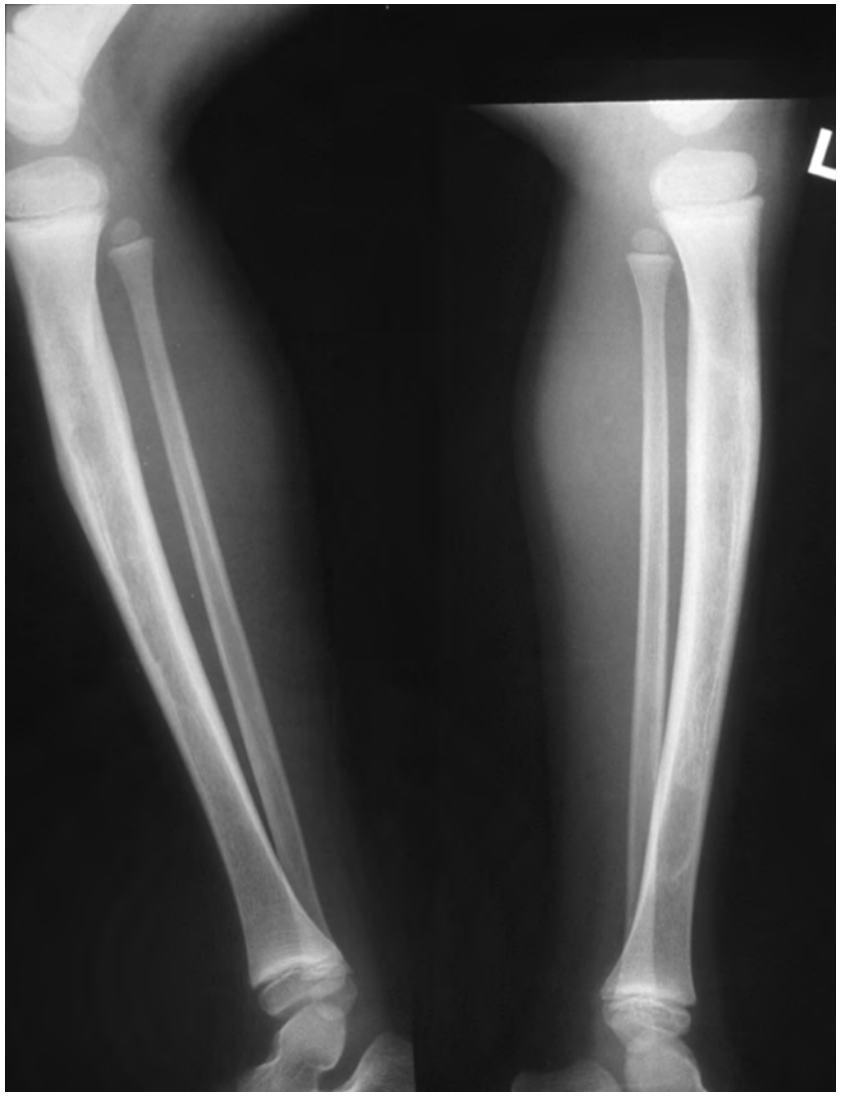
Site	Frequency	Bilateral
Lumbar spine	49%	
Abdominal pain	32%	
Femur	30%	28%
Knees	21%	68%
Sternum	18%	
Ribs	18%	47%
Shoulder	18%	53%
Elbows	17%	45%
Tibia/fibula	15%	57%
Humerus	12%	44%
Thoracic spine	12%	
Hips	11%	48%
“All over”	1%	

Medullary bone infarcts in SCA

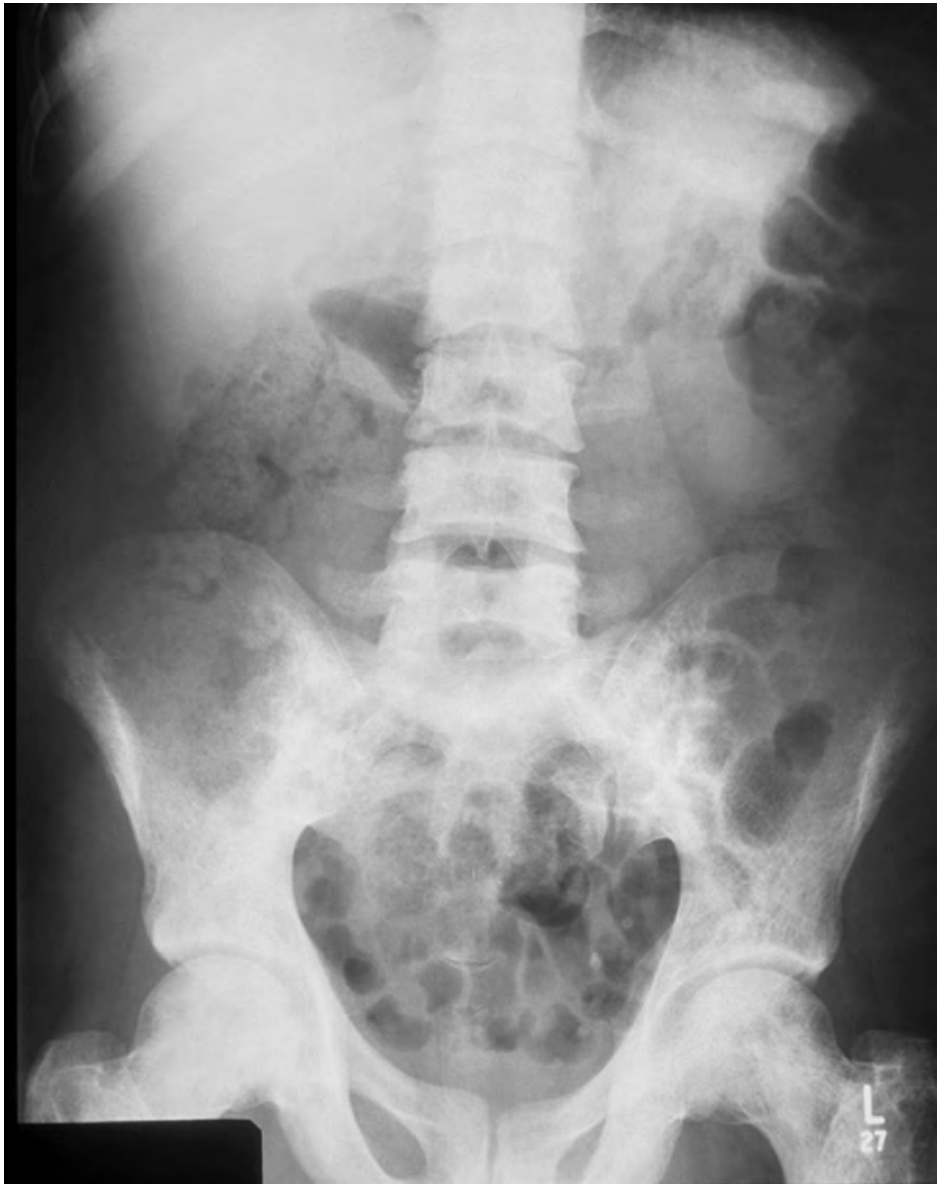


Bone infarction of the tibial diaphyses

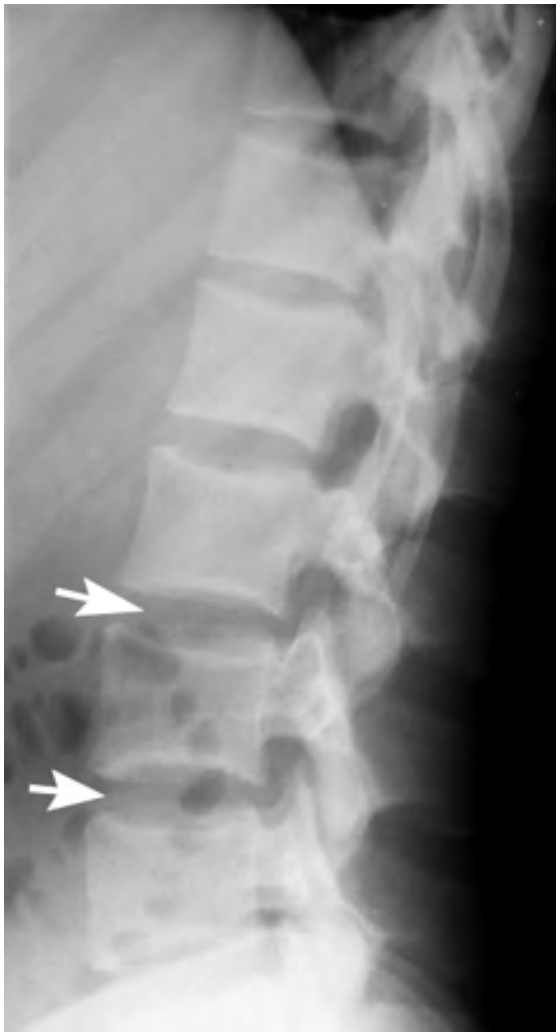




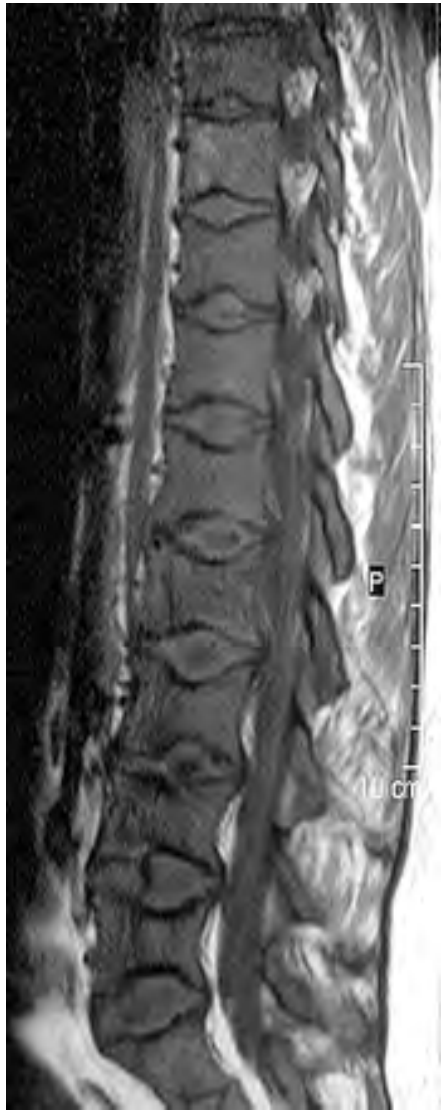
Increased bone density



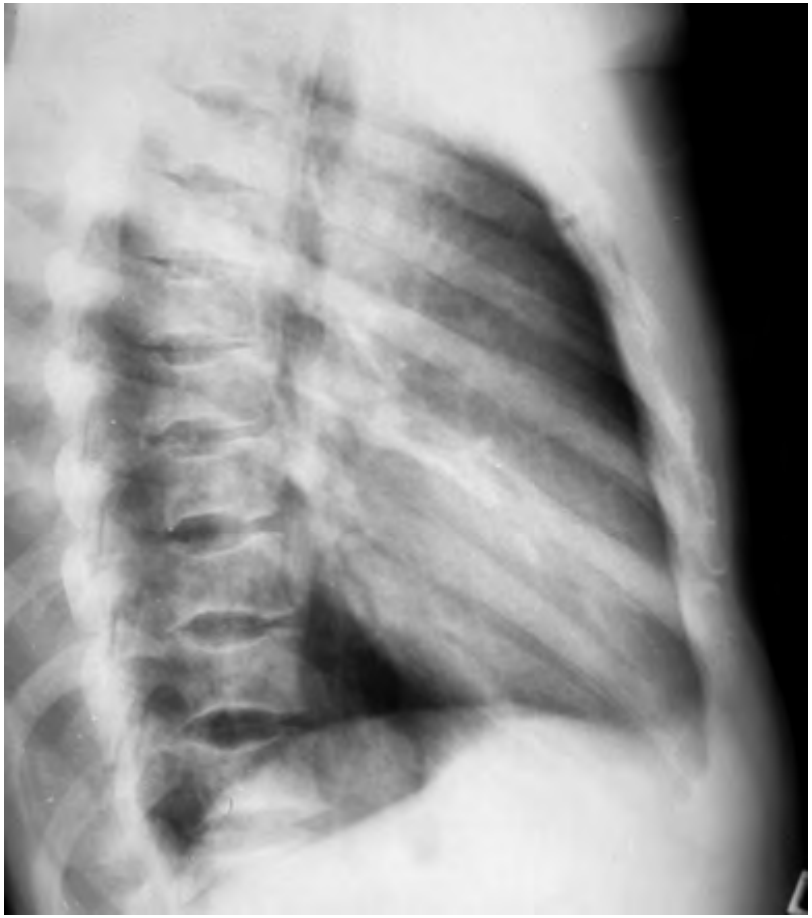
Fish-mouth vertebral deformities



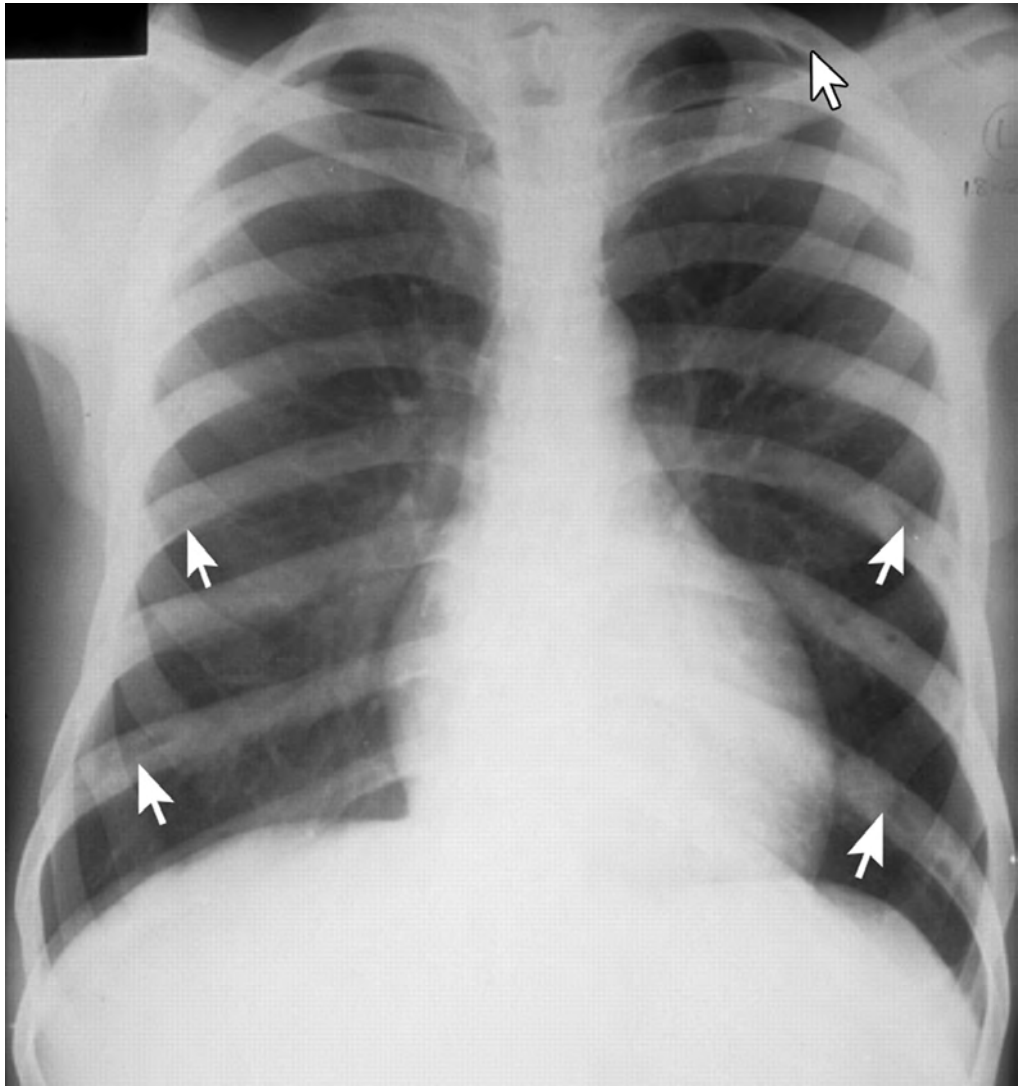
Vertebral end-plate concavity



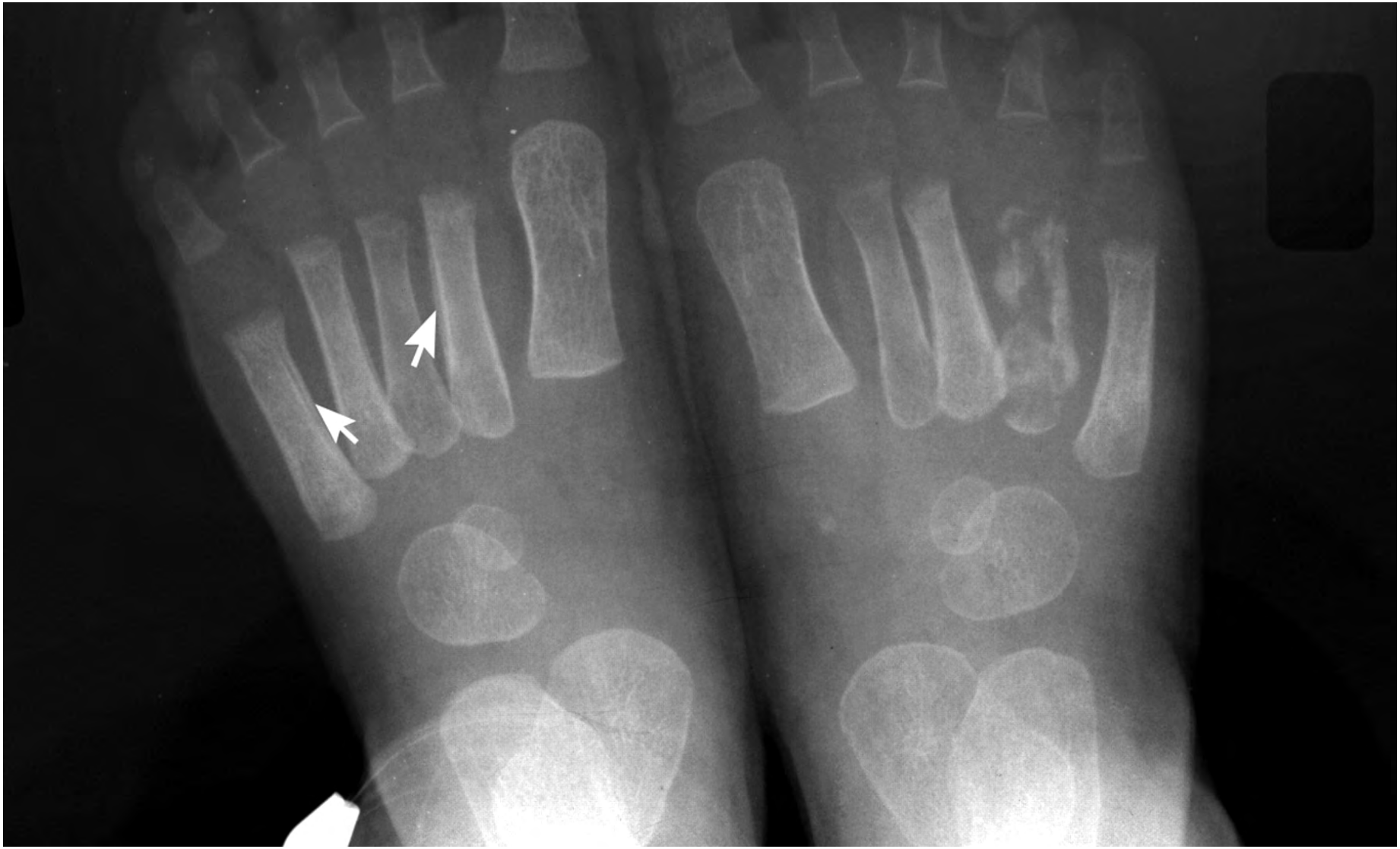
H-shaped vertebral deformity



Multiple rib infarctions



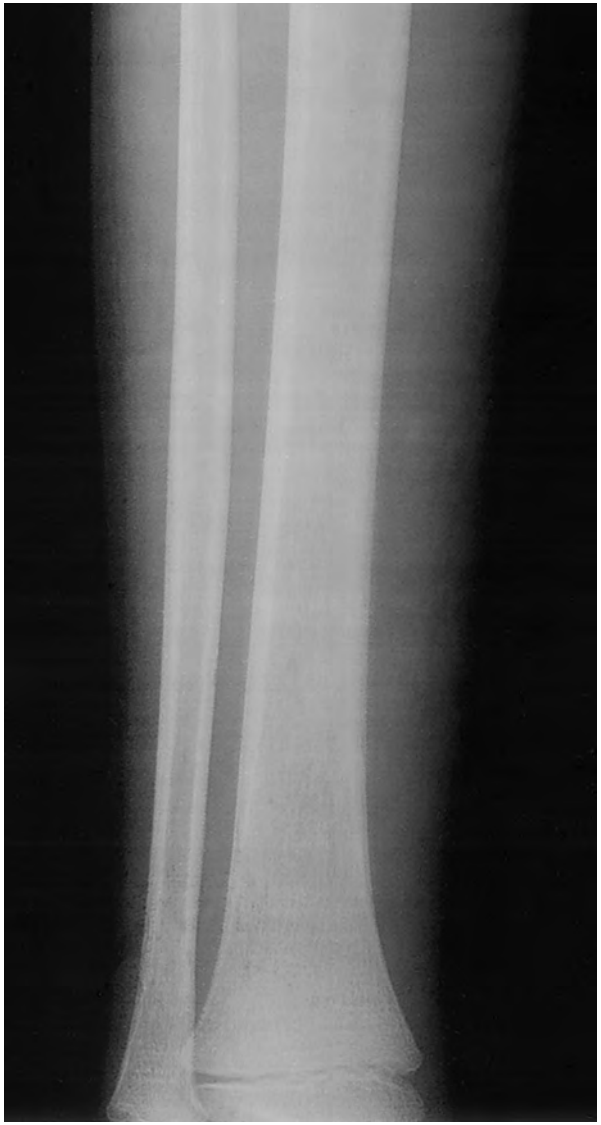
Dactylitis in the feet

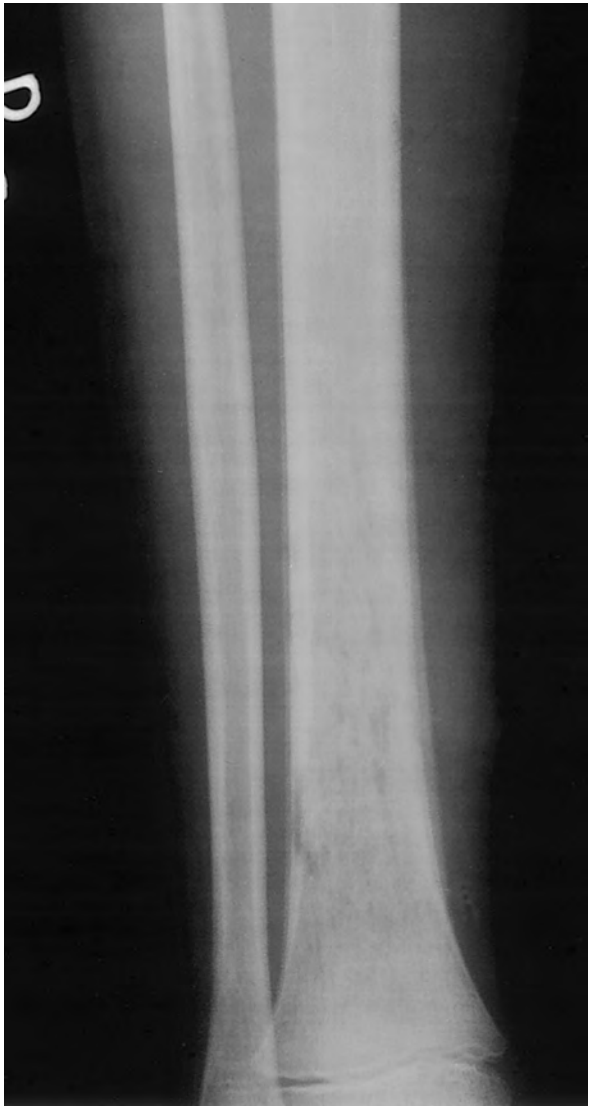


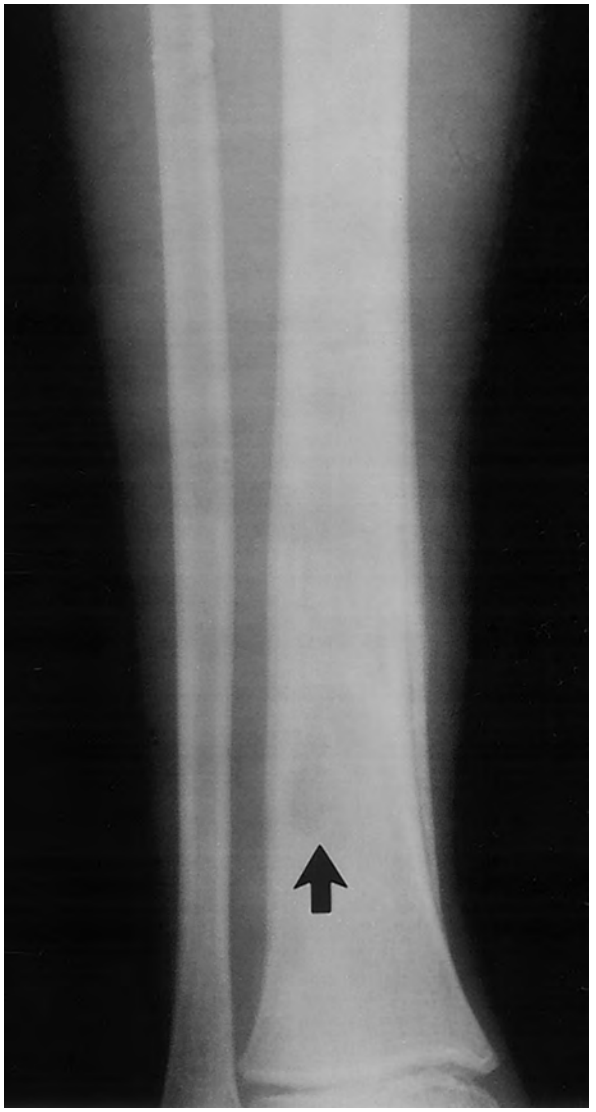
Infectious complications of Sickle cell anemia

- Related to absent spleen
  - Pneumococcus infections
  - Hemophilus infections
  - Dramatically improved with the use of prophylactic penicillin in childhood
- Related to frequent instrumentation
  - Staphyloccocal infections
- Related to tissue infarction
  - Osteomyelitis

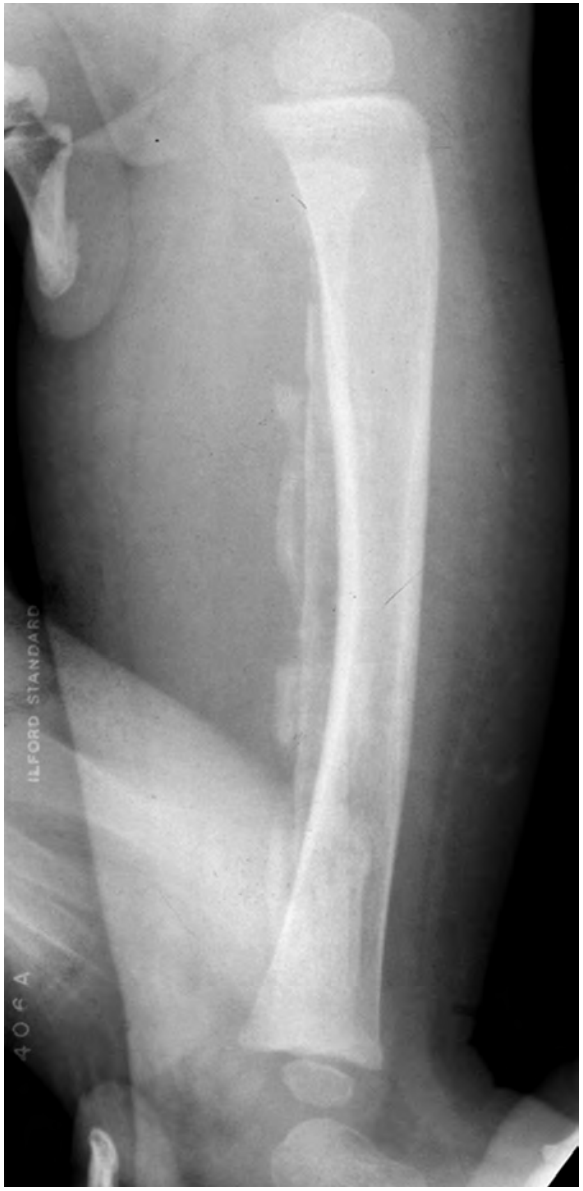
Salmonella osteomyelitis

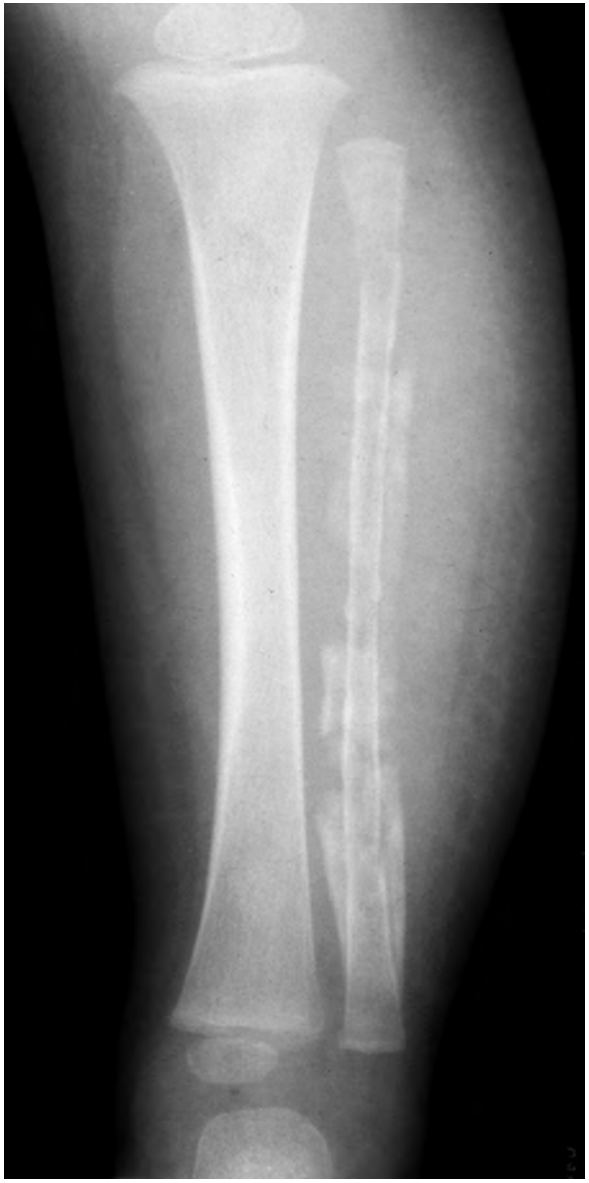




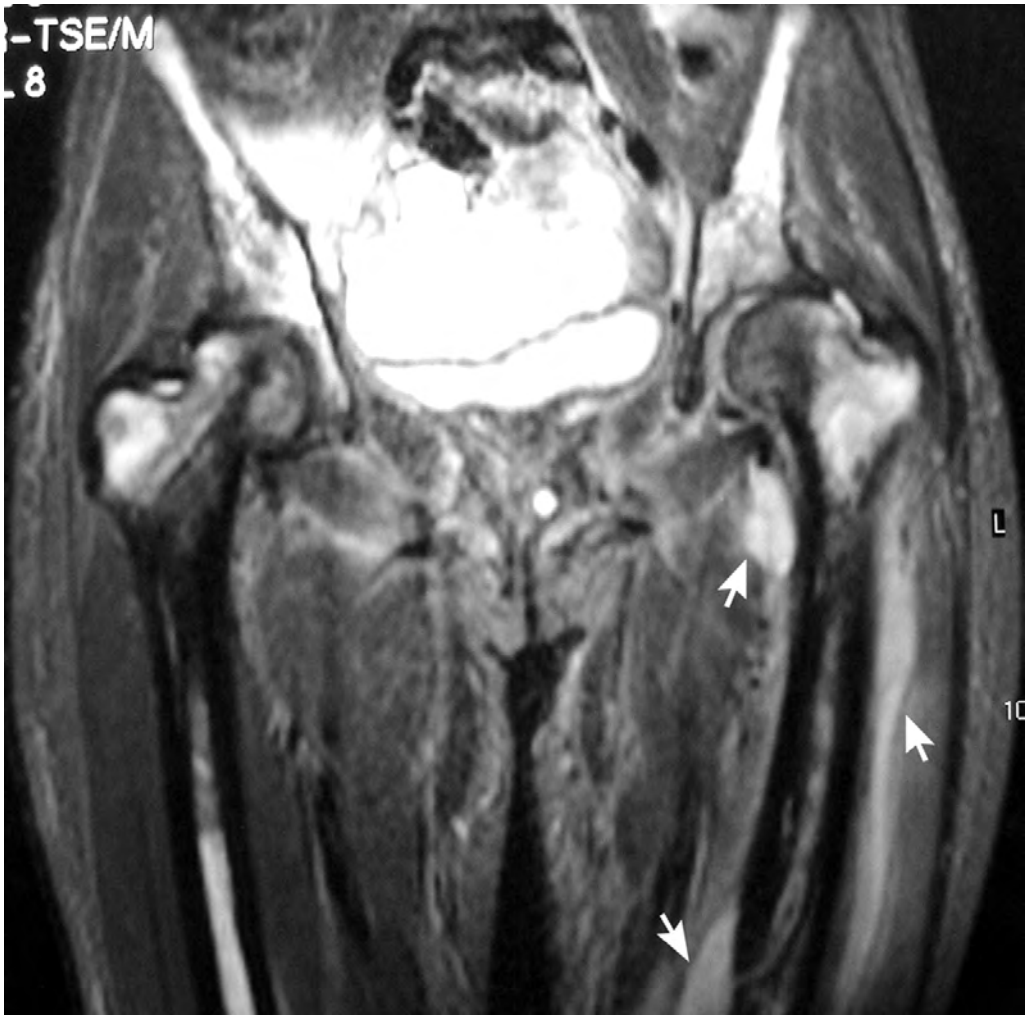


Chronic osteomyelitis





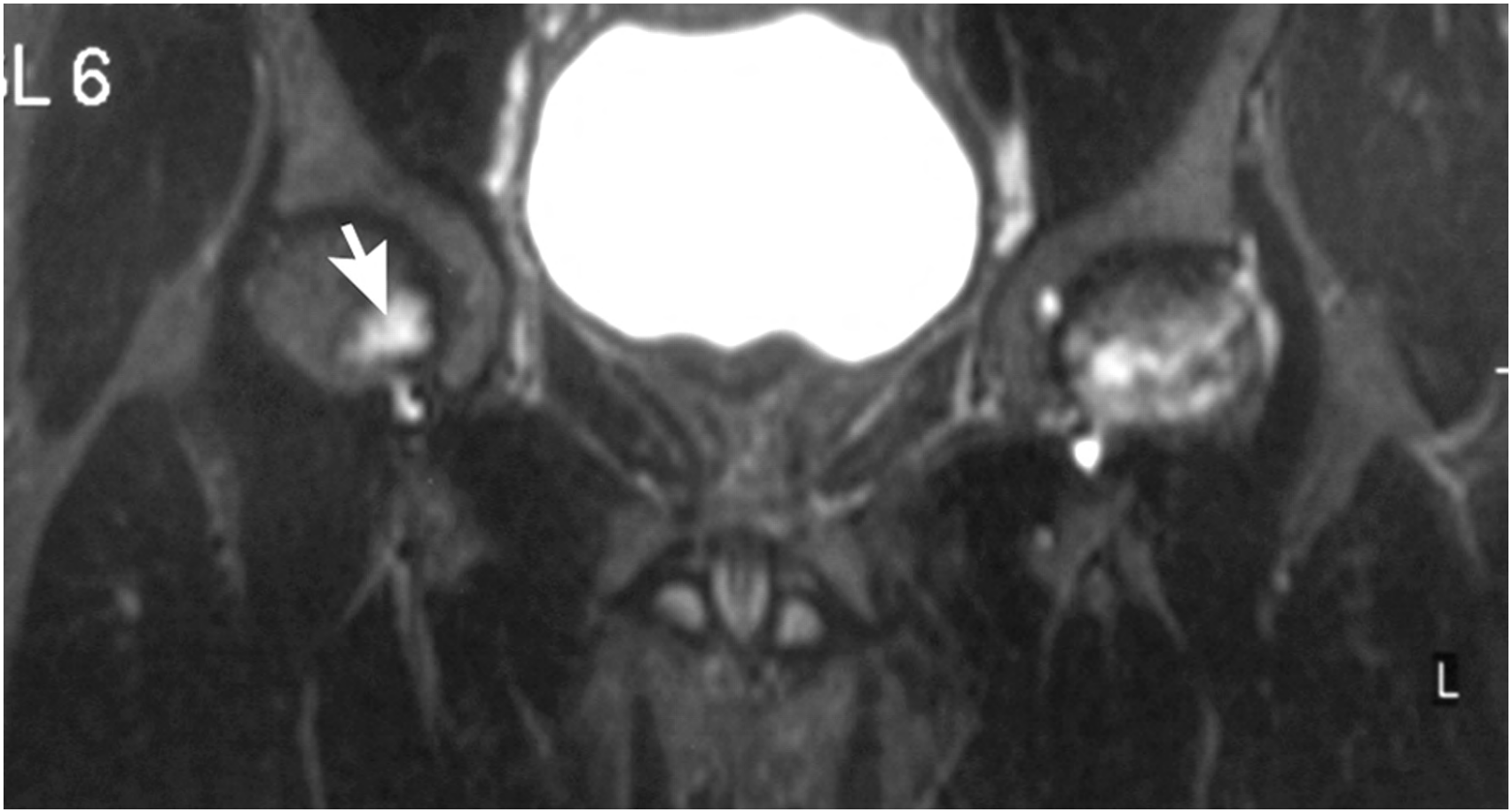
Chronic osteomyelitis in a 19-year-old woman with known homozygous sickle cell disease



Chronic bone problems in sickle cell disease

Osteonecrosis
Osteoporosis
Impaired growth
Chronic arthritis

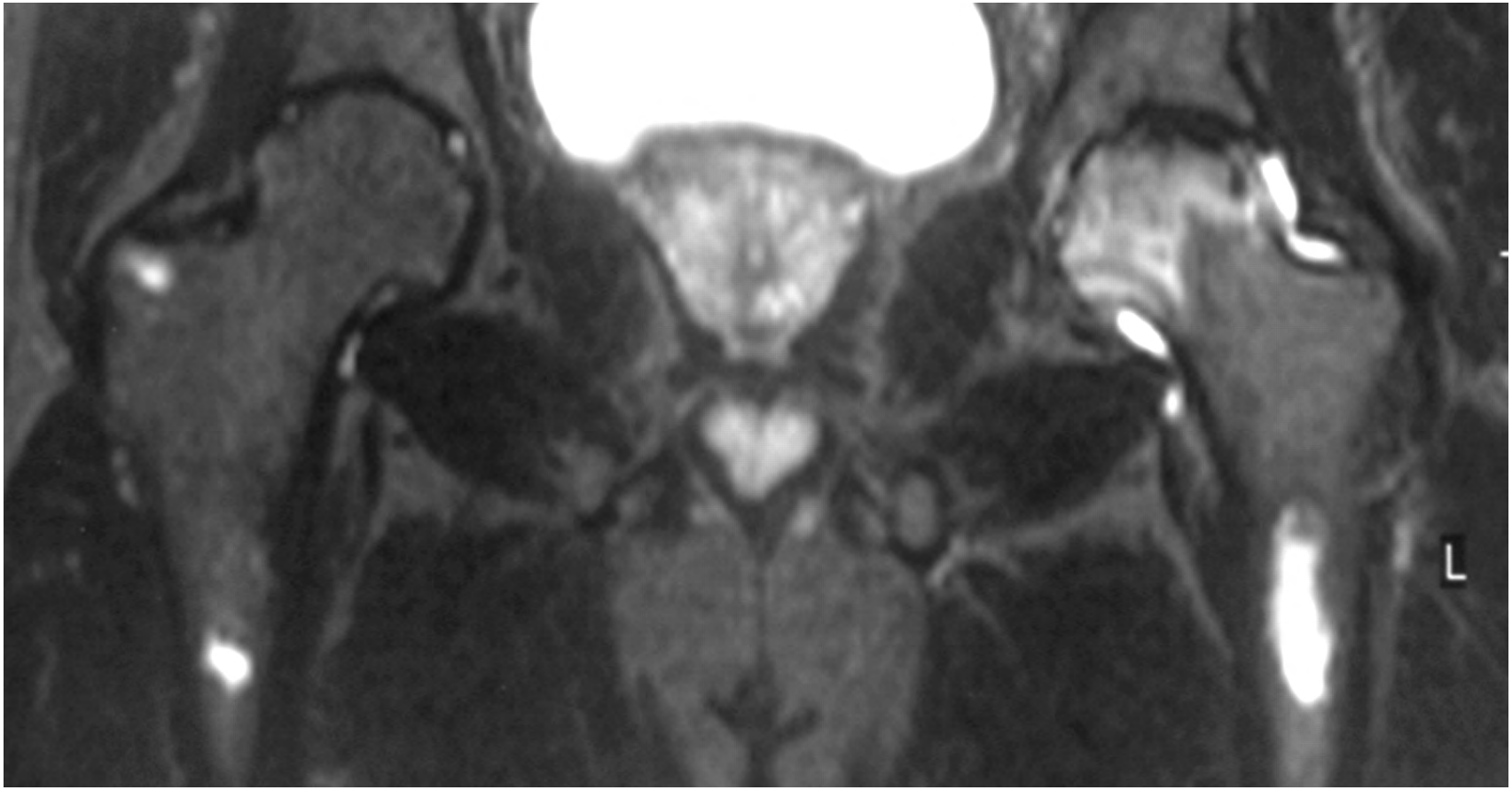
Figure 14b. (a) Anteroposterior radiograph obtained in a 44-year-old man shows stage IV avascular necrosis in the left hip and a normal right hip.



Ejindu V C et al. Radiographics 2007;27:1005-1021

RadioGraphics

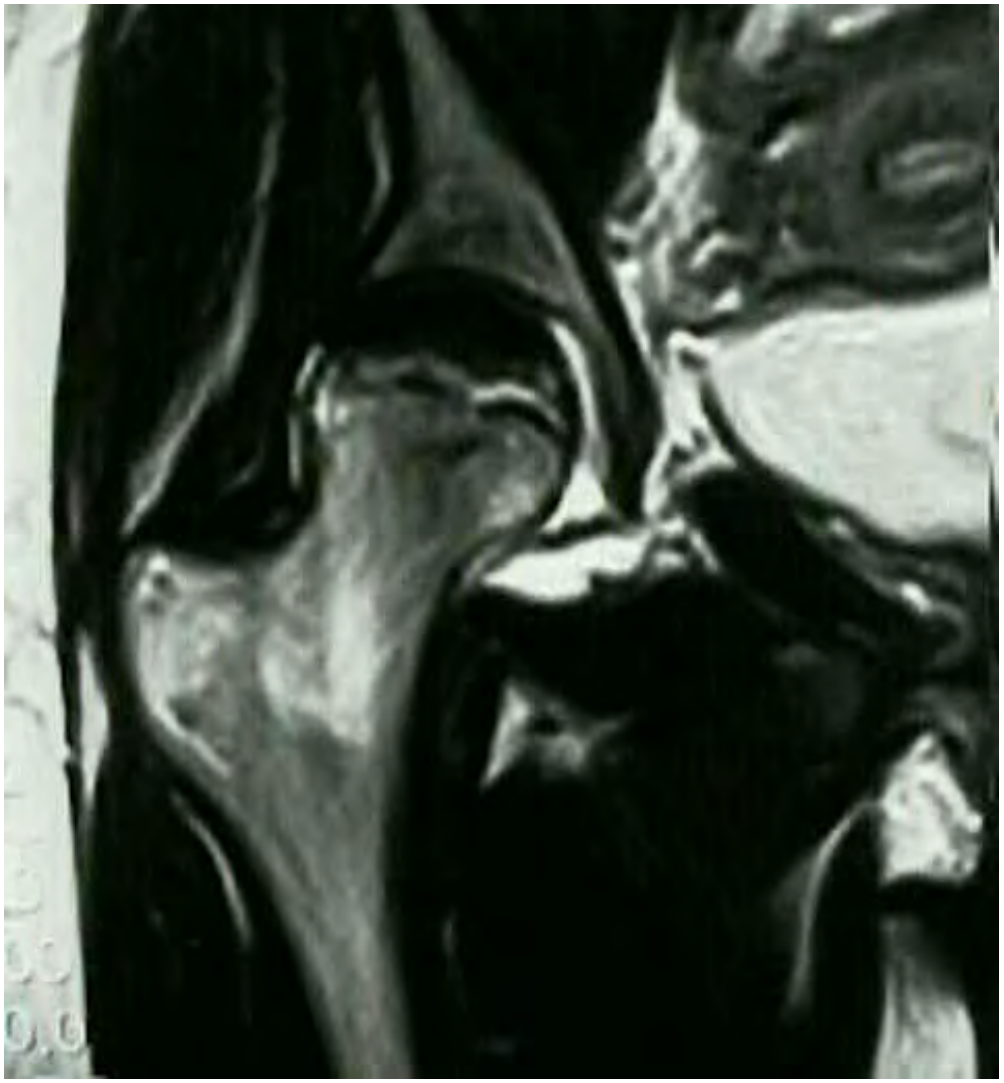
Figure 14c. (a) Anteroposterior radiograph obtained in a 44-year-old man shows stage IV avascular necrosis in the left hip and a normal right hip.



Ejindu V C et al. Radiographics 2007;27:1005-1021

RadioGraphics

Osteonecrosis of the femoral head



Hemophilia

- A hereditary disorder transmitted by the female to the male. These patients have a severe deficiency in blood clotting.
- Bleeding can occur spontaneously, after minor injury, or during a medical procedure, such as intravenous insertion.
- Bleeding can occur anywhere in the body, but bleeding into joints, deep muscles, urinary tract, and intracranial sites are the most common.

Types of Bleeding Disorders

- Hemophilia A (factor VIII deficiency)
- Hemophilia B (factor IX deficiency)

Incidence

- Hemophilia A: 1:5000 male births
- Hemophilia B: 1:30,000 male births

Type and Severity

- Normal factor VIII or IX level 50-150%
- Mild hemophilia
  - factor VIII or IX level 5-50%
- Moderate hemophilia
  - factor VIII or IX level 1-5%
- Severe hemophilia
  - factor VIII or IX level <1%

Types of Bleeds

- Joint bleeding - hemarthrosis
- Muscle hemorrhage
- Soft tissue
- Life threatening-bleeding
- Other common bleeding

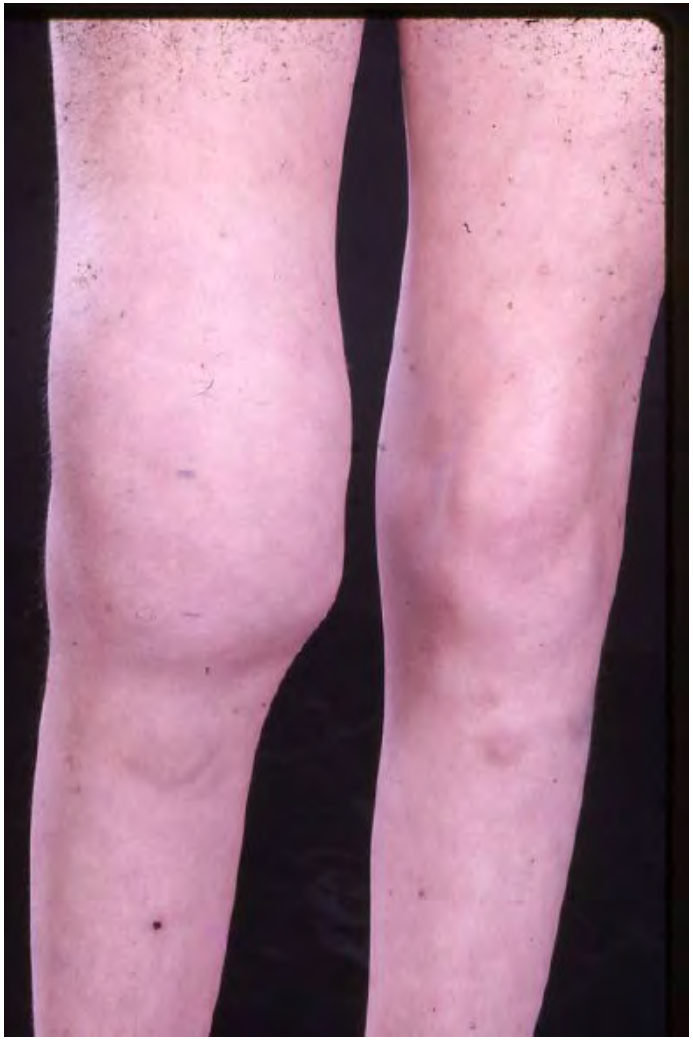
First Bleed/Diagnosis

- Mild
  - Often has bleeds at an earlier age but not identified till later in life, 3 to 14 years or older
- Moderate
  - usually before 2 years
- Severe
  - within first year

Joint Bleeds

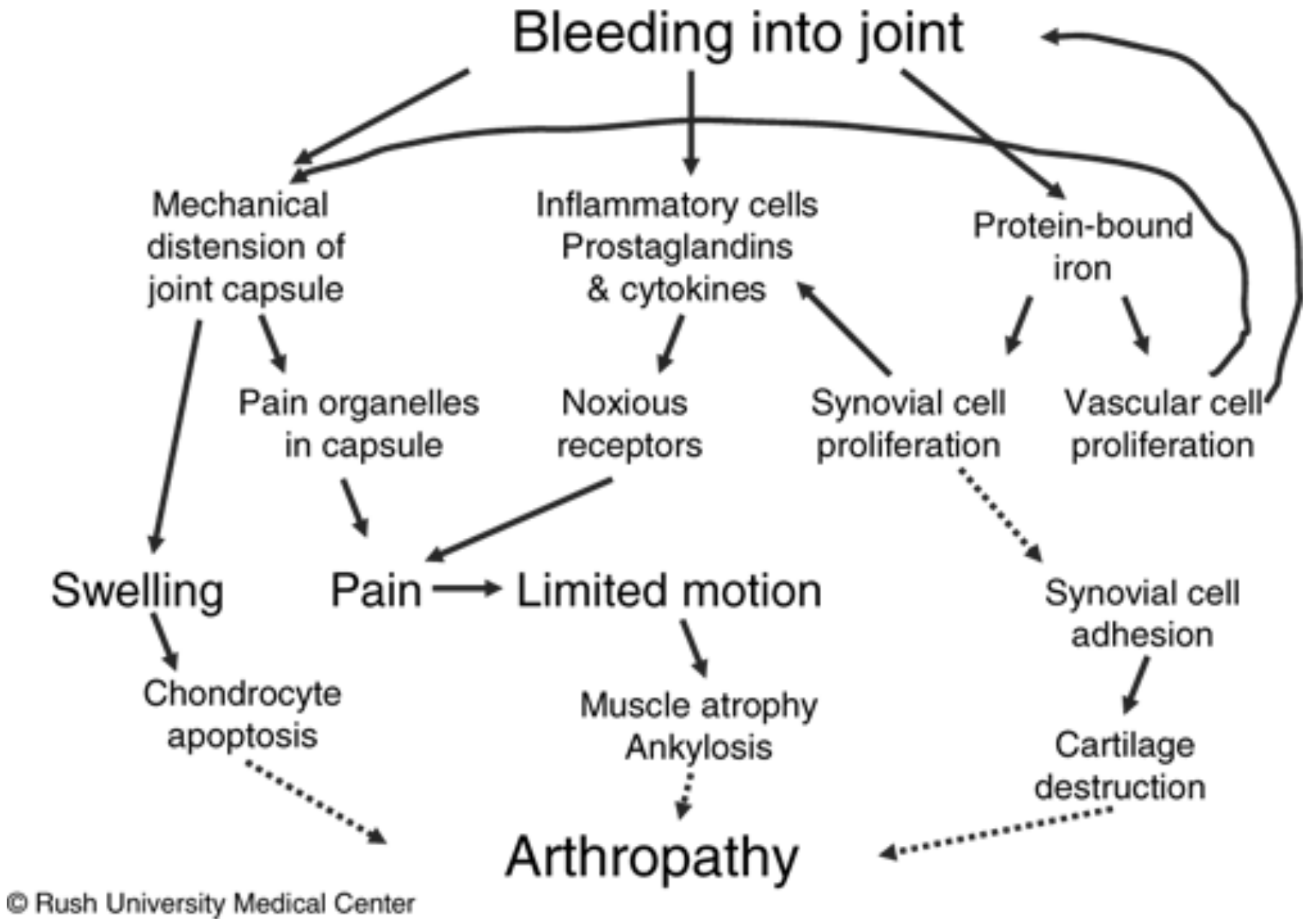
- Most common bleeding manifestation
- Most common joint Knees, Ankles, Elbows
- Collection of blood in joint space may cause joint to feel hot
- Initial symptoms of “tingling” or “bubbling” sensation
- Early sign: reluctance to move, swelling and joint pain as bleeding progresses
- Affected joint held in flexed position
- Usually no visible cutaneous bruising
- Treat with replacement factor, rest, ice,compression and immobilization

Joint Bleeds



Complications Joint Bleeds

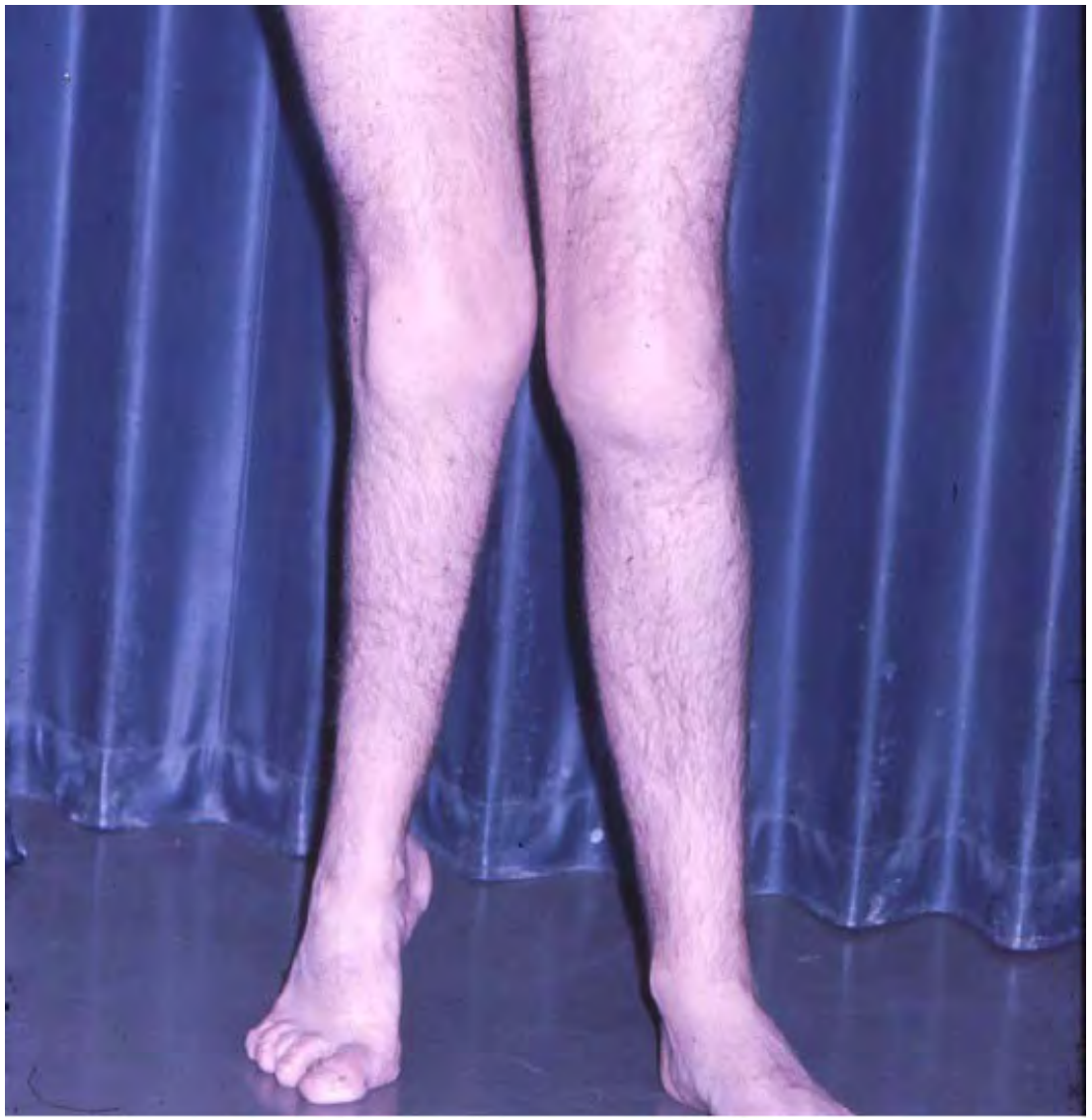
- Flexion contractures
- Joint arthritis / arthropathy
- Chronic pain
- Muscle atrophy



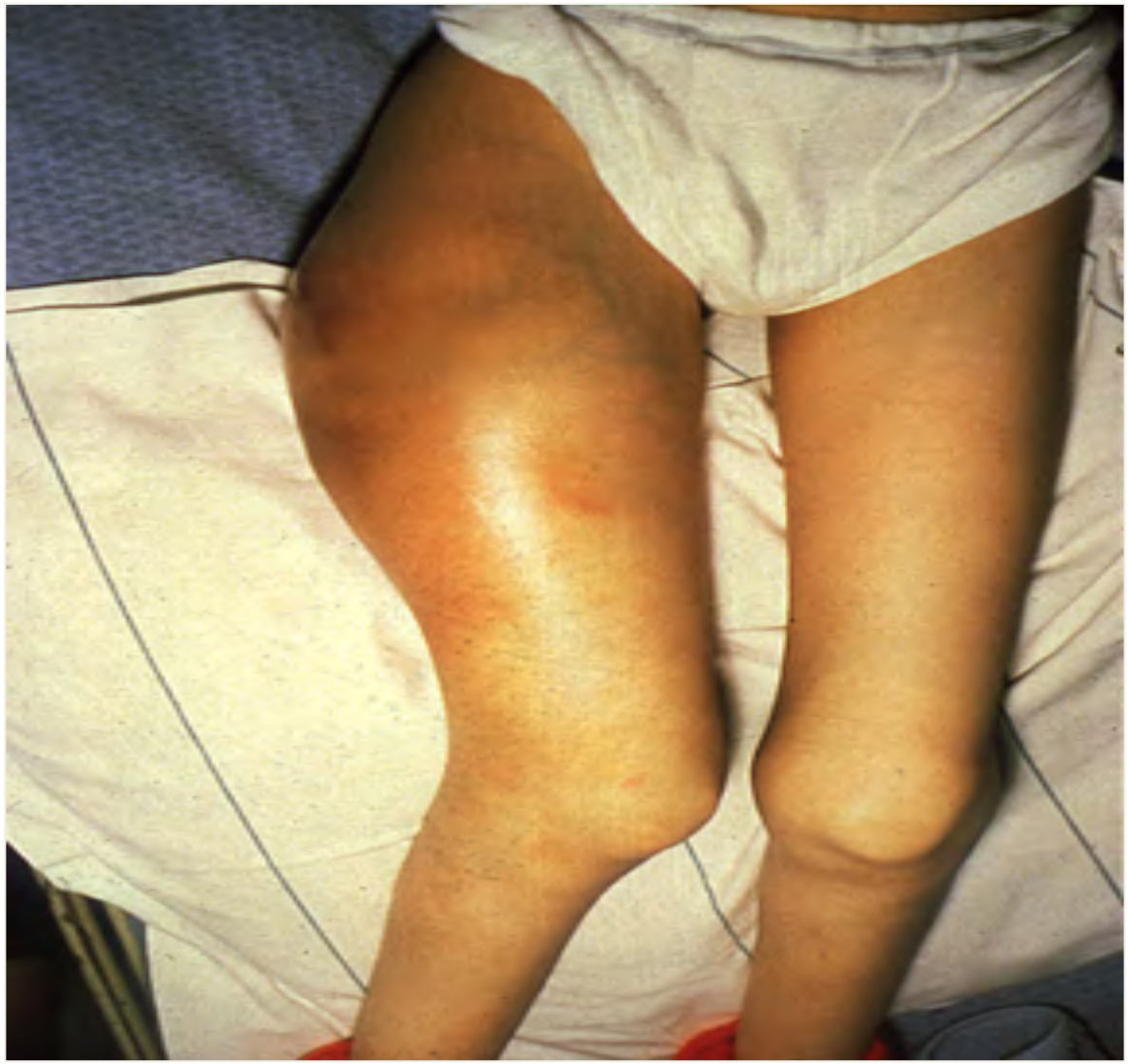
Background

- Mod-severe hemophiliacs develop 1st bleed as young as 2-5 years old
- Followed by hemarthrosis-synovitis-hemarthrosis cycle
  - Fe deposition → synovitis→ hypertrophy
  - Rich vascularization → rebleed ⇒ **Target joint**
- Target joint
  - Reduced range of motion
  - Muscle atrophy
  - Cumulative joint deformity

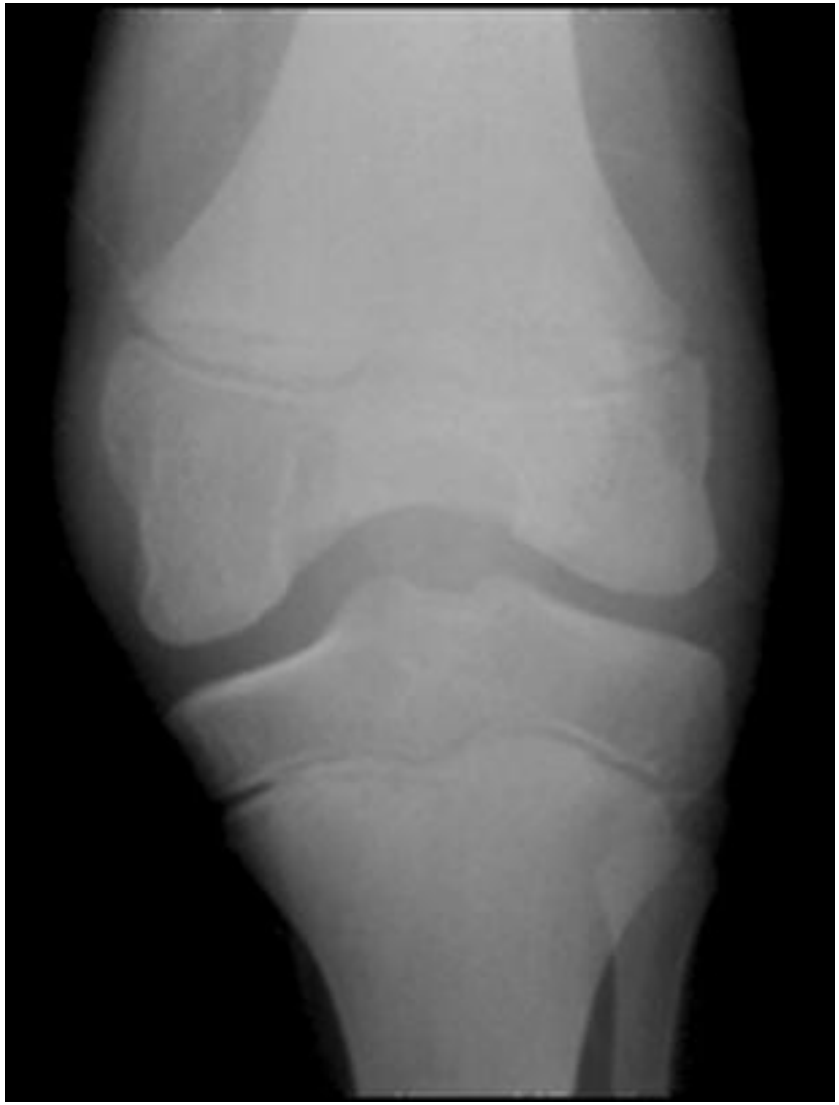
Hemophilic arthropathy



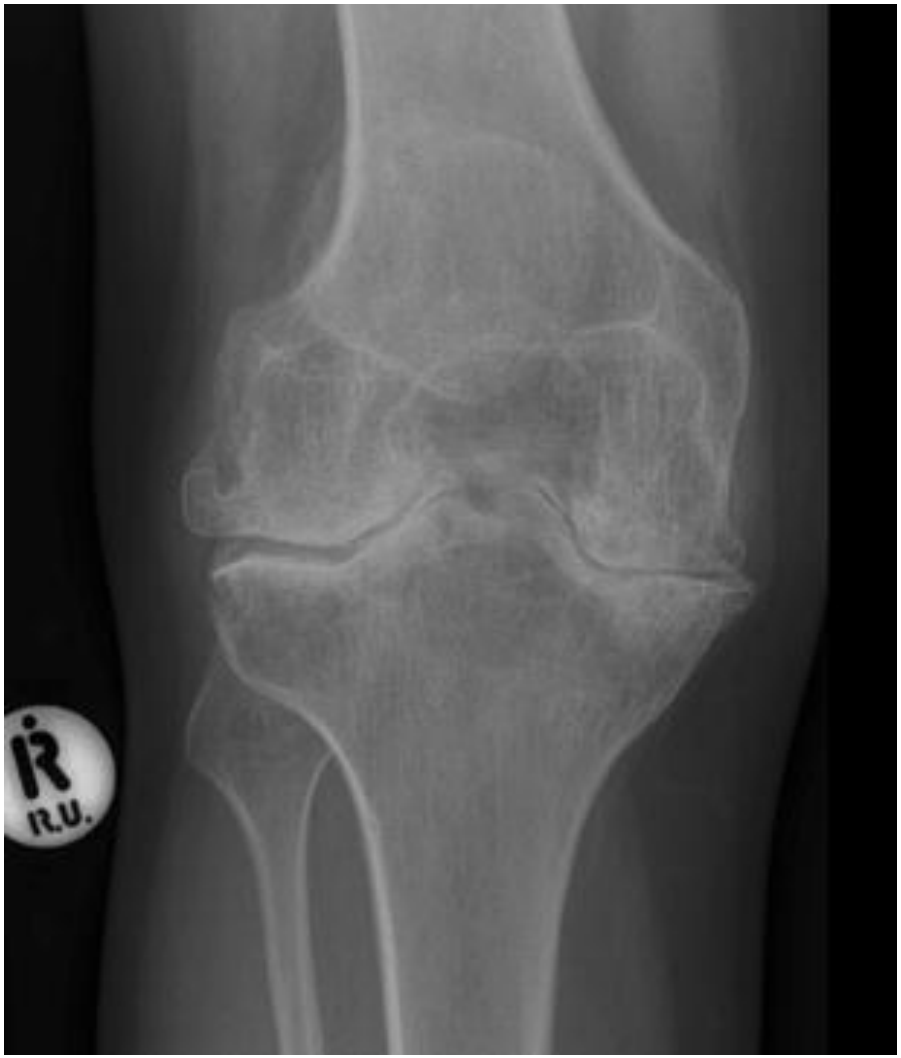
Advanced joint and muscle bleed



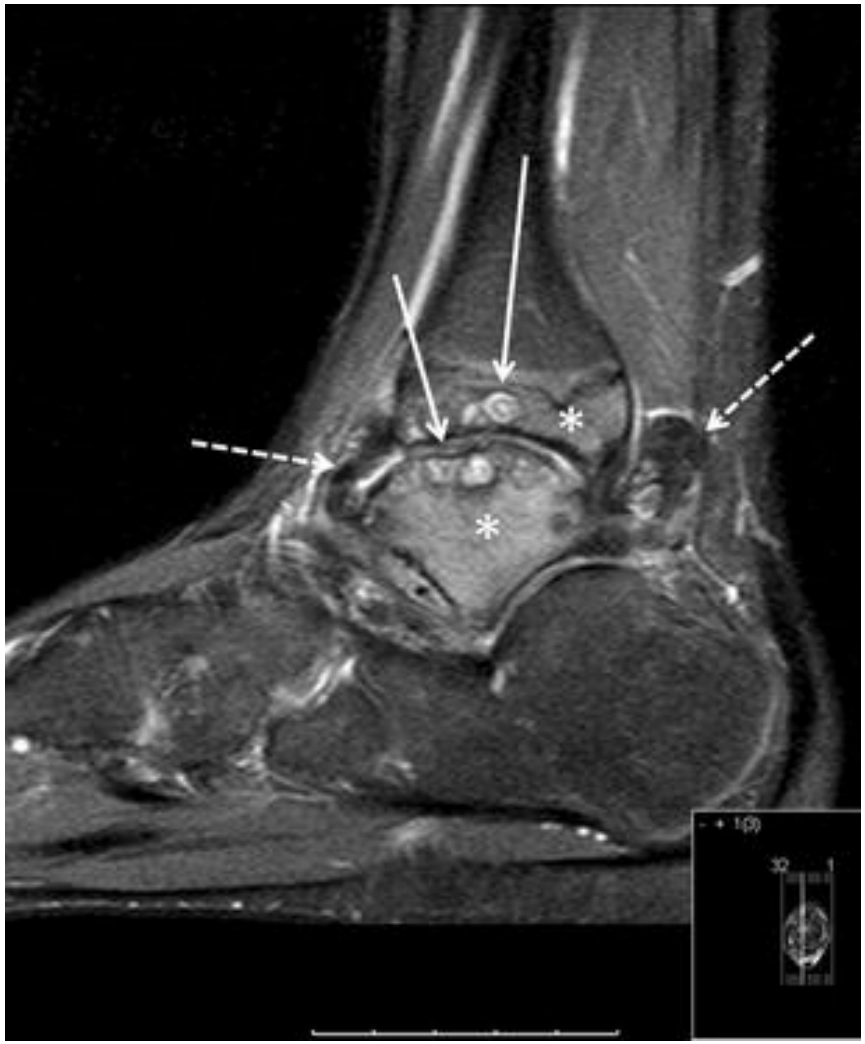
Hemophilic arthropathy in an 11-year-old boy with repetitive hemarthrosis

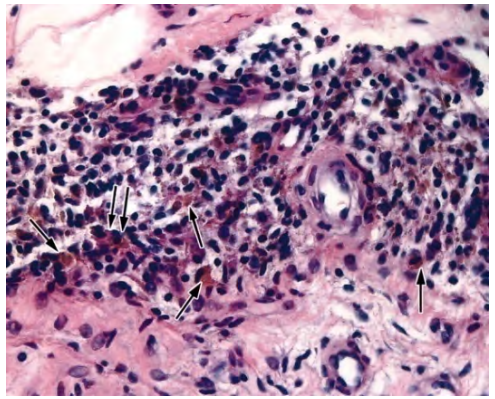


Hemophilic arthropathy

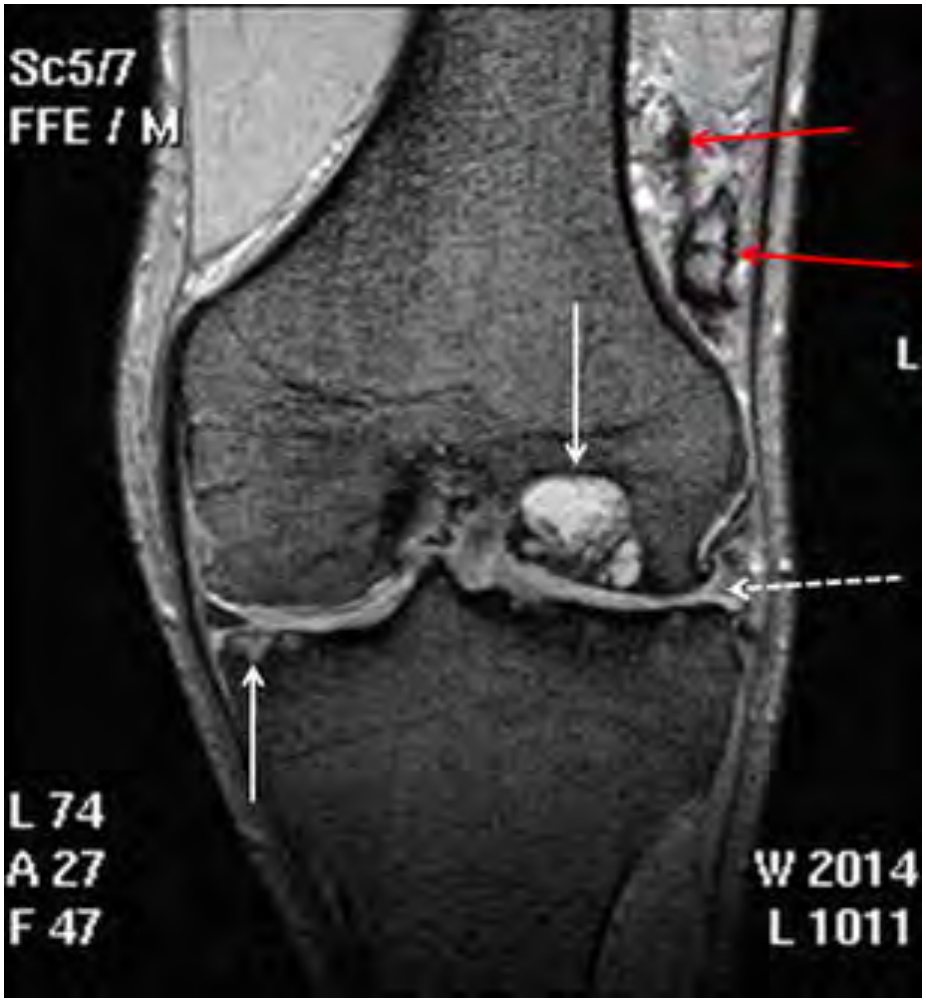


Hemophilic arthropathy

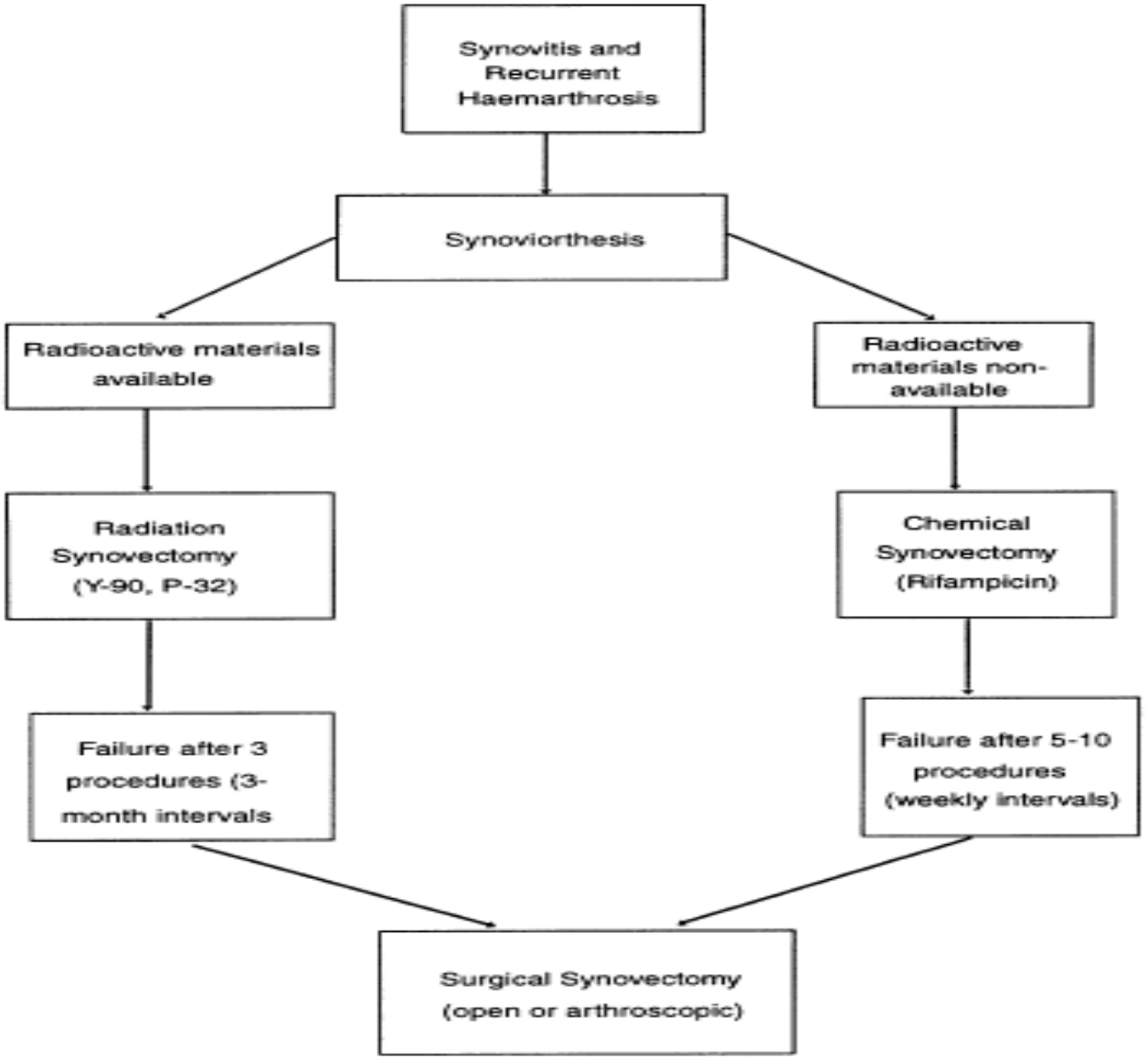




Chronic hemophilic arthropathy of the knee in a 35-year-old man with hemophilia A



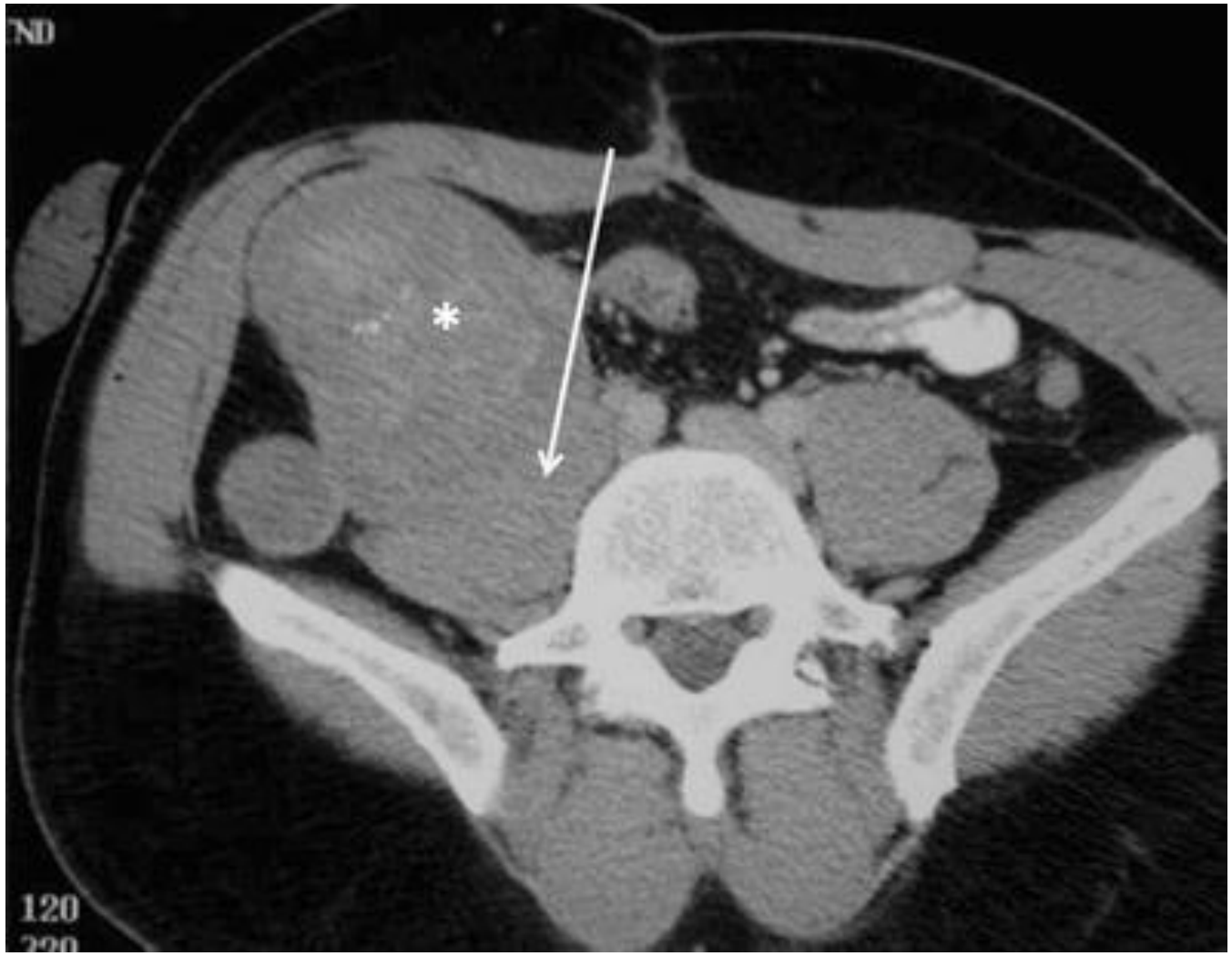
Treatment Algorithm for Hemophiliac



Muscle Bleeding

- Second common bleeding manifestation
- Bleeding leg, thigh, calf, forearm, and groin create pressure on nerves
- Early sign: reluctance to move, swelling and pain as bleeding progresses
- Affected extremity held in flexed position
- Usually no visible cutaneous bruising
- Treat with replacement factor, rest, ice , compression and immobilization

Muscle Bleeding



Complications Muscle Bleeds

- Compartment syndrome
- Neurologic impairment