

# Hyperostosis - an unusual radiographic presentation of Myelodysplastic Syndrome transformed to Acute Myeloid Leukemia

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## ABSTRACT

Acute myeloid leukemia (AML) is also referred to non-lymphocytic leukemia in the literature. It comprises about 15% of the childhood leukemia. There are multiple subtypes of AML from M0-M7 with approximately 45% of the cases being M0-M2 and the remaining subtypes being rare. The definitive diagnosis relies on bone marrow biopsy showing bone marrow infiltration with leukemic cells. We describe a rare radiographic presentation of myelodysplastic syndrome (MDS) transformed to AML in an 8 month old boy who presented with a orbital wall fracture, periosteal reaction, and mixed lytic and sclerotic lesions.

## CASE REPORT

### CASE REPORT

An 8-month-old boy was admitted with a 1-week history of left proptosis and periorbital swelling, low-grade fever, and increased fussiness. On physical exam, there was proptosis of the left eye and periorbital swelling. The infant had increased fussiness and irritability upon palpation of the mandible and long bones. There was a normal skin color and tone as well as normal abdominal girth. There were no signs of infection.

Laboratory profile revealed white blood count: 11.7 k/mm<sup>3</sup> (normal range 4.5-11 k/mm<sup>3</sup>), Hgb: 9.6 g/dL (normal range 10-15 g/dL), and Platelets: 87 k/mm<sup>3</sup> (normal range 150-400 k/mm<sup>3</sup>). Differential white count was normal. Red cells showed mild anisopoikilocytosis with tear drop cells. Spherocytes and schistocytes were not seen. White blood cells showed dysplastic neutrophils, and hypogranular and hyposegmented neutrophils were present. Blasts were increased ~8 % and morphologically resembled myeloblasts.

Mild thrombocytopenia was seen and platelets were of variable size and shape.

Facial computerized tomography demonstrated heterogeneous appearance of the osseous structures. There was bony expansion and increased bony density in the facial bones and the skull, consistent with hyperostosis. There was a soft-tissue mass-like density in the floor of the left orbit with fracture of the inferior left orbital wall (Figure 1). Initially this soft tissue density was thought to represent intraorbital hematoma due to the proximity to the fracture; however, later with the diagnosis of acute myeloid leukemia it was assumed that the mass-like density represents chloroma.

A radiographic skeletal survey demonstrated hyperostosis of the orbital walls, maxillary and mandibular bones. There was soft tissue swelling around the mandible (Figure 2). There was diffuse hyperostosis of the spine, pubis, iliac, and ischial bones (Figure 3). Periosteal reaction of the proximal femur was noted bilaterally with a lytic lesion of the proximal left femoral metaphysis (Figure 4). Delayed bone scintigraphy

demonstrated increased activity of the radiotracer in the maxillary bone. Patchy increased activity was noted in the skull and other bony structures (Figure 5).

The bone marrow aspirate was hemodilute and showed left shifted granulopoiesis with maturation arrest. Blasts were increased (Figure 6) and constituted 20-25 % of cells (type 2 blasts). Eosinophilia was present and mild dysgranulopoiesis was noted. Eosinophilic myelocytes having basophilic granules were seen.

The bone marrow biopsy was 100% cellular. The marrow space was completely infiltrated by sheets of myeloblasts (Figure 7) with marked decrease in normal hematopoiesis. The blast cells had irregular nuclear contours and moderate amount of pale cytoplasm. Only a rare megakaryocyte was seen on scanning. By immunohistochemistry the blasts were positive for CD34 (Figure 8), CD117 and MPO. They were negative for CD68, lysozyme, TdT, Factor VIII, spectrin, CD79a, CD20, CD3, S100 and CD1a. Flow cytometry also showed a subpopulation (25%) of MPO positive blasts that coexpressed CD33 with CD34. 3 to 4+ reticulin fibrosis was present in the biopsy. Morphologic and immunophenotypic findings were consistent with acute myeloid leukemia (AML).

Accompanying myelodysplasia in both erythroid and granulocytic lineage and 4 + reticulin fibrosis suggests underlying myelodysplastic syndrome (MDS) with transformation to acute myeloid leukemia. Only de novo AML cases are French-American-British (FAB) subtyped. The morphology in this case favors acute myeloid leukemia -M2 since some degree of maturation was also seen.

Chromosome analysis and fluorescence in situ hybridization (FISH) demonstrated trisomy 10 only in the blasts. Most cases of trisomy 10 reported had megakaryoblastic leukemia; however, in our case, blasts were negative for Factor VIII and were positive only for MPO, CD34 and CD117.

The patient was treated by our pediatric hematologists with chemotherapy and achieved remission.

## DISCUSSION

In this report we describe an 8-month-old boy who presented with hyperostosis. He had bilateral periosteal reaction of both femora, a mixed sclerotic lesion of the proximal left femoral metaphysis, irregular and symmetric bony sclerosis of the facial and pelvic bones, mass-like fullness of the lower left orbit and a fracture of the left inferior orbital wall. Clinically the patient presented with fever and irritability. These presenting radiographic features are similar to previously described cases of acute megakaryoblastic leukemia (subtype M7) [1]. Few previous reports document destructive and lytic lesions as a presentation of AML M7 [2] while other reports periosteal thickening and bone fibrosis [3]. Our patient had a lytic lesion as seen radiographically in the proximal left femur (figure 3b) and sclerosis surrounded this

lesion. Although, it was not proven pathologically, we assume that this is part of the general osseous irregularities and the radiological hyperostosis, part of the AML presentation, as documented in previous reports. In this case where AML was confirmed pathologically, it is unlikely that the mixed sclerotic lesion of the left femur is due to other etiologies. Differential diagnosis of this mixed lesion is vast and nonspecific and includes infectious or inflammatory bony process, healing traumatic or pathologic bone injury, and a focal neoplastic process. In our case it was considered to be part of the general bony manifestation.

The soft tissue mass-like density that is seen in Figure 1 most likely represents chloroma. This is an extramedullary manifestation of AML and is also seen in MDS. It is a solid collection of leukemic cells outside of the bone marrow. The differential diagnosis of this soft tissue density includes hematoma, as it is adjacent to a fracture site. A neoplasm arising from the bone or from the soft tissue, such as orbital rhabdomyosarcoma, and a vascular anomaly such as a hemangioma or lymphangioma are also part of the differential diagnosis.

The radiographic findings of leukemia were reported as osteoporosis, focal lytic lesions, metaphyseal bands, cortical lucencies and periosteal reaction [4, 5]. Our patient had symmetric periosteal reaction that involved proximal femora and hyperostosis of the spine, pelvis and facial bones. We did not find any previous report of hyperostosis either in MDS evolving to AML or in AML subtype M2. Almost 50% of patients with AML M7 have Down's syndrome and patients are usually younger than 3 years. Our patient did not have Down's syndrome and was healthy until presentation of the disease.

Myelodysplastic syndromes are bone marrow stem cell disorders resulting in disorderly and ineffective hematopoiesis manifested by irreversible quantitative and qualitative defects in hematopoietic cells. In a majority of cases, the course of disease is chronic with gradually worsening cytopenias due to progressive bone marrow failure. The incidence of MDS is 3-4 per 100,000 people. The disease occurs most frequently in the seventh or eighth decade of life and is very rare in children [6]. Approximately one-third of patients with MDS progress to AML within months to a few years.

The leukemic cell population also showed the genetic abnormality trisomy 10 [7]. Trisomy 8 is the most frequent chromosomal abnormality in the French-American-British subtypes. Trisomy 10 as a sole cytogenetic abnormality is rarely found in de novo AML. In childhood acute lymphoblastic leukemia, trisomy 10 is an indicator of a good prognosis. The prognosis of trisomy 10 in AML is not known. In other case reports, the incidence of CD 7 expression is as high as 75% in leukemic cells with trisomy 10 expressions. Our cell population did not follow that trend as the cells showed aberrant CD33/34 expression; however, CD33 is also correlated with trisomy 10 in the leukemic blasts [8, 9].

Radiology, with its different imaging modalities, plays an important role in the diagnosis. Although final diagnosis of MDS and AML is performed through bone marrow biopsy, images can guide the referring physician and narrow the

differential diagnosis. Plain radiographs demonstrate the different patterns of hyperostosis, such as expansion of the medullary space, periosteal reaction, and mixed lesions. Computerized tomography in bone windows helps to further explore and delineate this pattern. Soft tissue windows may demonstrate soft tissue abnormalities and masses if present. Magnetic resonance images will show low signal in T1 and T2 weighted sequences in cases of hyperostosis; however, in cases of leukemia and myelodysplastic syndrome, there will be low signal in T1-weighted sequences and high signal in T2-weighted sequences [10]. Bone scintigraphy will demonstrate increased activity in hyperostosis due to the increased blastic process. Reports of the pattern of fluorodeoxyglucose uptake in positron emission tomography are limited. A few reports document variable intensity of uptake in leukemia and in MDS [12, 13, and 14].

The differential diagnoses of hyperostosis include Infantile Cortical Hyperostosis (Caffey's disease), hypervitaminosis A, leukemia, and prostaglandin periostitis. Our patient did not have any therapy with prostaglandin or with vitamin A. The only differential diagnostic consideration in our patient was Caffey's disease which presents with fever, irritability, and with cortical thickening. Infantile cortical hyperostosis is usually seen in infants less than 6 months old and our infant was slightly older. The diagnosis was more confusing as our patient had the triad seen in Caffey's disease (fever, irritability, and hyperostosis). Our patient presented with symmetric periosteal reaction on the proximal femurs and symmetric hyperostosis of the pelvic and facial bones mimicking Caffey's disease. The patient had a pathologic fracture of the left inferior orbital wall and a soft tissue mass in the lower left orbit that represented a chloroma. A bone marrow biopsy was obtained which also showed AML and extensive myelofibrosis.

Not all patients with AML exhibit hyperostosis and the etiology of the bone changes remains poorly defined. The case suggests that massive periosteal reaction could reflect increased osteoblastic activity, possibly caused by the same factors that induce myelofibrosis [15]. Our patient had elevated alkaline phosphatase at presentation, most likely due to osteoblastic activity.

This case is unique due to its rare osseous presentation. Pathologic fractures were not previously reported in Caffey's disease and are rare in AML at presentation. The case mimicked Caffey's disease and the radiologist should be aware of this rare diagnosis when interpreting a skeletal survey or a facial CT that demonstrates hyperostosis.

#### TEACHING POINT

Hyperostosis is a rare radiographic presentation of myelodysplastic syndrome evolving to acute myeloid leukemia. Bone manifestations in plain radiographs include periosteal reaction, lytic lesions, thickening of the skull diploid space, heterogeneous density and thickening of the bones.

Although uncommon, this entity needs to be considered in the differential diagnosis among other more common diseases.

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FIGURES

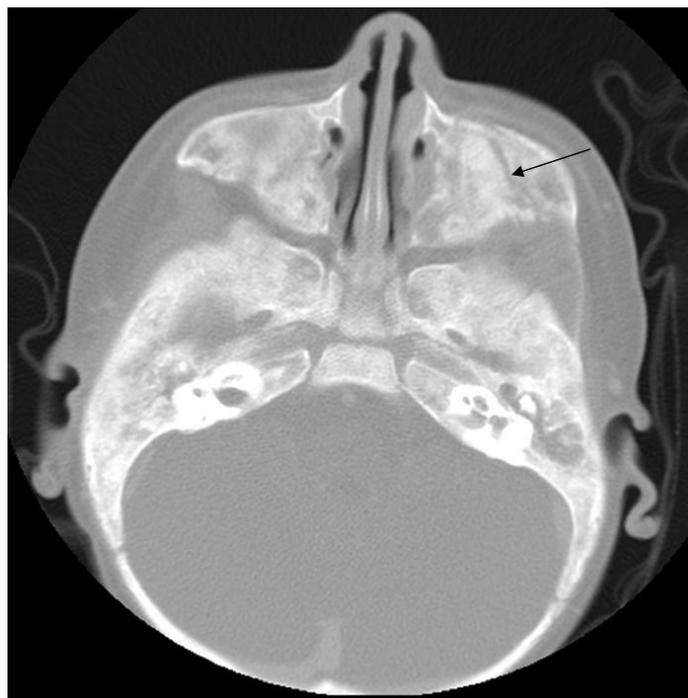


Figure 1a

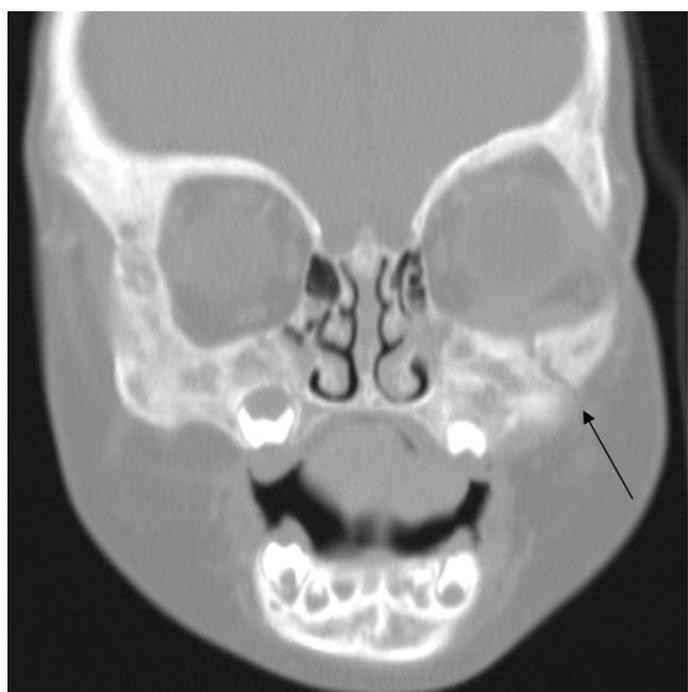


Figure 1b



Figure 1c

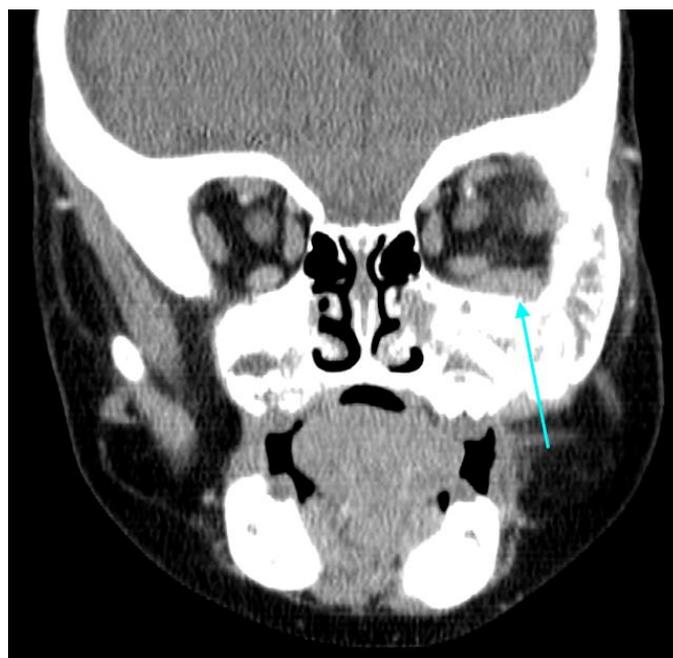


Figure 1d

**Figure 1:** 8-month-old male with acute myeloid leukemia, presents with hyperostosis. Maxillofacial CT images obtained following the intravenous administration of 18 mL of Omnipaque 240 on a CT (General Electric 64-slice with 120 kV and 9 mAs). Axial (a) and coronal (b) images formatted in bone windows demonstrate a heterogeneous appearance of the osseous structures. There is bony expansion and increased bone density consistent with hyperostosis. A fracture of the inferior orbital wall is seen (arrow). Axial (c) and coronal (d) soft tissue windows demonstrate a mass-like density in the floor of the left orbital wall (arrow). Initially the density was thought to be due to a hematoma; however, with the diagnosis of acute myeloid leukemia, it is assumed that the density represents a chloroma.



Figure 2a

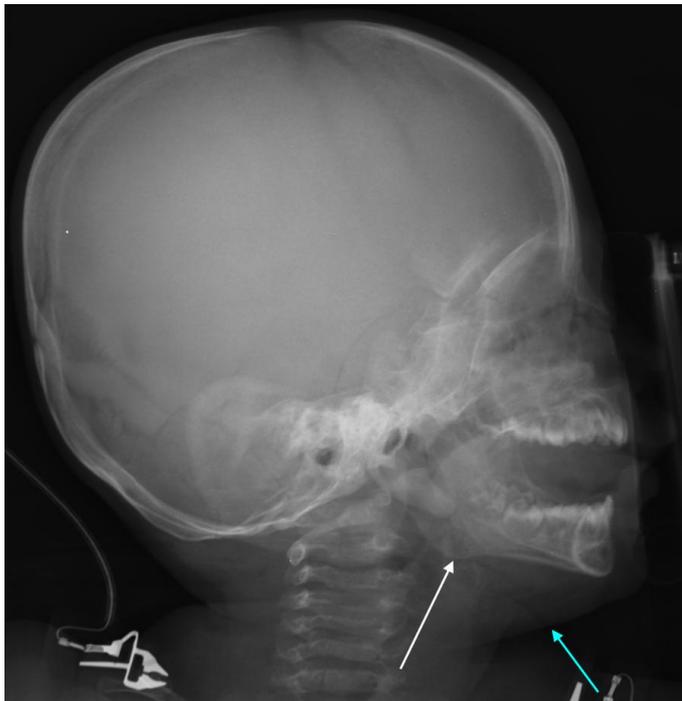


Figure 2b

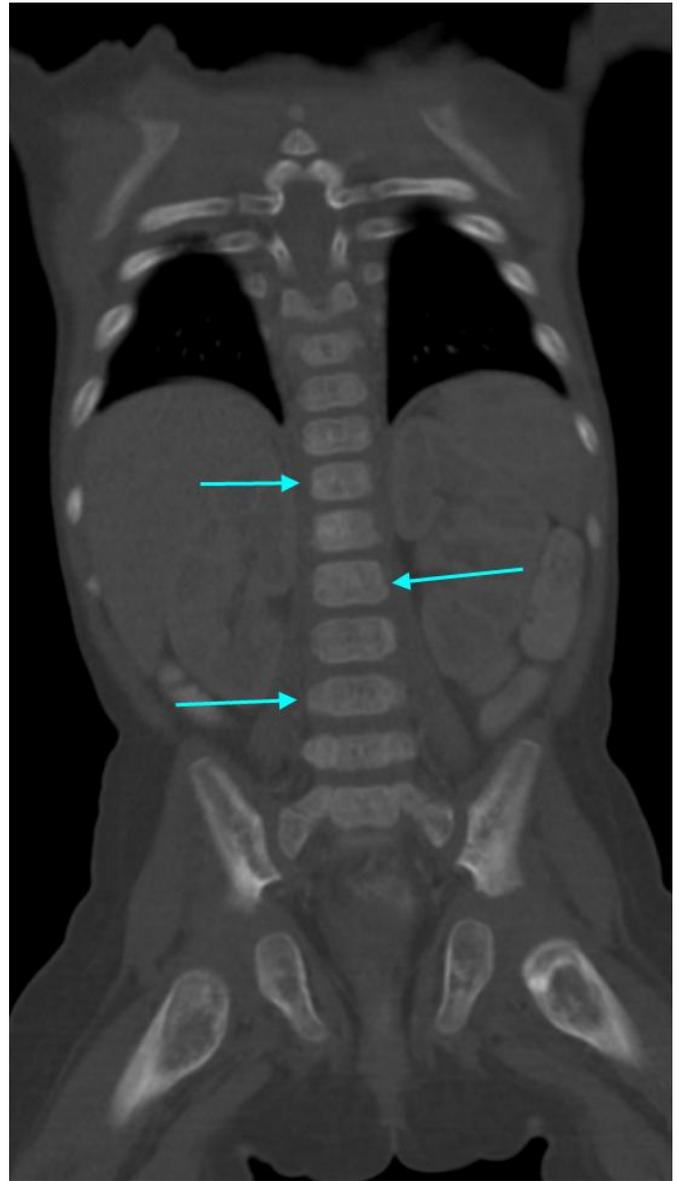


Figure 3a

**Figure 2:** 8-month-old male with acute myeloid leukemia, presents with hyperostosis. Frontal (a) and lateral (b) radiographs of the skull demonstrate irregularities and heterogeneity of the mandible (white arrows). There is soft tissue swelling around the mandible (blue arrows).

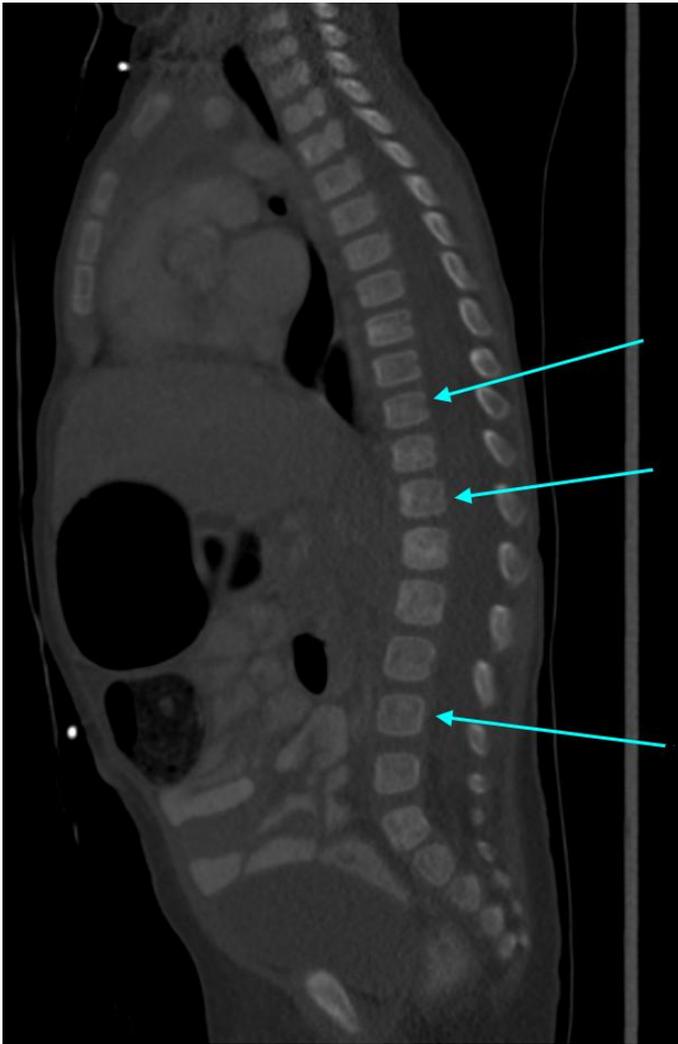


Figure 3b

**Figure 3:** 8-month-old male with acute myeloid leukemia, presents with hyperostosis. Coronal (a) and sagittal (b) CT (GE 64-slice with 100 kV and 3 mAs) with 15 mL of Omnipaque 350 intravenously formatted in bone window of the chest and abdomen demonstrates hyperostosis of the entire thoracolumbar spine (blue arrows) and pelvis.

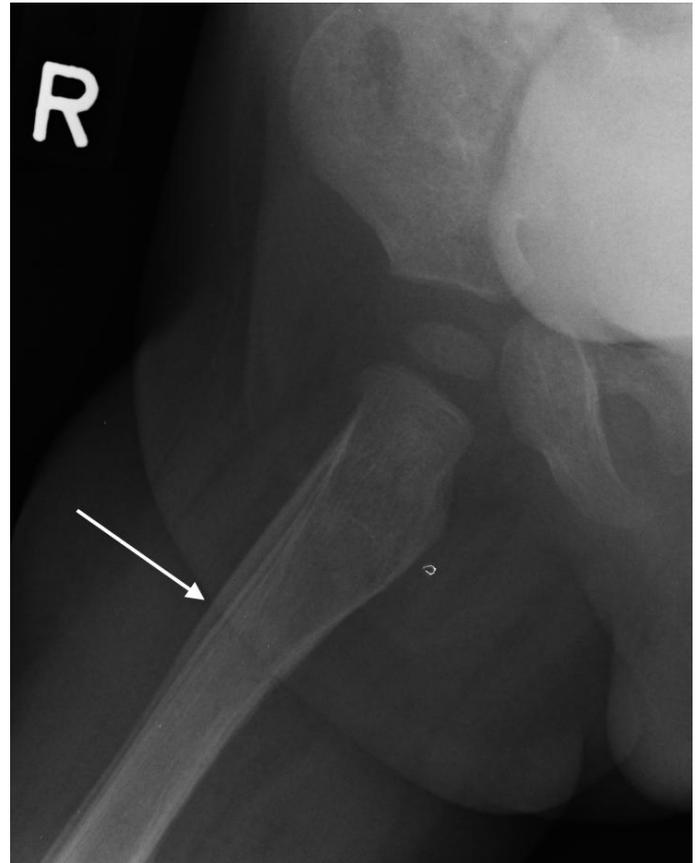


Figure 4a

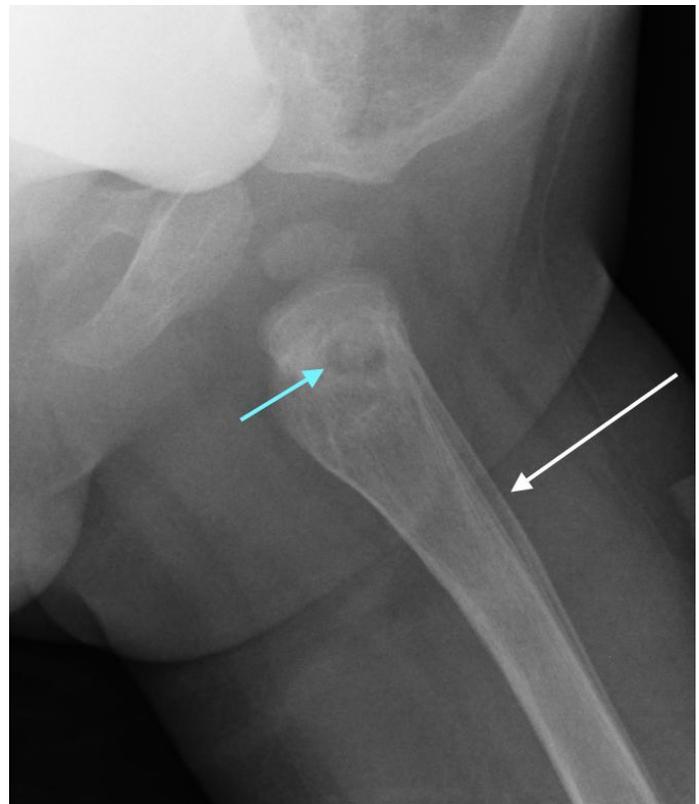
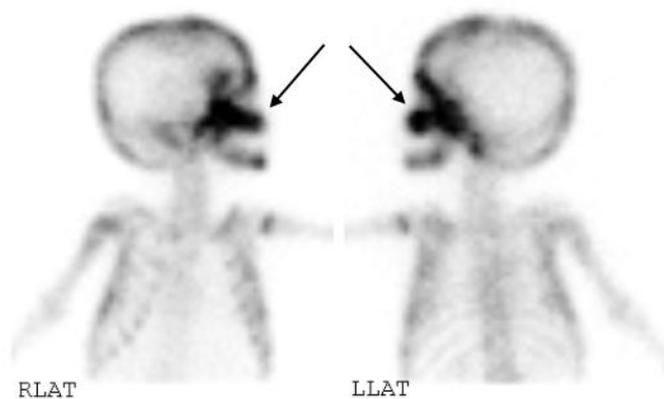
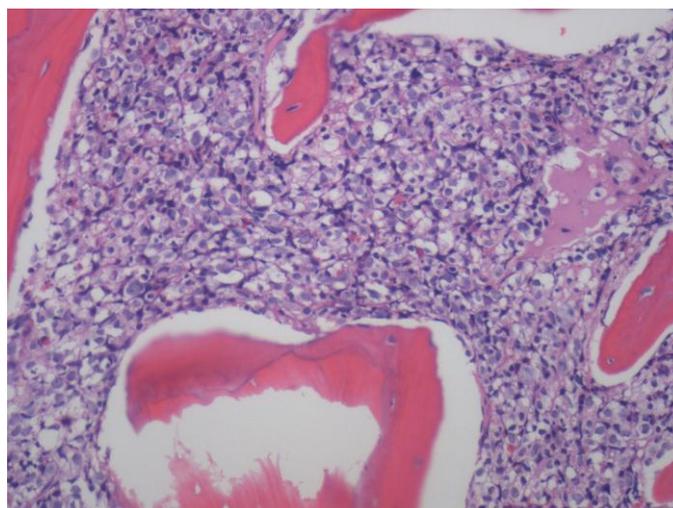


Figure 4b

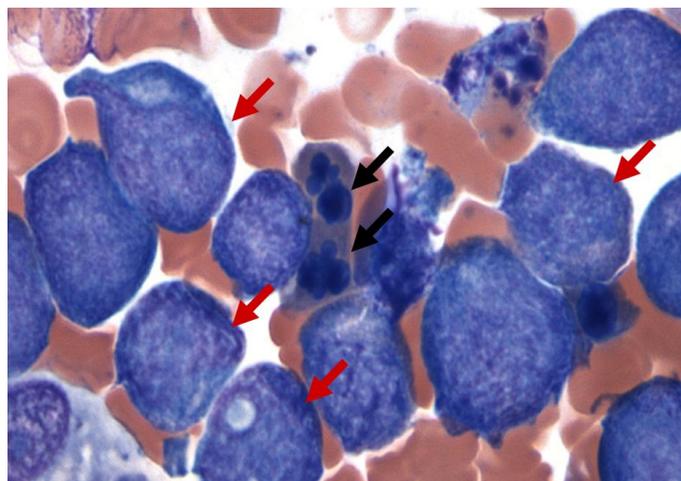
**Figure 4 (right column):** 8-month-old male with acute myeloid leukemia, presents with hyperostosis. Frontal radiograph of the right hip (a) and of the left hip (b) demonstrate periosteal reaction of the proximal femora bilaterally (white arrows). There is a lytic lesion in the proximal left femoral metaphysis with surrounding sclerosis (blue arrow).



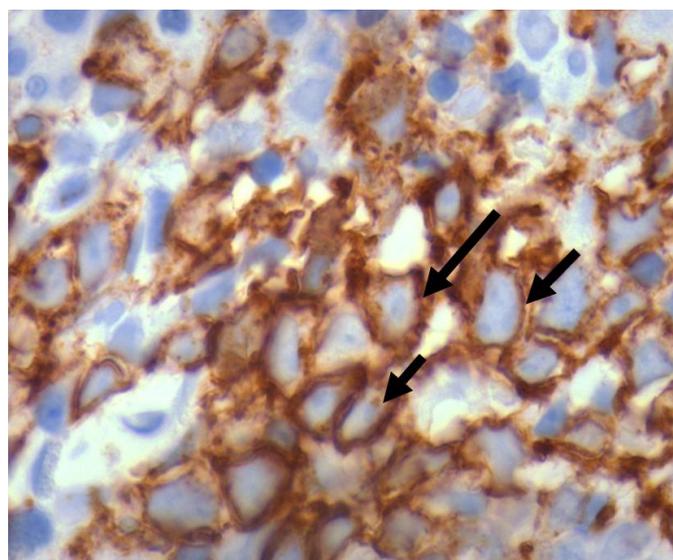
**Figure 5:** 8-month-old male with acute myeloid leukemia, presents with hyperostosis. Delayed phase of bone scintigraphy following the administration of 5.05 mCi of Tc-99m-MDP intravenously demonstrates increased activity in the maxillary bone. Patchy activity is noted in the skull.



**Figure 7:** 8-month-old male with Acute Myeloid leukemia, presents with hyperostosis. Bone marrow biopsy (hematoxylin and eosin stain, x 20) demonstrates packed marrow with sheets of blasts.



**Figure 6:** 8-month-old male with acute myeloid leukemia, presents with hyperostosis. Bone marrow aspirate (Wright stain, x 100, oil) demonstrates increased myeloblasts (red arrow) and dyserythropoiesis (black arrow).



**Figure 8:** 8-month-old male with Acute Myeloid leukemia, presents as hyperostosis. Immunohistochemistry (CD34 stain, x 100, oil) demonstrating that the blasts (arrows) were positive for CD34.

<b>Etiology</b>	Unknown (see risk factors below)
<b>Incidence</b>	3.4 per 100,000 people [6]; Rare in children and infants
<b>Gender ratio</b>	Male predilection [6]
<b>Age predilection</b>	Seventh or eighth decades [6]; Rare in children and infants
<b>Risk factors</b>	Advanced age, male gender, previous exposure to chemotherapy or radiation therapy, smoking, or, in rare cases, exposure to industrial chemicals [9].
<b>Treatment</b>	Chemotherapy; Drug therapy; Supportive care
<b>Prognosis</b>	Usually poor. Good if associated with Trisomy 10 [8, 9].
<b>Findings on imaging</b>	MRI: Low signal in T1 and High signal in T2. X-ray: Osteopenia; Rarely Hyperostosis

**Table 1:** Summary table for Myelodysplastic Syndrome

Disease	X-Ray	CT	MRI-T1	MRI-T2	Pattern of enhancement	Scintigraphy
<b>Myelodysplastic Syndrome</b>	Osteopenia [11]; Rarely hyperostosis	Hyperostosis	Low signal [10]	High signal [10]	Increased	Variable uptake of Tc-99m MDP
<b>Leukemia</b>	Osteopenia [11]; Lytic lesions [2]; Rarely hyperostosis [1,2,3]	Hyperostosis	Low signal	High signal	Increased	Variable uptake of Tc-99m MDP
<b>Infantile Cortical Hyperostosis</b>	Hyperostosis	Hyperostosis	Low signal	Low signal	None	Increased uptake of Tc-99m MDP
<b>Hypervitaminosis A</b>	Hyperostosis	Hyperostosis	Low signal	Low signal	None	Increased uptake of Tc-99m MDP
<b>Prostaglandin periostitis</b>	Hyperostosis	Hyperostosis	Low signal	Low signal	None	Increased uptake of Tc-99m MDP
<b>Fibrous dysplasia</b>	Hyperostosis	Hyperostosis	Low signal	Low signal	None	Increased uptake of Tc-99m MDP
<b>Cherubism</b>	Hyperostosis localized to mandibles	Hyperostosis	Low signal	Low signal	None	Increased uptake of Tc-99m MDP

**Table 2:** Differential diagnosis table for Myelodysplastic Syndrome. Differential diagnosis with imaging findings of Myelodysplastic Syndrome that presents with hyperostosis. (Hyperostosis means excessive growth of bone that may include periosteal reaction, increased bone density, heterogeneous osseous appearance, mixed lytic and blastic lesion, periostitis).

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**ABBREVIATIONS**

- MDS = Myelodysplastic Syndrome
- AML = Acute Myeloid Leukemia
- FAB = French-American-British
- FISH = Fluorescence in situ hybridization
- MPO = Myeloperoxidase
- MRI = Magnetic resonance imaging

**KEYWORDS**

Hyperostosis; Myelodysplastic Syndrome; Acute myeloid leukemia

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