

Review Article

Skeletal radiological findings in thalassemia major

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Skeletal changes in beta-thalassemia major (βTM) create a wide spectrum of bone radiographic features. The main pathology is extensive marrow proliferation due to ineffective erythropoiesis but the relative skeletal findings are encountered with a progressively reduced frequency and severity nowadays due to the regular hypertransfusion programs. The resulting hemosiderosis and particularly iron chelation therapy have been associated with dysplastic features which are found more often. Skeletal radiological appearances in βTM relate to a complex multifactorial pathogenesis (i.e. marrow expansion, direct iron and chelation toxicity, endocrine complications) and depend on the severity and duration of the disease, the type and effectiveness of treatment and the toxic effects of chelation therapy. Awareness of these findings is very important since early recognition can be an indicator for therapy adaptation.

Keywords: Bone, Chelation radiography, Skeletal, Thalassaemia major**Introduction**

Beta-thalassemia major (βTM) or Cooley's anemia or Mediterranean anemia was first described in 1925 by Cooley and Lee¹. The disease has a high prevalence in populations from the Mediterranean basin and refers to an inherited hematologic disorder characterized by reduced or absent synthesis of b-hemoglobin chains leading to ineffective erythropoiesis. If left untreated, βTM patients develop severe anemia, hepatosplenomegaly, several bone deformities, poor growth and usually die by heart failure in the first decade of life^{2,3}. Since 1965 long-term transfusion programs have been used from infancy to correct anemia and maintain acceptable levels of hemoglobin. From the late 1970s chelation therapy has been also instituted to remove the resulting iron accumulation and prevent its serious complications within the heart, liver and endocrine glands^{2,4}.

The modern radiologist should be aware not only of the classic well documented radiological findings caused by medullary expansion - although less common they may be seen in inadequately transfused patients - but of the skeletal deformities induced by therapeutic agents as well, since the latter are encountered more frequently nowadays and may indicate toxicity requiring dose adaptation⁵⁻⁷.

Pathophysiology and skeletal changes

In untreated or poorly transfused βTM patients skeletal changes result primarily from marked erythroid hyperplasia secondary to ineffective erythropoiesis⁸⁻¹⁰. Marrow

proliferation affects both cortical and cancellous bones causing widening of the medullary space - bone marrow can be expanded by a factor of up to 15 to 30 in untreated patients- cortical thinning and resorption of the secondary/tertiary bone trabeculae with subsequent prominent/coarse primary trabeculae creating a "lace-like" appearance. A generalized decrease in osseous density (osteopenia/osteoporosis) is resulting¹¹. Focal marrow proliferation may be also present causing small areas of lucency. Sometimes extra-medullary hemopoietic tissue extends to break through the bone cortex and grow beneath the periosteum forming a scalloped cortical edge. A periosteal reactive response may then initiate depending on the bone involved and the proliferation extent⁷. In some cases, extramedullary hemopoiesis creates large extraskeletal masses mimicking soft tissue tumors.

These skeletal findings are most often found in children older than 1 year old. Not all bones are involved to the same

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degree and at the same time. Intense skeletal changes are observed in the skull and hands, but are also found in the long bones, ribs and vertebral bodies. At first, both the axial and the appendicular skeleton are affected. Towards puberty, the findings in the appendicular skeleton diminish following the normal regression of hematopoietic marrow¹². In contrary, the deformities in the axial skeleton, e.g. skull, ribs, clavicles, spine and pelvis, which are sites of active persistent erythropoiesis remain throughout life or may even become more pronounced. Thus, according to Caffey¹³ "the distal portions of the skeleton (hands and feet), which are the optimal sites for radiological identification of the disease during infancy and childhood, become the least diagnostic after puberty". During the last decades these classic, well-documented in the past, bone radiological findings appear with a progressively reduced frequency and severity due to systematic hypertransfusion therapy. They have not disappeared though, as bone marrow remains hyperactive even with an optimal transfusion regimen¹⁰.

In *hypertransfused* patients and before the institution of chelation therapy a distinctive osteoarthropathy appeared. Hemosiderosis has been related to synovial and cartilaginous abnormalities which are probably caused by iron overload, abnormal calcium metabolism, vitamin D function and hyperuricaemia.

After the introduction of *iron-chelation* therapy in the late 1970s a new common pattern of skeletal changes emerged over the next decade¹⁴. Iron chelator agents may have a negative effect on bones and joints causing dysplastic deformities in the spine and the metaphyses of long bones, growth retardation and arthropathy. Different mechanisms may be implicated including abnormal metaphyseal collagen synthesis, inhibition of osteoblasts, a direct toxic effect and loss of minerals other than iron (e.g., copper). Post chelation dysplastic bone features are found nowadays more often than those resulting from marrow expansion or extra-medullary hemopoiesis¹⁵. Thus the literature recommends close monitoring of the toxic effects of chelation therapy, emphasising on the risks of chelation over-treatment and on the possible individual idiosyncrasy¹⁰.

To sum up, it is well known that in β TM many factors have an impact on skeleton including: marrow proliferation; iron overload/toxicity with direct negative effects on osteoblast and osteoclast activity; chelation therapy toxicity; associated endocrine complications (hypogonadism due to pituitary failure and gonadal dysfunction; growth hormone and insulin-like growth factor-I abnormalities; delayed puberty; hypothyroidism; insulin dependent diabetes; hypoparathyroidism and impaired calcium homeostasis); zinc deficiencies and low vitamin D levels; liver and kidney issues; nutritional deficiencies and little physical activity^{10,16,17}. The aforementioned factors contribute variably to skeletal changes with the severity of bony findings being associated with the extent and duration of the disease, the

type and effectiveness of treatment and the toxic effects of chelation therapy.

This review is a location based radiological skeleton guide covering the spectrum of bony appearances in β TM both in untreated and treated patients.

Radiological findings in axial skeleton

Skull

The attributed to marrow hyperplasia marked skull findings represent late skeletal manifestations and do not always agree with the degree of anemia or the changes in the rest of the skeleton^{8,18}. Initially, radiography may show only a slight thickening of the vault and the bones look "hazy" and "sandy" with increased porosity due to granular osteoporosis. At a later stage, the skull bones have a more spongy outline but well-circumscribed solitary or multiple lytic lesions may be also occasionally seen¹⁹.

As the disease progresses the hyperplastic marrow causes widening of the diploë –reported to become as much as four times wider than normal²⁰. The residual diploic trabeculae that don't get destroyed become thickened. The earliest and most severe deformities occur in the frontal bones, whereas the inferior part of the occiput is usually unaffected due to its lower marrow content^{12,13}. This asymmetry makes the calvarium become hollow and assume a camelback shape (helmeted aspect). The membranous skull bones do not expand adjacent to the sutures resulting in a "hot cross bun" skull configuration.

The hyperplastic marrow makes the outer table so thin as to be indistinguishable and perforates or destroys it. In contrary, the inner table may become notably thinner but remains intact^{8,12,13}. Once the outer table is perforated, the expanding marrow may proliferate under the invisible periosteum and cause reactive bone formation on the skull surface resulting in new bone spicules deposited vertically to the inner table²¹. These, along with the residual thickened, perpendicular in orientation, trabeculae create with the radiolucent marrow hyperplasia the characteristic "hair-on-end" sign or "crew cut" appearance, i.e. long, thin vertical lines that cross the thickened calvarium beyond the outer table looking like hair standing on end (Figure 1)²². The radiating spicules are easily seen in tangential radiographic projections²³. The hair-on-end pattern is a well documented but relatively uncommon finding that stops abruptly at the occipital bone due to lack of marrow activity within it. It is only evident in advanced stages in β TM and only sporadic reports exist for thalassemia minor and thalassaemia intermedia²⁴. The "hair-on-end" sign may be encountered in sickle cell disease, iron deficiency anemia and hereditary spherocytosis and is debatable whether may be reversed following treatment^{25,26}.

Another common finding in skull bones are the widened, elongated, tortuous and sharply delineated vascular impressions of middle meningeal vessels²⁷. Their size has been associated with the age at onset, the type of transfusion



Figure 1. Skull radiograph. Hair-on-end or crewcut appearance, marked calvarial thickening, external displacement and thinning of the inner table (From authors' archive).

therapy, the calvarium width and the nutrient foramina enlargement in the hands.

Following proper transfusion therapy, these findings may be either mild or even not present in approximately half the patients. Then, the lesion most frequently seen is widening of the diploë with osteopenia and a mottled appearance.

Facial bones

In infancy and early childhood, wall expansion and cortical thinning in the frontal, temporal and facial bones impedes the pneumatization of the paranasal sinuses and the mastoids, leading to their obliteration by marrow containing bone. The air spaces within the skull are not affected to the same degree^{20,21,28,29}. Maxillary sinus hypopneumatization and hypoplasia is most frequently present. The sphenoid and frontal sinuses are also often involved whereas the ethmoid air cells are usually spared due to little or even no active marrow potential within them. In the temporal bones, marrow activity varies considerably resulting in normal, slightly or completely suppressed pneumatization with more solid mastoids⁵. Changes in the sinuses are a classical x-ray finding in β TM not usually observed in other anemias. Increased incidence of sinonasal infections in β TM has been reported in the literature³⁰.

Involvement of the facial bones can create typical features giving rise to the terms "Cooley face" or "mouse face" or "mongoloid" or "rodent face" in describing thalassemic patients^{1,13,31,32}. The frontal and parietal bones are prominent appearing as frontal bossing, the zygomas protrude, the nasal bridge is depressed and maybe widened ("saddle nose") and the eyes have a mongoloid cant⁵. Marked hypertrophy of the upper maxilla appearing as bulging cheekbones is a distinctive pathognomonic sign of β TM, especially when accompanied by hypopneumatization of the antrum. In contrary, the mandible is generally less

protruded probably because its dense cortical layer resists expansion. Maxillary protrusion may cause marked orbital hypertelorism, overbite of the mandible and malocclusion.

The dentition is also affected showing protrusion and spacing of the upper anterior teeth³². Changes in morphology (i.e. reduced tooth size) may occur and dental development is delayed. Alveolar bone may also have a "chickenwire-like" appearance due to enlarged marrow spaces with coarse trabeculation.

Cephalometric radiography has been extensively used in orthodontics to study craniofacial morphology³³. The typical craniofacial features constitute a mild Class II skeletal pattern produced by the large intermaxillary discrepancy and characterized by reduction of the cranial base length, a shorter mandibular base length, a reduced anterior cranial base angle and an increased anterior face height³³⁻³⁵.

These facial deformities and oral alterations -overbite and openbite with malocclusion- may lead to speech, swallowing and eating difficulties and predispose to increased incidence of periodontal and caries diseases^{33,34}.

β TM patients may also show a shorter soft palate and a smaller tongue, small upper and middle airway spaces, a short length of the vertical airway and an hyoid bone lying close to the mandibular plane, findings that are attributed to the significant growth retardation^{33,36,37}.

The major determinants for the severity of facial deformities are marrow proliferation, the age at onset of transfusion therapy, the patient's age and the timing of splenectomy.

In the majority of patients undergoing systematic treatment from infancy, the changes in the skull and facial bones are prevented and/or markedly modified and by adulthood the bones develop quite normally. Facial bones deformities are rarely seen in other anemias and constitute an important finding for differential diagnosis.

Ribs

A variety of abnormalities have been described in the ribs even in Cooley's first report¹. The most common findings are widening and a characteristic trabeculated pattern due to osteoporosis involving the entire length of the rib (Figure 2)³⁸. Rib expansion may create a "finger-like" appearance whereas in some cases a halo is seen around the anterior or the posterior end of the rib. The feature has been described in other entities as well, e.g., diffuse neuroblastoma, Niemann-Pick disease and leukemia and may be followed by thoracic extramedullary hemopoiesis^{26,39,40}. Heterotopic marrow masses are depicted as "soft tissue" lesions. The rib cortex is usually thin and well defined and sharply marginated cortical erosions may be seen in the inferior margin of the ribs (possibly as an effect of subperiosteal marrow proliferation) mimicking the notching produced by aorta coarctation or neurofibromas²⁶.

Another relatively common finding, observed in sickle cell anemia as well, is a line of increased density in the rib's central



Figure 2. Chest radiograph. The visualized skeletal structures are diffusely osteopenic, with expansion of the medullary spaces (Courtesy of Dr A. Doulgeraki, Institute of Child Health, Athens).

area parallel to its long axis which is best seen at the middle to anterior aspect of the rib^{38,44}. This appearance, called as a “rib within the rib” sign (Figure 3), and subcortical fine linear radiolucency parallel and close to the superior margin of the rib^{26,38} seem to result from the provoked by marrow hyperplasia loss of the adjacent medullary trabeculae. The latter is the abnormality most commonly regressing after proper transfusion therapy. Another finding that may be also seen are small (1-2 mm), well-defined, localized lucencies in the medulla. The development of rib changes is believed to be prevented if hypertransfusion regimen begins early in life.

Following DFX therapy, a finding that may be seen on chest radiographs usually in the presence of other bone abnormalities is irregular sclerosis at the costochondral junction⁶.

Spine

In untreated or poorly transfused β TM patients vertebral changes are caused primarily by compensatory marrow hyperplasia^{41,42}. Marrow expansion and weight bearing on the vertebral column exert opposing forces on the vertebral bodies which present an initial increase in the height-to-width ratio and a slight bulging of their contour though having an average size. In severe cases medullary expansion can be complicated by spinal cord compression most commonly seen in the thoracic spine. Eventually, multiple small compression fractures may cause thinning of the subchondral bone plates and biconcave deformities of the vertebral bodies known as “fish-type” vertebrae (Figure 4). Rarely, central squared-off vertebral depressions or H vertebrae, characteristically observed in sickle cell anemia,

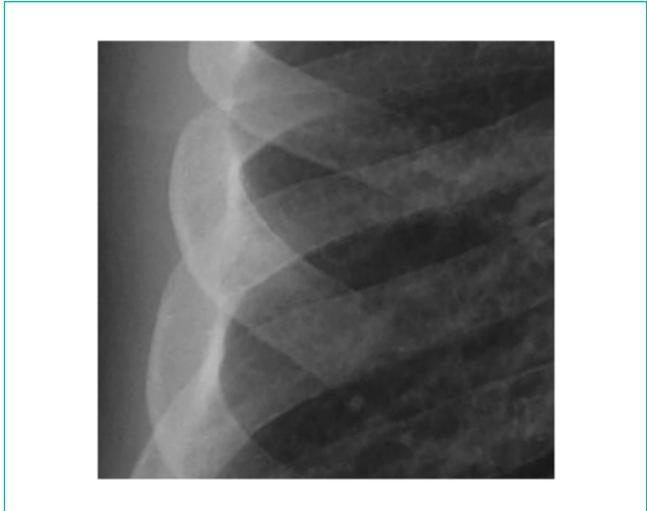


Figure 3. A “rib within the rib” appearance (Courtesy of Dr A. Doulgeraki, Institute of Child Health, Athens).

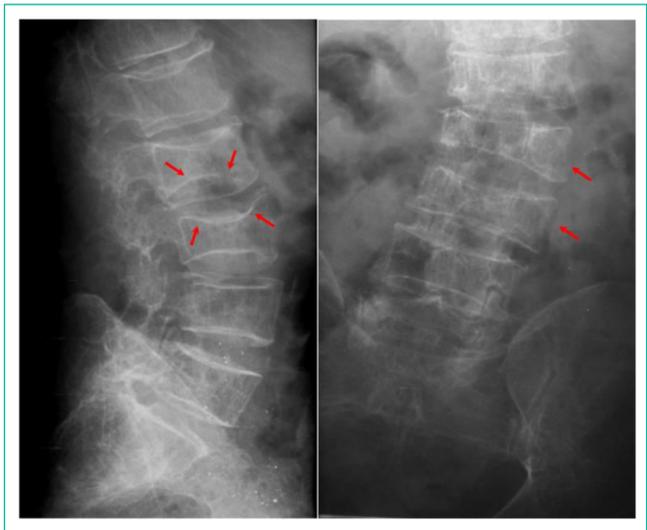


Figure 4. Plain radiographs of lumbar spine. Left image: Vertebrae have a coarse trabecular pattern. “Fish” vertebrae (arrows). Right image: Two flattened vertebrae resulting from compression fractures (arrows). (From authors’ archive).

may be seen, presumably due to growth disturbance at the chondro-osseous junction of the vertebral body. In advanced cases vertebral collapse may occur.

With improved maintenance of haemoglobin levels by transfusion therapy marrow hyperplasia and its resulting bony changes appear less frequently^{6,7,42-44}. Certain vertebral abnormalities occur though following DXF iron chelation therapy. Probably caused by interference with spinal growth plate development these changes differ both morphologically and pathologically from those due to marrow hyperplasia^{41,42}. Platyspondyly is a common



Figure 5. Lateral lumbar spine radiograph of a 32-year-old male β TM with hypogonadism. Vertebrae are flattened craniocaudally and elongated anteriorly (platyspondyly) (From authors' archive).

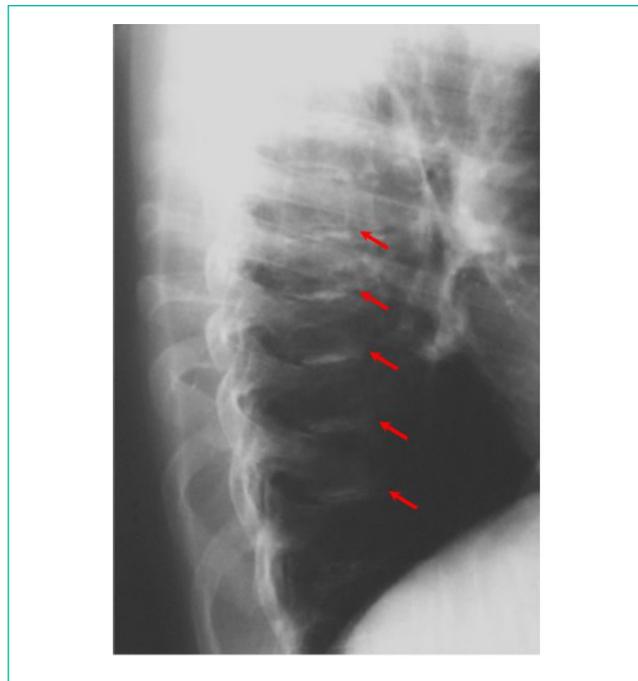


Figure 6. Lateral plain radiograph of thoracic spine showing calcified intervertebral discs at multiple levels (arrows). Note the increased radiolucency of vertebral bodies due to osteoporosis (From authors' archive).

finding observed in the entire spine with the vertebrae becoming flattened cranio-caudally and elongated anteriorly (Figure 5)⁴⁵⁻⁴⁷. The vertebrae may also acquire a biconvex contour -thoracolumbar spine is usually affected- while anterior tapering (wedging) of the upper thoracic spine may result in increased thoracic kyphosis. Osseous defects of ventral, upper and lower edges of vertebrae may resemble Scheuermann's disease, but the latter usually involves only a few vertebrae, its onset is around the time of puberty and platyspondyly is not seen⁶.

Spine osteoporosis is very common in thalassaemic patients as well. Diffuse demineralization with reduction in the number of trabeculae and accentuation of the primary vertically arranged trabeculation is most evident in the weight-bearing vertebral bodies giving them a vertical striated appearance in comparison to the pedicles, laminae, transverse and spinous processes (Figure 4). Despite optimal treatment with transfusion, chelation, sex hormones and bisphosphonates many β TM patients have vertebrae platyspondyly, endplate irregularities, osteopenia/osteoporosis and fractures.

In comparison to age- and sex-matched controls, β TM patients also show statistically significant more severe and extensive degenerative disc disease with no clear mechanism suggested by the literature so far⁴⁸. Its pattern is different exhibiting a multilevel involvement – the whole lumbar spine and several thoracic levels are affected-, intranuclear gas and calcification within discs (Figure 6)^{42,49}.

Similarly, in β TM patients there is an increased incidence of scoliosis in comparison to the general population. In a previously published study in a Greek population, 20% of patients (N=115) were found to suffer from scoliosis of the lumbar spine as compared with 6% in the general population, with an equal sex distribution⁵⁰. Long lasting DFX treatment, low haematocrit and high ferritin levels were all associated with an increased prevalence of scoliosis.

Pelvis

In the pelvis the expanded bone marrow causes cortical thinning and trabecular bone rarefaction with subsequent coarsening of the residual trabeculae. The above findings may result in the “cob-webbing” appearance.

Radiological findings in appendicular skeleton

Small tubular bones

The small tubular bones of the hands and feet are more commonly affected in children than in adults since in this age group red marrow is found in the entire skeleton. The earliest skeletal deformities are observed in the metacarpals, metatarsals and phalanges.

Marrow hyperplasia causes thinning of the cortex that also has a washed-out “worm-eaten” appearance with small, cyst-like lucencies or erosive defects. Due to absorption and/or destruction of the fine trabeculae, the spongy bone is sparse giving the picture of osteopenia^{13,26}. In most

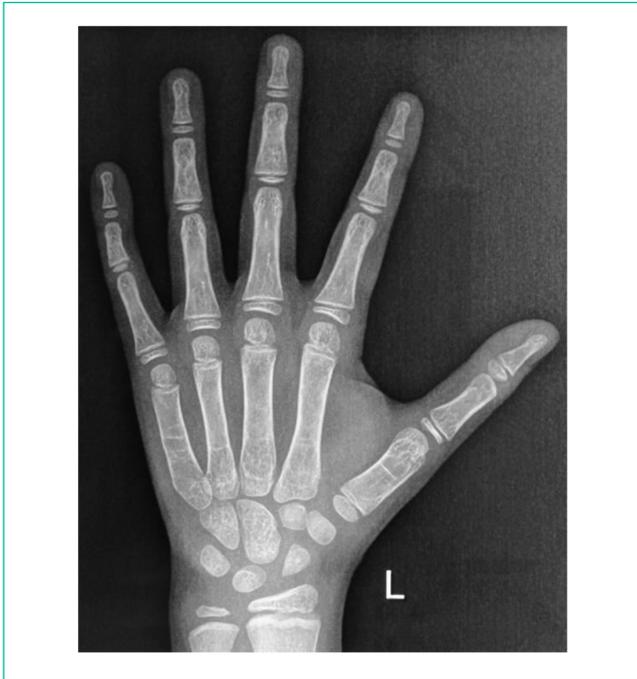


Figure 7. Hand radiograph. Thinned cortex and coarse primary trabeculae. Sausage shaped 1st metacarpal bone. (Courtesy of Dr A. Doulgieraki, Institute of Child Health, Athens).

typical cases, coarse trabeculation is seen in the shaft as the remaining trabeculae become thicker and appear even more conspicuous due to the concurrent cortical thinning^{6,26,46}. The coarse trabecular pattern may have a characteristic cystlike appearance that due to coexistent cortical atrophy becomes radiographically more conspicuous. Marrow hyperplasia and medullary widening may cause bulging of the normally concave shafts resulting in a squared or sausage-shaped configuration of the small tubular bones (Figure 7). Such abnormalities may be found in other diseases as well in which bone marrow overstimulation begins in childhood when the bones are relatively elastic and expansible. Sometimes a scalloped cortex edge is observed in hands and feet produced by extramedullary hemopoietic tissue growing beneath the periosteum⁷.

With advancing age and proper treatment, these lesions diminish and eventually disappear in the majority of cases. In contrary, all thalassemic patients and particularly those having improper treatment depict bone deficiency in metacarpal bones with increased medullary diameter and sometimes trabecular blurring except for the first metacarpal which remains clearly square in adult life independently of treatment when changes in the hand usually regress.

Enlargement of the nutrient foramina is another finding and presumably is related either to an increased arterial supply, an increased venous return or both, to or from the hyperemic hyperactive bone marrow. The enlarged foramina appear as round or oval lucencies in the center of

the metacarpals or phalanges -often in more than two-, vary in size (from <1 mm to >2 mm) and are usually found in the distal portion of the proximal or middle phalange of the hands^{27,51}. They are normal in β TM patients in whom transfusion therapy commenced at an early age and are largest in those who had a delay in therapy or never received one. Once enlarged the foramina size does not regress and hence remains as a permanent record of earlier marrow changes²⁷. However, this finding is not pathognomic of β TM because it may be also observed in Gaucher's disease⁵¹.

Long bones

In long bones marrow expansion causes widening of the medullary canal and pressure cortical atrophy similarly to small tubular bones. Coarse trabecular pattern and medullary lucencies involving the metaphyseal and diaphyseal regions of humeri and femori may be also evident⁵⁻⁷.

Due to marrow hypertrophy the long bones, commonly the humerus and femur, may lose their normal contour and normal concavity and appear "swollen" with a straight or convex appearance. In severe cases widening of the metaphyses and epiphyses resembles an Erlenmeyer flask.

In β TM children irregular transverse radiodense lines may be detected across the metaphyseal portions near the ends of the long bones. They represent growth arrest and recovery lines and are indicative of a significant childhood illness that interfered, at least temporarily, with normal osseous growth and development. These growth lines may be seen in adult life but they are not specific as they are encountered in innumerable other diseases.

Early fusion of epiphyses - Growth disturbances

Premature fusion of the growth plates in the tubular bones of the extremities was first described by Currarino and Erlandson in 1964 as a characteristic radiological appearance in β TM patients older than 10 years old⁵². This deformity is most commonly seen in children not have been transfused until late in childhood/adolescence⁶. It may be unilateral or bilateral, more frequently affects the proximal humeri and the distal femurs and rarely the proximal or distal tibia and fibula¹¹. Obliteration of the epiphyseal line tends to be asymmetric affecting only a segment of the epiphyseal plate -in the humerus almost always the medial segment of the proximal epiphyseal plate⁵². Paradoxically and in contrast with the premature fusion seen in the femur, secondary ossification centres (e.i. superior iliac crest) show delayed fusion^{6,8}.

Premature fusion may cause longitudinal growth retardation and bone shortening resulting in short stature or/and lower to upper limb length discrepancy that may require surgical intervention^{52,53}. Asymmetric segmental fusion may cause bone deformity that is characterized by an epiphysis tilt toward the fusion site and an axial deviation of the limb. In fact, the epiphysis is tilted medially in the humerus and posteriorly or anteriorly in the femur depending on the fusion position.

When the epiphyses are still open, the early segmental fusion can be depicted as an irregular transverse radiodense shadow crossing and bridging the epiphyseal line at the fusion site. In older patients with closed epiphyses, it is the presence of bony deformity or shortening that suggests an abnormal fusion originally segmental in location. In β TM patients, varus deformity of the humerus is characteristic and probably attributed to marrow hyperplasia, cortical perforation, compression of the medial surface of the weakened osteopenic bone (a Salter-Harris Type V injury) and ultimately premature fusion of the physis⁶.

Metaphyseal/epiphyseal dysplastic changes and growth failure associated with DFX chelation

Desferrioxamine therapy is associated with metaphyseal lesions and long bone dysplasia in about 30% of thalassemic patients receiving iron chelation therapy^{14,15,41,54,55}. The radiographic features have been well described including both spinal (see spine) and extraspinal abnormalities^{53,56}. Clinically, affected patients have a short trunk with moderate sternal protrusion, genu valgum, generalized joint stiffness and periarticular bone deformities.

The dysplastic bone changes predominantly affect the ends of fast-growing long bones, i.e. the metaphysis, the epiphyseal plate and epiphysis, whereas the diaphysis remains intact both radiologically and histologically^{14,15,41,53,55}. The bone abnormalities typically are bilateral and common sites with more dramatic alterations include the distal femur (being one of the fastest-growing regions), the proximal tibia and distal ulna^{56,57}. Other metaphyseal regions possibly involved are the proximal femur, proximal humerus, distal radius and distal tibia. In the absence of long bone changes, metacarpal dysplasia is uncommon. The epiphyses are less often involved but irregularity and sclerosis may occur. In cases of Severe epiphyseal dysplasia in the proximal and distal femur and tibia, surgery may be required for slipped upper femoral epiphysis, genu valgum or varum that are well documented secondary complications^{45,58}.

The commonest findings in DFX induced skeletal dysplasia is irregularity and coarse irregular sclerosis of the physeal-metaphyseal junction. Abnormalities in the metaphysis typically start to develop at the ages of 2 to 4, consisting initially of concavity and physeal widening with an intact metaphyseal line. Physeal widening is a frequent documented finding on radiography and has a more marked lateral location, differentiating DFX bone dysplasia from other dysplasias characterized by a uniform physeal widening across the bone width⁵⁹. Progressive changes subsequently occur including metaphyseal irregularity and cupping as well as indistinctness and fraying of adjacent bone. A broad band across the metaphysis may progress centrally toward the diaphysis creating a flame-shaped sclerotic lesion sometimes with lucent areas within it. The metaphyseal line eventually becomes thickened and irregular, with findings similar to those of rickets.

To sum up, DFX induced bone dysplasia can be diagnosed on conventional radiography when characteristic sclerotic and radiolucent cystic areas are seen in metaphysis. With a reduction of the DFX dose, healing of the metaphyseal abnormalities with partial or complete obliteration of the cystic defects and increased bone sclerosis may be encountered.

DFX exerts a further negative effect on growth velocity and dysplastic bone changes in the long bones exacerbate the observed growth retardation and short stature^{14,45,55,57}. De Sanctis et al. found that both the axial and appendicular skeleton are involved⁵. The trunk is disproportionately short, mainly owing to vertebral body deformities, frequently platyspondyly, and the extremities are affected due to decreased growth velocity of long bones.

Radiographic findings are identified 2–3 years after definite growth failure^{45,57} while premature closure of the physis does not appear to be a feature of this process. Diagnosis is very important given that a DFX dose reduction has been documented to revert the bone abnormalities and improve bone growth^{41,57}.

Avascular necrosis (AVN)

AVN of the femoral head was first described as a complication of β TM by Orzincolo et al⁶⁰. Despite its rarity - limited case reports are available- increased incidence has been reported in thalassaemic patients when compared with general population⁶⁰⁻⁶². The possible mechanism is probably multifactorial with the two basic factors being anaemia and osteoporosis. The chronic recurring hypoxia and the innately rigid and 'less-deformable' red blood cells could compromise the blood flow while marrow hyperplasia may compress the intramedullary branches of the nutrient artery. Additionally, an osteoporotic bone is liable to multiple microfractures that may contribute to osteonecrosis⁶³. The X-ray findings are those usually seen in Legg-Calve-Parthes disease, i.e. subcortical radiolucent zones and flattening of the femoral head and at a later stage deformity of the femoral head and subluxation.

Osteoarthropathy and crystal deposition

High serum iron levels have been associated with abnormal features of the synovium and articular cartilage. Articular deformities resemble that of primary hemochromatosis including symmetrical joint space narrowing, cystic lesions, flattening/collapse of the subchondral bone and osteophyte formation. However, they are less common and affect the large joints more frequently⁴².

Calcium pyrophosphate dehydrate crystal deposition may lead to chondrocalcinosis.

Hyperuricemia and acute gouty arthritis may also appear, though not commonly, and affect unusual locations such as the sacroiliac joints in addition to the small joints of the hands and feet. Radiological findings include well defined, sclerotic bordered erosions and soft tissue nodules⁶⁴.

Deferiprone related arthropathy

Arthropathy of large joints has been recognized as a toxic side effect of deferiprone (DFP) therapy. Bilateral knee involvement is most common, but ankles, hips, shoulders, elbows, wrists and small joints of the hands and feet can also be affected⁶⁵⁻⁶⁹. Clinically, the patients complain for musculoskeletal stiffness, joint pain, swelling and effusion, more frequently involving the knees⁷⁰. Radiographic abnormalities include irregular flattening of the subchondral bone and patellar beaks.

The long-term sequelae of DFP related arthropathy are not certain. Premature osteoarthritis may result from the damage to articular cartilage and the deformity of subchondral bone. Discontinuation of the drug may lead to clinical improvement but the structural damages seem to persist.

Osteopenia/osteoporosis and fractures

Osteopenia and osteoporosis represent main radiological manifestations in β TM children, adolescents and young adults of both genders and are more conspicuous in the lumbar spine⁷¹. Despite adequate treatment with transfusion program and chelation therapy, the bone mineral turnover shows an unbalance in β TM resulting in low bone mineral density (BMD) early in life. The reported frequency of osteoporosis varies from 13.6% to 50% in well treated thalassemic patients with an additional 45% affected by osteopenia^{5,10,16,43,72}.

The pathogenesis is complex and multifactorial including ineffective haemopoiesis, marrow expansion, direct iron and chelation toxicity on bones, genetic factors, endocrine complications (i.e. hypogonadism, thyroid/parathyroid dysfunction, diabetes, vitamin D and C deficiency), nutritional deficits and limited physical activity.

Nowadays osteoporosis represents the most clinically important skeletal manifestation being a prominent cause of morbidity in thalassemic patients^{16,73,74}. Severe osteoporosis may result in increased risk of fractures, skeletal deformities and growth failure. Thus, its early identification, quantification and follow-up are of paramount importance. Dual energy X-ray absorptiometry (DXA) is the method of choice for measuring BMD and close surveillance starting in adolescence is recommended. However in β TM two contributing factors may interfere with BMD reading in DXA method resulting in false diagnosis: spinal degenerative skeletal changes and short stature with the latter leading to underestimation of bone density. Alternative methods for precise measurement of osteoporosis are QCT, high resolution computed tomography and single energy quantitative computed Tomography (SEQCT) that should be regarded as sensitive and reliable in thalassaemia¹⁷.

Fractures are expected in view of the common severe osteoporosis and complicate falls in over 50% of β TM patients^{17,72,73}. The most commonly affected site is the upper limb, whereas fractures in spine, hips and pelvis occur

in approximately 10% of cases. Although the location of osteoporotic fractures follows that of the general population, young thalassemic patients have a particularly high incidence of vertebral fractures. Fractures of long bones, particularly those involving the femur, should be treated as pathological fractures owing to high bone fragility in β TM. In most cases they heal relatively slowly and may be associated with angulation and shortening of the limbs. Thus stabilization of the entire bone with intramedullary nailing may be required^{9,43,74-77}.

Summary

In β TM the skeletal deformities become radiologically distinct as age advances and diagnostic of the disease in long-standing severe cases. Novel transfusion programs and iron-chelation therapy have improved life expectancy of β TM patients and the marked osseous changes have been replaced by less severe bone abnormalities. Given that iron overload and high-dose DFX both result in a new pattern of bone lesions, careful balancing of the transfusion therapy and iron-chelation agents is required. Early recognition of radiographic findings caused by chelation toxicity is very important and could suggest reduction of the dose or change to another chelator drug. Awareness of the findings in hand radiographs performed for bone age estimation could be very useful in screening for DFX-induced skeletal dysplasia as the distal ulna is one of the first affected sites.

On the other hand osteoporosis represents probably the most clinically important skeletal complication of β TM. Close surveillance, early recognition of osteopenia and proper management are of paramount importance for thalassemic patients improving substantially the quality of their, prolonged by recent therapeutic modalities, life.

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