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Severe Thalassemia Bone Disease in a Young Woman with Transfusion-Dependent β-Thalassemia Major: Erlenmeyer Flask Deformity, Muscular Hemosiderin Deposition, and Profound Osteoporosis — A Case Report

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A B S T R A C T

Introduction: Beta-thalassemia major (β-TM) is a chronic transfusion-dependent hemolytic disorder in which thalassemia bone disease (TBD) is among the most frequent and least resolved long-term complications, driven by ineffective erythropoiesis with marrow expansion, iron-overload toxicity, and endocrine and nutritional deficiencies.

Case Presentation: We report a 27-year-old woman with β-TM diagnosed at the age of two years and a long history of iron overload, who presented with severe, movement-limiting pain of the right lower limb that had been intermittent since 2019 and acutely worsened over the preceding month. She had a documented hypersensitivity to deferasirox and was maintained on deferiprone. Examination revealed clinical anemia, hepatosplenomegaly, and a spontaneously painful, immobile right lower limb. Investigations confirmed hypochromic microcytic anemia (hemoglobin 5 g/dL), elevated ferritin, and low calcium and vitamin D levels. Pelvic radiography showed diffuse osteopenia; femoral radiography showed widening of the medullary cavity with an Erlenmeyer flask deformity; and magnetic resonance imaging revealed extensive hemosiderin deposition throughout the visualized bone and within the right rectus femoris muscle. Dual-energy X-ray absorptiometry showed a lowest Z-score of −3.5 at the left forearm, confirming profound, below-expected bone mineral density for age.

Conclusion: This case highlights the diagnostic and therapeutic complexity of advanced TBD — structural deformity, soft-tissue iron deposition, and profound osteoporosis compounded by chelation-limited iron control — and underscores the necessity of an urgent, individualized, multidisciplinary approach.

1. Introduction

Beta-thalassemia major (β-TM) is an autosomal recessive hemoglobinopathy in which partial or complete failure of beta-globin chain synthesis produces an excess of unpaired alpha-globin chains. These unstable chains precipitate within erythroid precursors, accelerate their apoptosis in the bone marrow, and generate the hallmark state of ineffective erythropoiesis and chronic hemolytic anemia. The cornerstone of management is therefore lifelong red-cell transfusion combined with iron-chelation therapy to mitigate the inevitable iron loading that accompanies repeated transfusion and increased gastrointestinal iron absorption.[1] Sustained advances in transfusion safety and chelation have transformed β-TM from a disease of childhood mortality into a chronic condition compatible with survival into adulthood; yet this very success has unmasked a

spectrum of chronic, multi-system complications that clinicians must now anticipate and treat over decades of life.[2,1]

From an epidemiological standpoint, thalassemia remains a major public-health burden across Asia. A systematic analysis derived from the Global Burden of Disease 2021 study reported that Southeast Asia carried the highest thalassemia mortality among the South, East, Southeast, and high-income Asian regions, accounting for 2,517 deaths (95% uncertainty interval 1,983–3,153), an age-standardized mortality rate of 0.37 per 100,000 population, and the highest age-standardized disability-adjusted life-year rate at 24.03 per 100,000 population.[3] Indonesia lies squarely within the global thalassemia belt and has been characterized as a hotspot for hemoglobinopathies, with an estimated 3.0–10.0% of the population carrying a β-thalassemia allele and approximately 2,500 infants born with β-TM each year.[4] Against this background, the long-term skeletal consequences of the disease represent a large and growing source of morbidity in the surviving adult population.

Thalassemia bone disease (TBD) is among the most frequent, persistent, and incompletely resolved complications of β-TM. It encompasses a continuum that ranges from reduced bone mineral density (BMD) and frank osteoporosis to skeletal deformity, chronic bone pain, fragility fracture, and the secondary loss of mobility and quality of life.[2,5] The magnitude of the problem is substantial. A recent cross-sectional study of 210 patients with thalassemia reported a 62.4% prevalence of low BMD, with transfusion dependency and lower body-mass index emerging as independent associated factors.[6] In a separate cohort of adults with transfusion-dependent thalassemia, BMD fell below the expected range for age in 58.0% of patients, osteoporosis was present in 38.4%, and fragility fractures had occurred in 20.5%, while a contemporary cross-sectional study of patients with β-TM has likewise confirmed a high prevalence of osteoporosis and identified its principal determinants.[5,7] Inadequate transfusion and chelation, in particular, have been linked to an increased prevalence of fractures in children and young adults with β-TM.[8]

The pathogenesis of TBD is multifactorial and is best understood as the convergence of three interacting pathways. The first is expansion of the erythroid marrow driven by chronic ineffective erythropoiesis; the hyperplastic marrow mechanically erodes and thins the trabecular and cortical bone, distorts metaphyseal modeling, and reduces the structural reserve of the skeleton.[2,9] The second is direct iron toxicity. Iron that is not adequately chelated is deposited in bone and in the endocrine glands, where it impairs osteoblast proliferation and collagen maturation, perturbs the receptor activator of nuclear factor-κB ligand and osteoprotegerin axis, and tilts bone remodeling toward net loss; iron overload has been shown to associate directly with reduced BMD in transfusion-dependent thalassemia.[10,11] The third pathway comprises the hormonal and nutritional deficiencies that accumulate over years of iron overload — hypogonadism, growth hormone deficiency, disturbed glucose homeostasis, and deficiencies of vitamin D and calcium — each of which further compromises the acquisition and maintenance of bone mass.[12,13] In most patients these pathways act simultaneously, so that the predominant lesion is a failure of bone formation superimposed on a variable increase in bone resorption.[2,10]

The clinical expression of bone disease in thalassemia is strikingly heterogeneous, which has important consequences for surveillance. Some patients accrue severe deficits in bone mass while remaining asymptomatic for years, whereas others present, as in this case, with disabling pain at a stage when the underlying loss is already advanced. The determinants of this variability include the adequacy of lifelong transfusion and chelation, the presence and treatment of endocrinopathy, genetic modifiers of bone metabolism, physical activity, and the cumulative duration of disease.[5,7] A practical implication is that chronological reassurance is unreliable: a young adult with apparently controlled hematological parameters may nonetheless harbor profound osteoporosis. This is precisely why objective densitometric and radiological assessment, rather than symptom-based

screening alone, is required to capture the true skeletal status of adults with β-TM.[6,14]

What makes TBD particularly challenging in clinical practice is that its structural manifestations may remain silent for years and then declare themselves abruptly, as acute pain, deformity, or pathological fracture, at a point when the underlying bone loss is already advanced. The radiological signature of long-standing marrow expansion — widening of the medullary cavity and the Erlenmeyer flask deformity of the distal femur — is a durable record of the disease, while soft-tissue and intramuscular hemosiderin deposition detectable on magnetic resonance imaging provides direct visual evidence of the iron burden that drives skeletal injury.[9] The co-occurrence of these findings in a single young patient, together with a Z-score in the profoundly low range, offers an instructive window onto the full pathophysiological spectrum of the disease.

The novelty of this report lies in the simultaneous, image-documented coexistence in one young adult of three otherwise separately described severe features of TBD: a classic Erlenmeyer flask deformity of the femur, magnetic-resonance evidence of hemosiderin deposition extending beyond bone into the rectus femoris muscle, and profound osteoporosis with a left-forearm Z-score of −3.5 — all unfolding in the additionally complicating context of incomplete iron control mandated by deferasirox hypersensitivity. The aim of this case report is therefore to describe the clinical presentation, the integrated radiological and densitometric diagnosis, and the multidisciplinary management challenges of severe TBD presenting as acute lower-limb pain, and to distil from this experience practical lessons on the early recognition and individualized treatment of bone disease in adults with β-TM.

2. Case Presentation

Patient identity and chief complaint

A 27-year-old woman presented with severe pain in the upper part of the right leg, extending from the right knee to the right groin. The pain had been present intermittently for several years, dating back to approximately 2019. During this period she had experienced repeated episodes of symptomatic improvement and had, at her best, been sufficiently mobile to undertake recreational mountain hiking. One month before the current admission, however, the pain recurred and then escalated sharply over the final week, to the point that the right leg could no longer be straightened or flexed and the patient became functionally immobilized. There was no clear history of antecedent trauma to account for the acute deterioration.

Past medical history and chelation therapy

The patient had been diagnosed with β-TM with iron overload at the age of two years and had since required repeated packed red-cell (PRC) transfusions. At the time of admission she was under regular follow-up at the medical hematology-oncology outpatient clinic. Her hemoglobin concentration was 5 g/dL, and further PRC transfusion was planned; this degree of anemia reflected ongoing, suboptimally controlled ineffective erythropoiesis. With respect to iron-chelation therapy, the patient had a documented history of hypersensitivity to deferasirox and was therefore being maintained on deferiprone at a dose of 1,000 mg three times daily. This history is clinically pivotal: the loss of deferasirox as a therapeutic option narrowed the available chelation strategy and contributed to an iron burden that could not be fully controlled, with direct consequences for the skeleton.[1]

Physical examination

On examination the patient was in a moderately ill general condition, with vital signs within normal limits. There were clinical signs of anemia together with hepatomegaly and splenomegaly, a constellation consistent with chronic iron overload and extramedullary hematopoiesis. The right lower limb was spontaneously painful, with marked restriction of active and passive movement at both the right knee and the right hip. No overlying skin changes, erythema, or local warmth suggestive of acute infection were noted. The contralateral limb and the remainder of the systemic examination were unremarkable.

Laboratory findings

Laboratory evaluation confirmed a hypochromic microcytic anemia accompanied by an elevated reticulocyte count, the expected hematological footprint of chronic hemolysis with a compensatory but ineffective marrow response. Iron-status assessment revealed a markedly elevated serum ferritin, confirming systemic iron overload. Evaluation of bone metabolism demonstrated reduced serum calcium and vitamin D concentrations, indicating the nutritional and hormonal deficiencies that commonly aggravate TBD. The principal laboratory findings and their clinical interpretation are summarized in Table 1.

Table 1. Summary of the principal laboratory findings at admission and their clinical interpretation.

Parameter	Finding	Clinical interpretation
Hemoglobin	5 g/dL (severe anemia)	Transfusion-dependent anemia; ineffective erythropoiesis not optimally controlled
Red-cell indices	Hypochromic, microcytic	Consistent with β-thalassemia major
Reticulocyte count	Increased	Compensatory but ineffective erythroid response / ongoing hemolysis
Serum ferritin	Markedly elevated	Systemic iron overload; incomplete chelation control
Serum calcium	Decreased	Nutritional/metabolic deficiency contributing to impaired mineralization
Vitamin D (25-OH)	Decreased	Deficiency aggravating osteopenia and bone-mineralization failure

Imaging findings

Pelvic radiography showed diffuse osteopenia without a visible fracture or joint dislocation within the visualized region. As shown in Figure 1, the reduction in radiographic bone density was generalized and symmetrical, in keeping with a systemic disorder of bone mass rather than a focal lesion.

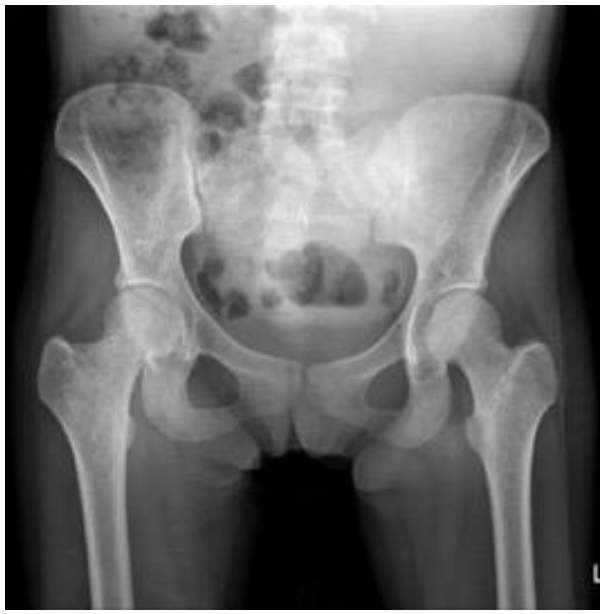

Figure 1. Anteroposterior pelvic radiograph demonstrating diffuse, symmetrical osteopenia of the pelvis and proximal femora, with generalized loss of bone density and no discrete fracture or dislocation in the visualized region.

Anteroposterior and lateral radiographs of the right femur demonstrated undertubulation of the distal third of the femur with widening of the medullary cavity, producing the classic Erlenmeyer flask configuration detailed in Figure 2. This appearance is a durable structural consequence of chronic marrow expansion and failed metaphyseal modeling, and in this clinical context is a recognized manifestation of β-TM.[9]

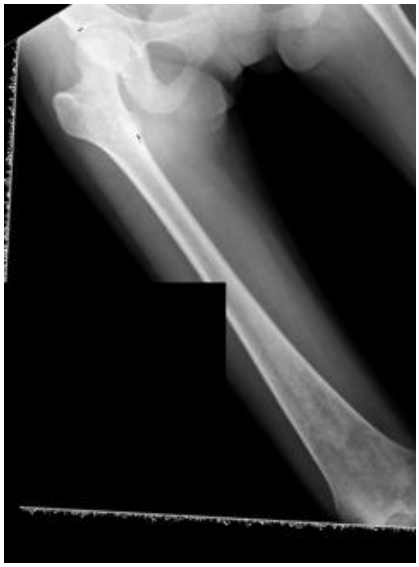

Figure 2. Radiograph of the right femur showing undertubulation of the distal femur with widening of the medullary cavity and thinning of the cortex, forming the characteristic Erlenmeyer flask deformity — a classic skeletal manifestation of long-standing marrow expansion in ß-thalassemia major.[9]

Magnetic resonance imaging (MRI) of the right femur was performed without contrast, using axial, sagittal, and coronal T1-weighted sequences together with coronal and sagittal T2 short-tau inversion-recovery and fat-suppressed sequences. As demonstrated in Figure 3, the study showed diffusely reduced marrow signal consistent with extensive hemosiderin deposition throughout the visualized bone, accompanied by hemosiderin deposition within the right rectus femoris muscle. These findings, detailed in Figure 3, provide direct imaging evidence of the iron burden affecting both the skeletal and the soft-tissue compartments and corroborate the systemic iron overload inferred from the elevated ferritin.[9,10]

A clinical photograph of the lower limbs, presented in Figure 4, documents the position of the affected right leg at presentation, when active movement of the knee and hip was severely limited by pain.

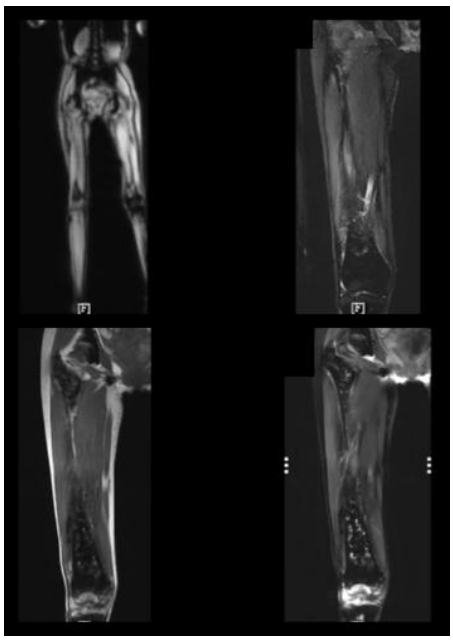

Figure 3. Non-contrast magnetic resonance imaging of the right femur (T1-weighted and T2 STIR/fat-suppressed sequences, multiplanar). There is diffusely low marrow signal consistent with widespread hemosiderin deposition throughout the visualized bone, together with hemosiderin deposition within the right rectus femoris muscle, providing direct evidence of iron toxicity in both bone and adjacent soft tissue.[9]

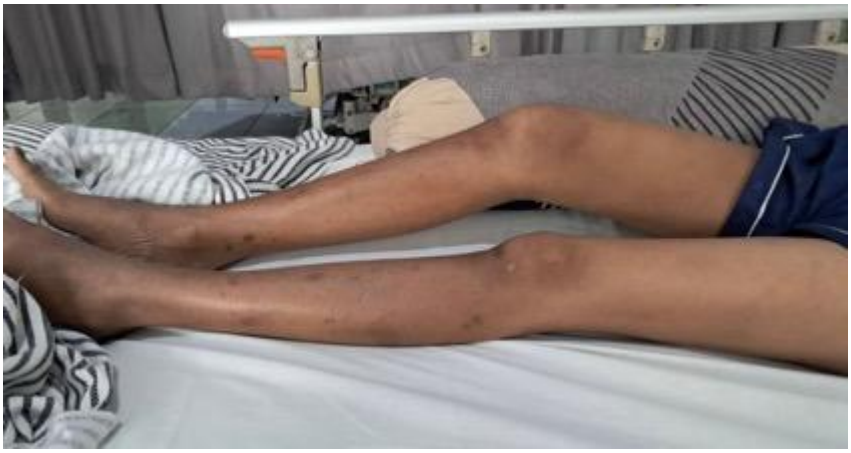

Figure 4. Clinical photograph of the lower limbs at presentation, documenting the painful, movement-restricted right lower limb. The patient's face is not included in order to preserve privacy.

Bone mineral density assessment

Bone mineral density was assessed by dual-energy X-ray absorptiometry (DXA) across multiple regions. The forearm was specifically evaluated because acute pain precluded reliable positioning and interpretation at the symptomatic right lower limb. The complete densitometric results are detailed in Table 2. The lowest value was recorded at the left forearm (total radius), with a Z-score of −3.5, confirming bone mineral density profoundly below the expected range for the patient's age. By contrast, and as also detailed in Table 2, the femoral neck and total femur Z-scores were near the age-expected mean (ranging from −0.4 to +0.3), while the lumbar spine could not be validly assessed because of multiple osteophytes and sclerosis of the vertebral bodies — a recognized pitfall in which degenerative and sclerotic changes spuriously elevate spinal BMD. The regional discordance illustrates why reliance on a single skeletal site, or on the spine alone, may substantially underestimate the true severity of bone disease in thalassemia.[14]

Table 2. Dual-energy X-ray absorptiometry (DXA) results by skeletal region.

Region	Parameter	Result
Right forearm	BMD radius 33% / Z-score	0.661 g/cm² / −2.0
Right forearm	BMD total radius / Z-score	0.526 g/cm² / −2.0
Left forearm	BMD radius 33% / Z-score	0.648 g/cm² / −2.2
Left forearm	BMD total radius / Z-score	**0.435 g/cm² / −3.5**
Right femur	BMD femoral neck / Z-score	0.814 g/cm² / −0.4
Right femur	BMD total femur / Z-score	0.861 g/cm² / −0.3
Left femur	BMD femoral neck / Z-score	0.881 g/cm² / −0.1
Left femur	BMD total femur / Z-score	0.931 g/cm² / +0.3
Lumbar spine	Evaluation	Not valid (multiple osteophytes and vertebral sclerosis)

Notes: The lowest Z-score (−3.5) was recorded at the left forearm; the lumbar spine was not valid for evaluation owing to osteophytes and sclerosis. Abbreviation: BMD, bone mineral density. Z-score compares the patient's BMD with the mean for an age-, sex-, and ethnicity-matched reference population; a Z-score of −2.0 or below is defined as below the expected range for age.

Working diagnosis

Integrating the acute presentation of severe pain and immobilization with the supporting investigations, the working diagnosis was transfusion-dependent β-TM complicated by thalassemia bone disease with severe osteoporosis (lowest Z-score −3.5), together with a suspected acute pathological fracture or osteonecrosis of the right femoral head, in the setting

of uncontrolled iron overload and combined vitamin D and calcium deficiency. This formulation framed the subsequent multidisciplinary management plan.

Management approach and clinical course

Management was structured around four parallel priorities that mirror the multifactorial nature of the disease. The first priority was acute symptom control and protection of the fragile limb, with analgesia and avoidance of weight-bearing pending dedicated orthopedic assessment of the suspected pathological fracture or osteonecrosis of the femoral head. The second was correction of the severe anemia: with a hemoglobin of 5 g/dL, PRC transfusion was planned in coordination with the hematology-oncology service, both to relieve symptomatic anemia and to suppress the ineffective erythropoiesis that perpetuates marrow expansion. The third priority was optimization of iron-chelation therapy in the difficult context of deferasirox hypersensitivity; the existing deferiprone regimen was reviewed with hematology with a view to achieving the most effective tolerated control of the iron burden reflected in the elevated ferritin and the hemosiderin load seen on MRI.[1]

The fourth priority addressed the bone disease directly. Calcium and vitamin D deficiencies were targeted for repletion as the indispensable metabolic foundation for any subsequent bone-directed pharmacotherapy, and the profound osteoporosis at the forearm was flagged for individualized treatment to be selected with rheumatology and endocrinology input. In parallel, referral for orthopedic evaluation was arranged to characterize the acute hip pathology and to define the risk of fracture and the need for any surgical intervention. The patient was thus managed not by any single specialty but through coordinated input across internal medicine, hematology, endocrinology, rheumatology, and orthopedics — an arrangement that the complexity of her presentation made essential rather than optional.

3. Discussion

Clinical relevance and the diagnostic triad

This report describes the clinical and radiological manifestations of severe TBD in a 27-year-old woman with β-TM, in whom the disease was characterized by profound osteoporosis (lowest Z-score −3.5) and by acute, movement-limiting pain of the right lower limb. Skeletal complications of this kind are a major cause of morbidity in adults with thalassemia and are entirely consistent with the global literature describing bone disease as a frequent and still unresolved problem in this population.[2,5] What distinguishes the present case is not the occurrence of any single abnormality but the simultaneous, image-documented coexistence of three severe features that together map onto the full pathophysiological model of the disease.

The diagnosis of TBD in this patient rested on a coherent triad of findings, each pointing to one limb of the three-pathway pathogenesis. First, the radiological evaluation demonstrated widening of the medullary cavity and an Erlenmeyer flask deformity of the right femur. This deformity is a classic structural hallmark of TBD: chronic ineffective erythropoiesis expands the erythroid marrow, which in turn compresses and thins the cortex and causes a failure of the normal metaphyseal modeling that would otherwise taper the bone, leaving the flask-like undertubulation seen on the radiograph.[2,9] Although the Erlenmeyer flask deformity is not pathognomonic — it is also described in lysosomal storage disorders such as Gaucher disease, in other skeletal dysplasias, and in certain anemias — its presence in a patient with established β-TM is a well-recognized reflection of marrow expansion.[9] Second, the iron-mediated component of the disease was supported by MRI, which showed extensive hemosiderin deposition in bone and, strikingly, in the rectus femoris muscle, in concert with a markedly elevated serum ferritin. These observations confirm the contribution of iron-overload toxicity as a direct driver of bone injury and as a cytotoxic influence on osteoblasts.[10,9] Third, the reduced serum calcium and vitamin D concentrations represented the nutritional and hormonal limb of the

model, acting as secondary factors that aggravate osteopenia and impair optimal mineralization.[15,13]

Pathophysiology: how three pathways converge on the skeleton

The skeleton in β-TM is injured by mechanisms that operate concurrently rather than in isolation. Ineffective erythropoiesis is the primary engine. The chronic anemia and tissue hypoxia of β-TM drive a massive but futile expansion of erythroid precursors, and the resulting marrow hyperplasia physically encroaches on trabecular and cortical bone. This is the same process that, in the appendicular skeleton, produces the widened medullary cavity and Erlenmeyer flask deformity observed in this patient, and that, in the axial skeleton and skull, produces the more familiar radiographic changes of thalassemia.[9,2] Beyond its mechanical effect, the expanded marrow is metabolically active and contributes to a milieu that favors osteoclastic resorption, a process in which the hormone erythroferrone — secreted by erythroid precursors — has recently been implicated in the dysregulation of iron and bone homeostasis.[16]

Iron toxicity constitutes the second pathway and is, in many respects, the most therapeutically tractable. Iron that exceeds the binding capacity of transferrin circulates as non-transferrin-bound iron and is deposited in the skeleton and the endocrine organs. Within bone, excess iron impairs osteoblast proliferation and differentiation, interferes with the incorporation of calcium into the hydroxyapatite lattice, and disturbs the balance between the receptor activator of nuclear factor-κB ligand and osteoprotegerin in favor of resorption; consistent with this, the degree of iron overload correlates with reduced BMD, and erythroferrone has been proposed as a predictor of low BMD and fracture risk in transfusion-dependent thalassemia.[10,11] In parallel, iron deposition in the pituitary, gonads, thyroid, parathyroid, and pancreatic islets produces the endocrinopathies that further undermine bone health.[12] The MRI demonstration of hemosiderin not only throughout the femoral marrow but also within the rectus femoris muscle in this patient is a vivid illustration of how widely distributed and how severe the iron burden had become, and it underscores the mechanistic link between inadequate chelation and skeletal failure.[9]

The third pathway comprises the endocrine and nutritional deficiencies that accrue over decades of disease and iron loading. Hypogonadism is the most consistently reported and is strongly associated with low BMD in thalassemia, but growth hormone deficiency, disturbed glucose homeostasis, hypoparathyroidism, and deficiencies of vitamin D and calcium all contribute to a state of reduced bone formation.[12,13] The reduced calcium and vitamin D levels measured in this patient are therefore not incidental laboratory abnormalities but mechanistically important, modifiable components of her bone disease; vitamin D deficiency in particular is prevalent in β-TM and is associated with poorer bone-health status.[15,13] The net biological result of these three converging pathways is a skeleton dominated by impaired bone formation, upon which a variable increase in resorption is superimposed — a distinction that, as discussed below, has direct implications for the rational selection of bone-directed therapy.[2,10]

Differential diagnosis of the Erlenmeyer flask deformity and the painful limb

Although the Erlenmeyer flask deformity is, in this clinical setting, a recognizable signature of marrow expansion in β-TM, it is not specific to thalassemia, and its appropriate interpretation depends on the clinical context. The deformity reflects a failure of metaphyseal remodeling and is described across a range of conditions, including Gaucher disease and other lysosomal storage disorders, osteopetrosis, metaphyseal dysplasia (Pyle disease), and other skeletal dysplasias, as well as hemoglobinopathies in which marrow hyperplasia is prominent.[9] In a 27-year-old with a two-decade history of transfusion-dependent β-TM, hepatosplenomegaly, and biochemical iron overload, the unifying diagnosis is parsimonious and secure; the value of recognizing the broader differential lies in avoiding diagnostic anchoring and in remaining alert to coexisting pathology.

The acute, immobilizing pain superimposed on this chronic deformity carries its own differential that must be resolved urgently. The leading considerations are pathological fracture through osteoporotic bone and osteonecrosis of the femoral head; both are well described in thalassemia and both can present with the loss of flexion and extension observed here.[8,9] Additional contributors include stress reaction within fragile bone, iron-related myopathy of the rectus femoris suggested by the soft-tissue hemosiderin on MRI, and, less likely in the absence of fever or local inflammatory signs, septic or inflammatory arthropathy. Cross-sectional imaging of the hip and orthopedic assessment are therefore not merely confirmatory but decision-altering, since the identification of a fracture or of advanced osteonecrosis would change management from medical optimization to potential surgical intervention.

Analysis of the acute presentation and densitometric interpretation

The temporal pattern in this case — years of intermittent pain culminating in an abrupt, immobilizing exacerbation — is a characteristic and clinically important presentation of advanced TBD. Chronic, fluctuating bone pain in thalassemia is commonly attributable to marrow expansion and to recurrent microarchitectural stress failure within osteoporotic bone, and it contributes materially to the impaired quality of life reported by adults with the disease.[17] An acute escalation that renders the limb unable to flex or extend, however, raises a higher-stakes differential — pathological fracture and osteonecrosis — that warrants urgent evaluation.[8] The extension of hemosiderin deposition into the rectus femoris demonstrated on MRI introduces a further consideration, since iron-related myopathy and soft-tissue involvement may contribute independently to movement-related pain.[9]

The densitometric findings in this case also carry an instructive lesson about the interpretation of BMD in thalassemia. As detailed in Table 2, the patient's femoral Z-scores were close to the age-expected mean, yet her left-forearm Z-score reached −3.5 and her lumbar spine was uninterpretable because of osteophytes and sclerosis. Reliance on the hip or spine alone would have grossly underestimated the severity of her bone disease. Degenerative and sclerotic changes spuriously raise apparent spinal BMD, and site-to-site discordance is common in thalassemia; assessment of multiple skeletal sites — and emerging tools such as the trabecular bone score — can therefore add value where conventional axial measurements are unreliable.[14,7] In this patient the forearm measurement was the single most revealing densitometric result and anchored the diagnosis of profound osteoporosis.

Therapeutic challenge I: iron control constrained by drug hypersensitivity

Optimal control of the underlying disease is the foundation of TBD management, and in this patient that foundation was compromised by a documented hypersensitivity to deferasirox. The loss of a first-line oral chelator narrowed the therapeutic options to deferiprone, with or without deferoxamine, and contributed to an iron burden — reflected in both the elevated ferritin and the MRI hemosiderin load — that could not be fully controlled.[1] Because iron toxicity directly impairs osteoblast function and correlates with reduced BMD, incomplete chelation does not merely threaten the heart and liver in the conventional sense but also undermines any attempt to rebuild bone; the skeletal response to bone-directed therapy is unlikely to be optimal while the iron drive to bone loss persists.[10,11] Combination oral chelation with deferasirox and deferiprone is effective in lowering iron burden, but is precluded here by drug allergy, which makes the construction of an effective tolerated regimen with hematology all the more important — since every increment of iron control is also an investment in skeletal recovery.[1]

Therapeutic challenge II: treating profound osteoporosis in thalassemia

The patient's severe osteoporosis, with a Z-score of −3.5, demands aggressive and individualized treatment, and its rational design begins from the recognition that TBD is predominantly a disorder of reduced bone formation with a superimposed increase

in resorption.[2,10] This pathophysiology raises a legitimate question about how far purely antiresorptive therapy can go. Nonetheless, the available evidence supports a central role for bisphosphonates as first-line treatment of thalassemia-associated osteoporosis; a randomized controlled trial demonstrated that weekly alendronate 70 mg over 12 months significantly improved BMD with a favorable safety profile,[18] and a Cochrane systematic review of treatment for osteoporosis in people with β-thalassaemia concluded that bisphosphonates can increase BMD, although the certainty of evidence for fracture-related outcomes remains limited.[19] In this patient, correction of vitamin D and calcium deficiency is an indispensable foundation for any pharmacological strategy but is, on its own, insufficient to address a Z-score of −3.5.[15,13]

When osteoporosis is severe or refractory, further options merit consideration. Denosumab, a monoclonal antibody against the receptor activator of nuclear factor-κB ligand, has been evaluated in thalassemia-associated osteoporosis, where it improved bone density and alleviated pain, providing a useful antiresorptive alternative for patients in whom bisphosphonates are unsuitable or insufficiently effective.[20] More fundamentally, because the dominant defect in TBD is impaired bone formation, anabolic therapy such as teriparatide, a recombinant fragment of parathyroid hormone that directly stimulates osteoblastic bone formation, is mechanistically attractive and offers a rationale for treating the formation deficit that antiresorptives do not address; its use in a young patient requires careful consideration of duration limits and monitoring, and the thalassemia-specific evidence base remains smaller than that for bisphosphonates.[19] The sequence and combination of these agents, layered upon optimized chelation and correction of endocrine and nutritional deficits, should be individualized to the patient's evolving response.

Toward a multidisciplinary, individualized strategy

The central message of this case is that bone-disease management in β-TM cannot be separated from hematological and endocrine control; the three pathogenic pathways must be addressed in parallel rather than in sequence. Several practical principles follow. First, proactive skeletal surveillance with DXA should begin early and should sample multiple sites, recognizing that axial measurements may be unreliable and that the forearm may reveal disease that the hip and spine conceal.[7,14] Second, care should be delivered by a coordinated multidisciplinary team spanning hematology, endocrinology, rheumatology, and orthopedics, so that chelation, hormone replacement, nutritional repletion, bone-directed pharmacotherapy, and the evaluation of acute orthopedic emergencies proceed in concert.[1,19] Third, bone therapy must be individualized — particularly in patients, such as this one, whose chelation options are constrained by drug hypersensitivity or whose response to standard therapy is suboptimal.[20]

Finally, this case is a reminder of the broader trajectory of β-TM in regions of high prevalence such as Indonesia. As transfusion and chelation extend survival, a growing adult population will live long enough to develop the cumulative skeletal consequences of the disease.[4,3] Anticipating TBD, screening for it before it becomes symptomatic, and treating it aggressively when it is found are therefore increasingly important components of comprehensive thalassemia care.

Monitoring, prognosis, and quality of life

Beyond the immediate management of the acute presentation, the longer-term care of this patient hinges on structured monitoring and on attention to quality of life. Serial DXA at consistent, reliably measurable sites allows the trajectory of bone mass to be tracked and the response to therapy to be judged objectively, while adjunctive tools such as the trabecular bone score may refine the assessment of skeletal fragility.[14] Iron status should be followed not only by serum ferritin but, where feasible, by organ-specific magnetic resonance quantification, so that chelation can be titrated against the true tissue burden rather than a single surrogate.[10] Endocrine surveillance for hypogonadism, thyroid and parathyroid dysfunction, growth hormone deficiency,

and disturbed glucose homeostasis is integral, because each of these, if identified and treated, removes a contributor to ongoing bone loss.[12,13]

The human consequences of advanced TBD are substantial. Chronic bone pain, deformity, fragility fracture, and the fear of immobility erode physical function, independence, and psychological wellbeing, and they compound the considerable burden already imposed by lifelong transfusion and chelation.[17] Framing the goals of treatment in terms of preserved mobility, pain relief, and the prevention of fracture — rather than BMD numbers alone — helps align the multidisciplinary plan with what matters most to the patient. In a woman of working age who had previously been active enough to hike in the mountains, restoring and protecting function is a central, not peripheral, objective of care.

Limitations

This report describes a single patient and therefore cannot establish causality or generalizability. Certain endocrine parameters that would have refined the pathophysiological picture — including gonadal, thyroid, parathyroid, and growth-hormone axes — were not detailed, and quantitative organ iron concentrations were not available to complement serum ferritin. The acute hip pathology suspected clinically (pathological fracture or osteonecrosis) warranted dedicated cross-sectional imaging and orthopedic assessment for definitive characterization, and longitudinal follow-up of the response to chelation optimization and bone-directed therapy was beyond the scope of this presentation. These limitations notwithstanding, the case offers a clear, image-documented illustration of severe, multi-pathway TBD and of the clinical reasoning its management demands.

4. Conclusion

This case of β-TM in a 27-year-old woman confirms that thalassemia bone disease is a complex, progressive, and highly morbid complication. The clinical picture — profound osteoporosis with a Z-score of −3.5, a classic Erlenmeyer flask deformity of the femur, and direct imaging evidence of iron toxicity in the form of hemosiderin deposition in both bone and muscle — reflects the simultaneous failure of the three pathways that maintain skeletal health: marrow expansion from ineffective erythropoiesis, iron-overload toxicity, and hormonal and nutritional deficiency. These abnormalities were compounded by a constrained iron-chelation strategy mandated by deferasirox hypersensitivity and by combined calcium and vitamin D deficiency.

Acute pain and immobilization in a patient with severe osteoporosis underscore the need for urgent orthopedic evaluation and a careful assessment of the risk of pathological fracture and osteonecrosis. The case further emphasizes that effective management of thalassemia bone disease requires a multidisciplinary strategy extending well beyond the correction of anemia and iron overload. Aggressive correction of hormonal and nutritional deficiencies, optimization of chelation, and individualized bone-directed therapy — bisphosphonates as a foundation, with denosumab or anabolic agents considered in severe or refractory disease — are required to rebuild bone mass and to prevent long-term disability. Early, multi-site densitometric surveillance and coordinated multidisciplinary care offer the best prospect of altering the natural history of bone disease in adults with β-thalassemia major.

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