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β - Thalassemia Intermedia with Severe Bone Abnormality

I Ketut Suyasa[1], I Gusti Ngurah Wien Aryana[2], Hendra Aryudi Hamzah[3]

[1, 2]Department of Orthopaedic and Traumatology, Sanglah Hospital/Faculty of Medicine, University of Udayana, Bali, Indonesia

Corresponding Author Email: *hendrahamzah3[at]yahoo.com*

Abstract: ***Introduction: β - thalassemia (βth) is a congenital hematologic disorder that affects the production of β - globin chains, resulting in impaired haemoglobin function. βth is classified into β - Thalassemia minor, β - Thalassemia intermedia (βti), and β - Thalassemia major. Bone abnormalities are common including osteoporosis and fracture in βti patients. This case study aims to highlightthe features of bone abnormalities in β - thalassemia intermedia patients. Case Description: A 25 - year - old woman with β - Thalassemia intermedia (βti) presented to our clinic with pain on her right knee and inability to bear her weight, after stumbling and falling during her way to the bathroom. Patient had previous history of trauma affecting her left leg. On radiographic examination, we found a right distal femoral fracture and a left subtrochanteric fracture. The patient was treated by packed red cell transfusion, internal fixation, and bisphosphonate. After two months of evaluation, the fractures had started to unite and the patient had improved her range of motion of her both leg. Bone abnormalities are common in βti patients including pathologic fracture in long bones. These patients should be treated comprehensively in order to improve bone density andlower the risk of fractures.***

Keywords: Case report, Pathologic fracture, Bone abnormalities, β - Thalassemia

1. Introduction

β - thalassemia intermedia (βti) is one of clinical subtypes of a congenital hematologic disorder that affects the production of β globin chains production, resulting in anemia, ineffective erythropoiesis, and bone marrow expansion. ([1 - 3]) Unlike the more severe type (β - thalassemia major), βti patients do not require regular blood transfusions to maintain normal haemoglobin level. Regular blood transfusions could lead to iron toxicity in multiple organs, including heart, liver, endocrine glands, and bone.[4 - 7]

One of the complications of βti is bone abnormalities. This condition is very common but poorly understood. Bone abnormalities are considered to be affected by multiple factors, including genetic factors, hormonal, iron overload, iron chelation therapy, nutritional deficits, and decreased levels of physical activity.1 βti patients were reported to develop more severe bone abnormalities, including low bone mineral density (BMD), fractures, deformity, and chronic bone pain. Most of the fractures were caused by minimal trauma. Bone abnormalities started to develop at second decade of life.8 [- 11] The prevalence of osteoporosis was reported to be 81.6% and the prevalence of fractures was reported to be 12% in βti patients.[4, 12 - 14]

Treatment of bone abnormalities in βti patients should be focusing on reducing the risk and prevention of fractures and disability to reduce the morbidity and mortality.[15] Fractures of long bones, especially those involving the femur in βti patients, were treated as pathological fractures.[1] Bone abnormalities can be minimized by maintaining normal haemoglobin value, iron chelation therapy, bisphosphonate, sufficient calcium and vitamin D levels, and physical activity.[8]

We presented a βti patient who suffered pathological fractures and a non - union fracture. In this report, we aim to highlight the features of bone abnormalities in β - thalassemia intermedia patient

2. Case Report

A 25 - year - old woman who was previously diagnosed with β - Thalassemia intermedia, presented to our clinic with complaints of pain on her right knee and inability to bear her weight, after stumbling and falling during her way to the bathroom. She landed on her right knee. Prior to this injury, she ambulated with assistance due to a previous injury in 2019, where she fell onto the left side of her leg from a standing position, and could not bear weight on her left leg afterwards. She did not get any treatment then. She also did not get regular blood transfusions and iron chelation therapy for her β - Thalassemia.

On examination, there was minimal swelling and deformity over the upper side of her right knee. Tenderness was found over the top of the knee area. The patient's skin was pale as well as the conjunctiva. Radiographic examination revealed right distal femoral fracture and left subtrochanteric fracture (Figure 1 - 2). Rarefaction of the cancellous bone, loss of cortical thickness, and widening of the intramedullary canal were seen on both femurs. Laboratory analysis showed moderate anemia (8 g/dL). We treated the patient with packed red cell transfusion, bisphosphonate, and internal fixation. Plate and screw fixation was performed for the right distal femoral fracture, and intramedullary nail was inserted into the left femur for the subtrochanteric fracture. Callus formation could be seen after a 2 - month follow - up (Figure 3). She is currently on physical therapy focusing on range of motion exercises.

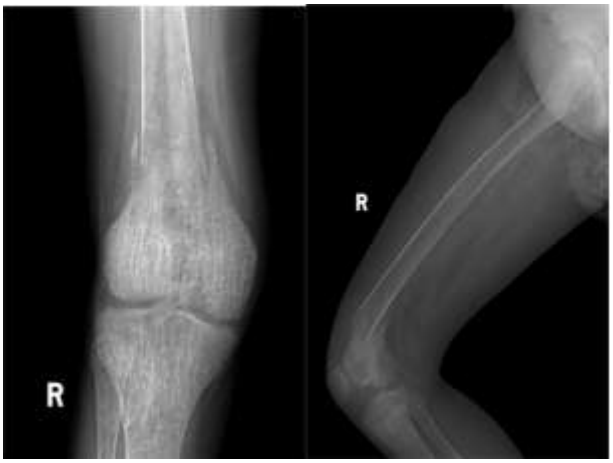

Figure 1: AP and Lateral View of Right Femur

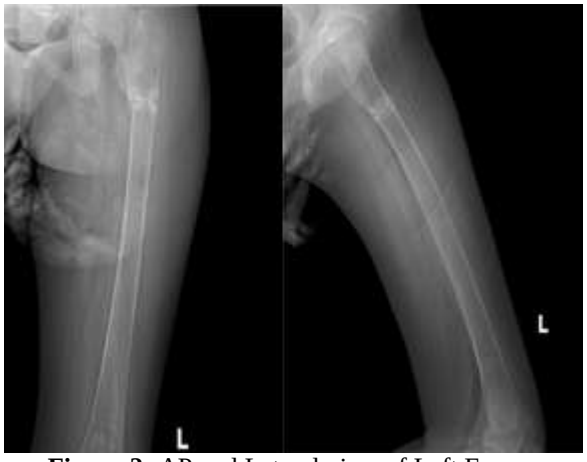

Figure 2: AP and Lateral view of Left Femur

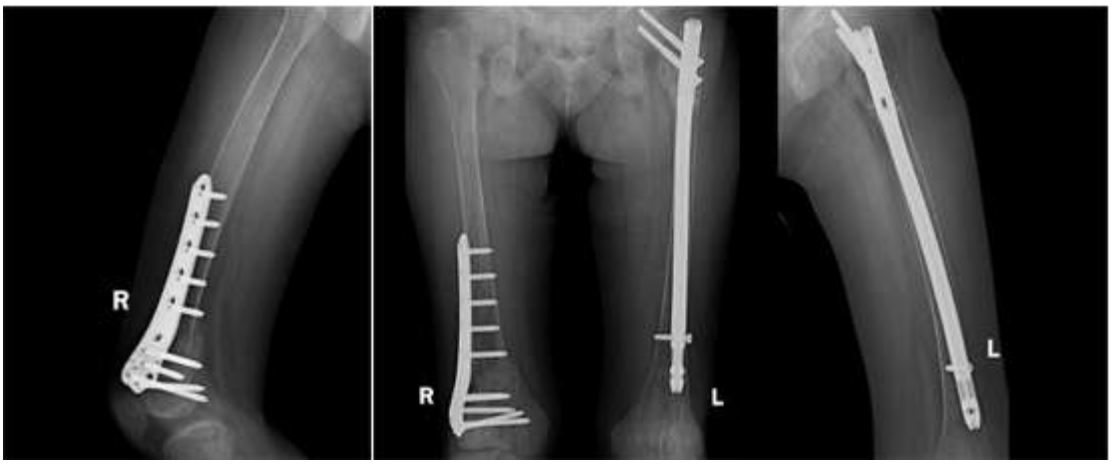

Figure 3: Locking plate on right distal femur and Intramedullary nail in left femur

3. Discussion

The pathogenesis of bone abnormalities in βti patients is considered to be multifactorial. It leads to diagnostic and therapeutic challenges. There were increased bone resorption and decreased bone deposition, resulting in reduced BMD. These conditions were considered due to impaired osteoblast activity and enhanced osteoclastic bone resorption.1, [16, 17] Genetic factors have been reported to have a role in osteoporosis in βti patients. Polymorphism in the Vitamin D receptor (VDR) and COLIA1 has been found to be associated with lower BMD than normal patients.[18]

Patients with βti displayed low serum IGF - 1 levels, which is a very important factor for bone remodelling and osteoblast differentiation. Insufficiency of the GH - IGF1 axis leads to impaired osteoblast proliferation and bone matrix formation while increasing osteoclast activation.9 Increased serum levels of Dickkopf - 1 and sclerostin, which inhibit Wntsignalling system and osteoblast function, have been demonstrated to correlate with reduced BMD.[19] Dickkopf - 1 and sclerostin have been considered to become good markers of bone resorption in βti patients.[1] Proliferation of osteoblasts, bone maturation, and mineralization are also impaired by iron toxicity in bone tissue.[8]

The receptor activator of nuclear factor kappa B (RANK) / RANK ligand (RANKL) / Osteoprotegerin (OPG) system has been shown to have a role in the mechanism of bone resorption as an important mediator of osteoclast differentiation and formation. βti patients showed higher circulation levels of RANKL with no differences in plasma levels of OPG, resulting in the increased osteoclastic activity of bone resorption.9 Iron overload stimulates the secretion of RANKL.[8]

Endocrine abnormalities in βti patients were due to harmful effects of iron overload to endocrine glands, including hypogonadism, hypothyroidism, hypoparathyroidism, and diabetes. Hypogonadism has been considered as the main endocrine abnormality that affects bone structure by increasing osteoclast activity and reducing bone formation.[19] Hypogonadal thalassemia patients have lower BMD compared to those with normal gonadal function.[8] Other factors, such as Low vitamin D levels and inadequate physical activity, may influence on bone changes in βti patients.[1]

Ineffective erythropoiesis due to defects in β globin chains production leads to bone marrow expansion and thinning of the cortex. Bone marrow expansion has been considered as one of the most important factors in determining bone destruction in thalassemia patients, which mainly involving trabecular bone.[20]

The frequency of decreased BMD has been observed in 2/3 of βti patients, especially in the spine, distal radius, and

femur. Meanwhile, the prevalence of osteoporosis has been reported to be 81.6% in βti patients. The relationship between low BMD and fracture is an acknowledged concept in osteoporosis. These progressive bone abnormalities start to develop at the age of 20s.[8, 17] The prevalence of fractures in βti patients was reported to be 12%. In 10% of the cases, fractures involve the spine, hips, and pelvis. Fractures of the femur should be treated as pathological fractures and require the stabilization of the entire bone with intramedullary nailing due to the fragility of the bone.[4, 21]

Bone healing time in βti patients is generally normal within the expected time frame.1[5] The causes of non - union in subtrochanteric fracture are the same as other fractures, including motion at the fracture site, inadequate vascular supply, fracture gap, and infection. Deforming forces caused difficulty in achieving anatomic reduction by close reduction.2[2] Without proper treatment of our patient previous injury, stability on the fracture site could not be achieved leading to a non - union left subtrochanteric fracture. We decided to treat our patient with internal fixation to provide stability to the fracture site and early mobilization. Our patient had reduced physical activity due to her previous injury. Physical activity and daily exercise are considered to have a positive impact on bone strength.4

A comprehensive treatment for bone abnormalities in βti patients includes prevention and curative treatment, which is a combination between specific pharmacological agents and general therapeutic measures. General therapeutic measures include blood transfusion, adequate iron chelation therapy, healthy nutrition, and adequate physical activity, vitamin D and Calcium supplementation.4 Blood transfusion and iron chelation therapy have led to improved bone health through a various mechanisms in reducing medullary expansion and cortical bone thinning, the incidence of hypogonadism, and other endocrine abnormalities that predispose to bone abnormalities. Current guideline suggesting to maintain haemoglobin levels greater than 9 – 10.5 g/L.1[5, 17]

Low BMD with low trauma fractures or progressive significant BMD loss without low trauma fracture should be considered as an indication for specific treatments such as bisphosphonates, denosumab, hormone replacement therapy, and other osteoporosis treatment.8 Bisphosphonates are potent inhibitors of bone resorption by reducing the induction, proliferation, differentiation, and lifespan of osteoclasts. It is widely used in the treatment of osteoporosis. Intravenously administered bisphosphonates are more preferred to be used and showing good results in increasing BMD. Denosumab is a fully human monoclonal antibody to RANKL. It prevents the binding of RANKL to RANK resulting in reduced bone resorption. Many trials using denosumab showed significant improvement in BMD.1[6] Specific pharmacological agent for bone abnormalities in βti still needs to be studied.

Progressive bone abnormalities in βti patients are bounded to take place over time and are at risk to suffer multiple pathological fractures. To prevent fractures in βti patients, they should be evaluated often with clinical assessment, routine screening for causes of secondary osteoporosis, and imaging procedures.

4. Conclusion

Bone abnormalities are common in βti patients including fractures which affecting morbidity. There are multiple factors affecting bone changes in these patients. A comprehensive therapeutically approach to bone includes adequate blood transfusion, prevention of iron toxicity, specific pharmacological therapy, and physical activity that could lower the risk of fractures. βti patient with pathologic fracture involving long bone should be treated using anti - osteoporosis medication to increase BMD and lower the risk of fracture. Considering all of the bone changes in these patients develop at young age, management of fracture in βti patients should include every aspect that could promote bone union and early ambulation.

5. Conflict of Interest

There is no competing interest regarding the manuscript

6. Ethic Consideration

Informed consent has been obtained from the patient according to the consideration of the ethics based on the COPE guidelines prior to the study being conducted

7. Funding

None

8. Author Contribution

All authors equally contribute to the study by selecting case, providing appropriate surgery procedures, and writing the case study through publication.

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