Dear Editor,

Thalassaemia is a genetic haemoglobinopathy secondary to a defect in globin chain production. Morbidity from thalassaemia can arise from the deleterious effects of ineffective erythropoiesis or the complications associated with multiple transfusions. Osseous complications can occur in patients with thalassaemia. The ineffective erythropoiesis leads to marrow expansion with a thinning of the cortices. In addition, endocrinopathy from transfusion-related complications can worsen bone density. These factors predispose patients with thalassaemia to a higher risk of fracture.

Osseous complications in thalassaemia have been documented previously. Data from the Thalassemia Clinical Research Network of North America showed that fractures occurred in 36% of their patients with thalassaemia, with 8.9% of the patients reporting 3 or more lifetime fractures. However, there is a paucity of literature on multiple pathological fractures occurring in a patient with beta thalassaemia major. We describe a patient with transfusion-dependent beta thalassaemia major complicated by hypogonadism secondary to transfusion haemachromatosis. The patient suffered multiple pathological fractures from minor trauma. This case report serves to highlight the features of multiple pathological fractures secondary to endocrinopathy from thalassaemia.

Case Report

The patient is a 38-year-old Chinese male with a known medical history of transfusion-dependent beta thalassaemia major. He was diagnosed with beta thalassaemia in childhood and underwent a splenectomy at the age of 16 years in an attempt to reduce haemolysis. He received blood transfusions twice a month to maintain a baseline haemoglobin level of 8 g/dL. In view of his transfusion-dependent thalassaemia, he was started on iron chelation therapy with desferoxamine (subcutaneous desferrioxamine 1500 mg, 5 times per week and oral deferiprone 1000 mg, 3 times a day). The ferritin levels remained stable at 6000.3 ug/L and 5833.4 ug/L at 25 and 30 years of age, respectively.

The patient first presented to our institution in 2001 with a left humerus supracondylar fracture after self-skidding whilst riding a motorcycle. Plate osteosynthesis was performed and the fracture went on to unite without complication. In 2006, the patient fell onto the right side from a standing position and suffered a right intertrochanteric fracture. A dynamic hip screw fixation was performed and the fracture united in 10 months. At the age of 32 years (2008), despite the iron chelation therapy, the patient developed endocrinopathies due to iron overload. He developed diabetes mellitus, hypothyroidism, hypoparathyroidism and hypogonadism. The biochemical investigations revealed a free T4 of 9.4 pmol/L, testosterone level of 2 nmol/L and a sex hormone binding globulin (SHBG) level of 183 nmol/L. The patient’s renal and liver panel was within normal range, as were the levels of calcium, vitamin D and parathyroid hormone. The patient was started on oral hypoglycaemic therapy, thyroid replacement therapy (thyroxine 50 mcg) and testosterone replacement therapy (intramuscular testosterone cipionate 150 mg monthly). The patient’s osteoporosis worsened after the development of endocrinopathies. Dual-energy x-ray absorptiometry (DEXA) bone mineral densitometry (BMD) of the proximal femur worsened from a Z score of -2.9 (in 2009) to -3.9 (in 2013). Despite worsening osteoporosis, the patient declined bisphosphonate therapy.

After the development of his endocrinopathies, the patient suffered several fragility fractures from trivial trauma (Table 1). At the age of 32 years, the patient fell from a standing position and suffered a right tibia and fibula fracture. The patient was treated with a cast. Unfortunately, a fall from a standing position later in the same year led to a right femoral periprosthetic fracture. The fracture occurred just distal to the previous dynamic hip screw. Removal of the right dynamic hip screw and intramedullary nailing of the right femur was performed. The right femur fracture united after 8 months.

At the age of 36 years, the patient fell again from a standing position and suffered a left proximal humerus fracture. He was treated non-surgically and the fracture united in 3 months. However, the patient was involved in a road traffic accident 2 months later and suffered a left humeral midshaft fracture. This was also treated non-surgically. At the age of 37 years, the patient fell from a standing position and suffered bilateral tibia and fibula fractures. These fractures were treated with plate osteosynthesis.
Three months later, the patient complained of pain over the right tibia and left humerus, with no history of trauma or fall. It was then noted on radiographs that there was a new right tibia periprosthetic fracture (Fig. 1) as well as a left humerus periprosthetic fracture (Fig. 2). This was the third fracture to occur in his left humerus in just under 1 year. An intramedullary nail was inserted into the right tibia. The left humerus was treated non-surgically. The left humerus and right tibia united after 7 months. The patient subsequently complained of low back pain with no history of trauma or fall. Radiographs revealed a L2 compression fracture. This was treated non-surgically.

The patient presented to us once more in 2014 with a left comminuted subtrochanteric fracture after a fall off his bed (Fig. 3). Surgical fixation with an intramedullary nail was performed. On postoperative day 3, the patient complained of right humerus pain after a routine blood pressure measurement. X-rays revealed a right pathological humeral shaft fracture (Fig. 4). Intramedullary nailing was performed for the right humeral fracture.

Unfortunately, the patient developed an unrelated perforated pyloric ulcer during the twentieth postoperative and demised.

Table 1. Fracture History

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at Injury (Years)</th>
<th>Fracture Characteristics</th>
<th>Mechanism of Injury</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>Left elbow supracondylar fracture</td>
<td>Road traffic accident (Motorcyclist self-skidded)</td>
<td>Plate osteosynthesis</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>Right femur intertrochanteric fracture</td>
<td>Fall from a standing position</td>
<td>Dynamic hip screw</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>Right tibia and fibula shaft fracture</td>
<td>Fall from a standing position</td>
<td>Non-surgical treatment</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>Right femur periprosthetic fracture</td>
<td>Fall from a standing position</td>
<td>Intramedullary nailing</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td>Left proximal humerus shaft fracture</td>
<td>Fall from a standing position</td>
<td>Non-surgical treatment</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>Left humerus midshaft fracture</td>
<td>Road traffic accident (driver at 40 km/hr)</td>
<td>Non-surgical treatment</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>Right tibia fracture</td>
<td>Fall from a standing position</td>
<td>Plate osteosynthesis</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>Left tibia fracture</td>
<td>Fall from a standing position</td>
<td>Plate osteosynthesis</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>Left humerus midshaft fracture</td>
<td>Fall from a standing position</td>
<td>Non-surgical treatment</td>
</tr>
<tr>
<td>10</td>
<td>37</td>
<td>Right tibia periprosthetic fracture</td>
<td>No known mechanism</td>
<td>Intramedullary nailing</td>
</tr>
<tr>
<td>11</td>
<td>37</td>
<td>L2 compression fracture</td>
<td>No known mechanism</td>
<td>Non-surgical treatment</td>
</tr>
<tr>
<td>12</td>
<td>38</td>
<td>Left femur subtrochanteric fracture</td>
<td>Fall from bed</td>
<td>Intramedullary nailing</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>Right humeral shaft fracture</td>
<td>Pressure from the blood pressure monitoring cuff</td>
<td>Intramedullary nailing</td>
</tr>
</tbody>
</table>

*Occurred after the development of hypogonadism.
Discussion

Osseous deformity, bone pain and fractures are some of the common osseous complications associated with thalassaemia. The ineffective erythropoiesis stimulates bone marrow expansion by up to 30 to 40 times, leading to a thinning of the cortices. Bone marrow expansion in bones such as the facial bones and long bones of the extremities can lead to the classical “chipmunk facies” appearance. Thalassaemia is associated with a low bone mineral density. It is postulated that an increased bone turnover in thalassaemia does not allow for positive bone accrual and attainment of optimal peak bone mass. Polymorphism of the collagen type Ia1 (COLIA 1) gene has been associated with reduced BMD in postmenopausal osteoporosis. Interestingly, polymorphism of COLIA 1 gene has also been noted in up to 30% of thalassaemic patients. This may contribute to the development of osteoporosis in thalassaemic patients. Other factors that may contribute to the development of osteoporosis include endocrinopathies, osteoblast toxicity from iron overload or bone toxicity from desferoxamine usage.

Regular transfusion was introduced in the 1960s in an attempt to maintain a normal haemoglobin level. Iron overload from multiple transfusions is a known complication. The body has no natural means of iron extraction and iron accumulation can occur in regions such as the myocardium, liver and endocrine glands. Iron chelation therapy with desferoxamine is widely used to assist in the excretion of chelated iron complexes from the body.

Endocrinopathy is a known complication in patients with transfusion-dependent thalassaemia. The anterior pituitary gland is sensitive to iron overload, and this can lead to a hypothalamic-pituitary axis dysfunction resulting in hypogonadism. Common endocrinopathies include thyroid dysfunction, hypogonadism, diabetes and dyslipidaemias. In adult-onset hypogonadism, there is a profound effect on the BMD, which may worsen the osteoporosis. Male patients with thalassaemia, endocrine dysfunction and fracture history are at particular risk for future fracture.

Hypogonadism can have a profound effect on the fracture risk of a thalassaemic patient. Androgens have a proliferative effect on osteoblasts and an inhibitory effect on osteoclasts. In hypogonadism, the diminished levels of androgens lead to a lowered BMD. In our patient, he suffered 2 fractures prior to the development of hypogonadism, with 1 fracture a result of minor trauma. There was an increased incidence of pathological fractures after the development of hypogonadism. He suffered a further 11 fractures after developing hypogonadism, of which 10 were due to minor trauma. In particular, a humeral fracture occurred from the use of an inflated blood pressure cuff. Notably, many of the fractures occurred from a low energy mechanism, with multiple fractures occurring in the same bone. The increase in pathological fractures after the development of hypogonadism reinforces the fact that hypogonadism is a strong independent predictor of fragility fractures in patients with thalassaemia. Patients with transfusion-dependent thalassaemia should be assessed regularly for hypogonadism. Alendronate therapy has been shown to increase the bone mineral density in thalassaemia-induced osteoporosis. Patients should be counselled for an increased risk of pathological fracture after the development of hypogonadism.
Patients with transfusion-dependent beta thalassaemia major complicated by hypogonadism are at a high lifetime risk of fracture due to worsening and profound osteoporosis.3,9 Such patients may suffer multiple pathological fractures from seemingly trivial trauma. These patients should be counselled appropriately for a high risk of fracture and their activities should also be modified to reduce risk. Surgical considerations in these patients include the use of locking plates and intramedullary devices where possible, due to the poor bone quality and propensity for implant failure.

Patients with transfusion-dependent beta thalassaemia major complicated by endocrinopathy tend to present later in adulthood. This is due to the delayed onset of endocrinopathy secondary to iron overload from multiple transfusions. As such, physicians should be aware of this clinical entity and conduct regular screening for the development of endocrinopathies in transfusion-dependent beta thalassaemia patients. If endocrinopathies develop, treatment should be started to prevent worsening osteoporosis.

Conclusion

Thalassaemia is a common haemoglobinopathy. Patients with transfusion-dependent thalassaemia should be placed on iron chelation therapy and monitored closely for development of endocrinopathies. Multiple pathological fractures can occur in transfusion-dependent thalassaemia complicated by hypogonadism. These patients should be counselled on the risks of multiple pathological fractures.

REFERENCES


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