TITLE OF CASE

Beware of bone pain with bisphosphonates

SUMMARY

A 71 year old lady who had been taking ibandronate for 10 years presented to an Endocrinology Department with persistent mid-thigh pain. Pelvic x-ray showed bilateral femoral cortical expansion, indicating impending atypical femoral fractures. Atypical femoral fractures have been linked to long-term bisphosphonate therapy and have morbidity and mortality similar to that of hip fractures. Such fractures can be averted by regular reviews of bisphosphonate therapy and vigilance for prodromal symptoms. This patient's bisphosphonate therapy was stopped and fractures were avoided by treatment with vitamin-D and parathyroid hormone.

BACKGROUND

It has been estimated that osteoporosis affects 2.8 million people in the UK. Bisphosphonates can reduce the risk of hip fractures by 30–50% and vertebral fractures by 30–70%.[1] Paradoxically, bisphosphonate therapy has recently been associated with an increase in risk of one particular type of fracture, namely a transverse femoral diaphyseal fracture that tends to occur with minimal trauma, the so-called 'atypical femoral fracture' (AFF). These result in morbidity and mortality similar to that of hip fractures. AFFs are often preceded by a typical prodromal thigh pain so doctors should therefore be vigilant for prodromal symptoms of atypical femoral fractures in patients on bisphosphonate therapy and adopt an appropriate therapeutic approach.[2]

CASE PRESENTATION

A 71 year old vegetarian lady of Indian origin presented to the Norfolk & Norwich University Hospital Endocrinology Department in 2012 with generalised aches and pains. Her past medical history included osteoporosis diagnosed in 1999 on a DEXA scan, bilateral Colles' fractures in 2008, and pernicious anaemia. Her regular medications were calcium carbonate 2,500 mg one tablet daily (Calcichew Forte), calcitriol (1,25-Dihydroxy-vitamin-D) 500ng daily, diclofenac 100mg daily, ibandronic acid 150mg monthly, started in 2002, and vitamin B12 injections. The ibandronic acid was started for osteoporosis and was chosen for the convenience of a once monthly oral preparation, the calcitriol had been prescribed for vitamin D deficiency.

INVESTIGATIONS

• DEXA 12/1/2011: T-scores -0.9 in the lumbar spine, -1.8 in the left hip, -1.6 left femoral neck (Z-scores of 1, -0.5 and 0 respectively)
Blood tests 21/5/2012:
• 25-OH-Vitamin-D 13 nmol/L (50 - 120)
• Adjusted Calcium 2.33 mmol/L (2.10 - 2.60)
• Alkaline Phosphatase 63 U/L (38 – 126)
Blood tests 20/11/2012:
• Parathyroid Hormone 3.7 pmol/L (1.6 - 6.9)
• 25-OH-Vitamin-D 53 nmol/L (50 - 120)
• Serum C-terminal telopeptide of type-1 collagen (CTX) 0.13 ug/L (0.10 - 0.50)
• Serum Procollagen Type-1 Amino Terminal Peptide 14 ug/L (19 – 69)
• Radiographs of hips and pelvis 10/12/2013: no bone or joint abnormality reported

DIFFERENTIAL DIAGNOSIS

Osteopenia with vitamin-D deficiency

TREATMENT

The patient was given 150000 IU of intramuscular vitamin-D (ergocalciferol) and continued ibandronic acid 150 mg monthly. Calcichew Forte was changed to Calcichew D3 Forte one daily. The generalised bone pain initially resolved but vitamin-D insufficiency recurred (25 OH D 36 mol/L) and right hip pain was present over the next year. 20,000IU cholecalciferol (vitamin-D) once weekly was administered commencing December 2013 for 8 months.

OUTCOME AND FOLLOW-UP

In August 2014, the patient now complained specifically of mid-thigh pain. Investigation results were as follows:

- Serum C-terminal telopeptide of type 1 collagen 0.23 ug/L (0.10 - 0.50)
- Serum Procollagen Type 1 Amino Terminal Peptide 24 ug/L (19 – 69)
- 25-OH-Vitamin-D 82 nmol/L (optimal 50 – 120)
- Plain X-ray femurs: bilateral femoral cortical expansion (figure 1 and figure 2)

Urgent bilateral femoral nailing was recommended following orthopaedic review but the patient did not want this treatment and after discussion the initial therapy was conservative management:

- Ibandronic acid was stopped
- Daily parathyroid hormone (Teriparatide 1-34 "Forsteo") injections were commenced 20 mcg od sc.
- The patient was still receiving calcitriol at this stage as it had alleviated some of her musculoskeletal pain and this was continued for the duration of her teriparatide therapy.
- 1000 IU vitamin D3 (cholecalciferol) daily for one year was also commenced.
- After completion of Teriparatide therapy, the thigh pain was much improved bilaterally and follow up radiographs showed that the femoral cortical expansion was significantly improved and the impending fractures had almost completely healed.

DISCUSSION

The lifelong risk of having a fracture related to osteoporosis is approximately one in two for women and one in four for men.[2] Bisphosphonates have successfully been used to reduce this risk by increasing bone strength and stiffness, but reduce bone-remodelling and have been associated with atypical femoral fractures if used for more than 3 years.[2,3] The patient in this case study had been on ibandronate for 10 years. Her bone marker results reflected low bone remodelling with CTX in keeping with decreased collagen resorption in response to ibandronate while her low serum procollagen type-1 amino-terminal peptide result reflected decreased type-1 collagen synthesis. The relative risk of atypical femoral fractures (AFFs) associated with bisphosphonate use has been estimated from 1.70 (95% CI, 1.22–2.37) to 55 (95% CI: 39–79) corresponding to an absolute risk of 11 (CI: 7–14) fractures per 10,000 person-years of use.[4, 5] These fractures are rare compared to typical osteoporotic fractures and so less of a public health concern but their impact on the individual warrants vigilance.[4] Mortality following atypical femoral fractures has been estimated to be 14% at 12 months and 25% at 24 months and morbidity is similar to that for hip fractures.[2,3].

AFFs are thought to be insufficiency fractures arising from a fatigue mechanism associated with repetitive loading [6]. Possible risk factors for atypical femoral fractures during bisphosphonate therapy include use of multiple anti-resorptive medications, glucocorticoids or proton-pump inhibitors, younger age when starting bisphosphonates, low pre-treatment bone turnover and normal bone mineral density.[3,7] The relative risk of atypical femoral fractures on alendronate compared to risedronate has been estimated as 1.9 (CI: 1.1–3.3).[5] Following cessation of bisphosphonate therapy the risk of atypical femoral fractures has been estimated to reduce by 70% per year.[5] Clinical features of atypical femoral fractures include prodromal pain for weeks to months, no significant trauma, and bilateral fractures in some patients.[2,7] Radiographic features include periosteal stress reaction, complete or incomplete, non-comminuted, transverse or short oblique subtrochanteric fractures, usually starting laterally and extending medially, proximal to the supracondylar flare with (often bilateral) thickening of the lateral femoral cortices.[2,3] Intramedullary nails are recommended for repair of complete fractures and symptomatic incomplete fractures.

Asymptomatic incomplete fractures can be managed conservatively with non-weight-bearing and re-evaluated after 2 to 3 months.[3] Imaging based on prodromal pain enabled cortical expansion to be identified in this patient before identifiable fractures occurred. Concentrations of bone-remodelling markers changed after bisphosphonate therapy was stopped and parathyroid hormone therapy was commenced (figure 3). Our report of a case with an impending AFF that healed with medical/conservative management is consistent with other reports in the literature [6] and adds support to the hypothesis that a partial AFF may be arrested and reversed before it has propagated through the cortex. Teriparatide therapy has been associated with increasing the speed of the healing process but good clinical trial evidence of this is lacking.

LEARNING POINTS/TAKE HOME MESSAGES

- Bisphosphonate therapy should be re-evaluated 6-monthly after the first 5 years of use and stopping or pausing (drug holiday) should be considered for patients with low fracture risk and T-scores >-2.5 [8]
- Patients on bisphosphonate therapy should be counselled to be vigilant for persistent thigh or groin pain.[2]
- X-rays of the entire femur are essential for symptomatic patients.[7] If X-rays are normal, consider MRI or Radionuclide bone scintigraphy.[3]
- If an atypical femoral fracture is confirmed, the contra-lateral femur should be evaluated radiologically.[3]
- Femoral cortical expansion secondary to prolonged bisphosphonate therapy can sometimes be successfully managed medically without surgical intervention.

REFERENCES

1. Klop C, Gibson-Smith D, Elders PJ, *et al*. Anti-osteoporosis drug prescribing after hip fracture in the UK: 2000–2010. *Osteoporos Int* 2015;**26**:1919–1928
2. Nieves JW, Cosman F. Atypical subtrochanteric and femoral shaft fractures and possible association with bisphosphonates. *Curr Osteoporos Rep* 2010;**8**:34–39
3. Shane E, Burr D, Abrahamsen B, *et al*. Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a task force of the American Society for Bone and Mineral Research. J ***Bone*** *Miner Res* 2013;**29**:1-23
4.Gedmintas L, Solomon DH, Kim SC. Bisphosphonates and risk of subtrochanteric, femoral shaft, and atypical femur fracture: a systematic review and meta-analysis. J ***Bone*** *Miner Res* 2013;**28**:1729-1737
5. Schilcher J, Koeppen V, Aspenberg P, Michaëlsson K. Risk of atypical femoral fractures during and after bisphosphonate use: Full report of a nationwide study. *Acta Orthop* 2015;**86:**100–107.
6. La Rocca Vieira R, Rosenberg ZS, Allison MB, et al. Frequency of incomplete atypical femoral fractures in asymptomatic patients on long-term bisphosphonate therapy. *Am J Roentgenol* 2012;**198**(5):1144-51
7. Black DM, Kelly MP, Genant HK, *et al*. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med* 2010;**362**:1761-1771
8. Nayak S, Greenspan SL. A systematic review and meta-analysis of the effect of bisphosphonate drug holidays on bone mineral density and osteoporotic fracture risk. *Osteoporos Int* 2019; https://doi.org/10.1007/s00198-018-4791-3

FIGURE/VIDEO CAPTIONS

Figure 1: Pelvic radiograph demonstrating bilateral femoral cortical expansion at the proximal third of the femora (arrows).
Figure 2: Left femoral radiograph showing periosteal stress reaction (arrow)
Figure 3: Graphs of markers of calcium and bone metabolic indices (25 OH vitamin D; 1,25 di OH vitamin D; serum C-terminal telopeptide cross links (CTX) and serum Procollagen Type 1 Amino Terminal Peptide (P1NP)) changes between 2012 and 2015. Ibandronic acid therapy was stopped in August 2014.

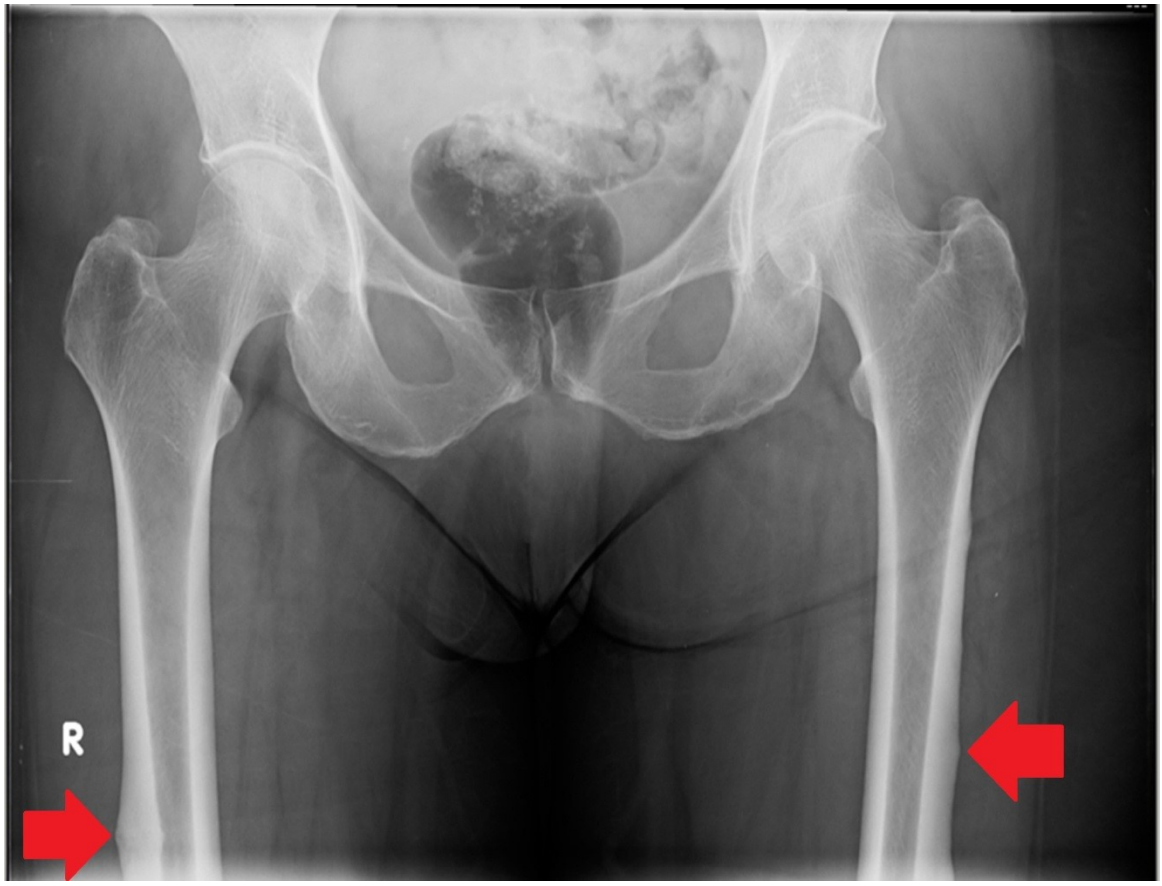


Figure 1:

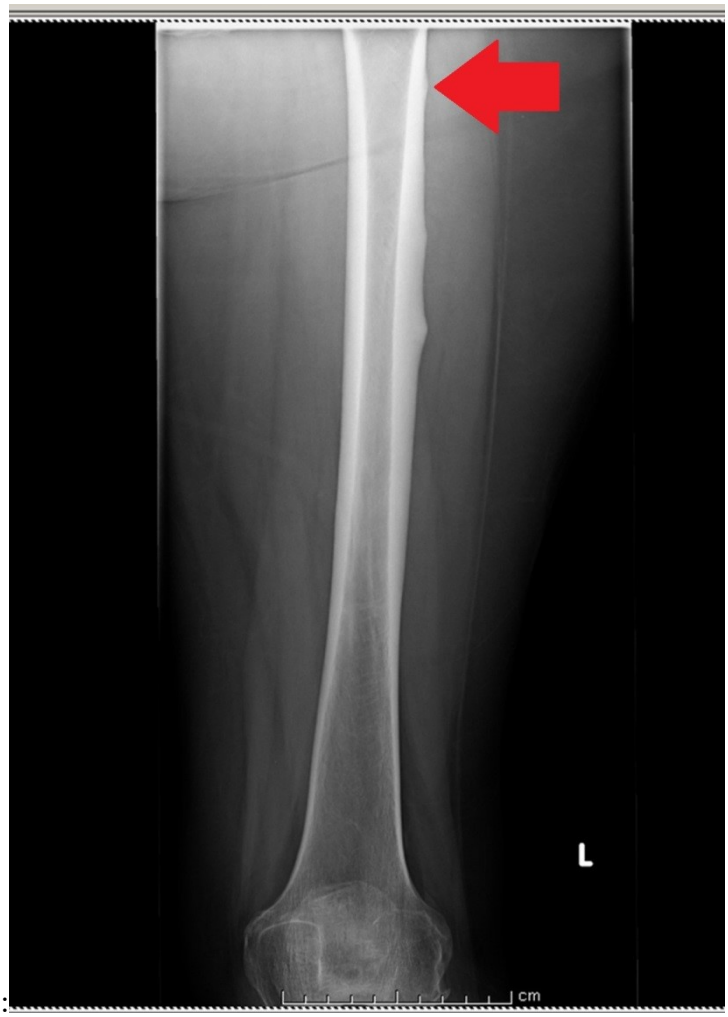
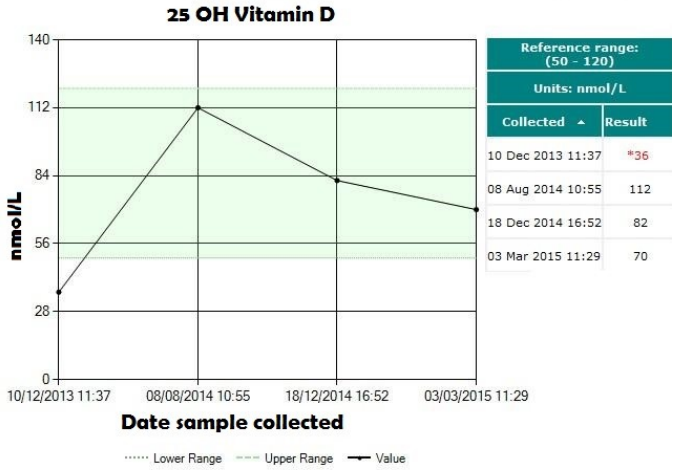
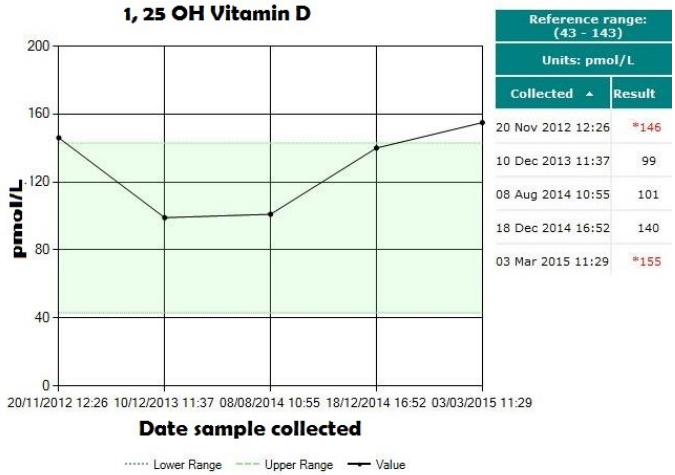


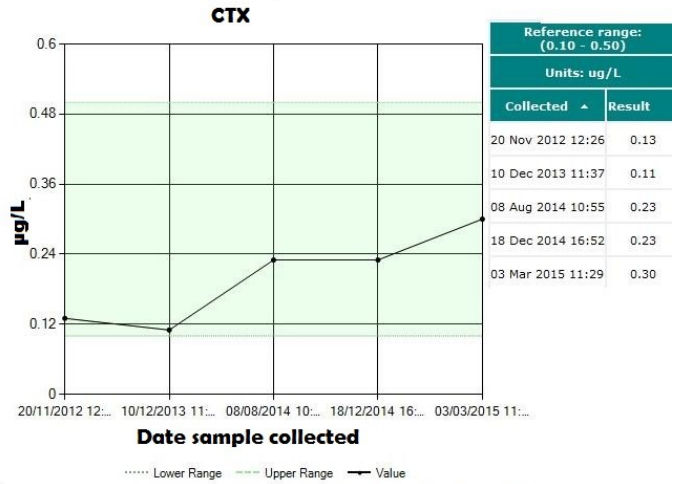
Figure 2:



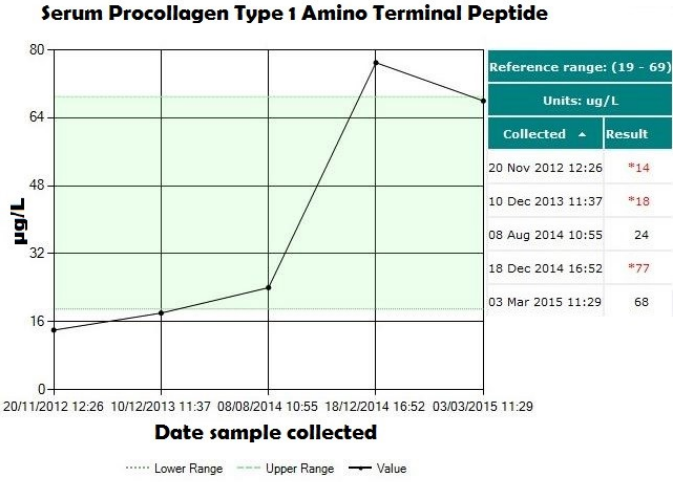
Reference range: (50 - 120)	
Units: nmol/L	
Collected	Result
10 Dec 2013 11:37	*36
08 Aug 2014 10:55	112
18 Dec 2014 16:52	82
03 Mar 2015 11:29	70



Reference range: (43 - 143)	
Units: pmol/L	
Collected	Result
20 Nov 2012 12:26	*146
10 Dec 2013 11:37	99
08 Aug 2014 10:55	101
18 Dec 2014 16:52	140
03 Mar 2015 11:29	*155



Reference range: (0.10 - 0.50)	
Units: ug/L	
Collected	Result
20 Nov 2012 12:26	0.13
10 Dec 2013 11:37	0.11
08 Aug 2014 10:55	0.23
18 Dec 2014 16:52	0.23
03 Mar 2015 11:29	0.30



Reference range: (19 - 69)	
Units: ug/L	
Collected	Result
20 Nov 2012 12:26	*14
10 Dec 2013 11:37	*18
08 Aug 2014 10:55	24
18 Dec 2014 16:52	*77
03 Mar 2015 11:29	68

Figure 3: