Unusual association of diseases/symptoms

Hypercalcaemia from genitourinary tuberculosis in a female with multiple exostoses

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Correspondence to Dr Mark Anthony Santiago Sandoval, markanthony_sandoval@yahoo.com**Summary**

The authors present a puzzling case of nephrolithiasis, hypercalcaemia, amenorrhoea, short stature and gross skeletal deformities in a 30-year-old female. Multiple pituitary hormone deficiency and metabolic bone disease were initially considered but were eventually excluded. The final diagnosis is genitourinary tuberculosis (TB) which caused the hypercalcaemia, nephrolithiasis and amenorrhoea, and also found to have the syndrome of multiple exostoses which explained the gross skeletal deformities and the short stature. After treatment with anti-TB therapy, there was resolution of hypercalcaemia and return of regular menstruation. The short stature and gross skeletal deformities remain as part of the congenital syndrome.

BACKGROUND

This case is significant for the following reasons: (1) It illustrates the investigation for short stature, amenorrhoea, hypercalcaemia and gross skeletal deformities; (2) It shows that tuberculosis (TB), specifically genitourinary TB, should be considered as a cause of hypercalcaemia and that treating TB leads to resolution of hypercalcaemia; (3) It shows that treatment of an underlying systemic illness may resolve the amenorrhoea which was initially thought to be from an endocrine cause; (4) It brings to our attention the rare syndrome of hereditary multiple exostoses which explains the short stature and gross skeletal deformities which have never been given much attention during the patient's life but which have been present since childhood; (5) It demonstrates that the 'diagnostic law of parsimony' does not always apply. In this case, there is no single entity that can explain her signs and symptoms, and that different disease entities need to be tied up together.

CASE PRESENTATION

A 30-year-old female was having left flank pains for 5 years, occasionally associated with dysuria and undocumented fever. She would also have nocturia, about four times a night. She did not seek consultation until 5 months prior to admission when she consulted a general practice clinic and was told to possibly have nephrolithiasis. On day of admission, she had severe flank pain and was brought to the emergency department.

She had an alleged fracture of the left forearm sustained several days after birth and had a gross forearm deformity since then. Patient has no other illnesses. She is at par with her peers in terms of physical activity and intelligence; however, her height is much shorter than her peers. There is no other member of the family with short stature and the gross forearm deformity.

Patient had her menarche at age 16 but did not have menstruation for 5 months prior to the admission. Pregnancy test was negative.

Patient was found to be hypotensive with blood pressure (BP) 80/60, relieved by intravenous hydration and dopamine at vasopressor dose. However, there would be recurrence of hypotensive episodes for which adrenal insufficiency was considered.

Patient had a height of 143 cm (4'8"), shorter than the midparental height of 147 cm (maternal height: 150 cm, paternal height 157 cm) (figure 1). She had an arm span of 136 cm but the left upper extremity was shorter due to the deformity of the left forearm. She weighed 37.5 kg and had a body mass index of 18.3 kg/m².

Aside from upturned nares, she did not have other facial abnormalities.

Chest and abdominal findings were normal. There was no costovertebral angle tenderness.

She had a grossly deformed left forearm (figure 2). The right small finger is also ulnarly deviated. There were palpable bony nodularities on the right wrist, base of the right 2nd finger and medial aspect of the proximal left leg. There was a dimple on the medial aspect of the left leg with no discharge. There were no shortened distal phalanges nor enlarged costochondral junctions.

She had well-developed (Tanner V) breasts. She never had axillary and pubic hair (Tanner I). She had normal external female genitalia.

DIFFERENTIAL DIAGNOSIS

Multiple pituitary hormone deficiency was considered on the basis of short stature (growth hormone (GH) deficiency), paucity of secondary sexual characteristics and secondary oligo-amenorrhoea (hypogonadism), recurrent hypotension not fully resolved with hydration and vasopressors (adrenal insufficiency) and nocturia and thirst (diabetes insipidus).

Figure 1 The patient (right) during her hospital admission with her father and mother. The patient stood at 143 cm (4'8") and was shorter than either parent.

Metabolic bone diseases such as vitamin D deficiency/rickets with secondary hyperparathyroidism and primary hyperparathyroidism, were also considered on the basis of short stature, gross skeletal deformity, and nephrolithiasis.

INVESTIGATIONS

Multiple pituitary hormone deficiency

Table 1 summarises the findings of the tests for possible multiple pituitary hormone deficiency. There is no deficiency in luteinising hormone (LH) and follicle stimulating hormone (FSH) while oestradiol, the peripheral hormone, was within normal levels. There is no central

hypothyroidism as free thyroxine (FT4), which is the peripheral hormone, is within normal levels. The low thyroid stimulating hormone (TSH) level can be explained by the administration of dopamine for the hypotension which was started 3 days prior to TSH determination. There is no glucocorticoid insufficiency as the serum cortisol level was appropriately increased in the patient who was in a state of physical stress. There is no deficiency in prolactin. GH and insulin-like growth factor-I (IGF-I) were not anymore measured when the above results came out as it is rare to get isolated GH deficiency. Patient had a dilute urine based on urine osmolality and specific gravity. But the urine output and serum osmolality (as derived from serum sodium levels) are both acceptable.

Metabolic bone disease

The diagnostic investigation for metabolic bone disease are also summarised in table 1. Total and ionised serum calcium levels were elevated while intact parathyroid hormone (iPTH) was suppressed. These suggest that there is parathyroid hormone (PTH)-independent hypercalcaemia.

Nephrolithiasis and urinary tract infection

Table 2 summarises the diagnostic tests performed for nephrolithiasis and urinary tract infection. There was an

ultrasonographically-demonstrated nephrolith, though no crystals were seen on urinalysis. There was sterile pyuria which prompted a search for other causes of infection. The finding of acid-fast bacilli (AFB), later on identified as *Mycobacterium* species, gave the diagnosis of genitourinary TB. Sputum AFB smears were negative.

Gross skeletal deformities

Skeletal survey radiographs revealed multiple bony extrusions, the cortices of which are continuous with the cortex,

Figure 2 On the left panel is a photograph of the patient during her hospital admission. On the right is the same patient after 1.5 years. Note that she has gained weight after successful treatment of tuberculosis. Note also the persistent bowing deformity of the left forearm (arrow).

Table 1 Results of diagnostic tests done for the consideration of multiple pituitary hormone deficiency and metabolic bone disease

	Result	Reference range
For multiple anterior pituitary hormone deficiency		
Follicle stimulating hormone (FSH)	15.8 mIU/ml	Ovulatory peak: 4.0 – 13.5 Pre and postovulatory: 0.6 – 9.5 Postmenopausal: 30 – 135
Luteinising hormone (LH)	25.5 mIU/ml	Ovulatory peak: 0.25 – 90 Pre and postovulatory: 0.7 – 80 Postmenopausal: 13 – 80
Oestradiol	154 pg/ml	Follicular phase: 57 – 227 Preovulatory: 127 – 476 Midluteal: 72 – 277 Postmenopausal <82
Free T4	16.4 pmol/l	11.0 – 24.0
Thyroid stimulating hormone (TSH)	0.09 uIU/ml	0.3 – 3.8
Random serum cortisol	3673.3 nmol/l	138 – 690
Prolactin	508 nmol/l	50 – 500
Urine specific gravity	1.000 – 1.010	1.001 – 1.035
Urine osmolality	139 mOsm/kg	500 – 800
Serum Na	131 – 147 mmol/l	135 – 145
For metabolic bone disease		
Corrected serum calcium	2.41 – 3.08 mmol/l	2.12 – 2.52
Ionised calcium	1.43 mmol/l	1.17 – 1.29
Intact parathyroid hormone (iPTH)	3 pg/ml	15 – 65
25-hydroxy vitamin D	52.51 nmol/l	47.7 – 144

in several areas: right acromion, proximal third and distal third of the left humerus, distal third of the right radius and ulna, distal third of left radius and ulna (figure 3), proximal third of both femora, medial and lateral aspect of the distal third of both femora (figures 4 and 5), proximal right tibiofibular articulation and lateral distal third of right tibia, medial aspect of left tibia (figure 5), tibiofibular articulation and lateral aspect of the distal third of left tibia.

There was bowing deformity of the left radius and ulna (figure 6), a lytic lesion in the anterior endplate of L4 vertebral body (figure 7) and a suspicious opacity on the apex of the left hemithorax overlying the left clavicle and 1st anterior rib.

These radiographic findings point to multiple exostoses or osteochondromas, and raise the suspicion of pulmonary and vertebral (Pott's disease) TB.

Genetic analysis

Chromosomal analysis revealed a normal female karyotype (46, XX). No gross chromosomal abnormalities were seen.

TREATMENT, OUTCOME AND FOLLOW-UP

BP eventually improved with hydration, with no need for glucocorticoids nor vasopressor agents. There was no recurrence of flank pain.

Patient was treated with anti-TB regimen of isoniazid, rifampicin, pyrazinamide and ethambutol for the first 2 months. Isoniazid and rifampicin were continued for the next 4 months. Urine AFB smears were done after the 2nd month of treatment and all three specimens were still positive. After the third month of treatment, three specimens of urine were already negative of AFB. The urine remained negative for AFB by the end of the 6-month anti-TB treatment period.

The corrected serum calcium remained elevated at 2.73, 2.76 and 2.76 mmol/l at 1, 2 and 3 months, respectively, of anti-TB treatment (normal range: 2.12–2.52 mmol/l). The corrected serum calcium eventually normalised to 2.47 mmol/l by the 6th month of anti-TB treatment.

After being amenorrhoeic for 7 months, menstruation returned after 3 months of anti-TB treatment and had been occurring at regular monthly intervals since then. She also

Table 2 Results of diagnostic tests performed for the consideration of nephrolithiasis and urinary tract infection

Urinalysis	pH 6.0 – 6.5, (–) sugar, trace to +1 protein, red blood cells 4–10/HPF with normal morphology white blood cells abundant, (–) crystals
Urine Gram stain	Polymorphonuclear (PMN) leucocytes 10–20/HPF Positive from Gram-negative bacilli
Urine culture	No growth
Urine acid-fast bacilli (AFB)	(+3) and (+1)
Urine mycobacterial culture	Positive for <i>Mycobacterium</i> species after 2 weeks of incubation Sensitive to isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin
Blood culture	No growth (2 specimens)
Abdominal ultrasound	Nephrolithiasis (0.3 cm) on the right Bilateral pelvocaliectasia, mild Others: cholecystitis and atrophic uterus

Figure 3 Exostoses on the left radius and ulna (encircled).

Figure 4 Multiple exostoses on the distal portions of both femora (encircled).

gained 2.5 kg in body weight during the course of anti-TB therapy (figure 2).

FINAL DIAGNOSES

- Genitourinary TB
 1. Hypercalcaemia from granulomatous disease
 2. Nephrolithiasis
 3. Secondary amenorrhoea
 4. Suspected pulmonary and vertebral TB
- Syndrome of multiple exostoses

DISCUSSION

This patient was admitted for acute flank pain due to nephrolithiasis and hypotension. But there were other features that did not seem to be related to nephrolithiasis. Among these were short stature, the gross skeletal deformities and the oligo-amenorrhoea. These were the findings that prompted more extensive diagnostic investigation.

Initially, the findings of short stature, oligo-amenorrhoea with absence of axillary and pubic hair and hypotension were thought to be from multiple pituitary hormone deficiency. These were thought to be manifestations of decreased levels of GH, gonadotrophins (FSH and LH) and adrenocorticotrophic hormone, respectively. However, the hormonal investigation did not show any deficiency in any pituitary hormone nor its peripheral hormone. Assay for IGF-1, however, was not done.

Metabolic bone disease was initially considered to explain the hypercalcaemia, short stature, gross skeletal deformities and nephrolithiasis. Primary hyperparathyroidism was ruled out by a suppressed level of intact PTH. Vitamin D deficiency has also been ruled out based on a normal 25-hydroxy vitamin D level. Secondary hyperparathyroidism has also been ruled out since this is expected to show low vitamin D, high PTH and an initially low

serum calcium which may eventually rise due to increased PTH secretion.

The diagnosis for short stature and the gross skeletal deformities was clinched upon the performance of the skeletal survey which showed multiple exostoses or osteochondromas. The syndrome of hereditary multiple exostoses is also known by various names such as osteogenic disease, chondral osteogenic dysplasia, chondral osteoma, dyschondroplasia, deforming chondroplasia, multiple hereditary osteochondroma, multiple cartilaginous exostoses or exostotic dysplasia.¹ These bony outgrowths are cartilage covered tumours (osteochondromas or exostoses) usually arising in the juxtaphyseal region of long bones. These exostoses prevent normal bone tubulation and are responsible for the metaphyseal widening and short stature of affected patients.¹ The shortening or bowing of the forearm is a striking feature in this syndrome.¹ For this patient, this was attributed by the parents to be due to a fracture which the patient sustained as a newborn. The radiograph, however, did not show any sign of a previous or healed fracture. Our patient had an upturned nares, and this finding was also seen in a previous case report.²

The syndrome of hereditary multiple exostoses is an autosomal dominant disorder, with 60–70% of patients having a positive family history.¹ This patient is the index case and does not have an affected relative, thus heredity is not established. Mutation is suggested to be at the EXT1 gene at chromosome 8q23-24. Gross chromosomal examination by karyotyping, however, failed to reveal any gross chromosomal abnormality in this case. There was a previously reported case of this syndrome having a translocation between chromosomes 8 and 11 (t(8;11)(q24.11;p15.5)).²

There are no reports which state that the syndrome of hereditary multiple exostoses is associated with hypercalcaemia. Hypercalcaemia in this case occurs in the setting of low level of parathyroid hormone. Common causes are

Figure 5 Multiple exostoses on the lateral portion of the distal femur (upper circle) and medial portion of the tibia (lower circle).

malignancy, granulomatous disease and the milk-alkali syndrome. No malignancy was identified in this patient, and she also is not taking exogenous sources of calcium. Granulomatous disease was proven in this patient upon the diagnosis of genitourinary TB after AFB were found in the urine which, on culture, were identified to be *Mycobacterium* species.

Granulomatous disease causes hypercalcaemia by the activated macrophages in the granulomas expressing the enzyme 1- α hydroxylase which converts 25-hydroxy vitamin D to the active form 1,25 dihydroxy vitamin D (calcitriol). The elevated levels of 1,25 dihydroxy vitamin D lead to increased intestinal absorption and increased renal tubular reabsorption of calcium, eventually leading to hypercalcaemia.³ Hypercalcaemia then could cause nephrolithiasis. Had an assay for 1,25 dihydroxy vitamin D been available, it would be expected to show an elevated value. For this case, the serum calcium level normalised upon completion of anti-TB treatment. This supports the hypothesis that the hypercalcaemia is from TB.

Hypercalcaemia occurs in as much as 15.5 % to 51% of patients with TB (⁴⁻⁶

Hypercalcaemia was reported in cases of miliary TB, pulmonary TB and hepatic TB.⁵⁻⁷ This case is proven to have genitourinary TB on the basis of the urine AFB smear and TB culture findings. She is suspected to have disseminated TB because of possible pulmonary and vertebral involvement. Pulmonary TB was suspected by chest x-ray but three sputum specimens were negative for AFB. Also, vertebral involvement was suspected as she had a lytic lesion on the anterior segment of the L4 vertebral body but there is no microbiologic or pathologic demonstration done to prove that there is really tuberculous involvement of the spine.

No reproductive hormone deficiency was noted for the patient's oligomenorrhea/ amenorrhoea. With anti-TB treatment, menstruation resumed and occurred in regular monthly intervals. This supports the clinical impression that the menstrual disturbance is due to the underlying systemic disease which, in this case, is TB.

Figure 6 Bowing deformity of the left radius and ulna.

Figure 7 Lytic lesion in the anterior portion of L4 vertebral body (arrow) suggestive of vertebral involvement by tuberculosis (Pott's disease).

This case is limited by the following: GH or IGF-I measurements were not done to complete the investigation of short stature. When the results of the other anterior pituitary hormones were already available, testing for GH deficiency was not done since an isolated deficiency of this hormone is rare. Also, the syndrome of multiple exostoses can explain the short stature. There is also no specific identification of *Mycobacterium tuberculosis* as the causative organism. The laboratory at that time can only identify the

organism as belonging to the genus *Mycobacterium*. Despite that, the patient was treated as *M tuberculosis* infection and microbiologic cure was documented in subsequent monitoring, evidence that she responded well to the anti-TB regimen. Biochemical markers of bone formation (ie, bone-specific alkaline phosphatase, osteocalcin and type I procollagen) and resorption (ie, cross-linked N-telopeptide, cross-linked C-telopeptide and free deoxypyridinoline) were not measured as well.

Learning points

- ▶ This illustrates the investigation for short stature, amenorrhoea, hypercalcaemia and gross skeletal deformities.
- ▶ TB, specifically genitourinary TB, should be considered as a cause of hypercalcaemia and that treating TB leads to resolution of hypercalcaemia.
- ▶ Treatment of an underlying systemic illness may resolve the amenorrhoea which was initially thought to be from an endocrine cause.
- ▶ The rare syndrome of hereditary multiple exostoses which explains the short stature and gross skeletal deformities which have never been given much attention during the patient's life but which have been present since childhood.
- ▶ The 'diagnostic law of parsimony' does not always apply. In this case, there is no single entity that can explain her signs and symptoms, and that different disease entities need to be tied up together.

Competing interests None.

Patient consent Obtained.

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