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Case Report

A haemodialysis patient with back pain: brown tumour as a cause of spinal cord compression under cinacalcet therapy

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Abstract

A 43-year-old haemodialysis patient was admitted to hospital because of paroxysmal pain in the upper abdominal region radiating to the back. Laboratory tests showed severe hyperparathyroidism [intact parathyroid hormone (iPTH) 69 pmol/L; reference range: 1.3–6.8 pmol/L], hypercalcaemia (2.79 mmol/L), hyperphosphataemia (1.6 mmol/L) and elevated serum total alkaline phosphatase (200 U/L). After developing a disturbed sensation and paraesthesia in both feet, epidural compression of the spinal cord was suspected. Magnetic resonance imaging showed a tumour that severely compressed the myelum of the thoracic spine. Histological investigation revealed a brown tumour or osteoclastoma, an erosive bony lesion caused by increased osteoclastic activity and peritrabecular fibrosis. A brown tumour is a benign tumour that is a rare complication of severe renal hyperparathyroidism. The brown tumour developed despite a 1-year treatment of the patient with cinacalcet, which, however, did not result in a major decrease in serum iPTH concentration (from 110 to 69 pmol/L: 37% reduction). Urgent decompressive neurosurgery and subtotal parathyroidectomy resulted in a complete recovery.

Keywords: brown tumour; hyperparathyroidism; osteoclastoma; spine

Case report

A 43-year-old man with a 1-year history of end-stage renal disease (ESRD) managed by haemodialysis therapy presented with paroxysmal pain in the upper abdominal region radiating to the back. Six years earlier, when presenting with chronic renal failure, severe secondary hyperparathyroidism already existed, for which he was treated with alphacalcidol and sevelamer (Figure 1). After an initial response to this therapy, over the last 2 years an aggravation of the hyperparathyroidism occurred and mild hypercalcaemia developed. Over the past years, a parathyroidectomy was considered but postponed owing to intercurrent hypothyroidism and an ischaemic stroke.

One week before presentation, the patient started to suffer from paroxysmal episodes of pain in the right upper abdomen radiating to the back that lasted about 20 min. Supine position aggravated the pain. There were no other symptoms such as nausea, vomitus, fever, weight reduction nor any nervous system deficits such as loss of motor function or urinary disturbances. Physical examination revealed no abnormality except for percussion pain in the mid-thoracic spine, which occurred only during pain episodes.

Laboratory investigations showed severe hyperparathyroidism [intact parathyroid hormone (iPTH) 69 pmol/L, reference range (rr): 1.3–6.8 pmol/L], with hypercalcaemia (2.79 mmol/L, rr: 2.20–2.65 mmol/L), hyperphosphataemia (1.6 mmol/L, rr: 0.8–1.5 mmol/L) and an increased serum total alkaline phosphatase (200 U/L, rr: 40–120 U/L). No data were available about serum 25 (OH) vitamin D levels. One year ago (June 2006), the patient had developed severe secondary hyperparathyroidism (iPTH 110 pmol/L). Because of concomitant hypercalcaemia, the dose of alphacalcidol was lowered and treatment with cinacalcet was started at a dose of 30 mg/day and gradually increased during 1 year to 180 mg/day. After an intercurrent increment, cinacalcet therapy had finally reduced the iPTH levels slightly from 110 to 69 pmol/L (a 37% reduction). Total alkaline phosphatase levels increased markedly after commencement of cinacalcet treatment (Figure 1).

Radiographs of the thoracic spine showed mild demineralization without evidence of focal lytic lesions or osteosclerosis. After a few days, the pain worsened rapidly and was more localized to the mid-thoracic spine. The sensation in both legs had changed. Coughing and sneezing provoked electrical shock-like symptoms in both legs (Lhermitte's sign). We found on physical examination percussion pain of the seventh thoracic vertebra. The combination of local thoracic pain and electrical sensation raised

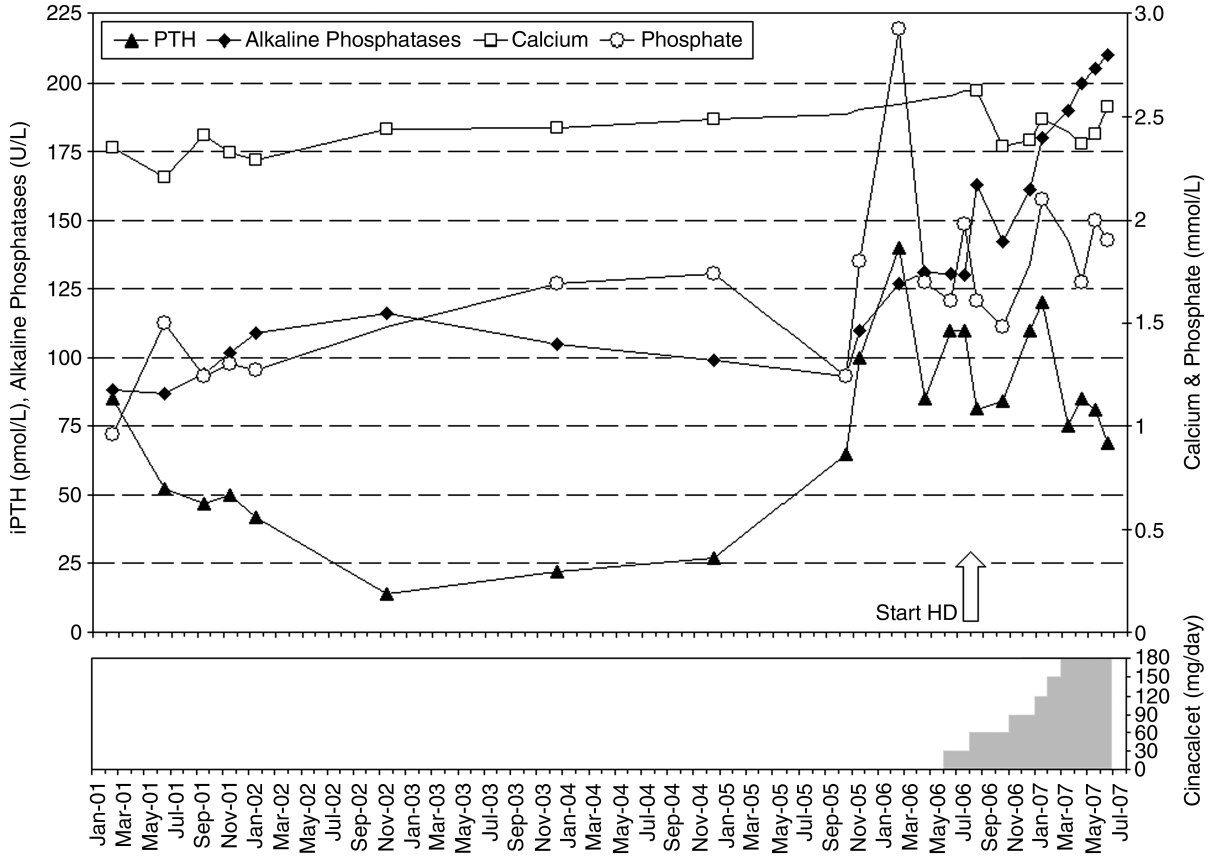

Fig. 1. Serum levels of intact parathyroid hormone (iPTH), total alkaline phosphatases, calcium and phosphate from 2001 (February) to 2007 (July). 7 June 2006: treatment with cinacalcet (30 mg/day) was started because of an iPTH of 110 pmol/L. Cinacalcet was gradually increased up to 180 mg/day and iPTH lowered to 69 pmol/L (37% reduction). 30 June 2007: after 1-year treatment with cinacalcet, a symptomatic brown tumour was discovered. HD: haemodialysis.

our suspicion of epidural compression of the spinal cord. Magnetic resonance imaging (MRI) (Figure 2A–C) demonstrated a soft tissue mass with a diameter of 3.5 cm in the posterior column of the seventh thoracic vertebra. This expansile lytic lesion almost completely replaced the bone of the spinous process and both lamina and transverse processes. Owing to a protrusion in the spinal canal, the myelum was severely compressed. Bone scintigraphy showed multiple hot spots in the ribs and pelvis, possibly caused by metastases, fractures or osteomalacia and an irregular distribution of activity in the thoracic spine, possibly due to degenerative changes. Echography showed an enlarged right parathyroid gland (1.5 cm). Histological examination of a percutaneous CT-guided biopsy of the spinal mass revealed proliferation of spindle-shaped cells and numerous multinuclear giant cells. Furthermore, small blood vessels and haemorrhagic changes were seen. Malignant features like cytological atypia or mitotic figures were absent. These findings correspond to a giant cell tumour or brown tumour (osteoclastoma). Deposition of haemosiderin gives the tissue, on gross examination, a brown appearance. Currently, no histological criteria are available to distinguish these two tumours. The diagnosis of a brown tumour rests on the presence of severe hyperparathyroidism. A true giant cell tumour is not associated with hyperparathyroidism. The brown tumour was discovered after 1-year treatment with cinacalcet.

We treated the patient with high dose dexamethasone to reduce the mass effect, and urgent decompressive surgery was performed. A T6- to T8-wide laminectomy and resection of transverse processes of vertebrae was performed. Via a dorsal approach, a red-brown tumour was resected. There was no need for additional stabilization of the vertebral column. The postoperative course was uneventful and the patient recovered completely. An MRI scan performed 6 weeks after surgery showed complete relief of the spinal cord compression without signs of myelopathy or residual tumour (Figure 2D). Because of the severe hyperparathyroidism, a subtotal parathyroidectomy was performed a few weeks later. Histopathological examination showed nodular hyperplasia of all four glands.

Discussion

Secondary hyperparathyroidism is a common complication of chronic renal failure that starts in stage 3 chronic kidney disease (CKD) and is aggravated when renal failure progresses. If left untreated, hyperparathyroidism will worsen and eventually lead to high-turnover bone disease, characterized by increased osteoblastic and osteoclastic activity, and fibroblastic proliferation, ultimately leading to the formation of a brown tumour, an extreme form of osteitis fibrosa cystica [1–5]. Brown tumours are

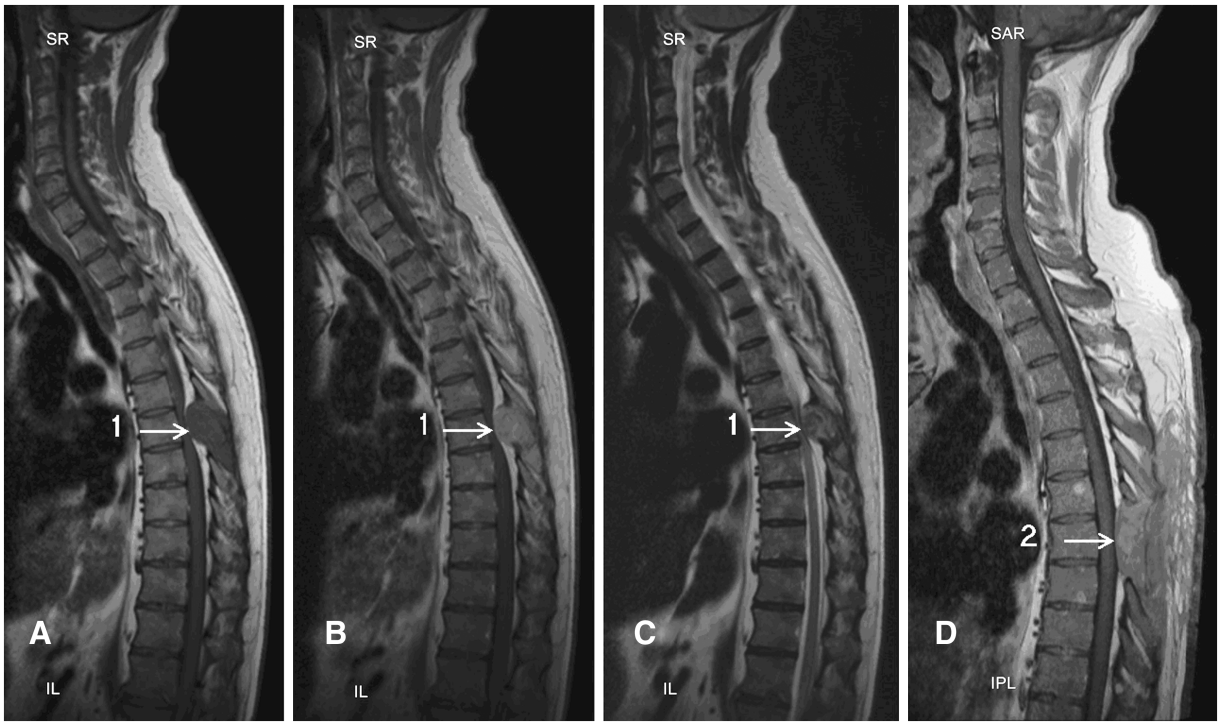

Fig. 2. Magnetic resonance imaging of the spine. Sagittal series show a soft tissue mass (1) originating from the neural arch of the seventh vertebra extending in the spinal canal and severely compromising the myelum. The lesion shows low signal intensity on a T1-weighted image (**A**) with clear but inhomogeneous enhancement after administration of gadolinium (**B**). Inhomogeneous moderately low signal intensity is seen on a T2-weighted image (**C**). Postoperative contrast-enhanced T1-weighted image confirmed decompression of the spinal cord. No evidence for remaining tumour was found, only fibrosis (2) (**D**).

known to only occur in the setting of primary or secondary hyperparathyroidism and are nowadays rare, which is considered to be the result of better diagnosis and more effective treatment of hyperparathyroidism [3]. The Kidney Disease: Improving Global Outcomes guideline for CKD 5D suggests maintaining iPTH levels in the range of two to nine times the upper normal limit [1]. A study among 73 haemodialysis patients, whose bones were periodically checked, showed three asymptomatic brown tumours within 5 years after starting dialysis (PTH varied between 5 and 15 times the upper limit) [6].

A brown tumour, also called osteoclastoma, is a benign tumour that usually resolves within 1–2 years after (subtotal) parathyroidectomy [2]. Any bone may be affected but involvement of the spine is extremely rare [2,3,7–9]. Table 1 shows 11 cases with CKD 3–5 and symptomatic brown tumours involving the spine. The PTH levels are markedly elevated, often more than 10 times normal. A brown tumour located in the spine may either cause slowly progressive symptoms due to compression of the spinal cord and surrounding tissue or acute symptoms due to pathological fractures [2]. Urgent surgery is required when myelum compression occurs [2,8].

Radiographically, brown tumours appear as lytic solitary or multifocal, sharply demarcated expansile lesions [7,18]. Bone scintigraphy shows multiple hot spots, owing to osteoclast activity, suggestive of a metastatic disease. However, the clinical history of renal failure and severe secondary hyperparathyroidism combined with increased alkaline phosphatase raises suspicion for a brown tumour. When diagnostic uncertainty persists, histological investigation of a lesion is recommended [3,8].

Our patient responded insufficiently to cinacalcet. A possible explanation is that enlarged parathyroid glands (>1 cm), with nodular hyperplasia, express less calcium-sensing receptors and may therefore be hyporesponsive to cinacalcet [4].

We have several hypotheses why our patient developed a brown tumour. First, most likely the duration of severe hyperparathyroidism plays a role. Our patient had severe secondary hyperparathyroidism for several years, which was refractory for medical treatment including cinacalcet. Recently, a case report described a patient who developed a brown tumour due to secondary hyperparathyroidism (PTH twice the upper normal limit) only 2 years after a biliopancreatic diversion for severe obesity [19]. Second, cinacalcet reduces PTH levels maximally 2–4 h after administration and therefore induces daily fluctuations. Intermittently high levels of PTH which increase osteoblast survival and stimulate the formation of fibroblasts [20], are known to have a different effect compared with continuously high PTH levels. Third, osteoblasts express calcium-sensing receptors [21]. Cinacalcet may induce mitogenic action on osteoblasts via calcium-sensing receptors in a high-calcium environment. The progressive increment of the level of serum total alkaline phosphatase (marker of bone formation) after starting cinacalcet suggests increased osteoblast activity.

We conclude that, although uncommon, a brown tumour of the spine should be considered in ESRD patients with

Table 1. Cases of symptomatic brown tumours due to secondary hyperparathyroidism involving the spine in chronic renal failure patients

Author	Year	Age (years)	Sex	Haemodialysis duration	Spinal involvement	Symptoms	PTH level pg/mL (reference range)	iPTH level pmol/L (reference range)
Ericsson *et al*. [10]	1978	47	F	CRF	Cervical	Paresis	14.9 (not mentioned)[a]	
Bohlman *et al.* [9]	1986	69	F	CRF	Thoracic	Back pain, paraplegia	3910 (230–690)[a]	
Pumar *et al.* [11]	1990	24	F	CRF	Thoracic	Paraplegia	Not mentioned	
Barlow and Archer [12]	1993	31	F	Yes, after failed renal transplant	Cervical	Neck pain, neuralgia	Not mentioned	
Fineman *et al.* [13]	1999	37	F	10 years	Thoracic	Incipient paraplegia	456 (10–55)	47.3 (1.0–5.7)
Azria *et al.* [14]	2000	40	F	Yes, after failed renal transplant	Thoracic	Back pain		
Masutani *et al.* [15]	2001	39	F	11 years	Thoracic	Paraplegia	139 191 (150–500)[a]	
Vandenbussche *et al.* [8]	2004	37	F	3 years	Thoracic	Back pain, incipient paraplegia	2500	259.3 (not mentioned)
Tarrass *et al.* [2]	2006	42	M	10 years	Sacral	Cauda equina compression	1456 (10–65)	151 (1.0–6.7)
Ren *et al.* [16]	2008	47	M	6 years	Thoracic	Incipient paraplegia	1301 (0–62)	134.9 (0–6.4)
Mak *et al.* [17]	2009	65	F	10 years	Thoracic	Back pain, incipient paraplegia		93.2 (1.2–5.7)
Current case	2010	43	M	1 year	Thoracic	Back pain		69 (1.3–6.8)

iPTH, intact parathyroid hormone; CRF, chronic renal failure; F, female; M, male; conversion factor PTH pg/mL into pmol/L (SI units): 9.643.
[a]These PTH measurements were not performed with an 'intact PTH assay' and therefore inactive PTH fragments were inaccurately measured.

severe secondary hyperparathyroidism and new onset neurologic symptoms. The brown tumour developed despite a 1-year treatment of the patient with cinacalcet, which however did not result in a major decrease in serum iPTH concentrations (from 110 to 69 pmol/L: 37% reduction). The tumour eventually caused severe myelum compression for which emergent decompressive neurosurgery to preserve neurologic function was required. With hindsight, a parathyroidectomy should have been performed earlier in our patient, given the persistently elevated PTH and alkaline phosphatase. Additional factors that could have supported the indication for parathyroidectomy include large parathyroid glands (>1 cm) on ultrasound or a bone biopsy revealing osteitis fibrosa cystica [4].

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Conflict of interest statement. None declared.

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