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Renal failure and progressive pancytopenia

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Abstract

Hyperparathyroidism may be a precipitating factor to the development of myelofibrosis; however, this is extremely rare with only a few documented case reports of myelofibrosis caused by secondary hyperparathyroidism. We describe a case of a 24-year-old female who had a failed live donor renal transplant and secondary hyperparathyroidism. While on haemodialysis she became increasingly pancytopenic despite erythropoietin injections and adequate iron, vitamin B12 and folate replacement. Her secondary hyperparathyroidism evolved to tertiary hyperparathyroidism despite vitamin D supplementation and phosphate binders. In order to determine the cause of her pancytopenia, a bone marrow biopsy was performed that confirmed myelofibrosis due to her secondary hyperparathyroidism. Following a successful parathyroidectomy in a tertiary hospital, her pancytopenia resolved and she is now awaiting a second transplant.

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Case presentation

We describe a case of a 24-year-old female with chronic kidney disease (CKD). She was first diagnosed at the age of 13 years with CKD as an incidental finding after being reviewed for short stature. She had normal cytogenetic studies and the underlying cause of her renal impairment was attributed to reflux nephropathy. She received a live donor transplant at the age of 15 years. Sadly, she developed chronic allograft nephropathy and recurrent allograft pyelonephritis resulting in graft failure, and was commenced on haemodialysis 5 years post-transplant.

She tolerated haemodialysis well but had a single episode of flash pulmonary oedema, secondary to renal failure, which required ventilation on intensive care.

In an attempt to prevent CKD mineral and bone disorder, she was treated with a variety of different agents and dietary modifications. This was largely successful, with her calcium levels remaining normal with mildly elevated phosphate levels. However, her parathyroid hormone (PTH) and alkaline phosphatase levels continued to rise.

Despite high normal ferritin levels, normal B12 and folate levels, and erythropoietin injections, her haemoglobin remained suboptimal, 78 g/l at its lowest (Figure 1). In addition, she developed leukopenia of 0.4×10^9/l and thrombocytopenia of 131×10^9/l. Her peripheral blood smear demonstrated a leukoerythroblastic film. Other abnormal biochemical tests included a raised lactate dehydrogenase level, hypocalcaemia and hyperphosphataemia. She did not have any paraprotein, normal free light chains and urine Bence-Jones protein. Her viral screen for cytomegalovirus, Epstein-Barr virus, parvovirus and adenovirus were negative.

Her peripheral blood cytogenetic studies for *JAK2*, *CALR*, *BCR-Abl* and *MPL* were normal. In light of the above findings, we proceeded to a bone marrow biopsy.

The patient and her family noted that her facial features had gradually changed during her time on haemodialysis and she had the appearance of cherubism. On examination, she had pale conjunctiva, no palpable lymphadenopathy, no hepatomegaly or splenomegaly. However, she had multiple bony swellings in her maxilla and mandible (Figure 2). CT imaging confirmed that the skeletal changes were consistent with brown tumours, which developed secondary to secondary hyperparathyroidism.

Despite optimal medical therapy, she had developed skeletal complications of secondary hyperparathyroidism. As such, a parathyroidectomy was deemed to be the next step in her management.

A parathyroid subtraction scan identified a single parathyroid adenoma just below the lower pole of the right lobe of the thyroid gland. She underwent elective parathyroidectomy

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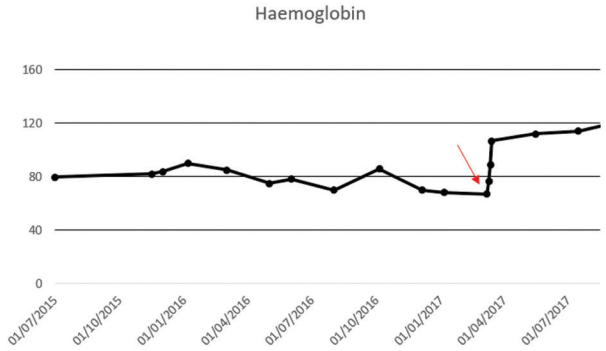
Figure 1 Haemoglobin level (g/l) pre- and post-parathyroidectomy with a rise in haemoglobin occuring postoperatively. The red arrow reflects the timing of the successful parathyroidectomy



to remove the single parathyroid adenoma in our hospital. However, her PTH levels failed to normalise postoperatively – they fell briefly before rising sharply to >500 pmol/l within the space of 1 month (Figure 3).

A bone marrow aspirate and trephine were obtained intraoperatively. It was a dry tap and only a trephine was obtained. Figure 4 illustrates the results of the trephine – reticulin grade 4 fibrosis was seen on scale of 0–4. As it was a dry tap no bone marrow cytogenetics could be performed.

As her initial surgery was only partially successful, she was referred to a tertiary hospital with expertise on thyroid disease. She underwent a wide local exploration of her neck with intraoperative parathyroid monitoring. The surgery was a success with three parathyroid glands being removed and

Figure 2 Skeletal changes that occurred in the patient – bony swellings over the maxilla and mandibular area

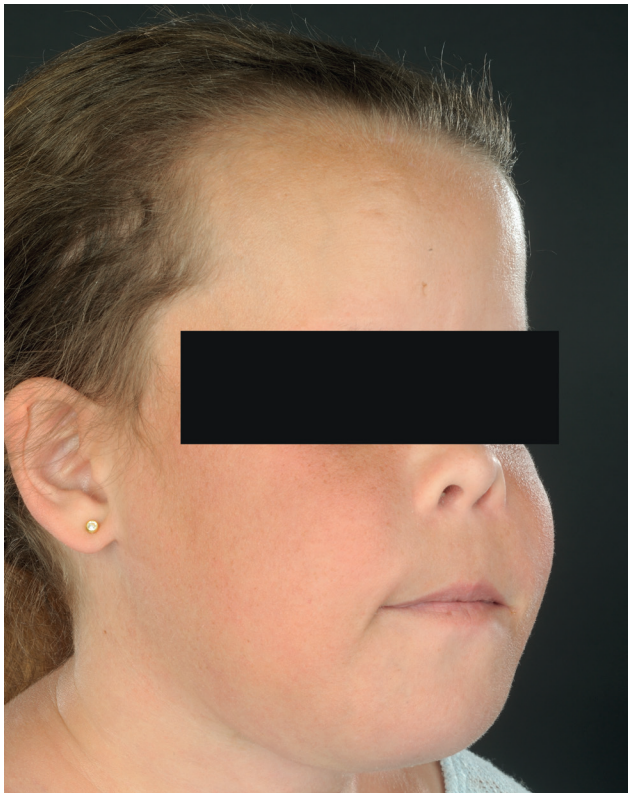
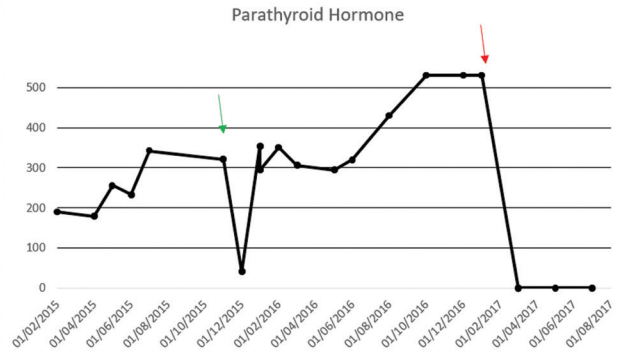


Figure 3 Parathyroid hormone levels (pmol/l), which peaked at 381 pmol/l just before the first parathyroidectomy (green arrow). After undergoing the first parathyroidectomy, an initial drop is seen, but levels rapidly doubled within the space of 1 month. The red arrow illustrates the timing of the second parathyroidectomy, which was successful in removing all the parathyroid glands



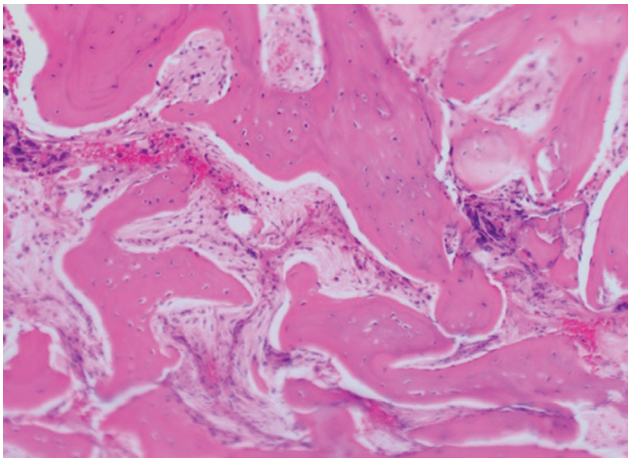
intraoperative monitoring of parathyroid levels demonstrated a drop to 35 pmol/l. Her PTH levels normalised within 5 days postsurgery. This postoperative drop is demonstrated by the red arrow in Figure 3.

Her pancytopenia resolved within 3 months post-parathyroidectomy, with her haemoglobin rising to 107 g/l, white cell count of 5.7 × 10^9/l and platelet count of 182 × 10^9/l. Her repeat blood film at 6 months postsurgery was unremarkable. The resolution of her blood counts postoperatively confirmed a diagnosis of secondary myelofibrosis due to secondary hyperparathyroidism. She remains on haemodialysis while awaiting a second transplant.

Discussion

Myelofibrosis is a rare disease in young individuals. The causes of myelofibrosis are diverse and can be broadly grouped into primary and secondary. There have been several case reports of primary hyperparathyroidism causing secondary myelofibrosis.[1,2] However, secondary myelofibrosis as a consequence of CKD is exceedingly rare with very few case reports in the literature.

Figure 4 Bone marrow trephine with reticulin grade 4 fibrosis



The pathophysiology of secondary hyperparathyroidism is a complex process, involving changes to bone and its mineral composition.[3] It occurs frequently in CKD especially in patients with glomerular filtration rate of <60 ml/min,[4] and is associated with increased morbidity and mortality in CKD patients owing to increased bone and cardiac disease.[3]

The pathophysiology of secondary hyperparathyroidism involves a complex interplay between PTH, calcium, phosphate and vitamin D.[3] Failure to maintain homeostasis can ultimately lead to autonomous production of PTH, which is termed tertiary hyperparathyroidism.[3]

Treatment of hyperparathyroidism in renal disease consists of dietary modification, phosphate binders and administration of active vitamin D.[3] Despite advances in medical management of hyperparathyroidism in end-stage renal disease, surgery is still required in about 5% of patients.[4]

Myelofibrosis is characterised by the accumulation of fibroblastoid cells and collagen fibres in the bone marrow.[5] The role of PTH in secondary myelofibrosis is not clearly defined. PTH has a direct toxic effect on erythropoietin synthesis and bone marrow erythroid precursors.[4,6] PTH causes the release of cytokines (interleukin-6, platelet-derived growth factor-α and tumour necrosis factor α) that stimulate fibroblasts resulting in myelofibrosis.[6] In experimental mouse models, where the transgenic mice express a constitutively active PTH-related protein, it has been demonstrated that marrow fibrosis is mainly formed by cells of the osteoblast lineage with mesenchymal stem cells being a potential contributing factor.[5] In addition, PTH receptor activation triggers cell signalling pathways, such as the cAMP pathway, and, consequently, the proliferation of bone marrow stromal cells.[6] The role of other physiological changes that occur in end-stage renal disease is not known.

Myelofibrosis causes a change in the architecture and cellular composition of bone marrow with excessive reticulin deposition in the bone. This leads to progressive anaemia, leukopenia and thrombocytopenia. In our patient, her haematological parameters improved within 1 month of successful parathyroidectomy. This demonstrated that her persistent anaemia and subsequent pancytopenia were due to PTH-induced myelofibrosis.

Conclusion

Our case highlights the importance of being aware of myelofibrosis as a potential complication of secondary hyperparathyroidism. Physicians should consider bone marrow biopsy as part of their investigations when faced with progressive pancytopenia in patients with end-stage renal disease.

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Informed consent

Written informed consent for the paper to be published (including images, case history and data) was obtained from the patient for publication of this paper, including accompanying images.

References

1 Gokosmanoglu F, Varim C, Ergenc H et al. Pancytopenia, secondary myelofibrosis and giant cystic parathyroid adenoma. *Eur J Biomed Pharm Sci* 2016; 3: 65–7.
2 Lim DJ, Oh EJ, Park CW et al. Pancytopenia and secondary myelofibrosis could be induced by primary hyperparathyroidism. *Int J Lab Haematol* 2007; 29: 464–8.
3 Tomasello S. Secondary hyperparathyroidism and chronic kidney disease. *Diabetes Spectrum* 2008; 21: 19–25.
4 Sharma SP, Siu K. Pancytopenia in secondary hyperparathyroidism due to end-stage renal disease. *Am J Med* 2013; 126: e11–12
5 Ohishi M, Schipani E. PTH and stem cells. *J Endocrinol Invest* 2011; 34: 552–6.
6 Nomura S, Ogawa Y, Osawa G et al. Myelofibrosis secondary to renal osteodystrophy. *Nephron* 1996; 72: 683–7.