Teaching Point
(Section Editor: K. Kühn)

Life-threatening vascular complications of severe hyperphosphataemia

Angel Argilés¹, Jean-Marc Frapier², Ronan Lorho¹,⁎, Marie-Françoise Servel³, Valérie Garrigue⁴, Sébastien Canet⁴, Guillaume Chong⁴, Bernard Albat² and Georges Mourad⁴

¹Institut de Génétique Humaine, CNRS UPR 1142, ²Department of Thoracic Surgery, University Hospital Arnaud de Villeneuve, ³Association pour l’Installation à Domicile, des Epurations Rénales (AIDER) and ⁴Department of Nephrology, University Hospital Lapeyronie, Montpellier, France

Introduction

Treatment of patients with renal bone disease and calcium–phosphate disturbances has changed over the last few decades. The available therapeutic arsenal has been enlarged in recent years and a more accurate and specific assessment of secondary hyperparathyroidism by biochemistry and imaging techniques is possible. New aluminium-free phosphate binders and vitamin D₃ derivatives have been developed [1,2] while dialysate solutions with variable calcium concentrations can be used [3,4] and new surgical techniques to control parathyroid gland over-function have been proposed [5]. However, despite this progress, renal bone disease and disturbances of calcium–phosphate metabolism remain the most worrisome long-term complications of chronic renal failure. Life-threatening calciphylaxis is observed with increasing frequency and other calcium–phosphate related complications might be under-reported [6,7].

We report here on a patient with systemic lesions due to calcium–phosphate deposition, which illustrates an extreme case of clinical evolution in association with protracted hyperphosphataemia.

Case

A 29-year-old woman presented with an isolated nephrotic syndrome and her renal biopsy was suggestive of focal and segmental sclerosis. Renal function and blood chemistries including calcium and phosphate serum levels were normal at the time of renal biopsy. She subsequently developed renal failure and hypertension and, in 1989, started dialysis at the age 39 years. She developed progressively worsening secondary hyperparathyroidism and underwent subtotal parathyroidectomy in 1994 (Figure 1A). Severe hyperphosphataemia recurred after parathyroidectomy and was associated with recurrent hyperparathyroidism (Figure 1A).

The patient was treated by haemodiafiltration using a polysulphone 1.7 m² dialyser. Her dialysis schedule consisting of 3 h thrice weekly was increased to 3 × 4 h and subsequently to 3 × 5 h per week in August 1997, because of protracted hyperphosphataemia (Figure 1A). In May 1999, daily dialysis (3-h sessions) with the same dialyser size and blood pump rate was initiated. She then presented multiple soft-tissue calcifications (Figure 1B).

Incidentally, atrioventricular block stage I was observed in 1996 and cardiac ultrasound suggested the existence of calcium deposits in the conduction system. P-R increased between 1996 and 1999 with the appearance of a Mobitz II disease and required the implantation of a pacemaker (Figure 2A).

At the same time pre-dialysis dyspnoea, which was exceptional during the patient’s first years of dialysis, was frequently observed and a clear diastolic murmur, compatible with mitral-valve stenosis, was recorded. Trans-oesophageal cardiac ultrasound showed an increase in maximal speed and mean pressure gradient, and a decrease in the slope of mitral fluxes (Figure 3), confirming mitral stenosis.

Chest X-ray showed an increase in right cardiac edges compatible with left atrial hypertrophy (Figure 2B). Daily dialysis was prescribed to improve dyspnoea episodes and valve replacement was scheduled after having excluded coronary-artery disease by coronaryography. Before the scheduled time for surgery, the patient was admitted to the university hospital with cardiogenic shock and suspicion of acute endocarditis (major dyspnoea, fever and systolic
blood pressure of 30 mmHg). Emergency surgery was performed and a JUDE type mitral prosthesis was put in place. The patient was discharged 1 month later with normal respiratory function and improved cardiac haemodynamics [Figures 2B(d) and 3]. Two years later she was admitted with a right-sided hemiparesis. CT scan showed a vascular lesion in Sylvian’s territory and trans-oesophageal cardiac ultrasound showed the presence of a floating vegetation arising from the mitral valve [Figure 3, lower panel (arrow)].

Comment

The clinical events linked to disturbances of calcium and phosphate metabolism associated with renal failure are mainly related to bone. Secondary hyperparathyroidism may present as pruritus, diffuse pain, functional limitation and pathological fractures [8]. Renal bone disease, although potentially disabling, does not carry a poor prognosis. Extra-osseous involvement with life-threatening complications may also be observed [8], but fortunately is less common. The present case illustrates particularly well this type of clinical course. It shows an atrioventricular blockade that, untreated, might have resulted in sudden death, and mitral-valve stenosis secondary to endocardial calcium deposits, which necessitated emergency valve replacement, and which still represents a clinically active disease 2 years after successful surgery.

The first case of metastatic myocardial calcification of the atrioventricular node in renal failure, presenting
as atrioventricular block, was reported by Henderson et al. [9]. Although moderate hypercalcaemia was not found to be associated with clinically significant effects on cardiac conduction in primary hyperparathyroidism [10], complete atrioventricular block has also been reported in primary oxalosis [11]. The poor prognosis of the involvement of the cardiac conduction system is well illustrated by the fact that the reports establishing a link between soft-tissue calcifications and cardiac arrhythmia were retrospective studies after sudden death [8,12,13]. Kuzela et al. [12] in an autopsy study of 56 dialysis patients observed soft-tissue calcifications in 79% of them (36% severe). The heart was the organ most frequently involved, and severe calcification of the cardiac conduction system was the established cause of death in seven patients [12]. Fujimoto et al. [13] observed calcium deposition in the cardiac conduction system post mortem in a dialysis patient, and atrioventricular blockade, which could be diagnosed retrospectively in earlier electrocardiograms, was found to have been evolving for more than 1 year before death [13]. In our unit, quarterly ECG studies are performed in all dialysis patients. Close cardiac control, especially in this patient, from the first signs of increased P-R segment >0.2 ms, permitted appropriate treatment and improved the outcome.

The association between disturbances of calcium and phosphate metabolism and mitral annulus calcification has received more attention in renal-failure patients. The aetiological factors seem to be age, elevated serum phosphate and calcium concentrations, as well as high intact PTH (iPTH) levels [14,15]. The patient presented here developed mitral calcification despite having a normal serum calcium concentration. However, the phosphate level was so markedly
elevated that the calcium–phosphate product was singularly high. At the same time she had elevated iPTH and decreased calcitriol serum levels, both predisposing factors for valve calcification [14,15].

The consequences of mitral annulus calcification are quite variable. The condition may remain undiagnosed and be a necropsy finding, or conversely it can cause clinically evident complications, particularly of the central nervous system. Our patient was admitted to emergency medicine with life-threatening endocarditis and haemodynamic failure that could only be countered by high-risk surgical replacement of the mitral valve. However, long-term follow-up after surgery was complicated by difficulties in controlling anti-coagulant therapy, and the appearance of a lesion in the Sylvian territory, responsible for hemiparesis, and probably secondary to the vegetation observed in the left atrium.

When analysing the clinical course of this patient, one cannot but wonder about the factors that resulted in such a severe hyperphosphataemia, despite having increased dialysis treatment time and frequency, increased phosphate binder prescription and avoidance of vitamin D3 derivatives. Although the patient regularly claimed to follow a strict low-phosphate diet, the first factor to think of is high oral phosphate intake. Additionally, an abnormal handling of absorbed phosphate cannot excluded (e.g. decrease in bone incorporation of phosphate in low-turnover bone disease, although this is unlikely with the iPTH levels observed in our patient). Finally, it must also be pointed out that every effort should be made to avoid the types of severe complication reported here. In this regard, the more extensive use of calcium- and aluminium-free phosphate binders, as well as the imminent introduction into clinical practice of the recently developed calcimimetics, are additional reasons for optimism.

**Teaching points**

Despite considerable progress in handling renal bone disease and secondary hyperparathyroidism, the pattern of the disease is changing, and complications with severe prognosis may be associated with the classically observed osteitis fibrosa.

Cardiac involvement is a life-threatening complication of protracted hyperphosphataemia that can be observed even after parathyroidectomy. It may present both as a conduction disease and cardiac arrhythmia and as valvular calcification. Indeed, should cardiac involvement be corrected in time by appropriate surgery (pace-maker and valve replacement), the complications associated with this surgery and the subsequent course, such as chronic anticoagulant therapy and possible embolic disease, will remain.

Therefore, particularly because we see hyperphosphataemia regularly in renal-failure patients, we must follow-up this type of patient closely and use all available means to control their serum phosphate levels.

---

**Fig. 3.** Trans-oesophageal echocardiograms (A) before, (B) immediately after, and (C) 2 years after mitral-valve replacement, when the patient presented with right-sided hemiparesis. Comparing echocardiograms (A) and (B) it can be seen that mean pressure gradient decreased from 21.6 to 10.3 mmHg (normal value 3 mmHg) and maximal speed decreased from 276 to 220 cm/s and the slope of the flow decrease was partially corrected (dotted lines). A vegetation 1.43-cm long can be observed arising from the valve and floating in the atrium (white arrow) in echocardiogram (C). This lesion was not present in previous echocardiograms.
The new non-calcium, non-aluminium phosphate binders, and the non-hypercalcaemic drugs currently being investigated in the control of secondary hyperparathyroidism, such as calcimimetics, are likely to provide valuable benefit, particularly in patients like the one described in this report.

Acknowledgements. The authors thank Drs G. Levy for cardiology advice and B. Laroche, S. Delmas, B. Canaud, A. Slingeneyer and H. Leray-Moragues for their help in treating dialysis patients. The work of Patrick Atger in preparing the iconographic material illustrating this observation is particularly appreciated.

References