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Case Report

Fatal Generalized Metastatic Calcifications

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Abstract

Metastatic calcifications are a rare but potentially fatal complication of primary hyperparathyroidism (PHPT). In this case, a 76-year-old man with a previously asymptomatic PHPT developed a hypercalcemic crisis with severe pancreatitis following elective urologic surgery. Despite initial treatment focused on pancreatitis and subsequent organ failure, hypercalcemia persisted, leading to rapid progressive metastatic calcifications in multiple organs. Parathyroidectomy during ongoing pancreatitis successfully reduced calcium levels but not the calcifications. After 4 months of complications and persistent pain, the patient declined further treatment and ultimately succumbed to the disease. The current literature primarily reports single-organ metastatic calcifications due to PHPT. This case represents the only lethal case of systemic metastatic calcifications in the current century. Physicians should be aware of the potential deterioration of hypercalcemia following elective surgery, particularly in the context of renal impairment. Rapid correction of calcium levels may prevent severe complications such as fatal metastatic calcifications.

Key Words: metastatic calcifications, organ calcification, primary hyperparathyroidism, parathyroid adenoma, hypercalcemic crisis, pancreatitis

Abbreviations: Ca*P, calcium and phosphate product; CT, computed tomography; CVVHDF, continuous veno-venous hemodiafiltration; ICU, intensive care unit; IV, intravenous; PTH, parathyroid hormone; PHPT, primary hyperparathyroidism; TURB/-P, transurethral resection of the bladder and prostate.

Introduction

Metastatic calcifications, first described by Virchow in 1855, are abnormal depositions of calcium salts in healthy tissues due to hypercalcemia and hyperphosphatemia [1-4]. Commonly affected organs include the lungs, kidneys, large arteries, heart, and stomach [5]. Multiple metastatic calcifications may be lethal due to complications of these calcifications or uncontrolled hypercalcemia [6, 7]. While typically associated with chronic renal failure, metastatic calcifications are an uncommon complication of primary hyperparathyroidism (PHPT) [8, 9].

Case Presentation

A 76-year-old man with a history of arterial hypertension, cholecystectomy, and subclinical stable PHPT for 3 years (see Table 1 for laboratory values) was admitted for an elective transurethral resection of the bladder and prostate (TURB/-P) for suspected in situ bladder tumor and prostate adenoma. His medications included telmisartan 80 mg and dutasteride .5 mg/tamsulosin hydrochloride .4 mg once daily.

Two days after the TURB/-P, the patient reported abdominal pain. A computed tomography (CT) scan revealed severe necrotic pancreatitis, portal vein thrombosis, and segmental pulmonary embolism.

Due to progressive tachypnea (34 breaths per minute), declining blood pressure (96/67 mmHg), and sinus tachycardia (122 beats per minute), the patient was transferred to the intensive care unit (ICU). On the same day, he developed respiratory failure due to exhaustion, and a pancreatitis-induced distributive shock was diagnosed. Treatment included intubation, mechanical ventilation, intravenous (IV) fluid therapy, and vasoactive drugs. Therapeutic anticoagulation with unfractionated heparin was initiated to treat thrombosis.

Diagnostic Assessment

On admission to the ICU (day 2; time specified in days after hospital admission), corrected serum calcium, ionized calcium, and parathyroid hormone (PTH) levels were elevated (see Table 1). In conjunction with the clinical findings of renal impairment, low urine output (.4 mL/kg/h), and stupor, a hypercalcemic crisis due to PHPT was diagnosed. Given the negative alcohol history, the absence of lithogenic signs, and no other plausible etiology, we considered the hypercalcemia as an etiologic factor for his pancreatitis. A positron emission tomography CT scan revealed 3 parathyroid adenomas as the underlying cause of PHPT. A parathyroidectomy was indicated and scheduled following the resolution of severe pancreatitis.

Treatment

Hypercalcemia was treated with salmon calcitonin (5 units/kg IV every 12 hours) and forced diuresis with Ringer acetate solution (600-1500 mL/day) alongside continuous IV furosemide infusion (20 mg/hour for 32 hours), resulting in a urine output between 3200 and 4400 mL/day over 3 days. Due to a positive fluid balance of 10 liters with signs of pulmonary edema and high intra-abdominal pressure, additional volume substitution was avoided. After initial treatment failed to resolve the hypercalcemia (see Fig. 1), citrate continuous veno-venous hemodiafiltration (CVVHDF) was started on day

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Table 1. Laboratory values of our patient before and during hospital stay

Parameter	Reference range	Day					
		−166	−17	2	59	60	64
Corrected calcium	2.05-2.55 mmol/L (8.2-10.2 mg/dL)	**2.76 mmol/L (11.0 mg/dL)**	—	**3.55 mmol/L (14.2 mg/dL)**	**2.81 mmol/L (11.2 mg/dL)**	**2.90 mmol/L (11.6 mg/dL)**	**2.64 mmol/L (10.6 mg/dL)**
Ionized calcium	1.15-1.27 mmol/L (4.60-5.08 mg/dL)	—	—	**1.81 mmol/L (7.24 mg/dL)**	**1.38 mmol/L (5.52 mg/dL)**	**1.36 mmol/L (5.44 mg/dL)**	1.25 mmol/L (5.00 mg/dL)
Phosphate	.74-1.52 mmol/L (2.3-4.7 mg/dL)	—	—	1.17 mmol/L (3.6 mg/dL)	.98 mmol/L (3.0 mg/dL)	1.17 mmol/L (3.6 mg/dL)	1.44 mmol/L (4.5 mg/dL)
PTH	10-65 ng/L (10-65 pg/mL)	**130 ng/L (130 pg/mL)**	—	**333 ng/L (333 pg/mL)**	**226 ng/L (226 pg/mL)**	**3.64 ng/L (3.64 pg/mL)**	**2.53 ng/L (2.53 pg/mL)**
25-hydroxyvitamin D	35-150 nmol/L (14-60 ng/mL)	—	—	**25 nmol/L (10 ng/mL)**	—	—	—
1,25 dihydroxy- vitamin D	60-108 pmol/L (25-45 pg/mL)	—	—	99 pmol/L (38 pg/mL)	—	—	—
Alkaline phosphatase	.5-2.0 µkat/L (30-120 U/L)	1.9 µkat/L (116 U/L)	—	**2.2 µkat/L (129 U/L)**	—	**3.0 µkat/L (181 U/L)**	**2.9 µkat/L (173 U/L)**
Creatinine	53-106 µmol/L (.6-1.2 mg/dL)	77 µmol/L (.9 mg/dL)	80 µmol/L (.9 mg/dL)	**169 µmol/L (1.9 mg/dL)**	81 µmol/L (.9 mg/dL)	87 µmol/L (1.0 mg/dL)	94 µmol/L (1.1 mg/dL)
Urea nitrogen	2.9-8.2 mmol/L (8-23 mg/dL)	—	—	**17.7 mmol/L (50 mg/dL)**	**9.1 mmol/L (25 mg/dL)**	**9.1 mmol/L (25 mg/dL)**	**12.8 mmol/L (36 mg/dL)**
CRP	<5 mg/L (<.5 mg/dL)	**5 mg/L (.5 mg/dL)**	<5 mg/L (<.5 mg/dL)	**86 mg/L (.9 mg/dL)**	**77 mg/L (.8 mg/dL)**	**98 mg/L (1.0 mg/dL)**	**119 mg/L (1.2 mg/dL)**
Lipase	.5-3.2 µkat/L (31-186 U/L)	—	—	**23.9 µkat/L (1429 U/L)**		.7 µkat/L (41 U/L)	**.3 µkat/L (19 U/L)**
Triglyceride	<1.8 mmol/L (<160 mg/dL)	.9 mmol/L (80 mg/dL)	—	.8 mmol/L (71 mg/dL)	—	**2.6 mmol/L (230 mg/dL)**	**1.8 mmol/L (160 mg/dL)**

Time specification in days after admission to the hospital (day −17 = preoperative clarification; day 2 = admission to intensive care unit; day 59 = parathyroidectomy). Abnormal values are shown in bold font. Values are indicated in System International units; values in parenthesis are conventional units. Hyphen indicates that no values are available.

Abbreviations: CRP, C-reactive protein; PTH, parathyroid hormone.

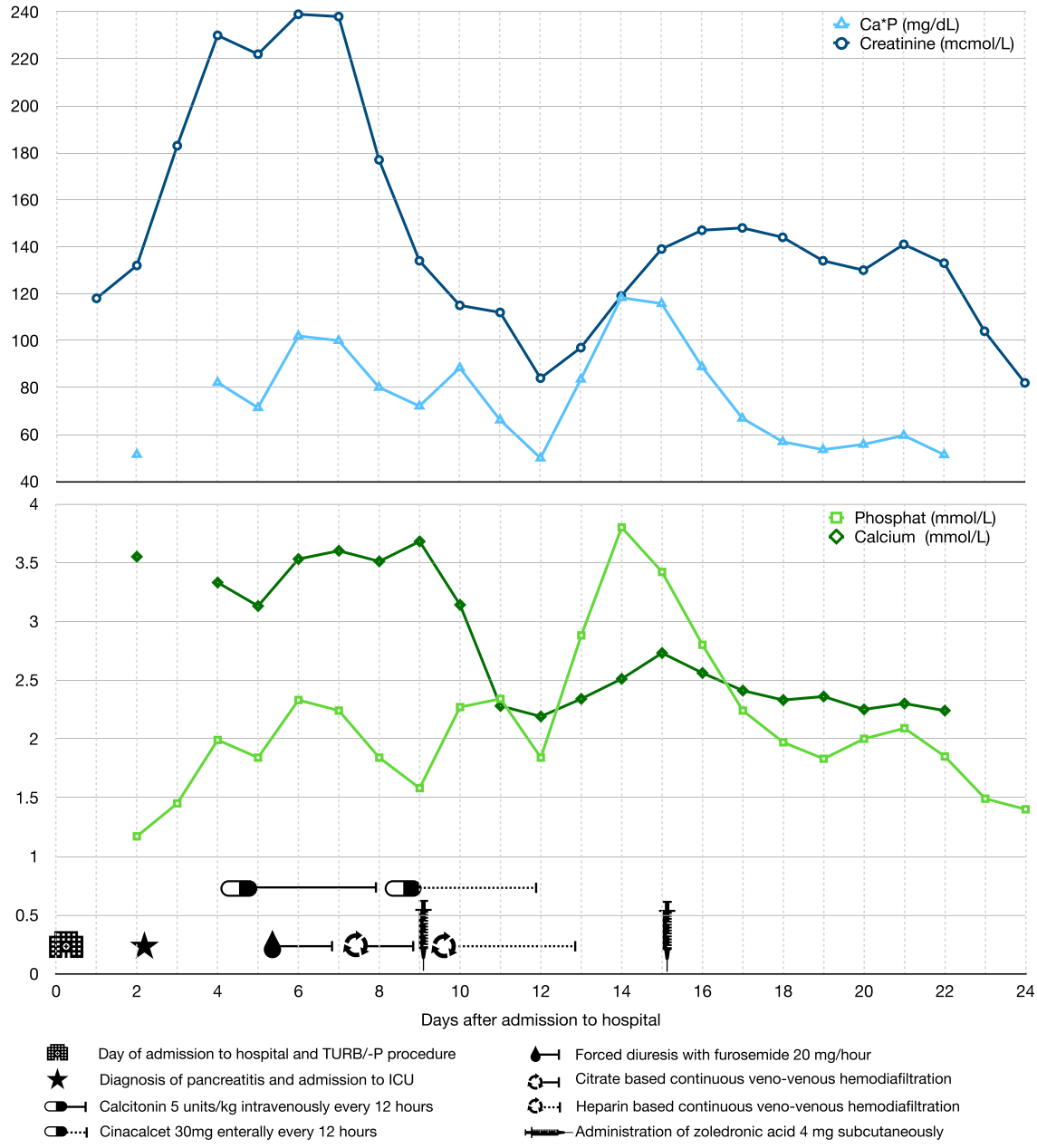

Figure 1. Initial treatment of hypercalcemia and trend of serum calcium, phosphate, creatinine, and Ca*P.

Abbreviations: Ca*P, calcium and phosphate product; ICU, intensive care unit; TURB/-P, transurethral resection of bladder and prostate.

5. However, the necessity for postfilter calcium substitution to neutralize citrate anticoagulation and prevent citrate toxicity resulted in insufficient serum calcium reduction, prompting a switch to a heparin-based CVVHDF. A calcimimetic, cinacalcet 30 mg, was added to the regimen and administered enterally every 12 hours. The first bisphosphonate, zoledronic acid 4 mg subcutaneously, was administered on day 9, followed by a rapid decrease in serum calcium (see Fig. 1) with marked neurological improvement. Zoledronic acid injections were repeated on days 15 and 38.

Outcome and Follow-up

The pancreatitis course was complicated by a paralytic ileus on day 9 with perforated megacolon on day 19, requiring an immediate right hemicolectomy and resection of the terminal ileum. The subsequent septic shock was treated with antibiotics and antifungals. Surgical revision was performed the following day, with open abdomen treatment using vacuum-assisted closure until day 109.

Hypercalcemia persisted despite the aforementioned treatment (see Fig. 2). Over time, calcifications emerged: a tracheotomy on day 13 revealed narrow tracheal clips. Replacing the tracheostomy tube and placing the arterial catheter on day 50 were challenging due to extraordinary calcifications of the tracheal cartilage and artery wall. The patient experienced severe, persistent painful muscle contractions. Moreover, repeated colonoscopies for gastrointestinal bleeding (days 50, 81, and 93) revealed severe calcified bowel wall areas (see Fig. 3). Repeated CT scans demonstrated progressive metastatic calcifications of lungs, pancreas, urinary bladder wall, colon wall, arm, shoulder, and pelvis muscles (see Fig. 4).

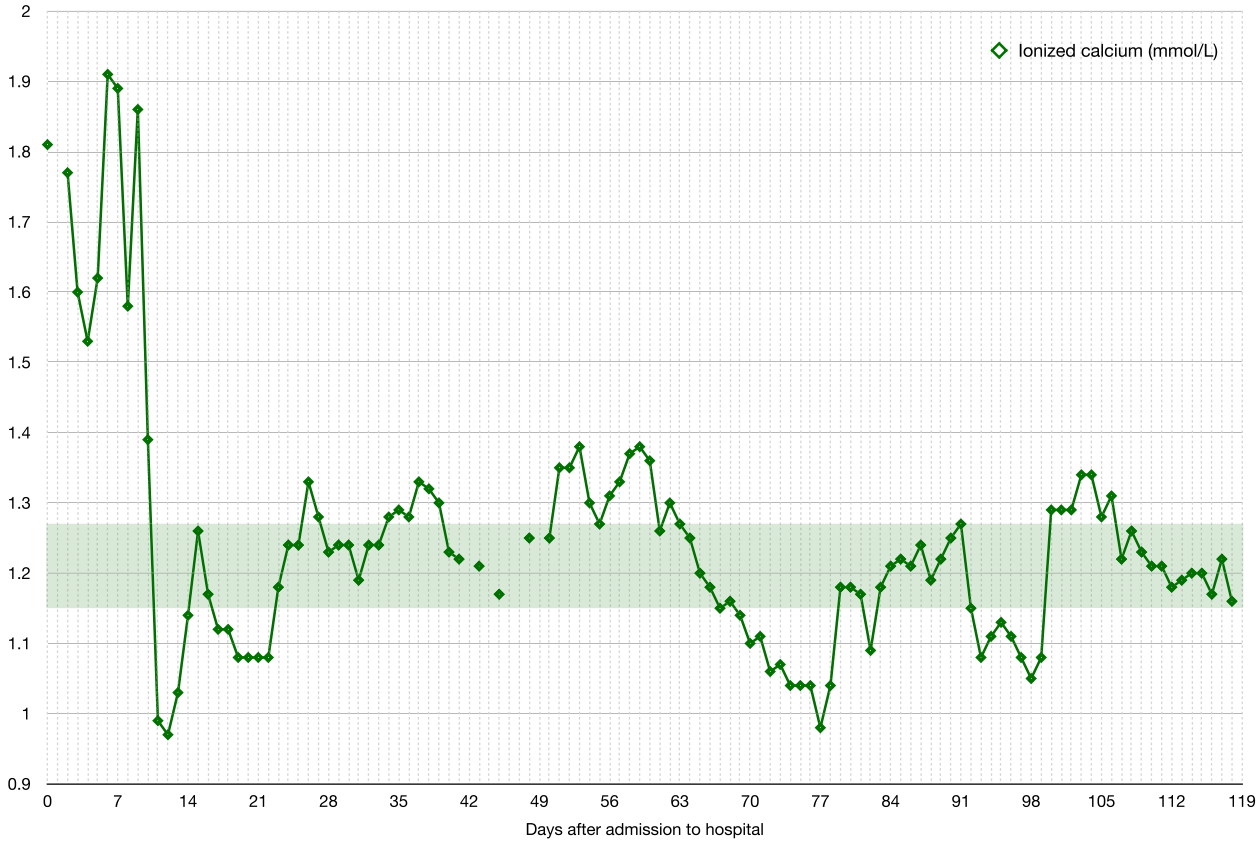

Figure 2. Trend of ionized calcium during hospital stay. The horizontal bar indicates the reference range of ionized calcium [1.15-1.27 mmol/L (4.60-5.08 mg/dL)].

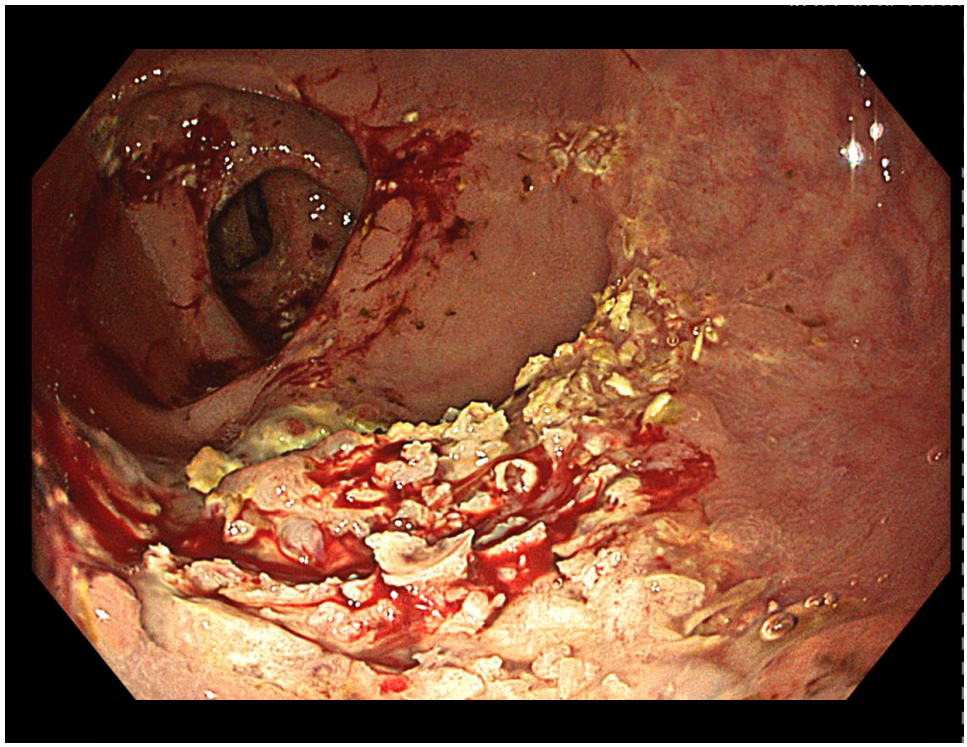

Figure 3. Calcified areas in the residual colon. This figure shows an image of the colonoscopy conducted on day 93 due to rectal bleeding. The colonoscopy revealed multiple areas of intestinal mucosa with calcifications that were markedly sensitive to tactile stimulation. In the rectum, the calcifications appeared almost circular.

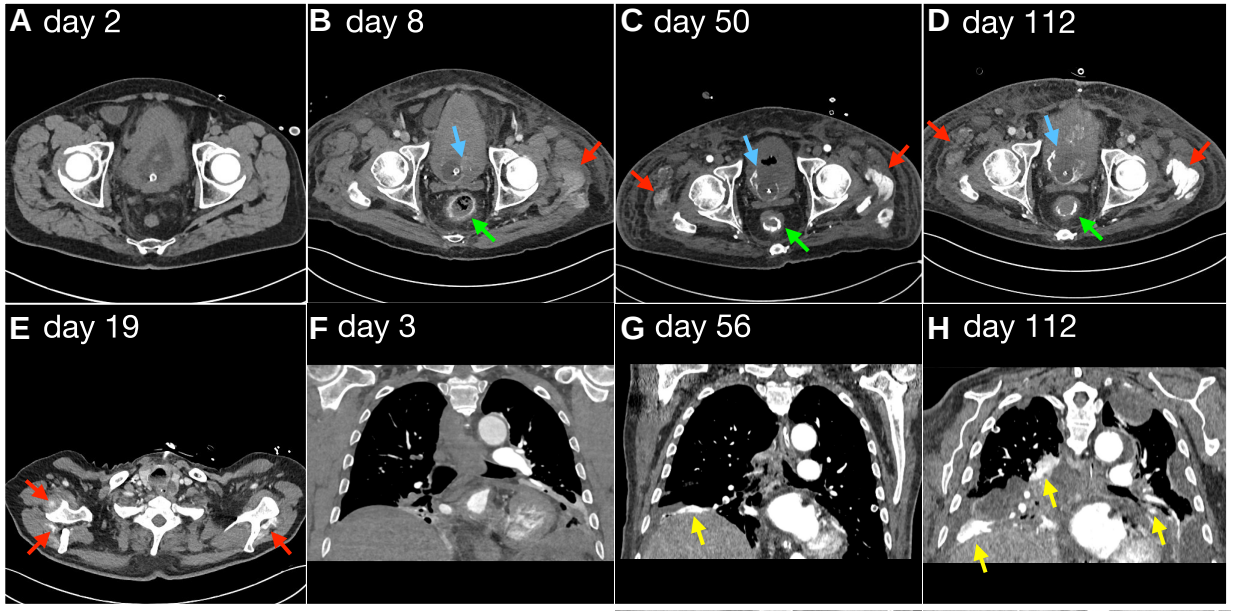

Figure 4. Evolution of selected metastatic calcifications on CT. The figures presented here illustrate the progressive formation and evolution of the calcifications in various anatomical locations. Initial CT scan (time specification in days after hospital admission) without evidence of calcifications (A, F). Six days later moderately dense calcifications begin to form in the pelvic muscles and the mucosa of the bladder and rectum (B), which progress in density and size in the following CT scans (C, D). Formation of upper extremity calcifications in the rotator cuff (E). Appearance of new calcifications in the right lower lobe (G) with new locations and progression in size over time (H).

Abbreviation: CT, computed tomography.

Due to the presence of progressive calcifications, a parathyroidectomy was performed on day 59, despite the ongoing open abdomen treatment and elevated C-reactive protein levels (see Table 1). Three out of the 4 parathyroid glands had adenomas, which were removed. Postoperatively, PTH levels decreased and serum calcium was effectively controlled (see Fig. 2). Afterwards, calcium substitution was required; IV calcium gluconate (13.5-27 mmol/hour) was administered for 16 days, followed by enteral calcium/vitamin D3 (500 mg/800 units twice daily).

After weaning from mechanical ventilation, the patient was transferred to the normal ward on day 91. However, he was shortly readmitted to the ICU on day 113 with respiratory failure due to pleural effusion requiring video-assisted thoracoscopic surgery, showing left-sided pus and calcifications. Antimicrobial and antifungal therapies were initiated. In the following days, on the general ward, the patient declined further therapeutic interventions due to prolonged suffering without improvement. Consequently, palliative care was initiated, and the patient passed away on day 119.

Discussion

To the best of our knowledge, this represents the first case report to detail acute decompensation of hypercalcemia following elective surgery, resulting in lethal pancreatitis and metastatic calcifications in a patient with long-standing stable PHPT. Benign PHPT-associated hypercalcemia causing metastatic calcifications is rare [8-10], as evidenced by the limited number of reported cases. We searched in PubMed and Google Scholar using the terms metastatic calcification "OR" calcification "AND" primary hyperparathyroidism "OR" parathyroid adenoma. This search yielded 45 case reports of metastatic calcifications due to benign PHPT, excluding single calcifications at joints or eyes. Only 10 documented cases have been reported in the 21st century. This decline may be attributed to the earlier detection of PHPT through routine serum calcium analysis and improved accessibility to PTH measurement since the 1970s, allowing early identification, closer monitoring, and timely intervention of asymptomatic patients [8, 11].

In our patient, calcifications were observed in multiple organs. In this century, only 1 case of multiple metastatic calcifications (lungs, cardiac muscle, and spleen artery) due to parathyroid adenoma and renal failure has been reported, showing a reduction of calcifications after medication-based treatment of hypercalcemia and resection of parathyroid adenoma [12]. All other 20 cases of multiple metastatic calcifications were published before 1996, with all but 1 resulting in a fatal outcome [4-7, 13-16]. Newer cases predominantly describe single-organ calcifications (lungs in 6 [17-22], heart in 1 case [23]) or involvement of 2 organs (lungs and trachea [24], lungs and stomach [25]), without fatal outcome. The high mortality associated with metastatic calcifications is attributed to uncontrolled hypercalcemia or complications arising from the calcification process, such as respiratory failure in metastatic pulmonary calcifications [10]. In our case, the fatal outcome resulted from the persistent painful calcifications, complicated pancreatitis, and calcification-induced gastrointestinal bleeding leading to the decision for palliative care because of extensive suffering.

Different studies emphasize that a serum calcium and phosphate product (Ca*P) greater than 60 mg^2/dL^2 (4.79 $mmol^2/L^2$) (reference range ≤ 55 mg^2/dL^2, ≤ 4.40 $mmol^2/L^2$) is necessary to cause precipitation of calcium salts [7, 8, 10, 20, 26]. Therefore PHPT, usually accompanied by hypophosphatemia, can induce calcifications only in combination with very high calcium levels or in the presence of severe renal

failure-induced hyperphosphatemia [10]. In our patient, the Ca*P exceeded 60 mg^2/dL^2 (4.79 $mmol^2/L^2$) in the first 15 days of the ICU stay (see Fig. 1). His elevated phosphate was likely caused by shock-induced acute kidney injury. Among all cases reviewed, renal function parameters were reported in 16 cases, with impairment observed in 14 (88%).

It remains unknown how long a high Ca*P is required to lead to clinically relevant calcifications. Most published cases cannot delineate the time needed for calcium salts to deposit, as patients often already present with metastatic calcifications. In the present case, a high Ca*P produced CT-visible metastatic calcifications within 6 days and symptomatic metastatic calcifications within 11 days. The literature reports only 6 cases with new calcifications emerging during hospitalization over a short period, ranging from a few days to 3 weeks [7, 12, 20, 25, 27]. Notably, all cases involved pulmonary calcifications. It is assumed that newly formed calcifications are unstable and therefore reversible after the rapid decrease of serum calcium and phosphate values [8]. This is supported by the clear clinical and radiological improvements described in 3 of the aforementioned cases [12, 25, 27]. We could not observe any recovery after the reduction of calcium and phosphate. One explanation for this irreversibility could be the very high Ca*P, up to 120 mg^2/dL^2 (9.58 $mmol^2/L^2$), almost twice the amount needed for precipitation. Only 1 case with reversible calcifications reported a similar Ca*P of 112 mg^2/dL^2 (8.94 $mmol^2/L^2$) for a maximum of 3 weeks [4]. The other cases with recovery exhibited a maximum Ca*P of 75 mg^2/dL^2 (5.99 $mmol^2/L^2$) [12, 17, 19, 21-25, 27, 28].

Considering the rapid onset of metastatic calcifications in our case, the question arises whether bisphosphonate administration or parathyroidectomy should have been performed earlier. Despite medical treatment, proper control of hypercalcemia was not achieved, suggesting that an early parathyroidectomy might have expedited calcium reduction. In our case, a prompt parathyroidectomy was assessed as an exceedingly high-risk procedure due to the persistence of shock. Given that metastatic calcifications were already present after 6 days, even a parathyroidectomy after initial stabilization would probably not have prevented calcium salts deposition. Therefore, pharmacological treatment of hypercalcemia was indispensable. Elevated calcium levels alone, without concurrent abnormalities in potassium, urea, pH, and other parameters, do not typically justify the initiation of renal replacement therapy. Therefore, the effect of calcitonin and fluid management was evaluated before proceeding with CVVHDF. Although bisphosphonates are often contraindicated in cases of reduced renal function, their use should be considered promptly when parathyroidectomy is not an option. Additionally, in cases with severe renal impairment, human monoclonal antibodies targeting osteoclasts, such as denosumab, could have been a viable alternative to bisphosphonates. In our case, as early parathyroidectomy was considered and due to concerns about the following potential for "hungry bones," prompt administration of bisphosphonates was discussed but not performed. Retrospectively, heparin hemodiafiltration and bisphosphonate injection, known as highly effective methods (despite surgery) for reducing serum calcium levels [29], may have been started earlier.

In accordance with guidelines for asymptomatic PHPT [30], a preventive preoperative parathyroidectomy was not indicated for our patient, who had stable annual serum calcium levels. Parathyroidectomy prior to elective surgery is recommended only for patients receiving medical treatment to manage hypercalcemia [31]. In our case, the absence of preoperative serum calcium measurements complicates the assessment of whether progressive hypercalcemia had already begun before TURB/-P or was exacerbated by the surgery, associated with sobriety, dehydration, and immobilization. The lack of calcification in the CT scan 2 days after TURB/-P supports the hypothesis of postoperative worsening.

In conclusion, based upon our case, we recommend monitoring of calcium and phosphate levels before and after surgery in all patients with PHPT to enable prompt intervention if levels rise. Early treatment with bisphosphonates (or denosumab in case of renal impairment), citrate-free hemodiafiltration, and urgent parathyroidectomy should be considered to manage acute symptoms of hypercalcemia and to prevent long-term complications, including metastatic calcifications.

Learning Points

- Metastatic calcifications represent a severe condition associated with significant morbidity and mortality.
- Optimal management necessitates strict control of calcium and phosphate levels to prevent the formation and progression of metastatic calcifications.
- Monitoring of calcium and phosphate levels before and after surgery in all patients with PHPT is strongly recommended.
- Bisphosphonates (or denosumab in cases of renal impairment) and citrate-free hemodiafiltration are the most effective nonsurgical treatments for hypercalcemia.
- When metastatic calcifications are diagnosed, prompt parathyroidectomy is essential, regardless of the presence of comorbidities or complications.

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Contributors

All authors were actively involved in the management of the patient during his time in the ICU. J.S. first identified the issue of metastatic calcifications. J.R. and F.D. conducted a detailed case analysis. The manuscript was collaboratively written by all authors, with F.D. initiating and coordinating the writing process. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient's relatives or guardians.

Data Availability Statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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