

Parathyroidectomy in Hyperparathyroidism-Associated Calciphylaxis in End-Stage Renal Disease Should be Prompt and Radical – a Case Report with Two Original Therapeutic Modifications and Successful Outcome

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ABSTRACT

We present a case of severe calciphylaxis in both thighs and calves in a patient with end-stage renal disease and advanced secondary hyperparathyroidism with successful outcome after modified therapeutic approach. The cause of calciphylaxis is multifactorial. In our case, not only severe hyperparathyroidism and mediocalcinosis, but also medication (warfarin, calcium and active vitamin D) was involved. Because the initial conservative therapy was not successful, we indicated parathyroidectomy. However, we were not able to localize parathyroid glands and we contraindicated bilateral neck exploration due to the patient's critical status. Therefore, we decided for total thyroidectomy with total parathyroidectomy. Surgery was uncomplicated and histology confirmed that all four parathyroid glands were removed. The expected post-operative hypocalcaemia was asymptomatic and we did not use any calcium supplementation or vitamin D. Thyroid hormone replacement was easy. After surgery, the large and multiple subcutaneous defects started to heal. We achieved complete healing within several months of continuing dedicated care. There is no recurrence after three years. Prompt and radical surgical parathyroidectomy was extremely useful in our patient.

KEYWORDS

calciphylaxis; thyroidectomy; parathyroidectomy; haemodialysis; hypocalcaemia

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Received: 23 June 2017

Accepted: 20 July 2017

Published online: 5 October 2017

Acta Medica (Hradec Králové) 2017; 60(2): 85–88

<https://doi.org/10.14712/18059694.2017.99>

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BACKGROUND

Calcific uremic arteriolopathy (CUA; calciphylaxis) is a rare but very serious disease affecting (not exclusively) kidney failure patients (1, 2). Mortality is high and sepsis is the usual cause of death.

Diagnosis and treatment of CUA is multifactorial and multidisciplinary (1–5). Therefore, wide spectrum of medical specialities should be familiar with this disease. Thanks to the multidisciplinary approach, the treatment of our case was finally successful.

The first clinical sign of CUA is usually pain, subcutaneous induration and skin patches resembling livedo reticularis. Within few days black cutaneous and subcutaneous ulcers and necrosis develop. The affected area could be larger than 10 cm. CUA typically affects inner sides of calves, inner and outer sides of thighs and, sometimes, abdominal areas. On the contrary, periphery of extremities is not involved (6). Sometimes, rhabdomyolysis is the initial clinical sign.

There is no single cause of CUA. Abnormal calcium (Ca) and phosphorus (P) homeostasis, sometimes associated with a disorder of parathyroid glands predisposes to this disease. Other risk factors include vitamin K antagonists (warfarin), low anticoagulant activity of protein C and S, hypoalbuminemia/malnutrition, inflammation, obesity, diabetes mellitus, etc. Especially warfarin is dangerous (7).

The treatment of CUA is local and systemic. This latter includes correction of all the above mentioned predisposing conditions. In addition, intravenous sodium thiosulphate is useful, as well as parenteral antibiotics, nutritional support, etc. In CUA associated with hyperparathyroidism, surgical parathyroidectomy (PTX) should be considered (7, 8) but the opinions are not unequivocal (4). Comprehensive reviews of CUA therapy have recently been published (2–4, 6).

CASE REPORT

A 62-year-old man with known renal disease presented to the Emergency Department of our hospital in June 2014 with severe breathlessness and general oedema. His past medical history was notable for a deep vein thrombosis in 1992 treated with warfarin for several years and advanced kidney disease (“end-stage kidney disease” in renal biopsy in 2012) associated with secondary hyperparathyroidism. Medications on admission included paricalcitol (1 µg/day), calcium (1000 mg/day), sodium bicarbonate and acetylsalicylic acid.

On examination, his blood pressure was 160/114 mm Hg, respiratory rate 22 per minute. Heartbeats were regular, 85 per minute. Weight gain was 10 kg during the last 10 days. Arteriovenous fistula created in 2012 on left forearm was malfunctioning. There was a small skin defect on the right lower limb. Serum creatinine was 632 µmol/l, urea 23.4 mmol/l, C-reactive protein 30 mg/l (reference range 0–5), total serum calcium 2.02 mmol/l. Parathyroid hormone (PTH) measured as whole molecule (1–84 PTH) was 37 pmol/l.

The patient underwent an acute haemodialysis (HD) with ultrafiltration through central dialysis catheter inserted in the right internal jugular vein and then we started regular HD.

Shortly thereafter, catheter-related sepsis, right internal jugular vein thrombosis and bronchopneumonia developed. The local skin defect became larger and new extensive skin ulcers appeared on inner sides of thighs and calves bilaterally, with typically visual appearance of CUA. We immediately stopped paricalcitol, Ca supplements and sodium bicarbonate and started sevelamer carbonate. The systemic therapy included sodium thiosulphate (magistraliter preparation), 100 ml 25% solution after HD, with controls of serum Ca and acid base balance (9), calcimimetics, antibiotics, nutritional support, daily HD (2, 5). Local care was carried out daily.

Despite intensive conservative treatment calciphylaxis did not improve (Figures 1a, 1b). In some areas, the lesions healed partly, but new lesions appeared (Figure 1b). In other areas, no improvement was observed (Figure 1a). The lesions were extremely painful and the patient became bed-ridden and suffered a lot. PTX was indicated but a detailed search for enlarged parathyroid gland was negative



Fig. 1: Calciphylaxis. Photography was taken before the surgery, at the end of intensive conservative therapy period. Patient was fully bed-ridden at that time. a) no healing after conservative local treatment, b) large area with some improvement, but also with new lesions at the edge of the scars.

on four times repeated ultrasound examination. Scintigraphy and magnetic resonance imaging were also negative.

Without proven localization of parathyroid tissue, bilateral neck exploration is the treatment of choice (11). However, several comorbidities and patient's critical health state contraindicated this rather lengthy approach. Therefore, we decided to surgically remove parathyroid glands together with thyroid gland (total thyroidectomy with total parathyroidectomy), which is shorter and less risky surgery. We were aware that this would lead to iatrogenic hypothyroidism, but also to the mandated (total) PTX.

The surgery was uncomplicated and successful. Histology confirmed total removal not only of thyroid tissue, but also of all four (nodular) parathyroid glands. Interestingly, all parathyroid glands were only slightly increased (max. 10 mm) and all were located within thyroid tissue. Histology of thyroid gland was normal and thyroid hormone substitution was easy, targeted at normal thyrotropin (TSH) levels.

The patient's serum PTH level dropped below the detection limit shortly after PTX. He also developed hypocalcaemia (mean total serum Ca 1.7 mmol/l). Because of our fear of new vascular calcium deposits, we did not use any calcium supplementation. Surprisingly, no clinical signs of hypocalcaemia occurred (i.e. paresthesia, spasms or cardiac rhythm disorders).

After surgery, the skin defects were improving day by day and finally they healed up completely (Figure 2). The pain disappeared and the patient's mobility improved dramatically. Six months after admission the patient was discharged. On outpatient basis, he has been dialysed three times a week. Now, he takes very low dose of calcium acetate per day and 5000 IU of cholecalciferol once in two weeks. His is asymptomatic.



Fig. 2: All lesions were successfully healed using careful local care with no recurrence. Photography was taken in June 2017. The patient is pain-free, moving without help, with active life with haemodialysis.

DISCUSSION

The treatment approach in our case has two unique and novel characteristics, not yet described in the literature:

- 1) Surgical total parathyroidectomy performed at the cost of iatrogenic hypothyroidism (total thyroidectomy with parathyroidectomy).

- 2) Iatrogenic hypocalcaemia not treated by calcium substitution and fully asymptomatic.

Ad 1) Based on our previous unpublished experience and on the unsatisfactory course in the presented patient during the first weeks after admission, we decided for parathyroidectomy. However, we were not able to find enlarged parathyroid glands on four-times repeated ultrasound examination performed by a skilled sonographer. Magnetic resonance and scintigraphy were negative as well. Due to the patient's poor clinical status, bilateral neck exploration, which is a lengthy procedure, was contraindicated. Our selected approach, i.e. curative total parathyroidectomy at the cost of total thyroidectomy, is quite unusual. We have not found any similar case in the literature. The neck surgery in our patient was successful, and it definitely contributed to the cure of CUA.

Brandenburg (4) has recently reported on the experts' discussion about important issues associated with CUA, namely on their opinion about surgical treatment of CUA associated with secondary hyperparathyroidism. There was a wide spectrum of answers, ranging from no recommendation of PTX to very strong support of PTX. Our own results support PTX without delay. We can also confirm another conclusion from this work: warfarin is a strong risk factor of CUA.

The explanation why we did not locate the parathyroid glands was probably their relatively small size (despite nodular structure and autonomic features) and namely their intrathyroid localization. So, if the clinical and laboratory findings are in accord with hyperparathyroidism, then negative imaging using ultrasound, scintigraphy and even nuclear magnetic resonance cannot serve as a document against this disorder.

Ad 2) As expected, hypocalcaemia developed shortly after surgery. We stopped sodium thiosulphate right after parathyroidectomy because it could intensify hypocalcaemia (10). We were afraid of calciphylaxis recurrence in our patient because of his preexisting mediocalcinosis. Therefore, we decided not to provide calcium substitution. We only carefully observed the patient's clinical and laboratory condition. Fortunately, there were no clinical symptoms of hypocalcaemia during immediate post-operative period and in the long-term course. The asymptomatic course of long-lasting hypocalcaemia can be, at least hypothetically, explained by previous significant positive calcium balance with resolving calcium tissue deposits. We were not able to find any case without calcium supplementation after total PTX in the literature, but we wish to encourage this approach for other similarly complicated patients.

CONCLUSION

Our patient had severe painful cutaneous and subcutaneous necroses in both lower extremities due to calciphylaxis. The initial approach, despite its complexity, did not help. Marked improvement and finally full healing was only achieved after total parathyroidectomy, together with total thyroidectomy. We have not found any publication describing this surgical approach in this setting. Also, to

our best knowledge, withholding of calcium supplementation in postsurgical hypocalcaemia has not been reported yet. Because of complex systemic and local care provided by a co-operating team of several dedicated specialists, this unique mode of treatment was fully successful.

ACKNOWLEDGEMENTS

Supported by the PROGRES Q40-14. We wish to thank to our colleagues who participated in the diagnostic process and who took care of the patient. Namely Luboš Sobotka, Vladimír Bláha and Jakub Víšek (metabolic care), Jan Maňák, Pavel Vyroubal, Joao Fortunato (intensive care), Jiří Kotlář (pharmacy), Milan Pospíšil (long term postintensive care), Miroslav Podhola, Dimitar Hadži Nikolov (histopathology), Ludovít Hofman Klzo (nuclear magnetic resonance), Jan Tilšer (PT scintigraphy), Josef Kovalský, Kateřina Jirmanová (anesthesiology), Petr Kordač, Jan Mejzlík, Jaroslav Růžička (surgery and otorhinolaryngology) and many others for their successful collaborative work.

CONFLICT OF INTEREST

None declared.

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