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Acute renal failure in the course of hypercalcemic crisis due to parathyroid carcinoma – the case study

Ostra niewydolność nerek w przebiegu przełomu hiperkalcemicznego u chorego z rakiem przytarczyc – opis przypadku

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Key words

parathyroid carcinoma, hypercalcemic crisis, calcimimetics, cinacalcet

Słowa kluczowe

rak przytarczyc, przełom hiperkalcemiczny, kalcimimetyki, cynakalcet

Summary

Parathyroid carcinoma is an uncommon cause of PTH-dependent hypercalcemia. The clinical features of parathyroid carcinoma are due primarily to the effects of hypercalcemia due to excessive secretion of PTH. Thus, signs and symptoms of hypercalcemia often dominate the clinical picture. The therapeutic goal at this point is to control the hypercalcemia.

A history of the 56-years man admitted to the hospital with acute renal failure in course of the hypercalcemic crisis is described. He was treated with saline hydration and furosemide, with improvement of renal function, however of very little effect on serum calcium levels. Extremely elevated serum PTH-intact of 1789 pg/ml confirmed the diagnosis of primary hyperparathyroidism and a possibility of parathyroid carcinoma had been considered. Since renal failure prevented the use of bisphosphonates, eventually a calcimimetic cinacalcet (Mimpara®), has been used to treat. Satisfactory reduction of serum calcium and PTH enabled to complete the necessary diagnostic procedures and refer the patient for surgery. Histopathological diagnosis of the parathyroid carcinoma had been confirmed.

Cinacalcet appears to have been highly effective at controlling acute hypercalcemia in patients with primary hyperparathyroidism.

Streszczenie

Rak przytarczyc stanowi rzadką przyczynę pierwotnej nadczynności przytarczyc. Manifestuje się przede wszystkim objawami nadmiernej produkcji parathormonu, a w obrazie klinicznym choroby dominują konsekwencje hiperkalcemii. Dlatego podstawowym wyznacznikiem terapeutycznym jest jej objawowe zwalczanie.

Przedstawiono przypadek 56-letniego mężczyzny, przyjętego do szpitala z objawami ostrej niewydolności nerek w przebiegu przełomu hiperkalcemicznego. Intensywne nawodnienie dożylnie i furosemid spowodowały poprawę czynności nerek, bez istotnego wpływu na stężenie wapnia w surowicy. Wybitnie podwyższone stężenie PTH w surowicy potwierdziło rozpoznanie pierwotnej nadczynności przytarczyc, zaś ostry przebieg kliniczny wraz ze skrajnie wysokimi stężeniami wapnia i PTH wskazały na możliwość raka przytarczyc. Ponieważ niewydolność nerek uniemożliwiła zastosowanie bisfosfonianów, standardowego objawowego leczenia ostrej hiperkalcemii, zdecydowano podać choremu kalcimimetyk – cynakalcet (Mimpara®). Po uzyskaniu zadowalającej redukcji kalcemii stan chorego znacznie się polepszył, co umożliwiło ukończenie niezbędnych badań diagnostycznych i skierowanie chorego do leczenia operacyjnego. Badanie histopatologiczne potwierdziło wstępne rozpoznanie raka przytarczyc.

Cynakalcet wydaje się lekiem wysoce skutecznym w objawowym zwalczaniu ostrej hiperkalcemii w przebiegu pierwotnej nadczynności przytarczyc.

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Parathyroid carcinoma is an uncommon cause of primary hyperparathyroidism. Approximately only 400 cases of this disease were reported in the English since 1930 (1-28). The clinical features of parathyroid carcinoma

are due primarily to the effects of hypercalcaemia due to excessive PTH secretion and do not consist the typical features of advanced neoplastic disease (1-6, 9-10, 12, 18, 27-28). Thus, unlike in the majority of

present-day benign primary hyperparathyroidism cases, signs and symptoms of acute hypercalcemia often dominate the clinical picture in parathyroid carcinoma, the controlling of which becomes, in consequence, the primary goal of the therapy. The critical, life-threatening hypercalcemia (hypercalcemic crisis) of parathyroid carcinoma is treated in the same way as hypercalcemia due to any other case (28-30). Due to the persistently excessive PTH secretion, saline hydration and loop diuretics rarely suffice to control the hypercalcemia, and addition of agents that interfere with osteoclast-mediated bone resorption is always necessary. However, in the case described here, the classic inhibitors of osteoclastic bone resorption, i.e. bisphosphonates, could not be used because of acute renal failure. Upon application the cinacalcet (Mimpara®, Amgen) – a calcimimetic, a drug of a new therapeutic class, a satisfactory reduction of calcemia was achieved.

CASE STUDY

A 56-year-old male was admitted to the hospital lethargic and fell asleep during examination. He also experienced intermittent nausea, vomiting, and watery diarrhea, however he denied having any fever, chills, or any other associated symptoms. He also noted excessive thirst and increased in urination but denied dysuria or hematuria. His past medical history was only significant for nephrolithiasis. He was not taking any medications regularly. However, he complained of worsening pain in the spine and pelvis and noted a painful deformation of the right knee and the lower leg. Physical examination revealed blood pressure of 160/80 mmHg, heart rate 96/min regular. His cardiopulmonary exam was unremarkable. Abdominal exam revealed mild tenderness in the epigastrium area and left lower quadrant without any signs of guarding or rigidity. Bowel sounds were active. Acute abdominal series X-ray did not show any acute process. Bedside glucose reading was 115 mg/dl. Laboratory investigation showed normal CBC and urine analysis. Serum creatinine level was 5.4 mg/dL (0.5-1.4 mg/dL). Serum calcium was 14.5 mg/dL (reference range 8-10.5 mg/dL), and ionized calcium was elevated at 1.78 mmol/L (reference range 1.10-1.30 mmol/L) and the acute renal failure in the course of hypercalcemic crisis was diagnosed.

Patient was treated with intravenous fluid hydration and loop diuretic while the etiology of hypercalcemia was being sought. Extremely elevated serum PTH-intact level of 1789 pg/ml confirmed the diagnosis of primary hyperparathyroidism and a possibility of parathyroid carcinoma had been considered. Left knee and lower leg X-ray and CT revealed a typical picture of *osteitis fibrosa cystica* (fig. 1). Renal failure excluded the possibility of using the standard symptomatic treatment of hypercalcemia, which are bisphosphonates. Hydration and furosemide treatment improved significantly renal function, however had a very little effect on serum calcium level. Eventually, it was

decided to treat patient with calcimimetic – cinacalcet (Mimpara®), recently registered for symptomatic control of hypercalcemia due to primary hyperparathyroidism. After the administration of the drug at the smallest recommended dose of 30 mg twice a day, the serum calcium began to reduce at a quick rate, dropped to 12.24 mg/dL after the third day of the treatment, and after increase of total daily dose to 90 mg/d, subsequently decreased above 12.00 mg/dL. Consequently, the saline hydration was stopped, which in turn did not affect the serum calcium values. After two weeks of cinacalcet treatment the PTH levels also decreased from 1789 pg/ml before the start of the treatment to 785 pg/ml, respectively. Improving the general condition of the patient allowed to perform the parathyroid imagining studies. Technetium 99mTc-MIBI scan as well as computed tomography indicated the enlarged left inferior parathyroid gland (fig. 2). The patient underwent surgery. Enlarged parathyroid tumor (3.0 x 3.0 cm) had been removed with left thyroid lobe and isthmus, and with surrounding, not enlarged and macroscopically unaffected lymph nodes. The left recurrent laryngeal nerves was preserved with neuromonitoring use. Twenty-four hours after surgery, serum calcium was 6.8 mg/dL, phosphorus was 1.6 mg/dL, and PTH was 24 pg/ml, with subtetany symptoms and positive Chvostek's sign. Patient had been treated with calcium gluconate iv and then with oral calcium carbonate (3.0 g daily) and alphacalcidol up to 3.0 µg/daily. He was discharged two week later. Histopathological diagnosis of the parathyroid carcinoma had been established.

DISCUSSION

Parathyroid carcinoma is characterized by slow development and rather low potential for malignancy. It tends to recur locally at the operative site and spread to surrounding tissues. Distant metastases occur only at later stages of the disease with spread via both lymphatic and the haematogenous routes. The most frequently affected organs are the cervical nodes (30%), lungs (40%) and liver (10%), much less often – bones, pleura and pancreas (19). A complete resection of the primary tumor proves to be the single most effective method of treatment (2-6, 10, 22, 23, 27, 28). In the case of tumors localized in the neck, the surgery should involve en block removal of the lesion, together with the ipsilateral thyroid lobe and the thyroid isthmus. Also the paratracheal and the tracheo-esophageal lymph nodes should be excised. If the recurrent laryngeal nerve is involved with tumor, it must be resected. An extensive lateral neck dissection should nevertheless be limited to the cases of documented spread to the anterior cervical nodes. Are there any presenting features of a patient with primary hyperparathyroidism that, when present, should suggest a malignant rather than a benign etiology (9, 10, 27, 28)? Parathyroid carcinoma is not directly sex-linked: the affected female to male ratio is 1:1 in most series compared with benign



Fig. 1. Left lower leg x-ray (A) and CT scan (B) revealing osteitis fibrosa cystica features.



Fig. 2. Anterior ^{99m}Tc – MIBI SPECT image show the intense uptake and delayed washout in a large left inferior parathyroid gland.

primary hyperparathyroidism, where there is a marked female predominance (3-4 vs. 1). Parathyroid carcinoma also affects younger population: a average parathyroid carcinoma patient is 40 years old, approximately 10 years younger than typical patients with parathyroid adenoma.

The serum calcium levels of most patients with parathyroid carcinoma are typically high, usually exceeding the upper limit of normal by 3-4 mg/dL (i.e. above 14 mg/dL), almost invariably associated with clinical signs and symptoms of hypercalcemia. This clinical picture is dramatically different to the presentation of the mild, asymptomatic hypercalcemia (within 1 mg/dL above the upper limit of normal), which is nowadays found in the majority of patients with primary hyperparathyroidism, often discovered by accident at routine evaluation. Also serum PTH levels in parathyroid carcinoma patients are usually significantly increased, several, or even more than ten times above the upper limit of normal for the assay employed. Such elevations in PTH levels are unusual in benign hyperparathyroidism, where serum PTH concentrations usually do not exceed the upper limit of normal by more than two or three times (31-33). It is of great importance that parathyroid carcinoma be considered in the differential diagnosis on the basis of the clinical picture as a potential cause of primary hyperparathyroidism, as the optimal outcomes are associated with complete resection of the tumor at the time of the initial surgery (3, 4, 6, 7, 9, 18, 20, 27, 28). Unfortunately, too often parathyroid carcinoma is diagnosed retrospectively only when local recurrence or distant metastases have appeared. As in the case with other endocrine, hormonally active neoplasms, parathyroid carcinoma is difficult to diagnose in histopathologic examination. In 1973 Shantz and Castleman identified a set of criteria facilitating an easier microscopic diagnosis of the parathyroid tumor malignancy (2). However, none of these features is pathognomonic of parathyroid carcinoma (7, 34, 35).

Even a very small recurring parathyroid carcinoma, as well as its distant metastases remain able to produce bioactive PTH, consequently causing hypercalcemia. Therefore, the clinical manifestation and the prognosis are significantly more dependent on the excessive production of PTH in the neoplastic tissue than on the advancement of the carcinoma itself. The main therapeutic goal in this case is to treat hypercalcemia symptomatically. The method of choice in the event of recurrence or parathyroid carcinoma metastases is the surgical resection of the pathologic tissue. In patients with recurrent hypercalcemia, localization studies should be performed before reoperation, In the recurring parathyroid carcinoma localized in the neck and the upper mediastinum, the best course of action seems to be scintigraphy with the use of ^{99m}Tc-MIBI or subtraction examination with thallium 201-technetium ^{99m} (36-38). ^{99m}Tc-MIBI scanning used concurrently with a hand γ -detecting probe seemingly improves the intraoperative localization of abnormal parathyroid tissue (16). Computed

tomography and magnetic resonance imaging may be used to examine the neck and mediastinum structures, as well as to identify the distant metastases of the parathyroid carcinoma. Arteriography and selective venous catheterisation can be useful when non-invasive methods prove ineffective (28).

Recurring parathyroid carcinoma localized in the neck region should be treated with extensive excision of the suspected area together with the regional lymph nodes and other involved structures. In many cases, however, described above included, even repeated explorations of the neck prove ineffective. In the event of extensive neoplastic process, significant palliation may result from resection of the distant metastases to the lymph nodes, liver or lungs (8, 11, 36). Attempts at use of radiotherapy to control the tumor growth and decrease the PTH production has been ineffective in majority of cases in which it has been attempted (2, 4). Due to the parathyroid carcinoma's low occurrence, the experience in chemotherapy of the disease is limited to scattered case studies. Thus there is no reliable method of assessing the usefulness of any of the described courses of treatment and the hitherto attempts at controlling the parathyroid carcinoma with chemotherapy are discouraging (39-43).

The treatment of critical, life-threatening hypercalcemia (hypercalcemic crisis) secondary to parathyroid carcinoma is no different to the treatment of hypercalcemic crisis arising from any other cause (29, 30). Due to the persistently elevated secretion of PTH and the subsequent extreme intensity of bone resorption, saline hydration and loop diuretics rarely suffice to control the hypercalcemia. That is why, it is highly recommended to consider treatment with inhibitors of osteoclastic bone resorption. Intravenous mithramycin (plicamycin) at a dose of 25 µg/kg usually reduces calcemia in the parathyroid carcinoma patients, and maybe repeated at daily intervals for up to 7 days. However, it rarely leads to normalization the calcium levels, and the effects of the treatment are not only transient but the effectiveness of the drug decreases with repeated courses (28, 29, 44). Furthermore, mithramycin toxically affects the parenchymal organs, in particular the liver, the kidneys and the bone marrow. Each administration of the drug intensifies the toxic effects. Intravenous calcitonin administered at a daily dose of 400-800 IU reduces the serum calcium levels only temporarily and only in some patients with primary hyperparathyroidism. The nagging side effects make the therapy practically unacceptable nowadays (3, 40, 45-47). Gallium nitrate inhibits the bone resorption by preventing dissolution of hydroxyapatite crystals. When administered as a continuous 5-day infusion at a dose of 200 mg/m²/24 h, it reduced calcemia in some parathyroid calcemia patients, however, its use must be limited due to its significant nephrotoxicity (12, 48). Bisphosphonates, now the first choice in the treatment of hypercalcemia of malignancy, directly inhibit the metabolic activity of the osteoclasts. Moreover, some

of them increase the osteoclasts' apoptosis. It has been proved that intravenous clodronate reduces calcium levels in parathyroid carcinoma patients (49-51). An intravenous infusion of pamidronate, which has stronger antiresorption effects than clodronate, administered at daily doses of 45-90 mg, reduces calcemia at least temporarily (11, 14, 19, 52-54). High hopes are attached to the new, more potent bisphosphonates: ibandronate and zoledronate, which prove highly effective in the treatment of hypercalcemia secondary to other neoplastic diseases. What needs to be stressed, however, is the fact that neither pamidronate, nor zoledronate influenced our patient's serum calcium levels in any significant way. However, the main limitation of bisphosphonates use is renal failure, and in fact, renal deterioration progressing to renal failure and dialysis with the use of zoledronic acid was reported (55).

Cinacalcet (Mimpara[®], Amgen) is the first available allosteric modulator of the calcium receptor (calcimimetic). The calcium receptor, first described by Brown, belongs to the class of membrane receptors linked to the G protein and the adenylyl cyclase system, the cascade of protein kinase C and the phospholipase A2 (56). The receptor may be found in many tissues, however, its presence on the surface of the main cells of the parathyroids enables it to directly control the PTH secretion. The activation of the receptor by ionized calcium inhibits the PTH secretion and seemingly plays a role in inhibiting the proliferation of the parathyroid cells. The discovery of the sequence and spatial conformation of the calcium receptor and its subsequent cloning made it possible to synthesise the complex particles activating (calcimimetics) and blocking (calcilytics) the calcium receptor (57). The majority of them is still being tested pharmacologically. The first calcimimetic, which had successfully passed the clinical tests, and was registered for the treatment of secondary hyperparathyroidism in patients with endstage renal failure on maintenance dialysis therapy and for the symptomatic treatment of hypercalcemia in patients with parathyroid carcinoma, is cinacalcet (Mimpara[®], Amgen) (N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride). By binding to the transmembrane fragment of the calcium receptor, the substance alters the receptor's conformation, increasing its sensitivity to extracellular calcium and consequently reduce the PTH secretion (58). Cinacalcet has been shown to lower serum PTH and serum calcium in hypercalcemia in patients with parathyroid carcinoma without any undesirable side effects (59-62). Also in patients with mild primary hyperparathyroidism, cinacalcet was highly effective in normalizing serum calcium levels and reducing PTH, and this effect was maintained over long-term administration (63). In the described case of life-threatening hypercalcemia, resulting in acute renal failure, cinacalcet lead to a quick and sustained reduction of the serum calcium levels, made it possible to complete the necessary diagnostic procedures and patient undergo effective surgical treatment.

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