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OPIS PRZYPADKU CASE REPORT

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Hypercalcemic crisis in patient after thyroidectomy due to suspected thyroid cancer**

Przełom hiperkalcemiczny u chorej po tyreoidektomii z powodu podejrzenia raka tarczycy

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Keywords

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Słowa kluczowe

przełom hiperkalcemiczny, jatrogenia, działania niepożądane, tyreoidektomia

Summary

Severe hypercalcemia represents a life-threatening emergency. The most common cause is hypercalcemia of malignancy (70%), previously undetected primary hyperparathyroidism (20%), and there are a few rarer causes (10%) including medication-induced hypercalcemia.

The clinical presentation and prognosis depend on the acuity of the development, the degree, and the underlying cause of hypercalcemia. Patients with levels of total serum calcium between 2.3 and 3 mmol/l are usually asymptomatic, but when the serum calcium level rises above this stage, hypercalcemia induces functional disturbances in a group of organs, which are considered together as the "hypercalcemic syndrome".

Drug related adverse events in ambulatory clinics occur with a prevalence of 12.8 per 100 patients or even higher, and are associated with various symptoms ranging from minor illness to death. In 2013 it was estimated that approximately 210,000 deaths per year were associated with preventable AEs in U.S. hospital. In Poland there were a reported 1903 deaths associated with AEs between 2006 and 2008. As adverse drug events seem to be an important medical issue we present a case of a young women after thyroidectomy due to suspected thyroid cancer with iatrogenic hypercalcemic crisis.

Streszczenie

Ciężka hiperkalcemia stanowi stan zagrożenia życia. Najczęstszymi jej przyczynami są: choroba nowotworowa (70%) oraz wcześniej niewykryta pierwotna nadczynność przytarczyc (20%), natomiast wśród rzadszych przyczyn, odpowiedzialnych za 10% przypadków, wymienić należy m.in. hiperkalcemię jatrogenną wywołaną stosowaną farmakoterapią. Obraz kliniczny i rokowanie zależą od: tempa rozwoju, stopnia oraz przyczyny hiperkalcemii. Chorzy ze stężeniem wapnia całkowitego w surowicy pomiędzy 2,3 a 3 mmol/l są zwykle bezobjawowi, ale gdy stężenie wapnia przekracza powyższą granicę, hiperkalcemia wywołuje szereg zaburzeń narządowych. Zaburzenia te określa się jako przełom hiperkalcemiczny.

Zdarzenia niepożądane związane ze stosowaną farmakoterapią występują, w warunkach ambulatoryjnych, u 12,8 na 100 chorych lub częściej, a związany z nimi obraz kliniczny może być różnorodny, począwszy od błahych objawów do zgonu włącznie. W 2013 roku szacowano, że około 210 tys. zgonów u hospitalizowanych chorych w USA związanych było z – dającymi się zapobiec – niepożądanymi efektami stosowanej farmakoterapii. W Polsce w latach 2006-2008 zgłoszono 1903 zgony związane z niepożądanym działaniem leków. Jako że działania niepożądane leków wydają się być ważnym problemem medycznym, prezentujemy przypadek młodej kobiety po tyreoidektomii z powodu podejrzenia raka tarczycy z jatrogennym przełomem hiperkalcemicznym.

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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**As a tribute to professor Franciszek Kokot, great physician, scientist and teacher; master of masters who taught us to think pathophysiologically.

INTRODUCTION

15% of adverse events (AEs) reported in hospitalized patients are drug related (ADEs), while in ambulatory care they occur with a prevalence of 12.8 per 100 outpatients (1, 2). Gandhi et al. reported that the incidence of ADEs was even higher, 27 per 100 outpatients (3). ADEs, which represent the most frequent cause of injury due to medical care in developed countries, are an important medical issue because they place an additional burden on the health care system and are associated with various symptoms ranging from minor illness to death (4, 5).

Adverse events are either preventable or unpreventable, and AEs associated with medical errors (MEs) are preventable. According to the Institute of Medicine, MEs kill between 44,000 and 98,000 people every year in U.S. hospitals (6). In 2013 James estimated that approximately 210,000 deaths per year were associated with preventable AEs in U.S. hospital (7). In Poland between 2006 and 2008 there were a reported 1903 deaths associated with AEs. As adverse drug events seem to be an important medical issue we present a case of a young women after thyroidectomy due to suspected thyroid cancer with iatrogenic hypercalcemic crisis.

CLINICAL PRESENTATION

A 44-year-old woman was admitted to the department of internal medicine because of nausea, vomiting, headache, dizziness, pain and paresthesia in both the upper and lower limbs and progressing weakness. The symptoms were observed since at least three days.

Two weeks earlier the patient underwent thyroidectomy due to follicular tumor (histopathologically: hyperplastic nodule). Since surgery, she has been provided with calcium carbonate (6 g per day), alphacalcidol (2 ug per day), hydrochlorothiazide (37.5 mg per day) and levothyroxine (75 ug/day). Her past medical history includes arterial hypertension, polyps in the right maxillary sinus and the suspicion of epilepsy. She has also been operated due to carpal tunnel syndrome and cholecystolithiasis 11 years ago. Pharmacological treatment includes bisoprolol, lisihexal and lamotrigine.

On admission the patient presented with dehydration and muscle weakness, blood pressure of 110/70 mmHg, heart rate 100 per min.

Laboratory findings (tab. 1, 2) revealed hypercalcemia (total and ionized serum calcium was 4.77 and 2.37 mmol/l, respectively) with very low serum PTH concentration (2.5 pg/ml), acute kidney injury (serum creatinine 1.8 mg/dl) and mild primary hypothyroidism (TSH 7.6 mIU/L).

Electrocardiography showed nonspecific repolarization abnormalities, which disappeared in subsequent days. Ultrasound examination revealed increased renal parenchymal echogenicity.

The patient was treated with intravenous saline, furosemide and corticosteroids. The dose of levothyroxine was increased up to 100 ug per day. With each passing day of hospitalization we observed clinical improvement and a decrease in ionized calcium.

The patient was discharged on the fourth day with the recommendation of taking 20 mg of prednisone only for another two days, calcium carbonate (2 g per day) and cholecalciferol (2000 Units per day). We recommended a follow-up test of ionized calcium, serum creatinine and electrolytes within 4 days.

One week after discharge from hospital the patient was in much better clinical condition without additional complaints. In laboratory findings ionized calcium was

Tab. 1. Hematological parameters

Parameter	Value		Normal range
	1st day of hospitalization	3rd day of hospitalization	
Erythrocytes (RBC) (M/μl)	4.9	4.07	3.5-5.4
Hematocrit (HCT) (%)	45.4	36	37-47
Hemoglobin (HGB) (g/dl)	16.1	11.3	12-15
MCV (fl)	93.2	88.4	81-99
MCH (pg)	33.1	27.8	26-34
White blood cells (WBC) K/μl	14.4	13.1	4-10
Neutrophils (K/μl)	11.1		2.5-5
Lymphocytes (K/μl)	2.1	11.2	1.5-3.5
Monocytes (K/μl)	1.0	1.5	0.2-0.8
Eosinophils (K/μl)	0.1		0.04-0.4
Basophils (K/μl)	0.0		0.02-0.1
Thrombocytes (PLT) (K/μl)	294	199	150-450

Tab. 2. Biochemical results

Parameter	Value				Normal value
	day of hospitalization				
	1	2	3	4	
Total protein (g/l)	79.23				60-80
CRP (mg/l)			1.04		5
Creatinine (mg/dl)	1.8		1.3		0.7-1.3
Glucose (mg/dl)	138 (post--prandial)				70-99
Chloride serum (mmol/l)	86		97	106	96-108
Potassium (mmol/l)	3.8		3.3	3.8	3.5-5.5
Sodium (mmol/l)	136		139	143	135-145
Total calcium (mmol/l)	4.77				2.15-2.50
Ionized calcium (mmol/l)	2.37	1.9	1.55	1.48	1.15-1.27
pH (venous blood)		7.43	7.48	7.44	7.35-7.45
TSH (mIU/l)	7.62				0.2-4.2
iPTH (pg/ml)	2.5				11.1-79.5
Carbon dioxide pressure (%)	59			53	35-48
Phosphorus, inorganic	0.99				0.81-1.45

normal, but with tendency to increase in consecutive tests, therefore the patients was recommended to discontinue calcium carbonate substitution. Serum PTH concentration was found to be in the normal range – 27.8 pg/ml (N: 15-65 pg/ml) which proved our theory of preserved, hormonally active, parathyroid gland. Because of the significant decrease in serum TSH level, the patient required a reduction of levothyroxine dose to 75 ug per day.

Further tests performed ambulatory revealed normal kidneys ultrasound image and normal serum creatinine level.

DISCUSSION

Severe hypercalcemia represents a life-threatening emergency. The most common cause is hypercalcemia of malignancy (70%), previously undetected primary hyperparathyroidism (20%), medication-induced hypercalcemia, and a few rarer causes (10%) may result in this endocrine emergency as well (9). The clinical presentation and prognosis depend on the acuity of the development, the degree, and the underlying cause of hypercalcemia. Patients with levels of total serum calcium between 2.3 and 3 mmol/l are usually asymptomatic, but when the serum calcium level rises above this stage, multisystem manifestations become apparent (10). The constellation of symptoms has led to the mnemonic "stones, bones, abdominal moans, and psychic groans", which is used to recall the signs and symptoms of hypercalcemia. They represent kidney, gastrointestinal tract, skeleton, and psychologic disturbances, respectively. In other words hypercalcemia induces functional disturbances in a group of organs, which are considered together as the "hypercalcemic syndrome". In our patients serum total calcium level was above 4 mmol/l. In such situations two organs are primarily at risk for decompensation. Polyuria may develop into oliguria and finally anuria, thus untreated hypercalcemic renal insufficiency may be lethal. The other organ at risk is the brain. Psychologic disturbances may develop into somnolence and finally coma. Our patients did not have "typical symptoms". She complained mainly about nausea, vomiting, headache, dizziness, pain and paresthesia in limbs. Taking into account her medical history, being unaware of her laboratory tests, we initially suspected primary hypoparathyroidism, which is one of the most common complications after thyroidectomy performed due to oncologic reasons. The incidence of postoperative hypoparathyroidism after thyroid surgery, mostly transient, resolving in a few months, or permanent, requiring lifelong oral calcium and vitamin D supplementation is approximately 9.1-21.6% and 0.9-15%, respectively (11-13). Hypocalcaemia, as a result of significant decrease or lack of serum parathormone, is usually observed within 24-48 hour after surgery (14). Thus patients are routinely supplemented with oral calcium.

To our surprise, both total and ionized calcium were at the level of severe hypercalcemia, with the PTH serum level 2.5 pg/ml. The patient was treated with saline infusion, loop diuretics and corticosteroids. In the following days we observed clinical improvement and normalization of both total and ionized calcium levels. However there was still one unanswered question – what was a mechanism of hypercalcemic crisis after total strumectomy, as it should not have happened even when the patient was supplemented. In addition, such a situation is poorly documented in medical literature. One possible explanation was the unadjusted treatment (oral calcium followed by increased calcium absorption from gastrointestinal tract, thiazide diuretics, alphacalcidol), the other was the preserved, hormonally active parathyroid gland. Consumption of large amounts of calcium carbonate in patients with normal kidney function should not result in hypercalcemia (with exception for milk-alkali syndrome). Thiazide diuretics increase renal calcium resorption and may cause mild, but not severe, hypercalcemia that is resolved when the medication is discontinued. Alphacalcidol has a weaker impact on calcium metabolism and parathyroid hormone levels than calcitriol (15, 16). It is the most commonly prescribed vitamin D metabolite for patients with end stage renal disease, as being an active vitamin D_3 metabolite, does not require the second hydroxylation step in the kidney. However, it should be noted the dose used in our patients (recommended by the surgeons) were twice too high as it should be. As it turned out in the following days of observation, our suspicion of the presence of preserved, hormonally active parathyroid gland was justified. The serum PTH level gradually increased up to 27.8 pg/ml and the patients did not require calcium and vitamin D supplementation. As is was mentioned above, permanent postoperative hypoparathyroidism after total strumectomy is rare. The cause of hypercalcemic crisis was multifactorial. It resulted from preserved parathyroid function combined with the treatment predisposing to increased calcium serum level.

The presented case serves as an example of an adverse outcome resulting from the routine application of pharmacological therapy that, we strongly believe, was preventable by the application of common sense. No two patients are the same and medical treatment should always be individualized. A lesson for the future is as follows: hypoparathyroidism after thyroidectomy requires careful patient monitoring with drug dosing adjusted appropriately.

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