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Case Report

Long-term hypercalcemia due to parathyroid adenoma resulting in hypercalcemic crisis; an autopsy case report

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Abstract

We present a case of parathyroid adenoma resulting in hypercalcemic crisis with lethal outcome and subsequential autopsy findings pointing out to long term hypercalcemia. A 51- year-old female was admitted to hospital due to vomiting, constipation, general weakness, hypotension and uncorrectable hypokalemia. A couple of hours after the admission her general appearance deteriorated and she became disoriented, more pale and developed both eye blindness. Laboratory findings revealed leukocytosis, increased values of urea, hypokalemia, thrombocytopenia, high blood calcium (26 mg/dL) pointing out to hypercalcemic crisis. Hypercalcemia was immediately treated, but unsuccessfully leading to lethal outcome. Autopsy revealed presence of pulmonary oedema, ascites, acute pancreatitis, diffuse calcification of arteries, bone osteopenia, left pulmonary artery thromboembolism, heart hypertrophy and nodule under the right thyroid lobe which was later pathohistologically described as parathyroid adenoma. Presence of chronic hypercalcemia due to parathyroid adenoma is difficult to be recognized since most cases are asymptomatic, but it is necessary in order to avoid chronic complications of calcium deposition and possible development of hypercalcemic crisis which is life threatening condition demanding immediate treatment.

Keywords: Parathyroid adenoma, Hypercalcemia, Hypercalcemic crisis, Pathology, Autopsy, Hyperparathyroidism

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Introduction

Parathyroid adenoma is the most common cause of primary hyperparathyroidism in approximately 85% of cases, gland hyperplasia and multiple adenomas in 15%, parathyroid carcinoma in around 1% of cases (1). Hyperparathyroidism is classified as primary, secondary which means increase in parathyroid hormone levels due to hypocalcemia in conditions such as chronic renal failure, and then tertiary caused by chronic stimulation of parathyroid glands (2). Incidence of primary is 1 in 500 women and 1 in 2000 men older than 40 years of age (3). Primary hyperparathyroidism is usually asymptomatic and chronic but it is believed that parathyroid adenomas can start to secrete large amount of parathyroid hormone which results in extreme increase in calcium levels and hypercalcemic crisis (4). Here we describe a case of a patient in hypercalcemic crisis with fatal outcome and emphasize the importance of recognizing causes and presence of hypercalcemia in order to avoid negative consequences.

Case Presentation

A 51-year-old woman visited her family physician because of vomiting and general weakness that lasted for 4 days. No abdominal pain, nausea or increased body temperature were present. She had no stool for the past 4 days. Urination was normal, without any pain or discomfort. Due to prostrated appearance of the patient, the physician sent her to department for infectious diseases under the suspicion on acute gastroenterocolitis. During examination by the infectologist findings were these: the patient was afebrile, oriented, prostrated, dehydrated and hypotensive (RR was 90/60). Auscultation of heart and lungs revealed no abnormalities. Abdominal examination was normal, lumbar areas were painless, no melena or rectal bleeding were found. No rash was present on skin. Meningeal signs were negative. Laboratory findings demonstrated leukocytosis (18.7×10^9/L), thrombocytopenia (57×10^9/L), increased C-reactive protein (33 mg/L) with increased values of urea (20.86 mg/dl) and hypokalemia (8.99 mg/dL). Urine analysis revealed increased number of leukocytes (30-40) and large amount of bacteria. The patient was kept for observation. During that time she received infusion of 0.9% NaCl and KCl and antibiotic therapy with cephalosporin was included. The patient was afebrile and no vomiting was observed during observation. She was further sent and admitted to department of internal medicine for further analysis of hypokalemia and acute renal insufficiency. During admission the patient was still afebrile, oriented, prostrated, pale, eupnoic. Blood pressure was 120/75 mm Hg. The examination

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Implication for health policy/practice/research/medical education

This case is important for practitioners since it implicates the significance of recognizing disorder of calcium levels which often remains undiagnosed due to lack of symptoms and can lead to life threatening conditions such as hypercalcemic crisis. It educates practitioners on symptoms of hypercalcemia and hypercalcemic crisis and points out to possible causes of this disorder focusing on parathyroid adenoma as the most common cause of primary hyperparathyroidism.

of lungs, heart, abdomen, lumbar area and rectum was normal. EKG demonstrated normal sinus rhythm with frequency of 90 beats/min, first degree atrioventricular block and S-T denivelation. The patient complained only on pain in her knees. Her anamnestic data have so far revealed long term knee pain and renal colics 7 years before this admission. She demonstrated so far no allergies. Few hours after the admission the patient became more prostrated, extremely pale, disoriented and hypotensive. In addition, she complained on blindness on both eyes. Neurologist was consulted and suggested head CT-scan. Laboratory examination was repeated and showed leukocytosis (21.5× 10^9/L), increased values of urea (21.7 mg/dL), hypokalemia (12.12 mg/dL), thrombocytopenia (20×10^9/L), values of amylases in both blood (89 IU/L) and urine (142 IU/L) were under reference range. Creatine kinase was increased (490 IU/L). Also, liver enzymes demonstrated increased values: lactate dehydrogenase (341 IU/L), alkaline phosphatase (139 IU/L), aspartate aminotransferase (42 IU/L). C- reactive protein was increased (52 mg/L). Blood calcium was increased (26 mg/dl), phosphorus was 4.49 mg/dl. According to symptoms and values of calcium that pointed out to hypercalcemic crisis the patient was immediately treated with pamidronate, furosemide, glucocorticoids and intravenous infusions of 0.9% NaCl. Despite the therapy, the patient's condition deteriorated and she developed ventricular tachycardia with subsequential cardiorespiratory arrest. Cardiopulmonary resuscitation was performed but without success. Lethal outcome was recorded on second day after the admission.

Autopsy was performed 56 hours after patient's death. Results of the examination demonstrated cyanosis of the entire body skin. In the area of the neck, below the thyroid gland under the right lobe, nodule 4 cm in its longest diameter was noticed which was later pathohistologically examined and characterized as parathyroid adenoma. Further, fibrosis of myocardial muscle was found with hypertrophy of all heart chambers, especially left ventricle. Lungs were filled with fluid characterized as pulmonary oedema. Also, thromboembolism of the left pulmonary artery was observed. Abdominal cavity was filled with 200 mL of thick, blood-tinged ascites. Liver was regularly sized but with fatty changes. Pancreas demonstrated inflammatory changes meaning acute hemorrhagic pancreatitis. Both kidneys were filled with cysts. Arteries demonstrated atherosclerotic changes with extreme calcification of vessel walls. Osteopenia due to long term hypercalcemia was visible on all bones, especially on bones of the skull which were extremely thin (as paper) and were able to be cut by using regular scissors.

Pathological examination was performed on removed tissue. It was solitary tan nodule 4 cm in its longest diameter well circumscribed from the surrounding tissue. Routine hemalaun & eosin staining revealed encapsulated lesion consisted of unimorphous small cells arranged in nests (Figure 1). No capsular or invasion to adjacent tissues were noticed. Immunohistochemical staining for parathyroid hormone revealed strong positivity for this marker suggesting the diagnosis of parathyroid adenoma (Figure 2).

Discussion

In our case, cause of patient's symptoms was parathyroid adenoma and after immunohistochemical positivity for parathyroid hormone we demonstrated that this benign tumor secreted this hormone, led to long term hypercalcemia (we concluded based on autopsy findings such as bone osteopenia, artery calcifications, but also on anamnestic data of renal colics probably due to renal stones and knee pain) and finally led to extreme increase in calcium levels meaning hypercalcemic crisis.

Normal levels of total calcium are 8.82-10.42 mg/dL, normal values of ionized calcium are 4.4-5.6 mg/dL (3). Patients with calcium levels of 10.42-12.02 mg/dL usually demonstrate no symptoms, but above those serum calcium levels, clinical manifestation appear involving multiple organs (3). In most patients with hyperparathyroid-

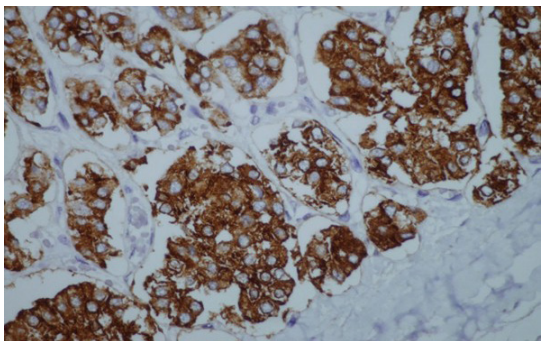

Figure 1. Parathyroid adenoma consisted of unimorphous small cells arranged in nests (H&E, 60×).

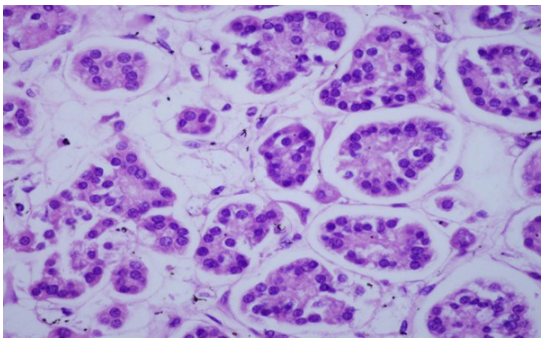

Figure 2. Strong positivity of parathyroid adenoma cells on parathyroid hormone (PTH, 60×).

ism, symptoms of hypercalcemia are not apparent which makes determination of the correct diagnosis difficult. When recognized and treated in time the disease can be adequately resolved (3). Chronic hypercalcemia in case of parathyroid adenoma can present with symptoms like weakness, fatigue, anorexia, nausea, vomiting, polydipsia, polyuria, weight loss, constipation, headaches, musculoskeletal pain and disorders, pathological fractures, renal stones, pancreatitis, anemia, peptic ulcer (5). Hypercalcemic crisis in primary hyperparathyroidism is rare condition, but medical emergency and life threatening condition which requires early recognition, immediate treatment of hypercalcemia and early parathyroidectomy as definite treatment to avoid patient's adverse outcome (1,6,7). Its incidence is around 1.6%-6% (7) Calcium level above 3.5 mmol/L is treated as hypercalcemic crisis and requires urgent treatment (8). It is considered that patients with chronic hypercalcemia in hyperparathyroidism, like in our case, can develop hypercalcemic crisis in case precipitating causes like trauma, surgery or infection occur (9). Prompt treatment of hypercalcemic crisis is necessary since critical levels of calcium lead to organ failure (7). Symptoms include gastrointestinal symptoms, dehydration, renal damage, deterioration of mental status, multiple organ failure and possible death (5,7). Blindness that the patient developed can be explained as neurocognitive symptom of hypercalcemic crisis. Neurocognitive symptoms appear due to hypercalcemia induced change of neurotransmitters (1). We have so far found no papers describing blindness in hypercalcemic crisis. It also leads to appearance of cardiac arrhythmias such as Q-T shortening, ventricular tachycardia, ventricular fibrillation, atrioventricular block (1). We believe that our patient suffered chronic hypercalcemia since calcifications were present. They led to destruction of blood vessels and organ damage. Finally, pulmonary oedema occurred due to destruction of alveolar/capillary barrier (10). As differential diagnosis of hypercalcemia these causes can be considered: hyperparathyroidism, vitamin D intoxication, malignant tumors (parathyroid carcinoma, multiple myeloma, breast cancer, lung, renal carcinoma, head and neck malignancy), medications (lithium, thiazide diuretics), endocrine disorders (adrenal insufficiency), genetic disorders (familial hypocalciuric hypercalcemia) and other causes (immobilization, Paget's disease) (11). Diagnosis is determined through anamnestic data, clinical examination, total and ionized serum calcium, electrolytes, urea, creatinine, phosphate, x-ray of lungs, ultrasound (12). Treatment for hypercalcemia includes saline hydration, diuretics, bisphosphonates, steroids, calcitonin and haemodialysis in case of hypercalcemia refractory for standard treatments (3,8). Parathyroidectomy is considered to be the most effective therapy for primary hyperparathyroidism (3).

Conclusion

To conclude, early recognition of hypercalcemic crisis and prompt lowering of calcium with recognition of the cause is necessary for adequate patient treatment and avoidance of lethal outcome. Also, recognition of chronic hypercalcemia due to parathyroid adenoma presence is difficult to be recognized since most cases are asymptomatic, but it is necessary in order to avoid chronic complications of calcium deposition and possible development of hypercalcemic crisis.

Authors' contribution

BP; acquisition and analysis of data, critical revision of the manuscript. SM; acquisition of data, design, drafting and critical revision of the manuscript. ZH; analysis of data, critical revision of the manuscript. VM; drafting and critical revision of the manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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