Case report

Recurrent diabetic ketoacidosis: a rare presenting manifestation of primary hyperparathyroidism

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Summary
We report a rare case of primary hyperparathyroidism in a young female who presented with recurrent diabetic ketoacidosis. The patient had suffered an episode of acute pancreatitis in the past. On evaluation patient was found to have primary hyperparathyroidism and after removal of left inferior parathyroid adenoma her insulin requirement decreased by twelve units.

KEY WORDS: primary hyperparathyroidism; acute pancreatitis; diabetic ketoacidosis.

Case report

19-years-old female presented to accident and emergency department with complaints of abdominal pain and vomiting from last one day. Her previous medical records revealed that patient suffered from similar episode of pain abdomen and vomiting in 2014 and serum amylase (603IU/ml, N 39–117 U/L) and contrast enhanced computed tomography (CECT) of abdomen was suggestive of acute pancreatitis at that point of time. On the 4th day during recovery, patient suffered from an episode of diabetic ketoacidosis (DKA) for which she was managed with intravenous insulin therapy and subsequently was discharged on premix insulin therapy. Patient remained all right until June 2015 when developed second episode of pain abdomen and vomiting and was found to have diabetes ketoacidosis, which occurred because patient missed 2 doses of insulin. Again, treatment for DKA was given and was discharged on twice a day premix subcutaneous insulin therapy. Now this was her third episode of admission with pain abdomen and vomiting. Patient is non-alcoholic, was not having gallstones in the past and there was no family history of diabetes. On examination, she was dehydrated with pulse rate of 120/min and blood pressure of 110/70. Systemic examination including cardiovascular, neurological, respiratory and gastrointestinal system were normal. On evaluation, patient was again found to be in DKA with a plasma glucose of 500 mg/dl, strongly positive urine ketones and arterial blood gas analysis with serum electrolyte suggestive of high anion gap metabolic acidosis and she was shifted to the department of endocrinology for management. In the next 24 hours, she improved with fluids and intravenous insulin therapy. Serum lipase level, renal function and liver function test were normal. Serum calcium was 12.30 mg/dl (N: 8.5-10.5 mg/dl), serum phosphate was 2.8 mg/dl (N: 3.5-5.5 mg/dl) and serum alkaline phosphatase level was 1832units/l (N: 39-117 U/L). In view of hypercalcemia and hypophosphatemia detected incidentally on biochemical reports, the past medical records of patient was reviewed and it was found that during the previous episode of pancreatitis serum calcium was 10.4mg/dl that is contradictory to expected hypocalcaemia usually observed during acute pancreatitis. However, she never underwent any further investigation for this observation during any of her past admissions. In view of recurrent DKA, history of acute pancreatitis and hyperparathyroidism with hypophosphatemia, a presumptive diagnosis of hyperparathyroidism was made and blood sample for serum 25(OH) vitamin D and serum parathyroid levels were sent. Her serum 25(OH) vitamin D levels was normal i.e. 78.88nmol/l (N: 75–250 nmol/l) and serum parathormone levels came to be raised 1900 pg/ml (14-72 pg/ml). Thyroid function test was normal. The other autoimmune workup including glutamic acid decarboxylase (GAD) Antibody levels 3.2 IU/ml (<10 IU/ml), IgA tissue transglutaminase (TTG) 8 Units (normal levels ≤20 IU/L) and thyroid peroxidase antibody (TPO) were normal. X-Rays of skull, hands, and pelvis showed multiple lytic lesions and DEXA scan at lumber spine showed a T score of –4.1. CECT Abdomen showed small pancreas with dense calcification noted in head and uncinated process with associated focal pancreatic duct dilatations in uncinated process. These findings on CECT abdomen were suggestive of chronic pancreatitis with atrophic pancreas body and tail. CECT also showed multiple well-defined lytic lesions in virtualized bones (pelvis, femur) which were suggestive of brown tumor. In view of hypercalcemia, hypophosphatemia, multiple lytic lesions and raised parathormone levels, a 99mTc sestamibi parathyroid scan was performed which showed left inferior parathyroid adenoma (Figure 1). A final diagnosis of Primary Hyperparathyroidism with hypercalcaemia causing recurrent pancreatitis resulting in secondary diabetes and DKA was made. Serum calcium was lowered with use of normal saline and furosemide and left inferior parathyroid adenoma was resected. Repeat parathormone hormone level was 165pg/ml. After resection of parathyroid adenoma patient’s insulin requirements decreased by 12 units and she was discharged on twice-daily premix subcutaneous insulin and calcium therapy.
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Discussion

Primary hyperparathyroidism (PHPT) is a rare disorder in young age with an estimated incidence of around 2-5/100,000 and only about 200 cases have been reported in the world literature (1). Presentation of the disease is similar to their adult counterparts except for more severe bone disease and less severe renal disease. Various atypical clinical presentations are recurrent pancreatitis, behavioral disturbances, seizures, encephalopathy, arrhythmias, myopathy, oliguria, intractable constipation and paraparesis (2). Our patient, initially had acute pancreatitis when diagnosis of PHPT was missed, presented to us in diabetic ketoacidosis and to the best of our knowledge DKA as presenting manifestation of PHPT has not been reported in the literature. Although most cases of PHPT in older children and adolescents are sporadic, caused by parathyroid adenoma, around 30% of the cases are familial and caused by hyperplasia of parathyroid glands. In our patient family history was negative and no features suggestive of MEN syndrome were present and solitary parathyroid adenoma was localised by sestamibi parathyroid scan (1, 2). Acute pancreatitis is a rare complication of PHPT and has been reported in 1.5 to 13% of the cases (3). The various mechanisms described for development of acute pancreatitis in patients with PHPT includes de novo activation of trypsinogen to trypsin by hypercalcemia resulting from PHPT resulting in auto digestion of the pancreas and subsequent pancreatitis, hypercalcemia resulting in formation of pancreatic calculi, ductal obstruction, and subsequent attacks of acute or chronic pancreatitis and finally factors other than calcium, such as genetic risk factors, may predispose patients with PHPT to acute pancreatitis (3). Serum calcium levels are usually low during an episode of pancreatitis and development of hypocalcemia has been included in prognostic scoring system for acute pancreatitis. Although the exact mechanism for development of hypocalcemia in acute pancreatitis are not clear, the various likely reasons include utilization of calcium in enzymatic necrosis and precipitation of calcium by fatty acids released from body of pancreas as calcium soap (4). Our patient had high normal serum calcium value during the acute phase of pancreatitis that is contradictory to expected hypocalcemia usually observed during acute pancreatitis. The finding of high normal serum calcium during an episode of acute pancreatitis may make one to think of alternate diagnosis but somehow the treating physician had not investigated this patient further and that might have resulted in delay in diagnosis of PHPT. Primary hyperparathyroidism also causes alterations in carbohydrate metabolism including insulin resistance and hyperinsulinemia. Hypercalcemia and diabetes both worsen each other. The prevalence of diabetes mellitus in primary hyperparathyroidism is approximately 8%, and that of primary hyperparathyroidism in diabetic patients is approximately 1% (5). Although hypercalcemia directly stimulates insulin secretion, high PTH level, hypercalcemia and hypophosphatemia impairs peripheral insulin sensitivity by interfering with the tyrosine kinase activity of insulin receptor, impairs suppression of gluconeogenesis and causes reduced binding of insulin to its receptors due to decreased number of insulin receptors (6-8). On the other hand, osmotic diuresis caused by uncontrolled diabetes will lead to dehydration and worsening of hypercalcemia. Mild hyperglycemia also occur transiently in acute pancreatitis in up to 50% of the cases and has been used as a marker for the severity of disease (9). Long-term follow-up of such patients after a single episode of acute pancreatitis indicated that they had chronic painless pancreatic inflammation and an increased frequency of abnormal glucose tolerance compared with an age-matched population. The prevalence of abnormal glucose tolerance in patients with chronic pancreatitis was 60-70% and of overt diabetes was 30-40% (9). The presence of pancreatic calcification increased the occurrence of endocrine dysfunction, resulting in a 70% prevalence of diabetes. Our patient had chronic pancreatitis as suggested by findings of atrophic pancreas body and tail with dense calcification noted in head and uncinated process along with associated focal pancreatic duct dilatations in uncinated process in CECT Abdomen. However, DKA has never been reported in context of PHPT and it is likely that apart from various reasons associated with development of glucose intolerance in PHPT and pancreatitis, the complex interplay of insulin, glucagon and various other counterregulatory hormones might have precipitated DKA. DKA results from insulin deficiency combined with excess of counterregulatory hormones like glucagon, catecholamines, cortisol and growth hormone. Both insulin deficiency and glucagon excess in particular are necessary for DKA to develop. Hyperglucagonemia without hypoinsulinemia was the most consistent hormonal pattern seen in acute pancreatitis, suggesting that elevated glucagon release is the major pathogenetic factor in causing the transient hyperglycemia of acute pancreatitis (10). The exact cause for abnormalities of insulin and glucagon secretion during chronic pancreatitis are unclear as there is lack of evidence of islet cell damage on histopathological examination. It is likely that impaired islet vascularity as a result of exocrine tissue fibrosis and altered secretion of gut-derived insulin-releasing peptides (incretins) due to malabsorption may contribute to abnormal insulin secretion in chronic pancreatitis (10, 11).

In view of negative family history of diabetes, absence of GAD antibody, patient had developed diabetes secondary to primary of hyperparathyroidism and chronic pancreatitis. Several reports had suggested that treatment of primary hyperparathyroidism may lead to improved control of diabetes. The reports by Walsh et al. (12) and Akgun et al. (13) each include one diabetic patient whose insulin requirement decreased after parathyroidectomy. In our patient insulin requirement decreased in post parathyroidectomy period by twelve units. To conclude with keeping a high index of suspicion for primary hyperparathyroidism in patient with pancreatitis and diabetes is rewarding and will avoid delay in proper diagnosis and treatment.

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References