Case Report

A case report of reactive hypoglycemia in a patient with pheochromocytoma and it's review of literature

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ABSTRACT

Pheochromocytoma, a tumor characterized by catecholamine excess, is usually associated with impaired glucose tolerance. Hypoglycemia may occur after the abrupt withdrawal of catecholamines in the postoperative period. Rarely, insulin secretion by stimulation of β-2 adrenoreceptors may overwhelm the glucagon production, thereby causing hypoglycemia. Here, we describe a female with pheochromocytoma, who presented with postprandial hypoglycemia.

Key words: Hypoglycemia, pheochromocytoma, postprandial/reactive hypoglycemia

Introduction

Pheochromocytomas are adreno-medullary tumors characterized by catecholamine excess. Impaired glucose tolerance and diabetes mellitus have been reported in 26-50% cases of pheochromocytoma in different series.[1] This has been attributed to multiple mechanisms including insulin resistance at the level of skeletal muscle and liver, enhanced gluconeogenesis but the major effect is inhibition of insulin release from the pancreas.[2]

Hypoglycemia in patients with pheochromocytoma has usually been reported in the postoperative phase.[3-5] There have been anecdotal case reports of hypoglycemia in patients with pheochromocytoma prior to surgical removal of the tumor. In these six cases, hypoglycemia was attributed to the predominant β-adrenoreceptor stimulatory effect for the release of insulin. Here, we describe an unusual case of pheochromocytoma who presented as reactive hypoglycemia.

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Case Report

A 51-year-old female initially presented to the Department of Surgery with complaint of recurrent nonbilious vomiting. USG abdomen revealed cholelithiasisand a right adrenal mass. Patient denied complaints of episodic palpitations, headache, sweating or weight loss. There was no history of early satiety or constipation. There was a history of frequent intake of meals at an interval of 3-4 hrs. She denied any history suggestive of postprandial hypoglycemia. She was diagnosed to be hypertensive around 3 years back, but she was not taking regular medication. She had been taking tablet Amlodipine 10 mg and Olmesartan 40 mg and referred to the Endocrine Unit. There was no family history suggestive of Hypertension, DM, CAD or MEN.

Examination revealed a thin built female of height 5'3", weight 43 kg, BMI: 16.79 Kg/m^2. Blood pressure was 115/80 mmHg in supine position and 104/80 mmHg in standing position. There was no postural drop in blood pressure. Systemic examination was unremarkable. Biochemical investigations revealed normal hemogram, liver function test and kidney function test. The 24-hour urine catecholamines were elevated [VMA: 36.63 mg/g creatinine (1.6-4.2 mg/g), Epinephrine: 81.42 pg/ml (<67 pg/ml), Norepinephrine: 876.47 ng/ml (95-446 ng/ml), Dopamine: 51.61 pg/ml]. Postprandial glucose levels were reported as 30 mg/dL and 54 mg/dL on two different occasions. An extended oral glucose tolerance test was done

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which showed reactive hypoglycemia and hyperinsulinemia at 3 hrs [Table 1]. HbA1C was 6.20%. Thyroid function test and serum cortisol levels were normal. CT abdomen and pelvis showed partially necrotic, otherwise well defined mass in the right adrenal measuring 42 × 39 mm in size. An incidental finding of mural thickening of antrum of stomach was found. Echocardiography revealed severe concentric Left ventricular hypertrophy, mild MR, AR and LV diastolic dysfunction with left ventricular ejection fraction of 60%.

Patient underwent surgery after appropriate hypertensive management with α and β-blockers. Histopathology revealed tumor cells with abundant amphophilic granular cytoplasm, vesicular nuclei and few cells showed nucleoli with occasional mitotic figures suggestive of pheochromocytoma [Figure 1].

Discussion

Abnormalities in glucose homeostasis are frequently reported in patients of pheochromocytoma. Impaired glucose tolerance and diabetes mellitus has been reported to be in as many as 26-50% patients in a semilogical study

Table 1: Extended oral GTT with 75 g of glucose

Time point (hr)	OGGT 1		OGGT 2	
	Glucose	Insulin	Glucose	Insulin
0	126	1.15	111	2.90
½			156	25.30
1	257	93.31	257	96.60
1½			98	60.20
2	115	49.31	117	28.30
2½			85	18.50
3	54	3.68	53	10.90
4	65	0.246	65	2.10
5	71	0.08		

OGGT: Oral glucose tolerance test

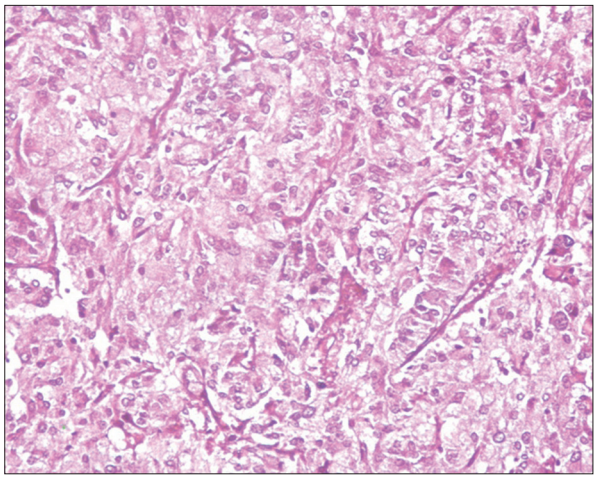

Figure 1: Histopathology showing tumor cells of pheochromocytoma

of 2585 patients, including 11 with pheochromocytoma.[1] Anecdotal reports of diabetic ketoacidosis have also been described in patients with pheochromocytoma. Isotani *et al.* reported a young patient with NA predominant pheochromocytoma presenting with DKA.[6] Another case of DKA in a 29-year-old patient was reported by Edelman in the year 1992 which was attributed to catecholamine excess.[7]

Catecholamines exert their action on glucose homeostasis through α and β-adrenoreceptors. Stimulation of β-adrenoreceptors by catecholamines causes enhanced glycogenolysis and gluconeogenesis by the liver resulting in transient increase in glucose production.[8] Direct stimulation by noradrenaline on α-adrenoreceptors of pancreas, causes inhibition of insulin release whereas stimulation of β-adrenoreceptors by adrenaline, results in insulin release, specially in conditions where glycogen stores are depleted.[9] In most situations the α-receptor-mediated insulin inhibition predominates over β-insulin-releasing actions causing impairment of glucose homeostasis.[10,11]

Some cases of hypoglycemia after surgical removal of pheochromocytoma have been described. Hypoglycemia in these cases is believed to be due to sudden loss of catecholamine effect on glucose homeostasis. There are only anecdotal case reports of hypoglycemia in patients of pheochromocytoma in the preoperative phase. Till date only six such cases have been reported [Table 2]. Reactive or postprandial hypoglycemia, occurs exclusively after meals, typically within 4 hours after food ingestion. The biochemical criteria for defining postprandial hypoglycemia are a plasma glucose concentration less than 3.0 mmol/L (54 mg/dL) and an insulin concentration greater than 18 pmol/L (3.0 pmol/L).[12,13]

The first case of hypoglycemia in a normotensive pheochromocytoma was reported by Hagiwara in the year 1981.[14] Innerman and his colleagues in 1982 reported a patient of pheochromocytoma that had metastasized to the liver. The author proposed that hypoglycemia was due to secretion of insulin or a substance with insulin-like activity by the tumor, increased utilization of glucose by the malignant cells and a local effect of the tumor on the hepatic parenchyma.[15] Oki *et al.* reported a case of pheochromocytoma of paroxysmal type with paradoxical response to glucose tolerance test.[16] In 1987, Kazuko Hiramatsu reported a case of pheochromocytoma with dilated cardiomyopathy, in whom transient hyperinsulinemia and reactive hypoglycemia were reported on one occasion during extended GTT, which could not be reproduced on subsequent glucose load. The author pointed out that the glucose tolerance abnormalities were transient.[17] Frankton *et al.* (2008) reported a case of pheochromocytoma crisis presenting with profound

Table 2: Previous cases of hypoglycemia reported in patients with pheochromocytoma

Name of the author	Year	Clinical background
Hagiwara M, *et al*.	1981	A case of normotensive pheochromocytoma with hypoglycemia
Innerman SC, *et al*.	1982	A patient presenting with hypoglycemia and a pheochromocytoma metastatic to the liver
Oki S, *et al*.	1985	A case of pheochromocytoma of a paroxysmal type who had a paradoxical response to GTT with ten years' clinical course
Hiramatsu K, *et al*.	1987	A 57-year-old man with pheochromocytoma who had reactive hypoglycemia with transient hyperinsulinemia
Frankton S, *et al*.	2009	A patient who presented with four days of vomiting, sweating, hypoglycemia and hypertension. Shortly after initial improvement with glucose, he developed acute pulmonary oedema and became hypoglycaemic again; a phaeochromocytoma crisis was suspected. He later deteriorated and died and autopsy examination confirmed a phaeochromocytoma in the left adrenal, with haemorrhage within the head of pancreas, but no evidence of a pancreatic tumor
Habra MA, *et al*.	2010	Patient with metastatic pheochromocytoma, who developed progressive and fatal hypoglycemia that did not respond to high-dose glucose infusion, corticosteroids, or glucagon therapy. The pattern of glucose uptake on (18) F-2-fluoro-2-deoxy-D-glucose positron emission tomography, with preferential tumor glucose uptake in association with a marked reduction in normal uptake in the heart, muscles, and brain, was highly suggestive of direct consumption of glucose by the tumor rather than insulin-like growth factor-2 mediated hypoglycemia

GTT: Glucose tolerance test

hypoglycemia and subsequent hypertension. The author postulated that in conditions of depleted stores of glycogen in liver and skeletal muscles, stimulation of β-adrenoreceptors by adrenaline, causes increase release of insulin thereby causing hypoglycemia.[18] Recently fatal hypoglycemia in malignant pheochromocytoma, was reported by Hambra in 2010. He postulated that hypoglycemia in this patient was because of increased consumption of glucose by the rapidly dividing tumor cells.[19]

Our patient had impaired fasting glucose with glucose levels rising to more than 250 mg/dl at 1 hr. Postprandial glucose fell down to 54 mg/dL at 3 hrs. There was an earlier report of postprandial glucose level of 30 mg/dL. Hyperinsulinemia was observed at 1 and 2 hrs. While the patient had frequent food intake and occasional headaches, classical symptoms of hypoglycemia were not elicited. An incidental finding of mural thickness at gastric outlet cannot explain postprandial hypoglycemia in our patient, rather delayed absorption and delayed increase in plasma glucose levels would be expected. Since the patient has presented with vomiting, it is possible that the glycogen stores in muscle and liver were depleted further contributing to hypoglycemia. Another interesting thing in our patient is that she is never been symptomatic for hypoglycemic symptoms even when the plasma glucose levels were 30 mg/dL.

Conclusion

The present case was rare case of pheochromocytoma presenting as reactive hypoglycemia.

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