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CASE REPORT

A paradoxical reaction after an oral glucose tolerance test revealed a pheochromocytoma

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Abstract

A 33-year-old Japanese man with a history of atopic dermatitis and asthma had never been diagnosed with any apparent glucose intolerance but had been aware of palpitations for >10 years. A 75g oral glucose tolerance test (OGTT) at his physical examination in March 2021 revealed fasting hyperglycemia and post-load hypoglycemia. An OGTT recheck was performed in May 2021 and was normal. We hypothesized that gluconeogenesis from the liver had caused his fasting hyperglycemia and performed abdominal echocardiography, which revealed a right adrenal tumor with abnormal catecholamine production. We diagnosed pheochromocytoma and performed a right adrenalectomy in September 2021. Postoperatively, the patient's palpitations disappeared and his laboratory findings normalized. Glucose intolerance is well known to occur before surgery in patients with pheochromocytoma, but it is extremely rare that hypoglycemia is indicated by a presurgery OGTT, as in our patient's case. Only three similar cases are reported to date, and in all three, hypoglycemia occurred ≥2 hr after loading, accompanied by excessive insulin secretion compared to the plasma glucose level. Our patient's case is the only one in which preload hyperglycemia was observed. Before his OGTT, he had run from the train station to the hospital, which was likely to be the cause of the preload hyperglycemia. We speculate that the stimulation of adrenergic β2 receptors may be involved in the enhancement of insulin secretion in patients with pheochromocytoma, but the mechanism is unknown. Further reports may clarify the mechanism of hypoglycemia induced by pheochromocytoma.

Abbreviations:

GLP-1	- glucagon-like peptide-1
OGTT	- oral glucose tolerance test
RET	- rearranged during transfection
MEN2	- multiple endocrine neoplasia type 2
IRI	- immunoreactive insulin
Epi	- epinephrine
Norepi	- norepinephrine

INTRODUCTION

Pheochromocytoma is a tumor of the adrenal medulla that is characterized by an abnormally high production of catecholamines. It has been estimated that approximately half of patients with pheochromocytoma have impaired glucose tolerance (Elenkova *et al.* 2020). This is due to the release of free fatty acids via adrenergic alpha and beta receptors, an enhanced secretion of glucagon, suppressions of glucagon-like peptide-1 (GLP-1) and insulin secretion, and an increased glucose uptake into skeletal muscle (Abe *et al.* 2020). Although hypoglycemia can occur after the resection of a pheochromocytoma (Aygun & Uludag 2020), few reports have described preoperative hypoglycemia in a patient with a pheochromocytoma. In this report, we present the case details of a patient with a pheochromocytoma that was diagnosed after he experienced a paradoxical reaction following an oral glucose tolerance test (OGTT).

CASE REPORT

The patient was a 33-year-old Japanese male who had a history of atopic dermatitis, bronchial asthma, and high plasma glucose detected on physical examinations ~10 years ago; he was taking no medication. He reported having experienced palpitations over the past ~10 years when lying down or jogging. At his physical examination in September 2019, his 2-hr postprandial blood glucose was 5.94 mmol/L (normal range 3.89–6.06 mmol/L) and the HbA1c level was 5.8% (normal range 4.6%–6.2%). In November 2020, he presented with an average blood glucose level at 9.22 mmol/L. An OGTT performed in March 2021 revealed fasting hyperglycemia and postload hypoglycemia (Table 1). He was free of hypoglycemic symptoms during the OGTT, and his vital signs were normal: heart rate 91 beats/min and blood pressure 99/67 mmHg. The OGTT recheck in May 2021 was normal (Table 2), and continuous glucose monitoring did not detect hyperglycemia or hypoglycemia during the 2-week course of the study.

Tab. 1. The patient's plasma glucose and IRI responses to the 75g-OGTT in March 2021

Min.	0	30	60	120
Glucose, mmol/L	11.2	9.0	4.1	2.3
IRI, pmol/L	129.2	577.6	485.7	95.4

IRI, immunoreactive insulin; OGTT, oral glucose tolerance test.

Tab. 2. The patient's plasma glucose and IRI responses to the 75g-OGTT in May 2021

Min.	0	30	60	120
Glucose, mmol/L	5.3	8.2	4.8	4.9
IRI, pmol/L	18.7	297.8	106.2	218.8

IRI, immunoreactive insulin; OGTT, oral glucose tolerance test.

We confirmed that the OGTT specimen used in March 2021 was accurate and that the patient's fasting hyperglycemia was due to gluconeogenesis from the liver. We thus performed abdominal echography, which revealed a tumor of the right adrenal gland, as well as an abnormal catecholamine production. Thus, pheochromocytoma was diagnosed. There were no other endocrine abnormalities.

In September 2021, a right adrenalectomy was performed. Postoperatively, the patient's palpitations disappeared and his laboratory findings normalized. The OGTT in March 2021 is likely to have been affected by the fact that the patient had run from the train station to the hospital to avoid being late before that examination.

The patient's mother had a history of medullary thyroid carcinoma, and genetic testing was done for suspected multiple endocrine neoplasia. The results indicated a mutation in the rearranged during transfection (RET) gene, and the patient was diagnosed with multiple endocrine neoplasia type 2 (MEN2) and is being followed regularly.

DISCUSSION

About half of patients with pheochromocytoma, a catecholamine-producing tumor, have impaired glucose tolerance (Elenkova *et al.* 2020). Hypoglycemia is also known to occur after pheochromocytoma resection (Aygun & Uludag 2020), but there are few reports of preoperative hypoglycemia in patients with a pheochromocytoma. Only three cases of postload hypoglycemia after an OGTT have been reported (Hagiwara *et al.* 1981; Hiramatsu *et al.* 1987; Thonangi *et al.* 2014). The data of each of these patients and the present patient are summarized in Table 3. In our patient's case, hypoglycemia was triggered by excessive insulin secretion relative to the plasma glucose level. Moreover, his hypoglycemia occurred at least 2 hr after loading, and preload hyperglycemia was not observed. Thus, a rare paradoxical reaction of pre- and post-loading hyperglycemia and hypoglycemia was observed. The fasting hyperglycemia can be attributed to the patient running from the train station to the hospital. It has also been reported that insulin secretion from isolated human islets of Langerhans is stimulated by adrenergic β2 receptor stimulation (Lacey *et al.* 1993), causing postload hypoglycemia, but the underlying mechanism is not yet known.

In conclusion, although the number of such cases is very small, patients with a pheochromocytoma can exhibit a paradoxical reaction following an OGTT, and our present observations are supported by prior findings in the literature. A further accumulation of case reports could clarify the mechanism of hypoglycemia induced by pheochromocytoma.

Tab. 3. Plasma glucose levels and IRI responses to 75g-OGTT, epinephrine, and norepinephrine levels in four patients with pheochromocytoma and hyperinsulinemia

		OGTT (min) and epinephrine, and norepinephrine levels				
	75g-OGTT	**0**	**30**	**60**	**120**	**180**
Present case	Glucose (mmol/L)	11.2	9.0	4.1	2.3	
	IRI (pmol/L)	129.2	577.6	485.7	95.4	
	Epi (pmol/L)	1413.9				
	Norepi (nmol/L)	3.1				
	100g-OGTT					
Hagiwara *et al.* (1981)	Glucose (mmol/L)	4.4	7.8	11.7	6.7	3.3
	IRI (pmol/L)	35.9	861.0	1435.0	502.3	143.5
	Epi (pmol/L)	109.2				
	Norepi (nmol/L)	11.8				
	75g-OGTT					
Hiramatsu *et al.* (1987)	Glucose (mmol/L)	8.3		20.7	11.8	1.9
	IRI (pmol/L)	107.6		5431.5		>7,175
	Epi (pmol/L)	12774.1				
	Norepi (nmol/L)	28.3				
	75g-OGTT					
Thonangi *et al.* (2014)	Glucose (mmol/L)	7.0		14.2	6.4	3.0
	IRI (pmol/L)	8.3		669.5	353.7	26.4
	Epi (pmol/L)	444.4				
	Norepi (nmol/L)	5.18				

IRI, immunoreactive insulin; OGTT, oral glucose tolerance test; Epi, epinephrine; Norepi, norepinephrine.

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