

Carcinoid Crisis After Injection of 6-¹⁸F-Fluorodihydroxyphenylalanine in a Patient with Metastatic Carcinoid

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A carcinoid crisis is a severe complication of the carcinoid syndrome that can arise in patients with advanced metastatic neuroendocrine tumors. It can be initiated by stress, catecholamines, and tumor manipulation. In this article, we report a case in which an injection with the catecholamine tracer 6-¹⁸F-fluorodihydroxyphenylalanine, used for PET, induced a carcinoid crisis. Octreotide can be used for treatment and should be available. Tracer injection should be slow.

Key Words: ¹⁸F-DOPA; carcinoid syndrome; carcinoid crisis; neuroendocrine tumors

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The carcinoid syndrome can occur in patients with a metastasized midgut carcinoid. This syndrome is characterized by episodes of flushing, diarrhea, abdominal pain, and wheezing (1–3). A carcinoid crisis is a serious complication of the carcinoid syndrome. A crisis is characterized by a sudden onset of different symptoms at once; these symptoms can consist of prolonged cutaneous flushing, severe dyspnea, peripheral cyanosis, tachycardia, and sometimes hemodynamic instability, which can be fatal (4–6).

In recent years, PET with 6-¹⁸F-fluorodihydroxyphenylalanine (¹⁸F-DOPA) has emerged as a new and accurate modality for the imaging of neuroendocrine tumors (7,8). ¹⁸F-DOPA is an amino acid but is also an important precursor in catecholamine metabolism. In this article, we report a case in which the rapid intravenous administration

of a bolus of ¹⁸F-DOPA, used for a PET study, initiated a carcinoid crisis.

CASE REPORT

A 61-y-old woman with extensive liver metastases from a carcinoid tumor was referred to our PET center for an ¹⁸F-DOPA PET scan. She participated in a diagnostic research project that was approved by the local institutional review board and had given informed consent. One and a half years earlier she had been diagnosed with carcinoid disease and elevated 5-hydroxyindoleacetic acid (5-HIAA) excretion on the basis of a primary tumor in the ileum and extensive liver metastases. To alleviate symptoms of diarrhea she received 20 mg of slow-release octreotide intramuscularly every 4 wk. Despite this treatment, she was still experiencing episodes of diarrhea and flushing at the time of referral for the PET scan. During the last 2 visits to the outpatient clinic, her blood pressure was 190/100 mm Hg. In the preceding month, her urinary 5-HIAA level had risen slightly from 102 to 124 mmol/mmol of creatinine. Since the age of 52 y, she had had type 2 diabetes, for which she received glibenclamide.

In accordance with our scanning protocol, she received 150 mg of carbidopa orally after 6 h of fasting. One hour later, a bolus of 160 MBq of ¹⁸F-DOPA with a specific activity of 6 GBq/mmol was administered intravenously in a few seconds. The total injected volume was 8 mL and consisted of 5.63 mg of ¹⁸F-DOPA and 6 mL of 0.9% NaCl. Radiosynthesis of ¹⁸F-DOPA had been performed according to the method described by De Vries et al. and was no different from previous syntheses (9). At approximately 3 min after injection, she complained about a strange feeling in the abdomen extending to her chest, shortness of breath, and nausea but no itching. These symptoms were followed by severe vomiting. A physical examination revealed facial flushing with facial edema, peripheral cyanosis, and tho-

As an exception to the JNM policy of not publishing case reports, the editors deemed the information presented in this study to be of importance for clinicians and investigators using ¹⁸F-DOPA for clinical studies.

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racic erythema. Her blood pressure was 185/90 mm Hg, and her heart rate was regular, at 72 beats per minute. An electrocardiogram was normal. Her blood glucose level was 8.6 mmol/L. She was given 2 mg of the antihistamine clemastine (Tavegil; Novartis) intravenously. At approximately 10 min after this injection, her vomiting stopped, and her other complaints slowly diminished in the next 30 min. She believed that she was fit to be scanned, and 1 h after injection of ^{18}F -DOPA, the scan procedure was started (Fig. 1). When the scan was finished, blood and urine samples were collected to evaluate for histamine, catecholamines, and serotonin metabolites. These data could be compared with measurements that had been obtained in the morning, before the PET scan. Finally, she went home in good condition approximately 2 h after the injection.

Two weeks later, she told us that she had experienced similar, but less severe, episodes (without vomiting and peripheral cyanosis) spontaneously before. On the basis of these symptoms and the increase in the urinary 5-HIAA level, the slow-release octreotide dose was increased from 20 mg to 30 mg monthly.

DISCUSSION

Initially, we ascribed the symptoms of this patient to an anaphylactic reaction caused by the injection of ^{18}F -DOPA. We treated her for this reaction by administering an antihistamine. However, on the basis of additional clinical and biochemical information, it appears that this incident was a carcinoid crisis induced by the injection of ^{18}F -DOPA.

Laboratory parameters are important for determining the nature of such incidents. During anaphylaxis, mast cells and basophils degranulate on activation by cross-linking of mast cell-bound IgE with antigen or complement components. Products released during this degranulation include hista-

mine, prostaglandins, leukotrienes, platelet-activating factor, and tryptase. Evidence in support of a diagnosis of anaphylaxis includes increased serum tryptase levels and increased levels of urine *N*-methylhistamine, a histamine metabolite that remains elevated for several hours (10,11). In our patient, tryptase and urine *N*-methylhistamine levels were within normal ranges (Table 1), a finding that virtually excludes an anaphylactic reaction as the cause for the incident.

A carcinoid crisis is the result of a massive release of serotonin and other products, such as histamine, kallikreins (12), or catecholamines (13). In particular, levels of serotonin and its metabolites (5-HIAA) are elevated and remain so for several hours (14–16). In our patient, the urinary 5-HIAA level doubled within a few hours. In addition, the serum tryptophan level declined by 50% (Table 1). From these values, it can be concluded that there was a period of massive serotonin production and release that, together with her symptoms and history, was diagnostic of a carcinoid crisis (17). The low level of tryptophan, the first precursor in the serotonin pathway, confirms the increased activity of this pathway.

Various causes for the carcinoid crisis have been reported. Besides mechanical stimulation of the tumor and triggering by catecholamines (especially noradrenaline), a carcinoid crisis also can be triggered by stress, hypercapnia, hypothermia, hypotension, hypertension, initiation of chemotherapy, or drugs that cause a release of histamine (5,12,15,18–20). In our patient, rapid injection with the catecholamine tracer ^{18}F -DOPA triggered the release of serotonin by the tumor cells, thus initiating the carcinoid crisis.

Possible mechanisms for the initiation of a carcinoid crisis by ^{18}F -DOPA include the local conversion in tumor tissue of ^{18}F -DOPA to noradrenaline, induced by the enzymes aromatic acid decarboxylase and dopamine β -hydroxylase. These enzymes, especially aromatic acid decarboxylase, can be abundantly present in carcinoids and remain active even in the presence of carbidopa (21,22). Noradrenaline then can stimulate the tumor cells to release serotonin. This mechanism seems most likely, because the amount of the injected tracer was relatively high (5.63 mg) as a result of the low specific activity. Another mechanism may be local irritation of the vessel walls of the adrenal gland by ^{18}F -DOPA. The adrenergic system then can release noradrenaline, which in turn can stimulate the tumor cells to release serotonin. Similarly, it has been proposed that the rapid uptake of ^{123}I -metaiodobenzylguanidine in chromaffin granules, either in the normal adrenal gland or in tumor tissue, may cause rapid noradrenaline secretion.

Every neuroendocrine tumor that produces and stores serotonin and catecholamines in secretory granules could react with a massive outpouring of hormones, thus initiating the carcinoid crisis. However, patients most at risk are probably patients with preexisting carcinoid syndrome and the existence of extensive liver metastases or of metastases

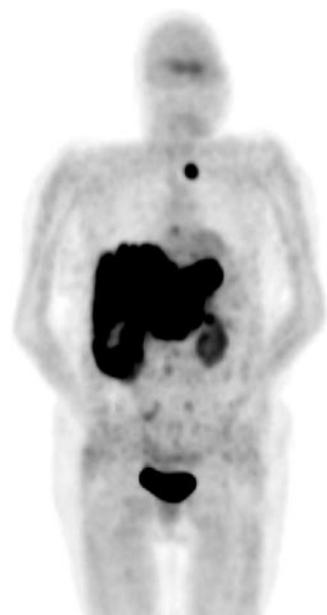


FIGURE 1. Anterior projection image from ^{18}F -DOPA PET scan showing extensive liver metastases and supraclavicular lesion. Note physiologic uptake in striatum, kidneys, and bladder.

TABLE 1
Blood and Urine Measurements Before and After Scanning

Parameter	Reference value	Value		
		Before*	After†	1 mo later‡
Plasma				
Noradrenaline	<4.31 nmol/L		3.34	
Adrenaline	<0.22 nmol/L		0.11	
Dopamine§	nmol/L		0.11	
Serotonin	2.8–5.4 nmol/10 ⁹ thrombocytes	26 ↑	27 ↑	21 ↑
Tryptophan	40–70 μmol/L	45.1	25.7 ↓	26.4 ↓
5-HIAA§	nmol/L	3,939.0 ↑	3,407.0 ↑	3,502.0 ↑
Tryptase	<11.4 μg/L		4.72	
Urine				
Creatinine	7.1–13.5 mmol/L	6.6	3.9	6.4
5-HIAA	0.8–3.8 mmol/mol of creatinine	124.2 ↑	247.3 ↑	101.1 ↑
Noradrenaline	<30 μmol/mol of creatinine		17	
Adrenaline	<10 μmol/mol of creatinine		2.1	
Dopamine	<300 μmol/mol of creatinine		41	
POHPAA	10.0–20.0 mmol/mol of creatinine		—	—
HVA	1.1–5.5 mmol/mol of creatinine		4.1	3.7
VA	5.0–15.0 mmol/mol of creatinine		1.3 ↓	11.0
MOPEG	0.4–1.5 mmol/mol of creatinine		1.1	0.8
VMA	0.5–2.5 mmol/mol of creatinine		2.2	1.4
DOPAC	<2.0 mmol/mol of creatinine		0.5	0.8
Metanephrine	33.0–99.0 mmol/mol of creatinine		96	91
Nonmetanephrine	64.0–260.0 μmol/mol of creatinine		181	221
3-MT	45.0–197.0 μmol/mol of creatinine		444 ↑	519
M-histamine	<150 μmol/mol of creatinine		52	50
MIMA	0.9–1.9 mmol/mol of creatinine		2.1 ↑	
Serotonin	0–66 μmol/mol of creatinine	274 ↑	271 ↑	294 ↑

*Blood and urine samples routinely taken 5 h before ¹⁸F-DOPA injection.

†Blood and urine samples taken directly after PET scanning, 2.5 h after ¹⁸F-DOPA injection.

‡Blood and urine samples taken 1 mo after ¹⁸F-DOPA PET scan to obtain individual baseline reference.

§Not detectable in healthy subjects.

POHPAA = *p*-hydroxyphenylacetic acid; HVA = homovanillic acid; VA = vanillic acid; MOPEG = 3-methyl-4-hydroxyphenylethylene glycol; VMA = vanillylmandelic acid; DOPAC = 3,4-dihydroxyphenylacetic acid; 3-MT = 3-methoxytyramine; M-histamine = *N*-methylhistamine; MIMA = methylimidazoleacetic acid.

— = not measured; ↑ = increased level; ↓ = decreased level.

in another part of the body where the venous blood flow directly enters the systemic circulation. There are currently no risk factors that can indicate which of these patients will develop a carcinoid crisis (1).

Differentiating a carcinoid crisis from a severe episode of the carcinoid syndrome can be difficult, and there is a gradual transition. However, the hallmark of a carcinoid crisis is the sudden (violent) onset of different symptoms at once. Our patient developed symptoms that were much more severe and diverse shortly after the injection of ¹⁸F-DOPA than the symptoms that she usually experienced during an episode of her carcinoid syndrome. Also, her biochemical findings suggested that she had gone through an episode with a massive release of serotonin. Therefore, it seems more likely that our patient experienced a carcinoid crisis instead of a severe episode of her carcinoid syndrome.

Considering the severity of a carcinoid crisis, preventive measures should be taken, and nuclear medicine workers

must be aware of this risk and its treatment. These caveats have become more relevant, because the application of ¹⁸F-DOPA PET seems to have become increasingly valuable for patient care. A preventive measure could be to administer ¹⁸F-DOPA slowly instead of as a bolus. By avoiding rapidly building peak first-pass concentrations, slow injection most likely can prevent a rapid secretion of noradrenaline by tumor cells. This strategy is similar to the advice given for the administration of ¹²³I-metaiodobenzylguanidine. Treatment of a carcinoid crisis should consist of blocking the release of the mediators from tumor tissue by administering somatostatin analogs, such as octreotide (20,23). In the acute situation, 100–500 µg of octreotide can be safely administered intravenously (6). Ketanserin has been used successfully in patients with a carcinoid crisis to block the actions of mediators. It is a selective antagonist of the 5-hydroxytryptamine receptor 2, the α₁-adrenoreceptor, and the H₁-histamine receptor and decreases the central

sympathetic outflow (23). Ketanserin can be given as a 10-mg intravenous bolus injection. Catecholamines should never be used for the treatment of hypotension, as they may stimulate tumor cells to release even more serotonin.

CONCLUSION

We present a case of a patient who had a carcinoid tumor and extensive liver metastases and who developed a carcinoid crisis after injection with ^{18}F -DOPA. As a carcinoid crisis can be fatal, PET centers using ^{18}F -DOPA for the imaging of patients with biochemically active and metastasized carcinoid disease should be aware of this rare syndrome. The tracer must be administered slowly, and intravenous somatostatin analogs and perhaps also ketanserin should be available to treat this condition.

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