Posterior Reversible Encephalopathy Syndrome Due To Carcinoid Crisis Complicating Transarterial Chemoembolization for Metastatic Carcinoid Tumour

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Abstract

Introduction: We present a case report of posterior reversible leukoencephalopathy syndrome (PRES) following transarterial chemoembolization (TACE) of liver metastasis of an intestinal neuroendocrine tumour.

Case presentation: A 62-year-old female was evaluated for progressive bilateral vision loss following transarterial chemoembolization (TACE) of hepatic metastasis of a midgut carcinoid tumour with cisplatin. Vital signs were remarkable for significant hypertension (170-210/85-110) since having undergone TACE (baseline BP 136/74), despite pre-procedure administration of octreotide. Blood pressure failed to correct with administration of amlodipine, hydralazine, captopril and labetalol infusion but responded promptly to octreotide infusion. Magnetic resonance imaging showed findings compatible with PRES. The patient's vision gradually corrected to her baseline over 2 days.

Conclusion: TACE for neuroendocrine tumours can be complicated by carcinoid crisis despite pre-administration of octreotide. Rarely, this may present as a hypertensive emergency of which PRES is a manifestation. Prompt recognition and treatment with high dose octreotide are important and can avoid permanent neurological injury in patients.

Résumé

Introduction: Il s'agit d'une étude de cas de syndrome de leuco encéphalopathie réversible postérieure (SERP) consécutive à la chimioembolisation transartérielle (CETA) d'une métastase hépatique d'une tumeur neuro-endocrine intestinale.

Présentation du dossier: Une femme de 62 ans a été évaluée pour une perte de vision bilatérale progressive suite à la chimioembolisation transartérielle (CETA) d'une métastase hépatique d'une tumeur du tube digestif par cisplatin. À l'examen des signes vitaux, une importante hypertension (170-210/85-110) a été constatée depuis la CETA (p.a. de base 136/74) malgré l'administration d'octéotide préalable à l'intervention. La pression artérielle ne s'est pas corrigée avec l'administration d'amlodipine, d'hydralazine, de captopril et de labétalol en perfusion, mais a répondu promptement à une perfusion d'octéotide. Une imagerie par résonance magnétique
Carcinoid syndrome is a syndrome classically consisting of diarrhea, paroxysms of cutaneous flushing with or without hypotension and bronchospasm arising most frequently in the setting of hepatic metastases originating from midgut carcinoid tumours. However, these neuroendocrine tumours can synthesize a wide variety of polypeptides, prostaglandins, and biogenic amines and hence present atypical clinical manifestations such as pellagra, abdominal pain, right-sided heart failure from valvular lesions and paroxysmal hypertension. Tumour manipulation may result in a massive influx of hormones into the systemic vasculature, potentially resulting in life threatening swings in blood pressure, cardiac arrhythmias and bronchoconstriction, even in patients without liver metastases or preoperative carcinoid syndrome.1

We present a case report of hypertensive emergency presenting as posterior reversible leukoencephalopathy syndrome (PRES) after transarterial chemoembolization (TACE) of a hepatic metastasis of carcinoid tumour.

Case Presentation

A 62-year-old caucasian female was evaluated on the surgical ward for progressive bilateral vision loss about 10 hours following transarterial chemoembolization (TACE) of a hepatic metastasis of a midgut carcinoid tumour (Figure 1, Figure 2) with Lipiodol and cisplatin. Premedication with octreotide 100 mcg subcutaneously and dexamethasone 8 mg IV pre-procedure was given, and post-procedure orders were given for dexamethasone 4 mg bid, ondansetron as needed and D5% NaCl 0.9% at a rate of 150 mL/h. The rest of her past medical history was unremarkable, specifically without history of hypertension, cerebrovascular disease, or clinical manifestations of carcinoid syndrome prior to admission. She had undergone two intra-abdominal surgeries without complication including resection of the primary. Her usual medication was limited to inhaled glycopyrrolate and indacaterol.

Upon evaluation, the patient was somnolent but otherwise well oriented. Eye exam confirmed bilateral 0/20 vision though pupils were 4 mm and reactive. On motor exam, the patient had diffuse hyperreflexia with upgoing plantar reflexes but without focal weakness. Chart review was remarkable for blood pressures ranging from 170-210/85-110 since TACE (pre-procedure resultats compatibles avec un diagnostic de SERP. La vision de la patiente s’est graduellement corrigée pour revenir à son état habituel en deux jours.

Conclusion: Dans le cas de tumeurs neuro-endocrines, la CETA peut être compliquée d’une crise carcinoïde malgré l’administration d’octréotide au préalable. Cette condition peut, quoique rarement, engendrer une urgence hypertensive dont le SERP est une manifestation. L’identification rapide de la condition et un traitement à l’aide d’octréotide à dose élevée sont de la plus haute importance et peuvent éviter des dommages neurologiques permanents.

Figure 1: Axial computed tomography scan of hepatic metastasis. A mass is visible in hepatic parenchyma corresponding to a metastasis of the midgut carcinoid tumour.

Figure 2: Fluroscopic image of transarterial chemoembolization of hepatic metastasis.
blood pressure 136/74). A presumptive diagnosis of PRES due to cisplatin was made.

Initial cerebral computed tomography scan was suspicious for a right occipital sub-cortical hypodensity of 3 cm, possibly of ischemic nature. IV fluids were discontinued (D5%NaCl 0.9% at a rate of 150 mL/h) and anti-hypertensive agents were begun. After failure of improvement of blood pressure or symptoms despite amlodipine, hydralazine, labetalol, and captopril, a diagnosis of carcinoid crisis was suspected and octreotide 300mcg IV bolus followed by an infusion of 50 mcg/h was started. The suspected diagnosis of carcinoid crisis was later confirmed by 24h urinary 5-HIAA dosing at 141.4 umol/day (normal 0–42, previously within normal limits pre-operatively). Serum chromogranin A was also elevated at 138.2 ug/L (normal 0–82), compatible with a neuroendocrine tumour.

Characteristic changes of PRES were seen on cerebral magnetic resonance imaging (MRI) (Figure 3) including predominantly sub-cortical hyperintensities in the bilateral parietal and occipital lobes on T2 and FLAIR sequences which were also hyperintense on diffusion-weighted imaging (DWI), likely from T2 shine through, and apparent diffusion coefficient (ADC) maps without restricted diffusion, hence confirming the finding of vasogenic edema compatible with PRES.

Discussion
Carcinoid tumours are classically described as slow growing, mainly affecting the gastrointestinal (GI) tract. They are known to internists mainly for their capability to produce the carcinoid syndrome. However, only about 25% of carcinoids actually produce the mediators which produce the carcinoid syndrome and less than 10% of patients actually develop the carcinoid syndrome.2 The syndrome usually presents when midgut carcinoids metastasize to the liver, hence bypassing hepatic metabolism. Typical symptoms include secretory diarrhea (80%) and flushing of the head, neck, and upper torso (90%) which may be associated with hypotension and tachycardia. Less frequent manifestations are right heart failure due to carcinoid valve disease (30%), bronchospasm (15%) and pellagra (5%).3 The classic triad of flushing, diarrhea and wheezing is infrequently found. Foregut (e.g., bronchial) and extra-digestive midgut (e.g., ovarian) tumours bypass the liver and may result carcinoid syndrome without hepatic metastasis, although symptoms are usually atypical in these cases.

Perioperative carcinoid crisis occurs in 10–30% of patients undergoing operative resection. Absence of preoperative carcinoid syndrome decreases the risk of carcinoid crisis, however it may still occur.1 This has led to the recommendation by some that patients be premedicated with somatostatin analogues to block bioactive peptide release and action, with or without other hormone antagonists (e.g., anti-histamines).3 However, the benefit of octreotide prophylaxis has been questioned by other studies.1 Once a carcinoid crisis has occurred, bolus doses of 25–500 mcg and intravenous infusions at rates of 50–150 mcg/h have been effective in case reports and case series, with higher doses being potentially required in patients on maintenance octreotide therapy or with carcinoid heart disease.4

Despite a lack of data comparing it to surgical management, transarterial chemoembolization (TACE).5 is a frequent management strategy for patients with liver metastases, especially when patients present with hormonal symptoms and multiple metastases preclude resection. Rates of complication from TACE are difficult to estimate ranging from 0 to 100%, likely due to variable definitions and reporting. Only one study reported on the incidence of post embolization carcinoid crisis,6 with 2 of 12 patients developing the complication. Both had a history of carcinoid syndrome and had been premedicated with octreotide 200 mcg SC before procedure and q8h afterward. One group7 did report a patient who developed transient cortical blindness following TACE which possibly could have been due to PRES.

PRES is a syndrome of failure of cerebral blood pressure autoregulation with acute onset elevations of blood pressure from baseline and a combination of altered level of consciousness, visual symptoms, headache and seizures.8 Blood pressure is
often only moderately elevated, though significantly above the patient’s baseline. Etiologies are varied but include cytotoxic chemotherapy, eclampsia and other causes of hypertensive emergency. It was originally felt that the patient’s PRES was due to the cisplatin received during TACE with contribution from dexamethasone and iatrogenic fluid overload (D5%NaCl 0.9% at 150 mL/h had been running for several hours) as she had no history of carcinoid syndrome, had been premedicated and had no other findings associated with the disease. However, her lack of response to standard anti-hypertensives and prompt response to octreotide suggest carcinoid crisis as the cause.

Neuroimaging with MRI confirms the diagnosis. Findings are compatible with symmetrical white matter edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions. The cortex, basal ganglia, brainstem, and cerebellar may also be involved though less so than the subcortical white matter, while anterior cortical involvement is seen only with the most severe cases. Importantly, the distribution is not confined to a single vascular territory. Classically lesions appear as punctate or confluent areas of hyperintensity on T2 and FLAIR sequences. DWI usually shows hypo or iso-intense signal (though sometimes mildly hyperintense from T2 shine through) while ADC maps show increased signal, thus distinguishing PRES from ischemic stroke. With prompt recognition and management, full recovery over a period of days to weeks can be expected.

**Conclusions**

Carcinoid crisis is a well-known and dreaded complication of surgical manipulation of carcinoid tumours. Transarterial chemoembolization of these tumours may also result in carcinoid crisis and our report suggests that pre-procedure carcinoid syndrome is not a prerequisite for this. Presentation may be atypical, as it was in our patient, and so clinical suspicion should be high. When suspected, prompt management with octreotide and other supportive therapies should be instituted.

**Key Points**

1. Patients undergoing transarterial chemoembolization for carcinoid tumour metastases are at risk for carcinoid crisis, even if they have been premedicated with octreotide and have no history of carcinoid syndrome.
2. Carcinoid crisis may present as hypertensive crisis rather than hypotension, and may give rise to PRES.

**References**