CASE REPORT

Circulatory collapse in a patient with gastrinoma after metoclopramide administration

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A patient who was given metoclopramide for vomiting and diarrhoea developed circulatory collapse with his blood pressure dropping to 50/20 mm Hg. A gastrinoma was diagnosed histologically. The extent of the tumour was defined by octreotide scanning and magnetic resonance imaging. Metoclopramide was again given for colicky abdominal pain and the patient developed circulatory collapse a second time. A laparotomy involving extensive resection of the tumour was performed. The *MEN1* mutation was not detected in blood or tumour tissue. Follow-up octreotide scanning did not show any residual tumour. Possible causes for the circulatory collapse are discussed. Our case is probably the first patient with gastrinoma to develop circulatory collapse after being given metoclopramide.

Case report

Our patient is a 17-year-old boy who had a 3-year history of ulcer symptoms, diarrhoea, and abdominal colic. A year ago he developed gastro-intestinal bleeding, which required blood transfusion. Oesophagogastroduodenoscopy showed a peptic ulcer so he was treated with omeprazole and became asymptomatic. He presented with vomiting and diarrhoea and was admitted with a diagnosis of traveller's diarrhoea.

He was given metoclopramide intravenously to manage his symptoms. His clinical condition deteriorated rapidly with his blood pressure dropping to 50/20 mm Hg. He was admitted to the intensive care unit with pneumonia, rhabdomyolysis, renal tubular necrosis, and disseminated intravascular coagulation.

Enteroscopy showed mild haemorrhagic gastritis and a small mucosal nodule in the antrum. Histological examination of biopsy specimens showed carcinoid tumour. An octreotide scan (6.3 mCi In-111 octreotide IVI, planar imaging from skull vertex to knees at 4, 24 and 48 hours, and single photon emission computed tomography of abdomen at 4 and 24 hours) showed three discrete foci with increased somatostatin receptor expression in the upper abdomen, compatible with tumour lesions at the gastric antrum, near the free edge of segment III of the liver and at the hepatic hilum (Fig a). Magnetic resonance imaging (MRI) demonstrated the segment III lesion in the liver. Contrast computed tomographic scanning of the abdomen showed a 2.7-cm nodule posterosuperior to the gastric antrum and two 2-cm nodules in the left lateral lobe of the liver. Endoscopic ultrasonography showed a 6 mm x 9.5 mm hypoechoic submucosal lesion in the antrum and a 2-cm metastasis at the left lobe of the liver.

His daily urinary excretion of 5-hydroxyindole acetic acid (5-HIAA) was normal but his whole blood serotonin level was raised (428 ng/mL; reference range, 50-200 ng/mL). His serum chromogranin A was also increased (395 ng/mL; reference level, <160 ng/mL) [Table]. His serum histamine and vasoactive-intestinal peptide levels were normal. He was given omeprazole, and all his symptoms resolved. Both his body weight and haemoglobin increased.

His serum gastrin was measured preoperatively and omeprazole was withheld for hormonal assessments. The night before the hormonal assessment, he had abdominal pain and vomiting although an H_2-antagonist had been prescribed, so he was given metoclopramide. His condition deteriorated rapidly and his blood pressure dropped to 90/50 mm Hg. He was resuscitated with a plasma expander and inotropes. His fasting serum gastrin was 3651 pmol/L (reference level, <55 pmol/L) and gastric pH was 1.4. Subcutaneous octreotide and oral omeprazole were given and continued until surgery. Postoperatively both medications were decreased gradually.

During surgery, a 4-cm tumour mass at the hepato-gastric ligament and a 1-cm tumour mass near the free edge of segment III of the liver were seen (Fig b). Enlarged lymph nodes were noted at the first and second part of the duodenum, the tail of the pancreas and the origin of the hepatic artery. All tumours and enlarged lymph nodes were excised. Histological examination of the stomach and lymph node specimens showed features of

Key words
Dopamine antagonists; Gastrinoma; Metoclopramide; Neuroendocrine tumors; Serotonin

Hong Kong Med J 2009;15:478-81

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carcinoid tumour. The tumour cells were found to be diffusely positive for neuroendocrine markers and for gastrin by immunohistochemical studies (Fig c). The final pathological diagnosis was gastrin cell tumour or gastrinoma with secondary carcinoid tumour.

Four weeks postoperatively, his serotonin level was 331 ng/mL, and his chromogranin A was 77 ng/mL (Table). He gave his informed consent for genetic analysis and genomic DNA was extracted from peripheral blood and resected tumour tissue. All coding exons with the flanking intronic regions of the *MEN1* gene were amplified with primer sequences previously described by Jap et al[1] and both strands were sequenced. No mutations were detected. An octreotide scan was repeated at 3 months and 10 months, with no new focus of tracer uptake seen.

一名患有胃泌素瘤的病人服食甲氧氯普胺後出現循環衰竭

一名有嘔吐及腹瀉的病人服食甲氧氯普胺（metoclopramide）後出現循環衰竭，血壓降至50/20 mm Hg。組織學分析顯示病人患有胃泌素瘤，利用奧曲肽掃描及磁共振術評估腫瘤的大小。病人因腹痛而再次服食甲氧氯普胺，其後再度出現循環衰竭。檢測病人的血液及腫瘤組織並未發現多發性內分泌瘤病一型的突變，奧曲肽掃描亦未顯示任何殘餘腫瘤。本文討論循環衰竭的病因。這可能是胃泌素瘤病人服食甲氧氯普胺後出現循環衰竭的首個病例。

TABLE. Biochemical results

	Preoperative	Postoperative	Reference range/level
Whole blood serotonin (ng/mL)	428	331	50-200
Serum chromogranin A (ng/mL)	395	77	<160
Fasting serum gastrin (pmol/L)	3651	53	<55
Daily urinary 5-HIAA* excretion (mmol/24h)	30	-	<32

* 5-HIAA denotes 5-hydroxyindole acetic acid

Discussion

Neuroendocrine tumours (NET) account for about 1.25% of all malignancies.[2] Their reported incidence has increased due to increased awareness, the availability of sensitive immunohistochemical markers and better imaging techniques.[3-5] The classical carcinoid presentation with diarrhoea, facial flushing, broncho-pulmonary constriction and right heart failure is uncommon.[2]

After a histological diagnosis of gastrinoma had been made, MRI and an octreotide scan were performed to chart the extent of the malignancy. Three lesion sites were identified: the gastric antrum, the lateral lobe of the liver, and the para-aortic lymph nodes superior to the coeliac artery. His treatment was aimed at symptom control and preparation for surgery. As many as 33% of small gut NET are multiple, the hypothesis being there is a common growth factor or initiating event that influences similar progenitor cells in different locations. About 15 to 25% of NET have a synchronous tumour, or metachronous association with other tumours, eg adenocarcinoma of the colon.[6] This high percentage of synchronous tumours suggests a common growth factor is inducing neoplastic transformation in susceptible cells. Despite being slow-growing tumours, NET are likely to have multiple metastases and the majority of patients with NET present with metastases beyond curative resection.[2,6]

Complete surgical resection is the treatment of choice when it can be performed.[7] Chemotherapy and radiotherapy have been used but have no convincing beneficial results.[5,7] Octreotide, a somatostatin analogue, has been used to control the symptoms but has no effect on the tumour size.[5,7]

There are several ways of classifying carcinoid tumours. They can be classified according to the embryonic origin of the tumour cells, the foregut (stomach, pancreas, and duodenum), midgut (beyond the Treitz ligament of the duodenum to the proximal part of the transverse colon), and the hindgut (the

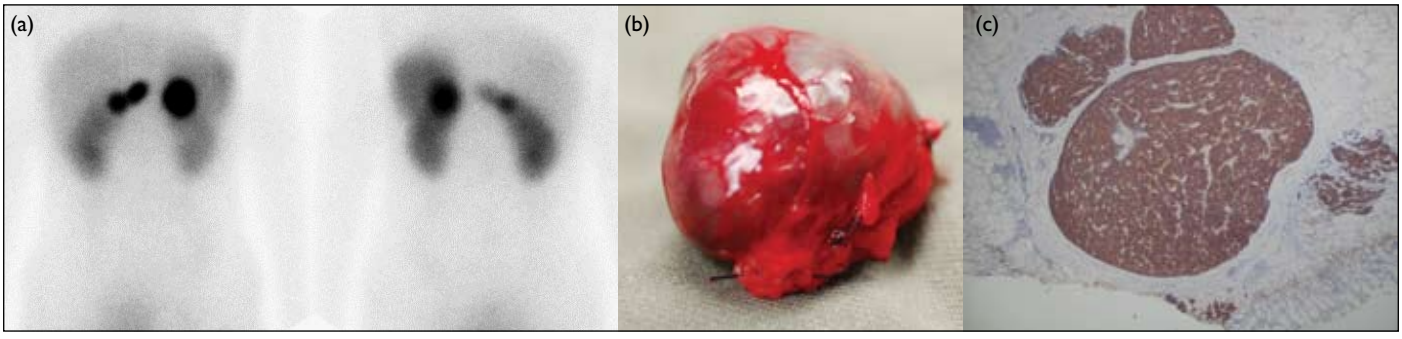

FIG. (a) Octreotide planar images: (left) anterior abdomen and (right) posterior abdomen. Three discrete increased uptake foci were seen in the upper abdomen. The one on the left side was larger in size while the two foci on the right side were lying close together. (b) The resected specimen of the largest nodules at the lesser sac. (c) Tumour cells showing diffuse strong gastrin staining on immunohistochemical study

distal part of the colon and rectum).[8] The World Health Organization has classified NET in accordance with their size, proliferation, localisation, degree of cell differentiation and hormonal production.[9] Neuroendocrine tumours are classified into well-differentiated NET, well-differentiated NET with low-grade malignancy, and poorly differentiated NET with high-grade malignancy.[9] The term carcinoid is not outdated and is synonymous with 'well-differentiated NET'.[5]

In our patient, the challenge was to search for the cause of his circulatory collapse, which was accompanied by several complications. There are a few possibilities. The first is an idiosyncratic reaction with hypotension. The second is an excessive response to serotonin autoinhibition. In the periphery, serotonin (5-HT) is present in both the enterochromaffin cells of the mucosa, which facilitates secretion, and neurons of the myenteric plexus, which facilitates peristalsis. In the central nervous system, serotonin is a neurotransmitter for anger, aggression, mood, appetite, and metabolism. Metoclopramide has both agonistic and antagonistic effects. Apart from being a dopamine D_2 receptor antagonist, metoclopramide is a mixed 5-HT_3 receptor antagonist and 5-HT_4 receptor agonist.[10] Its anti-emetic properties stem from its dopamine D_2 receptor antagonistic action in the chemoreceptor trigger zone. The catastrophic autonomic dysregulation seen in our patient may have been due to excessive serotonin autoinhibition.[11] In one reported case, metoclopramide was administered before the patient developed cardiac arrest.[12] The role of metoclopramide in this death was uncertain because several agents were given. In another report, six patients had transient hypotension for 60 to 90 seconds with no permanent damage.[13] Our patient was administered metoclopramide for its peripheral action. It was after the second episode of hypotension that we suspected metoclopramide might have caused his circulatory collapse.

The third possibility is the gastrinoma itself since shock is a rare presentation for gastrinoma. Our patient developed pain and colic when omeprazole was withheld for hormonal assessment. The onset of circulatory collapse after the metoclopramide injection may have been coincidental. A literature search failed to find any reports of metoclopramide-related circulatory collapse in patients with gastrinomas.

Gastrinomas can occur as either the sporadic form or the multiple endocrine neoplasia type 1 (MEN1)–associated form. The two forms have different management and prognosis. The familial syndrome is reportedly present in 25% of gastrinomas, and *MEN1* gene mutations are found in 31% of sporadic gastrinomas.[14] A mutation analysis was therefore performed to identify any germline mutations in the *MEN1* gene in this patient. Despite the young age of onset and the aggressive behaviour of the tumour, no germline mutation was identified in the *MEN1* gene, making familial MEN1 unlikely although our mutation analysis method did not rule out exonic mutations in promoter or other intronic regions.

Neuroendocrine tumours secrete several hormones, particularly those sited in the midgut.[15] Hormone secretion, such as plasma neurokinin A, has high prognostic value. An increase in neurokinin A deserves further imaging for detecting tumour recurrence.[15] In our patient, who has foregut NET, whole blood serotonin and serum chromogranin A levels returned to lower levels after surgery. Chromogranin A is a hydrophilic glycoprotein and is one of the hormones that can be detected in NET. Blood chromogranin A has high sensitivity (99%) for NET[5] but is not specific and can be detected in other tumours such as small cell lung tumours and prostate tumours. False elevation of chromogranin A has also been seen in chronic renal failure, atrophic gastritis and in patients using proton pump inhibitors.[5] Unfortunately, these markers are not easily available in most clinical laboratories, most of which only provide 5-HIAA as a routine screening test; 5-HIAA is usually normal in patients with foregut and hindgut carcinoids. It is important to use the right biochemical tests, maintain high levels of clinical suspicion and to persevere.

Conclusion

Our patient is probably the first patient with gastrinoma who developed circulatory collapse after metoclopramide injection. Repeated postoperative octreotide scans found no residual lesions. Biomarker assessments and radiological investigations are appropriate investigations for follow-up.

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