Preoperative localization of a gastrin-secreting tumour by total body imaging with $^{111}$ Indium-labelled pentetreotide

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H ALI, A HENDLER, B TAYLOR, S WOLMAN. Preoperative localization of a gastrin-secreting tumour by total body imaging with $^{111}$ Indium-labelled pentetreotide. Can J Gastroenterol 1994;8(3):189-192. A 41-year-old female presented with persistent diarrhea, and was diagnosed with Zollinger-Ellison syndrome when her gastrin level was greater than 3000 ng/L. All modalities for preoperative localization of her gastrinoma were unsuccessful, including trans-abdominal and endoscopic ultrasound, computed tomography, pancreatic angiogram, selective transhepatic portal venous sampling and magnetic resonance imaging. The gastrin-secreting tumour was visualized using the somatostatin analogue pentetreotide labelled with $^{111}$ Indium, combined with gamma camera imaging. A successful resection of the tumour resulted in the normalization of serum gastrin levels 3.5 years after presentation. A discussion of the merits and sensitivities of these tests for preoperative localization of gastrin-secreting tumours will be presented.

Key Words: Gastrinoma, $^{111}$ Indium-pentetreotide, Neuroendocrine tumours, Somatostatin receptor imaging

Localisation pré-opératoire d'une tumeur sécrétrice de gastrine à l'aide de l'imagerie totale au moyen de penta-tréotide marqué à $^{111}$ Indium

RÉSUMÉ : Une femme de 41 ans présentant de la diarrhée persistante a reçu un diagnostic de syndrome de Zollinger-Ellison lorsqu'en tant que patiente s'est révélée supérieur à 3000 ng/L. Toutes les modalités de localisation préopératoire de son gastrinome ont échoué, y compris l'échographie trans-abdominale et endoscopique, la tomodigraphie assistée par ordinateur, l'angiographie pancréatique, le prélèvement d'un échantillon veineux portal transhépatique sélectif et...

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l'imagem par résonance magnétique. La tumeur sécrétrrice de gastrine a été visualisée à l'aide de l'analogue de la somatostatine pentatréotide marqué à 111Indium, combinée avec une imagerie par caméra gamma. Le succès de la résection de la tumeur a entraîné la normalisation des taux de gastrine sérique 3,5 ans après l'apparition du tableau. Une discussion des avantages et des sensibilités de ces épreuves pour la localisation préopératoire des tumeurs sécrétrices de gastrine sera présentée.

Figure 1) Planar nuclear scan image of 111Indium-pentatreo­
tide-labelled gastrinoma 4 h after injection. The gastrinoma is indicated by an arrow.

ance of dairy products provided no relief of symptoms. There was no travel history, fevers or sweats. Despite her illness, the patient's appetite remained good. Physical examination was unremarkable with stable vital signs and no postural changes.

Investigations revealed stool samples were negative for culture, *Clostridium difficile* toxin and white blood cells. Colonoscopy was completely normal to the cecum. Gastroscopy showed a normal esophagus, but moderate to severe gastritis in the antrum and severe duodenitis. The patient was prescribed misopro­

trol 200 µg qid and diphenoxylate. Two months later, she continued to have symptoms and was referred to the authors' centre for further investigation. At referral the patient had experienced a weight loss of 6.8 kg. Further history revealed diarrhea occurred despite a diet of clear fluids or fasting in preparation for endoscopic investigations. Stool volumes were 1.6 to 2.0 L in 24 h collections.

Investigations revealed the following data. Red blood cell folate and vita­

min B12 levels were normal. A bile acid breath test was negative. Iron, ionized calcium, carotene, urine vanillylman­
delic acid and 5-hydroxyindoleacetic acid, prolactin, growth hormone, intact parathyroid hormone and morning cortisol levels were all normal. Calcitonin was less than 8 pmol/L (normal less than 15). The patient's gastrin level, however, was 3150 ng/L (normal less than 90). A diagnosis of Zollinger-Ellison syndrome was made. The patient was treated for symptoms, successfully at first, with omeprazole 20 mg bid; somatostatin 200 µg tid was added when the diarrhea returned, but this did not produce any change in the diarrhea. Later the patient required as much as omeprazole 80 mg bid to control the diarrhea.

Imaging studies were initiated to locate a gastrinoma. Computed tomogra­

phy of abdomen, chest x-ray and ultrasound were performed in duplicate and were read as negative for mass lesions. Repeat gastroscopy (seven months after the first) showed scattered erosive hemorrhagic areas in the stomach and duodenum, with enlarged folds and rugae consistent with a gastrin hypersecretory state. Pancreatic angiogram failed to reveal any tumour. Transhepatic portal venous sampling did not provide meaningful data which could have located a tumour. Magnetic resonance imaging did not show any mass lesions. Repeat gastrin level testing (two years after the first) was 2374 ng/L. Repeat gastroscopy showed normal mucosa except for prominent rugae.

Based on reports in the literature, an attempt was made by the radiopharm­

acy in the authors' hospital to attach a radiiodine label to commercially available octreotide (2,3). This was not successful because of inadequate binding of the radionuclide.

Recently, an indium-labelled somatostatin analogue – 111Indium-penta­

treotide (octreoscan 111, Mallinckrodt) – was made available for investiga­

tional use. A request made by the authors to the Health Protection Branch for emergency release of the compound was granted. The patient was given an intravenous injection of pentetreotide reconstituted with 12.3 mBq 111Indium-chloride.

Both whole body planar (Figure 1) and single photon emission computed tomography (SPECT) images of the ab­

domen (Figure 2) were obtained with an Elscint gamma camera (Haifa, Is­

rael) at 4 h, and planar images alone were obtained at 24 h. The images demonstrated an intense focus of abnormal activity anterior to the lower pole of the kidney, and the abnormality reportedly was located either in the tail of the pancreas or nearby.

Based on the 111Indium-pentatret­

teotide scan, the patient was taken to laparotomy. Intraoperative ultrasound confirmed that the mass was in the small bowel mesentery, not the pancreas. There was no evidence of another primary site. A 3 cm mass was
resected and pathologically confirmed as a gastrinoma. Follow-up gastrin levels, one and two months after surgery, were 80 and 56 ng/L, respectively. The patient is no longer on medications, and is asymptomatic. Her gastrin levels will be followed every three months for the first year.

**DISCUSSION**

Somatostatin inhibits secretion in various neuroendocrine tissues, in addition to its likely role as a neurotransmitter. Tumours from cells naturally containing somatostatin receptors often continue to express varying concentrations of somatostatin receptors, such as pituitary and islet cell tumours. In addition, some tumours not naturally containing somatostatin receptors may also occasionally do so, no doubt as part of malignant transformation. Examples of these are meningiomas and breast carcinomas (4). Somatostatin administered as therapy may relieve symptoms of tumour hypersecretion, and it has been shown to inhibit tumour growth (5,6).

Gastrinomas are often difficult to localize by conventional techniques if they are less than 2 cm in size – unfortunately they often are smaller (7), and only 50% of tumours are found with commonly used imaging procedures (8). Since tumours are difficult to find, and patients are being treated with more potent acid-inhibiting pharmaceutical formulations (H2 blockers, proton pump inhibitors), patients are presenting later with metastatic disease more often than they are with ulcer complications (1). Sixty per cent of gastrinomas are malignant, and metastatic gastrinaoma carries a 20 to 40% five-year survival (1,9,10). Therefore, although symptomatic control has improved, tumour localization for resection before progression to metastatic disease is still vital. The mortality associated with metastases is high and patients often go on to an exploratory laparotomy despite a lack of localizing information provided by conventional investigation. Intraoperative ultrasound combined with palpation improves the sensitivity of finding the tumour (11), yet 40% of gastrinomas are still not found at laparotomy (12,13).

In the past 20 years, a number of imaging techniques have tried to localize gastrinomas preoperatively. Initially abdominal ultrasound and computed tomography were employed, but their sensitivity relates to tumour size. In one study looking at islet cell tumours ranging in size from 0.7 to 2.0 cm, computed tomography visualized seven of 16 tumours, and ultrasound nine of 15. Sensitivity decreased with tumours in the tail of the pancreas (14). In another study, the sensitivity of ultrasound to detect extrahepatic gastrinomas was 20% and that of computed tomography was 45% (15). Magnetic resonance imaging is even less sensitive than ultrasound and computed tomography (15). If the tumour is not localized, pancreatic angiography and transhepatic selective venous sampling have been advocated. More recently, endoscopic ultrasound has shown promise. Its sensitivity exceeds that of angiography. Rosch's study (4) in 1992 showed that 82% of pancreatic neuroendocrine tumours not found by conventional ultrasound and computed tomography were localized by endoscopic ultrasound. Angiography can localize tumours 30 to 40% of the time (1,8). Transhepatic venous sampling has a 70 to 90% sensitivity, but only for tumours in the duodenum or pancreas (16). Furthermore, the correlation between hormone gradient and tumour localization, eg, head versus tail of pancreas, has a sensitivity of 35%.

The 111Indium-pentetreotide scan has the potential of a noninvasive method to localize tumours and provides the advantage of picking up metastatic disease in tumours containing somatostatin receptors (2,3). It appears that growth hormone pituitary adenomas, meningiomas, carcinoid tumours, gastrinomas, and some cases of breast carcinomas and insulinomas are most likely to contain somatostatin receptors (2,4). Of these, gastrinomas can be extrapancreatic 30 to 40% of the time (8,13,17). Duodenal and gastric sites may be visualized by experienced endoscopists with ultrasound. However, peripancreatic and periduodenal lymph nodes may be more difficult to locate.

**CONCLUSIONS**

Since the expertise for this procedure is not yet readily available, the 111Indium-pentetreotide scan combines the advantages of localizing tumours far from the endoscopist's and angiographer's view with an easily administered and noninvasive test in a nuclear medicine facility. In Lamberts' study (3), seven of nine pancreatic endocrine tumours were visualized. Larger studies are needed to evaluate sensitivity and specificity for this procedure. Nevertheless, because it is noninvasive and can scan the whole body, this technique provides significant advantages over other investigative methods. We conclude that 111Indium-pentetreotide imaging should be considered for gastrinomas (or any tumour expressing soma-
tostatin receptors) as the localization study to follow an unhelpful ultrasound and computed tomography scan.

REFERENCES