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Gastroenteropancreatic Neuroendocrine Tumour Presenting as Complete Large Bowel Obstruction: Literature Review Seizing upon a Case

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Abstract

Aim-Background: To review the rare entity of gastroenteropancreatic neuroendocrine tumours (GEP NETs) and to present multimodality therapeutic approaches for liver metastases in this group of patients.

Case Report: We describe the case of a 57-year-old gentleman who presented at the Emergency Department with symptoms of complete large bowel obstruction due to a splenic flexure tumour. The patient underwent tumour extirpation by an extended left hemicolectomy with end colostomy (transverse colon), while multiple liver metastases (both lobes) were also palpated. His postoperative course was without any major complications and he was referred to a tertiary centre for further evaluation and treatment. Histology of the specimen was remarkable for low grade large bowel neuroendocrine carcinoma (G3 WHO 2010) pT3, N2b (TNM 2009).

Results: Small NETs can be managed with local resection but larger tumours require formal resection of the involved organ with its adjacent lymph nodes, staging of the disease and planning of further treatment. Octreoscan identifies the need for adjuvant therapy with somatostatin analogues. Hepatectomy, with or without preoperative contralateral of the affected lobe portal vein embolisation, is performed on patients with metastases isolated to one lobe, while orthotopic liver transplantation is reserved for patients meeting standard criteria.

Conclusions: The rarity of GEP-NETs along with the variations in their presenting symptoms is a challenging diagnosis for the attending physician. Surgical therapy remains the cornerstone of treatment, while numerous adjuncts (RFA, PRRT, SIRT, TACE) serve in the multimodality approach for patients with unresectable liver metastases.

Key words: *Gastroenteropancreatic neuroendocrine tumour (GEP-NET); large bowel ileus; liver metastases; chromogranin A; somatostatin receptors; Ki67 index*

Introduction

Neuroendocrine tumours (NETs) arise from the chromaffin cells and their precursor's polypotent stem cells of the neural crest [1]. Stem cells normally differentiate to chromaffins or other cells of endodermal origin, scattered throughout the human body tissues (Figure 1). The differentiation process is through the Notch intercellular signalling pathway [2], which is mainly responsible for the intercellular recognition, binding and organization to tissues (Figure 2).

Chromaffins share common features: i) the production of biogenic amines from decarboxylation of amine precursors by a cell specialized rate-limiting enzyme (e.g. noradrenaline from dopamine in the adrenal medulla), and ii) peptide hormones biosynthesis (e.g. calcitonin in thyroid C- cells). These products are stored in specific cytoplasmic granules (stained in microscopy with chromium salts for catecholamines) and secreted after neural stimulation. [3]. They can be found as single units (e.g. in bronchial epithelium) or in clusters, such as adrenal medulla or the preaortic organ of Zuckerkandl.

The great variation in these tumours, regarding their location, product secretion, target organ and the biological function they exert, renders the NET family a unique category with a large constellation of signs and symptoms (or none in inactive tumours) at clinical presentation.

The term "carcinoid" refers to those tumours that derive from the enterochromaffin (Kultchinsky) cells and interpose in the submucosa of the gastrointestinal (GI) tract (Figure 3). These cells synthesize, store and secrete serotonin from

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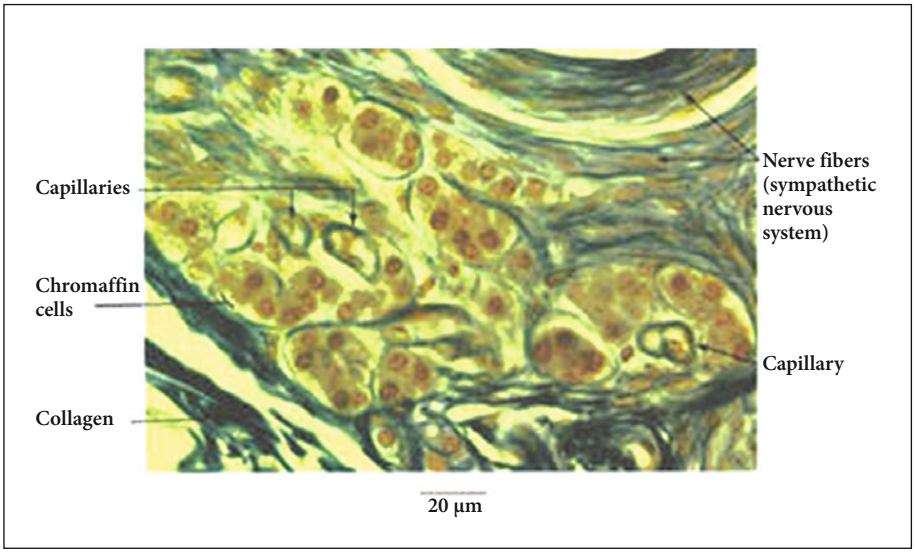

Figure 1. The chromaffin cell

tryptophan through the tryptophane hydroxylase -1 (TPH-1) enzyme [4]. First described by Lubarsh in 1888 [5], the terminology has now expanded to "GEP-NETs" in order to include all endocrine tumours of the GI track and its major glands (e.g. islet cell tumours)

Epidemiology:[6] The incidence of GEP-NETs is estimated to be 2-6 per 100.000 people per year, while their prevalence is about 35 per 100.000. The most common site of primary GEP-NET is the small intestine (28%), followed by the appendix (20%), pancreas (16%), rectum (15%), colon (13%) and stomach (9%). Metastases from the small intestine are commonest (45%), followed by the pancreas (42%), colon (40%), stomach (15%), rectum (6%) and appendix (3%). They tend to appear most frequently after the fifth decade.

Case report: A 57-year-old gentleman presented at the Emergency Department with a two-day history of soft abdominal distention, gas & faecal retention, and faecal stained vomiting. On repeated questions, he denied any recent change in bowel habits or signs of blood-mixed stools. His past medical history was remarkable for elective surgical repair for umbilical and right inguinal hernia performed a year earlier. He used to smoke heavily (30 pack/years), but did not consume alcohol on a daily basis. He did not report any drug abuse, known hypersensitivity reactions, allergies or exposure to toxic agents.

On admission, his vital signs included a temperature of 36.7 ^{0}C, blood pressure 104/59 mm Hg, heart rate 115/min, and respirations 27/min. The rest of the physical examination noted a gigantic but not overweight patient

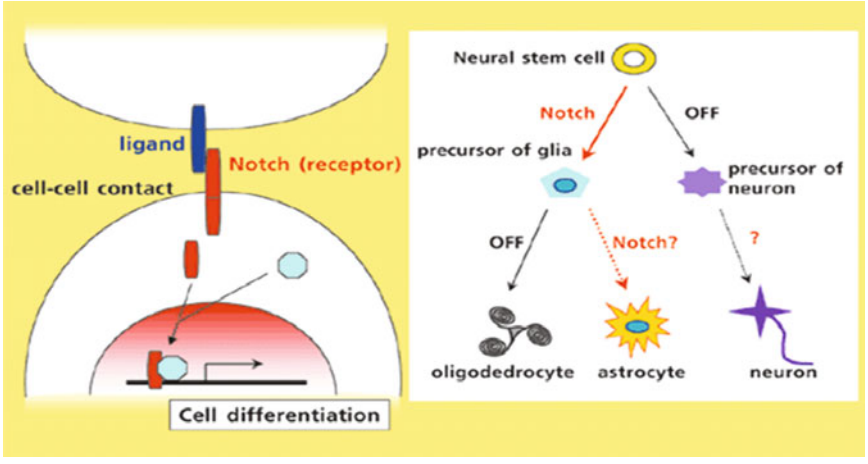

Figure 2. The Notch receptor protein

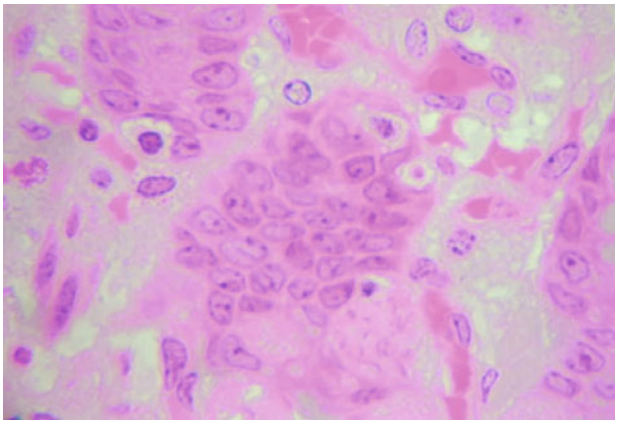

Figure 3. The Kultchinsky cell

with mild respiratory distress. His abdomen was distended with high pitched bowel sounds, without peritoneal signs on palpation at all quadrants. Heart and lung examination was unremarkable and no palpable lymph nodes or other gross pathology from the head, neck, limbs and genitalia was noticed. Rectal digital examination revealed an empty ampulla, no mass was palpated and there were no signs of a haemorrhage.

Preoperative imaging:

i) Plain X-rays of the thorax and abdomen showed large and small bowel ileus, an absence of subdiaphragmatic free air, normal cardiothoracic index and increased lung resonance, suggestive of COPD.

ii) Abdominal ultrasonography (U/S) revealed a normal-sized liver with increased echogenicity, probably due to "fatty liver", with more than nine hypoechogenic lesions of various sizes, suggesting metastases at both lobes. No intraperitoneal fluid was observed. The gallbladder, common bile duct, spleen, pancreas, kidneys and urinary bladder appeared normal. The prostate gland was slightly increased in size and of normal shape with benign hypertrophy.

iii) Computed tomography (CT) of the abdomen after per os and IV contrast disclosed obstructive large bowel ileus, due to a splenic flexure mass with concomitant enlarged mesenteric lymph nodes. Other findings were consistent with those shown by U/S.

CT of the lungs revealed emphysematic hypostroma with apex fibrosis. No metastasis was detected by CT of the brain.

Laboratory investigation: Leukocyte count 8.730/ μl (neutrophils -82%), Hct:44.1%, platelets 473.000/ μl, glucose 129 mg/dl, urea 21.8 mg/dl, creatinine 0.8 mg/dl, Na^+ 132 mmol/l, K^+ 4.0 mmol/l, AST 25 IU/l, ALT 23 IU/l, alkaline phosphate 85 IU/l, γGT 73 IU/l, bilirubin 0.4 mg/dl, amylase 55 IU/l, LDH 234 IU/l, and C-reactive protein 28.23; clotting factors and urinalysis were unremarkable. Arterial blood gas measurements were pH:7.45, pO2:56.2, pCO2: 32.1 Sat O2 90.3%, HCO3: 22.1

Medical intervention: Treatment was commenced with the placement of a nasogastric tube for gastric-bowel decompression, which produced approximately 3,500 ml of faecal stained liquid output. A central right subclavian vein and a urinary (14 Fr) Foley catheter was inserted. Intravenous (IV) repletion of fluid and electrolyte losses was guided by the measurement of central vein pressure (CVP), hourly urinary output and repeated blood analyses. Exploratory laparotomy was performed by a supra/infraumbilical incision with palliative intent. Complete extirpation of the large bowel tumour was accomplished by an extended left hemicolectomy with end colostomy (transverse colon) and closure of the peripheral stump in two layers. Metastases at both liver lobes was confirmed by palpation. The operation was completed by draining the left paracolic gutter and midline closure in two layers.

Postoperatively, the patient received IV peripheral parenteral nutrition for three days, fluids with electrolytes, antibiotics, proton pumps inhibitors, analgesia and subcutaneous low molecular weight heparin (prophylactic dose). The diet progressed from clear liquids to solids after colostomy function. Intense respiratory physiotherapy and early mobilization was also instituted. His course was complicated by surgical wound infection which was managed by opening and draining the purulent material, administering oral antibiotics based on the culture antibiogram, and reapproximation of the wound edges one week later by local anaesthesia. An urgent hypertensive crisis was successfully treated with IV clonidin, followed by oral calcium channel blockers.

Histology: A large bowel specimen revealed an undifferentiated neuroendocrine carcinoma (NET G3) according to WHO classification (2010), stage pT3, N2b according to TNM (2009). The specimen measured 32.5 cm length. At a distance of 13.5 cm from the one surgical limit, a white neoplasmatic tumour measuring 5.6 x 4.8 x 3.8 cm was seen obstructing the lumen and extending into the mesenterial adipose tissue. Fifteen lymph nodes ranging from 0.3-1.1 cm diameter were also included in the specimen.

Microscopy: A NET tumour with solid growth pattern and medium to sufficient degree of nuclear atypia. Tumour depth invasion reached the entire intestinal wall thickness up to <0.5 mm from the serosal surface. Vascular tumour emboli, nodules in the mesenterial tissue and >20 mitosis /10 HPF were observed. Ten of the 15 lymph nodes were metastatic infiltrates. Immunohistochemistry was positive for chromogranin A, CD 56 and synaptophysin. Ki 67 index

was > 50%. Surgical limits were free of tumour infiltration.

More specific blood analyses were then taken; somatostatin, chromogranin A, synaptophysin and neuron-specific enolase (NSE) levels had returned to normal. The absence of carcinoid syndrome (flushing, diarrhoea, bronchoconstriction, right-sided heat failure), notwithstanding liver metastases, led to the conclusion of an endocrine-inactive undifferentiated tumour.

Adjuvant chemotherapy: Three cycles of IV chemotherapy with cisplatin & etoposide were given. Imaging was repeated after completion of the regimens. An increase in liver metastases (>10) was noticed, the largest one (>10.5 cm diameter) being in the II lobe. The intrapancreatic part of common bile duct was found dilated (>1.2 cm). No ascitic fluid or peritoneal implantations were observed.

A radionuclide scan for somatostatin receptor (Octreoscan) was performed with IV111 MBq 30mCi and 99m Tc-Tektrotyde, which was found to be negative for uptake, and thus for somatostatin (sst2) receptors on the tumour cell surface. Given this finding, no somatostatin analogues were added to the overall treatment. The chemotherapeutic regimen hence progressed to vincristine-adriamycin- cyclophosphamide (VAC), but was discontinued early, due to patient intolerance and liver dysfunction.

Discussion

Diagnosis: GEP-NETs are diagnosed through a high index of clinical suspicion according to the patient's signs and symptoms, and neuroendocrine markers (NM).[7] Functional NETs lead to blood (or urine) detection of elevated NM, general or specific to each tumour. Chromogranin A (CgA), neuron-specific enolase (NSE), synaptophysin, 5-OH indoloacetic acid (5-HIIA), pancreatic polypeptide (PP), a-subunits of human chorionic gonadotropin (a-HCG) or the releasing hormone specific to each tumour (e.g. gastrin, insulin, somatostatin, VIP, etc) may be found elevated in such patients. Diagnosis can also be facilitated by imaging: newer technology CT or MRI protocols combined with angiography can detect even small tumours and metastases, while U/S is useful only for liver metastases. GI endoscopy combined with endoscopic U/S is helpful in the localization of small tumours. Somatostatin receptor scintigraphy (Octreoscan) [8] remains the gold standard for the diagnosis of active NETs (with the exception of insulinom).

Staging: Patients are staged according to the TNM classification system, which for GEP-NETs depends on the primary organ of origin. According to the European Neuroendocrine Tumour Society, staging is different for NETs originating from stomach, duodenum-ampulla-proximal jejunum, pancreas, lower jejunum-ileum and colon-rectum [9]. As concerns our case, TNM classification is as follows:

T	Primary tumour
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Tumour invades mucosa or submucosa T1a size < 1cm T1b size 1-2 cm
T2	Tumour invades muscularis propria or > 2cm size
T3	Tumour invades subserosa, pericolic, perirectal fat
T4	Tumour directly invades other organs/structures and/or perforates visceral peritoneum. For any T add (m) for multiple tumours
N	Regional lymph nodes
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
M	Distant metastasis
Mx	Distant metastasis cannot be assessed
Mo	No distant metastases
M1	Distant metastasis

Classification of GEP-NETs according to their i) localization, ii) biological behaviour, iii) hormone secretion and related symptoms/signs [10]

i)

GEP-NET	Localization	Classification
Foregut	Gastric NET	Type I (associated with chronic atrophic gastritis Type II (associated with MEN-1 syndrome) Type III (sporadic)
	Duodenal NET	a) Sporadic or associated with MEN-1 syndrome b) secretory (gastrinoma-somatostatinoma) or non-secretory
	Pancreatic NET	a)Sporadic or associated with MEN-1 syndrome b) secretory (gastrinoma –insulinoma,VIPoma, PPoma, glucagonoma, somatostatinoma, CRHoma,calcitoninoma, GHRHoma, ACTHoma, neurotensinoma, GRFoma, parathyroidoma) or non-secretory tumour
Midgut (fromTreitz ligament until left colonic flexure)	NET of jejunum, ileum, vermiform appendix, ascendic colon, transverse colon (up to splenic flexure)	Secretory (carcinoid syndrome) or non-secretory tumour

Hindgut (distally from left colonic flexure)	NET of transverse colon(distally of splenic flexure), descendic colon, sigmoid, Rectum	Non-secretory tumour

ii)

Biological behaviour	Differentiation grade	Tumour size	Ki-67 Index	Vascular invasion	Metastasis
Benign	High	< 1cm*	<2%	-	-
Benign or low malignant	High	< 2 cm	<2%	-/+	-
Low malignant	High	>2cm	>2%	+	+
High malignant	Low	Any	>30%	+	+

**Exception: the malignant duodenal Gastrinoma, usually <1 cm, limited in the submucosa*

iii)

Hormone/ Neurotransmitter	Tumour	Symptom/ Syndrome
Foregut (Stomach-Pancreas-Duodenum)		
Insulin	Insulinom	Fasting Hypoglycaemia
Gastrin	Gastrinom	Peptic Ulcer / Diarrhoea
Glucagon	Glucagonom	Diabetes mellitus, Exanthem
Somatostatin	Somatostatinom	Diabetes mellitus, Gallstones
VIP	VIPom	Watery diarrhoea
Midgut (Jejunum, Ileus, ascending colon)		
Serotonin, Neurotensin B	Function (with liver metastases)	Carcinoid syndrome
Foregut (Transverse-descending – sigmoid colon, Rectum)		
Chromogranin A*	Non-functional	Asymptomatic

**Chromogranin A is a universal tumour marker for NETs that can also serve as a tumour marker in non-functional tumours. Exceptions are rapidly proliferating undifferentiated NET Carcinomas*

Treatment: Only surgical intervention may offer cure or satisfactory long term palliation. Small tumours (<1 cm) can be managed with local resection (endoscopy or surgery). Larger tumours will require a type of formal resection of the involved organ with its regional lymph nodes (e.g. right colectomy for appendix carcinoids, partial gastrectomy for gastric carcinoid etc) [11].

Carcinoid crisis: [12] The carcinoid crisis may be the presenting symptom in undiagnosed secretory tumours and is due to a massive release of bioactive amines (serotonin). Symptoms range from mild to severe which consist of intense facial redness (flushing), accompanied by brochoconstriction, tachycardia and angioedema. Right-sided heart failure results from chronic exposure of the tricuspid valve to hormones secreting directly from liver metastasis into the hepatic veins. Treatment is directed towards general supportive measures and IV bolus administration of 100-500 μg octreotide (repeated after 5 minutes if necessary), 10 mg of mileinic chlorpheniramine (TPH-1 inhibitor), 200mg of hydrocortisone and H2 histaminic receptor blockers.

Management of neuroendocrine liver metastases (NLM)

Systemic chemotherapy of NLM usually has poor results, especially in the case of carcinoid tumours, due to cancer stem cell subpopulation in the tumour mass. [13] Surgical resection with Ro intent offers the only chance for potential cure. This can be accomplished with liver resection or liver transplantation providing a number of criteria are met. If radical resection is not feasible, cytoreductive surgery combined with tumour destructive techniques is preferred (multimodality therapy). Radiofrequency ablation (RFA), transarterial hepatic artery chemoembolization (TACE), selective portal vein ligation or preoperative embolizations, selective internal radiotherapy (SIRT) and peptide receptor radionuclide therapy (PRRT) all belong to the modern armamentarium.

Molecular genetics: [14] The biological behaviour of the primary tumour and metastasis is strongly considered before any decision for aggressive treatment is undertaken. In colorectal NETs, the intracellular product of the tumour suppressor gene ATM was found to be inversely correlated with Ki-67 protein, a nuclear protein implicated in ribosomal RNA transcription that serves to determine the growth potential of a specific cellular population. For metastatic NETs, Ki-67 index from both the primary tumour and one liver metastasis is determined to assess tumour behavior. Patients with low Ki-67(<2%) carry a high likelihood of a 5-year survival. Recently, a trial involving 51-genes was conducted for a more accurate prediction of tumour metastatic potential; however, further research is warranted.

Hepatectomy: [15] Imaging estimation of future liver remnant (FLR) is necessary to avoid postoperative liver

failure. Standard hepatectomies should accomplish tumour negative margins (Ro) and FLR equal to or above 25-30%. Suitable candidates are patients with grade I-II tumours and no extra hepatic disease on preoperative workup. Low differentiated (grade III) tumours represent a contraindication to hepatectomy, due to high recurrence rates.

Portal vein ligation (PVL) or embolisation (PVE). [16] Indicated in patients scheduled to undergo a lobectomy (commonly right) for anticipated Ro excision, but with an FLR estimated insufficient to preserve liver function postoperatively. PVL is performed in theatre at first operation; PVE can be done pre-or postoperatively depending on the patient's overall status. When performed on the side of anticipated lobe resection, the bloodstream that redirects towards FLR causes hyperplasia and an increase in volume. This technique is applied under local anaesthesia with sedation and results in contralateral lobe hypertrophy within approximately one month.

Orthotopic liver transplantation (OLP): [17] Patient eligibility for OLP for neuroendocrine tumour metastases varies among centres. The standard Milan criteria of HCC tumours are expanded by Mazaffero et al. for NET tumours: age<60 years old, complete removal of primary tumour in the GI track (except the lower rectum), absence of extrahepatic metastases (apart of perihilar lymph nodes), absence of severe carcinoid heart disease Ki-67 index <20% and stable disease six months prior to transplant are all prerequisites. Grade III tumours also represent a contraindication to OLP.

Palliative therapies: The following techniques are reserved for patients with unresectable liver metastases, no extrahepatic metastatic foci and non-end stage liver disease.

i) **RFA** [18] is performed either in theatre or percutaneously (U/S guided). After insertion of the probes, the tumour is destroyed by heating using a high frequency alternating current. Reports of tumour seeding after probe removal restricts RFA mostly to small (<1cm), peripheral multiple liver tumours or patients not physically suitable to undergo major resections.

ii) **Angiographic intra-arterial liver targeted therapies** [19] are given through catheterization of the hepatic artery (percutaneous or surgical implanted port: a) the TACE technique consists of delivering a mixture of chemotherapeutic agents directly to the liver metastasis and then permanently occluding the tumour feeding vessel; b) SIRT consists of delivering a high localized dose of radiation to metastases through permanently implanted radiolabelled microspheres (Yttrium -90 microspheres).

iii) **PRRT**: [20] This nuclear medicine technique holds promise for tumours expressing endocrine receptors (such as sst-2). Somatostatin analogues (octreotide) labelled with Yttrium or Lutetium are administrated IV; they bind and destroy tumour cells by emitting radiation. PRRT can be used for differentiated tumours and extrahepatic metastases.

Conclusions: The great heterogeneity and rarity of GEP-NETs can be misleading, making it difficult to achieve a correct diagnosis when first confronting the patient. Surgical therapy remains the mainstay of treatment, while numerous adjuncts serve in the multimodality approach of long term survival. Research is directed towards targeting specific intercellular and nuclear pathways involved in oncogenesis.

Ethical Approval - Informed Consent

The authors declare that the study has been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Written informed consent from the patient prior to his inclusion in the study.

Conflict of interest

The authors declare that they have no conflict of interest.

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