International Journal of Biomedical and Advance Research
ISSN: 2229-3809 (Online); 2455-0558 (Print)
Journal DOI: 10.7439/ijbar
CODEN: IJBABN
Case Report

Gastrointestinal carcinoids: A case report and review of literature

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Abstract

The gastrointestinal tract is the largest neuroendocrine system in the body. Carcinoid tumours are the commonest neuroendocrine tumours that arise from enterochromaffin cells throughout the gut. These tumours secrete bioactive substances producing characteristic immunohistochemical and clinical patterns. With the incidence and prevalence of carcinoid tumours rising, we present 2 cases of carcinoid tumours of the gastro intestinal tract.

Keywords: Quality Control rules, internal quality control

1. Introduction

Carcinoid tumours are the commonest neuroendocrine tumours that arise from enterochromaffin cells throughout the gut. These tumours secrete bioactive substances producing characteristic immunohistochemical and clinical patterns.

2. Case Reports

2.1 Case1

A 62 year old male came with complaints of Vomiting after every feed, burning sensations in lower chest since 1 month. He has history of loose motions 2-3 times / day with Loss of weight, and malena, General examination was unremarkable except for raised blood pressure. Per Abdominal findings were normal. Blood Investigations were essentially normal. Patient had done an endoscopic ultrasound which was reported as Duodenal GIST (Gastrointestinal Stromal Tumour).

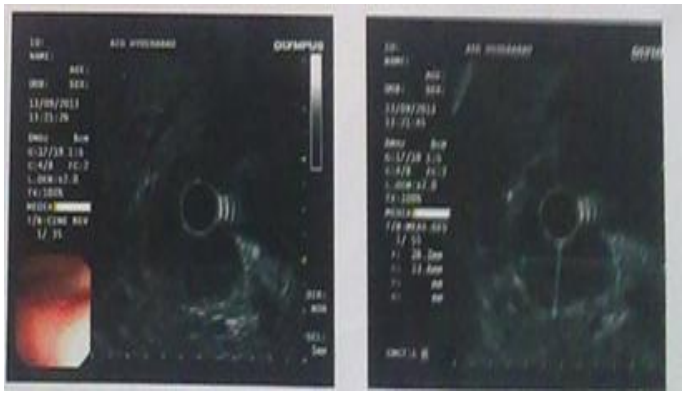

Figure 1: Endoscopic Ultrasound

A CT Scan was performed which reported A well-defined isodense enhancing Space occupying lesion along the medial wall of gastro duodenal junction projecting into the lumen of approx. 3x2 cm in size with no periportal or perigastric nodes. The hyper vascularity suggested possibility of GI stromal & neuroendocrine tumor.

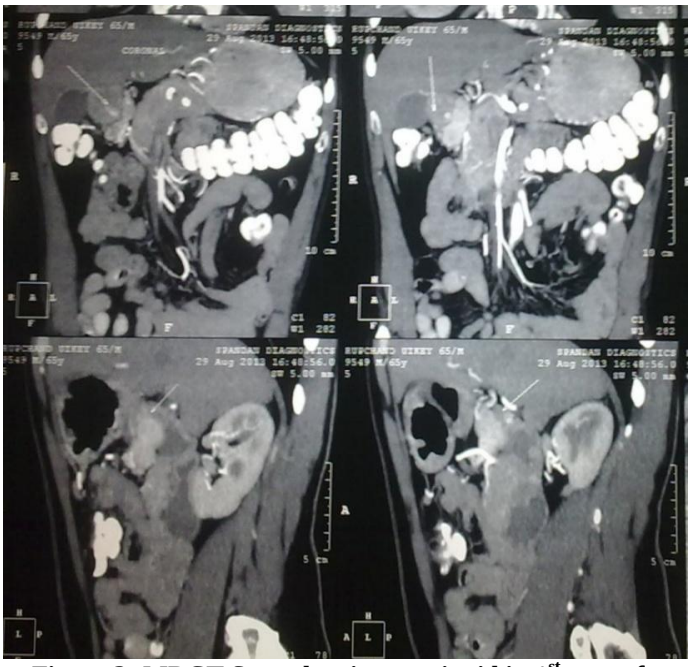

Figure 2: MDCT Scan showing carcinoid in 1st part of duodenum

Operation- Distal gastrectomy with Billroth II Anastomosis

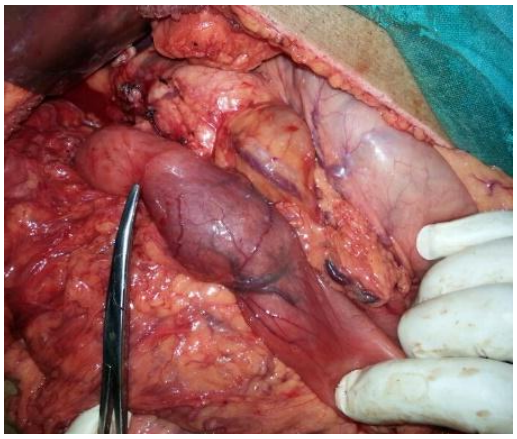

Figure 3: Intraoperative picture showing tumor in first part of duodenum

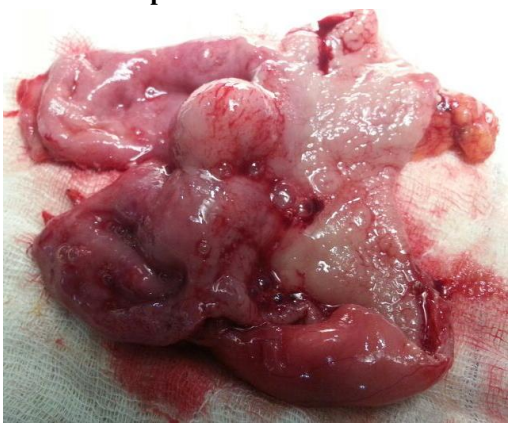

Figure 4: Resected specimen showing tumour

Patient was discharged after 10 days

Histopathological Reports had Cells having round nucleus with salt and pepper chromatin, eosinophylic cytoplasm, minimal mitosis, no necrosis seen. Surgical margins free from tumor invasion suggestive of Carcinoid Tumour-Duodenum.

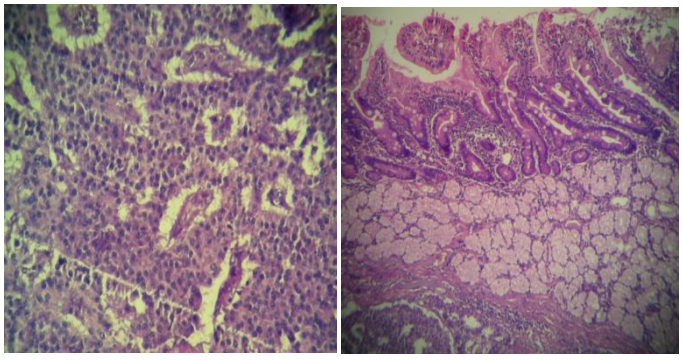

Figure 5: Histopathological Reports

2.2 Case 2

A 50 years old gentleman came with complaints of Pain in upper part of abdomen- 1 year, with history of vomiting abdominal distention on and off. His examination was normal. Per abdominaly he had normal findings with no pathology on per Rectal Examination

Patient was investigated outside with repots as Dudenitis on Upper G.I. scopy and his ultrasound was within normal limits. We had his X-Ray Abdomen which showed few air fluid levels, and an ultrasonography suggestive of subacute intestinal obstruction. We then did a CT scan showing concentric wall thickening forming a mass in mid-ileum.

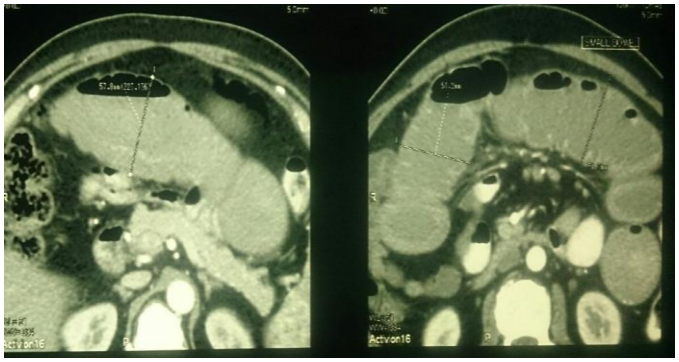

Figure 6: CT scan showing concentric wall thickening forming a mass in mid-ileum

We did a diagnostic laparoscopy which was converted to laparotomy with resection anastomosis. On Laparoscopy there was stricture in mid-ileal segment with proximal loop dilatation & collapsed distal loop. There were multiple enlarged mesenteric lymphadenopathies.

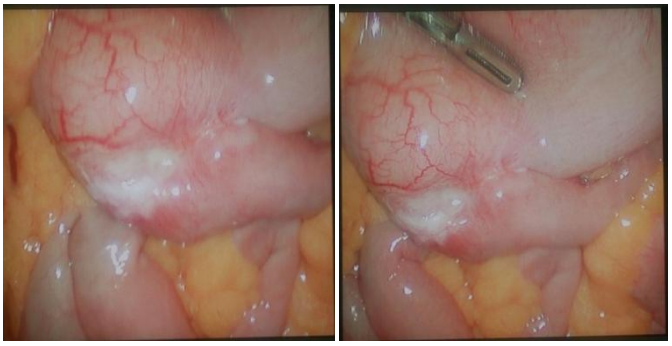

Figure 7: Diagnostic laparoscopy

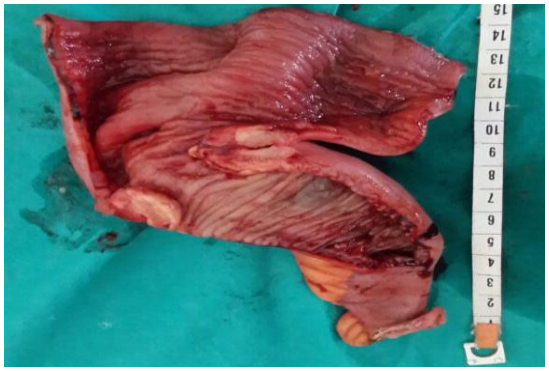

Figure 8: Resected specimen showing stricture and proximal dilation and distal collapse

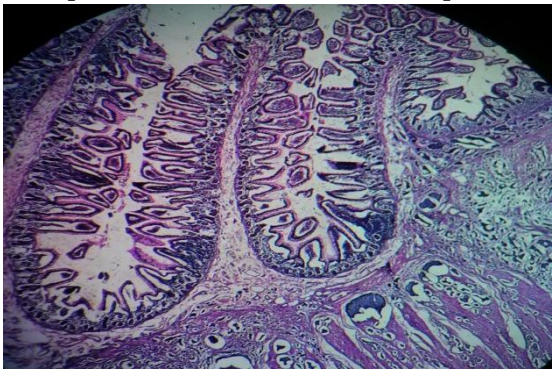

Figure 9: Histopathological examination: Multiple neuroendocrine cells ssuggesting the diagnosis of carcinoid tumor of small intestine.

3. Review of literature

Carcinoid *tumour* is a slow-growing type of neuroendocrine tumour originating in the cells of the neuroendocrine system. Another term used for these endocrine tumours is apudomas (amine precursor uptake and decarboxylation). They are most commonly found in the midgut at the level of the ileum or in the appendix. The next most common affected area is the respiratory tract [1].

The first histological description of what later became known as a carcinoid tumor was made in 1867 by Theodor Langhans. In 1888, Otto Lubarsch described similar findings in autopsy in two patients with ileal tumors. William Ransom described the first case of what is now known as carcinoid syndrome [2] in a 50-year-old woman with severe diarrhoea and attacks of wheezing. *Siegfried oberndorfer coined the term karzinoid (carcinoid means carcinoma like) in 1907 during the presentation at the german pathological society. In 1914, Gosset and Masson suggested that carcinoid tumours might arise in the Kulchitsky Cells in the glands of Liberkuhn* [1-3].

The clinical incidence of neuroendocrine tumours ranges from about 1.3 to 5.25 per 100,000.[4] Multiple studies have documented a significantly increasing incidence of neuroendocrine tumours over the past several decades. The increase is probably more because of the improvements in clinical awareness of the disease, the improvement in diagnostic and imaging technology [4-5]. Of all GI tract neuro-endocrine tumours, 38% are of small bowel origin. Carcinoid tumours are often considered quite rare; they are actually the second most prevalent gastrointestinal cancer, behind colorectal cancer. Of all small bowel carcinoid, at least 50% are located in the ileum.Duodenal carcinoids are extremely rare. The organ displaying maximum potential for malignancy is the pancreas.[5] A characteristic feature of neuroendocrine cells is the production of a wide variety of biogenic amines, peptides, tachykinins, and prostaglandinsSmall intestinal neuro-endocrine tumours are most commonly serotonine producing tumours [6-7-8].The wide varieties of substances produced by these tumors give variable clinical features. Patients with solitary tumors have a less aggressive nature compared with multiple tumors.

Table 1: Substances produced by Carcinoids

-Acid phosphatase	Kallikrein	Chromogranin A and B (CgA/CgB)
-α-glycoprotein	Histamine	Fibroblast growth factor (FGF)
-Amylin	Pancreastatin	Gastrin-releasing peptide (bombesin)
-α1-antitrypsin	Serotonin	Hydroxyindoleacetic acid (5-HIAA)
-Catecholamines	Substance P	Atrial natriuretic polypeptide
-A-Neuropeptide	Prostaglandins	5-Hydroxytryptamine (5-HT)
-Insulin	Secretin	Neuron-specific enolase (NSE)
-Motilin	Somatostatin	Platelet-dermal growth factor (PDGF)
-Neurotensin	Tachykinins	β-transforming growth factor (β-TGF)
-Calbindin-D28k	Glucagon/glicentin	Somatotropin release-inhibiting factor (SRIF)
-Dopamine	Gastrin	Pyroglutamyl-glutamyl-prolinamide
-Pancreatic polypeptide	-Insulin like factor	Vasoactive intestinal polypeptide (VIP)

The risk factor shown most significantly associated with development of a neuroendocrine tumor is the parental history of a carcinoid tumor in the small bowel.[8] There is an increase in the incidence of carcinoid tumors in the offspring of parents with cancers of the brain, breast, liver, endocrine system, and urinary tract. Some genetic disorders that are strongly associated with the development of pancreatic neuroendocrine tumors: Multiple endocrine neoplasia type 1 (MEN 1) about 65% of cases, Gastric carcinoids (7%), (Gastrinoma and Insulinoma), Von Hippel-Lindau (VHL) syndrome (15%), Von Recklinghausen syndrome (10%), Tuberous sclerosis. [9-12]

They can present with the symptoms most commonly being vague abdominal pain, bloating, diarrhea, weight loss, intermittent bowel obstruction.

Because of their vague symptoms, small bowel carcinoid often present in the metastatic state.

In neuro-endocrine tumours the laboratory evaluation should be undertaken, in that both *urinary* 5-*HIAA and serum chromogrannin* are particularly useful for midgut tumors. In terms of imaging studies, Cross sectional abdominal imaging, Octreotide scanning are done.[13]

Chromogranin is most useful circulating marker for carcinoid tumours and PNET. It is elevated in 60% to 100% cases of NET. Sensitivity (68%) and specificity (86%) of Chromogranin A (CgA) for the detection of NET. Levels of CgA are measured in the serum correlates with tumour burden.[12] False-positive tests can occur in patients with renal or hepatic impairment. High levels of CgA are predictor of poor prognosis [14].

5-Hydroxyindolacetic Acid urinary 5-HIAA, a metabolite of serotonin, is the principal laboratory test for the measurement of serotonin overproduction by carcinoid tumours. Normal value: 2 – 8 mg/24 hour has a sensitivity of 64% and a specificity of 98% for carcinoid tumours. The consumption of serotonin-rich foods (bananas, pineapples, or nuts) may alter urinary 5-HIAA levels, resulting in false positives. These foods should be avoided during the 5-HIAA specimen collection. [14-15]

Carcinoid tumors are particularly vascular, CT imaging with both arterial and portal phase imaging is helpful

in differentiating the tumor from surrounding tissues.NET are vascular tumours that enhance intensely with intravenous contrast during the early arterial phase of imaging and washout during the portal venous phase. The octreotide scanning is very useful for disease staging. [16-17]

Capsule endoscopy can be used only with caution given that in patients with small bowel narrowing and luminal disease from carcinoid, it may lead to obstruction.[17]

Endoscopic Ultrasound (EUS) Carcinoid tumours of the stomach can be imaged using EUS or endoscopy. It can detect whether larger gastric carcinoid tumours are invasive lesions. It detects 45% to 60% of duodenal lesions, and 90% to 100% of pancreatic lesions.EUS with fine-needle aspiration can also differentiate a non-functional PNET from an adenocarcinoma. [18-19]

Somatostatin receptor scintigraphy (SRS): It is the primary imaging modality for localization of primary and metastatic NET. It uses 111In–diethylenetriaminepentaacidic acid (DTPA)-labelled octreotide in order to locate small tumors that overexpress somatostatin receptors (particularly subtypes 2 and 5).[20] SRS is the most sensitive modality for identification of hepatic metastases.[21]

3.1 Positron Emission Tomography (PET) with Fluorodeoxyglucose (FDG)

Detects poorly differentiated or undifferentiated NET such as bronchus and thymus small-cell-like lesions, and highly aggressive NET. Single photon emission computed tomography (SPECT) and PET-CT permit the correlation of NET location with clinical function. PET imaging with radioisotope ^{131}I-metaiodobenzylguanidine (I-MIBG) detects carcinoid tumours in the jejunum, ileum, caecum, and appendix (midgut).[21]

3.2 Angiography

MRI angiography has replaced angiography. It demonstrates the degree of tumour vascularity, identify the sources of vascular supply, delineate the relationship of the tumour to adjacent major vascular structures, provide information regarding vascular invasion. Angiography may be useful as an adjunct to surgery, particularly in the case of large invasive lesions in proximity to the portal vein and superior mesenteric artery. Angiography provides a more precise topographic delineation of the tumour or tumour-related vessels and facilitates resection.[19-21]

4. Treatment

The curative therapy for GI carcinoids, is resection of the primary tumour and local lymph nodes.[22]Endoscopic surgery may be suitable for some tumours depending on the location, number, size, and degree of malignancy. Resection of non hepatic tumour primaries is associated with increased median survival. The extent of resection depends on the site of origin of a given tumour, the involvement of surrounding structures, and the extent of metastases.[21-22]

4.1 Gastric Carcinoids

Table 2: Types of gastric Carcinoid with treatment

Types of gastric Carcinoid		
Type 1	<1 cm	Endoscopic mucosal resection
	>1 cm/ Invasive	Local surgical excision
Type 2	Invasive	Duodenotomy with resection of lymph node metastases
Type 3	<2 cm	Gastric resection and regional lymphadectomy
	>2 cm or Gastric wall invasion or Atypical histology	Gastrectomy

4.2 Duodenal Carcinoids

Table 3: Duodenal Carcinoids with treatment

<1 cm	Endoscopic excision of primary duodenal carcinoids
1-2 cm	Full thickness excision locally
>2 cm	Operative full thickness excision and regional lymphadenectomy[regional lymphadenectomy includes lymph nodes from:- Posterior to the duodenum and pancreatic head, anterior to the inferior vena cava. - Posterolateral to the bile duct and portal vein - Anterior to the common hepatic artery]

4.3 Jejunal and ileal carcinoids

Early surgical treatment should include removal of the mesentery by wedge resection and resection of lymph node metastases surrounding the mesenteric artery and vein to preserve intestinal vascular supply and to limit the intestinal resection.[23]

Surgical treatment for advanced carcinoids involves prophylactic removal of mesenteric metastases early on because later the disease may become impossible to manage surgically. Repeat surgery may be necessary if mesenteric metastases are left during primary surgery or have progressed after primary surgery. These operations are difficult because of fibrosis between regions of the intestine, and surgery may result in fistulation, intestinal devascularisation, or creation of a short bowel.[23]

4.4 Appendiceal Carcinoids

Table 4: Appendiceal Carcinoids with treatment

<1 cm	Appendectomy
1-2 cm	Hemicolectomy may be appropriate if -invasion in the mesoappendix - residual tumour in the resection margins - presence of lymph node metastases
>2 cm/ Goblet cell variant	Right sided hemicolectomy and ileocaecal lymphadenectomy with chemotherapy -associated peritoneal metastasis delt with peritonectomy or oopherectom for ovarian metastases

4.5 Colonic Carcinoids

Colonic Carcinoids are Often exophytic and large (>5 cm), but they rarely bleed. They present with more liver metastases than regional lymph node metastases. Radical resection by hemicolectomy or subtotal colectomy with lymphadenectomy.[23]

4.6 Rectal Carcoinoids

Table 5: Rectal Carcoinoids with treatment

<1 cm	Endoscopic excision
1-2 cm	Endoscopic resection OR Surgical resection BOTH Both depending on:- atypia, high mitotic index, presence of muscularis invasion, regional metastases
>2 cm/ invasive/ malignant	Surgical resection with abdominoperineal resection(APR) -invasion of muscularis (APR) or low anterior resection (LAR) is recommended because of the high rate of nodal metastases and risk of distant metastatic disease

4.7 Somatostatin Analogs

They are important in the amelioration of symptoms of carcinoid syndrome Substantial improvement in quality of life with relatively mild adverse effects. The inhibitory effects of somatostatin on neurotransmission, motor and cognitive functions, smooth muscle contractility, glandular and exocrine secretions, intestinal motility, and absorption of nutrients and ions are mediated by cyclic adenosine monophosphate inhibition. Experimentally, somatostatin has been shown to have a cytostatic effect on tumour cells.[24]

Octreotide, a short-acting somatostatin analoglanreotide, a long-acting somatostatin analog administered every 10 to 14 days Adverse effects of somatostatin analog administration include: Nausea, Cramping, Loose stools, Steatorrhoea, Cardiac conduction abnormalities and arrhythmias, Endocrine disturbances (e.g., hypothyroidism, hypoglycemia, or, more commonly, hyperglycemia), gastric atony (rarely) and Biliary sludge and cholelithiasis. [24-25]

Interferon-alpha (IFN-alpha) Inhibition of disease progression and symptom relief, with approximately 75% of patients reporting the resolution of diarrhoea or flushing. Adverse effects, including alopecia, anorexia, fatigue, weight loss, fever, a flu-like syndrome, and myelosuppression However, IFN-alpha may show greater antitumor activity than somatostatin analogs.[26-27]

4.8 Treatment of Hepatic Metastasis

Surgical resection**,** hepatic artery embolization, chemoembolization with gelatin foam, cryoablation, radiofrequency ablation (RFA) orthotopic liver transplantation. **Radionuclides:** I131-MIBG (iodine-131-meta-iodobenzylguanidine), indium-111, yttrium-90, lutetium-177[28].

4.9 Management of Carcinoid Related Fibrosis

Bowel obstruction secondary to peritoneal fibrosis. It is most common presenting symptom. Surgical lysis of the adhesions often is technically demanding because of the cocoon-like effects of extensive fibrosis stimulated by the various tumour-derived growth factors. Valve replacements in cases of cardiac valve fibrosis [29-30].

4.10 Symptomatic Therapy

Advising to avoid factors, which induce flushing or bronchospastic episodes including the following: Ingestion of alcohol, certain cheeses, capsaicin-containing foods, and nuts. Stressful situations. Some kinds of physical activity. Diarrhoea: Antidiarrheal agents such as loperamide or diphenoxylate; more pronounced diarrhoea may be treated with the 5-HT receptor subtype 2 antagonist – cyproheptadine Histamine 1 receptor blockers: fexofenadine, loratadine, terfenadine, or diphenhydramine may be of benefit in treating skin rashes, particularly in histamine-secreting gastric carcinoid tumours. Bronchospasm can be managed with theophylline or beta-2 adrenergic receptor agonists such as albuterol.[29]

Treatments being tested in clinical trials include the following: Molecular-targeted therapies. VEGF monoclonal antibody - bevacizumab; tyrosine kinase inhibitors - sunitinib, vatalanib, sorafenib; mTOR (mammalian target of rapamycin) inhibitor – everolimus [29-30].

4.11 Carcinoid Syndrome

Carcinoid syndrome may occur when vast quantities of hormones are produced from the carcinoid, when it metastases to the liver or from a non-gastrointestinal (GI) primary tumor. The classic "carcinoid triad" associated with the syndrome includes flushing, diarrhoea, and cardiac involvement. The hormones largely responsible for the symptoms of carcinoid syndrome are serotonin, tachykinins, and vasoactive peptides. Carcinoid tumours located in the foregut (stomach), jejunum, ileum, appendix, and right colon can present with a carcinoid syndrome. Patients with longstanding uncontrolled or poorly controlled carcinoid syndrome can develop symptoms of niacin

deficiency, which include diarrhoea, dementia and dermatitis.[27]

4.12 Carcinoid Crises

Manifested by profound flushing, extreme BP fluctuations, bronchoconstriction, dysrhythmias, and confusion or stupor lasting hours or days and may be provoked by induction of anesthesia or an invasive radiologic procedure. This potentially fatal condition can also occur after manipulation of tumour masses (including bedside palpation), administration of chemotherapy, or hepatic arterial embolization. The use of calcium and catecholamine's should be avoided in carcinoid crisis because these agents provoke the release of bioactive tumour mediators that may perpetuate or worsen the situation. Plasma infusion and Octreotide (100µg IV) are used for hemodynamic support. This life-threatening complication can be avoided by pretreating the patient with Octreotide (200 µg subcutaneously three times a day) for several weeks prior to surgery and with continuous intravenous therapy intraoperatively (50 µg per hour).[27,30-32]

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