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Carcinoid tumor of the 4th part of duodenum a case report and review of literature

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Abstract
Carcinoid tumors are uncommon well differentiated neuroendocrine tumors. Primary duodenal carcinoids account for less than 2% of all gastrointestinal carcinoids. Duodenal carcinoids are seldom associated with carcinoid syndrome.
We reported a case of duodenal carcinoid tumor in a 25-year-old female presented by upper abdominal pain and intestinal obstruction. The tumor made wide spread intrabdominal and pelvic metastasis although the primary was small and of well differentiated neuroendocrine category.
Surgical excision of the primary tumor, histopathology and immunohistochemistry proved the diagnosis. The case underwent postoperative targeted therapy using Everolimus (Afinitor®). CT scan, 5-hydroxytryptamine (5HT) and 5-hydroxyindole acetic acid (5-HIAA) in urine were used for staging the tumor, confirming diagnosis and follow up. There was an excellent response after 3 months of postoperative targeted therapy without any recurrence locally, no lymph nodes, and complete disappearance of metastatic tumor in liver, peritoneum and pelvis. We recommended targeted therapy using afinitor for at least 6 months or more according patient response.

Keywords: cacinoid syndrome, duodenum, neuroendocrine, 5HT, 5-HIAA, targeted therapy

1. Introduction
Carcinoid tumors are rare and belong to the amine precursor uptake and decarboxylation system of tumors [1]. They account for less than 1% of visceral malignancies with the gastrointestinal tract carcinoids account for 67.5%-85% of them [1, 2]. They commonly arise in the small intestine with the terminal 60 cm of ileum is the commonest location [2, 3]. They most likely metastasize to liver or have bulky disease to produce the carcinoid syndrome [2, 4]. Serotonin, histamine, kinins, prostaglandins, and other hormonally active tumor-products are the humoral mediators of carcinoid tumors [5, 6]. Duodenal carcinoid are the least frequent of GIT carcinoid. Moreover, their association with carcinoid syndrome is extremely rare [5, 7]. We represent a case of duodenal carcinoid (G1 neuroendocrine tumor) in the 4th part of duodenum presented by upper abdominal pain, intestinal obstruction and carcinoid syndrome.

Case
A 25 year-old female, 49 kg weight, presented with vomiting and severe upper abdominal colic and absolute constipation. The patient is ill, exhausted, had mild ecterus and mildly dehydrated. She admitted to Al-Hamd Specialized Hospital in Ibb City (Yemen) for initial treatment and further investigations.
The condition started by episodes of watery diarrhea (2-3 times/ day) for a year. Then she had intermittent abdominal pain associated with constipation alternating with diarrhea for five months. Episodes of flushing involving the face and upper chest supervened for the last three months. Finally, the case came with absolute constipation, severe abdominal colic and repeated vomiting (intestinal obstruction).
She had no co morbid illness and family history was not significant. Her blood pressure and cardiac evaluation was normal. Examination of the rest of body systems and routine laboratory findings all were within normal.
Ultrasonography of the abdomen failed to detect any abnormality in liver, spleen, intestine, colon, pancreas, gall bladder and bile ducts, kidneys and pelvic organs.
CT scan revealed severe gastric and duodenal dilatation (involving the 1st, 2nd and 3rd parts) with no obvious mass lesion and no significant wall thickening, findings consistent with distal duodenal stenosis, advice barium meal study. Two enlarged lymph nodes noted above the 4th part of the duodenum measured 1.5cm and 2.5cm in diameter. Multiple highly vascular lesions noted in both hepatic lobes measured 7-10mm in diameter with marked enhancement during arterial phase only and became homogenous with the liver and disappeared later on. They interpreted as less likely to be metastasis and advice for regular follow up by ultrasound.
Upper endoscopy revealed grade A esophagitis, gastric dilatation with greenish contents. The duodenum showed greenish contents in its 1stand 2ndparts.

Operative data: laparotomy (upper midline) revealed sever stenosis (2.2cm long) at the 4thpart duodenum and sever gastric and duodenal dilatation. In addition, there were multiple tiny metastases (seeds) in liver, peritoneum and pelvis (white-yellow colored). Resection of 10 cm. of the duodenojujenal bowel and side to end anastomosis was done because of sever dilation. The clinical diagnosis was adenocarcinoma versus TB.
Pathological evaluation revealed 2.2cm long tumor stenosing lesion involves the whole wall thickness (figure 1).

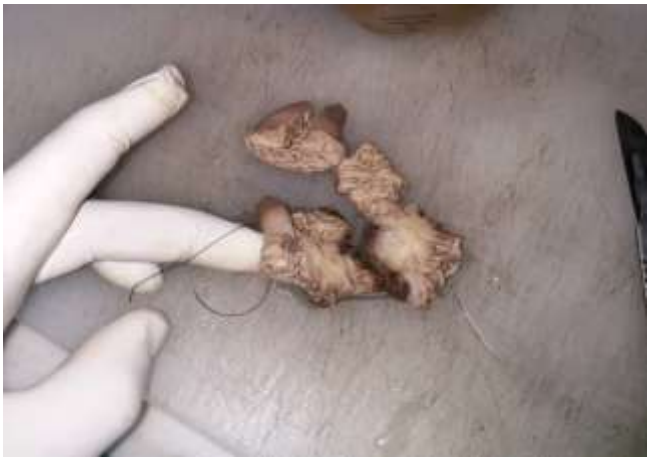
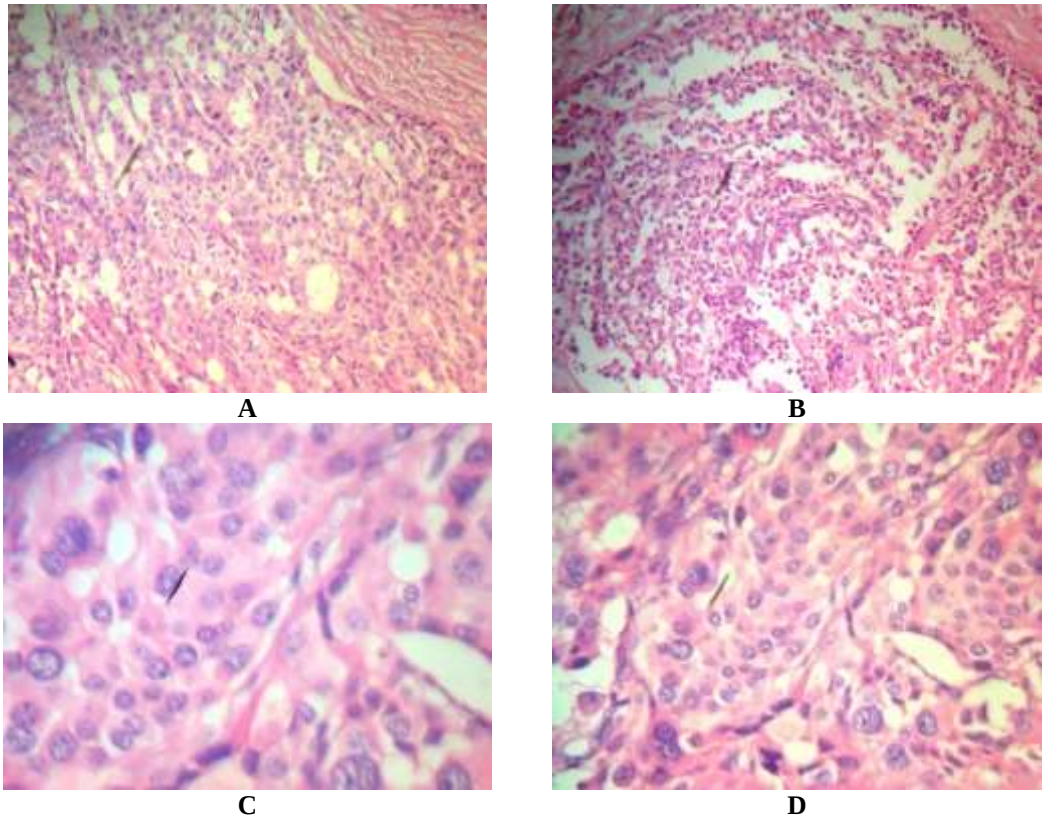


Fig 1: cracinoid tumor involves the whole wall thickness, tumor size is 2.2cm.

endocrine tumor formed of nests, glandular structures and trabeculae amid desmoplastic fibrotic stroma. The tumor cells are nearly monotonous rounded to polygonal with slightly granular cytoplasm and indistinct cell borders. The nuclei are rounded with salt and paper chromatin. There is mild to moderate variation in nuclear size. Mitotic count was 3/10HPF. No tumor necrosis detected. The tumor involves the whole wall thickness till serosa with impressive lymphovascular embolization and perineural invasion. The submitted lymph nodes (two in number) were infiltrated. A diagnosis of carcinoid tumor was made (well differentiated neuroendocrine tumor/ grade I)/ stage III (pT3N1Mx).

The histopathological diagnosis was confirmed by immunohistochemistry (figure 3). The tumor was strongly and diffusely positive for CK and NSE. Ki67 (a proliferation marker) was positive in <3% of tumor cells and c-Kit (GIST marker) was negative.

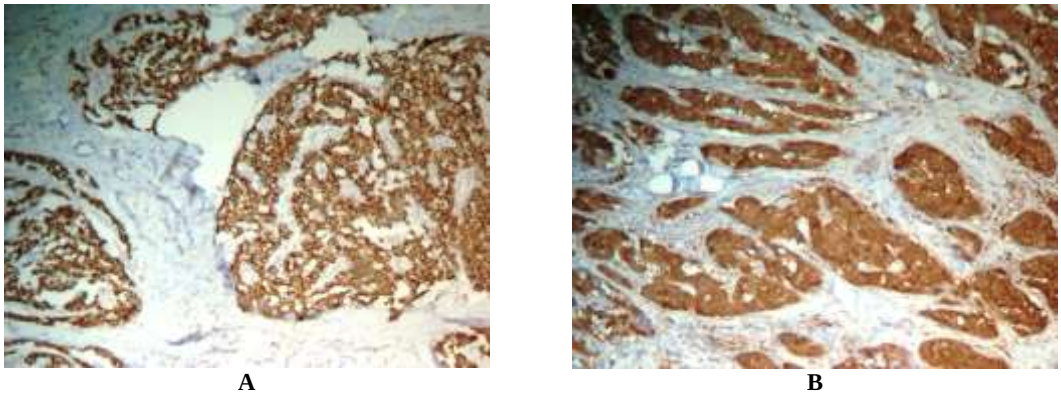
Microscopically (figure 2), a neuro



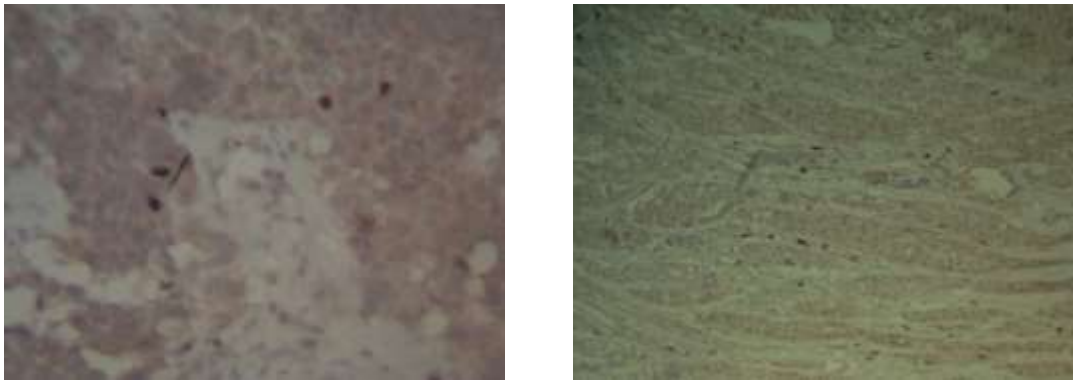
A **B**

C **D**

Fig 2: The tumor cells are monotonous, rounded to polygonal with indistinct borders and pink slightly granular cytoplasm. They form glandular structures (A) nests and trabecullae (B). The nuclei are rounded with salt and paper chromatin (C). There is moderate variation in nuclear size (C&D).



A **B**



C D

Fig 3: The tumor was strongly and diffusely positive for CK (A) and NSE (B). Ki67 (a proliferation marker) was positive in <3% of tumor cells (C) and c-Kit (GIST marker) was negative (D).

The final diagnosis was carcinoid tumor (well differentiated neuroendocrine tumor/ grade-1)

Follow up:

One month postoperative CT revealed residual lesion (mostly residual tumor/ less likely postsurgical granulation tissue) at the 4th part of duodenum encasing IVC and mesenteric vessels but not invading them, with multiple small mesenteric lymph nodes, all less than 12mm in diameter. Newly developed multiple minute hepatic nodules, all less than 10mm also detected. Other abdominal and pelvic organs are free. The duodenal obstruction was relieved although the proximal parts still dilated with delayed gastric empting. Chest CT was normal.

Post operative urinary 5HT was elevated 6.4 mg/24h (N= 0-5mg/24h) with a urine volume 4500ml/24h (N= 600-2500ml/24h), figure 4.

Fig 4: postoperative laboratory findings

Postsurgical therapy: the patient underwent targeted therapy using Afinitor® (Everolimus)

Afinitor® (Everolimus) capsules was used 2 months postoperative to control hepatic and peritoneal metastases in a dose of 10 mg/ day at night before dinner. After 20 days, the patient developed side effects like oral ulcerations, diarrhea, loss of appetite and nausea. Afinitor was stopped for a week and dexamethazone with oral hygiene was started. The side effects resolved and the dose reduced to a capsule every other day for a month. Side effects recurred again and managed as before. Afinitor continued for additional four months. Total period of afinitor was 6 months with stoppage of treatment when the side effects recur. After 4-months of treatment by afinitor, the patient clinical and radiological (CT) parameters improved completely and afinitor was stopped completely two months later (total afinitor period was 6 months). Radiological improvement by complete resolution of previously seen operative bed soft tissue nodular attenuation and all previously seen multifocal hepatic lesions, clear fatty planes at operative bed, no detectable measurable remnant or recurrent neoplastic lesions could be seen, no focal hepatic lesions with normal liver density, complete resolution of previously seen duodenal and gastric lumen dilatation, and free abdominal and pelvic organs.

A follow up CT scan one month and three latter (on the fifth month of afinitor) showed free stable stationary course of complete resolution. Two months after cessation of treatment (after 6 months), another CT was done and also free.

Discussion

Neuroendocrine neoplasms, defined as epithelial neoplasms with predominant neuroendocrine differentiation, can arise in most organs. The greatest incidence of carcinoid is noted in the gastrointestinal tract (67.5%), followed by the bronchopulmonary system (25.3%) and the rest are found in the thymus, liver, pancreas, ovaries, prostate and kidneys. Within the gastrointestinal tract, most carcinoid tumors occur in the small intestine (41.8%), rectum (27.4%), appendix (24.1%) and stomach (8.7%) [1].

Primary duodenal carcinoids account for less than 2% of all gastrointestinal carcinoids. The incidence of the duodenal carcinoid is highest in the first part and decrease distally (2nd, 3rd and 4th). The lesions are usually solitary; multiple lesions involving different parts of the duodenum are rare[2]. In our case, solitary nodular lesion of about 22x18mm was present in the 4thpart of duodenum making sever stenosis resulting in dilatation in proximal duodenum and stomach.

The most common symptoms of intestinal carcinoid are vomiting, intermittent upper abdominal pain, and abdominal distension[3]. All were found in our case.

The most common systemic manifestation of carcinoid tumors is carcinoid syndrome. This syndrome resulting from hormonally active tumor products such as serotonin, histamine, kinins, and prostaglandins. Flushing and diarrhea (present in our case) are the two most common manifestations of carcinoid syndrome, occurring in up to 73-89%. Cardiac disease is due to the formation of fibrotic plaques (serotonin mediated) involving the endocardium leading to stenosis and insufficiency of tricuspid and/or pulmonary valves, ending in heart failure usually seen in patients with metastatic disease. Less common clinical manifestations include asthma-like symptoms and pellagra-

like skin lesions (these tumors use tryptophan as the source for niacin synthesis, which results in niacin deficiency). Once the tumor invades the serosa and involves the retroperitoneum it causes severe desmoplastic reaction leading to retroperitoneal fibrosis and subsequent ureteral obstruction, peyronie′s disease of the penis, intra-abdominal fibrosis and occlusion of the mesenteric arteries or veins. In patients with duodenal carcinoid, carcinoid syndrome may occur in 4% [4, 5, 6].

Occasionally, carcinoid tumors can produce the adrenocorticotropic hormone and growth-hormone-releasing hormone causing Cushing syndrome and acromegaly respectively. This distinct entity is known as atypical carcinoid syndrome [6].

The neuroendocrine markers, chromogranin-A and 5-HIAA in serum and urine respectively may be useful for the diagnosis [5-6]. Measurement of 5-HIAA is used most frequently. It has 73% sensitivity and 100% specificity for carcinoid syndrome. The urinary 5-HIAA value more than 9mg/24h in patients without malabsorption and more than 30mg/24h with malabsorption is considered pathognomonic of carcinoid syndrome [5, 6, 7]. Our patient had urinary 5-HIAA of 5.6mg/24h, which is within normal range. This may be due to its measurement was post surgical (after removal of the main bulk of the tumor) as well as it was diluted by large urine volume of the patient i.e. dilutional (urine volume was 4500ml/24h).

Fasting plasma 5-HIAA (not done), platelet 5-hydroxytryptamine (5-HT), urinary 5-HT and urinary tryptophan (5-HTP) can also be used for the diagnosis of carcinoid syndrome. We measured 5HT+ 5HTP, and it was relatively high (6.4mg/24h) supporting the diagnosis of carcinoid [8].

Serum chromogranin A level (not measured in our case) is another marker for neuroendocrine tumors. It is elevated in 56-100% of patients with carcinoid tumors, and the level correlates with the tumor bulk.

Oesophagogastroduodenoscopy is the most useful method for diagnosis of the duodenal carcinoid. To improve the diagnostic index of the carcinoid tumor, deeper and multiple biopsies are required. Contrast-enhanced CT (CECT) and magnetic resonance imaging (MRI) do not usually identify small primary tumors, but may indicate liver and/or mesenteric metastases [7, 9].

Endoscopic ultrasonography (EUS) can define the tumor size, level of wall invasion and the presence of regional lymphatic metastases. Radioisotopes such as indium-111 or metaiodobenzylguanidine scan can identify carcinoid tumors [9, 10]. Such investigations not done, as they were unavailable for our case.

Endoscopic removal or surgery is the ideal treatment for duodenal carcinoids. Tumors up to 1cm in the submucosa away from the periampullary region without lymph node metastases on EUS or CT and no mitotic figures (pathologically) exhibit indolent behavior and no metastases. In such cases, endoscopic removal is the preferred treatment for these lesions [9, 10]. For tumors of 1–2 cm with invasion of the duodenal wall beyond the submucosal layer, the best treatment is transduodenal full-thickness resection[5] using laparotomy or laparoscopy [10, 11]. However, regardless of the depth of invasion; duodenal tumors smaller than 2 cm correlated with curability by endoscopic resection as they were not metastatic [11].

For carcinoid tumors larger than 2 cm (like our case), a full-thickness resection with a regional lymphadenectomy is recommended, especially when lymph node involvement detected by EUS/CT/MRI or mitotic index is higher than 2/HPF[11].

Ampullary and periampullary duodenal carcinoids deserve special consideration because they differ clinically, histologically and immunohistochemically from carcinoid tumors that occur elsewhere in the duodenum [12]. Although their rarity precludes the establishment of any definitive natural history, these tumors appear to behave unpredictably and might be viewed as a distinct category of the carcinoid tumor when treatment options are being considered[11]. Compared with tumors in other duodenal sites, even small (<1 cm) ampullary and periampullary carcinoid tumors exhibit distinctly different aggressive behavior, and may metastasize early [11, 12], radical surgical treatment of pancreaticoduodenal resection is favored [13].

Our case was 2.2cm tumor size with widespread metastasis so we did resection and anastomosis (duodenojejunal end to side) and this consistent with previous recommendations [11, 12, 13, 14].

It is important to prevent the occurrence of carcinoid crisis, a life-threatening form of carcinoid syndrome that may be triggered by tumor manipulation (e.g. biopsy and surgery) or by anesthesia. Carcinoid crisis results from the release of an overwhelming amount of biologically active compounds from the tumor. The predominant symptom is wide blood pressure fluctuations with predominance of hypotension. Administration of octreotide prior to resection reduces the incidence of carcinoid crisis [15].

Neuroendocrine tumors in general are classified into two categories, the first category is well differentiated neoplasms and called neuroendocrine tumors (NETs). These tumors are graded into G1, G2 and G3 corresponding to low-grade, intermediate-grade, and high-grade. This grading is organ specific and depends on three grading parameters of prognostic relevance. These parameters are 1- mitotic count, number of mitoses/mm^2 (ideally counted in up to 10 mm^2). In practice, tissue availability may restrict areas available for counting. It may also be best practice to specify the number of mitoses counted within the total area assessed for each case (i.e., X mitoses in Y mm^2); 2- the Ki-67 cell labeling index performed on regions of most intense labeling ("hotspots of at least 0.4 mm^2") using a validated antibody (i.e., MIB1 antibody) and 3- the presence or absence of necrosis, defined by morphological criteria. Necrosis may be focal (punctuate) or diffuse (geographic).The second of neuroendocrine neoplasms is the poorly differentiated neoplasms and called neuroendocrine carcinomas (NECs) and by definition are high grade. They may be either small cell neuroendocrine carcinoma (SCNEC) or large cell neuroendocrine carcinoma (LCNEC) [17].

Our case showed low mitosis <3/10HPF, Ki67-labeling index <3% and no necrosis. So according to these it is a NET-G1 (typical carcinoid), but it showed wide spread metastasis (aggressive behavior). Whether nuclear atypia be a risk factor for tumor aggressiveness like mitosis, necrosis and Ki67-labeling index, a point needs more review of reported cases of carcinoid and its behavior. Another point in this theme is why should classify neuroendocrine neoplasm in unusual pathologic manner as NET and carcinomas as all make metastasis like this case. Why we don't call them all carcinomas and putting the grade.

Therefore, G4 neoplasms are the most aggressive form either SCNEC or LCNEC.

In patients with liver metastases synthetic analogues of somatostatin (octreotide, lanreotide) are now the most widely used agents to control the symptoms in patients with carcinoid syndrome. They stabilize the disease and reduce the growth of metastases. However, a surgical resection and/or cytoreductive techniques may improve carcinoid syndrome symptoms to improve the quality of life and increase survival [18].

The role of systemic chemotherapy in patients with metastatic carcinoid is unclear, and the year 2012 guidelines from the European Neuroendocrine Tumor Society recommends against its use in these patients [19]. Consensus-based guidelines from the National Comprehensive Cancer Network suggest that anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon α (IFNα) and temozolomide can be used in patients with progressive metastases from carcinoid for whom there are no other treatment options. However, no chemotherapy drug or regimen has demonstrated an overall survival benefit or progression-free survival.

In our case we used afinitor® (everolimus) to control metastasis in liver and peritoneum. It is an inhibitor of mammalian target of rapamycin (mTOR). It currently used as an immunosuppressant to prevent rejection of organ transplants and in the treatment of renal cell cancer and other tumors. Much researches had also been conducted on everolimus and other mTOR inhibitors as targeted therapy for use in a number of cancers [20].

Afinitor 10mg/day was used in our patient to control hepatic and peritoneal deposits. The dose was tolerated by the patient initially, then usual side effects developed and was controlled as mentioned earlier. Stoppage of the drug for a week with dexamethazone therapy and oral hygiene were enough to control such symptoms. Reduction of the dose to the half was tolerated but symptoms recurred at quite longer intervals. So a dose of 5mg/ day is recommended [21, 22] preferably after initial dose of 10mg/day for 2 weeks. Six months therapy was enough to control metastatic disease in liver and peritoneum but longer periods should be considered in selected cases according to response.

Patient was followed up radiologically by CT and biochemically by monitoring 5-HIAA and this is consistent with others[23]. We recommend to repeat them every two months during and after stoppage of afinitor.

Conclusion: NETs are amenable for surgical removal especially if localized disease and for treatment using new-targeted therapies. The grade of NETs although a good predictor for aggressiveness, metastasis may occur early and widely in low grade NETs. Surgical resection of NETs is the main stay of treatment and other modalities are adjuvant and complementary. Afinitor® is a good choice for widely spread carcinoid tumors as a monotherapy with tolerable and easily controlled side effects. The side effects related to afinitor will respond to temporary discontinuation and simple therapeutic measures and don't mandate its termination. CT and 5-HIAA are good for monitoring therapy efficacy and follow up response.

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