Cancer Research Journal
2021; 9(3): 162-165
http://www.sciencepublishinggroup.com/j/crj
doi: 10.11648/j.crj.20210903.15
ISSN: 2330-8192 (Print); ISSN: 2330-8214 (Online)

Carcinoid Syndrome in a Patient with Duodenal Carcinoid Tumor

Khan Mohammad Nazmus Saqeb[1, *], Fariah Sharmeen[2], Farzana Hafiz[3]

[1]Department of Gastrointestinal, Hepatobiliary & Pancreatic Diseases, Jahurul Islam Medical College & Hospital, Kishoreganj, Bangladesh
[2]Department of Oncology, Square Hospitals Ltd., Dhaka, Bangladesh
[3]Department of Pathology, Square Hospitals Ltd., Dhaka, Bangladesh

Email address:
drsaqebk59@gmail.com (K. M. N. Saqeb), drfariahsharmeen29@gmail.com (F. Sharmeen), farzanahafiz@ymail.com (F. Hafiz)
[*]Corresponding author

To cite this article:
Khan Mohammad Nazmus Saqeb, Fariah Sharmeen, Farzana Hafiz. Carcinoid Syndrome in a Patient with Duodenal Carcinoid Tumor. *Cancer Research Journal*. Vol. 9, No. 3, 2021, pp. 162-165. doi: 10.11648/j.crj.20210903.15

Received: July 10, 2021; **Accepted**: July 27, 2021; **Published**: August 4, 2021

Abstract: Duodenal carcinoid tumors accounts for 5% of all Gastrointestinal Neuroendocrine Tumors (GI-NETs). Only 4% of all duodenal carcinoid tumors present with a full-blown carcinoid syndrome. We report a case of duodenal carcinoid tumor presenting as carcinoid syndrome in a 58 year old man, who presented with upper abdominal discomfort, diarrhoea, hot flushes and occasional wheezing. Histopathology following endoscopic resection of the tumor and 24 hour urinary 5-Hydroxyindolacetic acid (5-HIAA) confirmed the diagnosis. Duodenal carcinoid tumors are one of the rarest tumors of gastrointestinal tract and their association with a typical carcinoid syndrome is not that common. A high level of suspicion is required for an early diagnosis. With proper resection (endoscopic or surgical) of a localized tumor, recurrence and progression of the disease can be halted. Symptoms of carcinoid syndrome should be controlled by antidiarrheal agents, inhaled β-adrenergic agonist bronchodilators and somatostatin analogs (octreotide, lanreotide). Patients should be advised to avoid stress and conditions or substances that precipitate these symptoms. Dietary supplementation with nicotinamide can help in this regard. Patients with hepatic metastases are treated with synthetic analogues of somatostatin (octreotide, lanreotide). Systemic chemotherapy is not recommended in metastatic disease by the current guidelines. Patients should be followed up by monitoring serum chromogranin and urinary 5-HIAA. EUS, CT, MRI & somatostatin receptor scintigraphy can also be used for following up the patients.

Keywords: Carcinoid Syndrome, Duodenal Carcinoid, Gastrointestinal Neuroendocrine Tumors (GI-NETs)

1. Introduction

GI-NETs (carcinoid) comprise nearly 70% of all carcinoid tumors. GI carcinoids most commonly occur in the small intestine, rectum, appendix, or stomach. Within the small intestine, ileum is affected most commonly, followed by the duodenum and jejunum. Duodenal carcinoids comprise 22% of all small intestinal carcinoids, mostly arising from the first and second part of duodenum. Most of the patients present at the sixth decade, with a slight male predominance. Although various GI hormones are frequently found in duodenal carcinoids, no clinical syndrome is seen in 58% to 98% of patients. Only 4% of all duodenal carcinoid tumors present with a full-blown carcinoid syndrome. Here, we present a case of duodenal carcinoid tumor which presented as carcinoid syndrome. A similar case of duodenal carcinoid was reported by Nalla et al. from India in 2014. But no such case is reported from Bangladesh yet.

2. Case

A 58 year old nondiabetic normotensive man presented with the complaints of upper abdominal discomfort for 6 months, passage of loose watery stool for 3 months and recurrent hot flushes involving face and neck for the same duration. He also complained of occasional wheezing, which he has noticed for last few months and is precipitated by doing exercise. He didn't give any history of anorexia, weight loss, hematemesis or melaena. There was no

significant family history. He didn't give any relevant past medical history. His vitals were within normal limit. There was no icterus or anemia. Abdominal examination and other systemic examinations including cardiac examination were unremarkable.

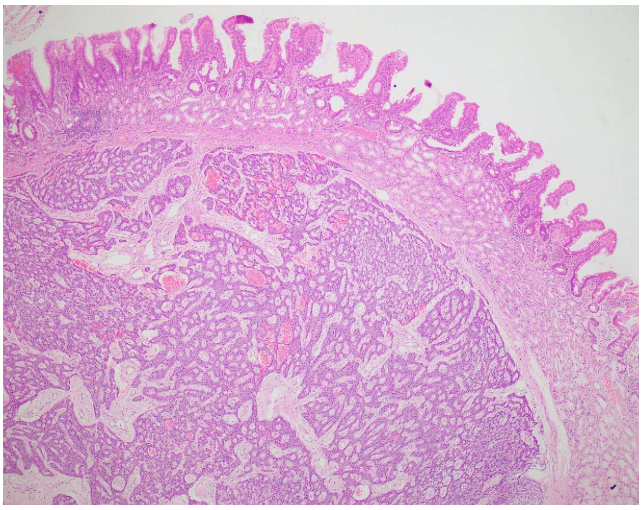

Figure 1. *Neuroendocrine tumor within the submucosa of duodenum (hematoxylin-eosin, magnification x40).*

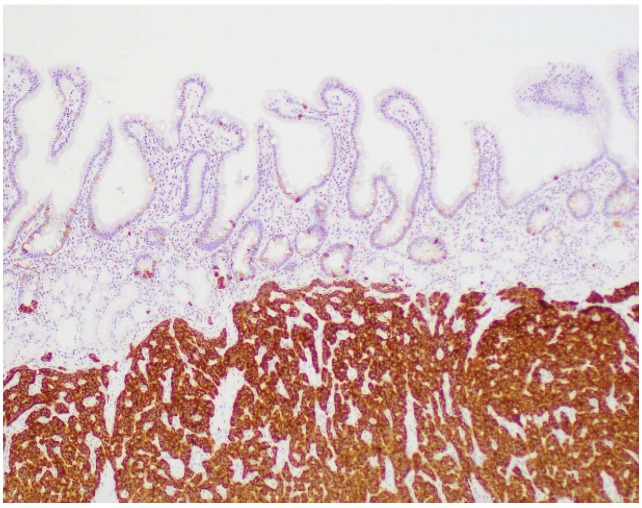

Figure 2. *Well differentiated duodenal neuroendocrine tumor (positive for synaptophysin) with tumor free margins (magnification x100).*

The routine hematological and biochemical blood tests, including SGPT, SGOT & serum lipase were all within normal limit. Stool routine examination was unremarkable and stool C/S revealed no growth. USG of whole abdomen revealed grade-I fatty liver with no other significant abnormalities. Thyroid function tests revealed no abnormality. Endoscopy of upper GIT showed presence of a suspicious looking single umblicated polypoid lesion with intact surface mucosa at the second part of duodenum. Chest Xray and serum IgE levels were within normal limit. A Contrast enhanced CT scan of whole abdomen was done to evaluate the polypoid mass at the second part of the duodenum. Contrast enhanced CT scan of whole abdomen revealed a polypoid intraluminal mass about 1.5 cm in diameter with contrast enhancement during arterial phase with no evidence of regional lymphadenopathy or hepatic metastases. Echocardiogram was normal. Contrast enhanced CT scan of whole abdomen revealed no evidence of regional lymphadenopathy or hepatic metastases. Therefore, endoscopic resection of the lesion was done. Following endoscopic resection of the duodenal mass, an immediate bleeding was noted from the site of resection and was subsequently controlled with injection of adrenaline. The mass was sent for histopathology after endoscopic resection, which revealed a duodenal carcinoid tumor. Immunohistochemical staining was done and it was positive for synaptophysin and chromogranin A. A 24 hour urinary 5-Hydroxyindolacetic acid (5-HIAA) level was done and it was 17 mg/24 hrs (normal range is 2-8 mg/24 hrs), which is consistent with the diagnosis of carcinoid syndrome.

The patient was on several pharmacological agents like proton pump inhibitors, antidiarrheals, beta-adrenergic agonist bronchodilators and somatostatin analogues before the surgery was done. Those drugs were effective only to a lesser extent. A second look endoscopy was done 2 days after the endoscopic resection, which revealed complete control of bleeding at the resection site. The patient was discharged three days after the endoscopic resection. The patient experienced a gradual reduction of symptoms after endoscopic resection. He is now absolutely asymptomatic after 6 months of resection with no evidence of recurrence or distant metastases.

3. Discussion

Duodenal carcinoids comprise 1% to 3% of primary duodenal tumors, 22% of small intestinal carcinoids, 5% of all GI-NETs (carcinoid), and just under 4% of all carcinoids. Most (>90%) duodenal NETs arise from the first or second part of the duodenum, with 18% to 20% occurring in the periampullary region [1]. Duodenal NETs are generally small, with a mean diameter of 1.2 to 1.5 cm; 75% of them are smaller than 2 cm [1]. Most (63%) are limited to the mucosa or submucosa, but they still can metastasize to lymph nodes (19% to 60% of cases), although liver metastases occur in less than 10% [1]. Most duodenal carcinoids are solitary, but they are multiple in 9% to 13%, particularly in patients with MEN-I, who comprise 6% of all patients with duodenal carcinoids [2]. Although various GI hormones are frequently found in duodenal carcinoids, no clinical syndrome is seen in 58% to 98% of patients.

Most of the patients present at the sixth decade, with a slight male predominance [1]. Because the vast majority of duodenal carcinoids are not associated with a clinical syndrome, they are usually diagnosed during EGD for nonspecific symptoms [1]. The most frequent functional syndromes are ZES (10%) and carcinoid syndrome (4%); other syndromes are rare (<1%). The 5-year survival with well-differentiated duodenal NETs is 80% to 95%.[1] Poor prognostic factors include distant metastases, advanced stage, larger primary tumor size, depth of invasion, increased

mitotic activity, and less differentiation [1].

EGD with biopsies is the most common method to diagnose duodenal NETs. Endoscopic ultrasound (EUS) should be done to assess the level of invasion. For patients with advanced disease, CT (or MRI) and SRS are indicated [3]. The carcinoid syndrome develops in approximately 8% of patients with carcinoids (range, 2% to 18%) [4]. The most frequent symptoms are spontaneous cutaneous flushing and diarrhea, followed by bronchospasm with wheezing and asthmatic symptoms and, later in the course of the disease, carcinoid heart disease with primarily right-sided heart failure [3]. The carcinoid flush usually presents with sudden appearance of an erythema involving the upper part of the body, primarily the face and neck. Diarrhea usually (85% of cases) occurs with flushing, but it may occur alone in 15% of cases [5]. Abdominal pain may also occur with the diarrhea or independently [5]. Cardiac valvular manifestations are common. Tricuspid regurgitation is the most common result (90% to 100%), followed by tricuspid stenosis (43% to 59%), pulmonary regurgitation (50% to 81%), pulmonary stenosis (25% to 59%), and mitral regurgitation (43%) [6]. *Carcinoid crisis* is one of the most serious complications of the carcinoid syndrome [7].

Symptoms of crisis include hypotension (sometimes hypertension), confusion, stupor, hot flushes, diarrhea, bronchospasm, hyperthermia & cardiac arrhythmias [7]. The measurement of urinary 5-HIAA levels is the current method of choice to diagnose the carcinoid syndrome [3]. The normal limit for urinary 5-HIAA excretion is 2 to 8 mg/day, although using a higher cut-off (15 mg/day) may reduce false-positive results [8]. The 24-hour urinary 5-HIAA excretion has greater sensitivity for detecting the carcinoid syndrome than urinary 5-HT excretion or a serum 5-HT assay [9].

Treatment of duodenal NETs:

1) Small (≤1 cm) non-ampullary duodenal NETs can be removed endoscopically if no metastases are present and tumor invasion is limited to the submucosa. [10] Duodenal carcinoid tumors located in the ampullary region should be removed surgically along with lymphadenectomy.
2) For medium sized (1 to 2 cm) duodenal NETs, surgical treatment is generally recommended, although various extensive endoscopic tumor removal procedures have been used successfully [10].
3) Large (>2 cm) duodenal NETs and those with lymph node involvement (any size) should be treated by surgical resection [11].

Patients with carcinoid syndrome should avoid stress and should stay away from conditions or substances that precipitate flushing. Dietary supplementation with nicotinamide may be helpful in this regard. Antidiarrheal agents like loperamide & diphenoxylate can be used to control symptoms of diarrhoea. Wheezing can be controlled by an inhaled β-adrenergic agonist bronchodilator and heart failure may require diuretics [3]. If patients continue to have bothersome symptoms, somatostatin analogs should be used [4]. To prevent a carcinoid crisis, patients with carcinoid syndrome undergoing procedures should receive an additional somatostatin analog [12]. Serum chromogranin and urinary 5-HIAA can be used for follow up. Other methods like EUS, CT, MRI & somatostatin receptor scintigraphy (SRS) can also be used for this purpose [13].

Treatment of metastatic disease is usually indicated when the metastatic burden is increasing, symptomatic, or associated with other poor prognostic factors [3]. Patients with hepatic metastases are treated with synthetic analogues of somatostatin, i.e., octreotide & lanreotide. These agents are effective in controlling the symptoms in patients with carcinoid syndrome. [13]. Surgical resection has been shown to be effective in reducing symptoms of carcinoid syndrome and in improving survival [1]. The 2012 guidelines from the European Neuroendocrine Tumor Society have recommended against the use of systemic chemotherapy in patients with metastatic carcinoid tumors [14].

A similar case of duodenal carcinoid was reported by Nalla et al. (2014) [13] from India. Our case was probably the first one to be reported from Bangladesh.

4. Conclusion

Duodenal carcinoid tumors are one of the rarest tumors of gastrointestinal tract and their association with a typical carcinoid syndrome is not that common. A high level of suspicion is required for an early diagnosis. Histopathology following endoscopic resection of the tumor and 24 hour urinary 5-Hydroxyindolacetic acid (5-HIAA) can be used to confirm the diagnosis. With proper resection (endoscopic or surgical) of a localized tumor, recurrence and progression of the disease can be prevented.

Author Contributions

Saqeb KM was involved in case identification, doing relevant investigations, collection of data, literature review, writing manuscript, final review & approval of the manuscript. Sharmeen F had substantial contribution in data collection, literature review & manuscript draft preparation. Hafiz F was involved in data collection & histopathology slide interpretation.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

No funding was received for this case report.

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