

ORIGINAL ARTICLE

Neuroendocrine Tumors of the Ampulla of Vater: Presentation, Pathology and Prognosis

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ABSTRACT

Context Neuroendocrine tumors of the pancreatic ampulla are uncommon. The final diagnosis is based on histology, and at times, it may be difficult to diagnose them pre-operatively since they present with a similar clinical picture to adenocarcinomas of this region. **Objective** To identify neuroendocrine tumors of the ampulla, as well as their presentation and management. **Design** A retrospective review of patients treated at a tertiary care institute was performed over a six-year period from 2005 to 2010. **Patients** Cases with periampullary cancers were investigated. **Main outcome measures** The case records were scrutinized for the clinical presentation, management and outcomes. **Results** A total of 4 cases (7.7%) of neuroendocrine tumors of the ampulla were identified from 52 patients with periampullary lesions, at a mean age of presentation of 49 years. The common mode of presentation was progressive jaundice (3 of 4 patients); pancreaticoduodenectomy was performed in 3 patients. One patient underwent palliative endoscopic stenting for metastatic disease. On histopathology, 2 of the patients had poorly differentiated (neuro)endocrine carcinoma (high grade), and 2 had well differentiated (neuro)endocrine carcinoma (1 low grade and 1 intermediate). All the tumors stained positively with chromogranin A. The patients who underwent pancreaticoduodenectomy are on regular follow-up and remain free of disease. **Conclusions** Neuroendocrine tumors of the ampulla are distinct entities presenting clinically with jaundice. They stain positive with chromogranin A on histopathology. Pancreaticoduodenectomy should be performed as it is associated with good outcome.

INTRODUCTION

A neuroendocrine tumor is defined as an epithelial neoplasm that shows neuroendocrine differentiation when analyzed by conventional histological, immunohistochemical, ultrastructural and biological evaluation [1]. Ampullary neuroendocrine tumor (ANET) are an extremely uncommon subset of pancreatic cancer that have a distinct clinical and morphological profile. ANET, formerly known as carcinoid tumors, account for only about 0.3 to 1% of all gastrointestinal neuroendocrine tumors, and even less than 2% of all periampullary cancers [2, 3]. To the best of our knowledge, a search of available English language literature revealed only about 139 patients with ANET that have previously been reported [1, 2, 3]. We report four cases of ANET with emphasis on their clinical presentation, pathology, treatment and outcomes.

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Key words Ampulla of Vater; Neuroendocrine Tumors; Pancreaticoduodenectomy

Abbreviations ANET: ampullary neuroendocrine tumor

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MATERIAL AND METHODS

A retrospective review of the records of all the patients diagnosed as periampullary cancer at our hospital was performed, over a 6-year period, from January 2005 up to December 2010. A total of 52 patients were identified as having periampullary neoplasms, in whom the initial assessment was done with endoscopic retrograde cholangiopancreatography (ERCP) and final histopathological diagnosis was made from endoscopic biopsy or pancreaticoduodenectomy specimen. Of these, 48 (92.3%) were adenocarcinoma and 4 (7.7%) were neuroendocrine tumors.

Depending upon the stage of the disease at presentation, these periampullary cancers were either taken up for surgery (46 patients, 88.5%) or palliative endoscopic stenting (6 patients, 11.5%). Of the patients who were operated, 30 successfully underwent pancreaticoduodenectomy (65.2%) whereas 16 (34.8%) could only be palliated for their biliary/gastric obstruction.

The indoor records of the 4 patients of ANET were scrutinized for information regarding presentation, histopathology and management.

ETHICS

The informed consent was not taken as the study was retrospective review of the last 6 years, as well as the

Table 1. Details of patient presentation.

Patient	Age (year)	Sex	Clinical presentation	ERCP	CECT/MRI	Treatment	Survival
#1	62	Male	Painless jaundice; lump lower abdomen	Dilated CBD with submucosal bulge at ampulla	Periampullary mass (3.5x2.5 cm); liver metastasis; mass in pelvis (11.7x13.0 cm)	Biliary stenting	Died (1 month)
#2	30	Female	Painless jaundice	Dilated CBD and bulky ulcerated ampulla	Dilated CBD with soft tissue mass at ampulla (1.5x2.0 cm)	Pancreaticoduodenectomy	Alive (20 months)
#3	70	Male	Pain upper abdomen	Dilated CBD with prominent ampulla with normal mucosa	Dilated CBD mass at ampullary region	Pancreaticoduodenectomy	Alive (42 months)
#4	35	Female	Abdominal pain and jaundice	Bulky ampulla with dilated CBD	Periampullary mass (3x2 cm)	Pancreaticoduodenectomy	Alive (4 months)

CBD: common bile duct



Figure 1. Clinical photograph showing submucosal lesion in periampullary region (Case #3).

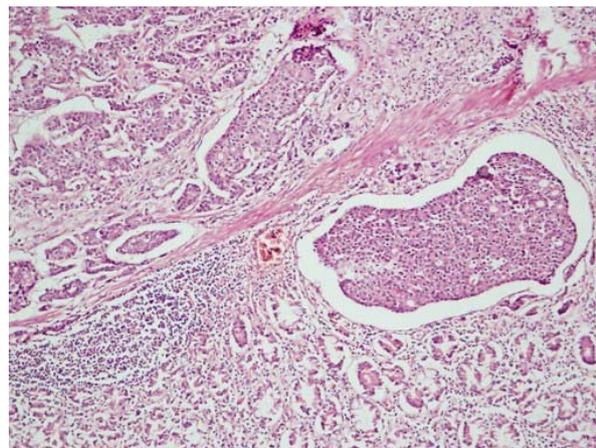


Figure 2. Photomicrograph showing nests of uniform looking tumor cells in the submucosa (Case #4; H&E x100).

Declaration of Helsinki/IRB approval are not required in our institute for retrospective review studies.

STATISTICS

Descriptive statistics only were used (absolute and relative frequencies).

RESULTS

Neuroendocrine tumors accounted for 7.7% (4 out of 52) of all tumors of ampulla. The details of these patients are tabulated in Table 1. Of these four patients, 2 were men and 2 were women. Although the mean age at presentation was 49 years (range 30-70 years), the female patients presented at a younger age as compared to the males. The common clinical presentation was with progressive jaundice (3 of 4 cases) and in the other, the presentation was with vague abdominal pain. One patient had associated neurofibromatosis. Endoscopic findings were similar in all the cases showing bulky ampulla with minimal mucosal ulceration. The diagnosis of ANET was made pretreatment only in one patient (Case #1). None of the patients had any symptoms/syndromes that could be attributed to hormonal hypersecretion by the ANET. Three patients underwent pancreaticoduodenectomy, but in the fourth, palliative biliary stenting had to be performed since the disease was metastatic. The tumor in resected specimens were in form of bulky ampulla (Figure 1) and measured 1.7-2.5 cm. One out of the

two patients with metastatic disease died within a month of stenting, but the other three patients who were operated are doing well on follow-up.

Histological diagnosis of neuroendocrine tumors was made on basis of typical neuroendocrine morphology seen on hematoxylin-eosin staining (H&E, Figure 2). Immunohistochemical staining was further used for establishing the diagnosis of ANET in these tumors; a positive stain for chromogranin A was seen in all our patients (Figure 3). Two patients had poorly differentiated (high grade) (neuro)endocrine carcinoma

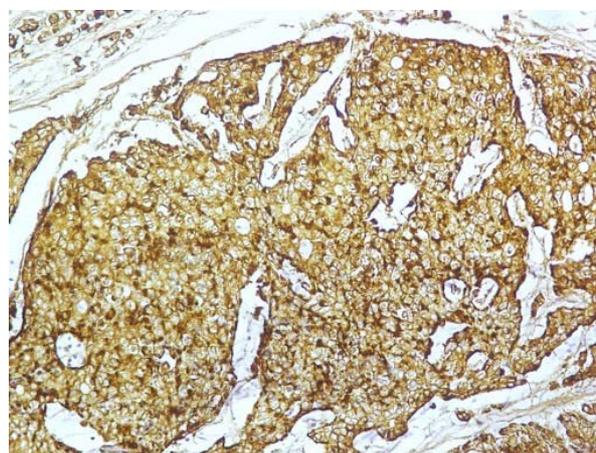


Figure 3. Photomicrograph showing nest of tumor cells positive for chromogranin A (Case #4; x200).

and two had well differentiated (one low grade and one intermediate grade) (neuro)endocrine carcinoma as per the WHO classification system (Table 2).

DISCUSSION

ANET are extremely rare tumors, accounting for less than 1% of all gastrointestinal neuroendocrine tumors and less than 2% of all tumors of ampullary region [3, 4]. To the best of our knowledge, only 139 cases have been documented in available English language literature till date, and only about 20% of these reported patients are of African or Asian Pacific origin [3].

Earlier, all neuroendocrine tumors arising in the gastrointestinal tract were called carcinoid tumors, but today, this terminology has been abandoned, and they are preferentially called neuroendocrine tumors (however, the term carcinoid is still used for low grade tumors). Histologically, although ANET are similar to neuroendocrine tumors arising from other parts of gastrointestinal tract, they have distinct ultrastructural and immunohistochemical behavior. Immunohistochemical staining is the main diagnostic method for these tumors, and ANET stain positively with chromogranin A and synaptophysin in 92-100% cases [4, 5].

According to the International Classification of Diseases of Oncology, published by the World Health Organization (WHO), the ampulla has been designated a site specific code “241” and neuroendocrine tumors are given specific codes: neuroendocrine not otherwise specified (8246); small cell neuroendocrine carcinoma (8041); and large cell neuroendocrine carcinoma (8013) [5]. The earlier system of identifying these tumors on the basis of hormones secreted or the clinical syndrome produced is no longer recommended, since the majority of these are not functional, and the prognosis of such tumors is based on their histological grade.

Various systems of nomenclature, grading and staging neuroendocrine tumors are prevalent which cause much confusion. But the majority of nomenclature system including WHO, European Neuroendocrine Tumor Society (ENETS) and TNM reflect differentiation and grading features of neuroendocrine

tumors [6]. Essentially, in all systems, these tumors are categorized as well or poorly differentiated on the basis of their proliferative rates assessed by amount of necrosis, mitotic figures/HPF or Ki67 labeling index [6, 7, 8].

ANET do not show any sex predilection, and are seen equally among males and females. The Surveillance, Epidemiology, and End Results (SEER) database reported 76 males and 63 females out of a total of 139 cases of ANET, with an average age of 61 years for carcinoids (low grade ANET) and 62 years for high grade neuroendocrine tumors [3]. Again, although we also had an equal incidence in males and females, the age of presentation was much younger in the female patients.

Owing to its location at the ampulla, ANET mostly present with obstructive jaundice (53%), non specific upper abdominal pain (24%), pancreatitis (6.0%) or weight loss (3.6%) [9, 10]. Jaundice was the common presentation in our patients also, and the other patient who presented with non specific abdominal pain without jaundice was diagnosed on ERCP that was performed for dilated extrahepatic biliary system seen on ultrasound examination. At times, the presence of neurofibromas in such patients may indicate the possibility of ANET, since neurofibromatosis type 1 has a well documented association with gastrointestinal tumors such as neurofibromas, gastrointestinal stromal tumors (GIST) and periampullary carcinoids, and these may be seen in up to 25% of patients with neurofibromatosis [11, 12]. In a recent review, 76 patients with neurofibromatosis type 1 were found to have periampullary or duodenal neoplasms. Of these, 31% were found to arise from the ampulla, and somatostatinoma (40%) was the commonest tumor type [12]. Less than 3% patients with neuroendocrine tumor of ampulla have hormonal hypersecretion syndrome [13].

ERCP is commonly used to diagnose ampullary tumors as well as to obtain tissue for histopathology. ANET characteristically proliferate under an intact mucosa [14]. The finding of a submucosal bulge at the ampulla on endoscopic examination should raise the clinical suspicion of ANET; this is the reason that the rate of preoperative diagnosis on endoscopic biopsy is as low

Table 2. Histopathological details of the patients.

Patient	Tumor size (cm)	Histological feature	Necrosis	Extent of invasion	Mitosis	Metastasis	Grade	Immunostains with chromogranin A	Final comment
#1	3.5x2.5 (CT scan)	Solid sheets	Yes	Could not be assessed ^a	>20 per HPF	Liver, pelvis	High	Positive	Poorly differentiated (neuro)endocrine carcinoma
#2	1.7x1.5x1.2	Nests and ribbons	No	Muscularis propria	2 per 10 HPF	-	Low	Positive	Well differentiated (neuro)endocrine carcinoma
#3	2.5x0.3	Nests and solid sheets	Yes	Muscularis propria	22 per HPF	-	High	Positive	Poorly differentiated (neuro)endocrine carcinoma
#4	2.0x1.2x0.6	Nests and sheets	No	Muscularis propria	8 per HPF	Lymph nodes	Intermediate	Positive	Well differentiated (neuro)endocrine carcinoma

^a Endoscopic biopsy

as 14% [4, 9]. Endoscopic ultrasound is helpful in detecting the depth of invasion and the presence of lymph node metastasis, but the facility may not be available at all the places. Computed tomogram scan and octreotide scan are helpful in a metastatic workup once the diagnosis of ANET is established [4, 15]. However, there are no specific features on imaging that can help in distinguishing ANET from the more common adenocarcinoma.

Tumor size has been regarded as a prognostic marker for adenocarcinoma of periampullary region. Singhal *et al.* in their comparison of adenocarcinoma and carcinoids of periampullary region observed that average size of carcinoid tumor was 5 cm and adenocarcinomas above 5 cm were seldom resectable [16]. However, tumor size does not predict the metastatic potential in ANET, and although a tumor size of more than 2 cm was found to be associated with lymph node metastasis, there are several reports of ANET up to 5 cm size without evidence of any metastasis [2, 17, 18].

Grossly neuroendocrine tumors of ampulla are small, solitary, polypoid and are covered with flattened mucosa. Microscopically the tumor is arranged in nests, microglandular, trabecular and rarely insular pattern. The tumor cells are small, uniform with scanty granular cytoplasm. The nuclei are regular, normochromic with scanty mitosis. Obvious evidences of malignant behavior are vascular invasion, gross local invasion or metastasis [3, 6].

The treatment protocol for ANET remains controversial, as they are rare tumors with an unpredictable biological behavior and prognosis [6]. Since tumor size has not been clearly established to correlate with lymph nodal positivity status, pancreaticoduodenectomy is often recommended as the treatment of choice for tumors of any size with no distant spread [10, 19, 20]. Although less invasive procedures like local excision and endoscopic resections have also been successfully attempted, especially for ANET less than 2 cm size or in high risk surgical candidates [13, 14, 21], extensive debulking surgery should be considered in patients with hormonal hypersecretion, even in the presence of advanced disease (extensive local or distant metastasis) since it offers survival rates of up to 80% at 5 years [6].

Tumor characteristics (grade) and distant metastasis are the most important prognostic factors in determining survival in ANET. Other tumor properties, like nodal involvement, tumor size and resection margins, appear to be of lesser significance in the long term survival [1, 22, 23, 24]. Low grade tumors show a 5- and 10-year survival rate to the tune of 80% and 71%, respectively, whereas high grade neuroendocrine tumors have dismal 5- and 10-year survival rates (15%) [3, 25].

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Conflict of interest The authors have no potential conflict of interest

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