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A Review on Neuroendocrine Tumor

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ABSTRACT

Cancer is a large group of almost 100 diseases. Cancer arises due to long term accumulation of genetic and epigenetic events. Cancer is one of the leading causes of death in the world while the long-term prognosis is still unfavorable, despite the enormous efforts in the search for effective anti-cancer drugs. A Neuroendocrine tumor (NET) begins in the specialized cells of the body neuroendocrine system. These cells have traits of both hormones producing endocrine cells and nerve cells. They are found through the body's organ and help control many of the body's functions. Neuroendocrine tumors (NETs) are unique group of malignant growths, best known for their ability to secrete bioactive peptides, which may cause symptoms such as flushing and diarrhea. NETs are considered to be rare tumors, but recent studies indicate that the incidence of NETs is increasing. They most commonly occur in the gastrointestinal tract (48%), lung (25%), and pancreas (9%), but may also develop in many other organs, including the breast, prostate, thymus and skin. In this review article we have discussed about types, treatments, complications, diagnosis and other related information of cancer and neuroendocrine tumor.

INTRODUCTION TO NEUROENDOCRINE TUMOR

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer is a broad term. It describes the disease that results when cellular changes cause the uncontrolled growth and division of cells. Cancer is not just one disease, but a large group of almost 100 diseases. Its two main characteristics are uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites. If the spread is not controlled, cancer can result in death. [1]

Neuroendocrine tumors (NETs) are a unique group of malignant growths, best known for their ability to secrete bioactive peptides, which may cause symptoms such as flushing and diarrhea. [2] The term "neuroendocrine" is applied to widely dispersed cells with "neuro" and "endocrine" properties. The "neuro" property is based on the identification of dense core granules (DCGs4) that are similar to DCGs present in serotonergic neurons, which store monoamines. [3] Neuroendocrine tumors (NETs) originate from enterochromaffin cells that are part of the neuroendocrine system of the bronchial and gastrointestinal tracts. At the beginning of the 20th century, Oberndorfer first described NETs and introduced the term "carcinoid," which combined the carcinoma-like characteristics of these tumors on the one hand and the relatively benign disease course on the other. Subsequently, the term carcinoid was coupled to tumor localization (for example, bronchial carcinoid, small bowel carcinoid, etc.) and to a clinical syndrome caused by overproduction of vasoactive mediators by midgut NETs e i.e., "carcinoid syndrome."

NETs are considered to be rare tumors, but recent studies indicate that the incidence of NETs is increasing. [4] The term "carcinoid" is no longer recommended, because it fails to convey the malignant potential that most NETs harbour. The term is also confusing, because it promotes the misconception that all NETs produce the carcinoid syndrome, when most do not. Currently, the term "neuroendocrine tumor" is preferred to describe grade 1 and 2 tumors, whereas the term "neuroendocrine carcinoma" is used to describe grade 3 tumors. Neuroendocrine neoplasms (NENs) occur in almost every organ or region of the body and originate from cells with a neuroendocrine phenotype. [5]

Given the body-wide distribution of NE cells, NENs have been described in the central nervous system, respiratory tract, the larynx, gastrointestinal (GI) tract, thyroid, skin, breast, and urogenital system. The GI tract and lungs are the most common primary tumor sites. [3]

They most commonly occur in the gastrointestinal tract (48%), lung (25%) and pancreas (9%), but may also develop in many other organs, including the breast, prostate, thymus and skin. [2]

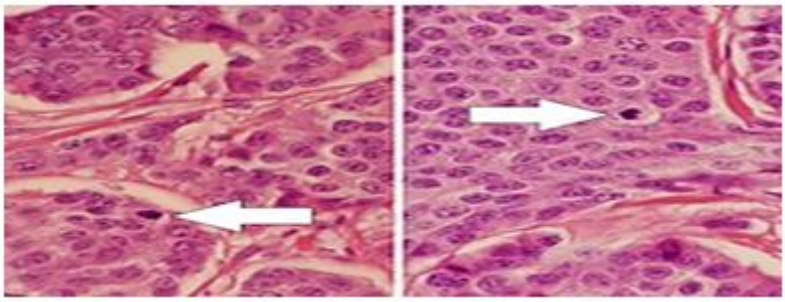

Fig. No. 1: Neuroendocrine Tumor

1. Gastrointestinal (GI) tract - NETs develop most commonly in the GI tract, specifically in the large intestine (20%), small intestine (19%), and appendix (4%). The GI tract plays a central role in digesting foods and liquid and in processing waste. GI tract NETs used to be called carcinoid tumors.

2. Lung - The lung is the second most common location of NETs. About 30% of NETs occur in the bronchial system, which carries air to the lungs. Lung NETs also used to be called carcinoid tumors.

3. Pancreas - Approximately 7% of NETs can develop in the pancreas, a pear-shaped gland located in the abdomen between the stomach and the spine. Pancreas NETs used to be called islet cell tumors.

The important neuroendocrine tumors are:

Sr. No.	**Name of the Tumor**
01	A Neuroendocrine Tumor of the Gastrointestinal Tract
02	A Neuroendocrine Tumor of the Lung
03	A Neuroendocrine Tumor of the Pancreas

1. A Neuroendocrine Tumor of the Gastrointestinal Tract

NETs can form in different organs including the gastrointestinal tract (GI), pancreas, lungs, gallbladder, thymus, thyroid gland, testes, ovaries and skin. Most of the NETs are in the GI (55%) or in the broncho pulmonary system (25%). NETs can develop throughout the GI (GI-NETs) in the following areas:

The small intestine (45%), rectum (20%), appendix (16%), colon (11%), and stomach (7%). [6] Gastrointestinal (GI) NETs were previously referred to as "carcinoids," which was first used by German pathologist Oberdorfer in 1907 as "karzinoide." [7] A recent evaluation of carcinoid tumors identified in the Surveillance, Epidemiology and End Results Program between 1973 and 1999 found the ileum to be the most frequent site of gastrointestinal NET followed by the rectum; the appendix accounted for only 4.8% of NET. [8]

NETs can be classified based on anatomical location or the degree of differentiation. They are also further graded as G1, G2, or G3 based on mitotic count and/or Ki-67 cell labeling index. [9] They are classified by tumor grade which describes how quickly the cancer is likely to grow and spread.

• **Grade 1** (low grade) - NETs have cells that look more like normal cells and are not multiplying quickly.

• **Grade 2** (intermediate grade) - NETs have features in between those of low and high-grade tumors.

• **Grade 3** (high grade) - NETs have cells that look very abnormal and are multiplying faster.

Cancers that are grade 1 or grade 2 are called GI neuroendocrine tumors. These cancers tend to grow slowly and can possibly spread to other parts of the body. Cancers that are grade 3 are called GI neuroendocrine carcinomas (NECs). Gastrointestinal NETs are mainly of epithelial origin. They are histologically characterized by positive silver stain and expression of certain proteins, such as synaptophysin, neuron-specific enolase, and Chromogranin A (CgA). [10]

Classification

Gastric NENs based on histomorphologic characteristics and pathogenesis. Gastric NETs are divided into 3 types-

(1) Type I are the most common subtype and associated with autoimmune atrophic gastritis.

(2) Type II are associated with gastrinoma/MEN-1.

(3) Type III is sporadic with normal levels of gastrin, normal gastric pH, and exhibit a more aggressive behavior pattern. [7]

Type I -Type I lesions correspond to the majority of gNETs found in the stomach (70-80%) and they are associated with autoimmune chronic atrophic gastritis. [11] In this setting, compensatory hypergastrinemia induces proliferation of enterochromaffin- like (ECL) cells, hyperplasia, and, ultimately, NET. Most type I g-NETs are small (<1 cm), G1 tumors, limited to the mucosa or sub mucosa (SM). [12]

Diagnosis of type I is made by upper gastrointestinal (GI) endoscopy with biopsy. Endoscopic findings consist of pale, yellowish and transparent blood vessels of the antral mucosa, contrasting with the smooth and reddish mucosa of normal areas. [13]

Type II -It is the least common type of G-NETs accounting for 5%-6% of all G-NETs. It occurs in response to hypergastrinemia in the setting of hyperchlorhydria (gastric pH $\leq$ 2) typically associated with MEN1-Zollinger-Ellison syndrome (ZES) and rarely sporadic ZES. [13] The frequency of type II gNETs is around 7% and the lesions are usually small and multiple. The metastatic potential is also low, although higher than in type I. [13] The non-compensatory hypergastrinemia induces ECL-cells hyperplasia in the stomach, leading to the development of these tumors. [12]

For diagnostic confirmation, upper GI endoscopy with gastric biopsy reveals normal or hypertrophic gastric mucosa. Hypergastrinemia and gastric pH<2 (hyperchlorhydria) are observed. Serial measurement of gastrin levels following intravenous administration of secretin can also be performed revealing an increase in gastrin levels for patients with gastrinoma, whereas they decrease in healthy individuals. [13]

Type III -These are sporadic G-NETs accounting for 15%-20% of all G-NETs. [6] G-NETs are sporadic tumors that account for 15–20% of gNETs and are more frequently found in men with a median age of 50years. [12] They develop from ECL cells in most cases in the absence of ECL hyperplasia and are not dependent on gastrin. Patients are often asymptomatic or may present with abdominal pain, weight loss and iron deficiency anemia (IDA). Hepatic

metastasis can be the initial presentation. Approximately 10–15% of gastric NETs are categorized as type III tumors. These lesions typically exist as solitary larger tumors, often >2 cm in size. [14] Diagnosis is made by upper GI endoscopy with biopsy, observing a single lesion in normal gastric mucosa. Although rare, carcinoid syndrome (due to the presence of liver metastasis) can be the initial manifestation. [13]

Diagnosis

Studies used to diagnose and differentiate gastric NET disease may be broadly divided into endoscopic, biochemical, histopathologic, and imaging studies. As symptoms related to carcinoid syndrome are rare, endoscopy is the gold standard for diagnosing gastric NETs. [14] EGD with biopsy is the most sensitive modality for the diagnosis. EUS with fine needle aspiration should also be performed in cases of non-diagnostic histopathology, for local staging (tumor invasion and LN metastasis) prior to ER, and in patients with MEN-1 with the additional ability to assess the pancreas for pancreatic gastrinomas. CT/MRI and PET-CT are also indicated. If liver metastases are detected, further MRI of the spine and bone scintigraphy should be performed.

1. Endoscopy

Endoscopy plays an important role in diagnosing NETs of the stomach, duodenum, colon, and rectum. With the popularization of endoscopy, more intestinal NETs are diagnosed. [7] GEP-NETs are frequently detected incidentally during upper or lower GI endoscopy performed for other indications. The majority being type I gastric NETs associated with autoimmune atrophic gastritis and frequently pernicious anemia with type III gastric NETs having the worst prognosis. [15] The majority of patients are diagnosed incidentally during esophagoduodenoscopy (EGD). On EGD, d-NETs are typically single, small (mean size 1.5 cm), sessile, pale, or reddish lesions found in the duodenal cap or bulb. [12]

Endoscopic management is predominantly utilized in type I and localized type II disease. In type III disease, endoscopy plays a smaller role given the higher likelihood of concurrent metastatic disease. [14]

2. Imaging

Multiple imaging modalities are used for NETs, including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US), endoscopy, and functional imaging. They are indicated for different purposes including localization, staging, assessing response to treatment, and prognostication. [7] These functional imaging techniques are sometimes more sensitive for detecting the presence of metastases than conventional cross-sectional imaging and additionally establish the somatostatin receptor status of the tumor. [15] Imaging includes a thoracic, abdomen, and pelvic CT in patients with lesions >1 cm and when LNM are detected, to assess for distant metastasis. [7]

3. Biochemical Markers

The National Institutes of Health (NIH) classifies biomarkers into 3 categories for different functions: type 0 for natural history of a disease, type I for effects of an intervention, and type II for prognosis. Current biomarkers for NETs are useful as type 0 and type I biomarkers but not sufficient in the prognosis of NETs. Currently, 5-hydroxyindoleacetic acid (5-HIAA) and CgA are the most commonly used biomarkers for GI NETs. [7]

Urinary 5-HIAA

The principle urinary metabolite of serotonin, 5-HIAA, is established as a valid and generally available molecular marker for the diagnosis, clinical monitoring, and prognosis of patients with carcinoid tumors. [16] 5-HIAA is the metabolic breakdown of serotonin, levels of which can be measured in 24-hour urine collections or fasting plasma. 24-hour urine 5-HIAA has a sensitivity of 73% and a specificity of 100%. A study of 31 patients comparing urinary to plasma 5-HIAA levels showed that there was no significant difference between the 2 measurements; however, fasting plasma 5-HIAA concentration was more convenient. [7]

Blood Chromogranin A

Chromogranin A is a member of a large family of high molecular weight acidic proteins associated with the secretory process in neuroendocrine cells and tumors. [16] Chromogranin A is an acid glycoprotein present in the secretory granules of most neuroendocrine cells and high in GI NETs. It is now the most widely used biomarker for evaluating NETs. The sensitivity ranges between 60% and 100%; however, the specificity is as low as 10% to 35%.

[7] Consistently with their generally poorer prognosis, patients with carcinoid heart disease have Chromogranin A levels approximately three times higher than carcinoid patients without heart disease. [16] Studies have shown that the level of CgA is associated with hepatic tumor burden and that a sudden increase to >1000 U/L can be associated with rapid tumor progression and shorter survival.74-76 However, CgA may not be as useful for colorectal NET. [7]

Management and Treatment

The treatment of gNETs depends on the clinical type, disease extent, the differentiation of the lesion and the presence or absence of poor prognostic factors. Factors determining management include site of primary tumor, stage, grade, functionality of the tumor, site of metastases, availability of specialized investigations and treatments/ surgery, patient fitness and choice, age and comorbidities. Treatment options depend on tumor type, size, and staging.

Type I -The prognosis of type I is excellent, with 5-year disease specific survival higher than 95%. Only one small retrospective study has compared endoscopic mucosal resection (EMR) and endoscopic sub mucosal dissection (ESD) in type I g-NETs but was restricted to < 1 cm lesions. Most of these lesions are small, well-differentiated and with excellent prognosis, treatment usually consists in the serial endoscopic resection of these lesions. Surgical treatment is necessary only when endoscopic resection is not feasible or when poor prognostic factors are present.

Type II -Treatment of type II gNETs consists in localizing and resecting the gastrinoma. As for gastric lesions, unless there is some factor of poor prognosis, endoscopic resection is enough.

Type III -These lesions should be managed aggressively with total or subtotal gastrectomy (depending on location) associated with lymphadenectomy. The prognosis is poor, with a mortality rate of 25–30% and 5-year survival of 50% or less. Since the majority of patients present with large lesions, MP invasion, LNM, and angioinvasion at diagnosis, guidelines still recommend surgery (partial or total gastrectomy with lymph node dissection) as the preferred approach.

Surgical Treatment for GI-NETs

The primary treatment goal for patients with GI-NETs should be curative surgery. Surgery to remove the primary malignancy and/or local lymph nodes (if affected) is currently the only possible cure and represents traditional first-line therapy; the minimum practical requirements include resectable, well differentiated liver disease with <5% mortality, and absence of right heart insufficiency, extra-abdominal metastases and diffuse peritoneal carcinomatosis. Type I GI-NETs occur in patients with chronic atrophic gastritis. They account for approximately 80% of gastric carcinoids. The chronic absence of gastric acid stimulates antral G cells to secrete excess serum gastrin, which, in turn, causes gastric neuroendocrine cell hyperplasia and the development of multifocal polypoid NETs. Type II gastric carcinoids are caused by hypergastrinemia in the setting of an underlying gastrinoma, primarily in patients with multiple endocrine neoplasia 1 (MEN1). [17]

Management of NETs

Medical Therapy

In addition to reducing bioactive substances, SSA is the first-line systemic treatment of NETs to inhibit tumor growth. In type I and II gastric NETs, somatostatin analogs (SSAs) have been shown to decrease levels of gastrin and have an anti-proliferative effect on ECL cells. SSAs (e. g. octreotide and lanreotide) can be considered in cases in which endoscopic resection is not feasible due to extensive multifocal disease or sub mucosal/lymph node involvement, as well as recurrent disease after repeated endoscopic resection. Somatostatin is an endogenous inhibitor of various hormones secreted from the endocrine system, including serotonin, insulin, glucagon and gastrin. It binds with high affinity to the five somatostatin receptor subtypes (sst1–5) on secretory endocrine cells, which have different inhibitory effects in the body.

Chemotherapy

GI-NETs with high proliferation need to be healed with cytotoxic agents. Poorly differentiated GI-NETs receive standard treatment with platinum-based therapies combined with etoposide. Temozolomide alone or in combination with capecitabine or bevacizumab is a new therapeutic concept for PNETs.

Interferon Therapy

Interferon therapy is generally recommended as a second-line approach in patients with functioning GI-NETs and low proliferation. The effect of interferons on symptom control is similar to that of somatostatin analogues and they may have greater anti-proliferative activity.

Radionuclide Therapy

The response rate of NETs to external beam radiation is limited. However, the introduction of systemic receptor targeted therapy (peptide receptor radiotherapy—PRRT) has provided beneficial effects in patients with unresectable somatostatin receptor-positive NETs. Current data suggest objective response rates of 30%–40% with disease stabilization in 40% of patients.

Symptoms by Tumor Location

The symptoms a person can have from a GI carcinoid tumor often depend on where it is growing.

1. The appendix

People with tumors in their appendix often don't have symptoms. If the tumor is discovered, it is usually when the appendix is removed for some other problem. Sometimes, the tumor blocks the opening between the appendix and the rest of the intestine and causes appendicitis. This leads to symptoms like fever, nausea, vomiting, and abdominal (belly) pain.

2. The small intestine or colon

If the tumor starts in the small intestine, it can cause the intestines to kink and be blocked for a while. This can cause cramps, belly pain, weight loss, fatigue, bloating, diarrhea, or nausea and vomiting, which might come and go. A carcinoid tumor sometimes can cause intestinal bleeding. This can lead to anemia (too few red blood cells) with fatigue and shortness of breath.

3. The rectum

Rectal carcinoid tumors are often found during routine exams, even though they can cause pain and bleeding from the rectum and constipation.

4. The stomach

Carcinoid tumors that develop in the stomach usually grow slowly and often do not cause symptoms. They are sometimes found when the stomach is examined by an endoscopy looking for other things. Some can cause symptoms such as the carcinoid syndrome. [18]

2. A Neuroendocrine Tumor of the Lung

Introduction

Lung NETs are the second most common site for NETs after the gastrointestinal system, accounting for 30.6% of all NETs. Neuroendocrine lung tumors are also characterized by secretory abilities to take up and decarboxylate the amine precursors (APUD system cells). According to the World Health Organization classification 2004, NETs of the lungs share common morphological, immunohistochemical and molecular characteristics and can be divided into three main entities:

• Carcinoid tumors (typical (TC)/atypical (AC)),

• Large cell neuroendocrine carcinomas (LCNEC),

• Small cell carcinomas (SCLC).

In contrast to typical and atypical carcinoids, LCNEC and SCLC are not closely related to each other regarding genetic and epigenetic characteristics. Contrary to carcinoids, no precursor lesions are known for SCLCs and LCNECs. [19]

Etiology

Although lung NETs are considered a distinct family of tumors with shared morphologic, ultra-structural, immunohistochemical, and molecular characteristics, there is evidence to suggest that TCs and ACs are morphologically distinct from LCNECs and SCLCs. Mechanisms for the development and progression of well-differentiated lung NETs are unclear. A recent study has proposed the presence of PNEC hyper plasia in at least three bronchioles associated with three or more tumorlets as the minimum pathologic criteria necessary to diagnose DIPNECH in pathologic specimens. Although poorly differentiated lung NETs (e. g. SCLCs) have a strong association with smoking, there does not appear to be

a relationship between well differentiated lung NETs and smoking, with TCs and ACs often occurring in nonsmokers. [11]

Classification

The 2004 World Health Organization (WHO) classification recognizes 4 major types of lung neuroendocrine tumors (NETs):

Typical Carcinoid

Carcinoid tumors are rare, accounting for 1% to 2% of all lung tumors. In the pediatric population, however, carcinoid tumors represent a common tumor type. Typical carcinoids are different from other types of lung cancers in their presentation at a relatively younger age (mean age range at presentation 45–55 years) and more frequent presentation at an earlier stage (more than 70% of the cases present as stage I disease), as well as good prognosis (more than 90% 5-year survival rate). There is no direct association with smoking because the prevalence of smoking in patients diagnosed for typical carcinoid is similar to the general population.

Atypical Carcinoid

Similar to typical carcinoids, atypical carcinoids are relatively common in the younger age group compared with other types of lung cancers and are frequently presented as early-staged disease. The prevalence of smoking in patients diagnosed for atypical carcinoids is twice as high as the general population. The prognosis of atypical carcinoid is significantly lower than typical carcinoid, with 5-year overall survival rate less than 80%.

Large Cell Neuroendocrine Carcinoma (LCNEC)

LCNEC, like SCLC, is associated with heavy smoking history. It is usually peripherally located in the lung. LCNEC is a highly aggressive neuroendocrine carcinoma. As its name implies, the tumor cells are larger than SCLCs and they have abundant cytoplasm.

Small Cell Lung Cancer (SCLC)

Small cell carcinomas or SCLCs comprise slightly more than 10% of all lung cancers. Smoking history is present in virtually all cases of SCLC. SCLC is a highly aggressive malignancy. Patients usually have metastatic disease at the time of presentation. Most patients

relapse within the first 2 years after treatment and the 2-year survival rate is less than 10% in metastatic patients. SCLC is commonly centrally located in the major airway. [20]

Diagnosis

The diagnosis of lung NENs is prerequisite for any adequate clinical decision-making process, but sometimes is demanding in small-sized diagnostic material. [21]

Diagnosis isn't straight forward. Once you have a diagnosis, some of the tests you have undergone will be used to monitor your health and the effects of your treatment.

Blood / Urine Tests

Full blood count, (B12 + serum Iron), Liver and kidney function, Chromogranin A (and B), Urinary 5-HIAA, CEA, Calcium, Glucose.

Endoscopy

Scans take pictures of your insides from outside your body. As detailed as they are, they don't always give a full view of what's happening inside the hollow organs of the body – for example if doctors want to see inside your airways. In situations like that, endoscopies and endoscopic ultrasounds can be very useful.

• Bronchoscopy

• Endoluminal Bronchoscopic Ultrasound (EBUS).

Scans and other investigations

• Chest x-ray

• Contrast or High Resolution chest CT or CAT scan

• CT / CAT scan abdomen/pelvis to exclude secondary disease – or confirm primary if lung tumor is a secondary (metastasis).

• Gallium-Dotatate PET/CT (SRS SPECT/CT if Dotatate PET n /a)

• FDG-PET – if High Grade / rapidly progressing disease. [22]

Treatment

Localized Disease

Surgical resection is the treatment of choice in patients with localized TCs or ACs, and it is the only curative option for resectable lung carcinoids. After surgical resection, the 5 and 10-year survival rates are both higher than 90% for patients with TCs, whereas patients with AC have a 5-year survival rate of 70% and a 10-year survival rate of 50%. [11]

For patients with peripheral lung tumors, the surgical extent of choice is complete anatomic resection (lobectomy and segmentectomy) with hilar/ mediastinal lymph node dissection or sampling. Small (<2 cm), peripheral typical carcinoid tumors with clinically negative lymph nodes can be successfully treated with sub lobar resection with frozen section confirmation of negative margins. There are multiple retrospective database studies comparing the survival difference between wedge resections and segmentectomies for stage I typical carcinoids. Although some report a survival advantage with anatomic resections, others have shown no difference in cancer-specific or disease-free survival with wedge resections for stage I typical carcinoids. [23]

Advanced/Metastatic Disease

Surgery may also be considered in patients with advanced/metastatic disease, and complete surgical resection of the primary tumor and metastases with curative intent can often be recommended for patients with limited sites of metastatic disease. In addition, an international, multi-institutional analysis reported the efficacy of cytoreductive surgery with or without ablation, particularly in patients with functional hepatic metastasis. However, there is a lack of consensus regarding recommended management approaches for unresectable advanced or metastatic disease owing to the lack of prospective clinical trials that include primarily patients with lung carcinoids. Systemic treatment options for advanced NETs of all primary tumor sites include SSAs (octreotide and lanreotide), targeted therapy (everolimus, sunitinib, and bevacizumab), interferon, chemotherapy, and PRRT (for SSTR-expressing NETs). [11]

Carcinoid Tumors

TCs and ACs, of low and intermediate grade, respectively, are almost always candidates for

surgery. In elderly patients with poor lung function and peripheral tumors, smaller resections, such as segmentectomy or wedge resection may be the only option, although these procedures are not considered adequate from an oncological point of view, given the small but real metastatic potential of these tumors. The most used CT regimen is based on platinum derivatives and etoposide (similar to the standard SCLC regimen), although limited experiences have also been published with other drugs, such as streptozotocin, doxorubicin with 5-fluorouracil, Temozolomide or everolimus.

Large Cell Neuroendocrine Carcinoma

As discussed above, LCNEC shares some morphologic features with other lineages and is often difficult to identify, particularly when the available biopsy specimens are small. Although LCNEC is classified within the group of non-microcytic large cell carcinomas, it is more similar in its molecular profile and biological behavior to SCLC. In any case, for TNM stages I and II, surgery is considered standard treatment. However, poor long term survival (between 27% and 67% at 5 years in stage I resected patients suggests that multimodal adjuvant treatment with CT and/or TRT may be appropriate. Various retrospective analyses have found greater survival in patients receiving adjuvant CT with platinum derivatives and etoposide, similar to the standard regiment for SCLC. [24]

Sign and Symptoms

Carcinoid tumors in the lung may cause:

Coughing, Chest pain, Shortness of breath. [25]

Frequent Symptoms

Some of the signs and symptoms of lung cancer are not obvious at first. You might think that they are being caused by a more common condition. However, if you have these symptoms you should not ignore them:

1. A cough that does not go away

2. Shortness of breath with activity

3. Repeated respiratory infections (e.g., bronchitis, pneumonia)

4. Coughing up blood

5. Shoulder, arm, chest, or back pain

6. Unexplained weight loss. [26]

3. A Neuroendocrine Tumor of the Pancreas

Introduction

A pancreatic neuroendocrine tumor (PNET) is a neuroendocrine tumor (NET) of pancreatic origin. [27] Pancreatic neuroendocrine tumors (PNETs), a group of endocrine tumors arising in the pancreas, are among the most common neuroendocrine tumors. [28] Pancreatic NENs (Pan NENs) are low incidence diseases accounting for less than 3% of all pancreatic malignancies but their prevalence is relatively high and is actually rising. [29] PNETs consist of both functional PNETs with clinical symptoms caused by hormones released by the tumors and nonfunctional PNETs with no distinguishable clinical manifestations. [27] The Pan NENs play a pioneering role in the classification of NENs because they are frequent among the NENs, have a very varied morphology, and may show a multifaceted functionality. [30] PNETs are divided into functional and non-functional tumors. About 90% of PNETs are classified as non-functional tumors and the remaining 10% as functional tumors. Functional tumors secrete particular hormones or peptides, such as insulin, gastrin, vasoactive intestinal peptide (VIP), glucagon, and somatostatin. [31]

Classification

PNETs are also divided into functional and non-functional tumor. A tumor is called functional when its hormone hypersecretion causes clinical syndrome and non- functional when clinical syndrome does not occurs, often in the presence of a hormone secretion. About 10 % of pNETs are functional with symptoms related to the type of hormone secretion; in this group, insulinomas are the most common (30-40%), followed by gastrinomas (16-30%), glucagonomas (<10%), VIPomas (<10%) and somatostatinomas (<5%).[32]

Functioning pancreatic neuroendocrine tumors

1. Insulinoma

Insulinomas are the most common functioning pancreatic endocrine tumors. [28] Insulinomas classically present with "Whipple's Triad:" a combination of symptoms of hypoglycemia, inappropriately high insulin levels with associated documented blood glucose levels of <50 mg/dL, and symptom relief with administration of glucose. [33] The diagnosis is confirmed with low serum glucose, inappropriately elevated serum insulin and C-peptide in exclusion of other causes of hypoglycemia. Insulinomas usually have a small size, and their accurate localization often requires a combination of preoperative imaging examination. [26]

2. Glucagonoma

Glucagonoma is a rare type of functioning PNET, with an estimated incidence of 1 per 20 million per year. Somatostatin analogs are generally successful in the initial management of patients with the glucagonoma syndrome. The diagnosis of glucagonoma requires a high index of suspicion. [28]

3. Gastrinomas

Gastrinomas are characterized by gastrin ectopic release and can be detected in pancreas, but, more often, they are located in the duodenum. [32] The diagnosis of gastrinomas is based on the association of hypergastrinemia/hyperchlorhydria associated with severe peptic ulceration with profuse diarrhea (*Zollinger-Ellison syndrome*). The first and urgent treatment of gastrinomas must be to control the hormonal hyper secretion with proton-pump inhibitors, sometimes at high doses. [26] Gastrinomas are sporadic or hereditary and representing the most common type of pNETs in MEN1 syndrome, with a worse prognosis than in the first case. [32]

4. VIPoma

VIPoma is a vasoactive intestinal polypeptide (VIP) - secreting tumor that commonly arises from the gastrointestinal tract. VIPoma syndrome is also known as WDHA syndrome and includes watery diarrhea, hypokalemia, and achlorhydria. [30] This syndrome was subsequently found to be due to ectopic vasoactive intestinal peptide (VIP) secretion. Treatment with somatostatin analogs is effective in treatment of diarrhea in these patients. [33]

5. Somatostatinoma

Somatostatinoma is the less frequent functional pNETs. This tumor shows different clinical features due to multiple somatostatin activity, such as inhibition of insulin, glucagon, gastrin secretions, and decrease of fat absorption and increase of bowel motility. [32]

Pathogenesis

The pathogenesis of PNETs is largely unknown but is growing as research topical. Approximately 10% of all PNETs are components of familial endocrine tumor syndromes such as multiple endocrine neoplasia syndrome type 1 (MEN1), von HippelL-indau disease (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis (TSC). The etiology of PNETs within the context of these familial syndromes is the inherited germline loss of the respective tumor suppressor gene. [28]

Diagnosis

The diagnosis of PNET is often delayed. Endocrine testing, imaging, and histological evidence are all required to accurately diagnose PNETs. If hormonal hypersecretion syndrome is suspected appropriate biochemical testing is performed to determine hormonal hypersecretion and followed by imaging, endoscopy, and biopsy**.** Biochemical testing should ideally be performed even if hormonal hypersecretion syndrome is not evident because it could be at the subclinical stage, and the hypersecreted hormones can be used as tumor markers during follow up evaluations. Chromogranin A (CGA), neuron specific enolase (NSE), and pancreastatin are the most useful PNET markers. [28]

Imaging

The goals of imaging in patients with pNENs are many and include detection, characterization, and localization of tumors; identification of malignancy and signs of aggressiveness, resectability, and local-regional spread; and detection of metastasis and the extent of disease. [34] Traditional cross-sectional imaging with triple phase computed tomography (CT) or magnetic resonance imaging (MRI) is generally the first step in attempting to localize these tumors. Endoscopic ultrasound may be more sensitive than CT or MRI for the detection of small lesions, and may also provide useful information regarding potential vessel involvement prior to plan resection.

Most pancreatic NET cells express at least two subtypes of somatostatin receptors (SSRs). SRS uses radiolabeled somatostatin analogs (SSAs) and can detect tiny primary lesions and distant metastases.

1. Computed Tomography

CT is the most common initial imaging study in the evaluation of patients with hormonal syndrome suspected with functional PNETs. Helical (spiral) triple-phase contrast-enhanced CT is the best option for the assessment of highly vascularized PNETs and liver metastasis.

2. Magnetic Resonance Imaging

Currently, with the advent of new technology in MRI sequences, PNETs are well visualized on MRI. They typically show low signal intensity on T1-weighted images and high signal intensity on T2 weighted images Similar to CT scan images, early arterial phase image is the best for detecting hyper vascular PNETs and small metastasis on gadolinium contrast-enhanced MRI. The sensitivity of MRI is over 85%, and its specificity is over 75%. Multiphasic MRI can detect PNETs that are less than 2 cm and small liver metastasis compared with CT scan.

3. Endoscopic Ultrasonography

EUS has become a very useful imaging modality to evaluate pancreatic lesions. With high-frequency transducer, it provides a high-resolution image of the pancreas. A recent study on 56 patients with PNETs showed that EUS is superior to multi detector CT for the detection of PNETs even though CT technology has improved. In the same study on 231 patients with PNETs, lesions smaller than 2 cm and insulinomas were usually missed by CT. [31]

Laboratory Evaluation

They take samples of blood, urine and stools to check for abnormal levels of hormones, glucose levels, and other substances.

The evaluation of hormones or peptides, including insulin, glucagon, gastric, VIP, and somatostatin, is essential for the diagnosis of functional PNETs when signs or symptoms are present. The serum level of insulin and C-peptide along with glucose during prolonged fasting (up to 72 h) is useful for the diagnosis of insulinoma if symptoms of hypoglycemia are

present or plasma glucose level is below 49 mg/ dL. Normally, insulin levels are decreased during hypoglycemia, but in patients with insulin-secreting tumors, they do not decrease and C-peptide levels are elevated during hypoglycemia. Proinsulin levels are also elevated in insulinoma. [31]

Management and Treatment

Surgical Management

Depending on the primary tumor location, the options are: simple enucleation, distal pancreasectomy, with or without splenectomy, central pancreasectomy, pancreatico-duodenal resection (Whipple's operation) and total pancreasectomy. [32] The prognosis following surgical resection of localized NET is often excellent. Isolated insulinomas, for example, are generally treated with enucleation; long-term survival following surgery in this patient population exceeds 90%. The role of surgical resection in patients with MEN1 syndrome remains more controversial because of the risk of additional tumors within the remaining pancreas and elsewhere. The reported survival rates for this surgical approach have been in excess of 60% at 5 years, which is twice that of patients with untreated liver metastases. [33]

Drug Therapy

1. Chemotherapy

Chemotherapy is the use of drugs to destroy tumor cells, usually by keeping the tumor cells from growing, dividing, and making more cells. Generally, chemotherapy is used for higher grade (grade 3) pancreas NETs, a large pancreas NET, or if hormonal or targeted therapies are no longer working.

At present, three kinds of chemotherapy schemes are recommended for pNETs: Temozolomide-based and streptozotocin-based chemotherapies (streptozocin mono- or plus 5-fluroracil) are mainly used for tumors with good differentiation and relatively fast growth, whereas the platinum-based scheme (cisplatin plus etoposide) is used for pNEC but not well differentiated NET.

2. Immunotherapy

Immunotherapy for NENs is still in the early stage of clinical trials and the efficacy of anti-programmed cell death protein 1 (PD-1) immunotherapy for GEP-NETs is lower, with an ORR < 10%. The expression of some potential immune-related biomarkers in pNETs has been preliminarily investigated. Expression of PD-L1 in pNET is rare, at 7.4%. Microsatellite instability was observed in 12.5% of patients with pNET. Stable microsatellite, low PD-L1 expression, and tumor mutation burden are associated with a poor response to immunotherapy in NENs. [35]

3. Targeted Therapy

Targeted therapeutic agents, especially those inhibiting molecules involving angiogenesis or growth factor receptor-related signal pathways, have revolutionized the treatment strategy of many cancers. A number of these agents have been tested and evaluated in pancreatic NET, including sunitinib, everolimus, bevacizumab, imatinib, gefitinib and bortezomib. In the following section, sunitinib and everolimus in the treatment of pancreatic NET are reviewed. The two drugs are currently the only targeted agents approved in the United States and Europe to treat patients with pancreatic NET. [36] The objective response rate (ORR) of sunitinib in advanced pNET ranged from 9% to 33.3%, higher than that of everolimus (5%-9.5%). [35]

4. Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) is efficient against well differentiated PNETs but is not widely available, so it is best for patients with large disease burdens that are resistant to other systemic therapies. [30] PRRT with Somatostatin-receptor (SSR) ligands is a novel and promising treatment modality for patients with SSR-expressing NET inoperable or with liver metastasis, because in the no SSR expressing tumors there is not peptide intake.

Principles of peptide receptor radionuclide therapy (PRRT): Radiopharmaceuticals are linked to the receptor ligand, which binds to its specific receptor at the surface of the tumor cell. The complex is subsequently internalized. Radioactivity is thereby specifically transported into target cells. [32]

Sign and Symptoms

Gastrinomas

These tumors make gastrin, too much gastrin causes a condition known as Zollinger-Ellison syndrome, in which the stomach makes too much acid. This leads to stomach ulcers, which can cause pain, nausea, and loss of appetite. Severe ulcers can bleed. Even if the bleeding is mild, it can lead to anemia (too few red blood cells), which can cause symptoms like feeling tired and being short of breath.

Glucagonomas

These tumors make glucagon, a hormone that increases glucose (sugar) levels in the blood. Most of the symptoms that can be caused by a glucagonoma are mild and are more often caused by something else. Excess glucagon can raise blood sugar, sometimes leading to diabetes. This can cause symptoms such as feeling thirsty and hungry, and having to urinate often.

Insulinomas

These tumors make insulin, which lowers blood glucose levels. Too much insulin leads to low blood sugar, which can cause symptoms like weakness, confusion, sweating, and rapid heartbeat.

Somatostatinomas

These tumors make somatostatin, which helps regulate other hormones. Symptoms of this type of tumor can include belly pain, nausea, poor appetite, weight loss, diarrhea, symptoms of diabetes (feeling thirsty and hungry, and having to urinate often), and jaundice (yellowing of the skin and eyes).

VIPomas

These tumors make a substance called vasoactive intestinal peptide (VIP). Too much VIP can lead to problems with diarrhea. This may be mild at first, but gets worse over time. By the time they are diagnosed, most people have severe, watery diarrhea. [36]

CONCLUSION

NETs account for a small proportion of all malignancies, but their incidence is on the rise. GI-NETs are increasing in incidence, in part due to expanding indications for endoscopy, so endoscopists need to be aware of specific characteristics regarding diagnosis, staging, and management. ER is a cornerstone of the management of these tumors, and the endoscopist should be familiarized with different technique modalities in order to maximize resection rates and long-term outcomes.

In some cases it is difficult to differentiate between the neuroendocrine tumors of the lung, atypical versus typical carcinoid and carcinoids versus small cell carcinoma and versus large cell carcinoma, but sometimes also the demarcation of NEs from non-NEs is a challenge.

Among pancreatic neoplasm, PNETs are rare tumor. However there incidence is increasing because of the advancement of imaging technology and increased opportunities for checking pancreatic diseases. The majority of PNETs are non-functional tumors and create symptoms due to the mass itself. Some patients present with symptoms secondary to hormone over production from functional PNETs. Insulinomas are the most common functional PNETs.

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