Pancreatic Cancer: Insulinoma and Gastrinoma — Diagnosis and Surgery

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Pancreatic cancer is one of the most aggressive malignant tumors worldwide. It is considered the 4th cause of overall cancer mortality among cancer patients. 5-year survival rate for stage 1A pancreatic cancer patients is less than 15%. Patients usually have vague complaints leading to late presentation and early metastasis which contribute to the high mortality rate. Tumors of the pancreas can arise from the exocrine part, mainly the duct system, which is the most common, or arise from the endocrine islet cells (neuroendocrine tumors) which are less common. Most of the pancreatic tumors arise in the head or neck of the pancreas with less frequent tumors arising from the body and tail.

Etiology of Pancreatic Cancer

There is no definite etiologic factor, but many risk factors are found those predispose to development of pancreatic cancer.

Risk factors for pancreatic cancer can be familial, smoking, chronic pancreatitis, diet, obesity or diabetes mellitus.
Genetic susceptibility

**Genetic mutations** associated with pancreatic cancer include KRAS2, P53, Smad4 and CDKN2 genes. **ABO Blood group system** has also been implicated in pancreatic cancer risk. Clinical studies have found a higher correlation between nonblood group O and pancreatic cancer. This means an increased risk in patients with blood groups A, B, and AB for pancreatic cancer. Another explanation is the susceptibility of these patients to **H pylori infection** associated with pancreatic cancer.

**Smoking** is responsible for almost one-fourth of pancreatic cancer cases. The risk increases proportionally to smoking index while cessation of smoking can lead to the reversal of the risk similar to the general population after 10 years.

**Chronic pancreatitis** increases the risk of transformation to malignant neoplasm to 2-4%. Prevention of pancreatitis has a major positive impact on decreasing pancreatic cancer mortality.

**Diabetes mellitus, diet, and obesity**

It has been noticed the correlation between obesity and diet with pancreatic cancer. Higher BMI is a risk factor, while diabetes mellitus can be a risk of pancreatic cancer and sometimes a result of the disease.

**Epidemiology**

The incidence of pancreatic cancer is though infrequent, it has a high mortality rate. It is one of the 4-5 most common causes of mortality due to cancer. Incidence varies greatly across the region suggesting the role of diet and other environmental factors such as smoking, exposure to vitamin D, alcohol consumption, and history of diabetes.

**Clinical Presentation of Pancreatic Cancer**

Patients commonly present with **epigastric or back pain**, general constitutional symptoms of **fatigue, anorexia** and **weight loss, GI symptoms** due to the duodenal obstruction; nausea and vomiting. Late manifestation with **jaundice, steatorrhea**, Pruritus (intolerable itching) and **dark urine** due to biliary obstruction.

Physical examination will be remarkable for **cachexia, jaundice, ascites, epigastric or right upper quadrant mass** and **palpable gallbladder** at the right costal margin known as **Courvoisier's sign**.

Other findings at physical examination

- Ascites, hepatomegaly, and palpable abdominal mass.
- **Blumer’s Shelf**-due to metastasis, mass in rectal pouch is found during rectal examination.
- **Sister Mary Joseph nodule**- This is subcutaneous metastasis in paraumblical area in advanced cases.
- **Virchow’s Nodes**- metastatic nodes found behind the medial aspect of left clavicle.
- Other cervical lymph nodes may be enlarged.
**Trousseau sign** is migratory thrombophlebitis and venous thrombosis which can be a common initial presentation indicating hypercoagulable state. **Pancreatic panniculitis** is nodular erythematous subcutaneous fat necrosis thought to be due to pancreatic enzyme digestion of the subcutaneous fat. It can occur in pancreatitis, cancer, and neuroendocrine tumors.

Pain associated with pancreatic cancer is a dull visceral **pain** of insidious onset and intermittent course. It is located in the epigastrium and referred to the back and to the sides. The pain slightly improves by leaning forward and is worse with eating and lying supine. Pancreatic head tumors give rise to **early cholestatic jaundice, dark urine, steatorrhea, itching** and **pale greasy stools**.

**Diagnosis of Pancreatic Cancer**

Laboratory evaluation of patients with jaundice and abdominal pain includes **serum aminotransferase enzymes, alkaline phosphatase, total and direct bilirubin** and **serum lipase**.

**CA 19-9** is a tumor marker that is more sensitive in large tumors and positive Lewis blood group antigen. High levels of the marker are associated with higher specificity. It can be used as a prognostic marker for follow up of disease response to treatment and recurrence.

Imaging with **abdominal ultrasound** is used initially to evaluate jaundice and visualize the biliary tract. A **CT scan** is used to evaluate patients with abdominal pain. It allows visualization of the pancreas and entire abdomen to detect small tumors and help with staging in case of metastases. **ERCP** is used for evaluation of jaundice due to biliary obstruction and allows decompression intervention by utilizing a stent to relieve biliary obstruction.

**MRCP** is an alternative way for biliary tract assessment but lacks any therapeutic intervention. **Endoscopic ultrasound** (EUS) allows visualization of small tumors and lymph node metastasis for better staging and percutaneous guided biopsy. **PET scanning** is mainly beneficial in detecting occult distant metastasis. **Fine needle aspiration** of the tumor can be performed percutaneously guided by ultrasound or endoscopic US and CT scan.

**Staging of Pancreatic Cancer**

Staging is the first step in management to evaluate for **resectability** of pancreatic cancer. Resectable tumors are confined to the pancreas without distant metastasis to the liver, peritoneum or distant organs. Invasion of the major blood vessels in the abdomen, e.g. aorta, superior mesenteric and celiac arteries is not a contraindication to surgery unless the tumor is unresectable.

**For tumor staging, TNM classification is considered**

**Tx:** The primary tumor can’t be assessed. T0: No evidence of primary tumor in the pancreas. Tis: Carcinoma in situ. T1: Tumor is less than 2 cm and limited to the pancreas. T2: The tumor is larger than 2 cm. T3: The tumor extends beyond the pancreas to adjacent structures. T4: The tumor invades the celiac or superior mesenteric arteries.

**Lymph nodes N; Nx:** LN cannot be assessed. N0: No LN metastasis. N1: Positive LN metastasis.
Distant metastasis M: Mx; cannot be assessed and M0 no distant metastases and M1 is positive for distant metastasis.

Treatment of Pancreatic Cancer

Surgical resection is the only curative treatment for pancreatic cancer; however, the long-term survival is still low even with resectable tumors. Pancreaticoduodenectomy (Whipple’s operation) is the most appropriate procedure for head tumors and cholangiocarcinoma. The procedure includes removal of the head of the pancreas, duodenum, gall bladder and gastric antrum. Complications of the surgery include high mortality rate, delayed gastric emptying or pancreatic leak.

Distal pancreatectomy is optimal for body and tail tumors, which usually present late. Complications of distal pancreatectomy are mainly a pancreatic leak. Surgical intervention may be used in the unresectable tumor for palliation, e.g., decompression and relieve of the obstruction and biliary drainage.

Celiac ganglion neurolysis is another intervention for pain control in patients with an unresectable tumor. Gastrojejunostomy is performed in patients with duodenal obstruction.

Gemcitabine-based chemotherapy regimens are approved for metastatic cancer with 1-year survival benefit and may be combined with erlotinib for better results. Neoadjuvant and adjuvant chemotherapy treatment is controversial. FOLFIRINOX regimen which combines leucovorin, fluorouracil, irinotecan, oxaliplatin was approved recently with a slightly better survival benefit in patients who can tolerate multiple chemotherapeutic agents.

Palliative therapy: Jaundice improves with endoscopic stent placement and decompression surgery. This is indicated to relieve the biliary obstruction, malabsorption, pruritus and guard against cholangitis. Pain control with opiates and radiation therapy should be considered in all patients with resectable tumor and palliative therapy.

Pancreatic Neuroendocrine Tumors

Neuroendocrine tumors arise from the islet cells of the pancreas that secrete hormones; insulin, glucagon, gastrin and vasoactive intestinal polypeptide; however, most of these
tumors are non-functioning and do not secrete hormones. These are rare tumors which constitute less than 5% of primary pancreatic tumors. They can be sporadic or associated with other syndromes, e.g., *multiple endocrine neoplasia I, Von Hippel Lindau disease* and *neurofibromatosis I*.

### Localization of neuroendocrine tumors

A **CT scan** is the best initial diagnostic modality with high sensitivity and specificity for pancreatic neuroendocrine tumors. The sensitivity increases with the tumor size and contrast enhancement.

**MRI with gadolinium enhancement** has excellent sensitivity and specificity. It is preferred in the detection and evaluation of liver metastasis.

**Endoscopic ultrasound (EUS)** is accurate in detecting small micro tumors that cannot be detected with CT or MRI. It is also useful in detecting duodenal wall gastrinoma and lymph node metastases. It allows the US-guided fine needle aspiration for tumor cytology.

**Octreotide scan** utilizes radiolabelled somatostatin analog for visualizing tumors with high somatostatin receptor expression. It is accurate in the localization of even non-functioning and poorly differentiated tumors.

**Pet scan** is accurate in localization and staging of NETs with high resolution, especially with functional tracers, e.g., gallium.

**Venous sampling** is sometimes used for localization of functioning tumors not visualized by conventional imaging. A sampling of the portal vein or hepatic vein with an assessment of hormonal levels, especially after injection of the stimulating agent, e.g., secretin. Intraoperative palpation of the duodenum and pancreas and intraoperative ultrasound are used for accurate localization and staging of the tumors that cannot be detected by conventional imaging.

**Insulinomas** are benign tumors which secrete insulin causing hypoglycemia. Patients present with symptoms of hypoglycemia and adrenergic stimulation including; palpitation, weakness, diaphoresis, amnesia, abnormal behavior, tremors and blurring of vision. Severe cases may present with seizures and coma. Symptoms improve dramatically with glucose administration.

Laboratory diagnosis depends on elevated serum insulin in patients with induced hypoglycemia for 72 hours or postprandial hypoglycemia. Elevated serum insulin more than 10 µU/mL with hypoglycemia below 40 mg/dL and C-peptide levels of more than 2.5ng/mL are considered for diagnosis.

### Pancreatic Insulinoma

#### Management

**Surgical resection:** After accurate localization of the tumor site, surgical intervention carries the most favorable prognosis. Surgical resection of the tumor varies according to the location. Enucleation of solitary tumors, distal pancreactectomy, total pancreactectomy and Whipple procedure are all used for resection. Resection, cryotherapy, radiofrequency ablation or embolization are all used for metastatic disease to the liver.
Laparoscopic surgery is less invasive than open surgery and can utilize endoscopic ultrasound for better localization of the tumor.

Medical therapy: Diazoxide is used to inhibit insulin secretion. Side effects include edema and hirsutism.

Octreotide: second line after diazoxide and can inhibit secretion of insulin, glucagon, and gastrin.

Verapamil has also been tried with positive results.

Glucagonoma originates from alpha cells of the islets of the pancreas. Mostly malignant and metastasizes early. The tumor secretes glucagon hormone responsible for hyperglycemic symptoms and necrolytic migratory erythema.

Clinical presentation

Patients present with diabetes mellitus, anemia, weight loss, diarrhea, hypercoagulability with thrombosis, cheilitis, and stomatitis and necrolytic migratory erythema. Necrolytic migratory erythema is painful pruritic lesions common in most patients in friction areas and range from maculopapular rash, blisters and pustular infective lesions. Early diagnosis of these lesions will help avoid complications of thrombosis and neurological involvement.

Laboratory evaluation: CBC, serum glucose, hepatic function tests are important to assess for diabetes mellitus and liver metastases. Radioimmunoassay (RIA) of glucagon level of more than 500 pg/mL is diagnostic.

Medical treatment: Nutritional support for patients with weight loss and nutritional deficiency is the first step. Octreotide can be used to inhibit glucagon secretion. Evorolimus and sunitinib are approved for unresectable malignant tumors.

Surgical intervention: Similar to insulinoma after tumor localization and assessment of respectability. Liver metastases can be treated with surgical resection, radiofrequency ablation or arterial embolization.

Gastrinoma are tumors that secrete gastrin hormone responsible for what is known clinically as Zollinger-Ellison Syndrome. The tumor arises from the pancreas, stomach, duodenum, jejunum and even lymph nodes. They can be malignant with metastases to the liver and regional lymph nodes.

Clinical presentation: Hyperacidity as a result of gastrin hormone leads to multiple peptic ulcers that are resistant to medical treatment. The most frequent symptoms are abdominal pain and diarrhea. Patients may present with complications of peptic ulceration including perforation, pyloric stenosis, GI bleeding and complications of acid reflux including oesophagitis and stricture. Diarrhea and weight loss develop due to irritation of the small intestine with acidic content.

Laboratory evaluation: Gastric PH and basal acid output are used to assess gastric hyperacidity while fasting serum gastrin level of more than 1000 pg/mL is a sensitive test for screening. Measurement of serum or venous sample gastrin and gastric acid secretion following secretin or calcium injection is more sensitive to localize gastrinoma.

Proton pump inhibitors are used to control the symptoms, while chemotherapy is used for a malignant metastatic disease. Surgical intervention is the definitive cure for resectable tumors.
**VIPoma** is a rare tumor characterized by hypersecretion of vasoactive intestinal polypeptide leading to diarrhea and hypokalemia.

**Prognosis**

Though pancreatic cancer survival rate has improved with time, still it is considered incurable. For all stages of pancreatic cancer survival rate for the first year is 20% that reduces to 7% for 5 years. The low survival rate is attributed to the fact that malignancy has been already metastasized grossly at the time of diagnosis. Moreover, surgery is not possible at every metastatic point.

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