The Endocrine System

☑ Sheet ☐ Slide ☑ Handout

PATHOLOGY

Number:	7
Subject:	Pancreatic Tumors
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This sheet was written according to the record that belongs to section 2

Everything in the slide is included, only refer to images

❖ Pancreatic neoplasia :

As you know by now the pancreas is divided into two main parts: Endocrine and Exocrine

The most common pancreatic tumor is **pancreatic carcinoma**:

- It arises from the exocrine part, mainly from the ducts
- It's very aggressive and we call it the worst human cancer

But our focus is on the endocrine part of the pancreas.

❖ Pancreatic Endocrine Neoplasia (PEN)

It was called (islet cell tumor)

PEN originates from the endocrine part of the pancreas

Epidemiology of the disease:

- It is a very rare tumor, constitute of only 2% of all pancreatic tumors
- It is much less aggressive than the pancreatic carcinoma
- It is a tumor of adulthood, not in children

To the right is a picture of Steve Jobs, founder of Apple Inc.

Jobs was diagnosed with PEN in 2003 and died of respiratory arrest related to the tumor on October 5, 2011.

Characteristics of the disease:

- It can be single or multiple
- It can be benign or malignant (benign tumors are usually small in size, less than 2cm)

How do we define malignancy in these tumors?

We don't define malignancy according to morphology, as it could be misleading, since we don't have polymorphism or abnormal cell appearance most of the time.

We rather define malignancy by invasion and metastasis (mostly to lymph nodes and liver)

These tumors (benign and malignant) can be functional (**secreting**) or non-functional (**non-secreting**)

❖ Types of PEN tumors :

1) Beta-cell tumor

- The most common one of all others
- Arises from the beta-cells of the endocrine pancreas
- It is an Insulin secreting tumor
- It can be called insulinoma
- 90% of cases are single, benign (but it can be multiple)
- Mostly it is a functioning tumor (secretes insulin)

What would the symptoms be?

When we have **high insulin** levels we expect the patient to be **hypoglycemic.**

Remember this: hypoglycemia is much more dangerous than hyperglycemia

WHY?

Hyperglycemia needs **long time** to develop clinical consequences while hypoglycemia needs **minutes** to kill the patient.

The symptoms of hypoglycemia are mostly related to CNS:

- Seizures
- Loss of consciousness
- Confusion.

These symptoms are **exaggerated** when the patient needs more glucose for example during **fasting or exercise**

20% of patients will develop **severe** symptoms, which can be fatal

Under the microscope:

- Proliferation of the islet cells (beta cells mostly but others as well).
- Normally these cells are found as islets, meaning that they are scattered and separated by fat and pancreatic tissue but due to the proliferation of the cells in the insulinoma **we don't see fat or pancreatic tissue we see sheets of cells**.
- Cells appear **monotonous**, there is no polymorphism in both benign and malignant tumors

How do we know if it's a beta-cell tumor or an alpha-cell tumor or whatever?

We do special staining by **immunohistochemistry**

We have insulin stain, if we use it and the results are **brown colored** cells (insulin-secreting cells) then it is positive, and this is a beta-cell tumor

If it's negative (no color) then we use other stains like alpha stains

2) **Gastrin secreting tumor (gastrinoma)**
   - Arises from gastrin secreting cells

What cells secrete Gastrin?

Normally, gastrin secreting cells **are not limited** to the pancreas.

- We see gastrin secreting cells in the peri-pancreatic fat, duodenum, and pancreas.
- We call this **gastrinoma triangle**; the tumor can arise in any of these areas
- 90% of them are severe (worse than insulinoma)
- **It has a similar histology to insulinoma, but they don't respond to the insulin stain**

What would the symptoms be?

90% Patients develop **peptic ulcer** (gastrin enhances acid secretion), and this syndrome is called **Zolinger-Elisser syndrome** (peptic ulcers secondary to gastrinoma)

These ulcers are very unique; they are multiple, located in the duodenum, stomach, and **they don't respond to treatment** (refractory to treatment)

In 50% of the cases the tumor becomes malignant (invasion and metastasis)

25% of the cases are part of MEN1 syndrome (discussed later)

We differentiate between gastrinoma and other PEN neoplasms under microscope by staining.

3) Alpha-cell tumor

- Arises from alpha cells
- Glucagon secreting tumors (glucagonoma)
- It is common in women specially in early menopause
- Also similar to insulinoma histologically

What would the symptoms be?

- When glucagon levels rise, it causes hyperglycemia, and mild diabetes.
- A feature of the disease is that it causes a special type of skin lesion, we call it **(Necrotic Migratory Erythema).** And as the name implies :

Necrotic: it is an ulcerative lesion

Migratory: starts in one place and then heals and then appears in another place

Erythema: type of skin rash

Most common site is in the upper part of the body, neck, mouth

Skin lesions are due to glucagon, not hyperglycemia.

Pathogenesis :

It is largely unknown, but it is thought to be secondary to nutritional deficiencies of some minerals like zinc

It is also differentiated from other tumors by staining.

❖ Multiple endocrine neoplasia (MEN)

- We have two subtypes:
    1. MEN1
    2. MEN2
- Both of them are inherited in an Autosomal Dominant fashion

❖ MEN1:

Pathogenesis:

- Due to a mutation in the **MEN1 gene** .
- MEN1 gene is normally found on chromosome 11 (11q13)
- The normal function of MEN1 gene: it is a tumor suppressor gene
- This gene is very active in endocrine cells

Commonly, in AD diseases, if one gene is mutated and the other is normal the disease will develop

In MEN1, both copies of the gene need to be mutated

Patients usually acquire a mutant gene on one allele (either from the mother or the father) and they lose the second one during life due to a mutation, so they will get the disease **later** in life (not born with it)

MEN1 is called the **3P** disease, it arises in:

1) Parathyroid (95%) the most common one, multiple tumors and hyperplasia
2) Pancreas (40%), often functional (insulinoma, gastrinoma), sometimes a mixed tumor, fatal hypoglycemia, behave aggressively with metastasis
3) Pituitary (30%), prolactinoma is the most common one

❖ **MEN2** :

- Mutation in RET protooncogene located on chromosome 10 (10q11.2)
- Patients who have the mutation 100% have **medullary carcinoma**
- We have different types of mutations that happen in RET gene, and the degree of severity of the disease depend on the type of mutation.
- The most severe type appears in childhood
- These tumors are **rare**, you may never face cases with MEN2, but we care about them clinically because it is one of the first tumors to be discovered

Suppose a patient presented to you with a RET gene mutation, or MEN2 syndrome, what would you do?

1. You are sure that this patient has medullary carcinoma in his thyroid gland, in the first two decades of life
2. Other siblings have 50% chance of getting the disease, so you do a genetic testing and counseling to test for a mutation
3. The patient is offered a prophylactic thyroidectomy, due to the bad prognosis of the disease

We have two further subtypes:

MEN2A

Tumors are:

1. Thyroid:
- Medullary carcinoma (100%) (The most common of all others)
- C-cells hyperplasia
2. Pheochromocytoma of the adrenal gland (50%)
3. Parathyroid hyperplasia (1/3 of cases)

MEN2B

- All the previous tumors but no parathyroid hyperplasia
- In addition, they develop other neuronal tumors like ganglioneuroma of mucosal sites (GI tract) or in the brain

These patients have **Marfan** like features (tall, thin, long limbs)

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I wish you all the best :D