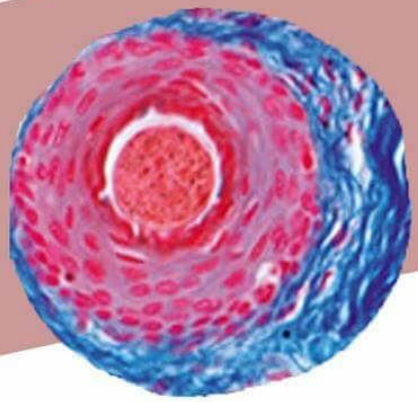
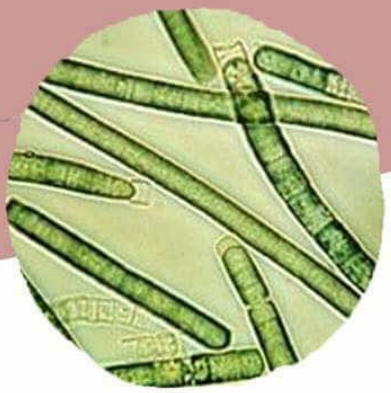
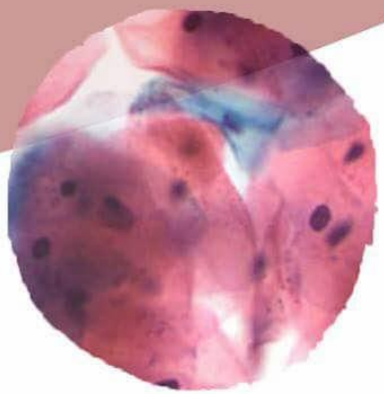
INTRODUCTION TO PATHOLOGY

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Sheet# 24

Clinical Aspects of Neoplasia:

[Note: Study this sheet with the slides simultaneously.**]**

During the entire lectures we have taken where cancer goes and how it does this and that, but we missed one important thing which is the patient. How cancer affects the patient and how it results in presentation to us.

Tumor effects on host:

We are going to illustrate some of them as clinical case scenarios:

- **Location**, how can location of cancer affect how patient presents to you;
    a) If you have a pituitary tumor that grow and destruct the blood supply that patient will present in hypopituitarism rather than a mass or a lump.
    b) A 55-year-old comes into the clinic looking particularly yellow, you will think "commonly" obstruction of the bile duct and other things related to liver but when you examine the patient the liver is not quite normal (when the patient takes a breath you can feel the edge of the liver) the edge is not straight you can feel something wrong may be a mass has compressed on the bile duct causing the jaundice or when you do work on the patient expecting to find a stone (common) you find a small tumor in the duct of the gall bladder that can cause the patient to present as obstructive jaundice.
    c) A 55-year-old male comes to you with problems initiating their urine stream, they feel full they want to go to the bathroom but they can't. They are standing there for 3 minutes trying to get the urine stream once it comes is not constant, they pee a little and stop, pee a little and stop, typical presentation for enlarged prostate. You will do colorectal examination trying to feel the prostate of the patient, the size of the prostate is large but it is not particularly smooth it feels craggy and it feels bumpy this must raise flag that this is may be prostatic cancer. However there are several presentations to benign prostatic hyperplasia, but if their tumor associated antigen is high which can also be high in benign prostatic

hyperplasia but when you feel the bumpiness this can tip the balance towards malignancy.

d) A patient comes in saying: “Doctor, I have been taking a shower the other day and as I was cleaning myself I felt something that is not quite right! It was not smooth there is a bump that did not used to be there!” You will feel the breast and you will find a lump that is a representation for a neoplasm, benign or malignant? You will take a biopsy.
e) A 22 years old comes to you with unilateral hear loss, hmm but there is no reason for it! The EMT doctor looked to his ear the membrane is normal no rupture and the entire ear is fine. Then, you do a MRI and you find a mass compressing the acoustic nerve, “the fact that the patient is young should tell you that either exposure to mass carcinogenic substances has occurred or hereditary.” What autosomal dominant genetic disorder causes acoustic neuroma that can cause hear loss? Neurofibromatosis type 2 (NF2).
f) A 27 year old female comes to you with a disturbing, increasing size mole. The mole is blacker than it used to be, it wasn't this big few months ago, and its edges are irregular. When you take the history of the patient, she turns out to be an avid sun bather. You think of melanoma! It potentially started from something benign and then transformed into something malignant.
g) A small tumor (leiomyoma) compressing the renal artery can potentially block the blood supply to the kidney causing its failure. Now, how a patient with renal failure will present? Edema, hypertension. Then you do different tests that are needed to diagnose the case.
h) A very large polyp (a benign growth) in the intestines. This growth may become caught in the peristaltic pull of the gut causing intussusception which is herniation of a bowel inside the bowel underneath it causing obstruction (think of a tube, and you've got something hanging from inside the tube and you're pulling this thing, the upper part of the tube could potentially go to the lower part of the tube). Now a patient has bowel obstruction, what will he present with? Abdominal pain, constipation (if it's low enough), if it's high enough (near the start of the intestine) it will cause vomiting, if it's a partial obstruction it'll cause bloating and the patient will

be having a hard time going to the bathroom. You know that colon absorbs water, so if the passage is reduced the fecal matter will get dryer and harder and the patient will come to you having hard defecation with pain and maybe bleeding.

- **Function**,
    1. A 32-year-old patient comes top you with flushing sweating, palpitation, hyperactivity and he has lost some weight recently. What are we describing? “Remember with adrenals we are worried about blood pressure.” With hyperthyroid we are worried about the above, then you go and feel the patient’s thyroid, if there is a cancer you might find a larger thyroid or a lump.
    2. A 55-year-old male patient who smokes 3 packs of cigarettes a day, presents with worsening of their cough, blood in their cough and shortness of their breath even more than before but there are also symptoms of a hormonal imbalance, what should this raise in your mind? Lung cancer, and what is the hormone being produced? ACTH, the basis of *Cushing's syndrome*, an example of the paraneoplastic syndromes (It was homework to check what is Cushing's syndrome, the doctor will not ask specifically about it in the exam but whenever you come across something you do not know have the curiosity to find something about it because otherwise it will not stick in your head, this was his advice!) This is an example of ectopic hormone production, hormones being produced at locations where they are not supposed to be produced.
    3. A 65-year-old female presents to you with paleness, palpitations, tiredness and shortness of breath; what are we describing? We did a CBC and found that she has anemia, but white blood cell count was normal, also it is an iron deficiency anemia, so an elderly patient who has iron deficiency anemia is a colorectal cancer patient until proven otherwise. This patient has a tumor in the GIT and this tumor began ulcerating and it bleeds, and many do not look after their bowel movements after they are done, so even if there was not blood it may not be seen esp. if the bleeding was little and over a long period of time they may not have noticed it and present

with symptoms of anemia. Keep in mind that whenever you have ulcerating in the epithelial tissue you are exposed to infections as part of your innate immunity being disrupted.

4. A 25-year-old secretary who likes to sun bathe in the Bahamas comes to you with a large pigmented mole that wasn't there recently and the edges are not uniform. Melanoma a malignant one as she is a sun bather and gets intense radiation.
5. A 22 year old medical student walking and then he faint, he is given some sugar. Every once and a while he faints. Why is his blood sugar constantly low? Something is not right, too much insulin! You think of a well-differentiated tumor the produces too much of a hormone, like insulin.

- **Cachexia**,

Very nonspecific symptoms of tiredness, weight loss, loss of lean body mass (anything but fat in your body) and losing their muscles, they are a bit anorexic and there is no good reason for his massive amount of weight loss! Unfortunately, advanced cancers in particular produce cytokines even your immune system like macrophages can produce cytokines like tumor necrosis factor TNF in their effort to fight the cancer and it will cause you to become anorexic and also keep your basal metabolic rate high. Normally, when you are starved the basal metabolic rate drops so if you stop eating and your basic metabolic rate is high, your body mass will decrease. These same cytokines will activate lipolysis, induce proteolysis, increase ubiquitin proteosomal meditated degradation of skeletal muscles, and inhibit lipoprotein lipase although it is not always the case of all tumor cells. All of this cause a reduction in fat mass and most importantly in lean body mass and patients end up in cancer cachexia and the **only** effective treatment is the removal of the cancer itself, no drug exists and pharmacists have no clue how to stop it. Keep in mind that cachexia is **not because the tumor has increased nutritional demands** it is because of the cytokines and growth factors produced by the tumor and the immune system. Almost all cancers can produce cachexia esp. if they are advanced cancers and for cancers that present late such as pancreatic cancer.

- **Paraneoplastic syndromes**, already mentioned, there is a table in the book do not memorize it all ,but there are three very common paraneoplastic syndromes, the most common is **Cushing's syndrome** which results from ACTH production from a lung cancer.

  The second is **hypercalcemia** resulting from the production of parathyroid-like hormone that releases calcium from bone to the blood stream**. However**, hypocalcaemia can also result from metastases. When a tumor goes to the bone (as it is a common metastatic site, not as common as lung or liver but it can happen), and this particular tumor cause destruction of the bone it is called lytic bone lesions, and the calcium will present in the blood stream and this is presented in hypercalcemia. Hypercalcemia that results from metastases is not a paraneoplastic syndrome. Paraneoplastic syndromes are effects that are not explained by the tumor original growth or by its metastases; not because of a mass effect or metastases so typically ectopic hormones or cytokines factor or …etc.

  The third one is that cancer patients are **hyper coagulant** i.e. they clot a lot easier than the general population, the syndrome is **non-bacterial thrombotic endocarditis**. The clot forms go somewhere else and blocks something and causes some sort of a problem and in this case we are talking about thrombosis in the heart. If the patient is undergoing surgery he should be receiving anticoagulant (e.g. heparin).

  These paraneoplastic syndromes are important in establishing a diagnosis so you should know them very well. If the patient comes to you with thyroid toxicosis you should keep it in the back of your mind, has patient been exposed to a carcinogen, has this patient a thyroid cancer patient? If the patient comes with all sorts of hormone imbalances you should wonder if this patient is a cancer patient or not? We are not saying all patients are cancer patients as the vast majority are not; cancer is rare. However, if you miss a cancer patient you and your patient are in trouble. Also, it is important in determining the pathology of a tumor. If a patient comes with cough sputum and Cushing's syndrome you should think of lung cancer. If a patient has a tumor in the pancreas that produces insulin ectopically this is going to present to you with hypoglycemia and this patient might die from hypoglycemia not the cancer so you are going to treat the

hypoglycemia first not the cancer. You should treat the most severe not the most life-threatening.

So a patient has presented to you and you have suspected cancer you found that there is lump and have taken a biopsy, you have done all different types of radiological tests in order to do two things **grade** and **stage** the cancer:

-They are already mentioned from lecture1-

Grading: how different it is from the normal tissue (from 0-4 with 0 being normal tissue) .Low grade or well differentiated cancer so "rule of thumb" it would be less aggressive and less able to metastasize. High grade anaplastic cancer is going to be more likely aggressive and more likely to metastasize (with exceptions to this rule).

Staging: Progression, how far along has the cancer got in its pathogenesis, is it a small tumor? Is it a big tumor? Are there lymph nodes? Are there distant metastasis?

There two major classifications for staging of cancer:

1) The TNM classification, it stands for "Tumor Node Metastasis" **T (tumor)**: is it a small tumor? Is it a large tumor? Has it gone through all the layers of the organ, has it pursued on to the next organ? **Nodes**: are there nodes that have been invaded by the cancer? How many nodes? How far away those nodes are? **Metastasis**: Is there metastasis or not?
2) The AJC classification, it stands for "American Joint committee", based on TNM basically meaning stage one>small tumor (NO invasion, NO lymph nodes), stage two>it is a larger tumor but still confined (invasion, still NO lymph nodes), stage three> means that there are lymph nodes involved, stage four>means that there are metastasis.

Designation	Description
Tumor	
Tis	In situ dysplasia or intramucosal carcinoma
T1	Tumor invades submucosa
T2	Tumor invades into, but not through, muscularis propria
T3	Tumor invades through muscularis propria
T4	Tumor invades adjacent organs or visceral peritoneum
Regional Lymph Nodes	
NX	Lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis or seeding of abdominal organs

Example: colorectal cancer "Do not memorize it (the figure). It is just for illustrations but you may next semester".

The numbers are not arbitrary, they are based on survival percentages, patients with three or less lymph nodes survive a lot better than patients with four or more lymph nodes. The number and distribution is different for each cancer based on the data we have.

When you see an X in front of N or M it means we haven't assessed it or we are unable to assess it. An (is) in front of T it means carcinoma in situ not an invasive carcinoma yet, it is a paraneoplastic syndrome.

Stage*	Tumor-Node-Metastasis (TNM) Criteria			5-Year Survival (%)
	T	N	M	
I	T1, T2	N0	M0	74
II				
IIA	T3	N0	M0	67
IIB	T4	N0	M0	59
III				
IIIA	T1, T2	N1	M0	73
IIIB	T3, T4	N1	M0	46
IIIC	Any T	N2	M0	28
IV	Any T	Any N	M1	6

The AJC classification for colorectal cancer:

[**Note**: As you go down the scale the survival rates decrease and as you are descending and finally reaching metastasis survival is very low, why? There are two major vital organs when metastasis reaches them there is not

much that you can do which are the liver and lungs as you cannot take them entirely! Now, what is the major difference between an older cancer and a younger one? It has become more aggressive, has gained more hallmarks became resistant to treatment and the patient who has metastasis means that the cancer is old; the aforementioned points are characteristics to it hence, survival rates drop! So you as a general physician or whatever you decide to be in the future your job is early detection, because we do not have a treatment for metastasis.]

Diagnosis:

How do we diagnose cancer? Biopsy! You never diagnose it by sight, radiology, or physical examination. You always have to confirm with a biopsy!

What are the types of biopsy?

We have **incisional biopsy** where you take part of the tumor. An **excisional biopsy** you excise, i.e. you remove the entire tumor because it is small and excisable (e.g. breast lump).

With excisional biopsy you send the whole thing to the histopathologist and then he will take a representative sample. Here is a good question, what do you need to send your biopsy with? You need to send it with a history and a physical examination.

The importance is illustrated in this example; let's assume you are an orthopedic surgeon a 15 years old boy comes to you with a broken leg because he fell of a bike or got hit by a car. You are not a particularly good orthopedic surgeon and when you do the cast you do not approximate the bone correctly, several weeks later when the cast is supposed to be removed, you noticed that the bone is still broken and it didn't heal correctly, thinking that the patient has a problem in bone healing you take a sample from the healing and send to the histopathologist and if he didn't get the history and physical examination he will say: Bone cancer(osteosarcoma) and it looks under the microscope exactly like a healing bone region. You will say,"what! The patient just broke his leg!" The histopathologist would say, "you moron didn't give the history of the patient and did not approximate the bones correctly!" So location, what happened to the

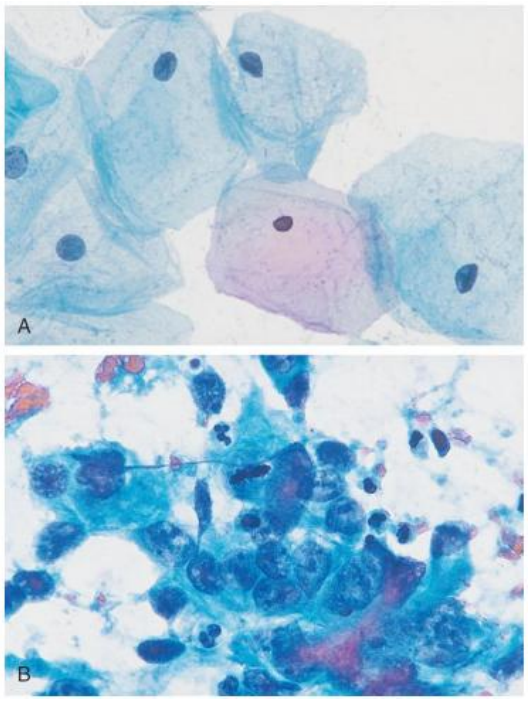
patient , how old is the patient, where did the tumor came from, what are the signs and symptoms and any ectopic hormone production will aid you and the histopathologist in diagnosing the sample.

Sometime tumors you can't get at surgically you can take what is called **needle biopsy** in the past these needle biopsies were preserved for tumors you can't get at easily thyroid or breast and take a representative sample. Where you take the representative sample from? Not from the edges as it is not going to be representative and not from the center as it is more likely to be necrotic. Send it with a proper history and documentation of what you think is going on.

Nowadays you can take needle biopsy from wherever you want from the liver, lung and even from brain. You use radiographic techniques or ultrasound assisted biopsies where you see where the needle is and decide the location of the representative sample.

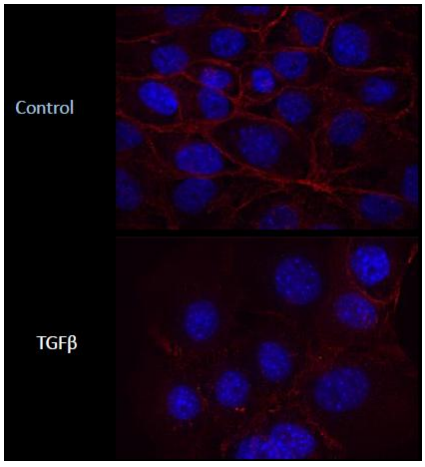
Sometimes you already have the patient open and you've taken out as much of the tumor as you can, now you ask the pathologist for a frozen section to know if you have it all or not. He quick freezes the tissue, puts it on the slide and looks at it. In specialized hands it can be a very quick and accurate way to know if you're done or not. But sometimes it won't be conclusive and you have to close the patient up and wait for a full histopathological diagnosis.

Taking bits of tissues is not the only type of biopsies. **Cytological biopsies**, scrapings or washings are also used to diagnose cancer, for instance, a pap smear, you use a long cotton bud (like the one you clean your ear with it but do not use this one) and put it in the patient's cervix, take a little scraping from the outside and from the inside put it on a slide and under the microscope you can decide. (Picture A is what a smear should look like. Picture B on the other hand is an unhealthy one "more nuclei, bigger, angrier, and darker.") You are looking for

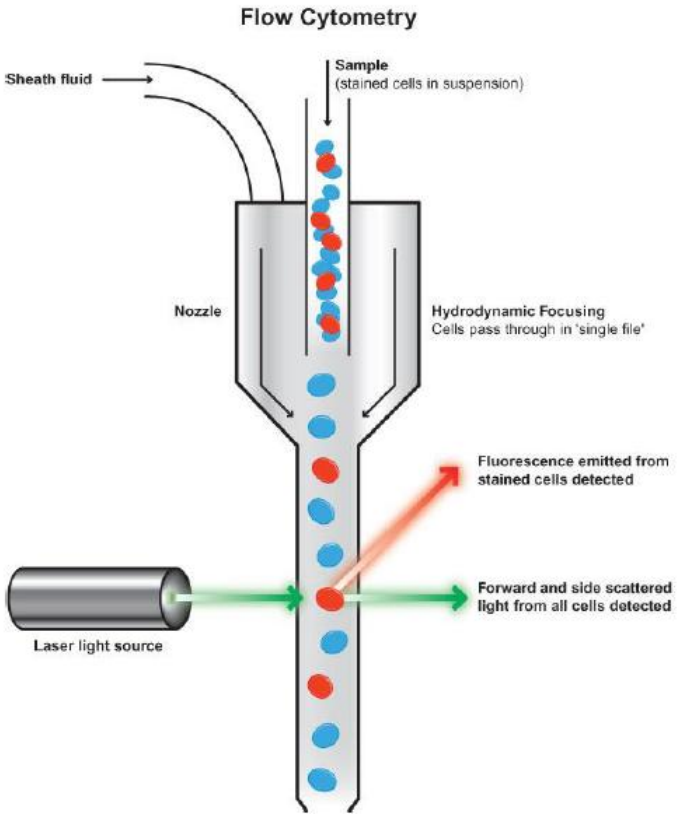


dysplasia and you want to catch it and treat it easily before it becomes cervical cancer. This is one of the main reasons cervical cancer has dropped over the years. Also, you can take scrapings and washings from urinary bladder. Also, during a bronchoscopy take the cells that might have sloughed of wash it and then look under the microscope, why is this a good technique? Take in mind that epithelial cancer is where you're getting these samples from; one of the things that epithelial cancer goes is epithelial to mesenchymal transition. Mesenchymal cells are not bound to other cells and they do not stick on basement membrane so they are going easy to scrape and wash of.

Immunohistochemistry, you can take the tissue from the patient but instead of putting an ordinary dye, you put an antibody to a specific protein which you know is associated with one type of cancer or another. Example, you are looking for E-cadherin. Take some purified human E-cadherin inject it into a mouse or a rabbit or a goat and this is going to be a non-self protein for the animal and the animal will produce antibodies for that, then you purify them a company does those steps not you in the lab. You are going to put them on the sample, and they have something that turns color or fluorescent therefore you can detect over expression or under expression of a particular protein.



These are Dr. Mazin's slides. After you add the antibody and see the colored picture you should expect to see it between the cells, and after adding TGF-ß (inducing epithelial to mesenchymal transition), e-cadherin is lost. Basically we can do this technique for any of the previously mentioned proteins in the neoplasia lectures, like when we a have a specific antibody for a mutated protein.



Flow cytometry, in this technique the cells are in a suspension rather than a slide i.e. the cells are floating singly in it. Which type of cancer we use this technique for? Leukemia lymphomas, they are already single cells suspension. Different white blood cells have different surface markers; CD4 is for T-helper cells, CD8 is for cytotoxic T-lymphocytes, therefore you can diagnose the different types of cancer by adding antibodies to those markers moving those cells in a single in front of a laser and allow the laser to read whether this cell is a B or a T cell or it has over expression of something or another. Nowadays, we can use this technique for solid tumors, we take a biopsy in the lab, digest the cells with certain enzymes so as to turn it into a single cells suspension, by this we can quantify over expression or under expression and the reason we use this is that we are counting cells as each cell passes the laser is counted and you are told which type of cell it is.

Immunohistochemistry qualitative data and flow cytometry quantitative data.

In lecture 1 we took two other techniques where we look at the gene and see what mutations are in them, and nowadays you can sequence a whole human being in two weeks using next generation sequencing, but it is still expensive and not practical to sequence every patient.

Microarrays: we still rely on them. There are DNA microarrays and RNA microarrays; one can detect mutations, the other can detect over expression or under expression of mRNA. The drawback is that you have to know the mutation in order to make the microarray chip and that you have to know the particular genes to put on the microarray chip, you have a different glass slide for each tumor and you can use those as a molecular diagnosis of the tumor. This should

tell if the patient have to be sent for genetic testing or whether we have the whole family should be checked. The patient turns out to have a mutation in RAF (downstream of RAS), its over-activity (caused by this mutation) results with turning on pro-growth pathways. Unfortunately this is not unique to a particular cancer, it has been found in melanoma, thyroid cancer, leukemia, Langerhans cells histiocytosis, and colorectal adenocarcinoma, and all of these tumors which are different in location and morphology respond very well to the inhibitor of RAF, so this signals that we may need to stop classify tumors based on what they look under the microscope and classify them based on their molecular pathway that can be targeted for treatment (this will make your life easier as an oncologist you receive a diagnosis from histopathologist as a BRAFoma, whereas if you receive a diagnosis of colorectal adenocarcinoma is he an APC mutation does he over express COX2 does he have an EGFR mutation,…).

The End

Good Luck