MECHANISMS OF HUMAN DISEASE: LABORATORY SESSION
CYTOPATHOLOGY
Monday, April 26, 2013

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GOAL:

1. **Understated the role of cytopathology in the clinical management of the patient and recognize the utility of various cytology techniques.**

OBJECTIVES:

1. **Describe the Papanicolaou test**
2. **Describe the cytologic characteristics of HPV infection in a cervical PAP test**
3. **Describe the role of cytology in diagnosing malignant tumors of the bladder**
4. **Describe how cytology affects ovarian carcinoma staging**
5. **Describe the process of a fine needle aspiration biopsy and its advantages**
6. **Describe the cytologic features of papillary thyroid carcinoma**
7. **Understand the molecular basis of treatment of GIST**

What is cytopathology?

Cytopathology is a branch of pathology that studies and diagnoses diseases on the cellular level.

The most common use of cytopathology is the Pap smear, used to detect cervical cancer at an early treatable stage.

Other type of specimens:

- **exfoliated cells: urines, fluids**
- **washings/brushings: bronchi, renal pelvis, esophagus**
- **fine needle aspirations**

CASE 1

CHIEF COMPLAINT: Annual routine physical examination.

HISTORY: The patient is a 24 year-old sexually active female, with a history of several partners. She feels well.

PHYSICAL EXAMINATION: Heart, lung, abdominal exams are normal. Breast exam is normal and without masses. Pelvic exam is unremarkable. A Pap test is obtained.

1. What are the possible Pap test interpretations in this patient?

    a. **Evidence of inflammation**
    b. **Sexually transmitted diseases – Herpes, Trichomonas**
    c. **Squamous intraepithelial lesion**
    d. **Carcinoma**
    e. **Normal findings**

2. Identify and describe characteristic pathologic findings seen on the Pap test.

Koilocyte: Pathognomonic for HPV (human papillomavirus) infection; causes a cytopathic effect in the squamous cells and results in the formation of a characteristic large halo surrounding the nucleus.

3. What is HPV infection?

-Considered to be the most important agent in cervical oncogenesis.
-Sexually transmitted disease

-Risk factors for CIN and invasive carcinoma include: early age at first intercourse, multiple sexual partners, male partner with multiple previous sexual partners, and persistent detection of high-risk HPV types

4. What is the link between HPV and cervical cancer?

-Cervical carcinomas are associated with specific HPV types (high-risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68)
-Condylomas are associated with low-risk types of HPV (6, 11, 42, 44, 53, 54, 62 and 66)
-HPV DNA particles are found in 95% of cervical cancer

5. The HPV test performed in this patient revealed the presence of a high-risk type of the virus. What is the chance that she will develop a cervical cancer?

The chance is minimal. At least 50% of the entire population is exposed to high-risk HPV. However, only 10% will have persistent disease and only 1.3% will develop a carcinoma.

CASE 2

CHIEF COMPLAINT: "I see blood in my urine".

HISTORY: The patient is a 72 year-old-male with a history of low-grade urothelial carcinoma.

PHYSICAL EXAMINATION: Physical examination is unremarkable

LAB TESTS: Urinalysis – Numerous RBC's.

1. What is the clinical problem?

Hematuria

2. What are potential causes of hematuria?

Recurrence of urothelial carcinoma, infection, lithiasis, carcinoma in situ.

Diagnostic work-up:
Cystoscopy did not reveal any papillary tumors, but did show focal erythematous areas.

Bladder washing (barbotage) was performed and the specimen was submitted for cytologic examination

3. Describe the findings in urine specimens.

There are numerous large, pleomorphic cells with eccentrically located and irregular nuclei.

4. What is your diagnosis?

Urothelial carcinoma, high grade. Since cystoscopy did not reveal any tumor, this is most likely a carcinoma in-situ.

5. What will urologist likely do now?

Bladder biopsy to confirm the diagnosis and establish whether there is invasion (stage).

6. What molecular changes can you expect in this patient's urothelium?

Initially, this patient developed a low-grade papillary carcinoma that was initiated by the deletion of tumor suppressor genes on 9p (p16INK4a) and 9q. Now, with the development of CIS, he most likely acquired a p53 mutation as well.

CASE 3

HISTORY: The patient is a 63 year-old-female who presents with abdominal discomfort. She feels bloated all the time and can longer button her pants. She is short of breath with minimal exertion. She has little appetite but feels that she has to frequently go to the bathroom to urinate.

Her last visit to a doctor was 2 years ago ago. A Pap test performed at that time was normal.

FAMILY HISTORY: Her sister died of breast cancer at age of 32.

PHYSICAL EXAMINATION: Physical examination showed shifting dullness on abdominal percussion. The abdominal wall was taut, the umbilicus was everted and a fluid wave was elicited.

1. What is the clinical problem?

Ascites

2. What radiographic examination should be performed?

Ultrasonography to detect any abdominal/pelvic masses. Abdominal ultrasound showed a left adnexal mass (5 cm).

Abdominal paracentesis was performed

3. Describe the characteristic cytologic findings.

Three-dimensional papillary clusters of malignant cells.

4. What is your diagnosis?

Malignant effusion, most likely of ovarian origin.

5. What is the significance of this finding?

Cytologic evaluation of peritoneal fluid in patients with ovarian carcinoma is a part of the staging process.

6. What genetic mutations are associated with this disease?

Mutations in both *BRCA1* and *BRCA2* increase susceptibility to ovarian cancer. The estimated risk of ovarian cancer in women bearing either of these mutations is 20% to 60% by age 70.

CASE 4

CHIEF COMPLAINT: "I found a lump in my neck."

HISTORY: The patient is a 55 year-old-female with a history of radiation to the neck 20 years ago for hyperthyroidism.

PHYSICAL EXAMINATION: A nodule is palpated in the right lobe of the thyroid gland (2 cm) and also an enlarged right cervical lymph node is present.

LAB TESTS: Thyroid function tests were normal. Ultrasound confirmed the presence of a 2 cm nodule in the right thyroid and an enlarged lymph node. It was a "cold" nodule on scintiscan.

1. What is the clinical problem?

Thyroid mass

2. Describe characteristic cytologic findings

The slides show a markedly cellular smear with papillary structures, papillary caps and tips. Concentric calcifications and giant cells are present. On high power, oval nuclei with nuclear grooves, intranuclear inclusions, fine powdery chromatin and eccentric nucleoli are seen.

3. What is your diagnosis?

Papillary thyroid carcinoma

4. What is the prognosis for this patient?

Excellent, even with a metastasis to the lymph node. Overall 10 year survival is 95%; local recurrence occurs in 5% - 20%; distant metastasis seen in 10% - 15%.

5. What molecular changes are associated with this lesion?

1. **Rearrangement of the tyrosine kinase receptors *RET* or *NTRK1* (neurotropic tyrosine kinase receptor 1).**
2. **Activation of mutation in the *BRAF* oncogene.**
3. ***RAS* mutation.**

CASE 5

CHIEF COMPLAINT:

"My stomach hurts".

HISTORY:
The patient is a 72 year-old female who complains of vague abdominal pain for the past several months. She denies nausea, vomiting and blood in her stool.

PHYSICAL EXAMINATION:

The patient is alert and oriented. Vital signs are normal. Her abdominal exam reveals normal bowel sounds with no tenderness to palpation or rebound tenderness.

LAB TESTS:

Hemoccult negative. CT scan reveals a 4 cm well-demarcated mass arising from the posterior wall of the gastric fundus and extending into the gastric lumen.

1. What is the clinical differential diagnosis?

Gastric mass: Adenocarcinoma, lymphoma, carcinoid, GI stromal tumor (GIST), schwannoma, lipoma, metastatic carcinoma.

2. Describe cytologic findings

Numerous cohesive fragments of spindle cells

3. What special studies would you do on the cytology material to narrow your diagnosis?

Desmin, keratin, S-100, C-kit (CD 117)

4. What is your diagnosis?

Gastrointestinal stromal tumor (GIST)

5. Name the cell of origin for this lesion.

Interstitial Cell of Cajal (which controls GI peristalsis).

6. With what syndrome is this tumor associated?

Associated syndromes include: Carney's triad of gastric GIST, paraganglioma and pulmonary chondroma and Neurofibromatosis type I

7. What genetic mutations are associated with this lesion?

85% of GISTs have *c-KIT* (receptor for stem cell factor) mutations and 35% of GISTs with normal *c-KIT* contain *PDGFRA* (receptor for platelet-derived growth factor) mutations.

7. What is Gleevec?

It is also known as Imatinib or STI 571 and it works by inhibiting the receptor tyrosine kinase for c-kit. It was approved by the FDA for the treatment of unresectable or metastatic malignant GIST on February 1, 2002. Currently, STI 571 is widely used as an agent to treat GISTs; this demonstrates the application of a targeted therapeutic approach to the treatment of human malignancies.