Unit 1

Cell injury, adaptation and death

■ Objectives

1. Master the concepts of adaptation, atrophy, hypertrophy, hyperplasia, metaplasia, and to be familiar with the morphologic characteristics of atrophy, hypertrophy and metaplasia.
2. Master the changes of common types of cell injury.
3. Master pathological changes and types of necrosis.
4. Master the concept and morphological changes of apoptosis.

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- **Key points of observation**

- **Adaptation**

1. **Atrophy**

   **Basic pathologic changes**

   **Gross morphology**
   - (1) decrease in size or shrinkage of organs
   - (2) organs become dark in color
   - (3) the texture of organ becomes firm
   - (4) decrease in the ratio of parenchyma to interstitium.
   - (5) the arteries on the surface of organs may be tortuous (heart?)

   **Histopathology**
   - (1) reduction in size or number of parenchymal cell
   - (2) proliferation of interstitial fibrous tissue and adipose tissue
   - (3) pigment deposition can be seen in cytoplasm of parenchymal cells

   - **Pressure atrophy of the kidney**

   **Case summary:** This was a 39 year old female with a recurrent left abdominal pain for 8 years. X-ray showed a stone in her left urinary tract. Then a nephrectomy was performed.

   **Gross specimen(No.8):**
   - (1) The kidney is enlarged with scraggy surface
   - (2) Significant dilatation of the renal pelvis
   - (3) Renal parenchymal is shrunken (normal: 2.0cm~2.5cm)
   - (4) The demarcation/boundary between cortex and medulla is not clear
   - (5) Medullary pyramid may disappeared

   **Questions:** Does the kidney expand or shrink? Why is it called atrophy? How will the functions of the kidney be compromised?
Granular atrophy of the kidney
Case summary: A 40 year old male patient had recurrent hematuria, proteinuria and hypertension for 10 years. One year ago there was oliguria and then he died of renal insufficiency. An autopsy was performed.

Gross specimen (No.9)
(1) The kidney is contracted
(2) There are fine granules diffusely scattered on the surface
(3) The cortex is thinner than normal
(4) The corticomedullary demarcations is not clear
(5) perinephric fat is increased

Question: What’s the difference between pressure atrophy and granular atrophy of kidney?

Pressure atrophy of the brain (hydrocephalus)
Case summary: A 4-year-old male had tuberculous meningitis. With the progressing of his sickness there was enlargement of his skull and varices of surface veins in head and neck. The boy had severe vomiting, dyspnea and died.

Gross specimen (No.105)
Please observe and describe the gross specimen by yourself.

Questions: How are the gyri? How are the ventricles? Why?

Chronic liver congestion
Case summary: The patient was a 37 year old woman with palpitation, dyspnea and edema in both legs for 3 years. Physical examination found cyanopathy of her lips and fingers, and enlargement of heart field. She died of heart insufficiency.

Tissue slide (No.1)
(1) the lobular structure of the liver is conserved
(2) Lobular central venous and hepatic sinus are full of red blood cells
(3) liver cells decrease and shrink
(4) fat vacuoles in the cytoplasm of liver cells

Question: How is atrophy of liver cells induced?

2. Hypertrophy
Basic pathologic changes
Gross morphology
(1) increase in size of organs
(2) the arteries on the surface of organs are straight
(3) parenchyma is thicker than normal

Histopathology
(1) increase in size of parenchyma cells
(2) nuclei of parenchyma cells become larger and darker than normal
(3) interstitial cells decreased in number
Hypertrophy of the heart
Case summary: The patient was a 60 years old man with headache and high blood pressure for more than 10 years. He expired by sudden death.
Gross specimen (No.20)
(1) Increase in size of the heart
(2) The heart is more than 350 gram (normal heart in a male adult is 250g~300g)
(3) The cut surface of the heart show thickened left ventricular wall and interventricular septum, trabeculae carneae and papillary muscle are thickened
Question: Why is the left ventricle wall thickened?

3. Metaplasia
■ Squamous metaplasia in bronchus
The bronchial tissue came from a heavy smoker with bronchiecasis (a disease condition characterized by dilatation of bronchus).
Tissue slide (No.36)
(1) dilated bronchial lumen (under low power)
(2) pseudostrantified ciliated columnar epithelial cells are replaced by stratified squamous epithelium
Questions: How did this pathological change occur? What’s the significance to the body?

■ Intestinal metaplasia of gastric gland
The tissue came from a female with chronic atrophic gastritis.
Tissue slide (No.115)
Please observe and describe the histological features of intestinal metaplasia of gastric gland by yourself.
Question: Do you find goblet cells and Paneth cells that normally are characteristic of the small intestine?

“Degeneration” and intracellular and extracellular accumulations

1. Cell swelling
Basic pathologic changes
Gross morphology
(1) The organs are swollen to various degrees
(2) The color is pale and cloudy
(3) The capsule is tense
Histopathology

Department of Pathology, West China Hospital, Sichuan University
(1) The parenchyma cells are swollen and crowded together
(2) The cytoplasm is pale

- **Hydropic change of the tubular epithelia of the kidney**
  
  **Case summary:** A 1 year old little girl died of lobular pneumonia. The tissue came from her kidney.  
  
  **Tissue slide (No.12)**
  (1) Look for the cortex area under low power field
  (2) Observe the proximal convoluted tubules. Note the narrowed lumen of the tubules
  (3) The cytoplasm of the epithelia is often translucent but may be filled with fine eosinophilic granule

- **Hydropic change of the liver cells**
  
  **Case summary:** This was a patient with chronic viral hepatitis. The specimen came from a needle aspiration biopsy.  
  
  **Tissue slide (No.20)**
  (1) Look for the portal area under low power field
  (2) The structure of hepatic lobule is conserved
  (3) Swelling of hepatic cord and narrowing of hepatic sinusoid
  (4) The swelling of hepatic cells with a pale, finely granular cytoplasm and relatively normal nuclei.

2. **Fatty change (intracellular fat accumulation):**

   **Basic pathologic changes**

   **Gross morphology**
   (1) The enlarged organs have tense capsule and obtunded edges
   (2) The cut surface is bright yellow, soft and greasy

   **Histopathology**
   (1) Round vacuoles in cytoplasm
   (2) Some vacuoles are large and may push the nuclei to the periphery of cells

- **Fatty liver**
  
  **Case summary:** A 3 years old boy had diarrhea, high fever, vomiting and seizures.
  
  **Gross specimen (No.10)**
  (1) The liver is swelling with tense capsule and obtunded edges
  (2) The cut surface is bright yellow, soft and greasy
  
  **Tissue slide (No.13)**
  ◆ There are many clear vacuoles of different sizes in the cytoplasm of liver cells
  ◆ Some vacuoles are large and push the nuclei to the periphery of cells.

**Question:** How do you confirm that these vacuoles contain fat?

3. **Hyaline change**
Gross morphology
(1) The tissue appears to be gray, homogenous and translucent
(2) The texture is firm

Histopathology
(1) The cells or tissue appears to be homogenous, eosinophilic and glassy

- **Hyaline change of connective tissue (extracellular accumulation)**
  
  **Scar**
  
  Tissue slide (No.11)
  (1) Under low power, you could see pink eosinophilic region consisting of thick collagen fibers merging with each other.
  (2) There are a few fibrocytes and the original normal structures of tissue may disappear.

- **Hyaline change of vascular wall (extracellular accumulation)**

  **Spleen in hypertension**
  
  Tissue slide (No.10)
  This slide is from a patient with primary hypertension.
  (1) Under low power magnification find the red pulp and white pulp. Look for white pulp and central artery.
  (2) Observe the increased thickness of the vascular wall and narrowed lumen. The vessel wall is eosinophilic, translucent and without normal structure. This is arteriolosclerosis. What could happen in the heart?

  **Kidney in hypertension**
  
  The kidney came from a patient with primary hypertension.
  Tissue slide ( - )
  Find the glomeruli under low power magnification and describe the histological changes of arterioles by yourself.

- **Intracellular hyaline change**
  (intracellular protein deposition)

  **Intracellular hyaline change of tubular epithelium in the kidney**
  
  Glass slide (No.58)
  (1) Under high power magnification look for the proximal convoluted tubules
  (2) Note the eosinophilic droplets in tubular epithelial cells

4. **Pathologic pigmentation**

- **Hemosiderosis of lung**

  The tissue came from a patient with chronic pulmonary congestion.
  Tissue slide (No.14)
  (1) Note the golden-brown, fine granular pigments in the alveolar spaces under high power magnification.
Most of them are located in the cytoplasm of macrophages.

**Question:** How do you confirm that this pigment is hemosiderin?

- **Pathologic calcification**
  - **Tissue slide**
  - **Lymph node involved by tuberculosis (No.17) and aorta involved by atherosclerosis (No.38, No.39)**
  - Look for the dark blue granules or pieces in caseous necrosis in tuberculosis or in areas of the hyaline change in aorta.
  - **Questions:** Why did calcium deposit in the necrotic area? Is it dystrophic calcification or metastatic calcification?

**Necrosis**

**Basic pathologic changes**

**Gross morphology**

1. Necrosis consists of a variety of morphologic appearances resulting from different causes
2. Coagulative necrosis: the lesion is grayish-white or yellowish-white, and exhibits a firm texture
3. Liquefactive necrosis: the necrotic tissue liquefies and may result in cyst formation
4. Caseous necrosis: the necrotic tissue is yellow-white, and looks like cheese

**Histopathology**

1. the necrotic nuclei show pyknosis, karyorrhexis and karyolysis
2. the cytoplasm shows increased eosinophilia
3. congested vessels and inflammatory cell infiltration are easy to be found in interstitial tissue

1. **Coagulative necrosis**

**Case summary:** The patient was a 25 year old man and died of subacute bacterial endocarditis (SBE).

- **Coagulative necrosis of the spleen**
  - **Gross specimen: (No.3)**
  1. Find wedge-shaped grey or yellow regions in the cut surface.
  2. The wedge-shaped region usually is surrounded by a narrow, dark red, congestive or hemorrhagic band.
  - **Question:** Why is the necrotic region wedge-shaped?

- **Coagulative necrosis of the kidney**
Glass slide: (No.16)
Look for a wedge-shaped pale region in the slide with naked eye.
(1) Under low power, compare the necrotic region with the non-necrotic, you can find ghost outlines of glomeruli and tubules in the necrotic regions.
(2) Under high power magnification, you can find the basic morphologic features of cell death: pyknosis, karyorrhexis and karyolysis.

2. Caceous necrosis

Case Summary: A female patient, 41 years old, had hematuria for six months. Physical examination: urine culture was positive for tubercle bacilli. A left nephrectomy was performed.

■ Renal tuberculosis
Gross specimen: (No.11)
(1) The kidney is enlarged and looks nodular in surface.
(2) On cut surface there are many cavities lined with yellow-white, cheesy caseous material.

■ Tuberculous lymphadenitis
Gross specimen: (-)
(1) A few enlarged lymph nodes fused with each other.
(2) There is yellow-white cheesy necrotic material on cut surface.

Tissue slide: (No.17)
Observe the slide with the naked eye and look for a pink area.
(1) Under low power magnification, notice where the normal structure of lymph node is destroyed.
(2) In the caseous necrotic region there is eosinophilic, amorphous and fine granular material.
(3) In comparison with coagulative necrosis, there is no ghost outline of original tissue.

3. Liquefactive necrosis

■ Brain abscess
Case Summary: A 17 years old female had headache, vomiting and loss of vision for 7 days. She had a previous history of tympanitis. Several days later she died of central respiratory insufficiency.
Gross specimen: (No.93)
(1) Brain. Notice congestion of blood vessels on the surface of the brain and broadened gyri.
(2) On cut surface, find one or two round space containing yellow to white necrotic material.
material.

- **Brain infarct**
  The patient had a history of thrombosis of brain blood vessel.
  **Gross specimen: (No.42 )**
  On cut surface of brain there is an irregular cyst located at the boundary of white matter and grey matter.

- **Amoebic liver abscess**
  **Case Summary:** The patient was a 37 year old male. He had a right epigastric pain for 4 months and died of cachexia.
  **Gross specimen: (No.79 )**
  (1) The liver is enlarged
  (2) On cut surface there are one or several cysts
  (3) In the inner wall there are many flocculent residual tissue pieces. The liquid material in the cysts is brown and sticky, just like jam, which may have been drained during dissection.

4. **Gangrene**

- **Dry gangrene of the foot**
  **Case Summary:** A 52 year old male had an intermittent pain of right toes for 3 years. Then his right toes lost sentience and became dark and dry. A surgical operation was performed to resect his toes in order to save his life.
  **Gross specimen: (No.12 )**
  (1) The toes are shrunk, dark and dry.
  (2) The boundary between the lesion and normal tissue is clear.
  **Note:** In which conditions does dry gangrene happen?

- **Moist gangrene of the small intestine**
  **Case Summary:** A 37 years old woman was hospitalized with acute abdomen. She had vomiting and severe abdominal pain. A laparotomy was performed. The surgeon found ileus and resected the lesional small intestine as well as a portion of normal intestine on both ends.
  **Gross specimen: (No.13 )**
  (1) The intestine is dark and swollen.
  (2) the boundary between dark bowel and adjacent bowel is not clear
  **Note:** Why did the surgeon resect not only the dark part of small intestine, but also a part of adjacent “normal” intestine?

5. **Fibrinoid necrosis**
Case Summary: A 13 year old girl was diagnosed to have rheumatic fever and died of heart failure. The tissue came from her heart or skin.

Tissue slide:
(1) Notice the focal, strongly eosinophilic, reflexible and amorphous material in connective tissue.
(2) Notice the original structure is destroyed by necrosis and the inflammatory cells surrounding the necrosis.

6. Sequelae of necrosis

- Cavity of the lung/ kidney
  Gross specimens: (No.84) / (No.11)
  (1) The cavities are located in the lesional lung or kidney
  (2) The wall of the cavity is covered with caseous material

- Ulcer of the stomach
  Gross specimens: (No.50)
  (1) A portion of stomach has been opened along the greater curvature of stomach
  (2) There is an oval deep defect in the mucosa of the lesser curvature
  (3) The ulcer penetrates deeply down to the muscular layer
  (4) The mucosal folds surrounding the ulcer converge in a star-shaped pattern toward the ulcer

- Calcification of the lung (-)

Apoptosis

Basic pathologic changes
Histopathology
(1) The affected cell shrinks
(2) The cytoplasm is intensely eosinophinic
(3) The nucleus is small and dense or may disappear.
(4) Apoptotic body

- Chronic hepatitis
Tissue slide: (No.120)
(1) There are single hepatocytes with eosinophilic change: shrunk, strongly eosinophilic cytoplasm with dark blue nuclei.
(2) apoptotic bodies : ssmall eosinophilic bodies without dark blue nuclear elements
(3) inflammatory cells infiltrate around the apoptotic cells

Note: Consider the difference between necrosis and apoptosis.
Questions for review

1. What is the influence of metaplasia on the human body?
2. What are the pathological diagnostic criteria for necrosis?
3. Contrast necrosis to apoptosis.
4. Compare coagulative necrosis with caseous necrosis.
5. Contrast dry gangrene with wet gangrene.
Unit 2

Tissue Repair: Cell Regeneration and Fibrosis

**Objectives**
1. **Master** the following terms regeneration, repair and granulation tissue.
2. **Recognize** the lesions of granulation tissue, fibrosis, wound healing (by first and second intention).

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**Key points of observation**

Granulation tissue

The tissue came from the base of ulcer or skin wound healing by second intention.

Glass slide: (No. 23)
(1) Find numerous dilated capillaries with swollen endothelium under low power magnification.
(2) Recognize of inflammatory cells and fibroblasts under high power magnification.

**Note:** Consider the roles of granulation tissue in wound healing and its sequelae.

Wound healing of the skin

A 28-year-old woman had pain of abdominal wall and a firm nodule in her abdominal wall was found on palpation. She had a caesarean operation one year ago. 10 months later she felt pain and induration in her abdominal incision. The time of pain was related with her menses. The clinical diagnosis was endometriosis and a second operation was done. The specimen is the resected skin scar.
In the center of the skin sample, there is a 10 cm long string like scar in grey to white color. Is this healing by first intention or by second intention? If you become a surgeon in the future, what kind of healing in your patients, would you try to achieve?

**Healing of bone fracture**

This is a long bone fracture. Please identify which bone it is. Find the swelling of the healing position. Note whether the bone marrow space is present in the healing area.

**Questions for review**

1. What are the functions of the granulation tissue in wound healing?
2. What are the factors influencing wound healing?
3. What are the conditions and features of first intention healing and second intention healing?
Unit 3

Hemodynamic disorders, thrombosis

**Objectives**

1. **Master** the concepts of hyperemia, hemorrhage, thrombosis, embolism, and infraction; recognize the major morphologic changes of hyperemia, thrombi and emboli
2. **Recognize** the subtypes of embolism and its possible effects to human body
3. **Understand** the mechanism of thrombosis

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**Key points of observation**

1. **Congestion and hyperemia**
   - **Acute pulmonary congestion**
     **Gross specimen:**
     (1) Volume of the lung is enlarged
     (2) The cut surface is dark red in color
     (3) If it is a fresh sample, the cut surface is hemorrhagic and wet.
     **Tissue slide:**
     (1) Alveolar capillaries is engorged with blood
     (2) Alveolar septa edema with or without focal intra-alveolar hemorrhage
     **Question:** what symptoms and signs may be found in patient with acute pulmonary edema?
   - **Chronic pulmonary congestion**
     **Gross specimen:**
     (1) Cut surface of the lung are gray and brown in color and looks compact
     (2) Pleural membrane may be thicken because of fibrous tissue proliferation
**Tissue slide:**
(1) The septa become thickened and fibrotic
(2) The alveolar spaces may contain numerous hemosiderin-laden macrophages (so called “heart failure cells”)

**Question:**
(1) When we find hemosiderin-laden macrophages under microscope, what does it mean?
(2) How to identify hemosiderin histologically based on the knowledge you have learned?

- **Chronic congestion of the liver (nutmeg liver)**

**Gross specimen:**
(1) The volume of the liver is larger or smaller than that in normal
(2) The central regions of the hepatic lobules are grossly red-brown and slightly depressed, and accentuated against the surrounding zones of uncongested tan liver

**Tissue slide:**
(1) Centrilobular necrosis with hepatocyte drop-out and hemorrhage
(2) Fatty change of hepatocytes in peripheral region of the lobules
(3) Fibrous tissue proliferation could be found in cases of long-standing hepatic congestion

- **Chronic congestion of spleen**

**Gross specimen:**
(1) The volume of the spleen is enlarged with thickened capsule which is gray-white in color
(2) There is brown pigmentation in the cut surface with or without infarction

- **Hyperemia of the meninges**

**Gross specimen:**
(1) It is a specimen of purulent meningitis
(2) On the surface of the brain, notice hyperemia of blood vessels

**2. Hemorrhage**

(1) Morphologic changes are related to the bleeding sites and the amount of the blood
(2) Hemorrhage presented inside solid organs and subcutaneous region, hematomas may be found
(3) When hemorrhage occurs in skin, serosa and mucosa, it often appears as petechia, purpura and ecchymoses
(4) Histologically, aggregated red blood cells (erythrocytes) could be found outside the blood vessels

- **Cerebral hemorrhage**

**Gross specimen:**
A hematoma could be found in the cut surface of the brain.

**4. Thrombus**
Thrombi may develop anywhere in the cardiovascular system: within the cardiac chambers; on venular cusps; or in arteries, veins, or capillaries.

Thrombi are of variable size and shape, depending on the sites of origin and the circumstances leading to their development.

Characteristic of thrombi is their attachment to the underlying endothelia, often being firmest at the point of origin.

Pay attention to the color of the thrombi. Are they white, red or of mixed color?

**Thrombus**

**Gross specimen:**
1. What organ is it?
2. Can you find lines of Zahn? These are produced by alternating pale layers of platelets admixed with fibrin, and darker layers containing more red blood cells.
3. What color is it?

**Vegetations on cardiac valves**

**Gross specimen:**
1. Which valve is involved?
2. How many thrombi?
3. What is the color of the thrombi can you identify?
4. Is there any difference between thrombi in rheumatic endocarditis and in infective endocarditis?

**Venous thrombus**

**Tissue slide:**
1. Trabeculae of platelets which are pink in color
2. Enmeshed red blood cells and some white blood cells

**Teaching demonstration:**

**Hyaline thrombi (lung or kidney)**

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**Note:**
1. How to distinguish postmortem clots from thrombi?
2. Why thrombi are always attached to the underlying endothelium?
3. What are vegetations on cardiac valves in infectious endocarditis? Is there any difference from venous thrombi?
5. Embolism

- Tumor cell embolism
  
  **Tissue slide:**
  (1) Find the small blood vessels under low power magnification, and there is a mass of tumor cell in the lumens
  (2) morphology of the tumor cells

6. Infarct

(1) Notice the volume of the organs
(2) The number, shapes and color of the infarction lesions, as well as the morphologic changes of the surrounding regions
(3) The histologic feature of infarction is coagulative necrosis

- Anemic infarct of the spleen
  
  **Gross specimen:**
  (1) Volume of the spleen is enlarged. Why?
  (2) Infarcted region is wedge shaped, with the occluded vessel at the apex and the periphery of the organ forming the base.
  (3) Infarcted region is gray-white in color with a narrow rim of hyperemia and hemorrhage

  **Tissue slide**
  Morphologic changes of coagulation necrosis
  - Anemic infarct of the kidney
    (1) The volume of the kidney may be normal
    (2) Coagulation necrosis under microscope
  - Cardiac infarct
    Grossly the infarcted lesion is irregular in shape. Why?
    Histologically the lesion is coagulation necrosis
  - Hemorrhagic infarct of the lung
    **Gross specimen:**
    One or more wedge shaped lesions in dark red color could be found on cut surface of the lung
    **Tissue slide:**
    (1) The structure outline of lung is preserved
    (2) The alveolar spaces are filled with red blood cells
    (3) There may be hyperemia and inflammation surrounding the infarcted region
  - Septic infarct of the lung
    **Gross specimen:**
    Abscesses may be observed in the hemorrhagic infarction regions
    **Tissue slide:**
    (1) Coagulation necrosis and hemorrhage
    (2) Abscess: a central necrotic region rimmed by many preserved neutrophils.
      Sometimes foci of bacteria may be found inside the abscess.
Notes:
1. If the vascular occlusion has occurred shortly (minutes or hours) before death of a patient, can you find the morphologic changes? Why?
2. How do you distinguish pale infarct from red infarct in clinicopathology?

Case study

Case 1

Clinical history: A 36 year old female suffered from joint pain eight years ago. She had dyspnea after movement for three years. The symptoms worsened with relapse of edema of both lower limbs, as well as swollen abdomen. One day before hospitalization, she had a cough, blood-tinged sputum and high fever. Physical examination showed body temperature: 38°C, Pulse: 98/min, Respiration rate: 35/min, cyanosis on lips and fingernails, jugular vein dilatation. Wet rales were detected in both lungs wall. Dullness area of the heart was enlarged by percussion. Grade III murmurs of both systolic period and relaxation could be detected in cardiac apex. Hepatosplenomegaly with positive hepatojugular reflux. She died of the disease.

Autopsy findings
Heart: the volume is enlarged with a weight of 320 grams (average weight in normal adult 250g). Both auricular and ventricular walls were thicked, and cardiac chambers were dilated. Mitral stenosis. Hydropericardium. Microscope examination showed that cardiac muscle fibers were enlarged.
Lung: Black and brown spots were found on the surface of both lungs. The cut surface was compact. Microscopic examination showed the alveolar walls were thickened with fibrous tissue proliferation and capillaries were congested. The alveolar spaces were compressed with red blood cells and clusters of hemociderin-laden macrophages.
Liver: the volume was enlarged, on cut surface, a mixed, intermingled. Microscopic examination: central veins and hepatic sinusoids were dilated and filled pattern could be observed with red blood cells. The surrounding hepatocytes dropped-out in the center of the lobules may be and hepatocytes in peripheral region of hepatic lobules showed fatty change.
Spleen: the spleen was enlarged and deep red in color on cut surface.
Brain: The brain is swollen with narrowed sulci and expanded gyri and there may be cerebellar tonsils.
Others: Both lower extremities were swollen with depression by pressing with fingers; There was fluid in both pleural cavities (200ml) and the abdominal cavity (400ml).

Discussion
1. Try to make a pathologic diagnosis and explain the reasons.
2. What is the possible cause of death
3. Discuss clinicopathological correlation (the relations between the clinical manifestations and pathologic changes)

4. How the disease start and develop in this case?

**Case 2**

**Clinical history:** A 52 year old male suffered bone rupture of left tibia and 4 ribs with contusion of left lung and hemorrhagic shock in car accident. 25 days after the accident, the patient had an operation for the ruptured left tibia. At the time the operation was finished and the tourniquet was loosened, the patient complained of dyspnea, and then respiration suddenly stopped and died.

**Question**
1. What is your diagnosis?
2. What was the major cause of death? How was it developed?
Unit 4

Acute and Chronic Inflammation

**Objectives**

1. **Master** the basic pathologic changes of inflammation, particularly exudation, and the features of the major types of inflammation.
2. **Recognize** the various components in inflammatory exudate.
3. **Be familiar with** the clinical presentation, the course, and the outcome of inflammation.
4. **Understand** the functions of the major inflammatory mediators.

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**Key points of observation**

**Basic pathologic changes of inflammation**

1. **Intracellular and extracellular accumulations and necrosis**

Inflamed tissues often have various degrees of morphological changes, including intracellular and extracellular accumulations and necrosis, either resulting from the direct
effect of the inflammatory agent(s) or as a consequence of the vascular changes. In some inflammatory diseases, these degenerative or necrotic changes are prominent. In old literature the term “alteration” was used to describe these disease processes. This term has fallen into disuse in recent years.

The common pathologic changes caused by injury to parenchymal and mesenchymal cells include cellular swelling, fatty change, coagulative necrosis, liquefactive necrosis, caseous necrosis, hyaline change, pathological calcification and fibrinoid necrosis, among others.

■ Amebic “abscess” of the liver
Gross specimen:
(1) “Abscesses” may arise in liver when there is dissemination of Entamoeba histolytica from the bowel via the portal venous circulation.
(2) There is collection of “pus” formed by disintegrated tissue in a cavity of the liver.
(3) The inner surface of the cavity is ragged.
   (Notice: the abscess in amebic abscess is usually not a true abscess, which is typically seen in purulent or suppurative inflammation. See below)

2. Exudation
(1) The involved organ or site is hyperemic.
(2) The exudation can be predominantly serous, fibrinous, or can form pus.
(3) Serous exudate is clear with little viscosity. The inflammatory organ or site appears edematous.
(4) Fibrinous exudate can form pseudomembranes on mucous membrane surface. In the lung, the exudate fills the alveolar spaces, causing “consolidation”. In the pericardial space, the exudate appears velvety.
(5) Neutrophils dominate the scene of purulent inflammation. Necrotic tissue and neutrophils constitute “pus”, which is the hallmark of suppurative inflammation.

■ Rheumatic pericarditis
Gross specimen:
(1) It’s a kind of fibrinous inflammation caused by rheumatic fever.
(2) The surface of epicardium and pericardium appear roughened with shaggy fibrinous exudates.
(3) The appearance of this specimen is reminiscent of buttered bread dropped on a carpet.
(4) Fibrinous pericarditis is also known as cor villosum.

■ Diphtheria
Gross specimen:
(1) It’s a bacterial infection usually affecting the mucous membranes of upper respiratory tract.
(2) Typically, the surface of mucosa is covered with a sheet of thick, gray fibrinous exudate, which was called pseudomembrane. (hence the name “pseudomembranous inflammation ”)
(3) Sometimes the exudate can block the airway, causing dyspnea.
- **Lobar pneumonia**  
  **Gross specimen:**  
  (1) In the lung, the fibrinous exudate fills the alveolar spaces, causing consolidation of the lobe.  
  (2) There is fibrinous pleuritis on the surface of pleura.  
  **Tissue slide:**  
  The fibrinous exudate accumulated in the alveolar spaces appears as an eosinophilic meshwork of threads or amorphous coagulum.

- **Lobular pneumonia/Bronchopneumonia**  
  **Tissue slide:**  
  (1) The alveoli are filled with serous exudate, which is watery, relatively protein-poor fluid.  
  (2) Serous fluid is red or pink staining on the HE slides.

- **Suppurative / Purulent meningitis**  
  **Gross specimen:**  
  (1) Subarachnoid space is filled with pus, which obscures the sulci.  
  (2) There is hyperemia of the blood vessels of the meninges.  
  (3) Pus is a yellowish or greenish cloudy liquid composed of tissue debris and abundant neutrophils, many of which are necrotic.

- **Suppurative / Purulent appendicitis**  
  **Gross specimen:**  
  (1) The appendix is swollen and hyperemic.  
  (2) On the surface of serous membrane, there is tan-yellow inflammatory exudates.

- **Granulation tissue**  
  **Tissue slide:**  
  (1) The granulation tissue is composed of capillaries, fibroblasts and various kinds of inflammatory cells.  
  (2) Please focus on the morphology of these inflammatory cells, including neutrophils, eosinophils, lymphocytes, plasma cells, monocytes and macrophages.

3. **Proliferation**

Proliferative changes of parenchymal cells can result from the inflammatory stimuli or can be a secondary reaction.

Vascular endothelial proliferation leads to budding of the capillaries and the formation of new blood vessels. There can be various amounts of collagen deposition by proliferating fibroblasts. Macrophages and macrophage-derived cells can form granuloma, sometimes containing multinucleate giant cells.

- **Typhoid fever of the intestine**
**Gross specimen:**

1. The hallmark of intestinal typhoid is the proliferation of Peyer's patches of the ileum.
2. The Peyer's patches are aggregations of lymphoid tissue that are usually found in the lowest portion of the small intestine.
3. On the surface of terminal ileum mucosa during fastigium phase of typhoid, the Peyer's patches become hyperemic, swollen, elevated, convoluted, and have a shaggy base.
4. The solitary lymphoid follicles of the ileum are enlarged and have a central dimple.
5. Commonly, the intestinal mucosa would progress to ulcerate in the late stage.
6. The ulcers are oval, ragged and with varying extent and depth. The location and shape of these ulcers usually coincide with the Peyer's patches. The long axis of the ulcers tends to be parallel to the long axis of the intestinal.

**Chronic cholecystitis**

**Gross specimen:**

1. The morphological changes are variable. The gallbladder maybe enlarged, contracted, or of normal size.
2. Usually, the submucosa and subserosa are thickened from fibrosis. The mucosa becomes coarse.
3. Gallstones are present within the gallbladder in many cases.
4. Acute phase inflammation can lead to edema, hyperemia, hemorrhage and necrosis.

**Posthepatitic cirrhosis**

**Gross specimen:**

1. The cirrhosis has a markedly bumpy external appearance on the liver capsule.
2. On cut surface, there is disruption of the normal hepatic architecture and formation of regenerative nodules, surrounded by fibrous septa.
3. The regenerative nodules have yellow-brown appearance and are about 3 mm in average diameter.
4. The cirrhotic liver tends to shrink in size at end-stage.

**Various types of inflammation**

1. **Serous inflammation**

   **Lobular pneumonia/Bronchopneumonia**

   **Tissue slide:**
   The key features of this slide have been listed above.

2. **Fibrinous inflammation**

   **Rheumatic pericarditis**

   **Gross specimens:**
   The key features of these specimens have been listed above.

   **Diphtheria**
Gross specimens:
The key features of these specimens have been listed above.

- **Lobar pneumonia**
  Gross specimens:
The key features of these specimens have been listed above.
  Tissue slide:
The key features of this slide have been listed above.

3. **Suppurative/purulent inflammation**

- **Purulent menigitis,**
  Gross specimens:
The key features of these specimens have been listed above.
  Tissue slide:
  (1) There is accumulation of a lot of neutrophils in the subarachnoid space.
  (2) The blood vessels of the meninges become dilated and hyperemic.

- **Purulent appendicitis**
  Gross specimens:
The key features of these specimens have been listed above.

- **Abscess of the brain**
  Gross specimen:
  (1) In the cerebral parenchyma, there are multiple abscesses.
  (2) The liquefactive necrosis of brain and purulent exudate lead to pus cavity formation.
    These cavities are surrounded by thick, irregular, rough surfaced walls.
  (3) The pus in these abscesses flow away.

- **Abscess of the lung**
  Tissue slide:
  (1) One or more abscesses can be found in the lung. They are localized purulent lesions, containing numerous neutrophils and focal necrosis.
  (2) There is no organizing abscess wall formation in the early stage.

- **Purulent appendicitis**
  Tissue slide:
  (1) The morphological feature of acute appendicitis is neutrophilic infiltration to varying extent within the wall.
  (2) In many cases, there is ulceration, necrosis and hemorrhage.

4. **Hemorrhagic inflammation**

- **Leptospirosis of the lung**
  Gross specimen:
There are extensive and irregular areas of hemorrhage in the lung.

Sometimes hemorrhage may diffusely spread to the pulmonary parenchyma.

5. Nonspecific chronic inflammation

- **Chronic cholecystitis**
  
  **Gross specimen:**
  The key features of this specimen have been listed above.

- **Chronic cholecystitis**
  
  **Tissue slide:**
  (1) The gallbladder wall becomes thickened because of the proliferating fibroblasts, blood vessels and the deposition of various amounts of collagen.
  (2) Chronic inflammatory infiltrates can be seen throughout the wall of gallbladder.
  (3) Some cases contain outpouchings of the mucosa, termed Rokitansky-Aschoff sinuses.

6. Granulomatous inflammation

Some inflammatory processes are featured by the formation of granuloma(s). A granuloma is composed of macrophages and macrophage-derived cells. Foamy macrophages, epithelioid cells, and multinucleate giant cells of the Langhans type or the foreign-body type are cells derived from macrophages.

- **Tuberculosis of the lymph node**
  
  **Tissue slide:**
  (1) The structure of the lymph node is destroyed by tubercles (with or without caseous necrosis).
  (2) The tubercles are composed of epithelioid cells and (or) Langhans multinucleate giant cells.

- **Foreign body granuloma**
  
  **Tissue slide:**
  (1) The foreign body granulomas are nodular lesions, containing macrophages and multinucleate giant cells.
  (2) Usually, the foreign bodies (e.g., suture, splinter, implant) can be found in the granulomas.

7. Outcomes of inflammation

- **Chronic fibrocavitary pulmonary tuberculosis**
  
  **Gross specimen:**
  (1) There is cavitation in the apical aspects of the lung when extensive caseous necrosis involves the wall of an airway and the necrotic material is discharged into the
bronchial tree.
(2) Parenchymal scarring can be seen around the cavity.
(3) The pleura of the upper lung or apex becomes thicker, and adhesive.
(4) The apical aspects or upper portion of the lung are more commonly affected because of higher oxygen tensions or impaired tissue clearance mechanisms.

- **Tuberculoma of the lung**

  **Gross specimen:**
  (1) Tuberculoma is a tumor-like lesion which is well demarcated from the adjacent normal lung in gross cut section.
  (2) This kind of tuberculous lesion is usually a single rounded nodule, but may be multiple.
  (3) In later phases of infection, some tuberculous lesions can evolve to fibrocalcific nodules to form tuberculomas.

**Case discussion**

**History:** A 23 year old house staff member had an apparently suppurative inflammation on the right toe for a couple of days after a mechanical injury. He made an incision on the inflamed site for drainage himself with a scalpel that was “disinfected” by burning on an alcohol burner. Local pain intensified and the patient started to have high fever. The patient was found to be in a delirious status by his colleagues.

**Physical examination** revealed a body temperature of 39.5°C, a pulse rate of 130/min, a respiratory rate of 40/min, and a blood pressure measurement of 10.6/6.6 kPa. The patient appeared delirious. He had tachycardia but no arrhythmia. There were rales in both lungs. The abdomen felt soft, and splenomegaly or hepatomegaly was not present. Numerous areas of ecchymosis scattered on the skin all over the body. The right leg was swollen and reddish with tenderness.

**Laboratory findings:** RBC 3.5 x 10^12/L, WBC 25.0 x 10^9/L, neutrophils 0.75, lymphocytes 0.23, monocytes 0.20.

Immediate administration of large doses of both antibiotics and steroids, blood transfusion, and local draining were performed upon hospitalization. Twelve hours after hospitalization, the patient was in shock with hypotension. Emergent measures did not help and the patient died on the third day after hospitalization.

**Brief findings of autopsy:** The deceased had a normal development, and a proper nutritional status. The skin on the upper part of the body as well as the had many areas of ecchymosis. There was a 1.5 cm long, suppurative wound on the right toe and a surgical draining incision on the right ankle. The right leg was reddish and swollen. There was fibrous adhesion of the upper lungs with the pleura and the chest wall. Both lungs were hyperemic and consolidated, with multiple hemorrhages and yellowish, miliary abscesses. There were indurated nodular lesions on the upper lobes of both lungs, one with a cavity of 0.8 cm diameter. Microscopically, the cavity wall was composed of epithelioid cells,
Langhan’s giant cells, lymphocytes, and fibroblasts, with caseous necrotic material in the cavity. Ziehl-Neelsen’s stain revealed a few acid-fast bacilli. All visceral organs were hyperemic. Parenchymal cells of solid organs appear degenerative. Petechiae were present on the epicardium, gastrointestinal tract, adrenal glands, and spleen. Gram positive streptococci and staphylococci were found in the lungs and the great saphenous vein.

**Discussion:**
1) List the diseases and the major lesions the patient had.
2) Describe the disease process, based on the clinical history and autopsy findings.
3) Describe the possible outcomes of an inflammatory process, and tell what kind of outcome was in this case.
Unit 5

Neoplasm

- **Objectives**

1. **To master** the following concepts and principles: neoplasm (tumor) and neoplasia; the general morphologic features; the differences between neoplastic hyperplasia and non-neoplastic hyperplasia; differentiation and atypia; nomenclature and classification of neoplasms; patterns of growth and pathways of metastasis of neoplasms; tumor grading and staging; effects of tumors on the host; the differences between benign and malignant tumors; pre-cancerous lesions, atypical hyperplasia and carcinoma *in situ*.

2. **To be familiar with** the gross and histological appearances of common tumors (papilloma, adenoma, squamous cell carcinoma, adenocarcinoma, etc.); the differences of carcinoma and sarcoma; the molecular basis of tumorigenesis.

3. **To acquire** a general understanding of the common tumorigenic agents; the common pathological methods of tumor diagnosis; and tumor immunology.
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Key points of observation

1. Appearances and growth patterns of neoplasms

Polypoid/Exophytic growth
(1) Commonly seen on the inner surface of gastrointestinal tracts
(2) The polypoid mass protrudes from the inner or outer surface of the involved organ, sometimes with a pedicle.
(3) Invasion at the base indicates malignancy.

Multiple polyps of the colon

Gross specimen:
(1) There are several “polyps” protruding into the lumen of the colon, often pedunculated, with diameters of 0.3cm-2.5cm.
(2) Most have slender stalks 1 to 2 cm long and raspberry-like heads.
(3) Of malignancy (with carcinoma) should be suspected if the “polyps” are sessile and invasion into deeper structures of the intestinal wall was observed.

Papillary/Cauliflower-like/Exophytic growth
(1) Commonly seen on the surface of the body or on the inner surface of gastrointestinal tracts.
(2) The Papillary/Cauliflower-like growth protrudes from the surface of the involved organ.
(3) On cut surface, a branching pattern composed of many fronds is prominent. Each frond has an outer layer of yellowish epithelial tissue and a whitish fibrovascular core.
(4) Necrosis and ulceration are common in malignant tumors. Invasion at the base indicates malignancy.

Papilloma of the skin

Gross specimen:
(1) The new growth protrudes from the surface of the skin with a papillary or cauliflower-like appearance.
(2) On cut surface, a branching pattern is prominent with outer layer of yellowish hyperplastic epithelial tissue (parenchyma) and whitish fibrovascular...
Carcinoma of the penis

Clinical history: Male, 59-year-old, with a history of redundant prepuce from childhood. A pea-sized red new growth has been found on the left side of the urethral orifice for 7 months. The size of the new growth increased gradually with a cauliflower-like appearance and odorous yellowish secretions. Inguinal lymph node enlargement was also present. Surgical remove of the penis and inguinal lymph node was performed after pathological diagnosis was established.

Gross specimen:
(1) A cauliflower-like mass was presented on the glans with necrosis and ulceration.
(2) On cut surface, the mass was whitish and invaded into the cavernous body of penis.

Nodular and lobular growth / Expansive growth
(1) Commonly seen in subcutaneous or deep tissues.
(2) The tumor mass forms a round or lobulated nodule, sometimes with a capsule.
(3) On cut surface, the tumor is well-demarcated, compressing adjacent tissues.
(4) The color of the tumor, which can best be appreciated on the cut surface, depends on several factors: the composition of the parenchyma, the production of pigments (if any), and secondary changes such as hemorrhage.

Leiomyoma of the uterus

Clinical history: Female, 45-year-old, presented with increased menstrual quantity for more than two years, and with palpitation and giddy tinnitus for one month. Physical examination: pale complexion; several non-fixed smooth masses connected with uterus were touchable at lower abdomen. Vaginal ultrasound examination showed enlargement of uterus with irregular shape. Several round low echo nodules were observed in the intramural/submucosal/subserosal layers.

Gross specimen:
(1) A complete uterus with increased size was demonstrated.
(2) There are several round nodules with clear boundaries in the intramural/submucosal/subserosal layers, pushing the surrounding tissue to form a pseudocapsule.
(3) On the cut surface, the nodules are gray, solid, arranged in braided or swirling pattern.
Lipoma

Clinical history: Male, 37-year-old, presented with a soft, painless, movable, well-demarcated dorsal subcutaneous mass.

Gross specimen:
The tumor is round or oval, soft, lobulated with fine fibrous capsule and trabeculae, greasy on cut surface.

Cystic/Expansive growth
(1) Often a round or oval mass with fine capsule.
(2) There may be (unilocular) or more (multi-locular) cysts on the cut surface, filled with serous or mucinous fluid.
(3) The inner surface of the cyst can be smooth or can have papillary projections.
(4) Invasion of adjacent tissue indicates malignancy.

Serous cystadenoma of the ovary

Gross specimen:
(1) A round or oval cystic mass with smooth surface.
(2) There is one (unilocular) cyst on the cut surface, filled with transparent light yellow serous fluid.
(3) The thickness of the capsule wall is uniform and the inner surface of the cyst is largely smooth with some papillary projections.

Mucinous cystadenoma of the ovary

Gross specimen:
(1) A round or oval cystic mass with smooth surface.
(2) There are (multi-locular) cysts on cut surface, filled with transparent jelly mucinous fluid.
(3) The inner surface of the cyst is relatively smooth.

Ulcerative/Infiltrating growth
(1) Often an irregular ulcer with thickened rims.
(2) Uneven and necrotic base.
(3) Invasion into adjacent tissue can be discerned on cut surface.

Ulcerative carcinoma of the stomach

Clinical history: Male, 45-year-old, presented with irregular upper abdominal pain for more than one year. The pain has nothing to do with the diet. Recently, he has
developed anorexia and weight loss (25kg one month). Physical examination: emaciation, chronic disease face with mild abdominal tenderness. Gastroscopy revealed a firm, ill-defined, 5cm x 6cm ulcer with necrotic base located in the lesser curvature of the stomach near the pylorus. Lab examination: fecal occult blood (++).

**Gross specimen:**
(1) An irregular large ulcerative mass is located in the lesser curvature of the stomach near the pylorus.
(2) The ulcer is hard with uneven necrotic base. On cut surface, the tumor is gray, solid, invade into the muscular layer.

- **Mucinous cystadenoma of the ovary**

**Gross specimen:**
(1) A round or oval cystic mass with smooth surface.
(2) There are several (multi-locular) cysts on the surface, filled with transparent jelly mucinous fluid.
(3) The inner surface of the cyst is relatively smooth.

**Note:**
How to determine whether a stomach ulcer is benign or malignant?

- **Deep-seated/Infiltrating growth**

  (1) Often an ill-defined, un-encapsulated tumor mass.
  (2) Growth or infiltration into adjacent tissues.
  (3) Often firm and fixed on palpation

- **Carcinoma of the breast**

**Clinical history:** Male, 58-year-old, presented with left breast mass for 2+ years. The mass had been growing recently associated with ipsilateral nipple inversion and discharge. Physical examination: Palpable, fixed mass of left breast associated with ipsilateral nipple inversion and skin changes (eg, dimpling and inflammation). Some bloody nipple discharges and enlargement of left axillary lymph node were also present. Core needle biopsy revealed invasive ductal carcinoma. Radical mastectomy of left breast was performed.

**Gross specimen:**
(1) Nipple inversion and skin changes (eg, dimpling and inflammation) are prominent.
(2) An irregular grey tumor can be identified beneath the nipple.
(3) The tumor is hard in consistency.
(4) The tumor invaded to surrounding tissue.

2. Histological structure and atypia of neoplasm

**Cellular atypia**
Tumor cells may have the following features:
(1) Increased N/C ratio
(2) Enlarged nuclei and/or nucleoli
(3) Hyperchromasia
(4) Pathologic mitosis
(5) Tumor giant cells
(6) Pleomorphism (prominent variation in size and shape of tumor cells).

**Architectural atypia**
(1) Tumor cells are disorganized, with loss of polarization, and other structure features of their normal counterparts.
(2) Malignant tumors have prominent cellular atypia and architectural atypia. Benign tumors usually have little cellular atypia, but may have architectural atypia to some extent.

■ **Squamous cell carcinoma**

Clinical history: Male, 68-year-old, presented with progressive dysphagia for 5 years. Esophagoscopy revealed a 5.5cm fungating mass located 35cm from the incisors protruding to the esophageal lumen and involving 2/3 of the esophageal circumference. The tumor had shallow ulcers on surface and with thickened rims.

Slide:
**Naked-eye view:** Try to identify the four layers of esophagus.

**Low-power view:** Tumor cells form nests of different sizes, with no orderly differentiation of squamous cells. Keratin peals are clear in well-differentiated tumors, but absent in poorly-differentiated ones. The tumor nests infiltrated the muscular or serosal layer.

**High-power view:** Tumor cells of well-differentiated squamous cell carcinoma are
strikingly similar to normal squamous epithelial cells, with basal-like cells surrounding the onion-like keratinization substances (keratin peals). Intercellular bridges sometimes are present. Tumor cells of poorly-differentiated squamous cell carcinoma lack differentiation; displaying marked pleomorphism (marked variation in size and shape). Characteristically the nuclei are hyperchromatic (darkly stained) and large. The chromatin is coarse and clumped, and nucleoli may be prominent size. Mitotic figures may be numerous and distinctly atypical. By comparing with the adjacent normal squamous epithelium, you can have better understanding of cellular and architectural atypia. Inflammation in the tumor stroma may result from tumor necrosis and secondary infection.

- **Papilloma of the skin**

**SLIDE:**

**Low-power view:** The new growth protrudes from the surface of the skin with a papillary appearance. A branching pattern is prominent with outer layer of yellowish hyperplastic epithelial tissue (parenchyma) and a whitish fibrovascular core (mesenchyma).

**High-power view:** The arrangement of cells (squamous cell epithelium) can still be retained with basal layer, spinous layer, granular layer and the horny layer, form bottom to top. Cellular atypia are not prominent.

**Questions:**

What constitute the tumor parenchyma and mesenchyma of a tumor?

Which part determines tumor differentiation and atypia?

3. **Metastasis**

**Lymphatic metastasis**

**Gross features:**

1. Regional lymph node(s) involved first, distant lymph node(s) in advanced stage

2. In advanced stage, involved lymph nodes can fuse to form a large mass.

**Microscopic features:**

1. Typically the metastatic tumor tissue is distinct from the normal lymphoid tissue, but is similar to the primary tumor.

2. The marginal sinus is firstly involved.
(3) In later stages, part or all of the lymph node can be effaced by the metastatic tumor.

- Gastric/colon carcinoma with lymph node metastasis

**Clinical history:** Male, 45-year-old, presented with upper abdominal pain for 1+ year. The pain has nothing to do with the diet. Recently, he had developed anorexia and weight loss. Physical examination: mild abdominal tenderness, and a palpable peanut size lymph node was noticed at left supraclavicular fossa. Gastroscopy revealed a new growth located at the lesser curvature near the pylorus. Adenocarcinoma with moderate differentiation is diagnosed by biopsy. Abdominal contrast enhanced CT showed the enlargement of gastric lymph nodes around the stomach. Stomach and surrounding lymph nodes were surgically removed.

**Gross appearances:**
A new growth is located at the lesser curvature near the pylorus in mucosa (pay attention the shape of it). There are several whitish, hard, enlarged lymph nodes around the stomach, indicating of lymphatic metastasis.

**Microscopic features:**
Swelling lymph node near the tumor

**Low-power view:** In early stage, atypical glands or cells can be noticed in the lymph node sinuses. In later stage, the structure of lymph node is destroyed and replaced by the metastatic tumor. The tumor tissue was arranged in glands or nests in the lymph node.

**High-power view:** Pay attention to the cellular atypia and architectural atypia.

**Hematogeneous metastasis**

**Gross features:**
(1) Metastases to the lung and the liver are the most common.
(2) Often multiple and peripherally located.
(3) Well-demarcated nodules of varying size.
(4) Central necrosis of tumor nodules on the surface gives an “umbilical” appearance.

**Microscopic features:**
Typically the metastatic tumor tissue is distinct from the surrounding normal tissue, without transition between them.

- Metastatic carcinoma of liver
Clinical history: Male, 70-year-old, diagnosed with adenocarcinoma of colon for 1 year. Four months earlier, an upper abdominal mass was found together with hepatalgia, fatigue and weight loss, and rapidly development of jaundice ascites and cachexia. CT reported multiple solid masses in the liver. After conservative treatment, the patient died. Autopsy revealed a huge ulcerative mass located at the right colon with multiple liver masses.

Gross description:
(1) Gray nodules of different sizes were noticed on the surface of liver with “umbilical” appearance.
(2) On cut surface, the nodules were round with clear border, often peripherally located and with necrosis in the middle.

Questions: Why can colon cancers easily metastasized to liver? What are the differences between primary liver tumor and metastatic tumor of liver?

Cancer embolus of lung

Low-power view: Aggregates of tumor cells are located in the lumen of small vessels and capillaries. Finding the blood vessels is the key to locate the lesion. Pay attention to the lining endothelial cells.

High-power view: Pay attention to the cellular and architecture atypia to identify the tumor cells.

Questions:
What kind of primary tumors can easily metastasize to liver?
Which organs are favored metastatic sites, in addition to liver?
How to distinguish primary tumor and metastatic tumor of in an organ?

Transcoelomic metastasis (seeding)

Gross description:
(1) Metastases to serous membranes via direct “seeding” of tumor cells.
(2) Numerous nodules with varied sizes.
(3) Adhesion may results.

Peritoneal metastases resulting from “seeding”

Gross description:
There are several tumor nodules (some are fused) on the greater omentum.

Questions: How do these nodules form?
4. Commonly encountered tumors in clinical practice

Benign tumor

Gross description:
(1) The benign tumors protruding from the surface of the skin, the inner surface of organ lumen or the body cavity usually have papillary, polypoid, fungating or cauliflower-like appearance.
(2) The deep-inside benign tumors show expansive growth and form round or lobulated nodules with capsules. The tumors are well-demarcated, compressing adjacent tissues.

Micro description:
(1) Tumors often have distinctive architecture atypia
(2) The cellular atypia is not obvious
(3) The demarcation between stroma and parenchymal part of mesenchymal tumors is obscure.

Malignant tumor

Gross description:
(1) Except for the outgrowing part of malignant tumors, deep infiltrating in the base always exists.
(2) The deep-inside malignant tumors often form a crab-like mass with obscure boundary by infiltrating to surrounding tissues.
(3) The fast growing malignant tumors often form pseudocapsule by pushing the surrounding tissues, accompany with central necrosis and hemorrhage of tumor.
(4) The amount of stromal connective tissue does determine the consistency of a neoplasm. The more the fibrous stroma is, the harder the tumor is.

Micro description:
(1) Tumors often have distinguishing cellular and architectural atypia.
(2) The demarcation between stroma and parenchymal part of mesenchymal tumors is obscure.
(3) Tumors infiltrate to surrounding tissues.

Common benign epithelial tumors
Papilloma of the skin
It’s a benign tumor origin from squamous epithelium. The macroscopical and microscopical characteristics are as previously described. The key point is to distinguish between benign and malignant papillary tumors.

Gross description:
Pay attention to the characteristics the papillary, especially whether there is any necrosis and ulcer, or any infiltration of the base of the papillary on the cut surface.

Micro description:
(1) Microscopically, please carefully observe the polarity and differentiation of the squamous epithelial cells.
(2) Whether there is any invasion of the tumorous squamous epithelial cells to the surrounding tissue?

Multiple polyps of colon or adenoma of the intestine
The macroscopical characteristics are as previously described.

Micro description:
Naked-eye view: Papillary and tubular structures.
Low-power view: The tumor protrudes from the mucosa and composes with varied-sized hyperplastic glands. The structure of the intestinal tube is preserved.
High-power view: The tumor cells are tall columnar in shape, hyperchromatic, somewhat disorderly cells, which may or may not show mucin secretion. The palisading nucleuses are located at base. The tumor cells of neoplastic glands resemble their normal counterparts with no cellular atypia. The stroma is connective tissue with some plasma cells infiltrating.

Common malignant epithelial tumors

Squamous cell carcinoma
It’s a malignant tumor origin from squamous epithelium. The macroscopical and microscopical characteristics are as previously descripted.
Microscopically, please carefully observe the polarity, differentiation and cellular atypia of the squamous epithelial cells. Whether there is any invasion of the tumorous squamous epithelial cells to the surrounding tissue? (Fig. 5-1)

Question: Where are the common sites for the occurrence of papillomas and Squamous cell carcinomas? How about their characteristics?

Adenocarcinoma of the intestine
It’s a malignant tumor origin from glandular epithelium.

**Clinical history:** Male, 50-year-old, presented with bloody stool and occasionally constipation for 2 years. In recent years, the constipation was getting worse accompany with thinning stool, abdominal pain, distention and emaciation. Colonoscopy found an ulcerative mass in colon sigmoideum. Adenocarcinoma was made by biopsy. The disease colon was removed by surgery.

**Macro description:**
A section of colon was shown with an irregular ulcerative mass on the mucosa. The ulcer had an uneven, necrotic base, and thickened rims. On the cut surface, the tumor is grey, solid, hard, and infiltrated the whole four layers of the colon. The corresponding serosa was very rough. Pay attention to the surrounding lymph nodes (if presents).

**Micro description:**
- **Naked-eye view:** the tissue is composed of the purple blue part (carcinoma) and pink part (normal).
- **Low-power view:** Firstly, you should locate the tumor part and compare it with the normal mucosa. The tumorous glands are vary in size, irregular in shape, chaotic in arrangements, and invade to sub-mucosa, muscular, and serosa. The normal structure of the four layers of colon is destroyed.
- **High-power view:** The tumor cells are vary in size, low cuboidal or columnar. Characteristically the nucleuses are large, and nuclei are variable and bizarre in size and shape. The chromatin is coarse and clumped, and nucleoli may be of astounding size. More important, mitoses figures are often numerous and distinctly atypical.

**Questions:**
1. What are the clinical manifestations of the patient may have considering the macroscopical features? What are the possible consequences?
2. Where are the common sites for the occurrence of adenoma and adenocarcinoma?
3. How about the characteristics?

- **Primary carcinoma of the liver**

**Clinical history:** Male, 56-year-old, presented with live pain, progressive live enlargement, loss of appetite, anemia, weight loss and weakness recently. He had a previous history of hepatitis 17 years ago. Physical examinations: Liver was palpable 3 cm under the rib. Abdominal ultrasound showed an occupying focus in the right lobe of liver. Hepatocellular carcinoma was diagnosed after biopsy. Partial
hepatectomy was performed.

**Macro description:**
The volume of liver is increase. On the cut surface, there is a huge tumor mass underneath the liver capsule. The tumor is grey and solid with necrosis and hemorrhage in the center. Several satellite nodules are scattered peripherally around the tumor.

**Question:**
What are the differences between primary liver carcinoma and metastatic carcinoma of liver?

**Common benign mesenchymal tumors**

**Lipoma**
The clinical history and macroscopical features are as previously descripted.

Micro description (Fig.5-7)
Naked-eye view: The color is light pink
Low-power view: Like normal fat tissue and lobulated with fine fibrous trabeculae.
High-power view: Lipoma is composed of mature adipocytes. Because of fixation, the fat has been dissolved, leaving only fat vacuoles. The nucleus is small, located on the periphery.

**Leiomyoma of the uterus**
The clinical history and macroscopical features are as previously descripted.

Micro description (Fig.5-7)
Naked-eye view: The color is pink. The boundary between normal uterine muscle and leiomyoma is clear in some slides.
Low-power view: Tumor is composed of uniform spindle cells, arranged in bundles, interlaced, whorled, with a sharp demarcation of normal tissue.
High-power view: tumor is composed bland spindle cells arranged in bundles, interlaced, whorled. Nuclei are spindled, have blunt ends and are normochromatic with generally inconspicuous nucleoli. Mitoses figures are rare.

**Common malignant mesenchymal tumors**

- **Liposarcoma**

**Clinical history:** Male, 67-year-old, presented with abdominal pain and distention for more than 2 months. Abdominal CT scan showed a huge retroperitoneal occupying mass. Surgical resection was performed for further pathological examination.
Gross description:
(1) The tumor is big, multi-nodular or lobulated, with a thin fibrous capsule.
(2) The color is light yellow, grey, or with partial transparent on the cut surface.
(3) Areas of necrosis and hemorrhage are common in larger lesions.
(4) Calcification is usually seen.

Questions:
(1) Is there any infiltration of liposarcoma which may lead to obscure demarcation between normal and tumor tissues?
(2) What is the growth pattern of liposarcoma?
(3) What is the most likely metastatic route?

Micro description

Naked-eye view: The color is pink.

Low-power view: Tumor is composed of varying sized fat cells, lobulated with fibrous trabeculae. Myxoid degeneration of stroma is common.

High-power view: Tumor is composed of mature adipocytes and lipoblasts. Lipoblasts are relatively specific, and are somewhat smaller than mature adipocytes. Lipoblasts have round, sharply demarcated cytoplasmic lipid (clear) vacuoles which scallop the nucleus and are smaller than vacuoles of mature adipocytes; spikes of chromatin may project between the vacuoles; may resemble signet ring cells or have central nuclei with small indentations by multiple fat vacuoles.

Osteosarcoma

Clinical history: Male, 16-year-old, presented with pain and swelling in the upper tibia for 1 year. X-ray showed a lump in the upper tibia associated with bone destruction. Codman triangle and sun burst pattern were visible.

Gross description:
A spindle lump is noticed at the end of a long bone. The tumor is grey or light red, fish like, with hemorrhage and necrosis on the cut surface. It often destroys cortical bone, elevates periosteum, and invades soft tissue and medullary cavity.

Micro description:

Naked-eye view: The tissue is dense and red in color.

Low-power view: Tumor cells are diffused distributed with marked cellular atypia and predominant pleomorphism.

High-power view: Tumor cells may be spindly, oval or round of variable size with bizarre giant cells in stroma. High grade tumor cells produces osteoid matrix. Mitoses
Others

- **Teratoma of the ovary**
  It’s a kind of germ cell tumor usually composed of more than one germ layer, and may differentiate in ways suggesting other germ layers.
  
  **Clinical history:** Female, 27-year-old, a cystic mass of her left ovary was found by ultrasound in physical examination.
  
  **Gross description:** A cystic mass with fine capsule. It contains greasy material composed of keratin, hair and teeth.

- **Malignant melanoma**
  
  **Clinical history:** Female, 27-year-old, a cystic mass of her left ovary was found by ultrasound in physical examination.
  
  **Macro description:**
  The tumor is dark, dry and solid.
  
  **Micro description:**
  
  **Naked-eye view:** The tissue is dense and red in color.
  
  **Low-power view:** Tumor cells may be spindly, polygonal or round of variable size, arranged in nests, cords or alveolar.
  
  **High-power view:**
  Tumor cells usually large with abundant eosinophilic and finely granular cytoplasm. Cellular atypia is marked with pleomorphic nuclei with large eosinophilic nucleoli. Melanin pigmentation and invasion of surrounding tissue are prominent. Mitotic figures are common.

**Question:**

(1) What is the reason for the malignant change of the mole of this patient?

(2) What are the clinical warning signs in daily life?

**Cytologic smear of adenocarcinoma**

- **Pleural (peritoneal) effusion smear or sputum smear**
  
  **Naked-eye view:** the color is light with some dark cell blocks scattering
  
  **Low-power view:** if it’s a pleural (peritoneal) effusion smear, some isolated abnormal cells or cell blocks with eccentric nuclei are scattered among lymphocytes/mesothelial cells background.
**High-power view:** Also scattered single cells with hyperchromatic nuclei, 1-3 nucleoli, mitotic figures, apoptotic bodies, watery diathesis.

**Notes:** Pay attention to distinguish adenocarcinoma cells from mesothelial cells and other inflammatory cells.
Case Discussion

Clinical history: A 61 year old male had upper abdominal pain and weight loss for over a year, which had been intensifying over the time. The patient also felt dizzy and weak in the past four months. During the last three weeks, he had melena. The abdominal pain was not related to eating.

Physical examination revealed a body temperature of 37°C, a pulse rate of 84/min, a respiratory rate of 20/min, and a blood pressure measurement of 7.34/9.34 kPa. The patient appeared pale with a slightly distended abdomen which was soft but tender upon palpation. Laboratory findings: RBC 1.92 x 10¹²/L, Hb 60g/L, WBC 4.1 x 10⁹/L, neutrophils 0.88, lymphocytes 0.10, monocytes 0.02. Occult blood test (OBT) of stool result is positive. X-ray imaging suggested a large ulcerative lesion on the lesser curvature of the stomach. Administration of antibiotics and transfusion together with other supportive treatment was not effective. Five days after hospitalization, the patient had severe jaundice and vomiting of dark brownish fluid, and more severe anemia. The patient died in a prominent wasting and comatous status.

Necropsy findings: The deceased had a normal development, but with poor nutrition. The skin, sclera and mucosa had a yellow tinge. No enlarged superficial lymph node was detected. Pitting edema was apparent on both legs. There was 2000 ml of yellowish, clear ascites, and a small amount of pleural perfusion of a similar nature. There was a 6 x 5 cm irregular ulcer 2 cm above the pylorus in the stomach, with an uneven base deep in the musculature. The rim of the ulcer appeared elevated and nodular. Peri-ulcer gastric wall was thickened with a hardened consistency, involving the gastric antrum and the pylorus. Microscopically, Intestinal metaplasia of gastric mucosa is prominent. There were numerous abnormally large columnar or cuboidal cells with abundant cytoplasm in the ulcerative lesion. The nuclei of the cells were large and pale with prominent nucleoli. Many mitotic figures were seen. The cells were arranged in irregular glandular structures, which were intermixed with fibrous stroma. There was destruction of the gastric musculature, as well as involvement of the duodenum and pancreas by these abnormal cells.
A mass was located in the lower common bile duct and the Vater’s ampulla, which appeared grayish white on cut surface. Microscopically, the mass composed of the abnormally-looking cells similar to that found in the stomach.

The liver weighed 1300g. The surface was smooth and yellowish green in color. There were multiple well-demarcated grayish white nodules in the liver, which were composed of cells morphologically identical to the abnormal cells found in the stomach. Hepatic cells showed degenerative and necrotic changes with cholestasis.

A thrombus was found in the portal vein, which extended to the upper mesenteric vein. Part of the thrombus was attached to the vascular wall. The thrombus was of a mixed nature upon microscopic examination, which did not contain any cells that looked like the abnormal cells found in the stomach.

Lymph nodes of the gastric lesser curvature and the pylorus region, and the hepatic and common bile duct lymph nodes were enlarged to about 1-2.5 cm in diameter, with some fused to larger masses. The cut surface was grayish yellow. Microscopically, numerous abnormal cells reminiscent to that found in the stomach replaced much of the lymphoid tissue.

**Discussion:**

1) Give your diagnoses and reasons for your diagnoses.
2) Describe the disease process, based on the clinical history and anatomic findings.
3) How the lesions of the various organs related?
4) What are the causes of the patient’s death?
**Questions for Review**

1. Please compare skin papillary with squamous cell carcinoma; adenoma with adenocarcinoma; lipoma with liposarcoma. Explain the differences between benign and malignant tumors.
2. What are the possible tumors of esophagus based on the normal 4-layer structure of it?
3. Please describe the differences between carcinoma and sarcoma by taking well differentiated squamous cell carcinoma and liposarcoma as examples.
4. Try to explain the nomenclature of tumor and give some examples.
5. What is tumor metastasis? What are the pathways for tumor disseminate? Why sarcoma is prone to metastasize hematogenously?
6. How to distinguish neoplastic mass from non-neoplastic mass for a subcutaneous mass? How to differentiate between benign and malignant if it is a real tumor? How to differentiate between carcinoma and sarcoma if it is malignant?
7. How to determine the benign or malignant of a subcutaneous mass through physical examination or clinical history taking?
8. What is the meaning of early diagnosis of tumor? How to make an early diagnose the carcinoma of cervix, lung, esophagus, stomach, intestine and liver?
9. Try to explain the cytological diagnosis standard of adenocarcinoma cells.