10

Pathology

Doctor 2018 | Medicine | JU

◉ Sheet ○ Slides

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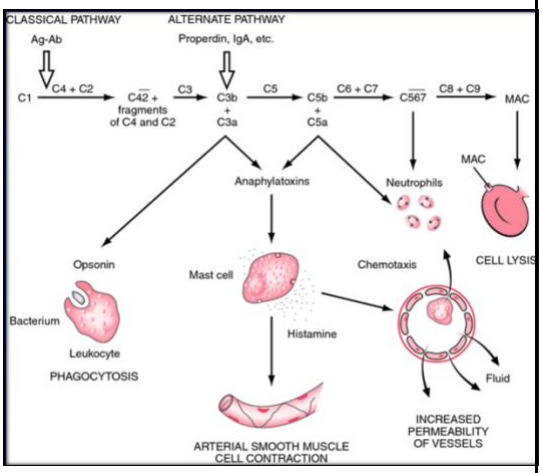
The complement system

- The complement system is a collection of soluble proteins that are normally inactive, and therefore need activation (fixation) to function.
  (In pathology the word fixation means activation)
- There are more than 20 complement proteins, some of which are numbered C1(complement protein number 1), C2, C3, through C9. They function in both **innate and adaptive** immunity for defense against microbial pathogens.

We said that they need to be activated (fixed), but how?

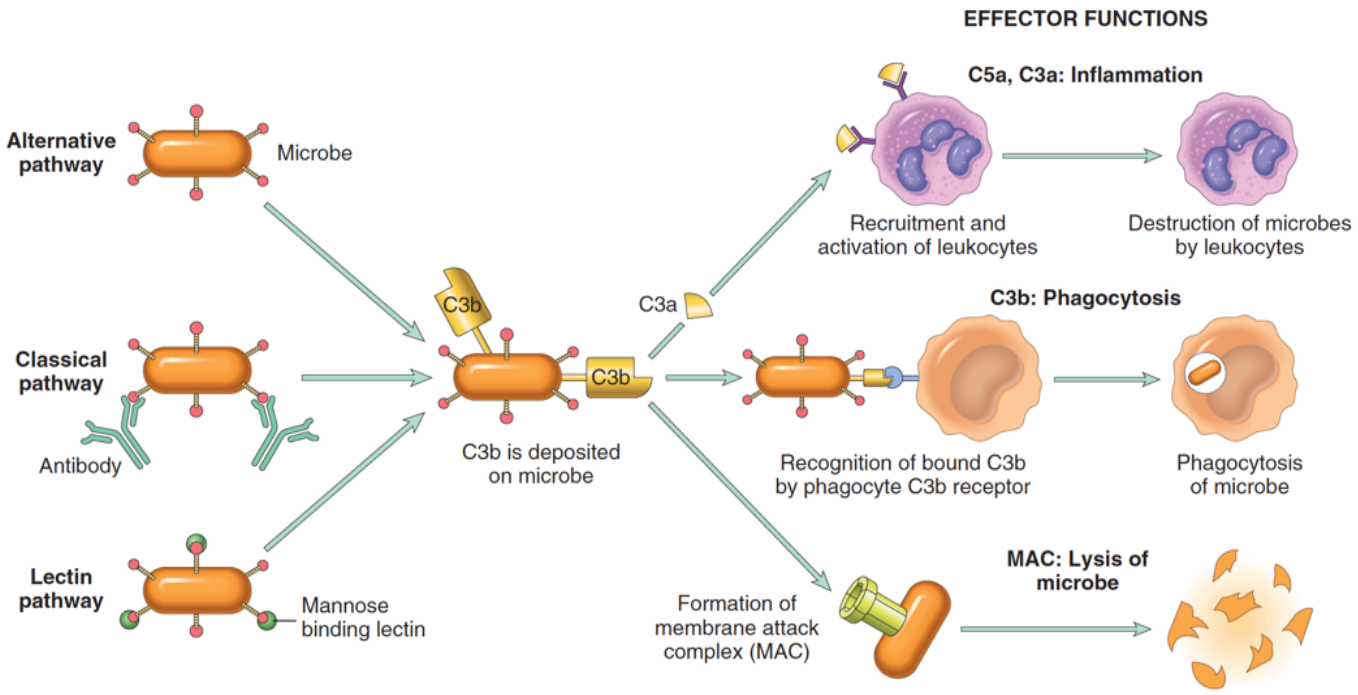
- Complement proteins get activated through the process of cleaving the protein into 2 units, a & b. For example, C5 will be activated when it is cleaved to C5a and C5b.
  (Both of the cleaved products have specific functions.)
- many of them are activated to become proteolytic enzymes that cleave other complement proteins, thus forming an enzymatic cascade capable of tremendous amplification.
- The cleavage products of complement proteins cause Increased vascular permeability, Chemotaxis, opsonization, cell lysis and many other functions that aid the complement system's main function; **host defense against microbes** and helping in **pathologic inflammatory reactions**.



What is the main gate to activate the complement system?

- **The critical step** (the main gate) in complement activation is the proteolysis(cleavage) of the third **(and most abundant)** component, **C3**.
- Cleavage of C3 can occur by one of **three pathways**:
  1- **The classical pathway**; is triggered by antigen-antibody (Ag-Ab) complexes that activate C1, starting an enzymatic cascade that cleaves C3.
  2- **The alternative pathway**; triggered by microbial surface molecules (e.g., endotoxin, or LPS), complex polysaccharides, some immunoglobulins and other substances.
  3- **The lectin pathway**; in which plasma mannose-binding lectin binds carbohydrates on microbes and directly activates C1 which in turn activates C3.

- All three pathways of complement activation lead to the formation of an enzyme called the C3 convertase, which splits C3 into two functionally distinct fragments: C3a and C3b.



The complement system is complicated with many cascades functions, but we are only required to know these points.

Complement system's functions

1- Inflammation

- **C5a** is the strongest chemotactic agent (chemoattractant).
- **C5a**, and to a lesser extent, C3a, stimulate **histamine** release from mast cells and thereby increase vascular permeability and cause vasodilation.
  They are called **anaphylatoxins** because they have effects that are involved in the reaction called anaphylaxis.

(Anaphylaxis is a serious allergic reaction that is rapid onset and may cause death, for example, some patients die from a strong allergic reaction towards penicillin)

2- Opsonization and phagocytosis.

- **C3b**, when fixed to a microbial cell wall, act as opsonins and promote phagocytosis by neutrophils and macrophages, which bear cell surface receptors for these complement fragments.

3- Cell lysis

- By the membrane attack complex (MAC), which is virtually multiples of C9.
  It was previously thought that the mac complex is a mix between C5,C6,C7,C8 and C9 (C5-9)
  It drills holes in the microbial cell membrane, making the cells permeable to water and ions and resulting in their osmotic death (lysis).

Regulatory proteins for the complement system

❖ **C1 inhibitor**

It blocks the activation of C1, the first protein of the classical complement pathway, which in turn blocks the cascade that activates C3. Inherited deficiency of this inhibitor is the cause of hereditary angioedema.

Angioedema is the rapid severe edema, or swelling, of the area beneath the skin or mucosa; could be fatal if not treated immediately.

Angio: means vascular

❖ **Decay accelerating factor (DAF) and CD59**

- DAF inhibits C3 convertases
- CD59 inhibits MAC (membrane attack complex).

Both DAF and CD59 are GPI anchored proteins, so an acquired deficiency in the production of GPI anchors leads to deficiency of these regulators which leads to:

1- excessive complement activation(✖ DAF → no regulation of C3 convertase)
2- lysis of red cells (✖ CD59 → no regulation of the MAC)

This gives rise to a disease called paroxysmal nocturnal hemoglobinuria (PNH)

- PNH is a disease characterized by the destruction of red blood cells, leading to accumulations of hemoglobin in the urine.
- Nocturnal means active at night.
- Paroxysmal means sudden attack.

❖ **Factor H**

Factor H is a plasma protein that serves as a cofactor and a regulator for the proteolysis of the C3 convertase; its deficiency results in excessive complement activation.
Mutations in Factor H are associated with a kidney disease called the hemolytic uremic syndrome (HUS).

To sum up:

Regulatory protein	function	Deficiency leads to
C1 inhibitor	Inhibits activation of C1	angioedema
Decay accelerating factor (DAF)	Inhibits C3 convertase	paroxysmal nocturnal hemoglobinuria (PNH)
CD59	Inhibits MAC	
Factor H	proteolysis of the C3 convertase	hemolytic uremic syndrome (HUS)

❖ Congenital deficiencies of complement proteins cause increased susceptibility to infections.

Other mediators

We talked about different inflammatory mediators like histamines, cytokines, leukotrienes, the complement system and here are some more:

• **Platelet activating factor (PAF):** like Thromboxane, it stimulates platelet aggregation and causes vasoconstriction alongside other functions.
• **Protease activating receptors (PARs):** also stimulate platelet aggregation.
• **Kinins:** they are vasoactive peptides. **Bradykinin** is the active form of kinins; it functions in vasodilation, increasing permeability, smooth muscle contraction and mainly producing **pain.**
• **Neuropeptides**: they are proteins produced by neurons like Substance P and neurokinin A.

Table 3.8 Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

This table summarizes the mediators we talked about (**memorize it!**)

Summary

Actions of the Principal Mediators of Inflammation

- Vasoactive amines, mainly histamine: vasodilation and increased vascular permeability
- Arachidonic acid metabolites (prostaglandins and leukotrienes): several forms exist and are involved in vascular reactions, leukocyte chemotaxis, and other reactions of inflammation; antagonized by lipoxins
- Cytokines: proteins produced by many cell types; usually act at short range; mediate multiple effects, mainly in leukocyte recruitment and migration; principal ones in acute inflammation are TNF, IL-1, and chemokines
- Complement proteins: Activation of the complement system by microbes or antibodies leads to the generation of multiple breakdown products, which are responsible for leukocyte chemotaxis, opsonization and phagocytosis of microbes and other particles, and cell killing
- Kinins: produced by proteolytic cleavage of precursors; mediate vascular reaction, pain

Morphology of acute inflammation.

- There are 2 types of morphology → **gross morphology** (by the naked eye), and **microscopic morphology** (using the microscope), for example frozen sections during surgery. The importance of recognizing distinct gross and microscopic patterns of inflammation is that they often provide valuable clues about the underlying cause.
- The morphologic markers of acute inflammation are:
- **1- Dilation of blood vessels**
- **2- Accumulation of leukocytes (WBCs) and fluid in the extravascular tissue.**
- these general features are characteristics of most acute inflammatory reactions:
  Redness, Warmth, Swelling, Loss of function and pain
- Although these are common features in acute inflammations, special morphologic patterns are often superimposed on them, depending on the severity of the reaction, its specific cause, and the particular tissue and site involved. For example, →

Edema	Fluid and proteins in interstitium
Redness	*rubor*
Warmth	*calor*
Swelling	*tumor*
Loss of function	*Functio laesa*
Pain	*dolor*

Serous inflammation

- Serous inflammation is marked by a cell-poor fluid**(transudate)**, for example **serous effusions**, **skin blisters** and **seromas.**
- Serous effusion: the accumulation of cell-poor fluids inside various body cavities. Examples of serous effusions are pleural serous effusion, pericardial serous effusion and Ascites (Peritoneal cavity fluid). Note that not all effusions are serous.

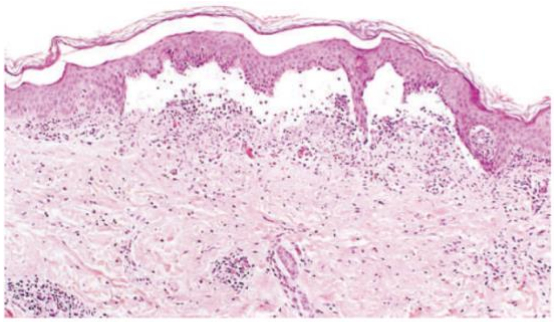
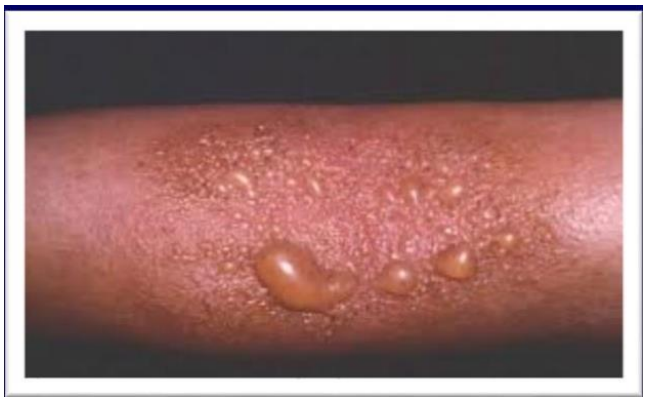


Fig. 3.12 Serous inflammation. Low-power view of a cross section of a skin blister showing the epidermis separated from the dermis by a focal collection of serous effusion.

- Seroma: is an accumulation of a fluid (serum) that builds up under the surface of your skin. Seromas may develop after a surgical procedure, most often at the site of the surgical incision or where tissue was removed.
- Serous inflammations are **transudate**



Fibrinous inflammation

- A fibrinous exudate (accumulation of **fibrin**) develops when the vascular leaks are large or there is a local procoagulant stimulus, we can see it in Pericarditis (inflammation of the pericardium) and pleuritis (inflammation of the pleura)
- Notes:
  - To properly diagnose pleuritis, a doctor examines the chest specifically around the area of pain and can often hear (with a stethoscope) the friction that is generated by the rubbing of the two inflamed layers of pleura with each breath.
  - When the pericardium is inflamed, doctors surgically remove a small part of the pericardium making a window called a pericardial window.

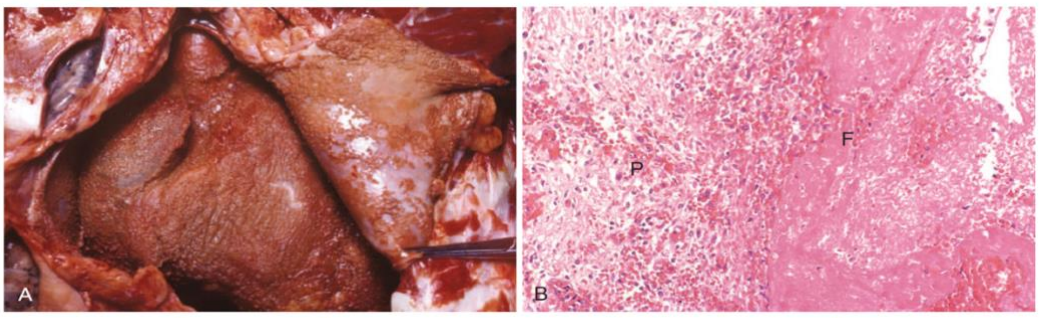


Fig. 3.13 Fibrinous pericarditis. (A) Deposits of fibrin on the pericardium. (B) A pink meshwork of fibrin exudate *(F)* overlies the pericardial surface *(P)*.

Purulent (Suppurative) Inflammation, abscess

- Purulent inflammation is characterized by the production of pus, an exudate consisting of neutrophils (PMNs), the debris of necrotic cells, and edema fluid.
- Purulent (Suppurative) Inflammation is a severe acute inflammation.
- The most frequent cause of purulent (also called suppurative) inflammation is infection with bacteria such as staphylococci.
- A common example of an acute suppurative inflammation is acute appendicitis (inflammation of the appendix).
- Abscesses are localized collections of pus.
- Purulent inflammations are **exudate**

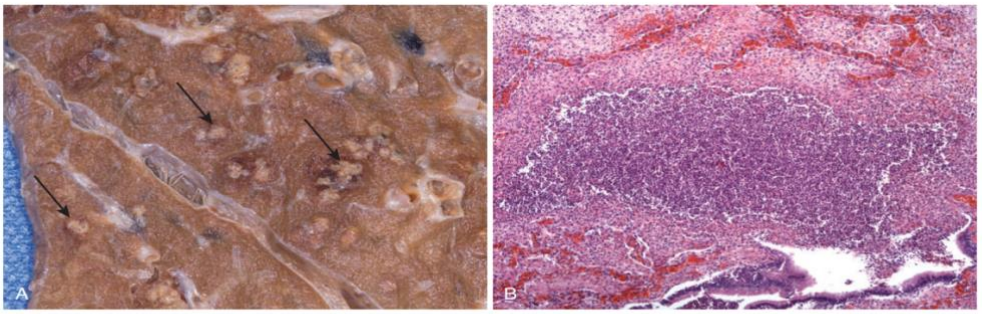


Fig. 3.14 Purulent inflammation. (A) Multiple bacterial abscesses *(arrows)* in the lung in a case of bronchopneumonia. (B) The abscess contains neutrophils and cellular debris, and is surrounded by congested blood vessels.

Ulcers

- An ulcer is a **local defect,** or a discontinuation of the surface of an organ or tissue, which mainly happens in **mucosal surfaces** and the **skin.**
- Examples are peptic ulcers of the stomach and duodenum ulcers.
- One of the most important procedures dealing with ulcers is taking a biopsy to check for cancer. The pathologist looks at the biopsy using the microscope and then decides if the ulcer is benign or malignant.
- Acute and chronic inflammations often coexist in ulcers.
- Acute ulcers (superficial erosion) are sometimes drug induced.
- With chronicity, the margins and base of the ulcer develop fibroblast proliferation, scarring, and the accumulation of lymphocytes, macrophages, and plasma cells.

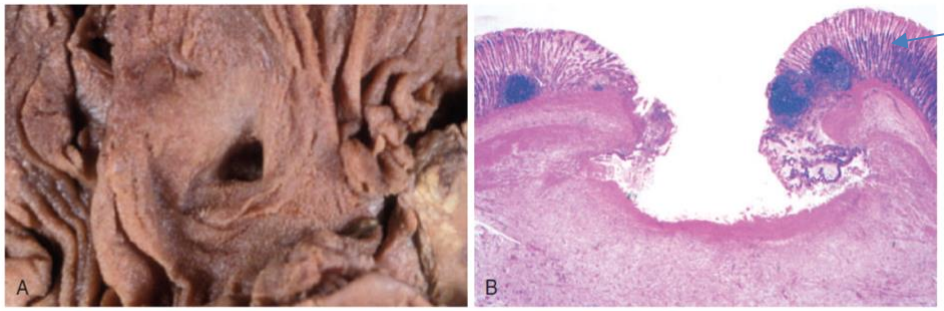


Fig. 3.15 The morphology of an ulcer. (A) A chronic duodenal ulcer. (B) Low-power cross-section view of a duodenal ulcer crater with an acute inflammatory exudate in the base.

Chronic ulcer, because of the accumulation of lymphocytes (the blue circles)