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Pathology

Doctor 2017 | Medicine | JU

◉ Sheet ○ Slides

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Doctor

Dr. Mousa

****We talked about the 5 inflammatory response steps briefly, now we will discuss them in more explanation:**

1 - Recognition of microbes and damaged cell:

- First step in inflammatory Response: this happened by the action of:

– Cellular receptors: Toll-like Receptors (TLRs); found on membranes (especially inflammatory cells and other cells) and endosomes (inside the cell structure). These receptors recognize certain protein sequence of invaders (especially alive invaders),

This protein pattern called **Pathogen Associated Molecular Patterns (PAMPs).**

– Not all the invaders are organisms so the second mechanism is:

– Sensors of cell damage: recognize **Damage Associated Molecular Patterns (DAMPs)** such as uric acid, ATP, K, & DNA. Consequently, multiple cytoplasmic proteins get activated (called inflammasomes).

– Circulating proteins: sometimes they are part of chemical mediators for inflammation,

Examples: complement system (proteins from C1-C9 each one activated the second like dominos, when the complement 1 activated then called C1a and so on), mannose-binding lectins and collectins.

2 - WBCs & Plasma proteins recruited to injury site:

Reaction of blood vessels in acute inflammation:

-One of the initial important event of inflammation is **Acute Initial Vascular Phase of inflammation** that explain multiple cardinal signs seen on inflamed organ (swollen, redness-erythema- ,pain – a symptom-, tenderness-when you touch the site of pain, heat)

- This phase composed of 3 steps:
    1- Blood vessel dilation
    2- Increased vessel permeability
    3- Emigration of WBCs

- Each step has its mediator which enhance and stimulate it.

** Blood vessels dilation step mediated by vasoactive amines (histamine)

Actually, the first mediate vascular response is a transient vasoconstriction followed by vasodilation (especially for quick sudden powerful stimulus)

**physiological properties of blood vessel:

-Normally, blood vessels consist of plasma proteins, cells and epithelial cells on the vessel wall attached by desmosomes. The inside components are in equilibrium with the outside ones. There is balance between Colloid osmotic pressure (depend on amount of plasma proteins) and the hydrostatic pressure (depend on amount of fluid inside the vessel).

- if hydrostatic pressure increase>> fluids (serum) will exit the vessel.
- if colloid pressure increase>> fluids will enter the vessel.
- If there is inflammation >> 2 major changes can take place:
***moving of fluid + cells + other molecules exit the vessel (Exudation)**
**** in exudation: severe acute inflammatory response very active process which open the gaps between the epithelial cells and holes in the membrane allowed to the cells and small amount molecular proteins to exit outside the vessel.**

- High protein, many cells and debris and higher specific gravity.

**however, in transudate, just fluid exit so:
Low protein, Low cell content, Low specific gravity.
** why there is 2 possibilities??
-The presence of different causes:
Exudate: Caused by increased vascular permeability and denotes inflammatory reaction. (more serious)
Transudate: Caused by osmotic/hydrostatic pressure imbalance.
Patient with liver failure>> hypoproteinaemia

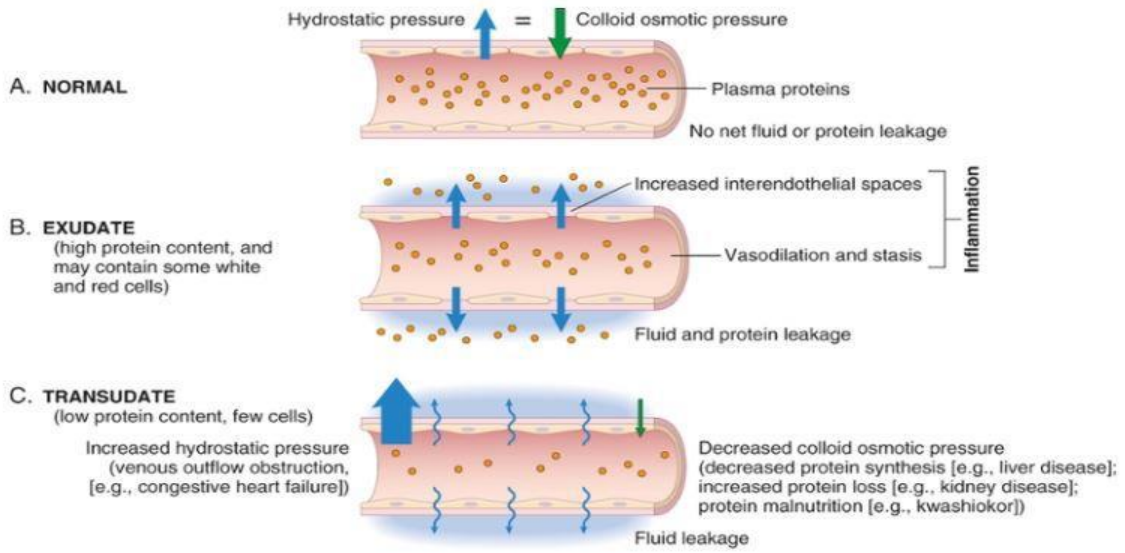
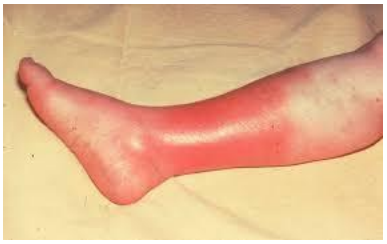


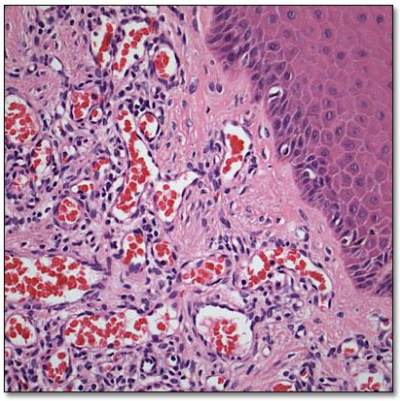
FIG. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue …*

* **Edema:** excess fluids in interstitium or serous cavities (lateral or abdominal cavities)>> either transudate or exudate depending on the cause.



* **PUS:** purulent exudate; inflammatory exudate, fluid rich in WBCs, debris, and microbes.

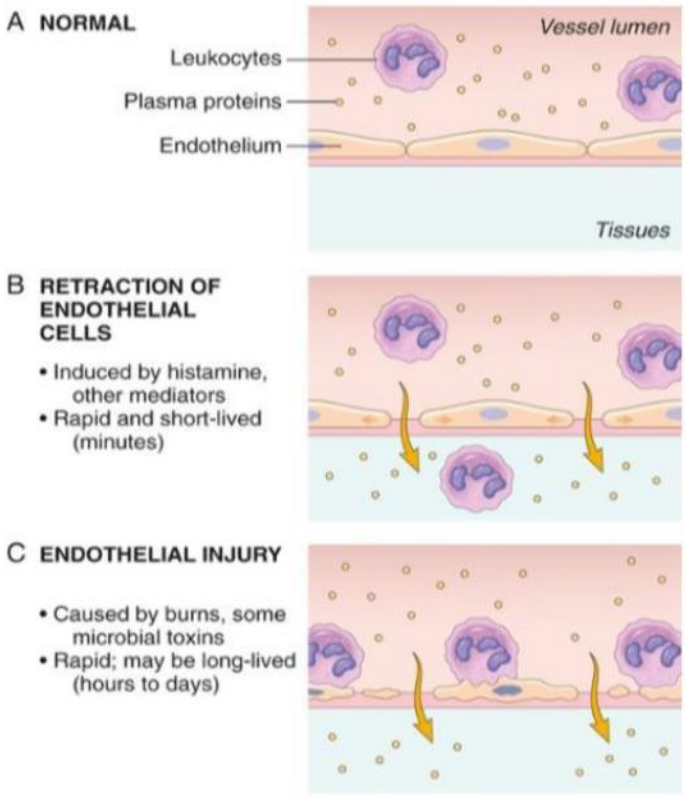
So early vascular events are:



* Vasodilatation: histamine; increased blood flow causing redness (erythema) and heat.
  * Followed by increased permeability (exudate).
* Stasis; congestion and erythema.
* congestion means that per meter square there are more structure, RBCs, and more inflammatory cells.
* PMNs: are the main acute inflammatory cells, accumulate and adhere to endothelium then migrate outside the vessel into the interstitium.

*those are the early vascular events, the main driver is histamine.

*Vasodilation has 2 phases:

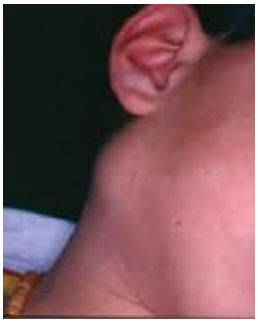


Initial phase: traction of the epithelial cells (not damage, still alive), basement membrane intact, small amount of small molecular proteins and fluids will come out.

*However, when the body need more cells, PMNs to go out, the body will actively damage epithelial cells and basement membrane, and this what happens in **phase 2** >> more proteins and fluids will come out.

Note: But what is the main structure of basement membrane? Collagen type 4 and laminin, the basement membrane is important for epithelial cells and in inflammation and cancer.

Responses of Lymphatic vessels and lymph nodes:



*It is important because it drains and repairs after acute inflammation.
*Enlargement of lymph nodes is not necessary to be bad news, it can be good or bad dependent on the case of the patient.
*In the emergency, if a patient come with pain, redness, tenderness in his lymph node>> it can be good news if there are bacteria and viruses (inflammatory lymphatitis) and by taking antibiotics he will come back to normal state, but if the cause is cancer the antibiotic will not make sense in his body and this case is bad news.
*The pathologists have to connect the 3D shape of the cell in the body with the 2D shape under the LM.
*Neutrophils and monocytes (macrophages when it goes to the tissue) *this is what the doctor said* are very important cells in the recruitment and migration, responsible for eliminating the enemy (we will talk about it later in phagocytosis).

TABLE 3.3 Properties of Neutrophils and Macrophages

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

HSC, Hematopoietic stem cells; *iNOS*, inducible nitric oxide synthase; *NET*, neutrophil extracellular traps.
This table lists the major differences between neutrophils and macrophages. The reactions summarized above are described in the text. Note that the two cell types share many features, such as phagocytosis, ability to migrate through blood vessels into tissues, and chemotaxis.

*Now, how WBCs move from inside (blood vessels) to outside (site of injury), when there is acute inflammation?

1- margination.
2- Rolling.
3- Adhering.
4- Transmigration.

** Each one of these steps has its stimulus and mediator.

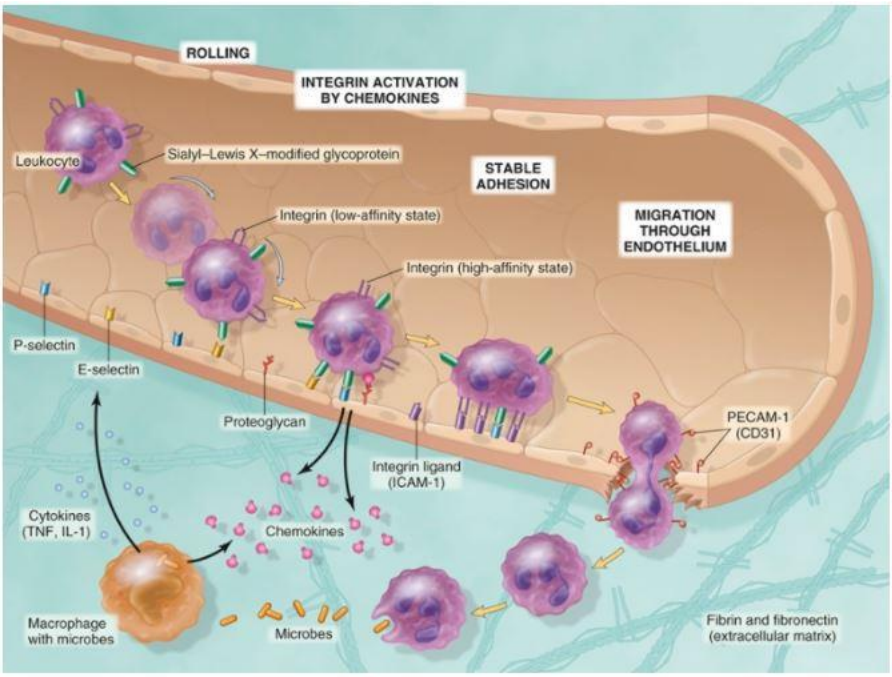


FIG. 3.4 The multistep process of leukocyte migration through blood vessels, shown he…

Cells, proteins and neutrophils normally flow (luminal flow) in the centre of blood vessels (in the inner 2/3 of the vessels).

*When the inflammation starts>> the WBCs move and become closer to the wall of blood vessels>> this step is called **migration**.

*The WBCs start rolling much closer to the wall >> **Rolling**.

*There are structures on the epithelial cells that attach to WBCs >> **Adhesion.**

Adhesion has two steps:
Initial weak adhesion >> selectins followed by stronger adhesion >> integrins (high affinity).
*The final step before WBCs go out is **Transmigration** and this happens by the stimulation of CD31 (PECAM-1) which secrete collagenase and pierce the basement membrane>> so WBCs can go to the site of injury.
If we multiply this process by **1000** >> edema and redness will occur.
*more severe stimulus >> more damage >> so more repair.