

Pathology of septicemia

Septicemia (sepsis) is a life-threatening condition and a global disease burden with significant morbidity and mortality even in the modern era of critical care management. Dysregulated host response to infection causes heterogeneous syndrome defined as severe organ dysfunction. Now, requested is a paradigm shift from the pathogen to the host response as a potentially more promising angle. Pathological changes associated with septicemia are presented herein.

Ref.-1: Tsutsumi Y. Pathology and pathophysiology of sepsis. In: Diagnosis and treatment of sepsis and their development strategy. Chapter 1-3-2. Technical Information Institute, Tokyo, 2013; pp. 87-95 (in Japanese).

Ref.-2: Remick DG. Pathophysiology of sepsis. Am J Pathol 2007; 170(5): 1435-1444. DOI: 10.2353/AJPATH.2007.060872

Ref.-3: Jarczak D, et al. Sepsis—Pathophysiology and therapeutic concepts. Front Med (Lausanne) 2021; 8: 628302. doi: 10.3389/fmed.2021.628302

Systemic inflammatory response syndrome (SIRS)

Septicemia (sepsis) represents a systemic inflammatory response syndrome (SIRS) against microbial infection in organs and tissues. Microbes intermittently invade the blood to provoke bacteremia and severe systemic infection. Bacteria or fungi are proven by microbial culture of the peripheral blood. Symptoms and signs include fever, chills, malaise, tachycardia, hypotension (septic shock) and consciousness disturbance. Neutrophilia is associated in the peripheral blood. Frequently, disseminated intravascular coagulopathy is complicated to provoke multiorgan failure (MOF).

Septic shock

Septicemia is caused by Gram-negative rods such as *E. coli*, endotoxin, a component of bacterial cell wall, provokes endotoxin shock. The lethality reaches 25%. Septicemia caused by Gram-positive cocci such as *Streptococcus* and *Staphylococcus* results in toxic shock-like syndrome due to exotoxins produced by the Gram-positive cocci. Mixed abnormalities of acid-base balance are seen with metabolic acidosis and respiratory alkalosis.

Primary infectious foci provoking septicemia

Severe infections such as pneumonia, cholangitis, pyelonephritis, peritonitis and meningitis commonly cause septicemia. When the patient has a deformity in the left cardiac valves (mitral valve or aortic valve) secondary to rheumatic fever or atherosclerosis, infective endocarditis may happen. Infective endocarditis is prompted by transient bacteremia due to the treatment for dental caries or catheterization in the artery, vein and urethra.

Neutropenia caused by aplastic anemia and chemotherapy against malignancy accelerates opportunistic infection by enterobacteria, *Pseudomonas* or *Candida*.

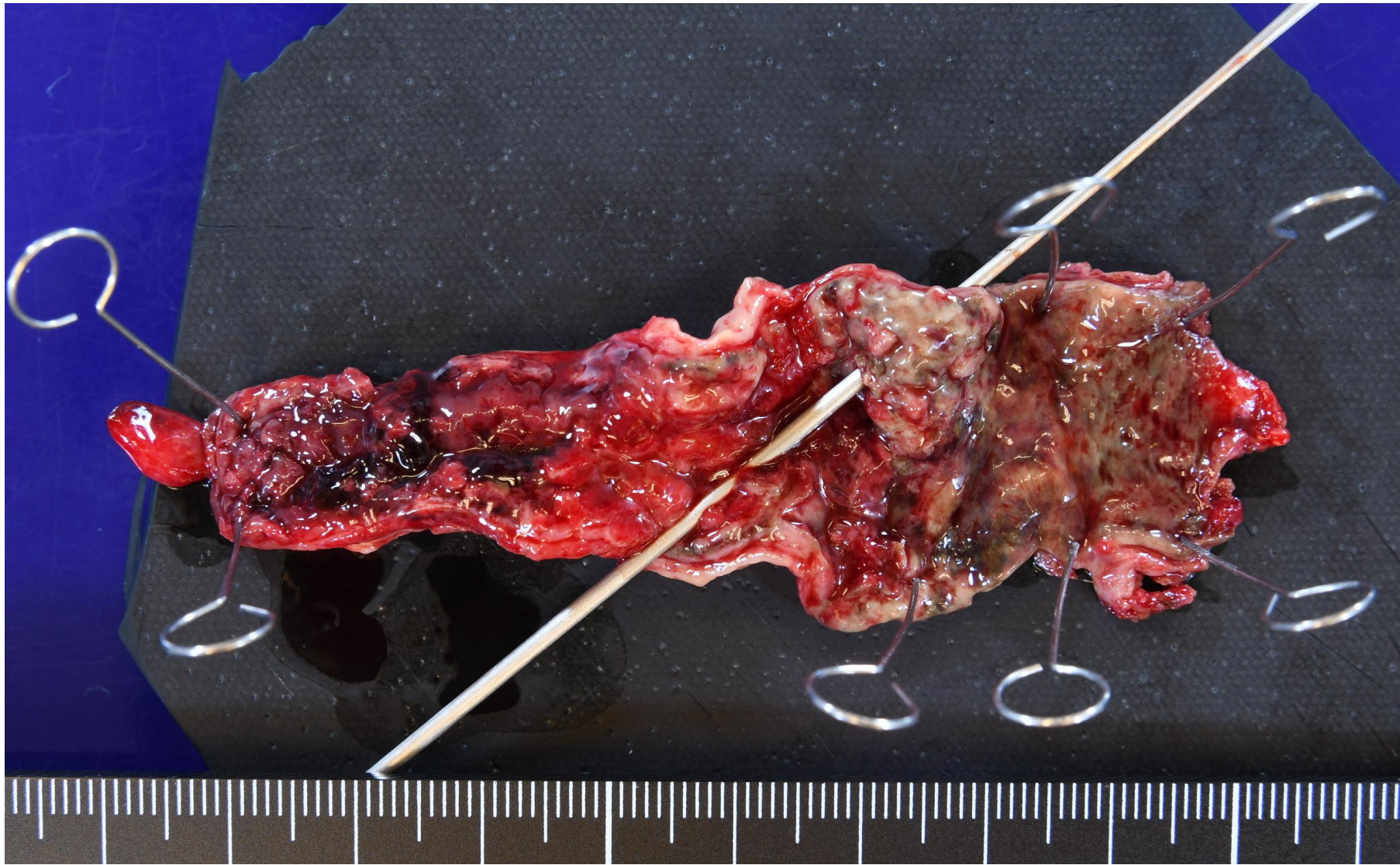
Infective endocarditis

Cardiac valve deformities in the mitral or aortic valve, caused by old rheumatic fever or atherosclerosis, may accelerate microbial infection to cause infective endocarditis. Septicemia is inevitable. Traditionally, infective endocarditis has been grouped into two: subacute and acute forms.

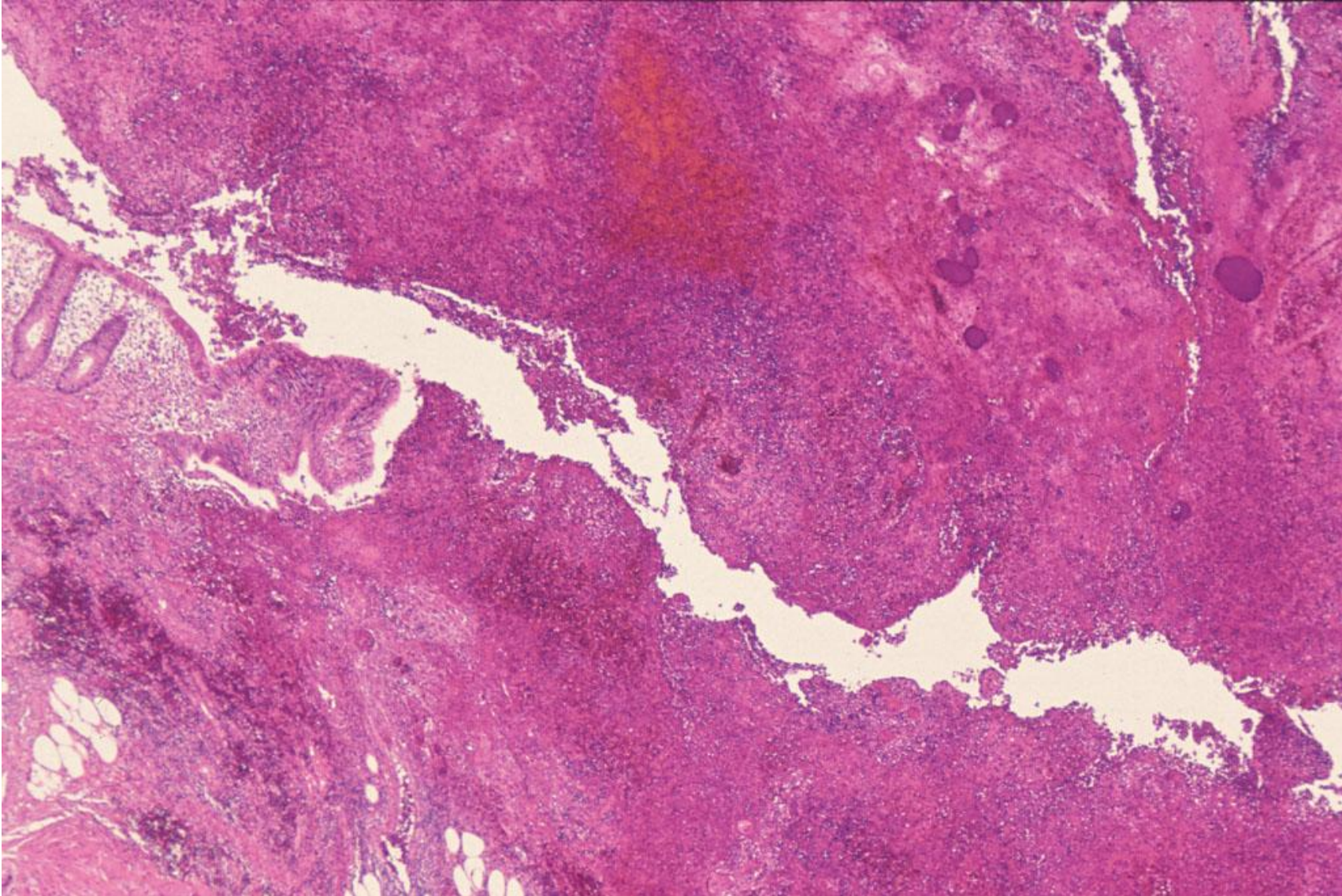
- 1) Subacute bacterial endocarditis (SBE): a prolonged course of septicemia results from infection of *Streptococcus viridans*, bacterial flora of the oral cavity.
- 2) Acute bacterial endocarditis (ABE): a severe form of septicemia results from infection of *Staphylococcus aureus*.

Histopathological features of septicemia

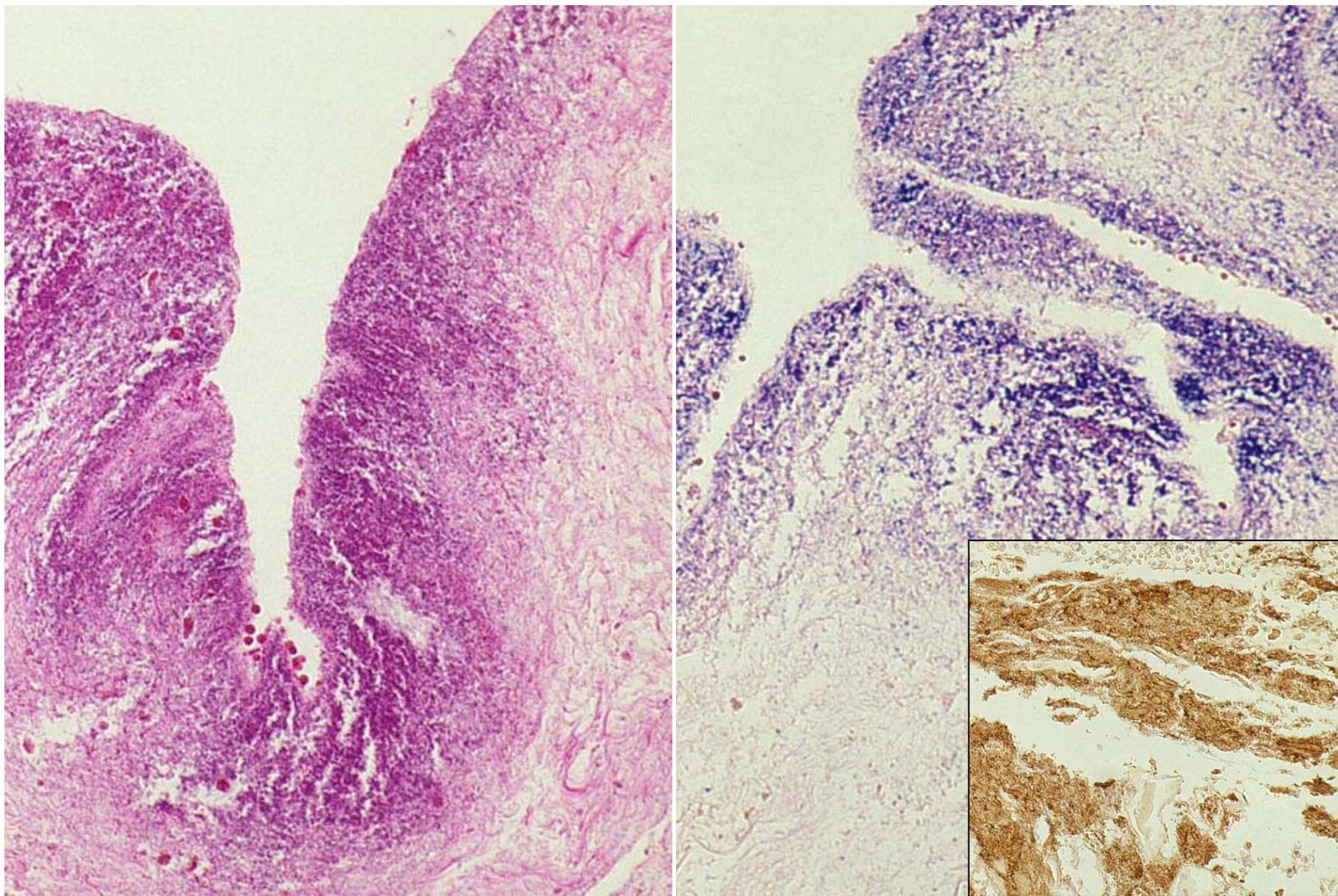
- 1) Infective endocarditis
- 2) Microabscess formation in systemic organs such as the heart, kidney, lung and brain.
- 3) Myeloid hyperplasia in the bone marrow
- 4) Acute splenitis with increase of neutrophils in the red pulp
- 5) Disseminated intravascular coagulopathy with fibrin microthrombi in the glomeruli, capillary vessels in the lung, and the splenic red pulp. Embolic infarction may be seen in the kidney, heart and spleen.
- 6) Septic shock-related lesions such as diffuse alveolar damage (lung), acute tubular necrosis (kidney), centrilobular necrosis (liver), congestion-related terminal hemorrhagic necrotizing enteropathy (intestine), and acute atrophy of lymphoid follicles (lymph nodes and splenic white pulp).



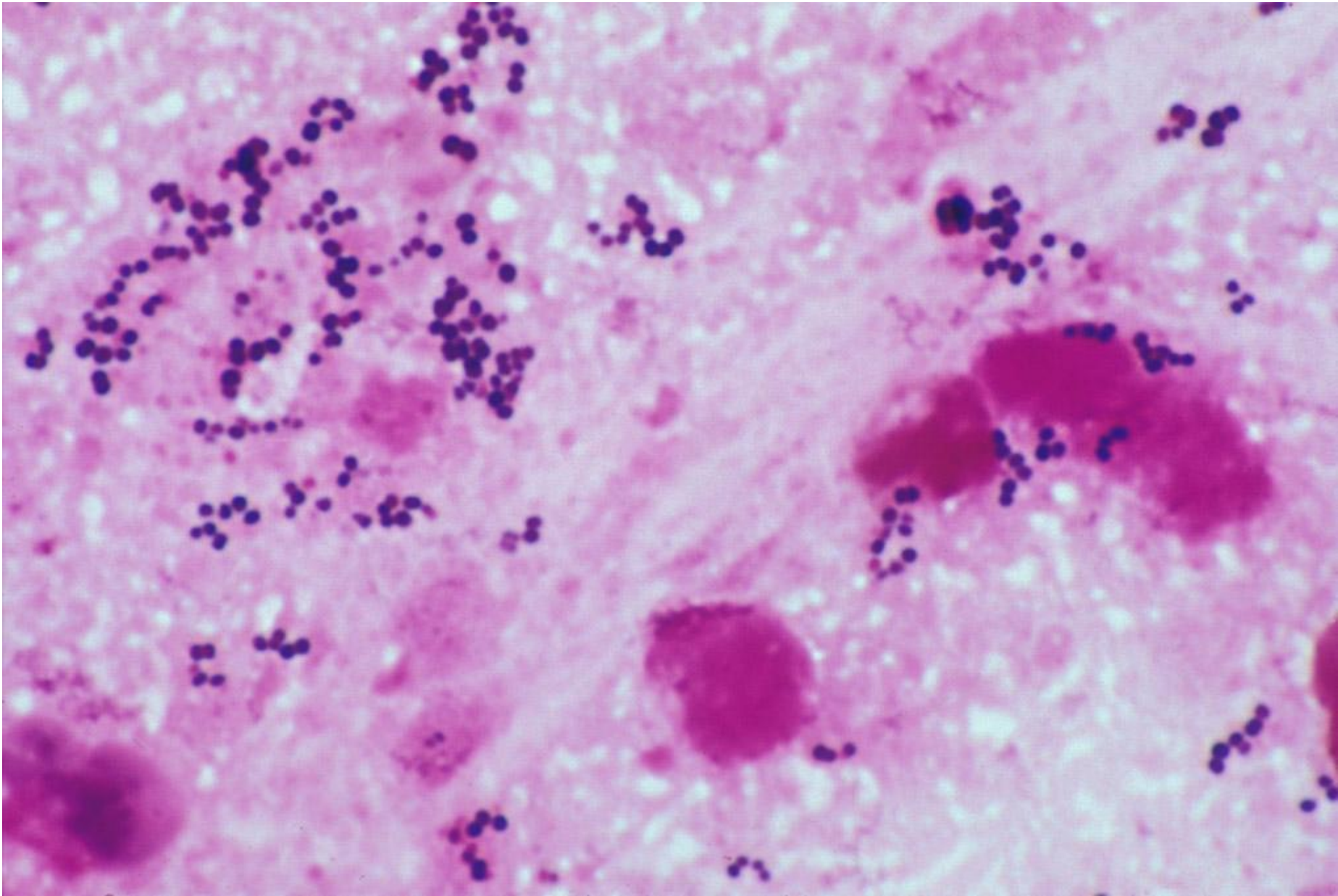
Gross appearance of acute gangrenous appendicitis with perforation



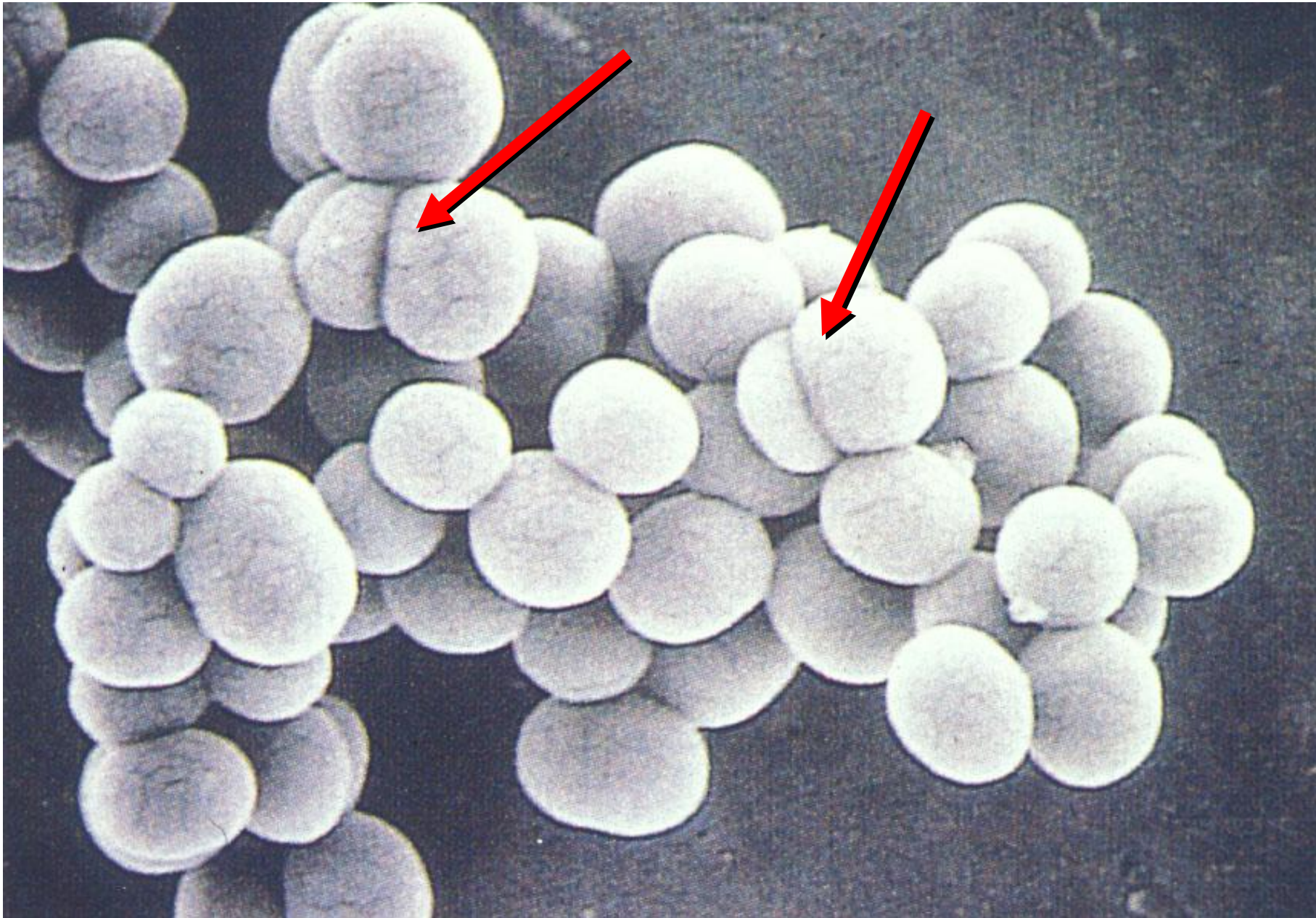
Acute gangrenous appendicitis with bacterial colonies. Hemorrhagic necrosis is extensive. Perforation provoked purulent peritonitis, a potential source of septicemia. H&E



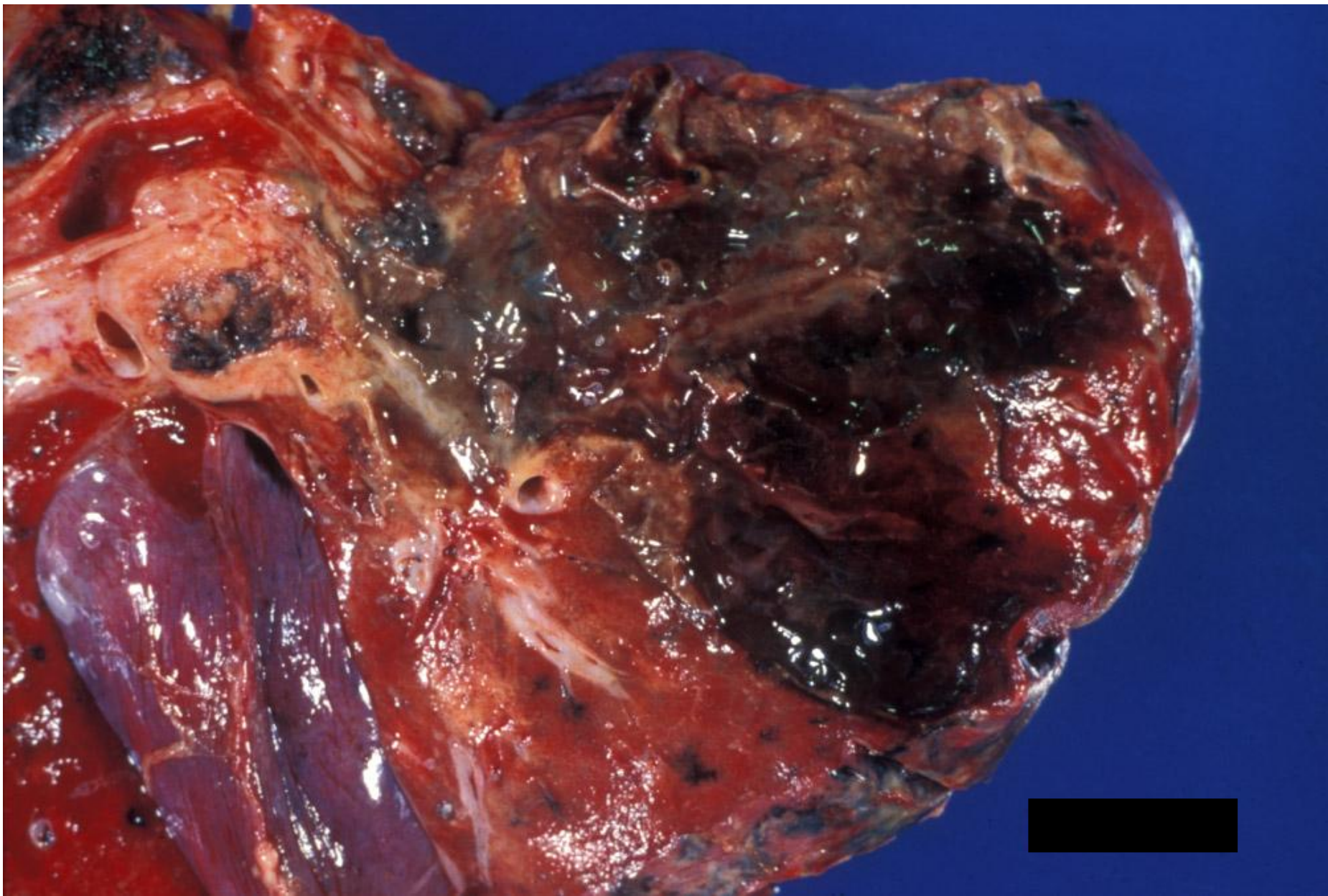
Acute gangrenous appendicitis. Massive mixed infection of Gram-positive cocci and Gram-negative rods (*E. coli*) is proven. left: H&E, right: gram, inset: immunostaining for *E. coli* antigens



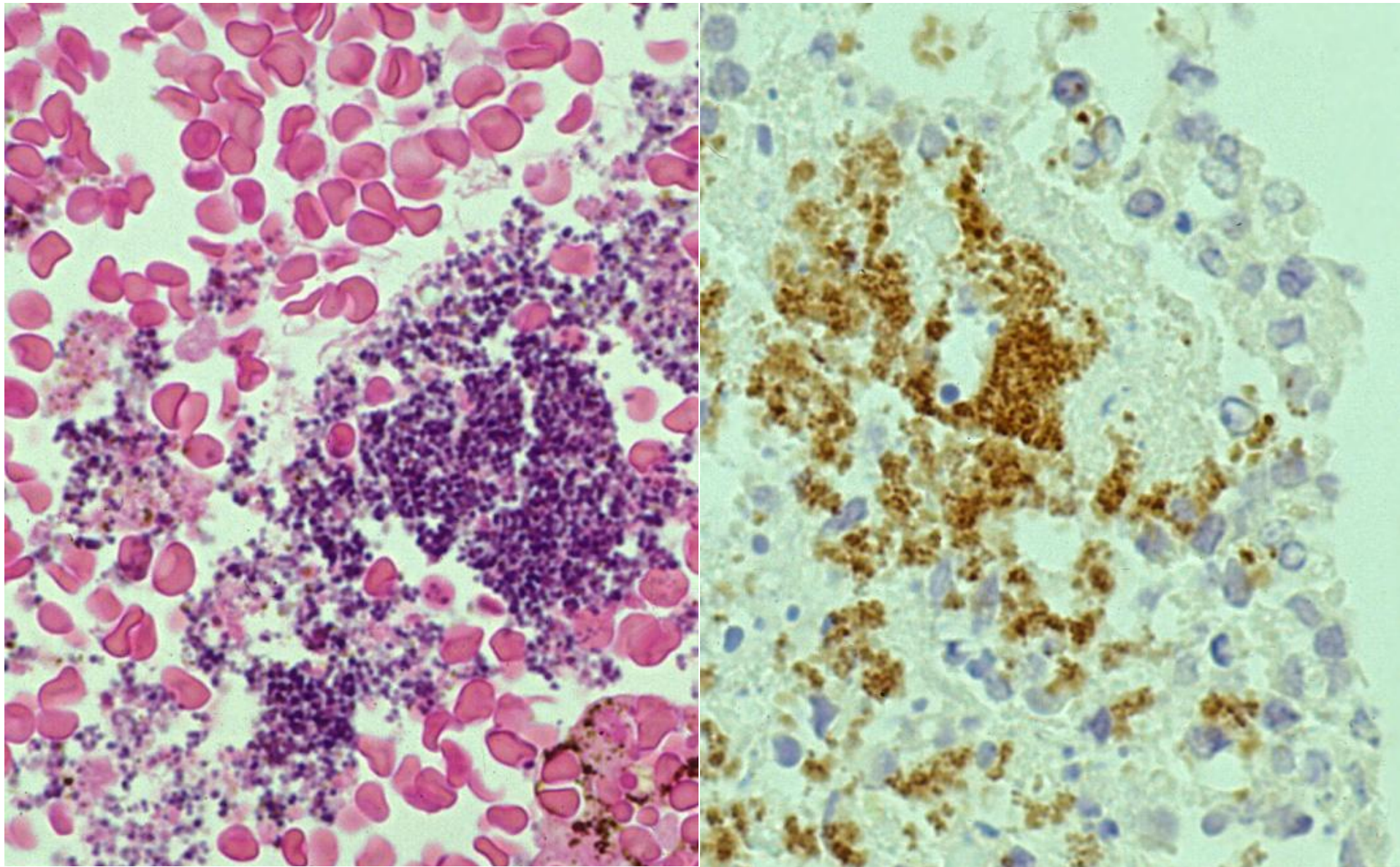
Sputum smear of Methicillin-resistant *Staphylococcus aureus* (MRSA) in a case of MRSA pneumonia (Gram)



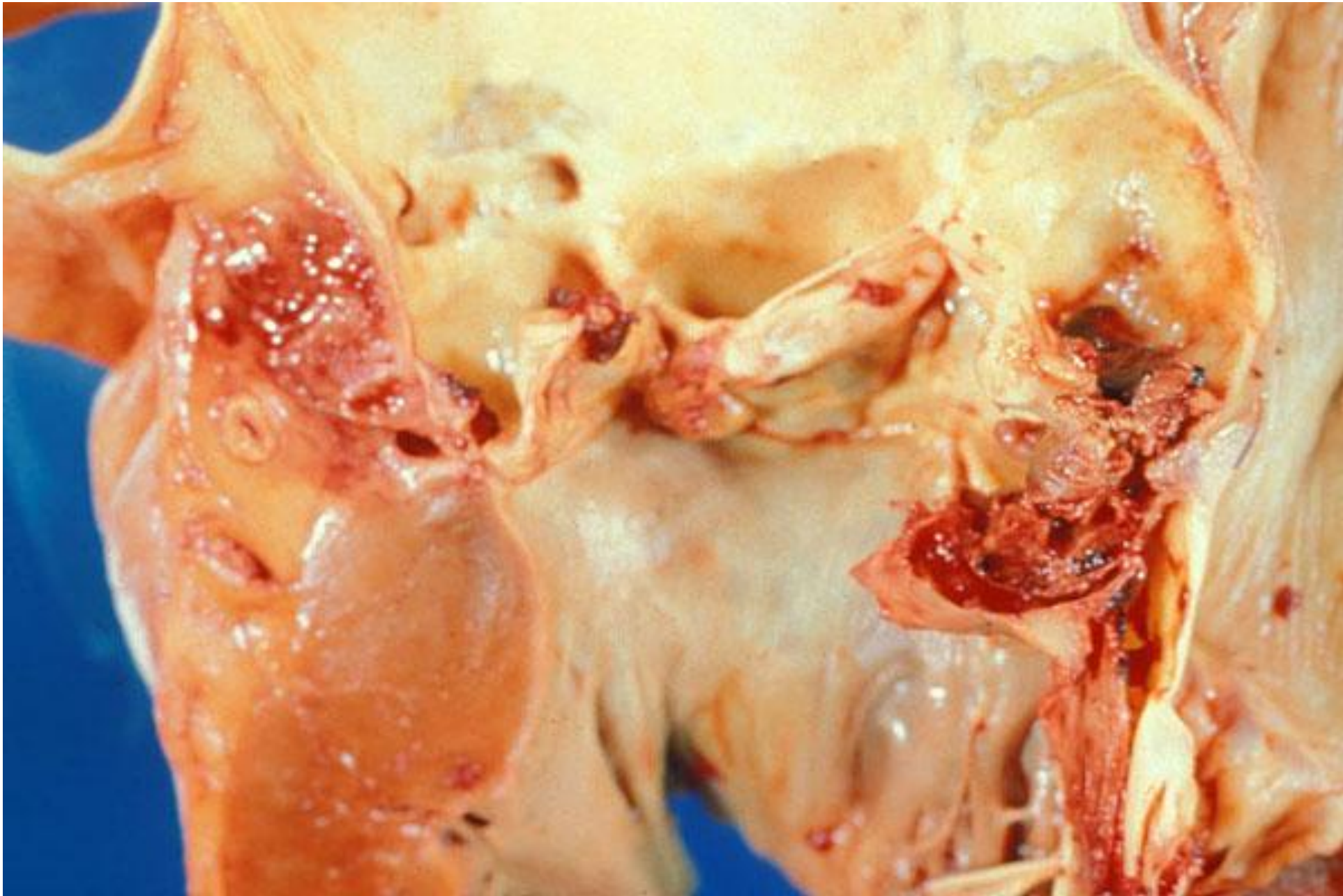
Scanning electron micrograph of *Staphylococcus aureus* (arrows indicating binary division)



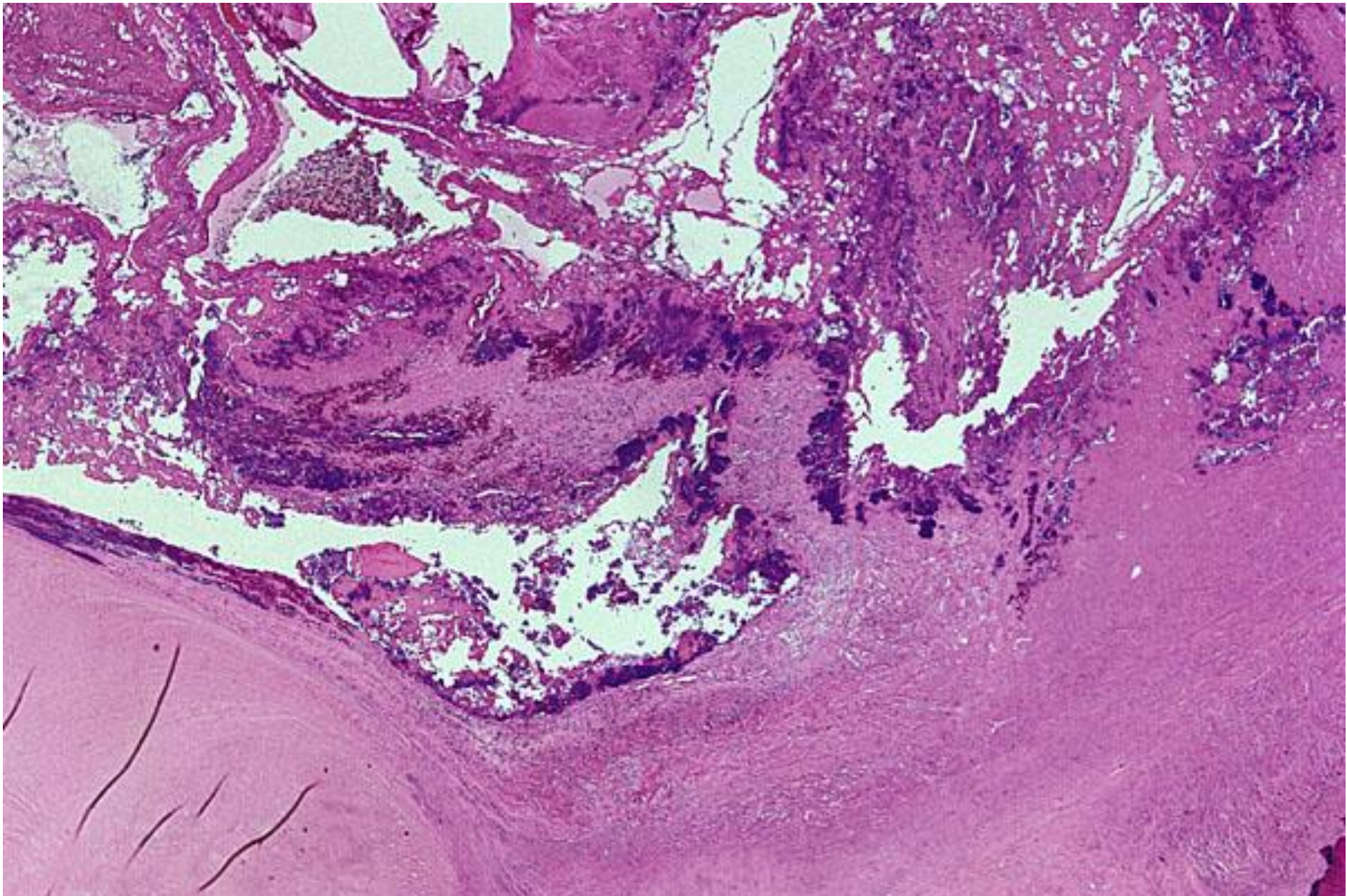
Gross appearance of MRSA pneumonia with hemorrhagic abscess formation (cavity-forming pneumonia)



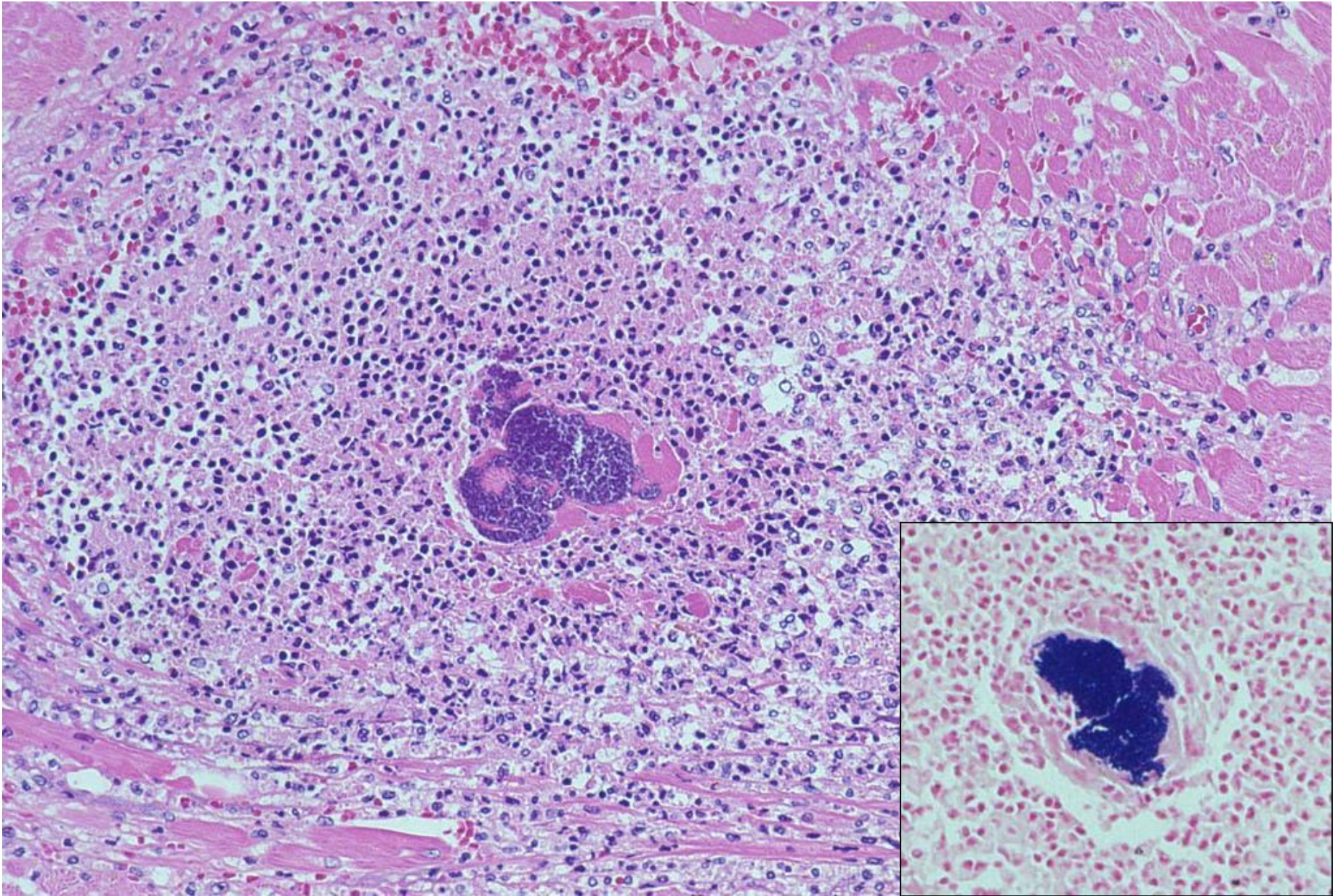
MRSA pneumonia (left: H&E, right: immunostaining for penicillin-binding protein 2': PBP2'). Expression of PBP2' represents the multidrug resistance of the bacteria.



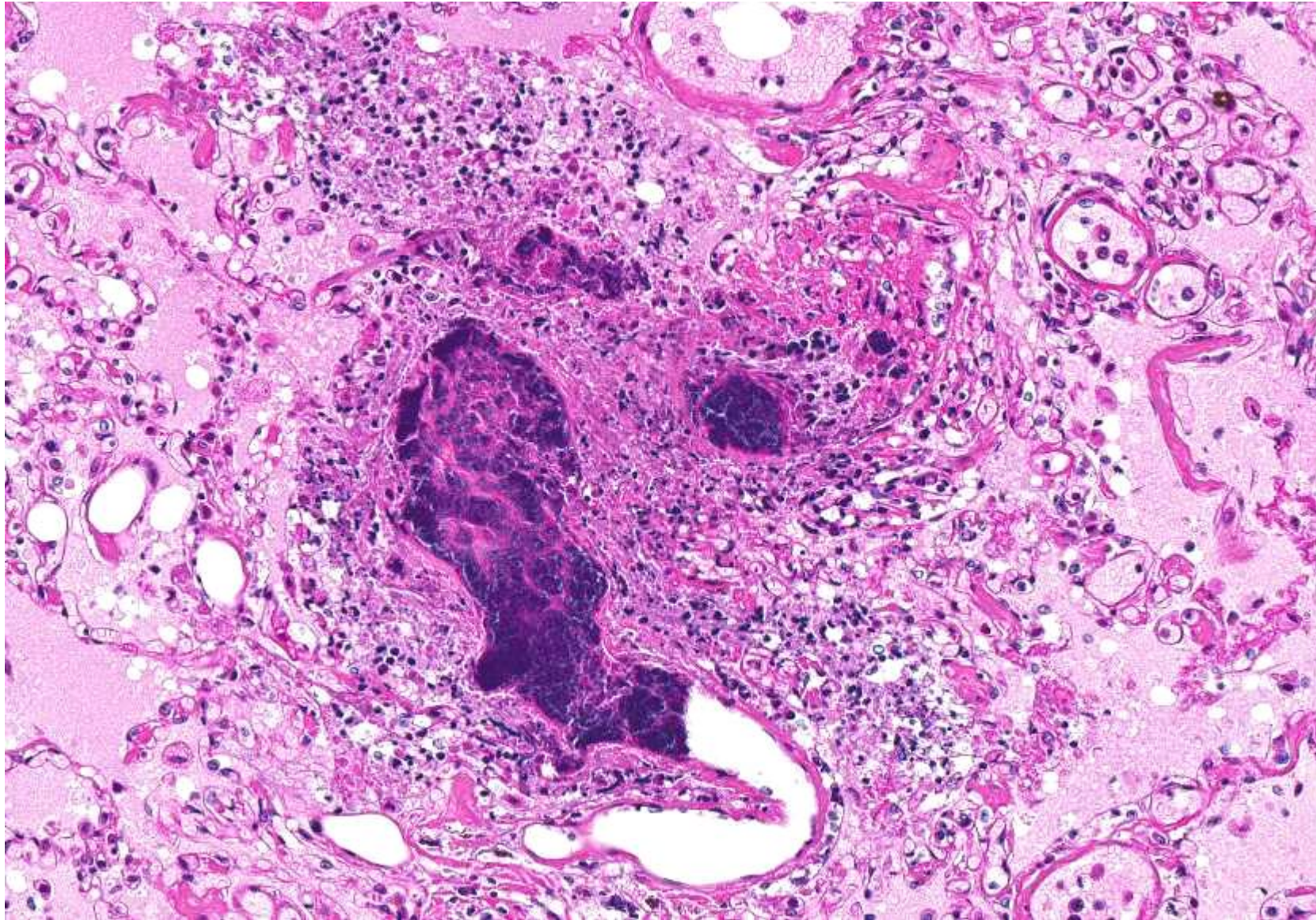
Gross appearance of MRSA endocarditis of the aortic valve, representing acute bacterial endocarditis



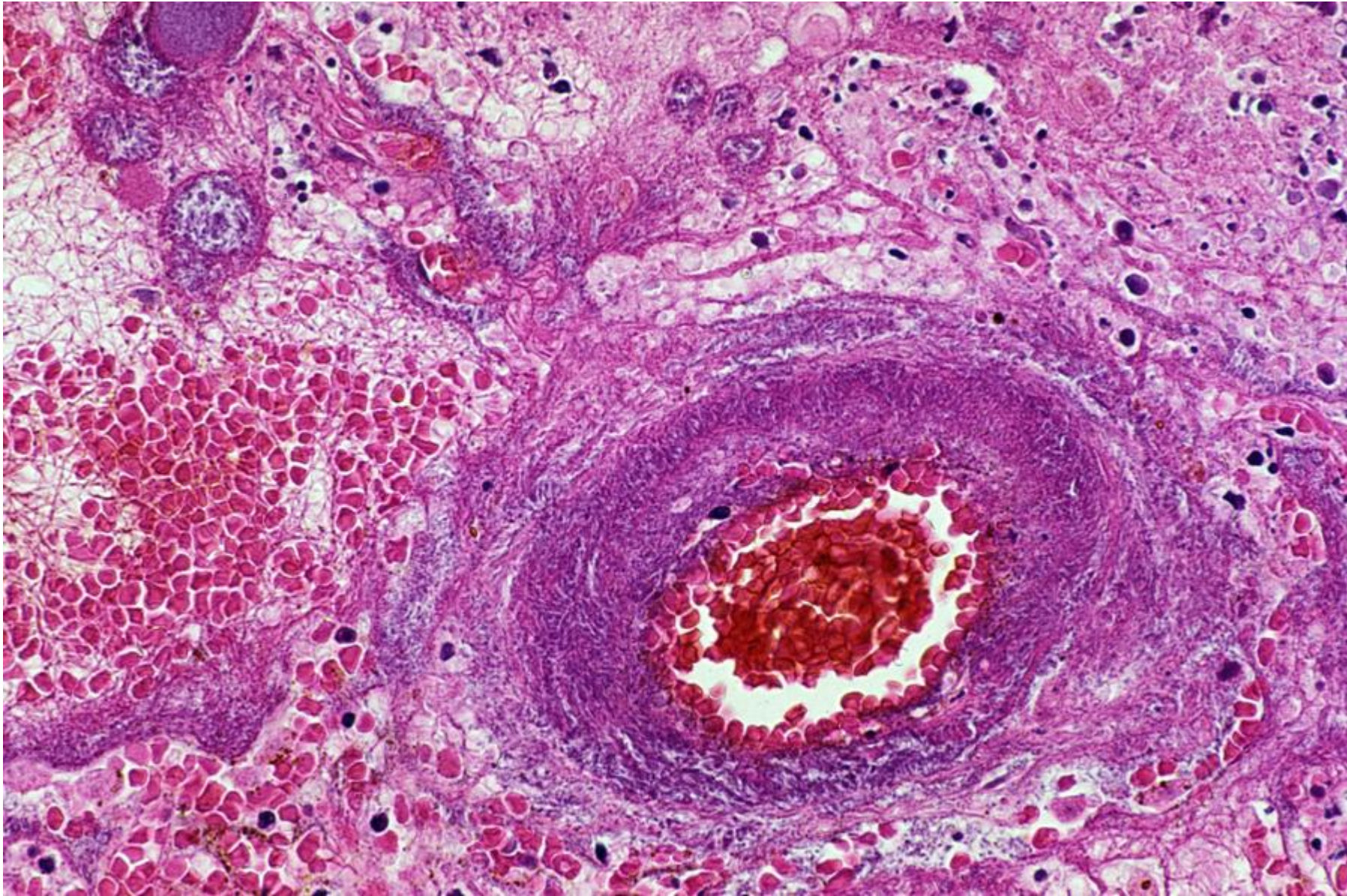
MRSA endocarditis of the aortic valve, representing acute bacterial endocarditis (H&E)



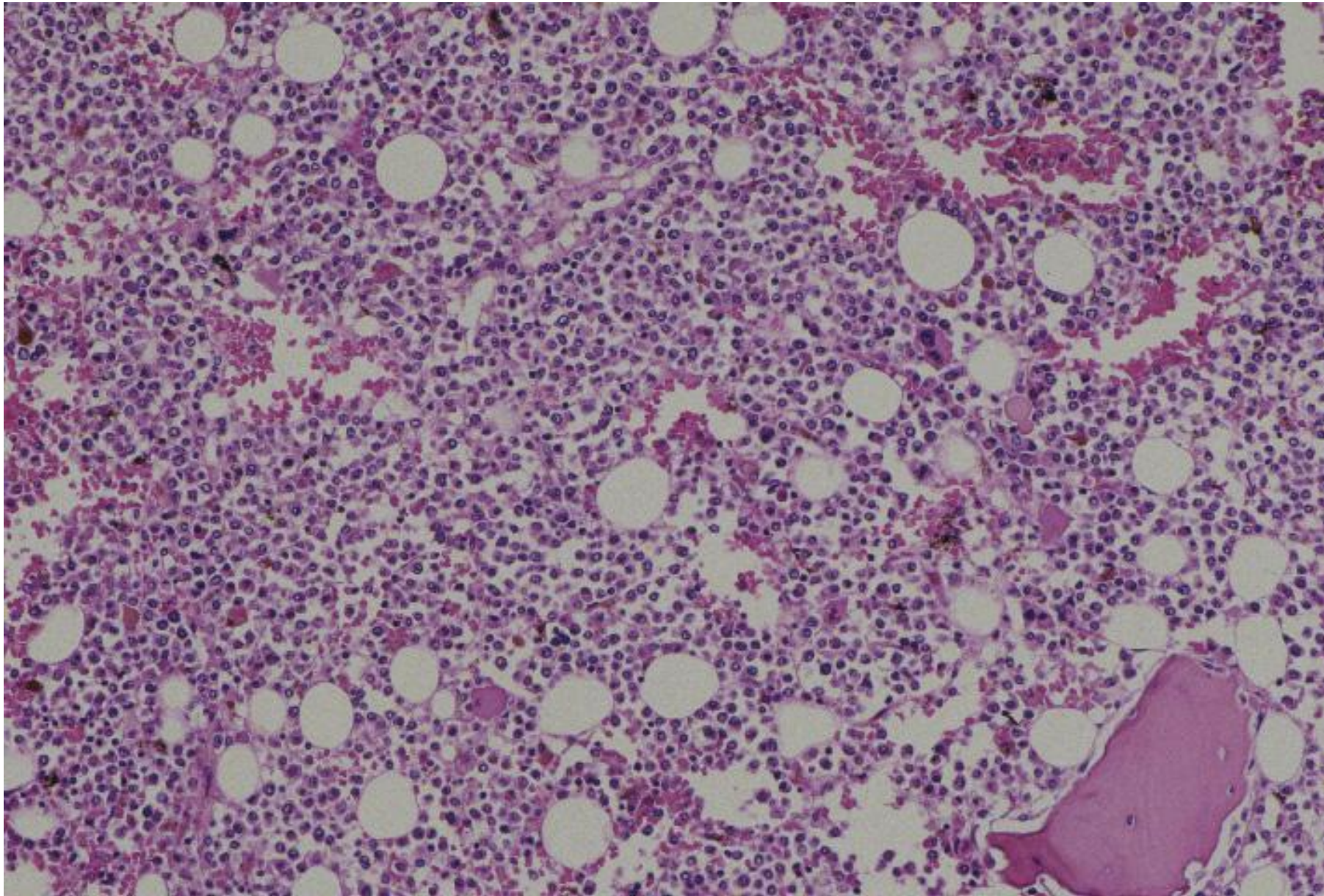
Microabscess of the heart in MRSA septicemia (H&E, inset: Gram)



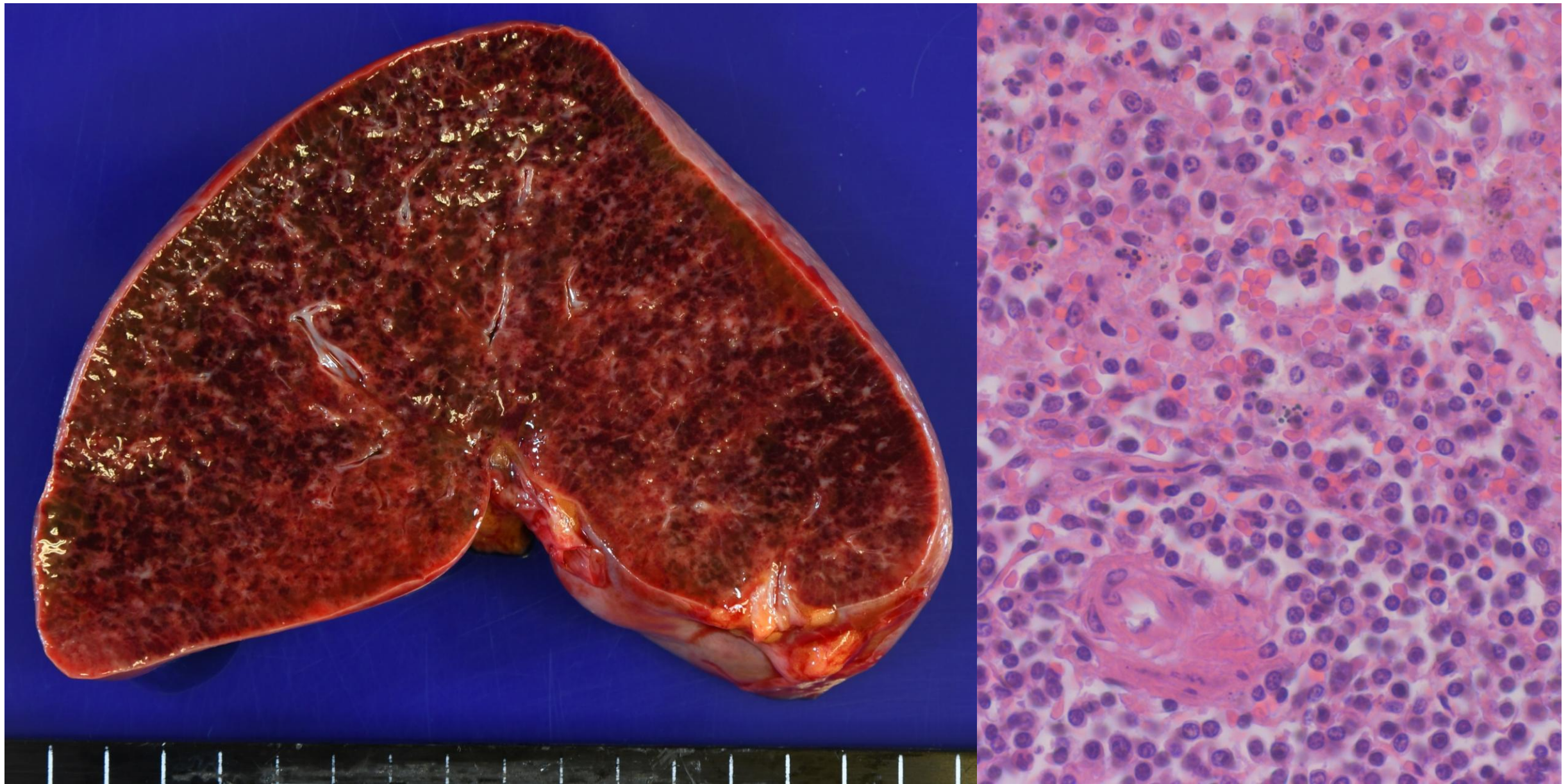
Mycotic emboli in pulmonary artery branches caused by MRSA septicemia (H&E)



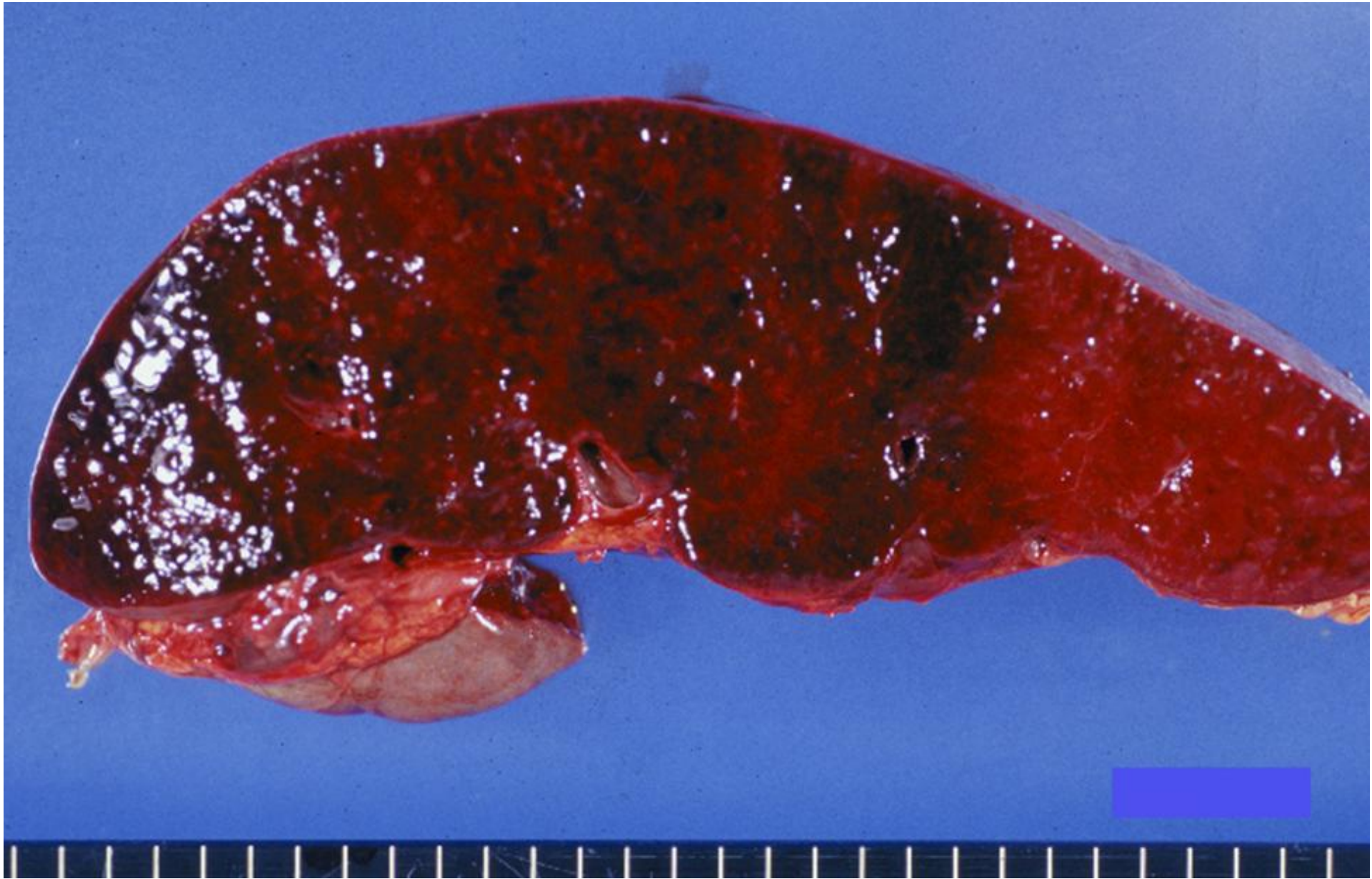
Perivascular cuffing seen in septicemia caused by *Pseudomonas aeruginosa* (H&E). Characteristically, Gram-negative rods are clustered in the vascular wall. Cellular reaction is minimal, because of chemotherapy-related neutropenia.



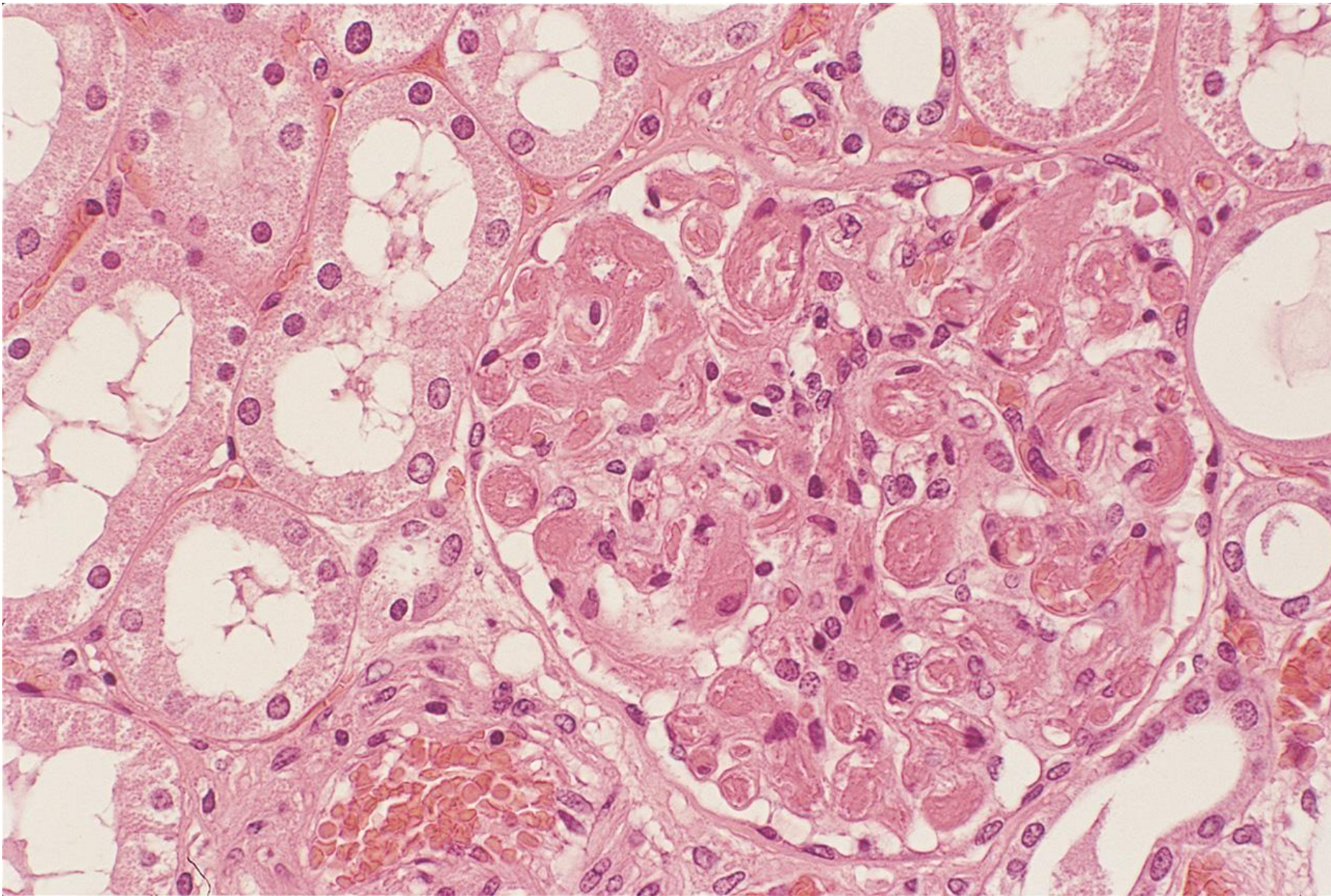
Myeloid hyperplasia in the bone marrow: septicemia-related reaction (H&E)



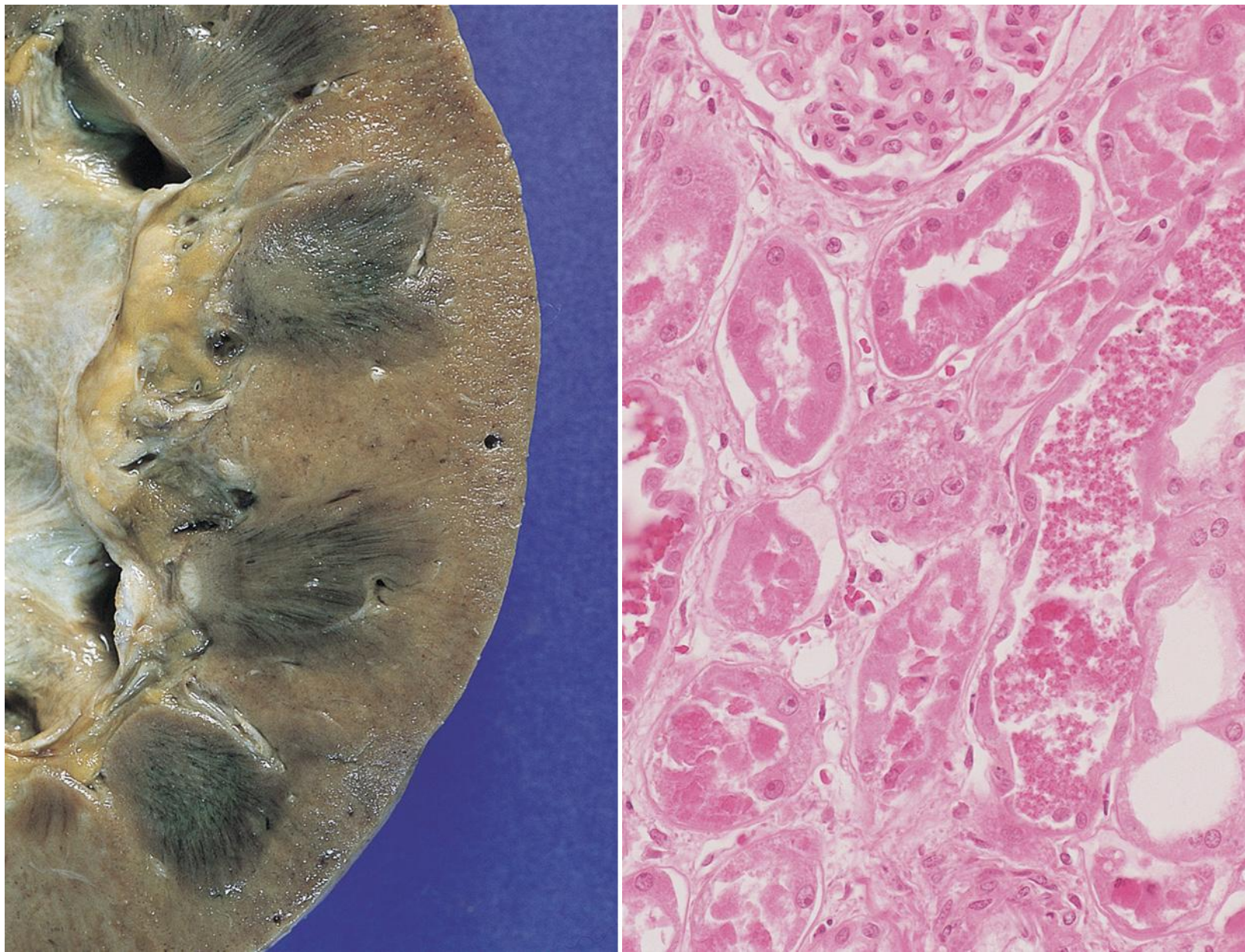
Septicemia-related acute splenitis with congestive splenomegaly (230 g).
Microscopically, neutrophilic infiltration is seen in the red pulp (right: H&E)



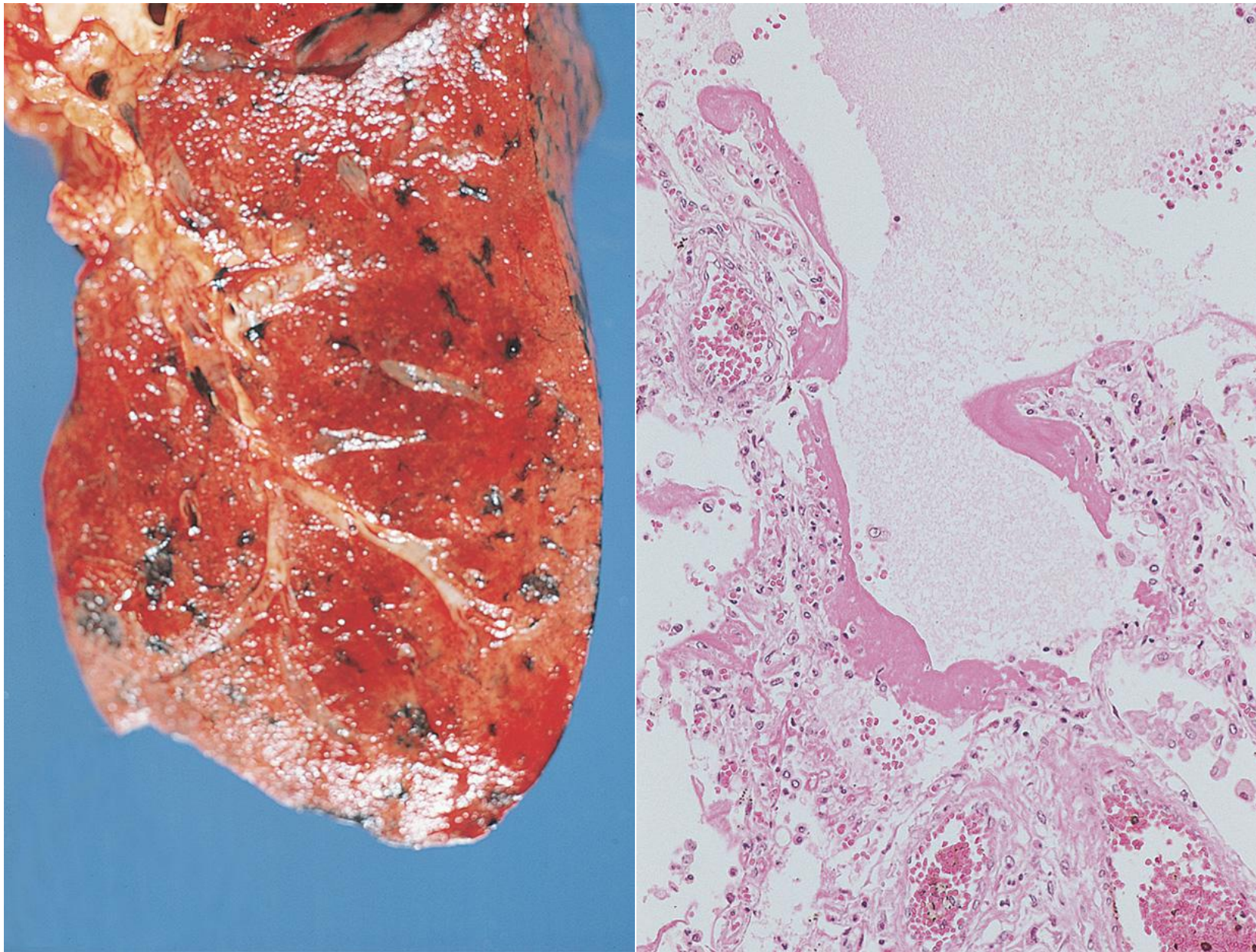
Another case of septicemia-related acute splenitis with congestive splenomegaly (350 g)



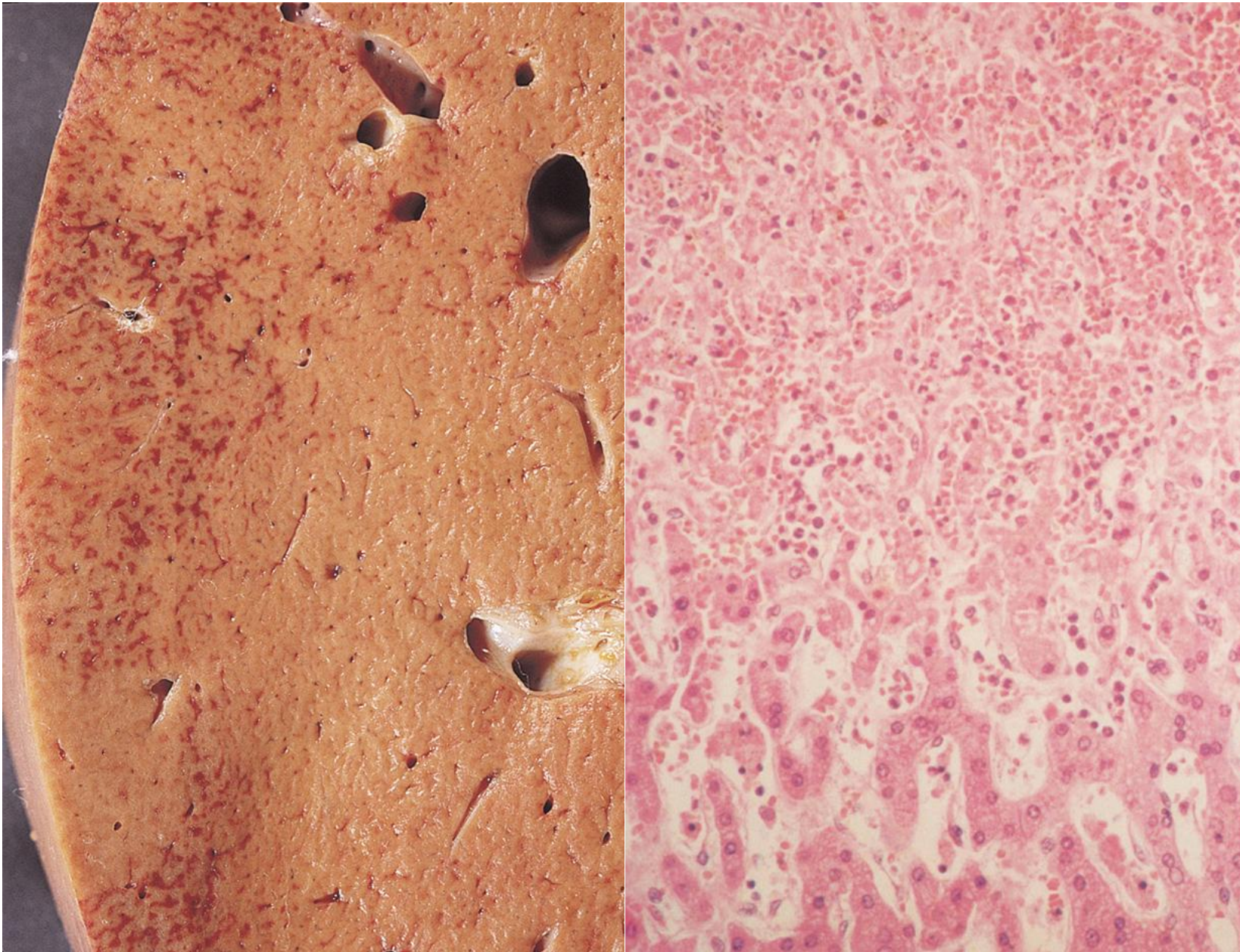
Disseminated intravascular coagulopathy (DIC). Fibrin thrombi in glomerular capillary vessels (H&E)



Septicemia-related acute tubular necrosis (shock kidney). The bilateral kidneys are enlarged. Necrosis of the proximal renal tubules is seen microscopically. Left: gross appearance of the formalin-fixed kidney, right: H&E



Diffuse alveolar damage (DAD). Diffuse hardening with decreased air content is seen in the lung. Hyaline membrane formation is seen microscopically. Left: gross appearance of the lung, right: H&E



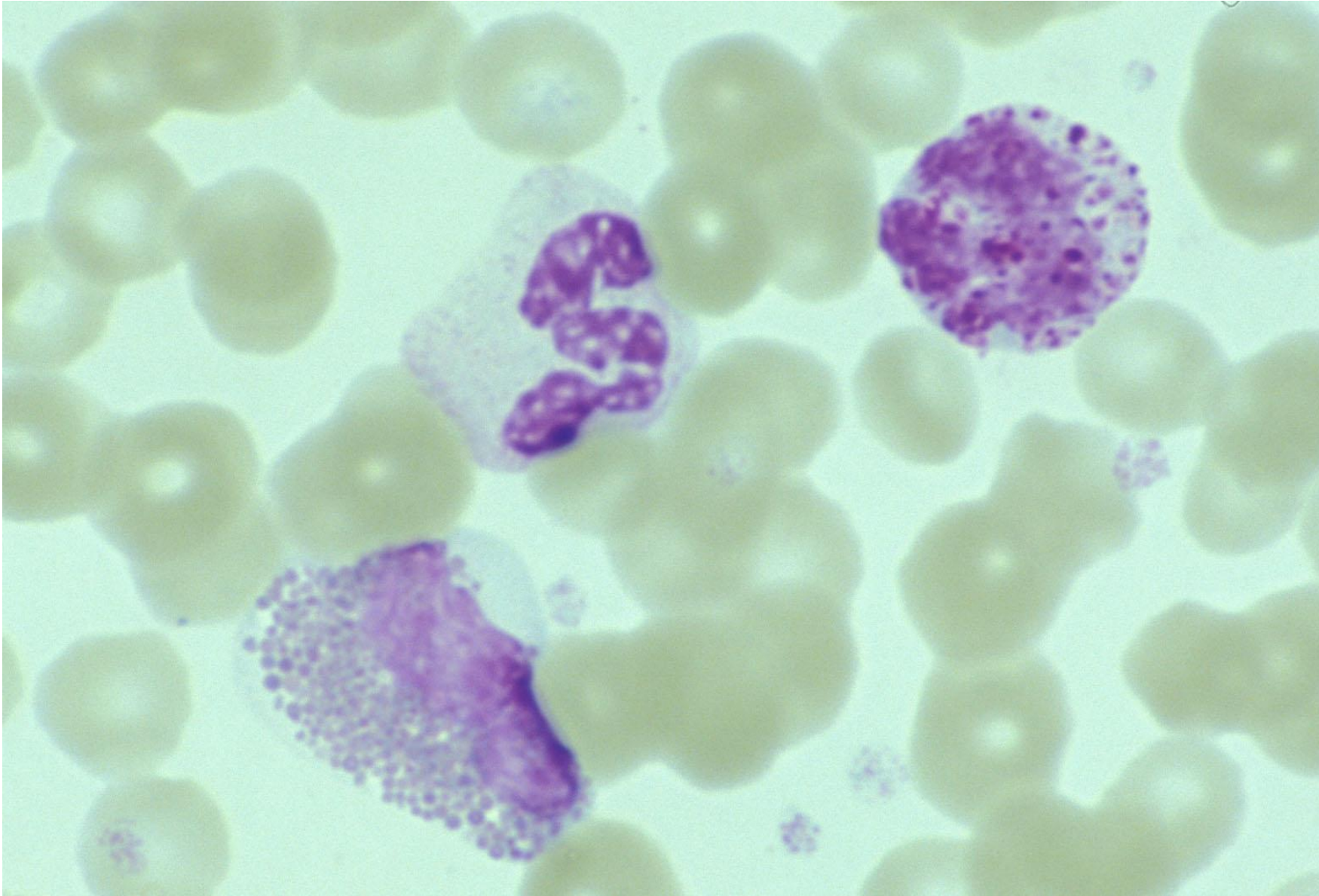
Acute liver congestion with centrilobular hepatocellular necrosis (left: gross appearance, right: H&E)



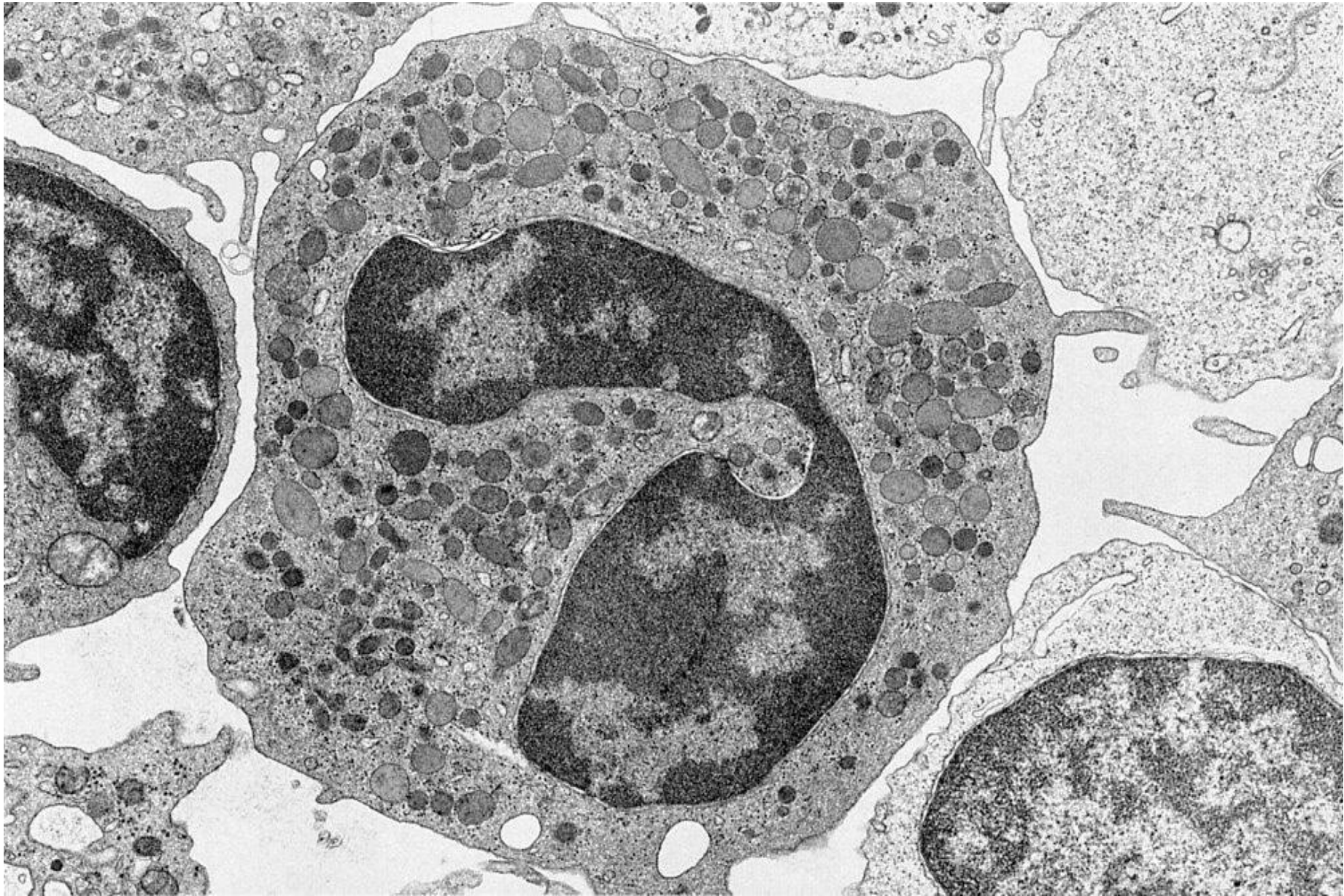
Congestion-related terminal hemorrhagic necrotizing enteropathy of the jejunum (H&E)

Inflammatory cells

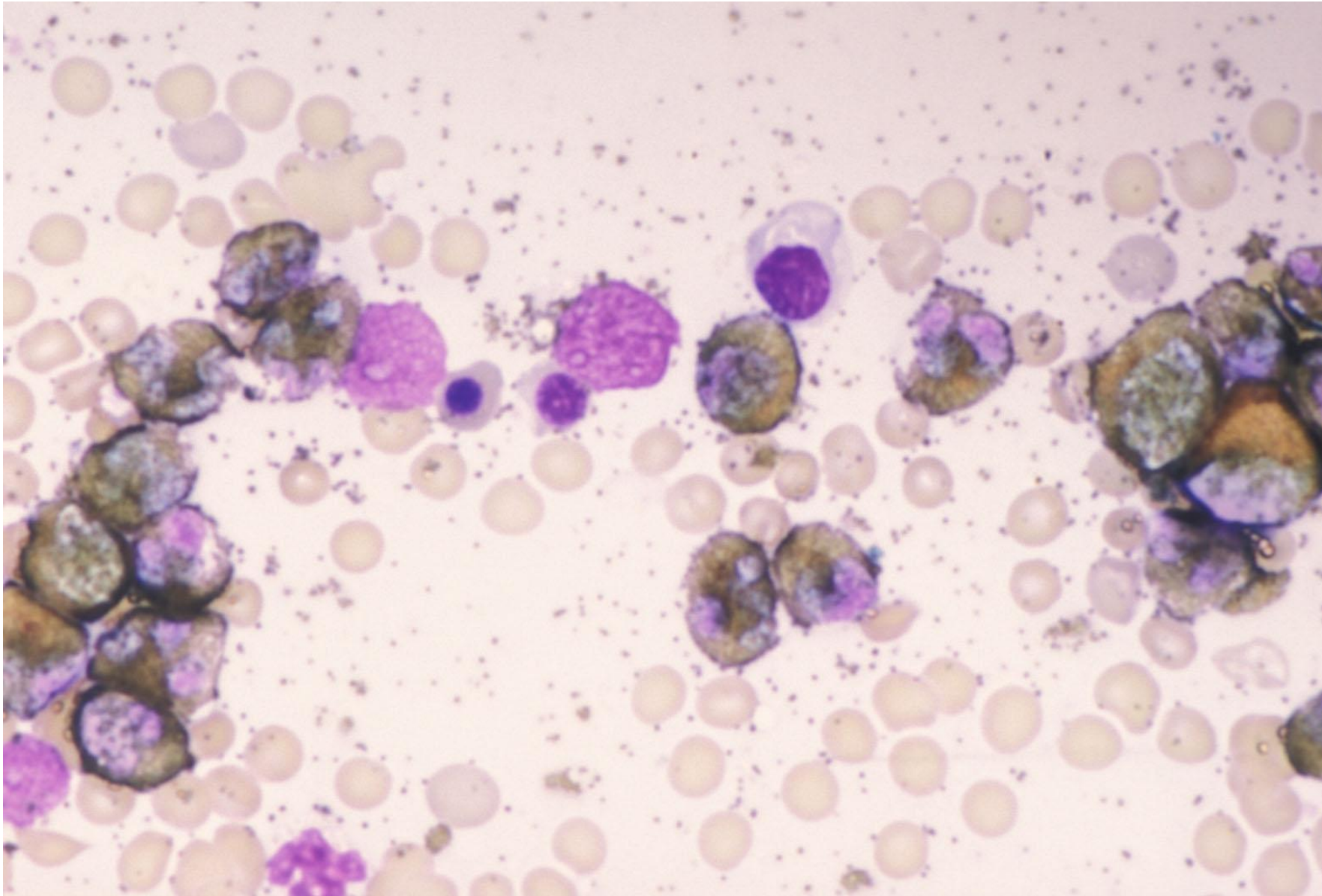
<u>cell</u>	<u>function</u>	<u>growth ability</u>
Granulocyte		
neutrophil	phagocytosis/NETs	absent
eosinophil	allergy/anti-parasite	absent
basophil	histamine production	absent
Mast cell	histamine production	present
Monocyte	phagocytosis	present
Macrophage	phagocytosis/granuloma	present
Lymphocyte	humoral/cellular immunity	present
NK cell	nonspecific immunity	present
Plasma cell	antibody production	absent
<u>Dendritic cell</u>	<u>antigen presentation</u>	<u>present</u>



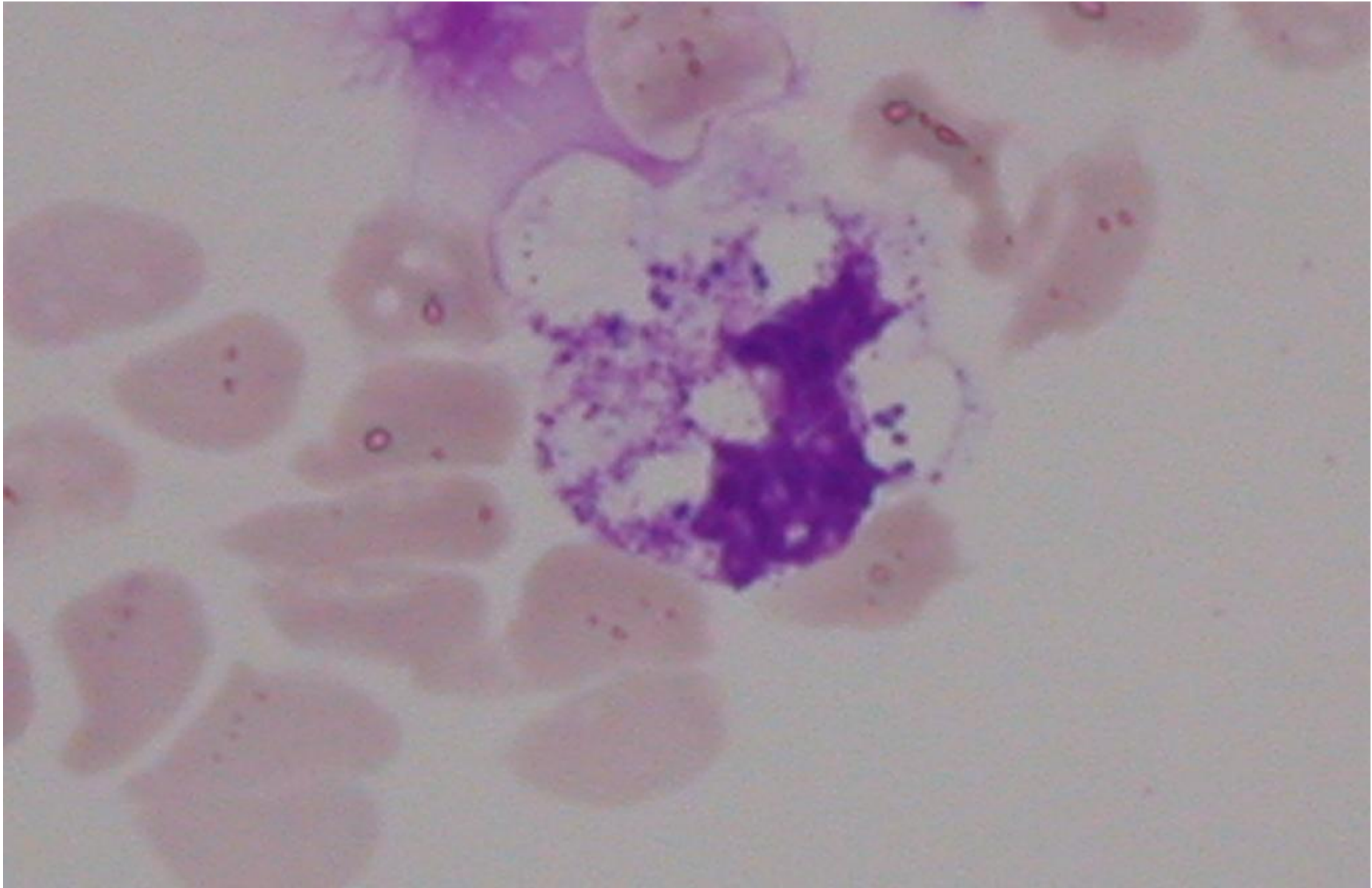
Three kinds of granulocytes: eosinophil (left), neutrophil (center) and basophil (right). May-Giemsa



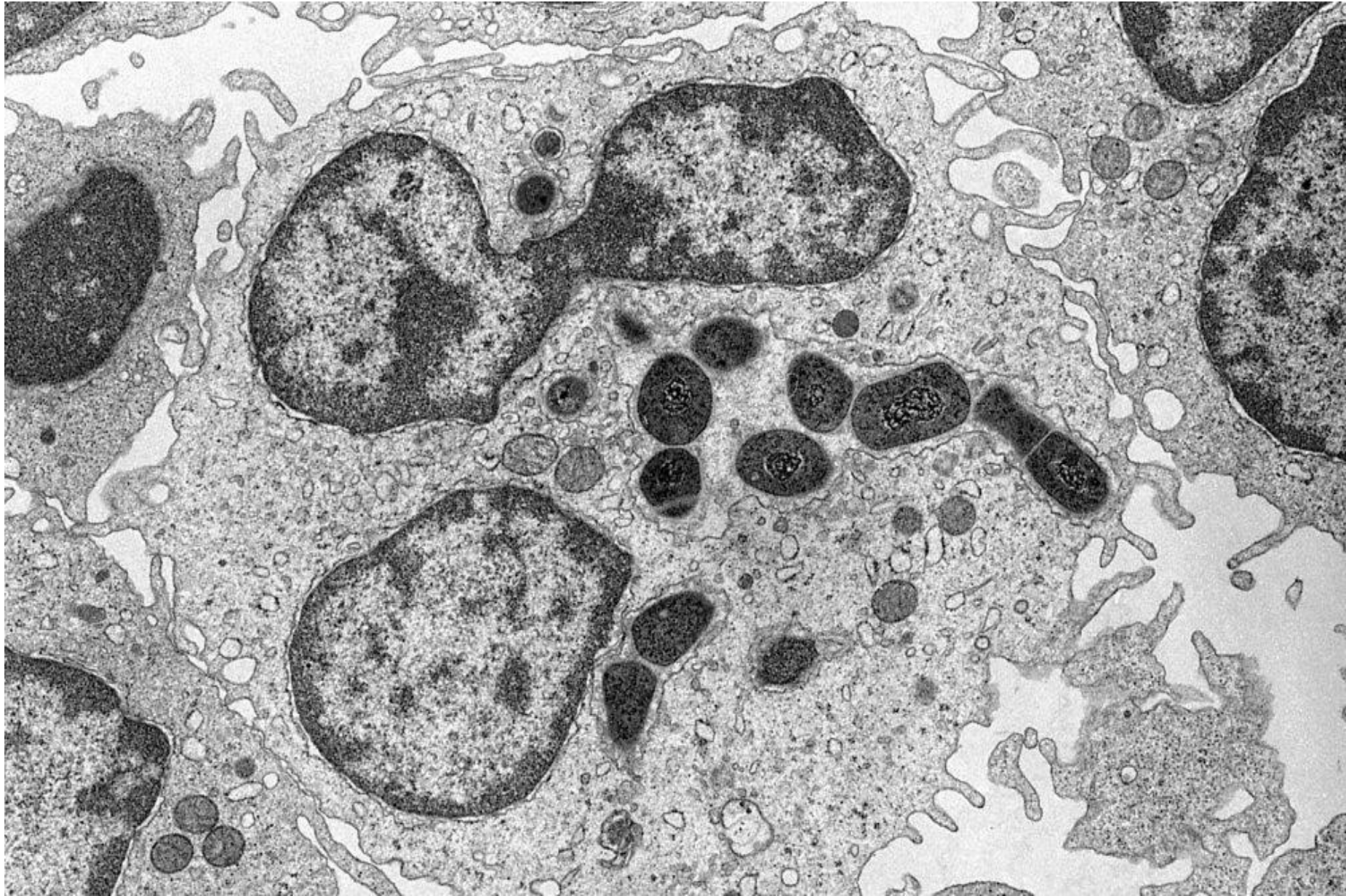
Granulocyte: lobulated nucleus and specific granules (EM)



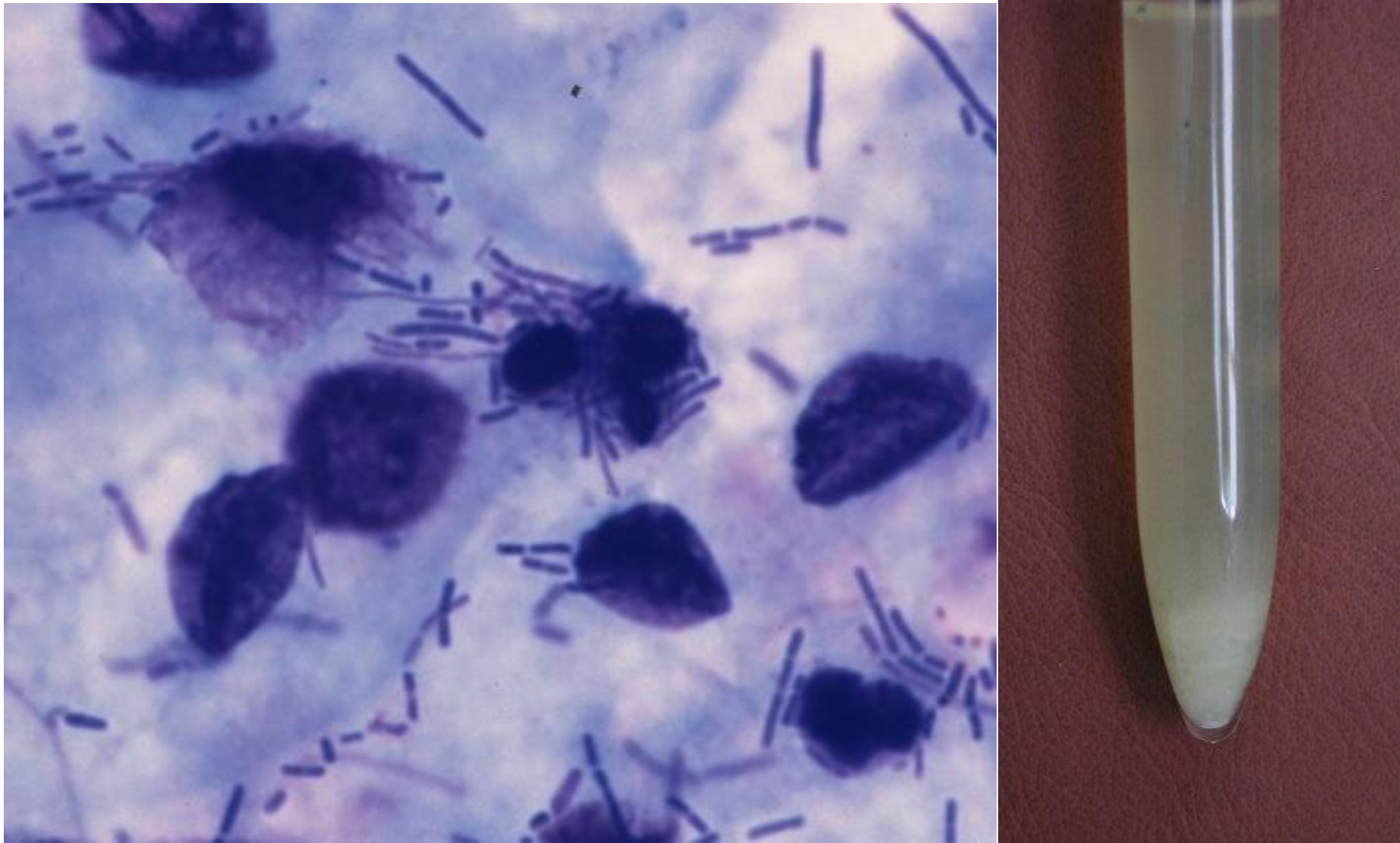
Peroxidase reactivity in neutrophils (peroxidase activity with May-Giemsa stain)



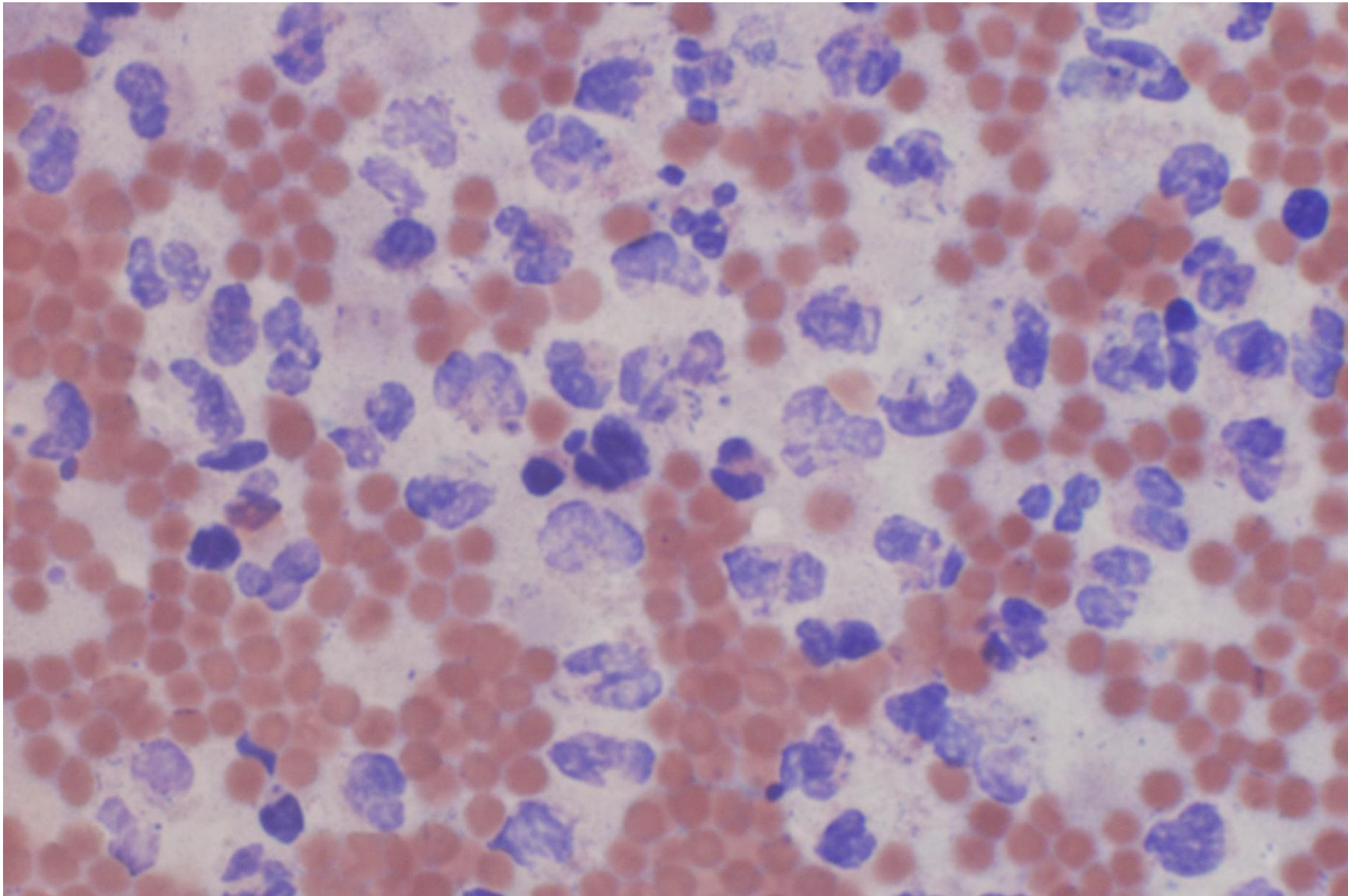
A neutrophil phagocytizing cocci (May-Giemsa)



A neutrophil phagocytizing rods (EM)



Pyuria (E. coli-infected acute cystitis, Giemsa)



Aspiration from perianal abscess (Giemsa). Rods are phagocytized by neutrophils.

Three kinds of cellular reactions against pathogens

Defense cell	Pathogen	Property	Tissue reaction	Susceptible state
neutrophil	Aspergillus deep-seated Candida Purulent bacteria Enterobacteria	Extra-cellular pathogen	abscess	Bone marrow suppression
T-cell/ macrophage	Cryptococcus Superficial Candida M. tuberculosis Protozoa Viruses (CMV/adeno)	Intra-cellular pathogen	granuloma	AIDS/ Steroid use
neutralizing antibody/ complements	Meningococcus Pneumococcus Haemoph. influenzae HSV, VZV, HBV Measles virus	Capsule-forming bacteria/ Persistent infection	Phlegmonous inflammation /Viral inclusion bodies	Complement deficiency/ Specific immune suppression

Bone marrow transplantation: neutropenia in early stage, T-cell dysfunction in mid-stage, and poor antibody formation in late stage

***Severe/fulminant opportunistic
infection: an representative case***

Burn of the foot caused by diabetic peripheral neuropathy and subsequent necrotizing fasciitis

(Necrotizing fasciitis: severe gangrenous inflammation of the soft tissue)

→complicated with septicemia, SIRS and DIC



Diabetic peripheral neuropathy with severe burn in a male patient aged 70's. Because of the loss of sensation, the burn occurred by foot warming with a fan heater in the winter season. Note dry gangrene of the second toe due to diabetes-related circulatory disturbance.



Emergency amputation of the lower leg saves the patient life. The patient is now under rehabilitation.