Gangrenous and fulminant bacterial infections

Gangrene is a lesion of ischemic tissue death. When severe infection is associated, fever and sepsis may follow. Certain pathogens cause fulminant and often lethal infection without gangrenous change. Risk factors of gangrene and fulminant infection include diabetes mellitus, atherosclerosis, smoking, major trauma, alcoholism, liver cirrhosis, renal insufficiency, immunosuppression, AIDS, drug abuse, malnutrition and pernio. Pathologic features of varied gangrenous and fulminant infections are described herein. In addition to gross findings, microscopic features are presented mainly with hematoxylin and eosin (H&E) and Gram stains. When needed, immunohistochemical approach is combined. Immunostaining using rabbit antisera raised against Bacillus Calmette-Guérin (BCG; *Mycobacterium bovis*), *Bacillus cereus*, *Treponema pallidum* and *Escherichia coli* (*E. coli*) is employed. These low-specificity (widely cross-reactive) antimicrobial antisera effectively yields clear high-sensitivity signals with a low background.

Ref.-1: Tsutsumi Y. Pathology of Infectious Diseases. 2003; https://pathos223.com/en/

Ref.-2: Tsutsumi Y. Pathology of Gangrene. IntechOpen 2020; doi: 10.5772/intechopen.93505

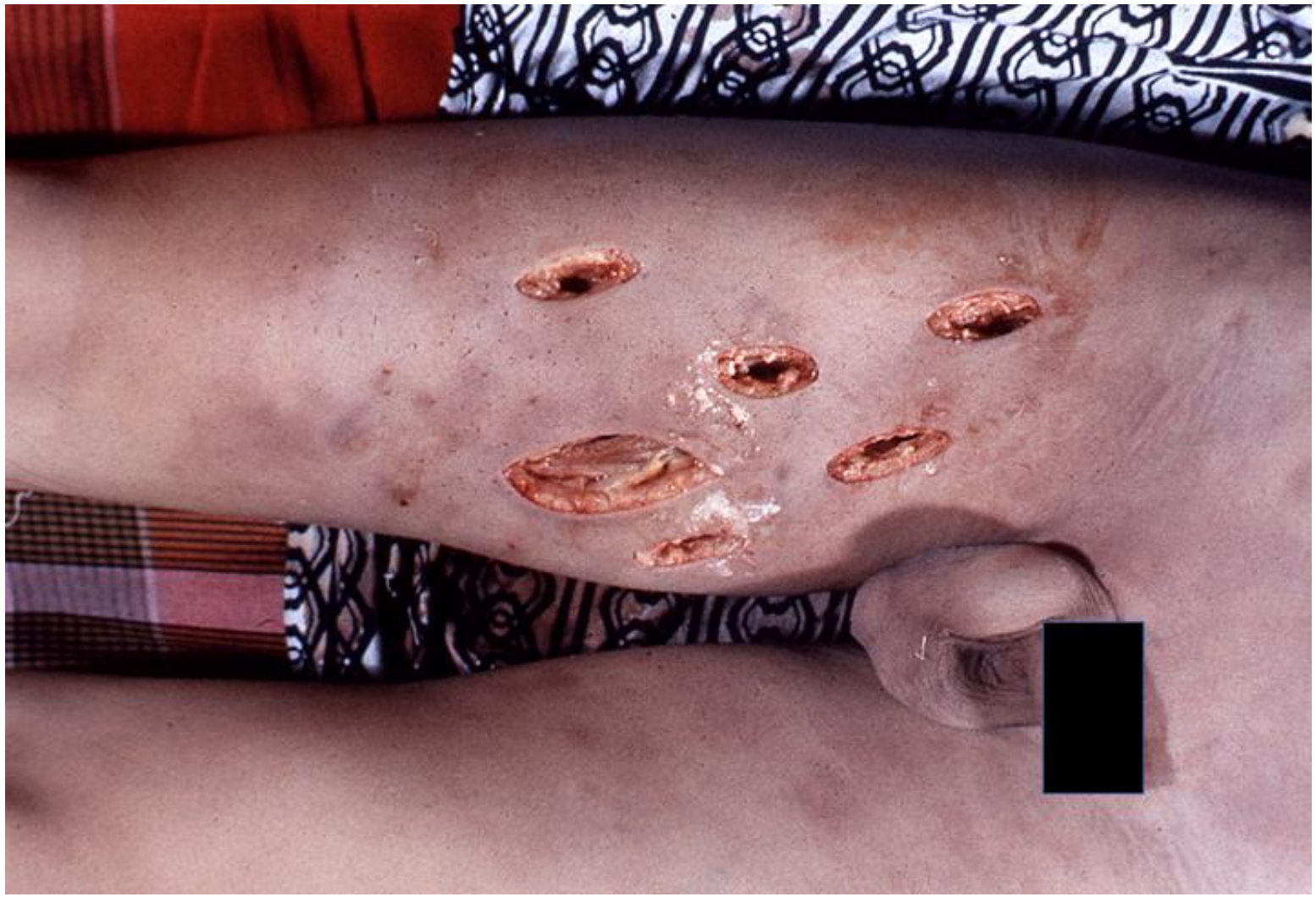
Ref.-3: Tsutsumi Y. Low-specificity and high-sensitivity immunostaining for demonstrating pathogens in formalin-fixed, paraffin-embedded sections. Intechopen 2019; doi: 10.5772/intechopen.85055

Clostridial gas gangrene

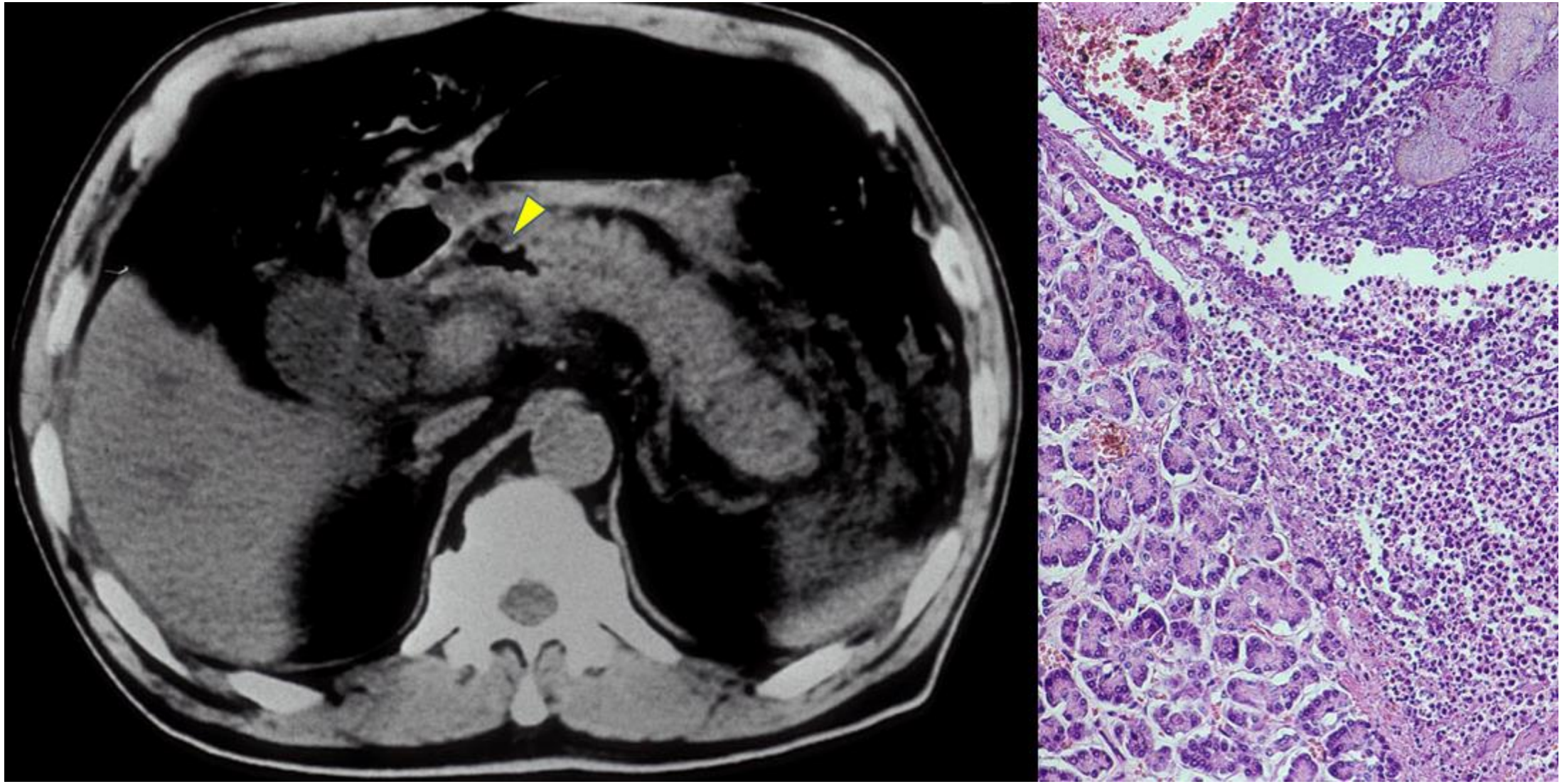
Gas gangrene caused by infection of *Clostridium perfringens* (formerly called *C. welchii*) is a life-threatening emergency, as a grave form of wet gangrene. C. perfringens is an obligate anaerobic Gram-positive bacillus forming spores on culture plates. Clostridial gas gangrene is grouped into 2: traumatic vs. non-traumatic. Tissue necrosis is accelerated by α-toxin production of the microbe. Putrid odor is associated. Intravascular hemolysis is a common event due to bacterial production of hemolysin. The liver often reveals foamy appearance. The prognosis is very poor.

1) In the traumatic gas gangrene, skin invasion of the microbe results in massive ischemic necrosis (gangrene) of the soft tissue involving the striated muscle. Gas production is quite characteristic, and the involved tissue thus reveals crepitation on touch.

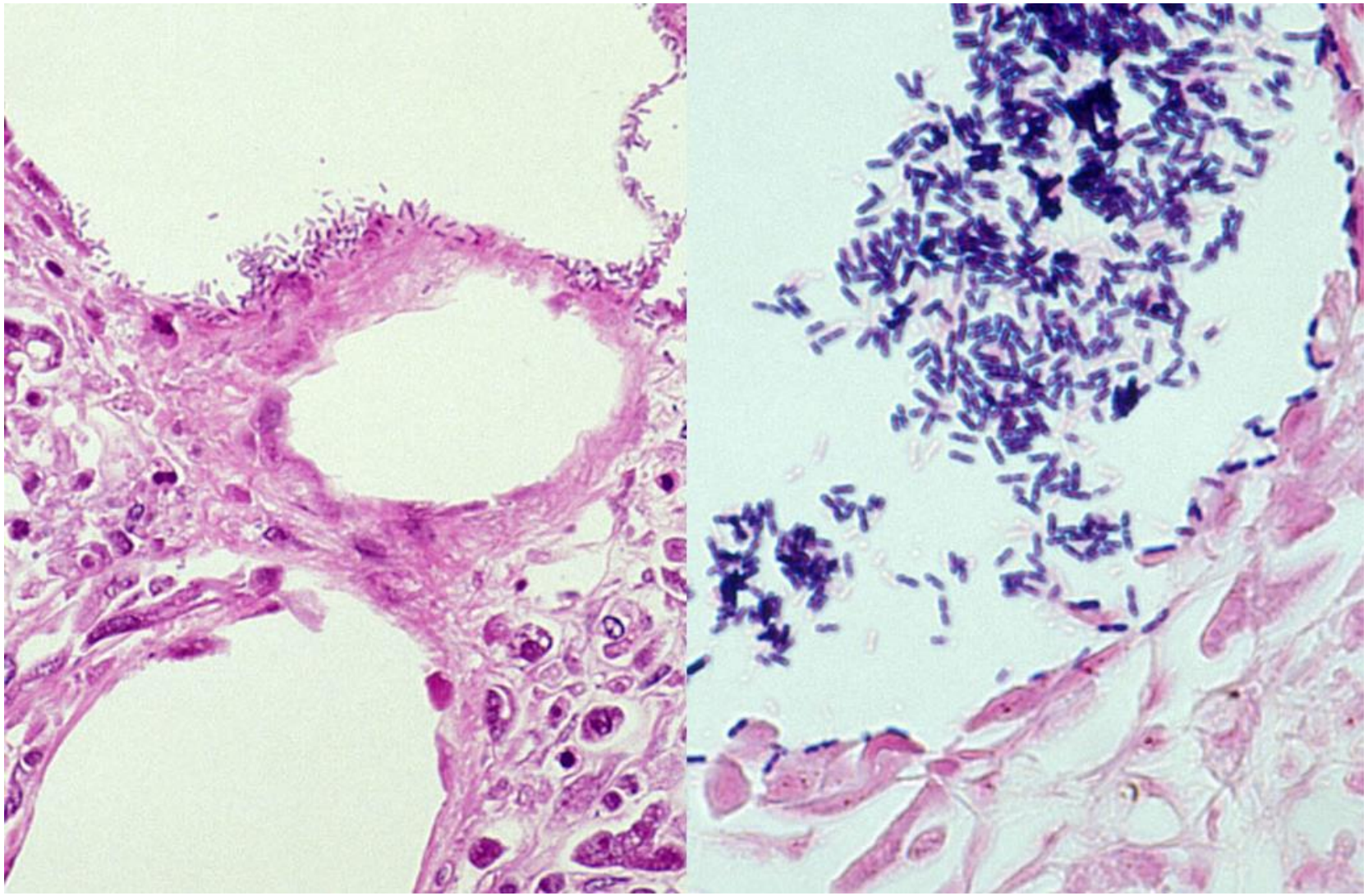
2) *C. perfringens* commonly resides in the gut lumen of healthy individuals, so that non-traumatic gas gangrene is encountered in the internal organs such as the gut, bile duct and pancreas. Representative autopsy cases of clostridial pancreatitis, colitis and gastritis are presented below.



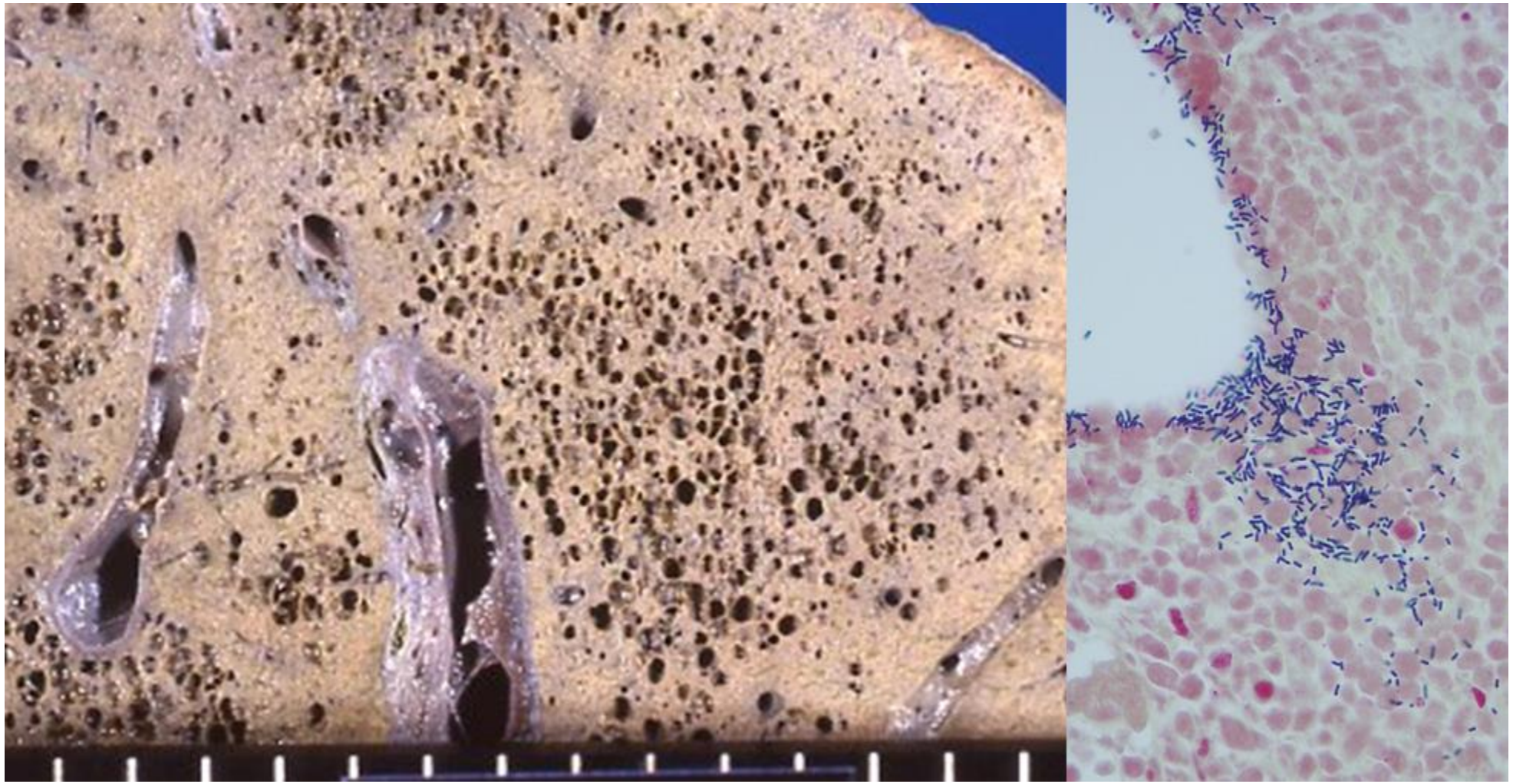
Traumatic gas gangrene of the right thigh (gross appearance). Gas-forming gangrenous process of the soft tissue results in marked swelling of the thigh. Crepitation was palpable on touch. Surgical debridement has been performed for the treatment purpose.



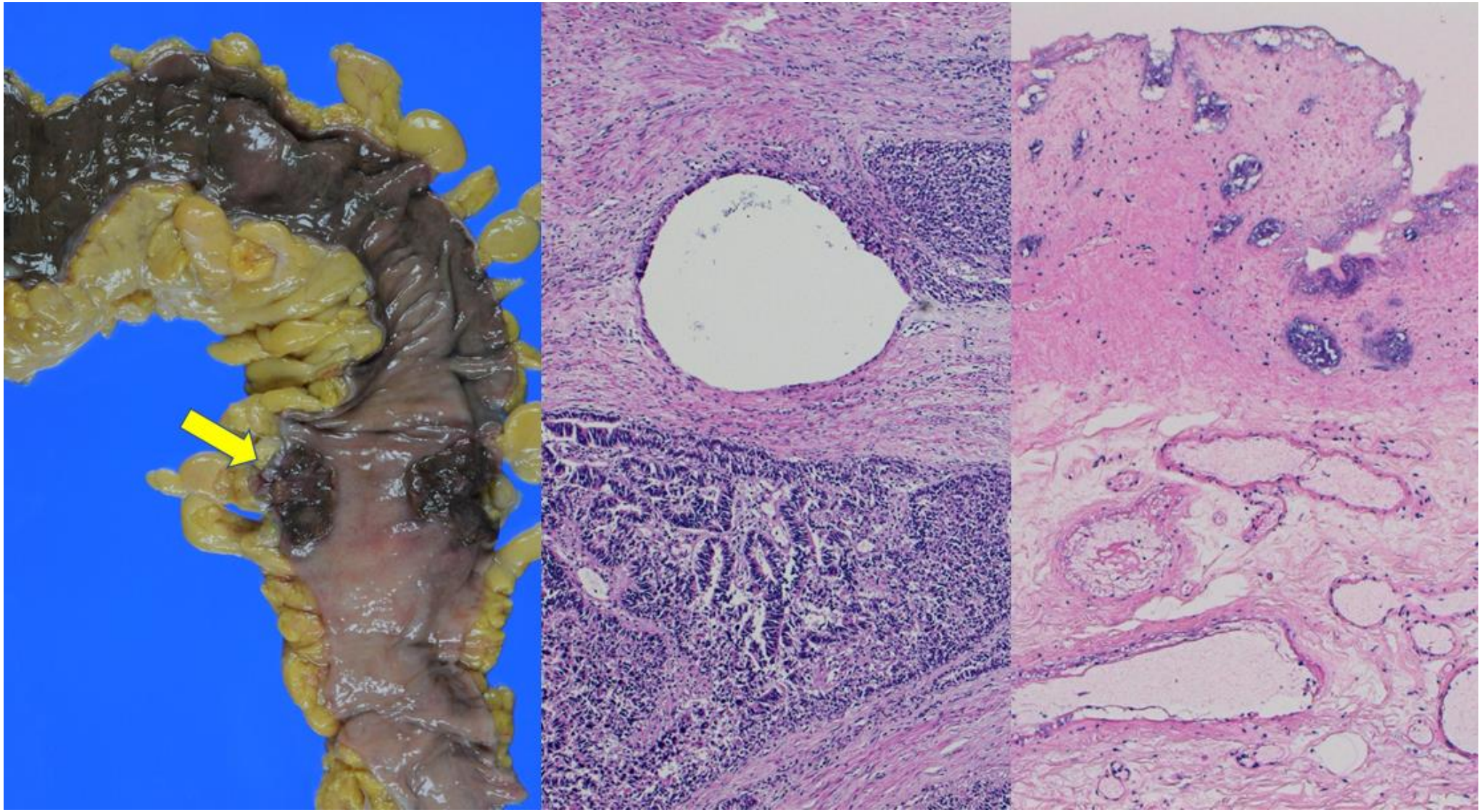
Non-traumatic clostridial gas gangrene (1-1). Pancreatic clostridial gas gangrene (CT scan and H&E). Computed tomography scan demonstrates gas formation in the pancreatic head (arrowhead). At autopsy, neutrophils are infiltrated in the pancreatic parenchyma, giving features of severe acute pancreatitis.



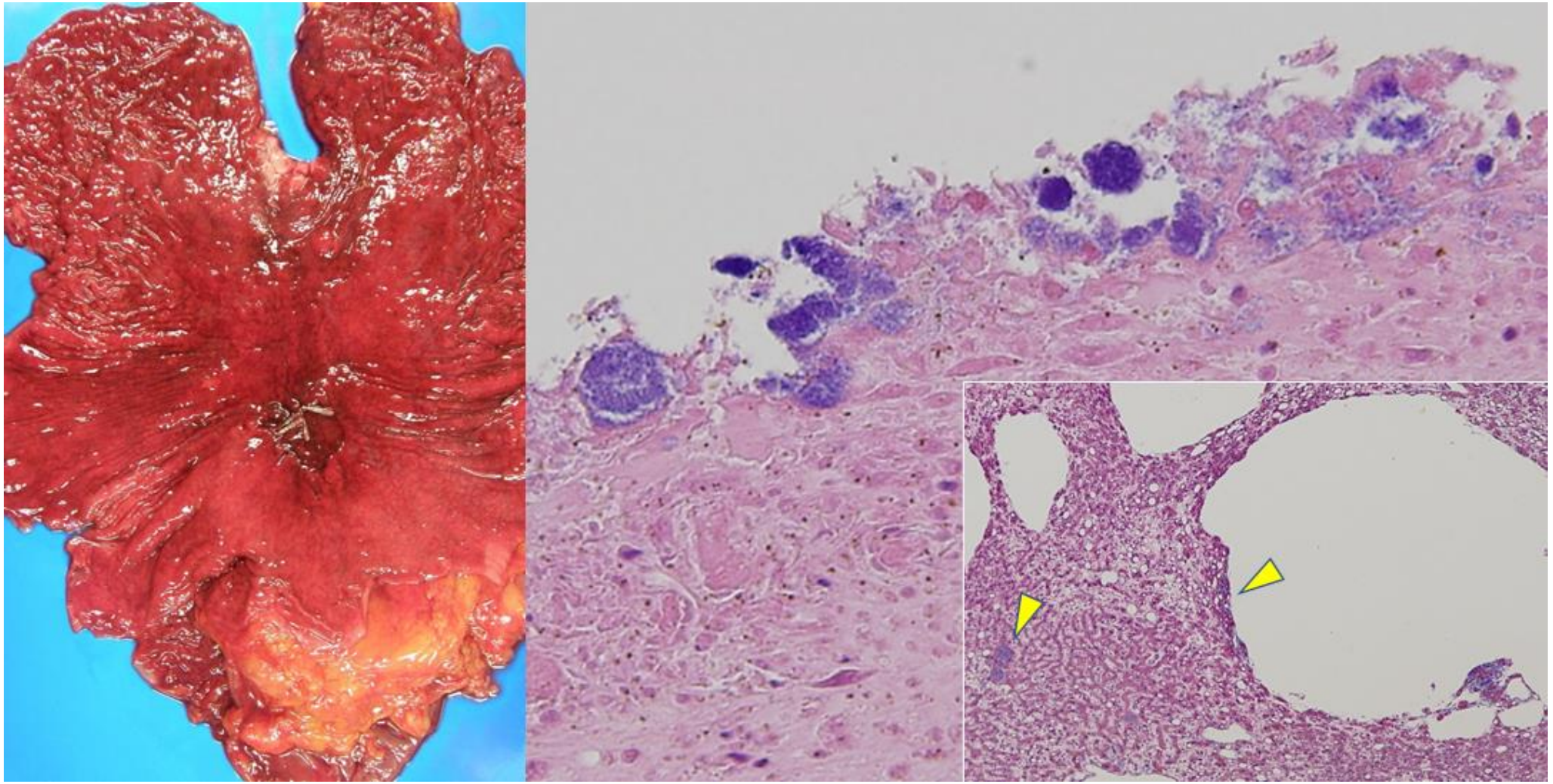
Non-traumatic clostridial gas gangrene (1-2). Pancreatic gas gangrene with growth of *Clostridium perfringens* in acute necrotizing pancreatitis (H&E and Gram). Gas bubbles are observed in the necrotic pancreatic tissue with sparse inflammatory infiltration. The rods growing in the bubble are unevenly Gram-positive (some bacilli are not stained blue). Spores (representing unstained dots in the bacterial body) are only focally recognizable in the living body.



Non-traumatic clostridial gas gangrene (2). Clostridial gas gangrene involving the liver (gross and Gram). Numerous gas bubbles replace the liver parenchyma, giving foamy or spongy appearance (foamy liver). The hepatocytes reveal ischemic changes, and Gram-positive rods are clustered around the gas bubble. Note that the condition allowing the growth of obligate anaerobic *Clostridium perfringens* must be highly hypoxic.



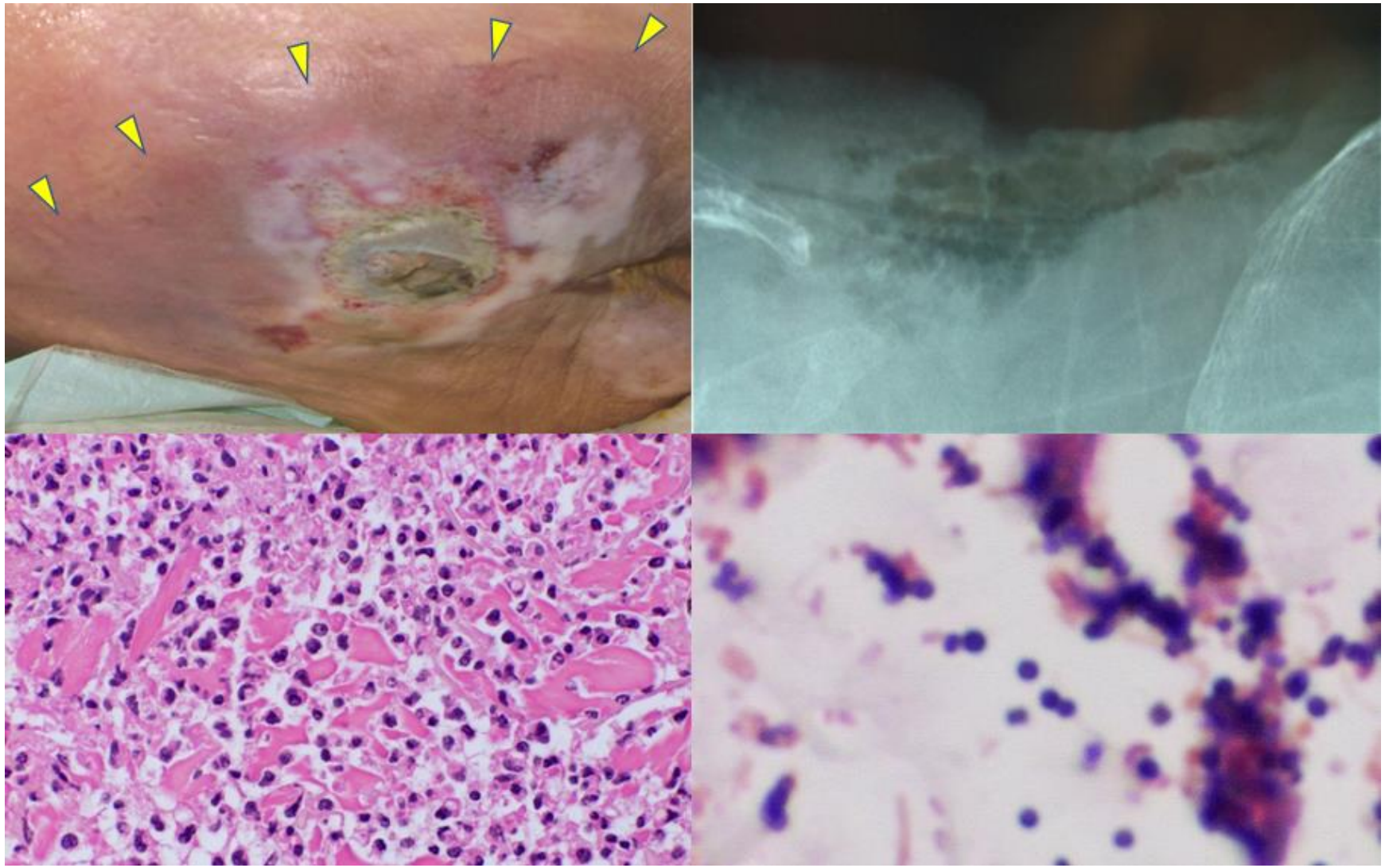
Non-traumatic clostridial gas gangrene (3). Rectal cancer-associated non-traumatic clostridial gas gangrene in an 81-year-old female (gross and H&E). The rectal cancer is hemorrhagic, and the edematous proximal colon reveals diffuse hemorrhagic necrosis. Gas formation is observed in the tissue of rectal adenocarcinoma with marked ischemic change. Large-sized rods colonize the crypts of the non-cancerous necrotic colorectal mucosa.



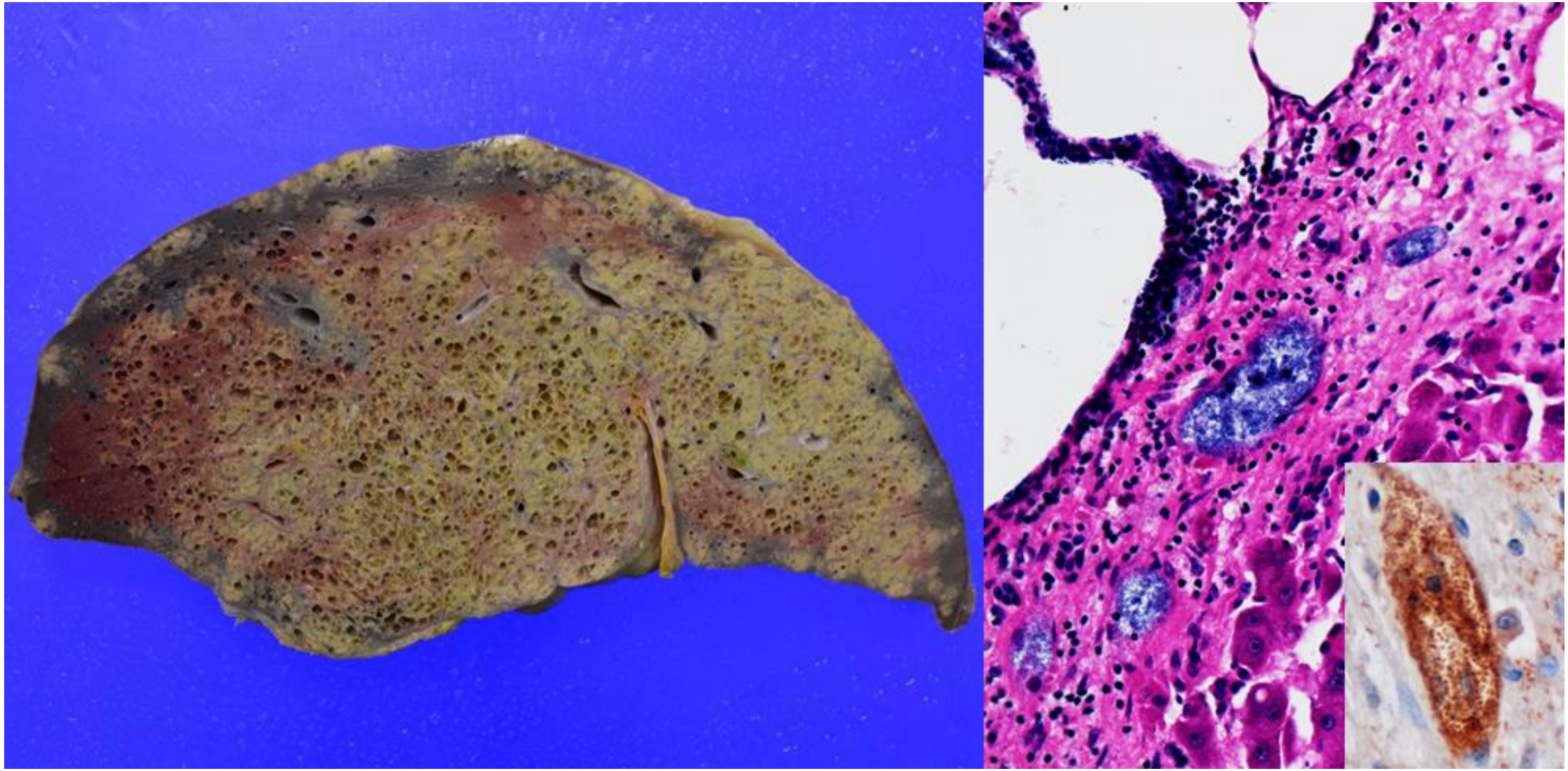
Non-traumatic clostridial gas gangrene (4). Gastric clostridial gas gangrene in a 65-year-old diabetic male (Gross and H&E). At autopsy, red-swollen stomach after endoscopic mucosal resection for early gastric cancer has an artificial ulcer at the gastric angle. Rods colonize the ulcer base. Gas formation is evident in the liver tissue (inset). Arrowheads indicate colonies of *Clostridium perfringens*.

Non-clostridial gas gangrene

Gas gangrene is commonly caused by clostridial infection, but non-clostridial bacteria may provoke gas gangrene mostly in the limbs. Early diagnosis and therapy are required, because the disease rapidly progresses to fatal toxemia. This unique dermatologic emergency is featured by the detection of non-traumatic subcutaneous emphysema of the leg with or without association of erythema, tenderness or bullous lesions. Non-clostridial gas gangrene most often results from polymicrobial infection of mixed kinds of microbes, and it is mainly seen in diabetic patients. The causative gas-producing bacteria include *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, *Aeromonas hydrophila*, *Bacteroides* spp. and *Streptococcus anginosus* group (former *S. milleri* group). Groups A, B and G streptococci also cause non-clostridial gas gangrene, as a form of fulminant streptococcal infection.



Lethal non-clostridial gas gangrene caused by group A β-hemolytic streptococcal infection (gross and radiologic findings, H&E and Gram). Infected sacral decubitus seen in a 72-year-old diabetic female with a history of brain infarction progressed to gas gangrene. The arrowheads indicate the red-colored skin area with crepitation on touch. X-ray examination discloses gas formation in the soft tissue. The debridement tissue reveals massive gangrenous inflammation with infection of Gram-positive cocci.



E. coli-induced non-clostridial gas gangrene accompanying foamy liver seen in a diabetic male aged 70's with advanced rectal adenocarcinoma (Gross and H&E, inset: immunostain). Transportal infection of *E. coli* has provoked foamy liver due to gas formation by the infected bacteria. The rods embolic in capillary vessels of the liver are immunoreactive with a monoclonal antibody against *E. coli* antigen (inset).

Severe gangrenous and emphysematous inflammation of internal organs

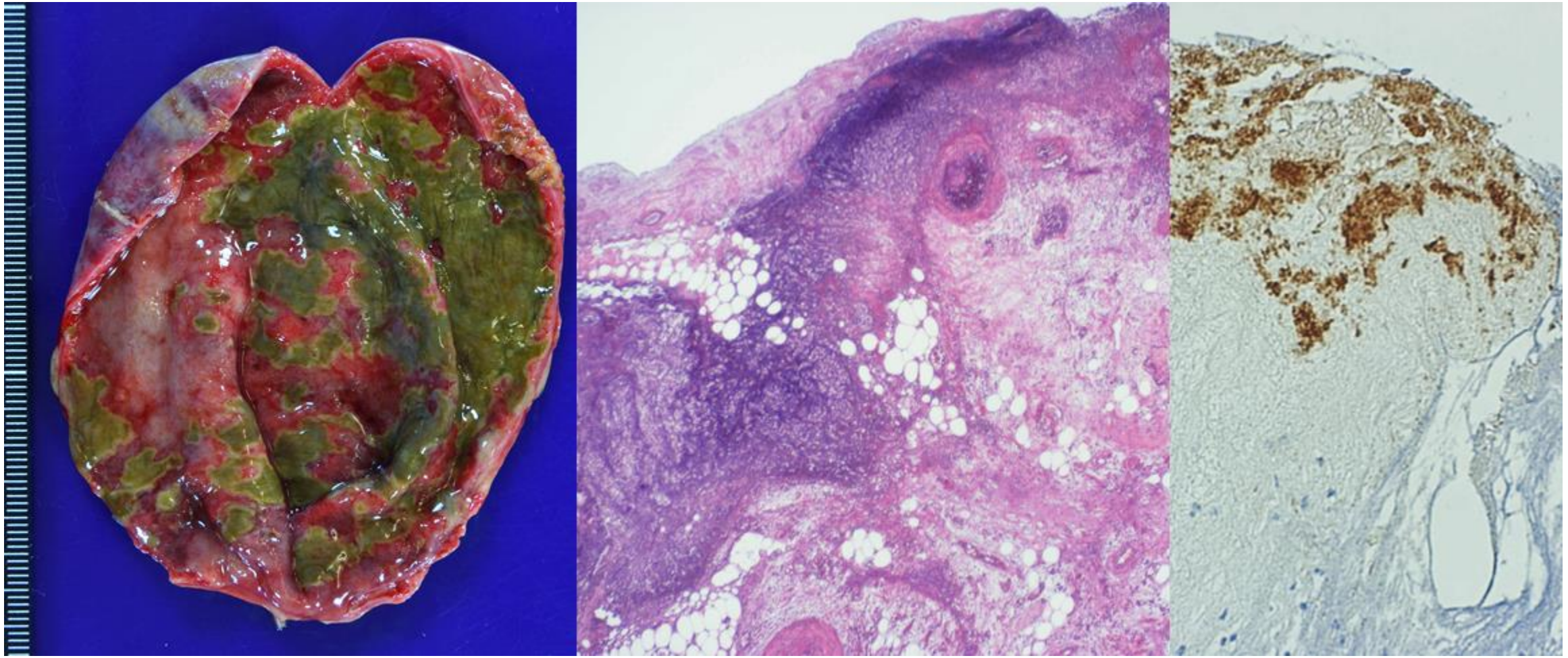
Gangrenous inflammation may occur in a wide variety of internal organs, such as the vermiform appendix, gallbladder, bile duct, pancreas, lung, kidney, eyeball, etc. The lesion may be localized within the organ, but it often extends to the surrounding tissues, so as to be fatal.
When the anaerobic pathogens produce gas, we call the serious condition as “emphysematous” inflammation (as a form of localized gas gangrene). Diabetic patients are susceptible to these severe infectious diseases.

Severe infection seen in diabetes mellitus under poor disease control

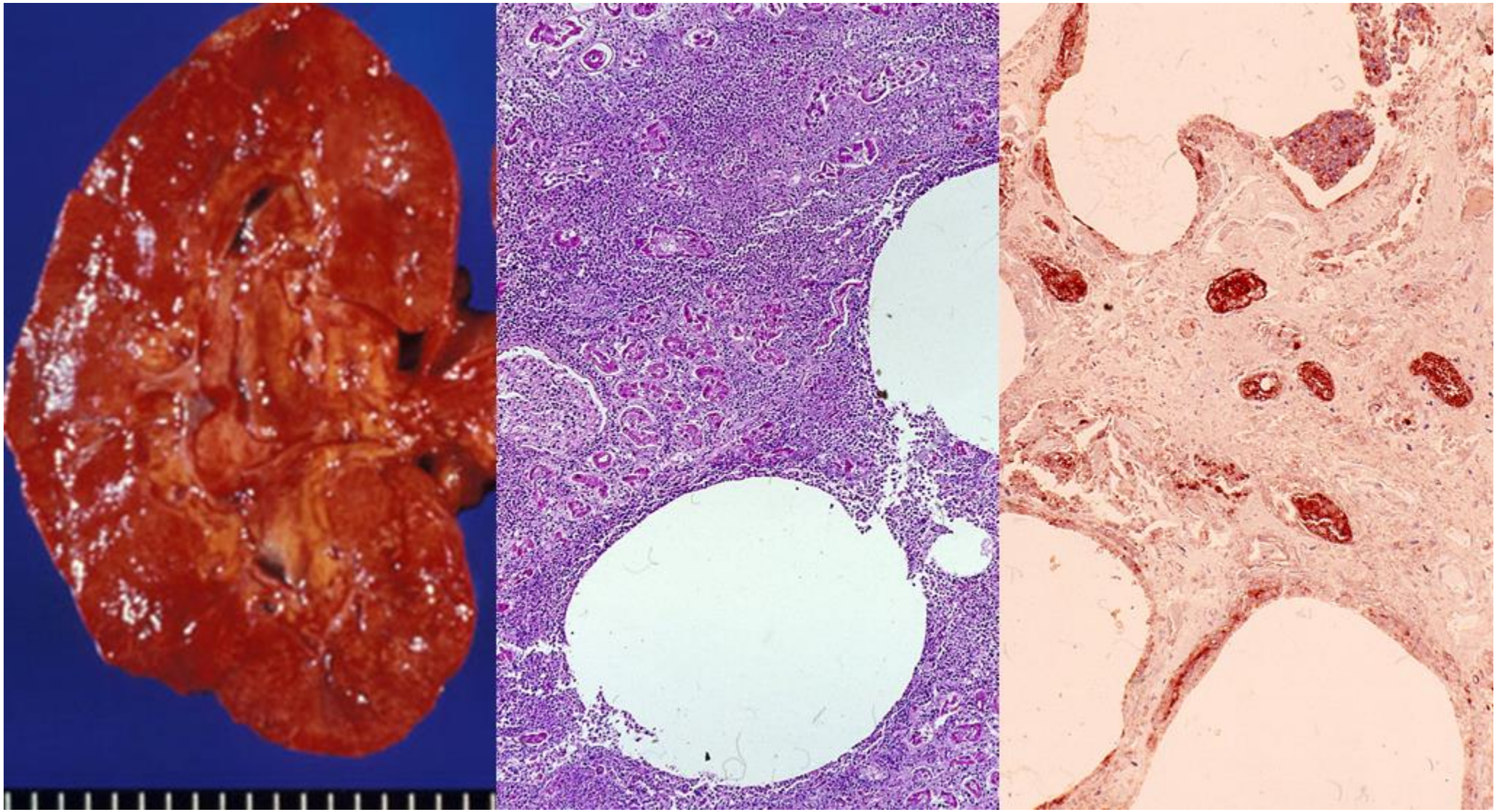
Diabetes mellitus is a complex metabolic disorder affecting the glucose status of the human body. Chronic hyperglycemia related to diabetes is associated with end organ failure. Early onset of metabolic deficiencies, namely dysregulated glucose homeostasis, peripheral insulin resistance and impaired insulin production are accompanied by both innate and adaptive immune. In particular, neutrophilic dysfunction is closely related to the susceptibility to infections. Those who suffer from diabetes mellitus are especially susceptible to the severe and advanced infectious conditions. Neutrophils protect infection of extracellular pathogens. Hence, extracellular pathogens often infect in patients with diabetes mellitus.

Ref.-1: Alba-Loureiro TC, et al. Neutrophil function and metabolism in individuals with diabetes mellitus. Braz J Med Biol Res 2007; 40(8): 1037-1044. doi: 10.1590/s0100-879x2006005000143

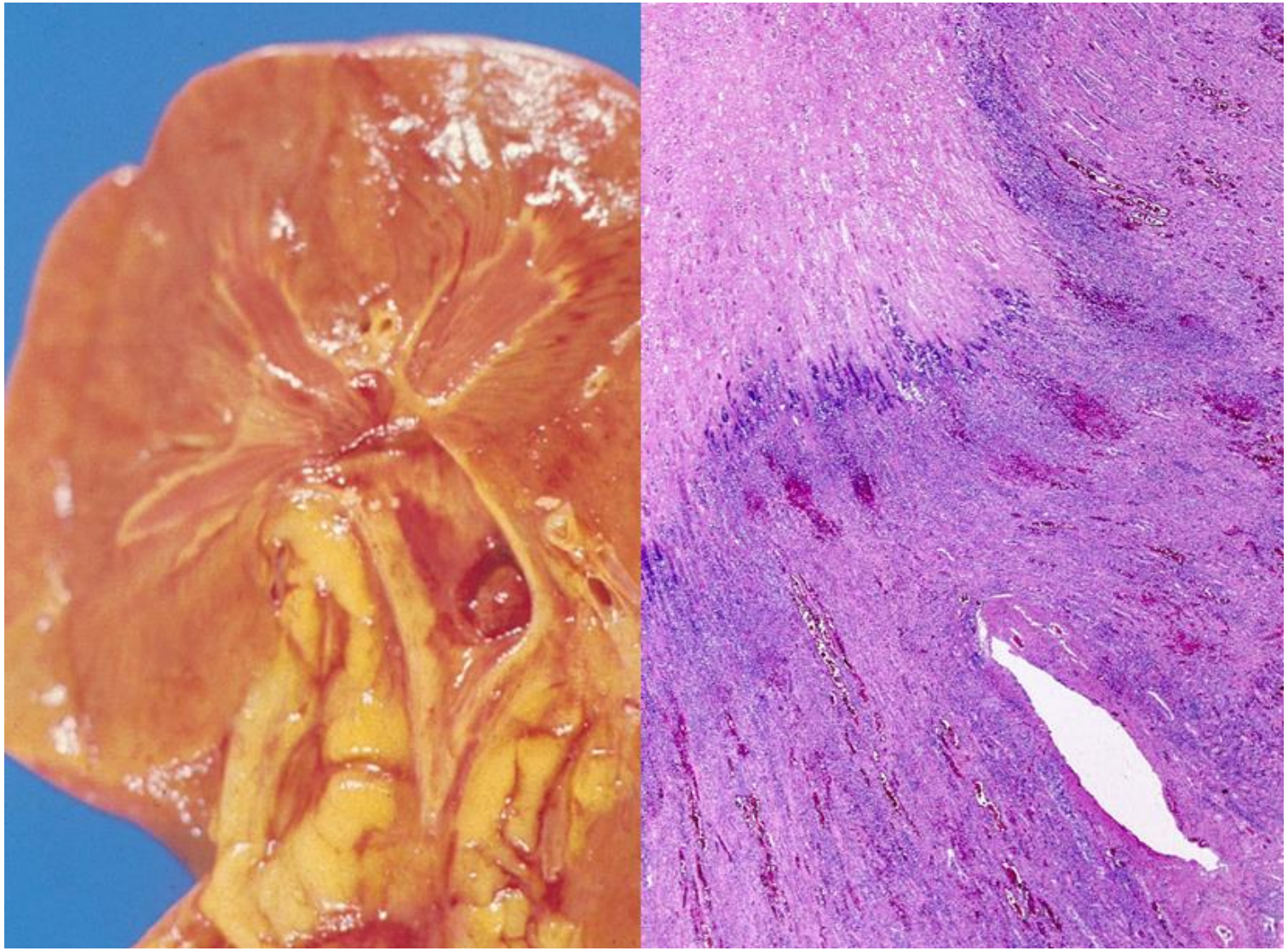
Ref.-2: Keeter WC, et al. Role of neutrophils in type 2 diabetes and associated atherosclerosis. Int J Biochem Cell Biol 2021; 141: 106098. doi: 10.1016/j.biocel.2021.106098



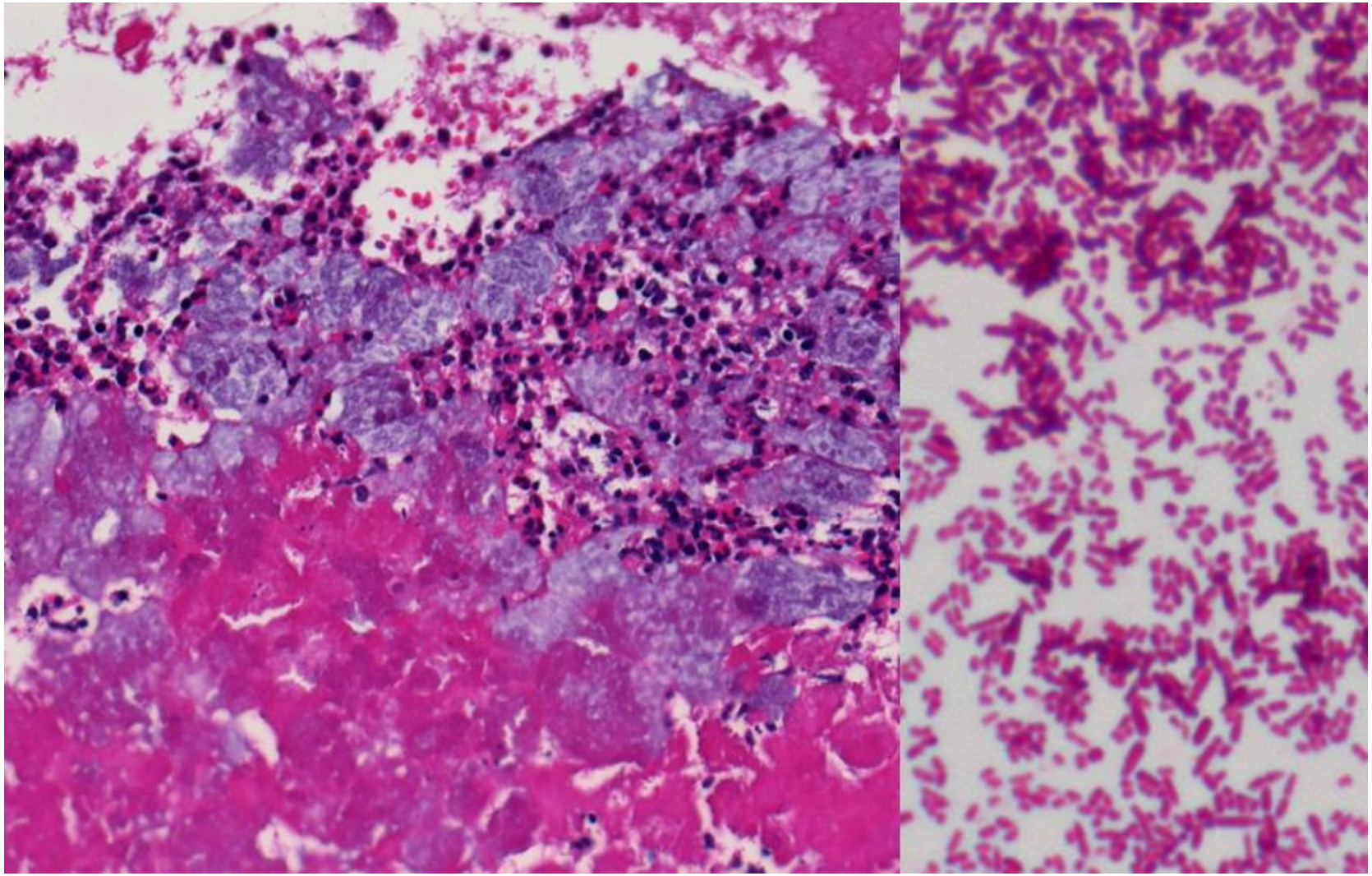
Diabetes mellitus-related infection (1). Gangrenous cholecystitis (gross, H&E and immunostain). The gallbladder surgically removed from a diabetic male patient aged 50's reveals marked necrotizing inflammation with bile-stained (green-colored) multiple mucosal ulceration. Bacterial colonies growing in the necrotic exudation are strongly immunoreactive for *E. coli* antigens.



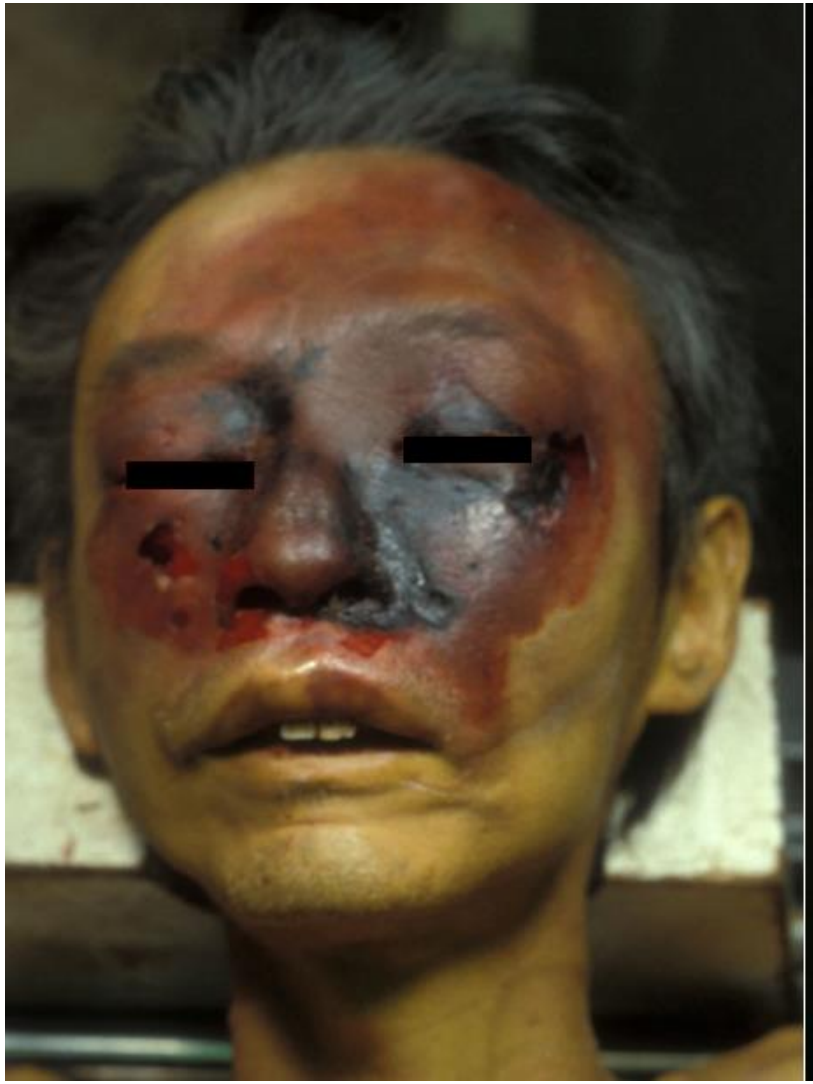
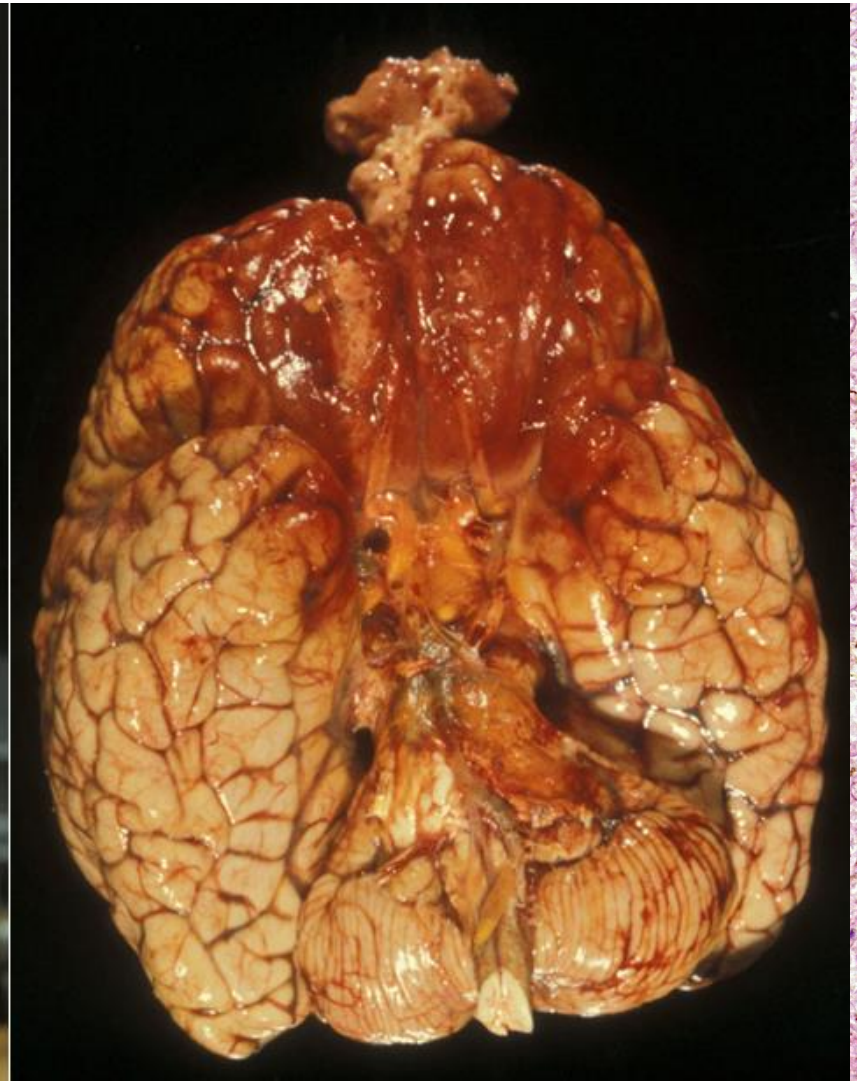
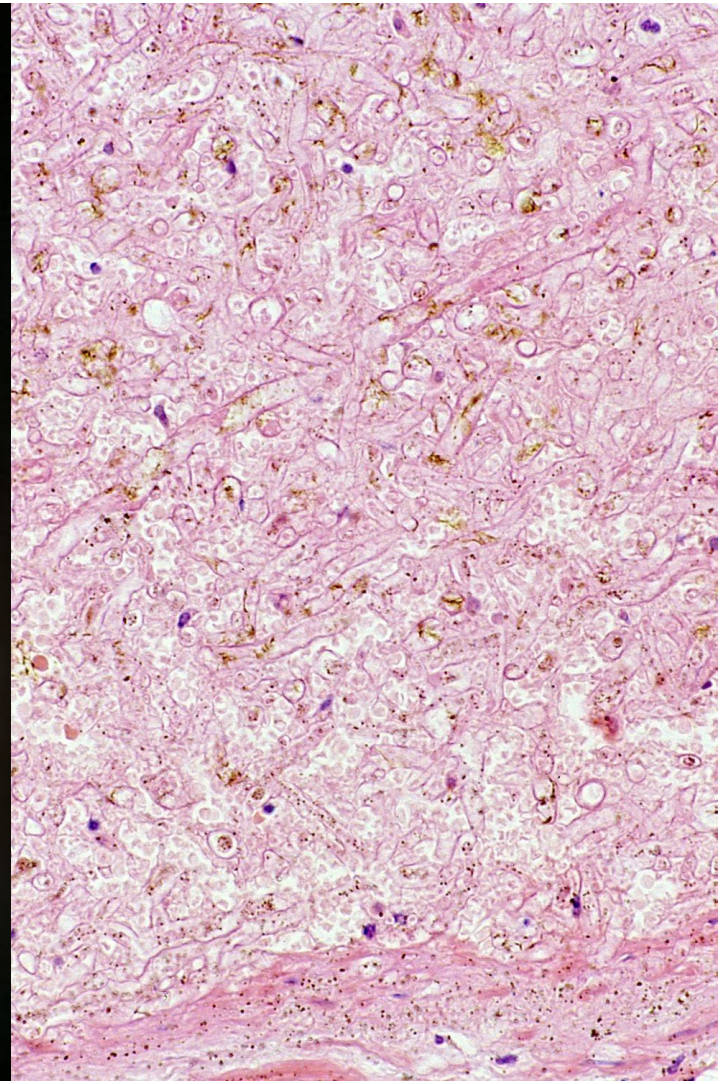
Diabetes mellitus-related infection (2). *E. coli*-infected emphysematous pyelonephritis in a diabetic male patient aged 70's (gross, H&E and immunostain for *E. coli* antigens). The enlarged kidney shows multifocal gangrenous changes with formation of small bubbles. Gas-forming infection of *E. coli* is evident both histologically and immunohistochemically in severe acute purulent pyelonephritis.



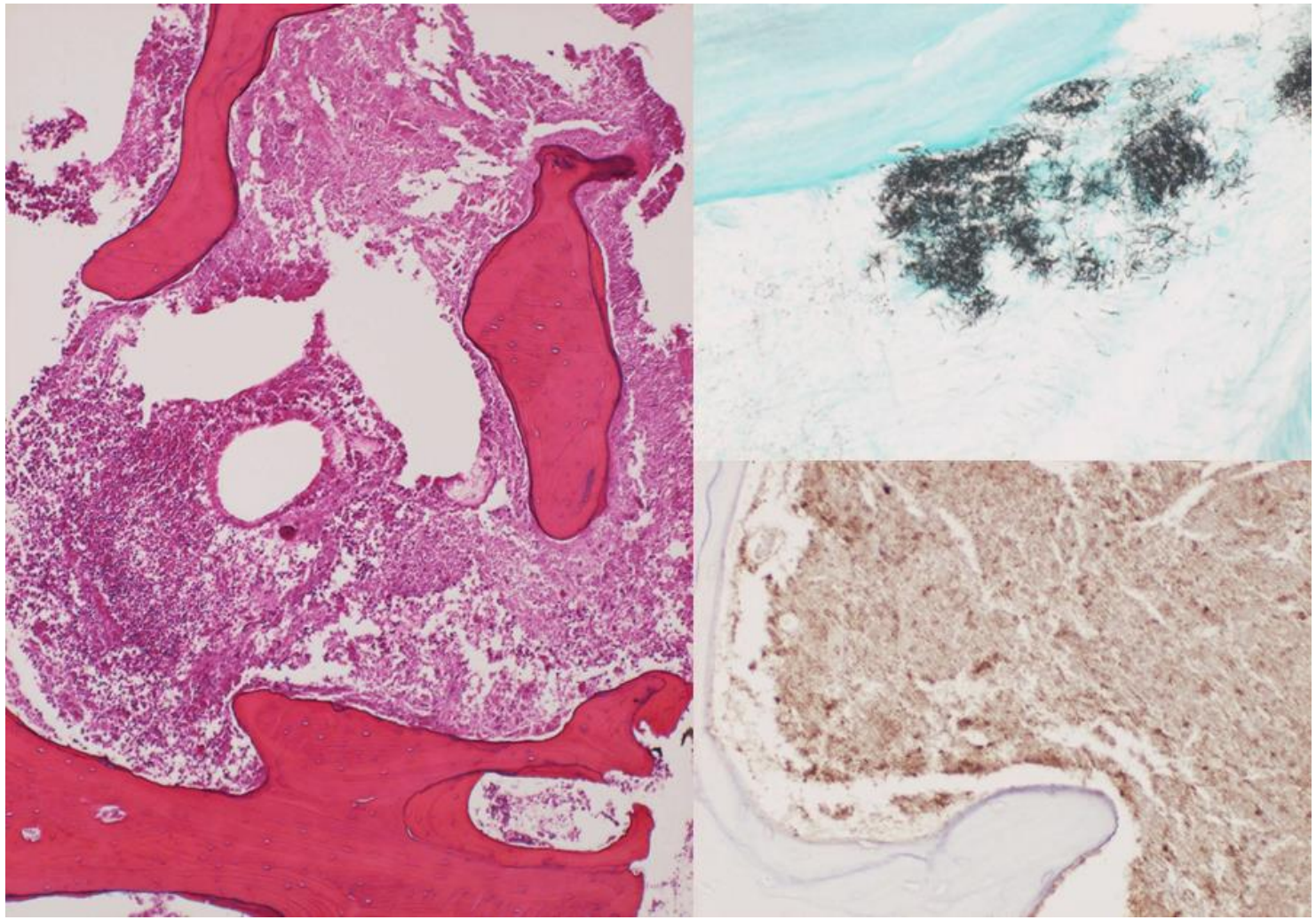
Diabetes mellitus-related infection (3). Renal papillary necrosis in an aged male patient with uncontrolled diabetes mellitus (gross and H&E). The patient manifested symptoms of acute pyelonephritis and died of acute renal failure. The renal papillae are necrotic and demarcated with yellowish zones. Ascending infection of *E. coli* is associated.



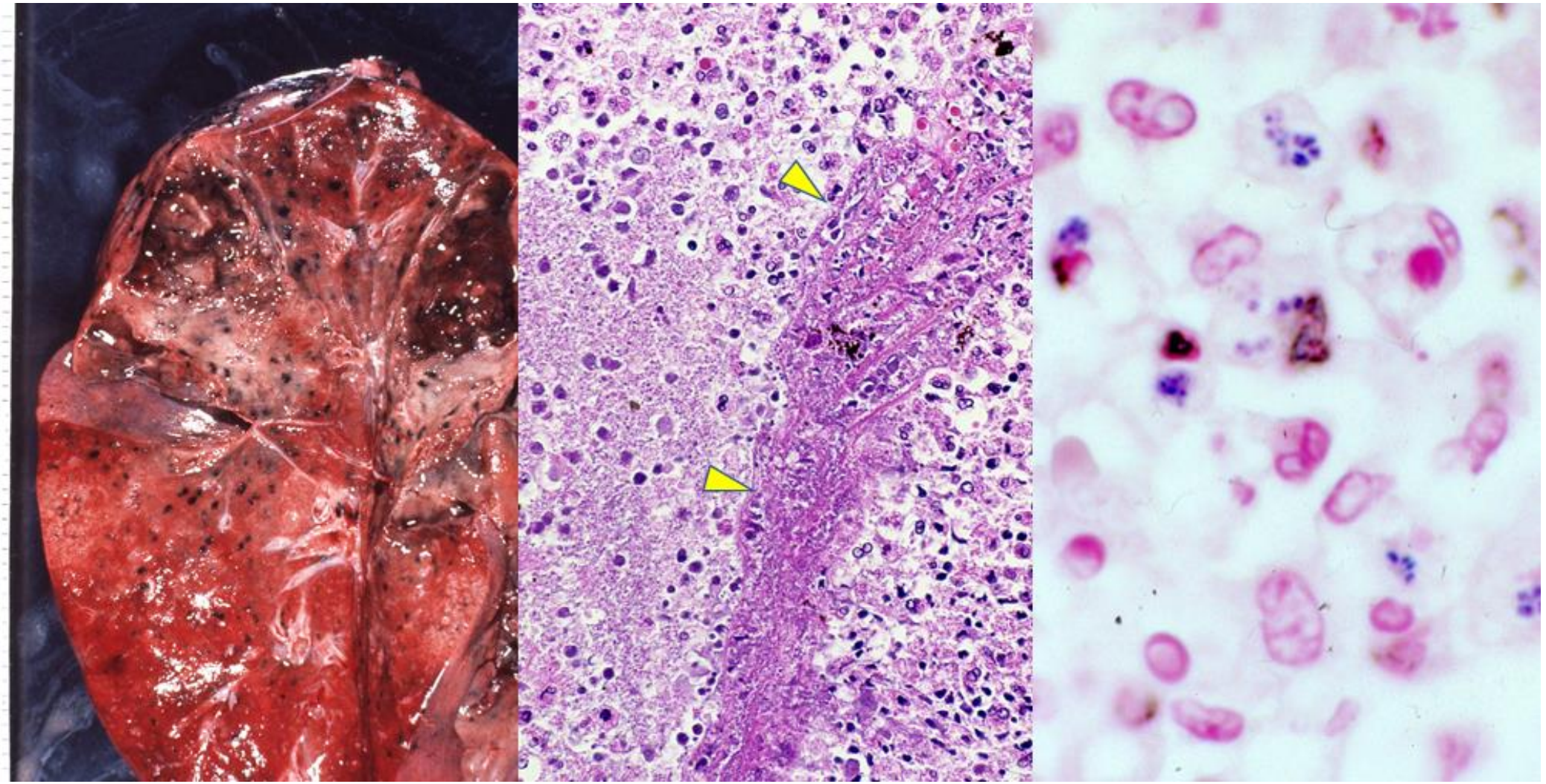
Diabetes mellitus-related infection (4). Malignant otitis externa (H&E and Gram stain on smear preparation). In this lethal diabetic case (49-year-old female) accompanying pseudomonal septicemia, Gram-negative rods densely colonize the necrotic debris in necrotizing petrosititis. Myxoid matrix of the colony indicates biofilm infection. Gram-negative rods are demonstrated in the smear sample.

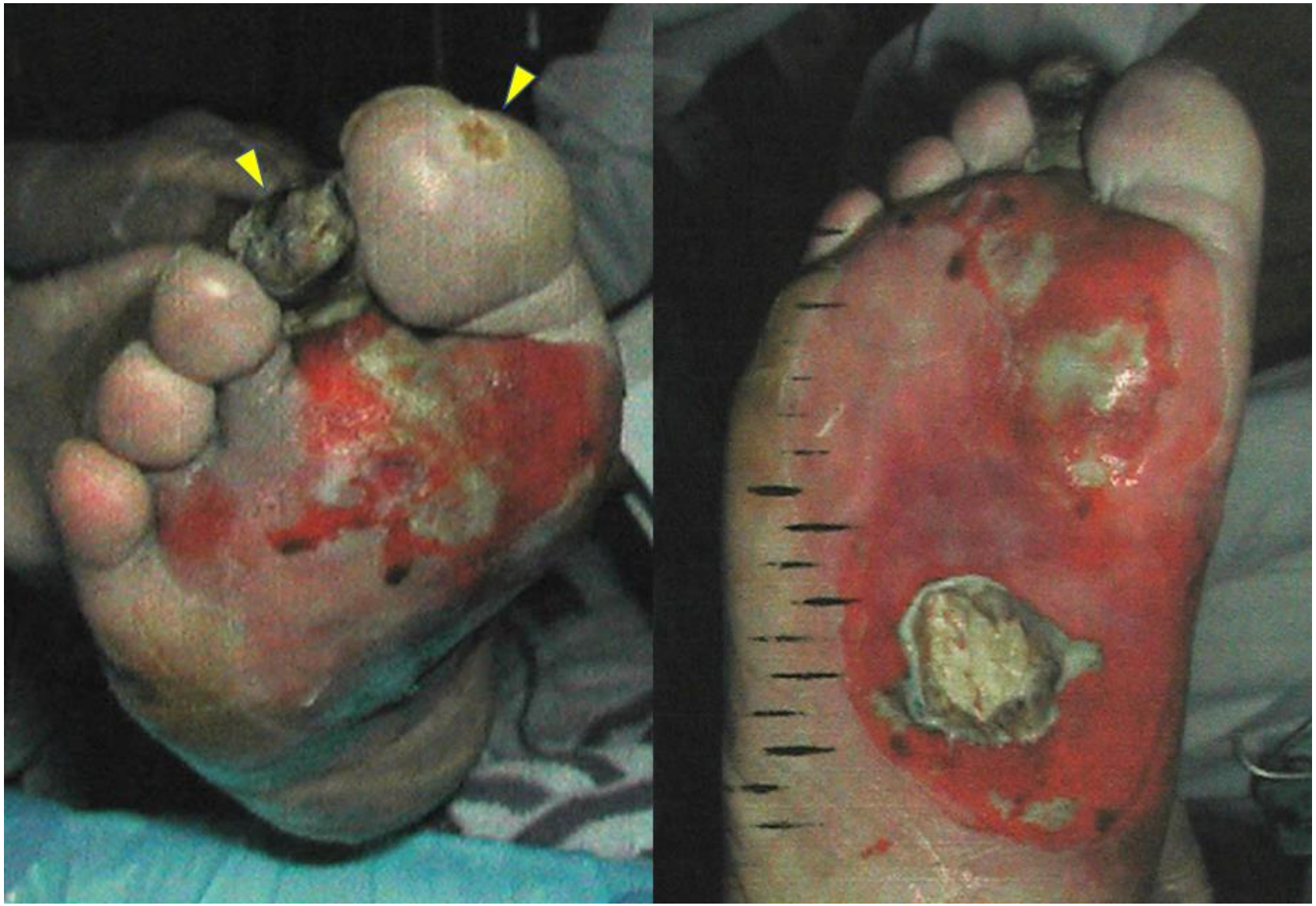
Diabetes mellitus-related infection (5). Lethal mucormycosis of rhinocerebral type in a poorly controlled diabetic patient (gross appearance/H&E). The patient has advanced pancreatic adenocarcinoma. Angioinvasive mucormycosis (right: H&E) resulted in hemorrhagic necrosis of the face, eye ball and anteroinferior part of the brain. Infection had been extended from the paranasal cavity.



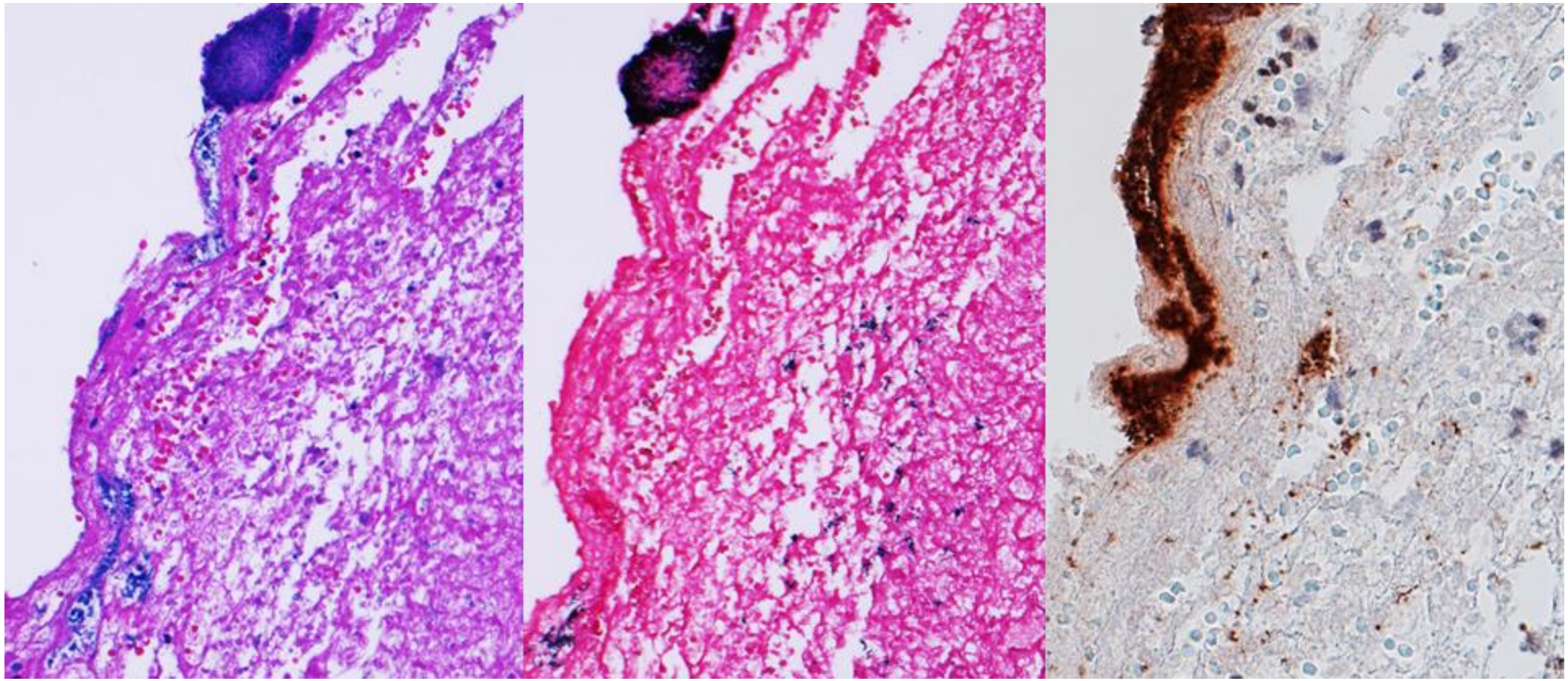
Diabetes mellitus-related infection (6). Noma-like condition (progressive ulcerative gingivitis) in a diabetic male patient aged 80's (H&E, Grocott and immunostain). A gas-forming, necrotizing lesion is observed in the biopsied maxillary bone. Grocott methenamine silver stain identifies colonies of filamentous bacteria in the lesion, probably representing Actinomyces colonization. The Gram-negative bacteria around the gas bubble are immunoreactive with a commercial antiserum against *E. coli*, which shows wide cross-reactivity to Gram-negative bacteria.



Diabetes mellitus-related infection (7). Pulmonary gangrene (gross, H&E, Gram) in a diabetic patient. Cavity-forming pneumonia is noted in bilateral lungs. Foul smell was associated. Gangrenous inflammation is evident histologically. Microbial culture from the lung lesion identified *Bacteroides*, *Pseudomonas aeruginosa* and *Peptostreptococcus*. Pseudomonal infection is indicated by arrowheads, and Gram-positive cocci (probably representing *Peptostreptococcus*) are phagocytized by neutrophils.



Diabetes mellitus-related infection (8). Localized severe burn on the sole of a diabetic male caused by a fan heater, resulting in necrotizing fasciitis (gross appearance). Because of diabetic neuropathy, deep ulcers occurred on the senseless foot. Dry gangrene on the first and second toes (arrowheads) indicates the association of diabetes-related atherosclerosis obliterans. The importance of foot care should be emphasized in diabetic patients.



Diabetes mellitus-related infection (9). *Bacillus cereus*-induced necrotizing fasciitis (H&E, Gram and immunostain). Trauma-related lethal soft tissue gangrene is formed on the hip of the diabetic patient. Gram-positive rods colonize the necrohemorrhagic soft tissue. Immunostaining for *Bacillus cereus* antigens is strongly positive, particularly on the spores.

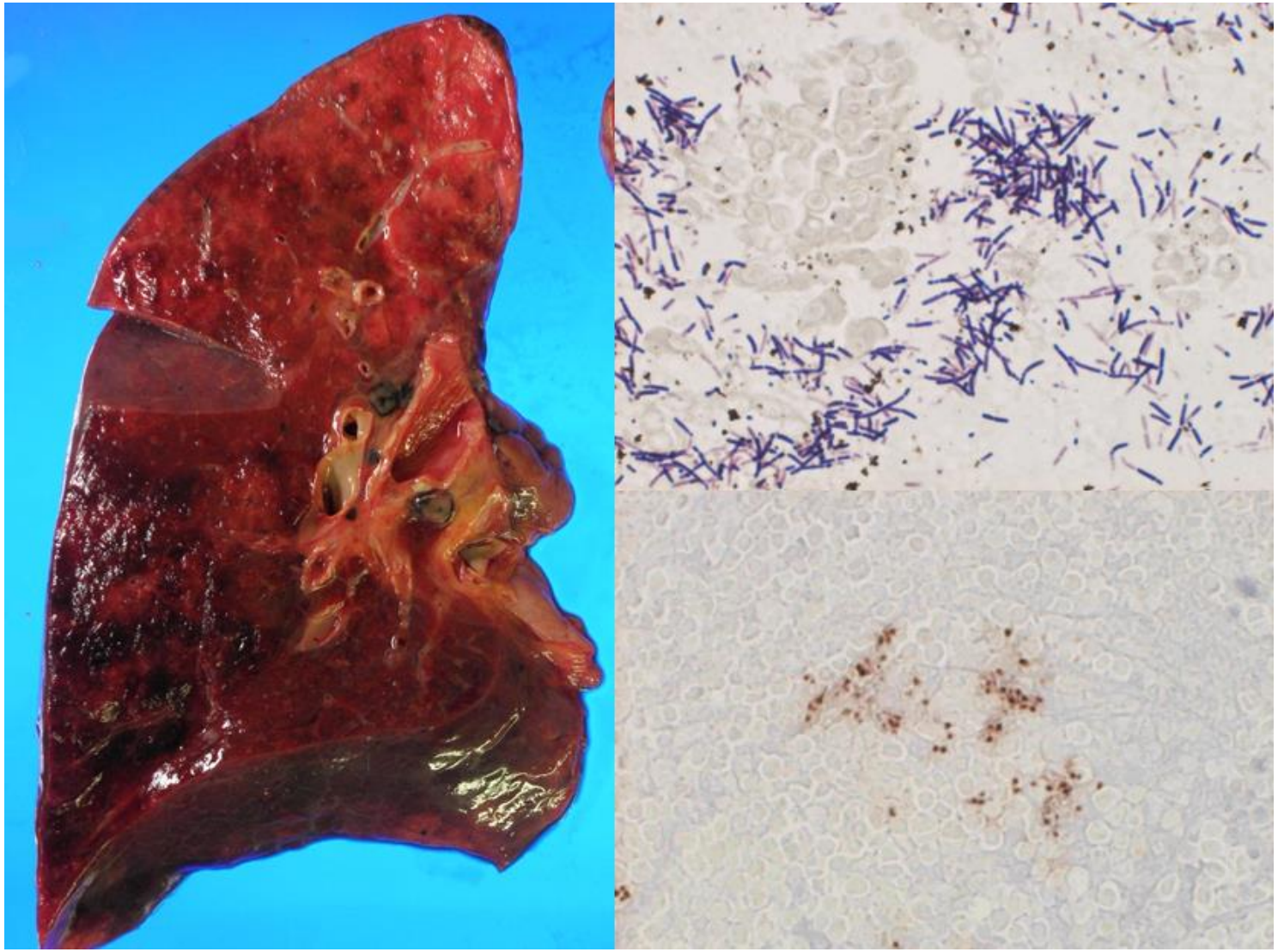
Severe infections related to immunosuppression and malnutrition

With immunosuppressive therapy, infections occur. Anti-cancer drugs may provoke myelosuppression to cause neutropenia, and infection by extracellular pathogens is quite susceptible. Steroid therapy or immuno-targeted therapy may result mainly in suppression of cellular immunity, and infection by intracellular pathogens is plausible.

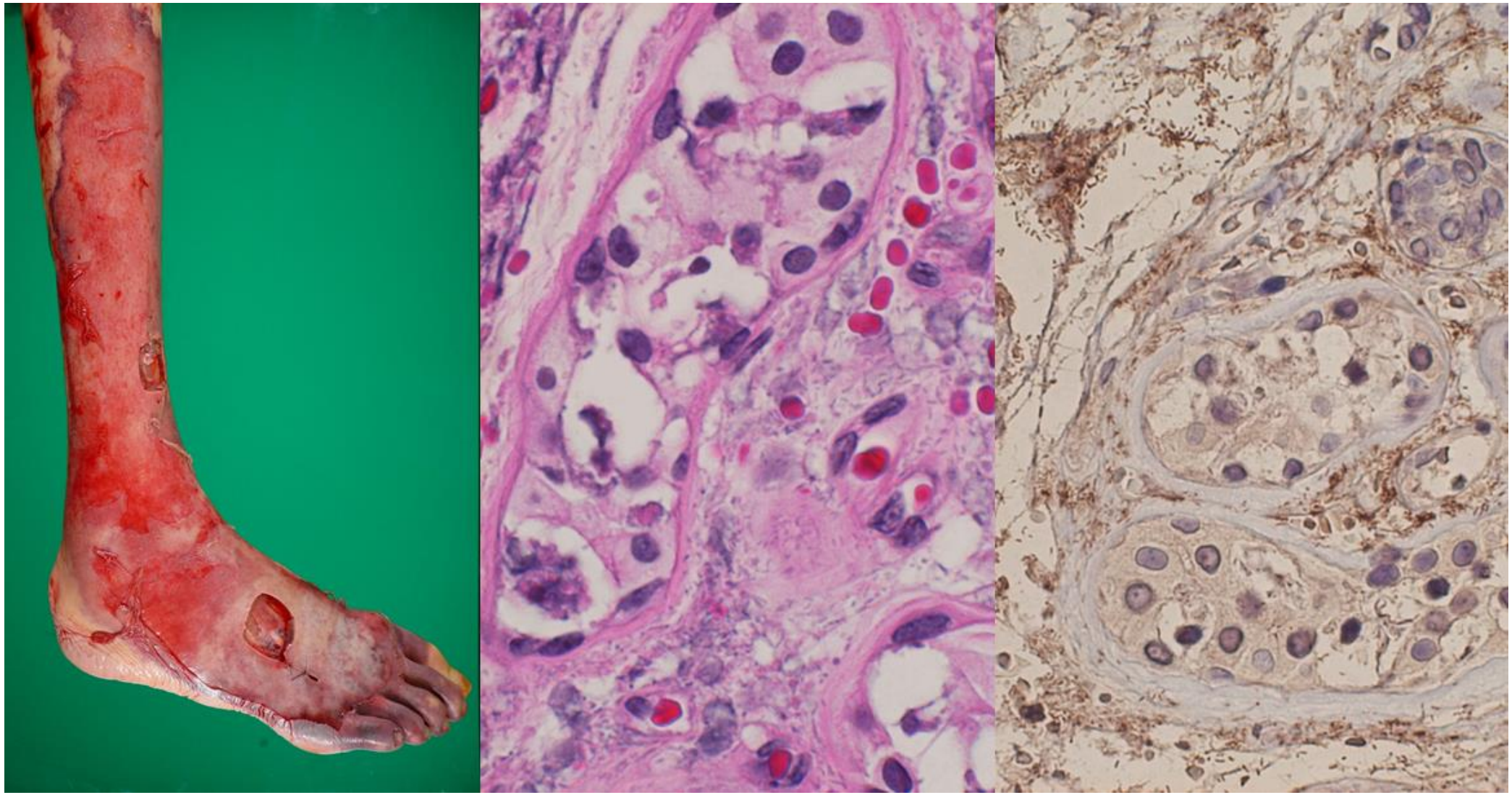
Infection and malnutrition have always been intricately linked. Malnutrition is the primary cause of immunodeficiency worldwide.

Ref.-1: Handley G, Hand J. Adverse effects of immunosuppression: infections. Handb Exp Pharmacol 2022; 272: 287-314. doi: 10.1007/164_2021_550

Ref.-2: Katona P, Katona-Apte J. The interaction between nutrition and infection. Clin Infect Dis 2008; 46(10): 1582-1588. doi: 10.1086/587658



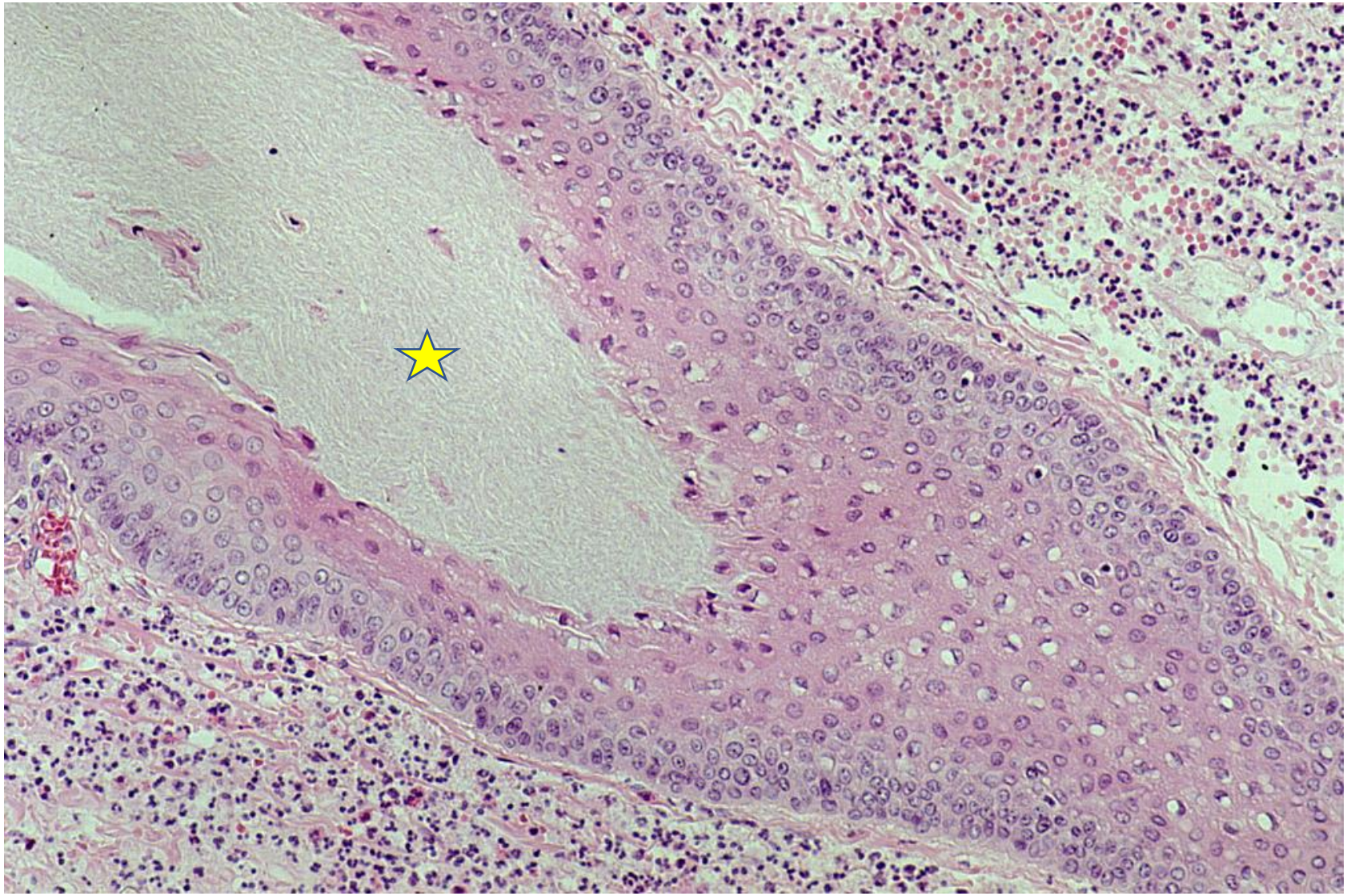
Lethal *Bacillus cereus* pneumonia in a female patient with indolent lymphoplasmacytic leukemia (Gross, Gram and immunostain). Severe necrotizing hemorrhagic pneumonia was caused by incidental aspiration of *B. cereus*-grown sweet-curdled milk. Gram-positive rods grow in the necrotic lesion. The antiserum against *B. cereus* labels spores in the rods. Leukemia-related immunosuppression accelerated the infection.



Pseudomonas aeruginosa-related necrotizing fasciitis in a young female aged 20's suffering from anorexia nervosa (gross, H&E and immunostain). Her leg with massive necrotic/gangrenous lesions was amputated (left, after sampling of histological specimens). Massive bacillary growth has provoked little inflammatory reaction. The bacteria are immunoreactive for *Pseudomonas aeruginosa* antigen detected by a monoclonal antibody. The malnutrition state is closely related to the infection.

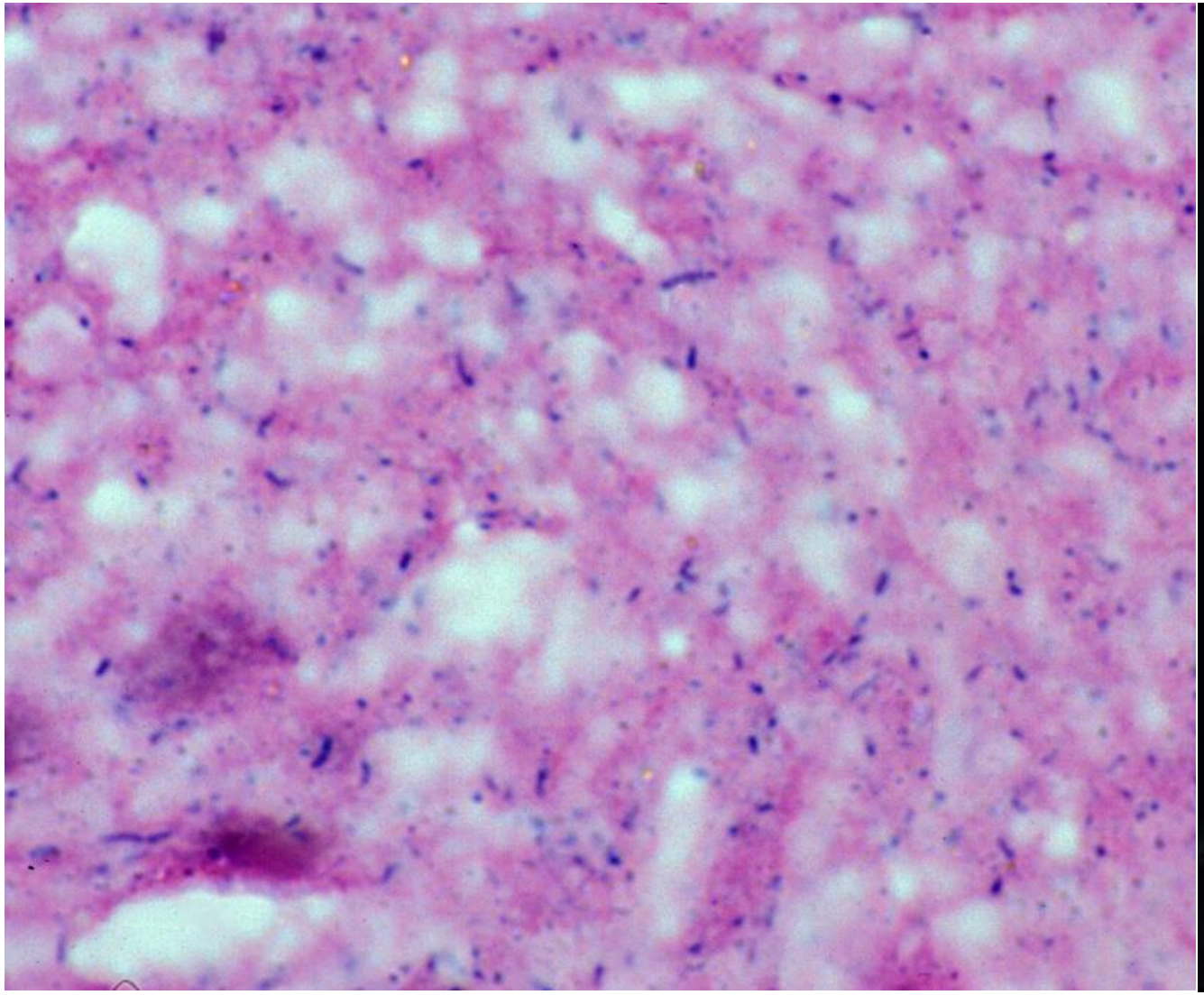
Community-acquired fulminant infections

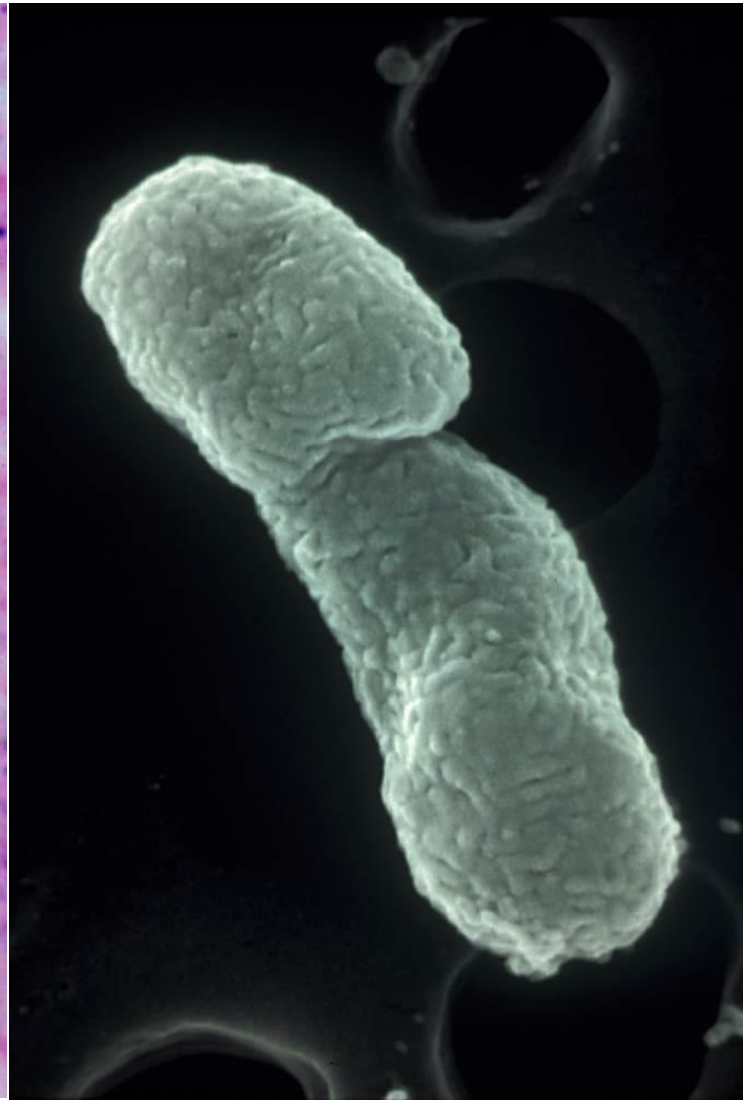
Fulminant and often lethal infections may occur in healthy individuals without underlying diseases such as diabetes mellitus, immunosuppression, malnutrition, splenectomy, liver cirrhosis or renal failure. Examples include diphtheria,lobr pneumonia caused by *Streptococcus pneumoniae* or *Legionella pneumophila*, purulent bacterial meningitis, Naegleria encephalitis, enterohemorrhagic *E. coli* infection O-157 of the colon, fulminant hepatitis, and flesh-eating bacterial infections, including fulminant streptococcal infection with or without gangrene of the extremities. Zoonotic infection of *Capnocytophaga canimorsus* septicemia and *Streptococcus suis* septicemia may happen in previously healthy individuals.



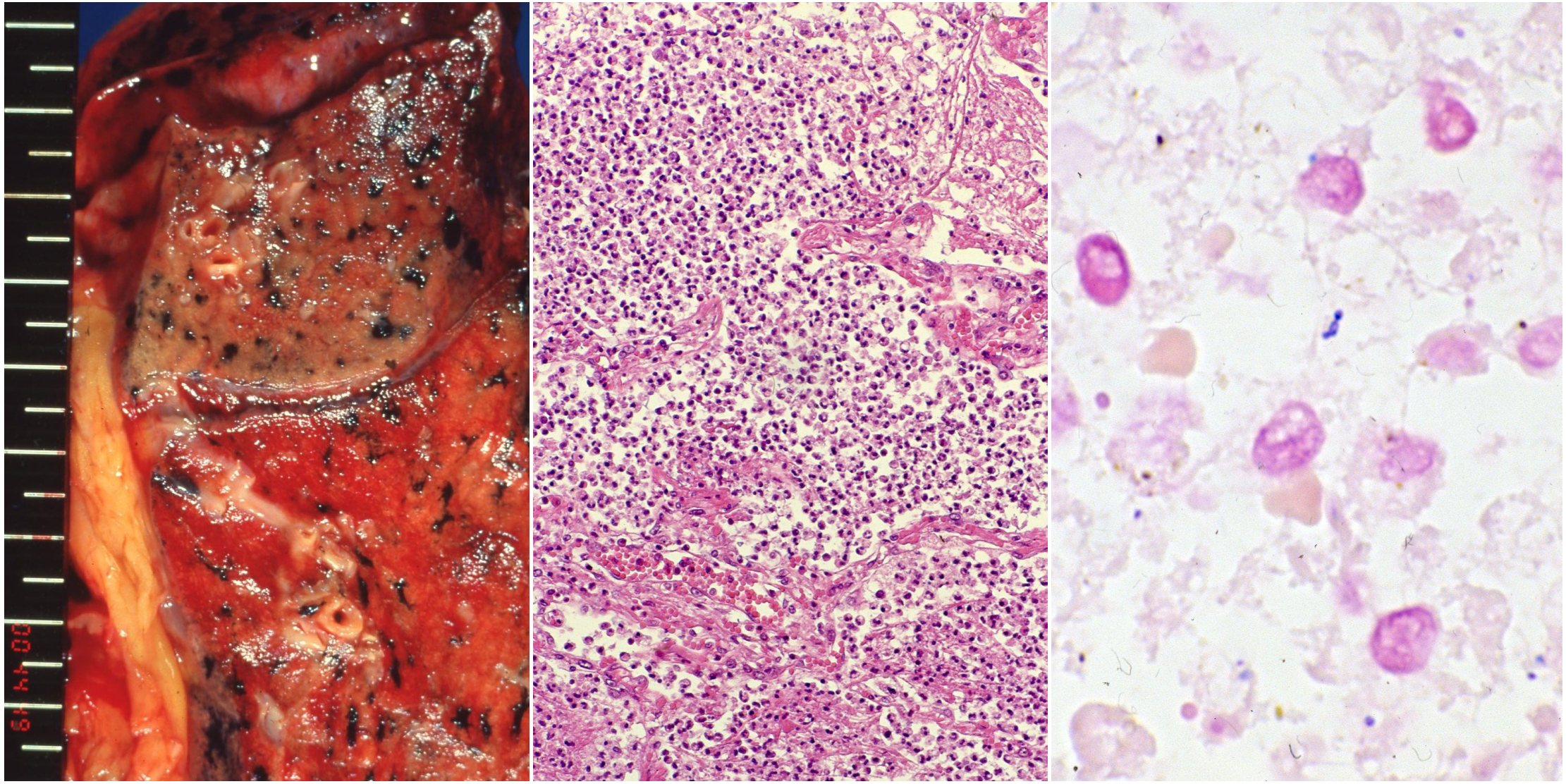
Diphtheria (pseudomembranous pharyngitis) (H&E). A 75-year-old Japanese male patient complained of acute respiratory distress without fever. The thick pseudomembrane hampered intubation at the emergency suite. A piece of pharyngeal mucosa was submitted to the pathology division for histopathological evaluation. The asterisk indicates the pseudomembrane. Patient died on the table. Consider a high biohazard during the patient care.

Importance of Gram staining

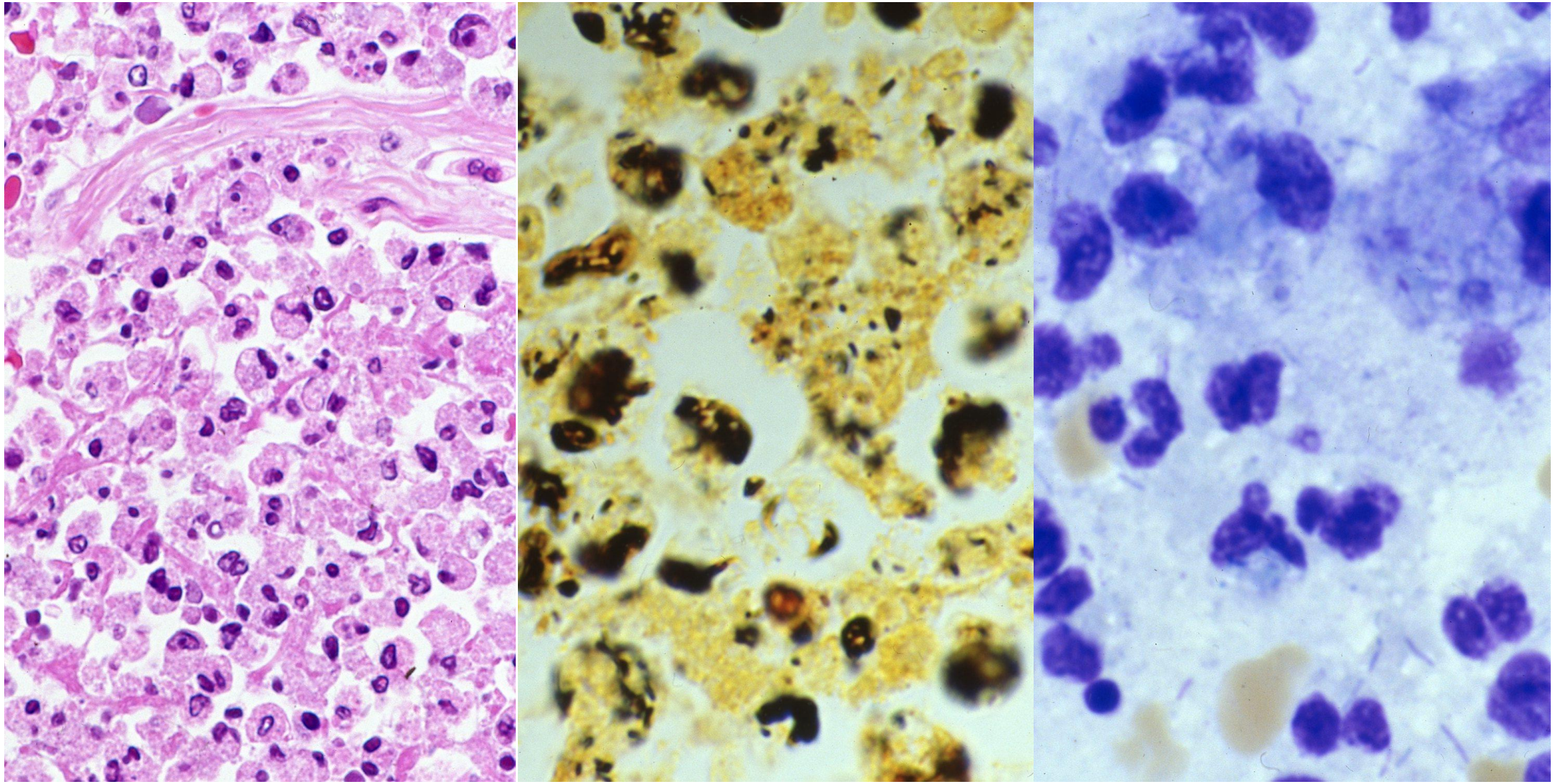




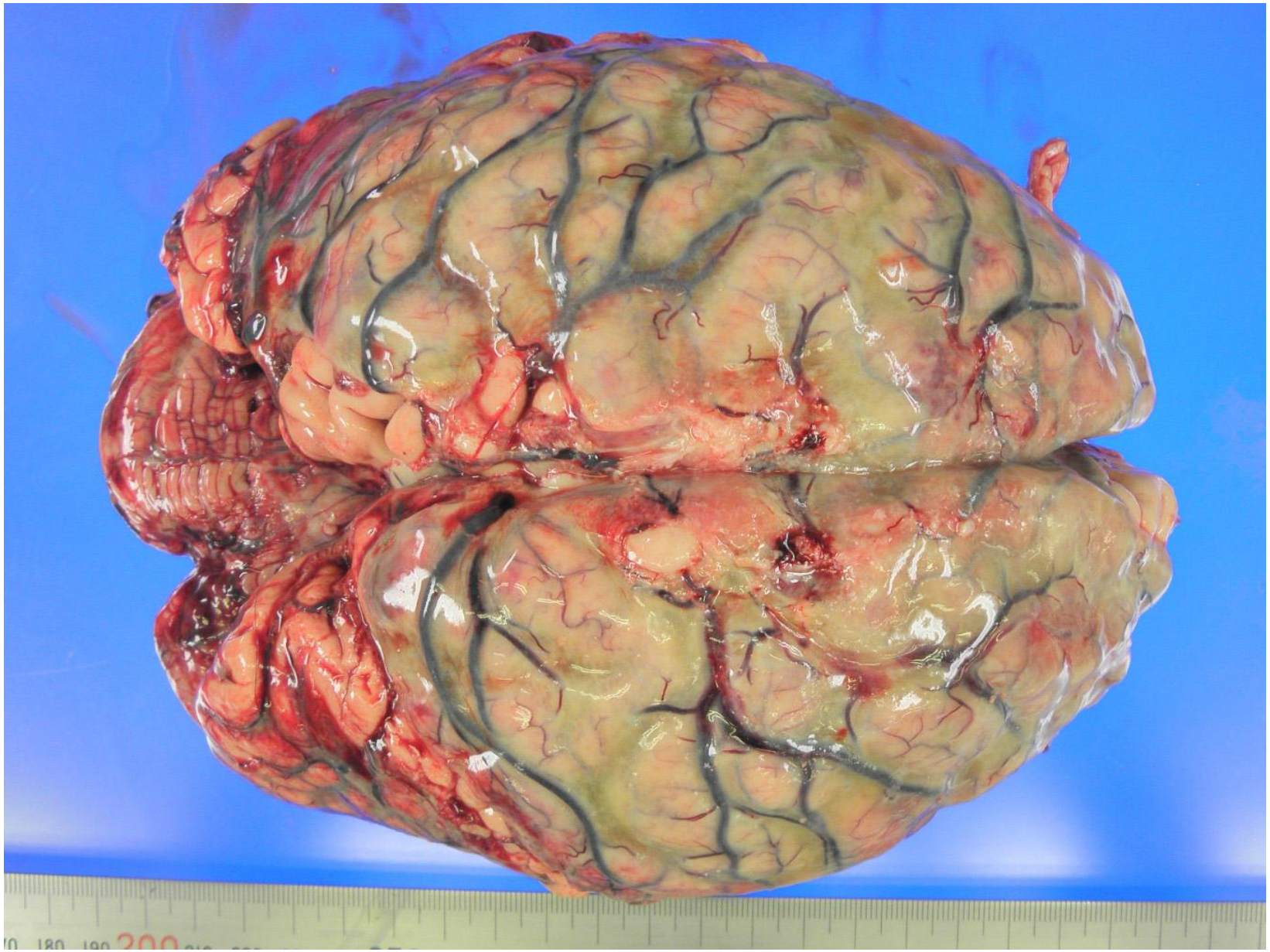
Diphtherial pharyngitis (Gram-positive rods & scanning EM) in a 75-year-old male patient. The pseudomembrane on the throat contains numbers of Gram-positive rods. *Corynebacterium diphtheriae*, a club-shaped, non-flagellated, non-capsulated, Gram-positive bacillus, is proven by the SEM study.



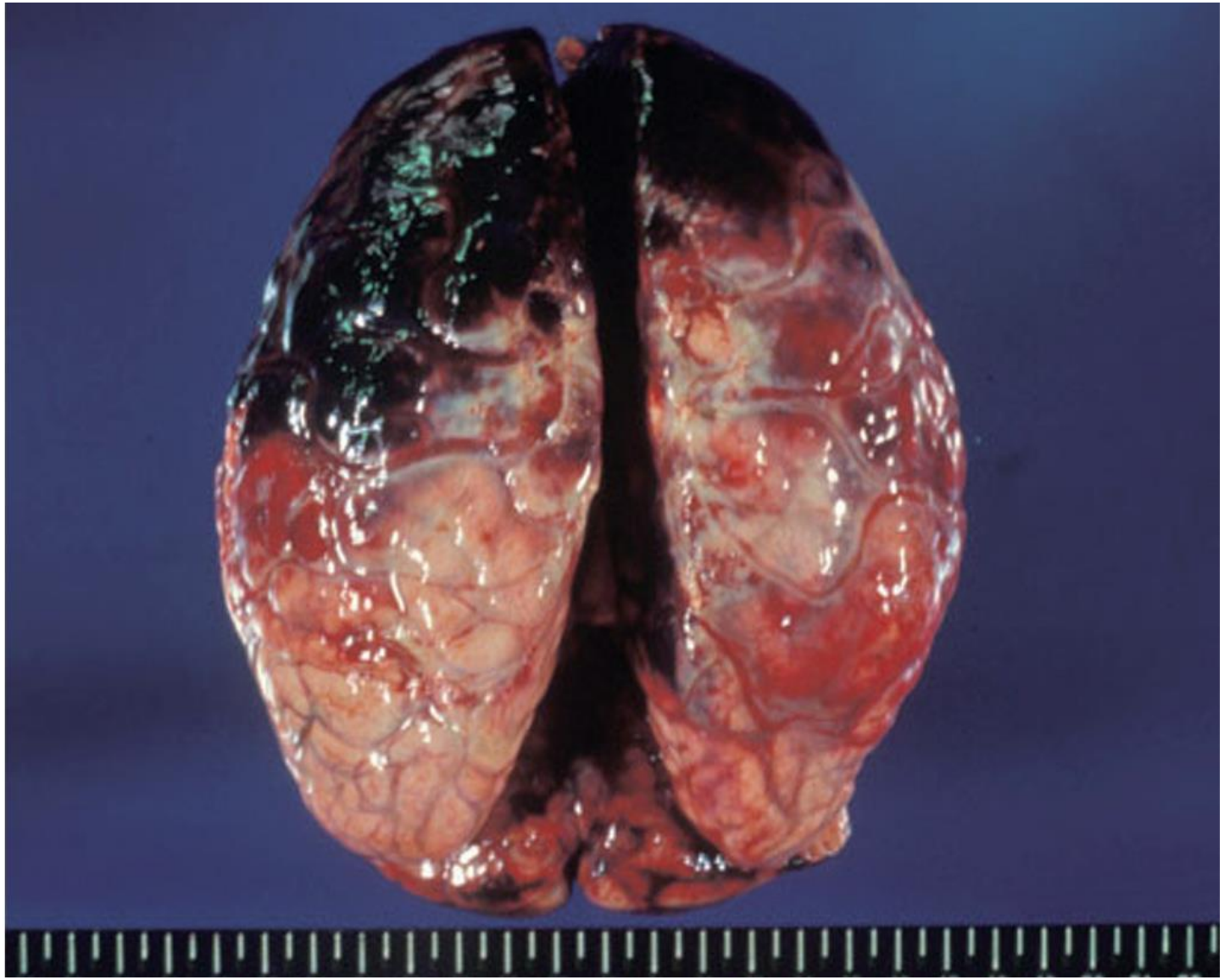
Pneumococcal lobar pneumonia in the aged man (macro/H&E/Gram). The right middle lobe of the lung is diffusely involved by exudative lesion. Microscopically, exudation of neutrophils is evident, but the pre-existing alveolar structure is retained. Gram-positive diplococci are scattered in the alveolar space, The bacteria are fundamentally not phagocytized by the neutrophils because of capsule formation.



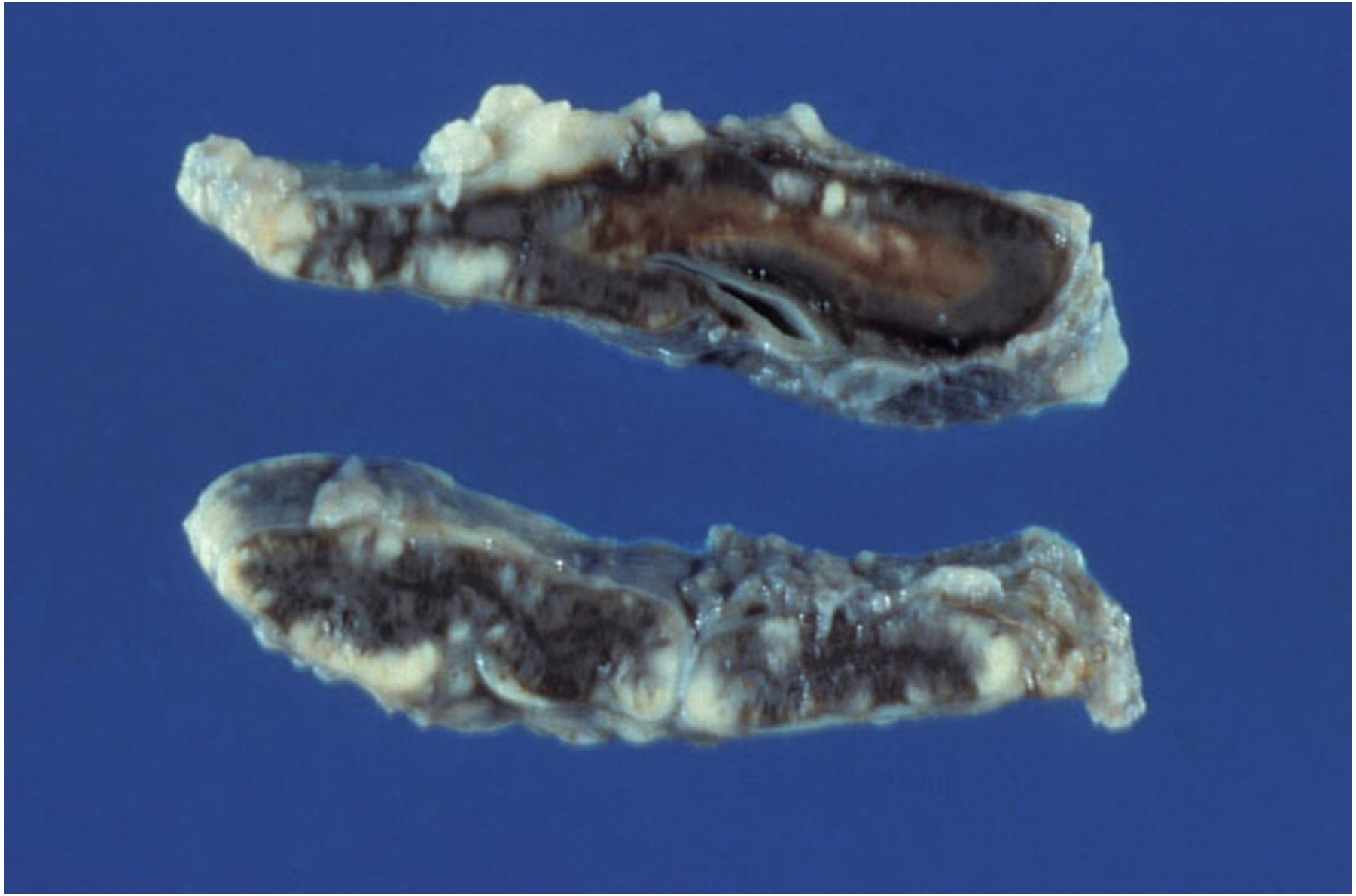
Legionnair's pneumonia (HE/Warthin-Starry/Giemsa). Acute lobular pneumonia is caused by *Legionella pneumophila* infection. Diffuse alveolar exudates mainly consist of macrophages. Warthin-Starry stain discloses argyrophilic rods phagocytized by macrophages. Stamp smear preparation of the pneumonia lesion demonstrates long rods in the cytoplasm of macrophages.



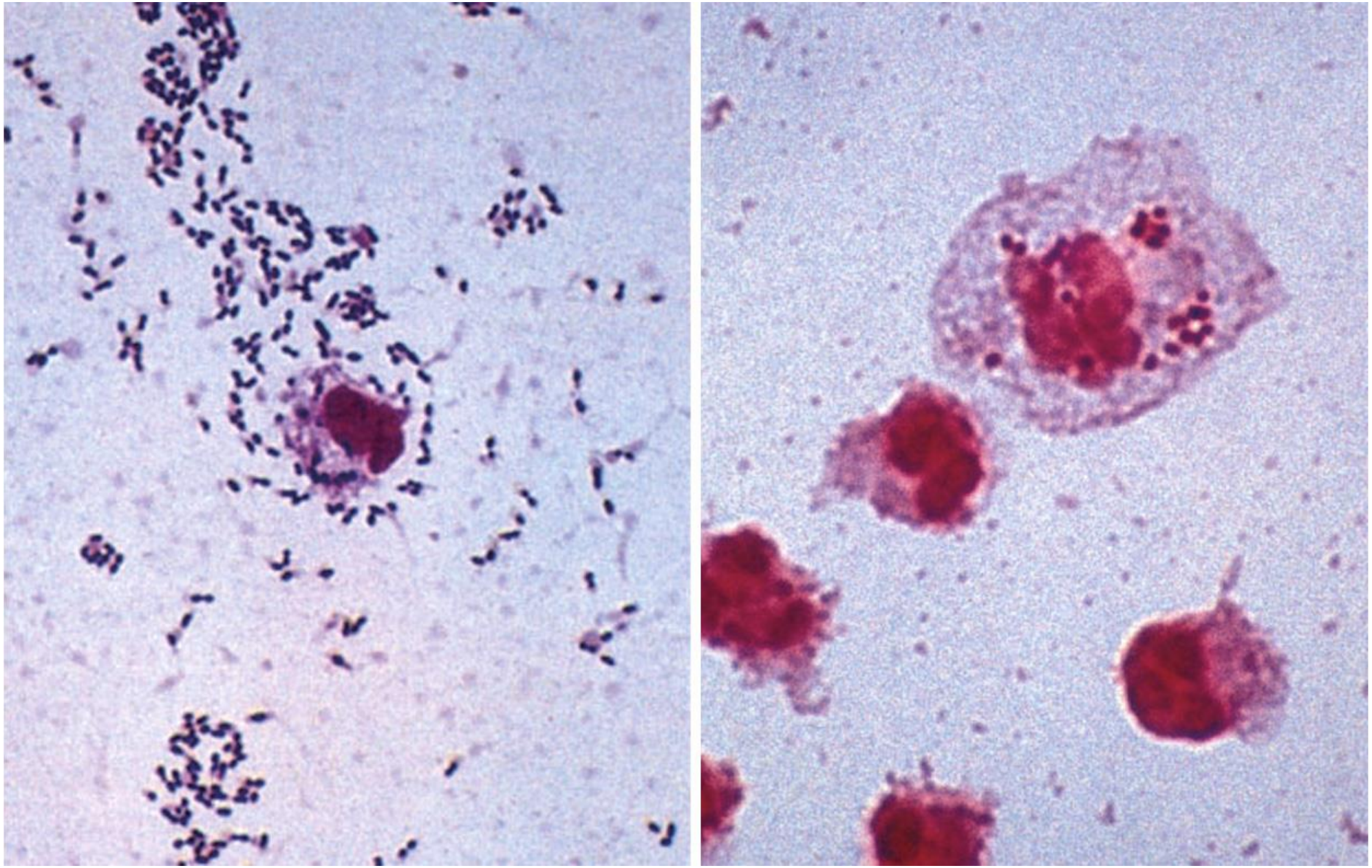
Gross appearance of acute purulent meningitis caused by *Streptococcus pneumoniae* (pneumococcus). The cocci have spread from extradural abscess of the lumbar spinal cord.



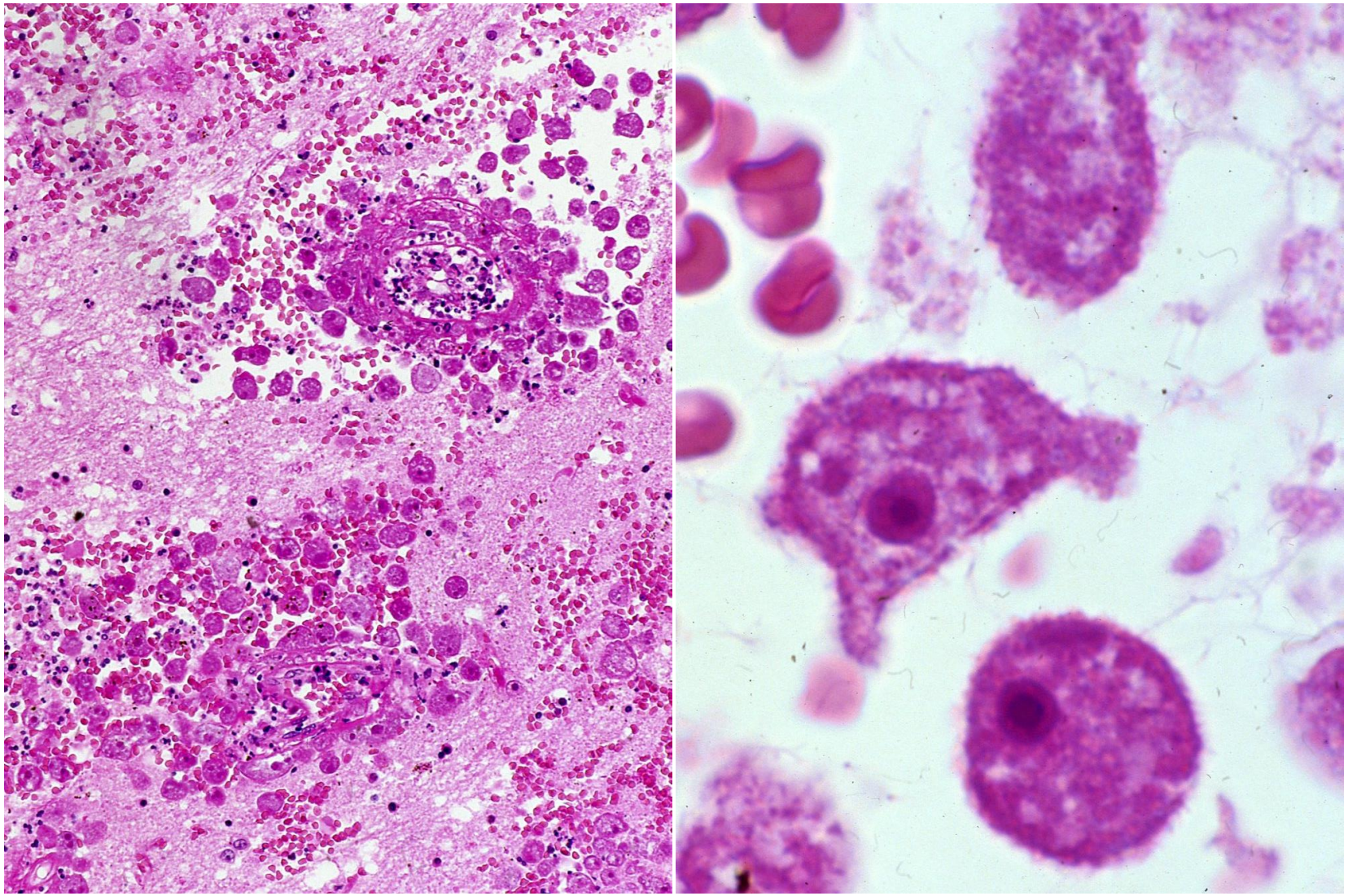
Meningococcal meningitis (acute purulent and hemorrhagic meningitis) in a 25-year-old female patient, who has traveled abroad. She complained of fever, headache and consciousness disturbance. The total clinical course was 3 days.



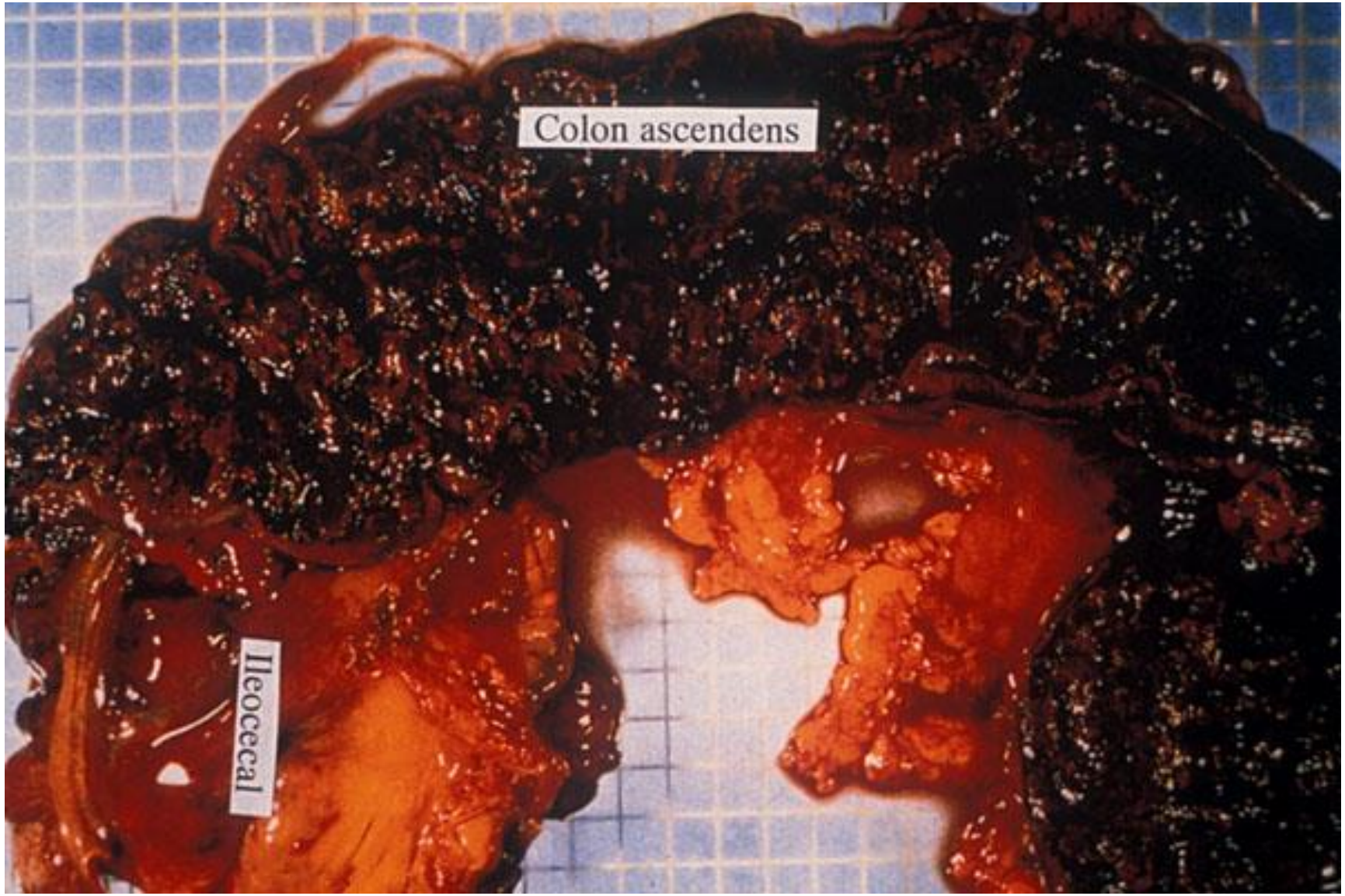
Waterhouse-Friderichsen's syndrome (bilateral adrenal hemorrhage causing acute adrenocortical failure). Meningococcal meningitis has provoked DIC and a shock state.



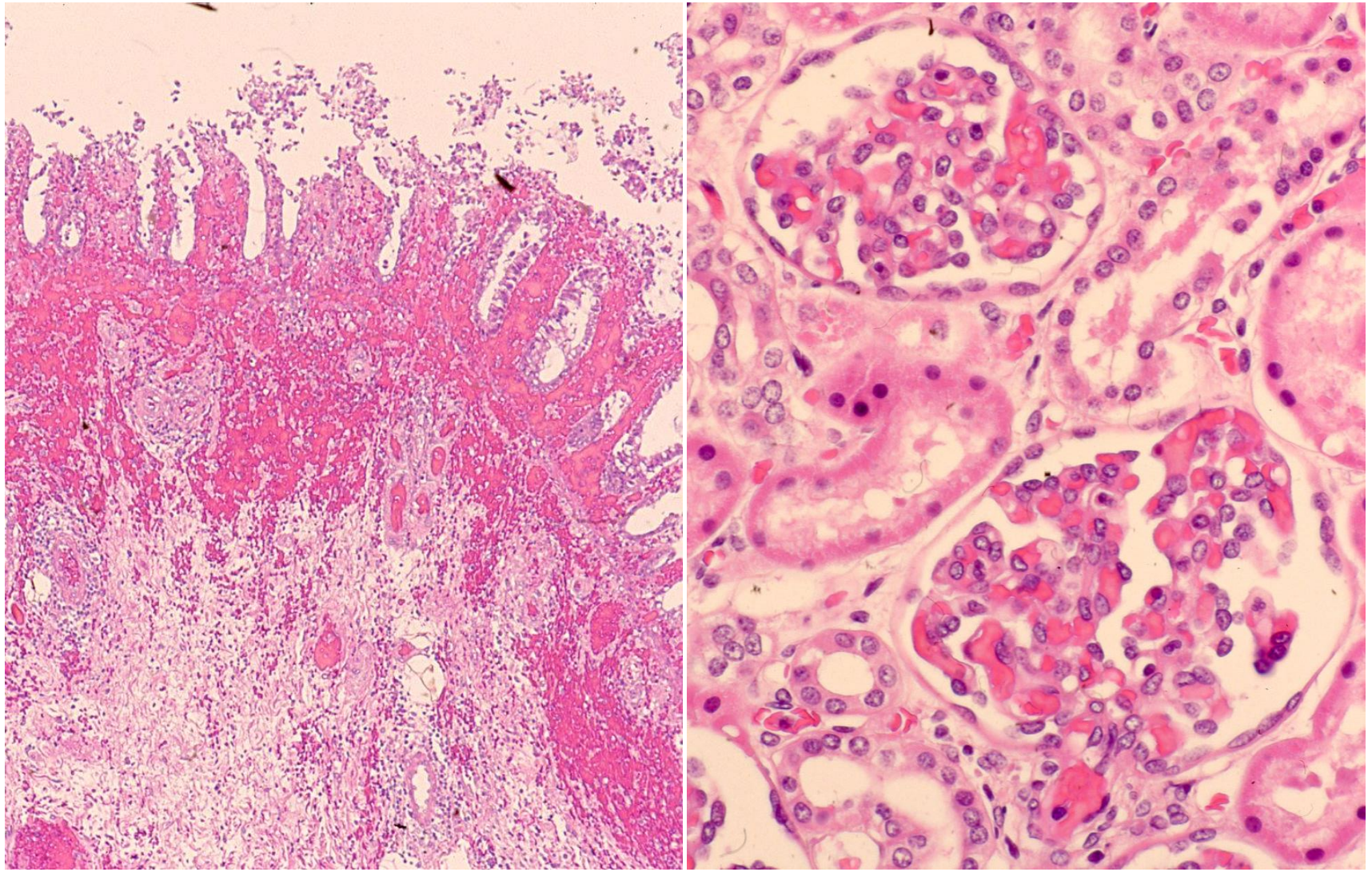
Two representative cocci causing acute bacterial meningitis (left: *Streptococcus pneumoniae*, right. *Neisseria meningitidis*, cerebrospinal fluid, Gram stain)



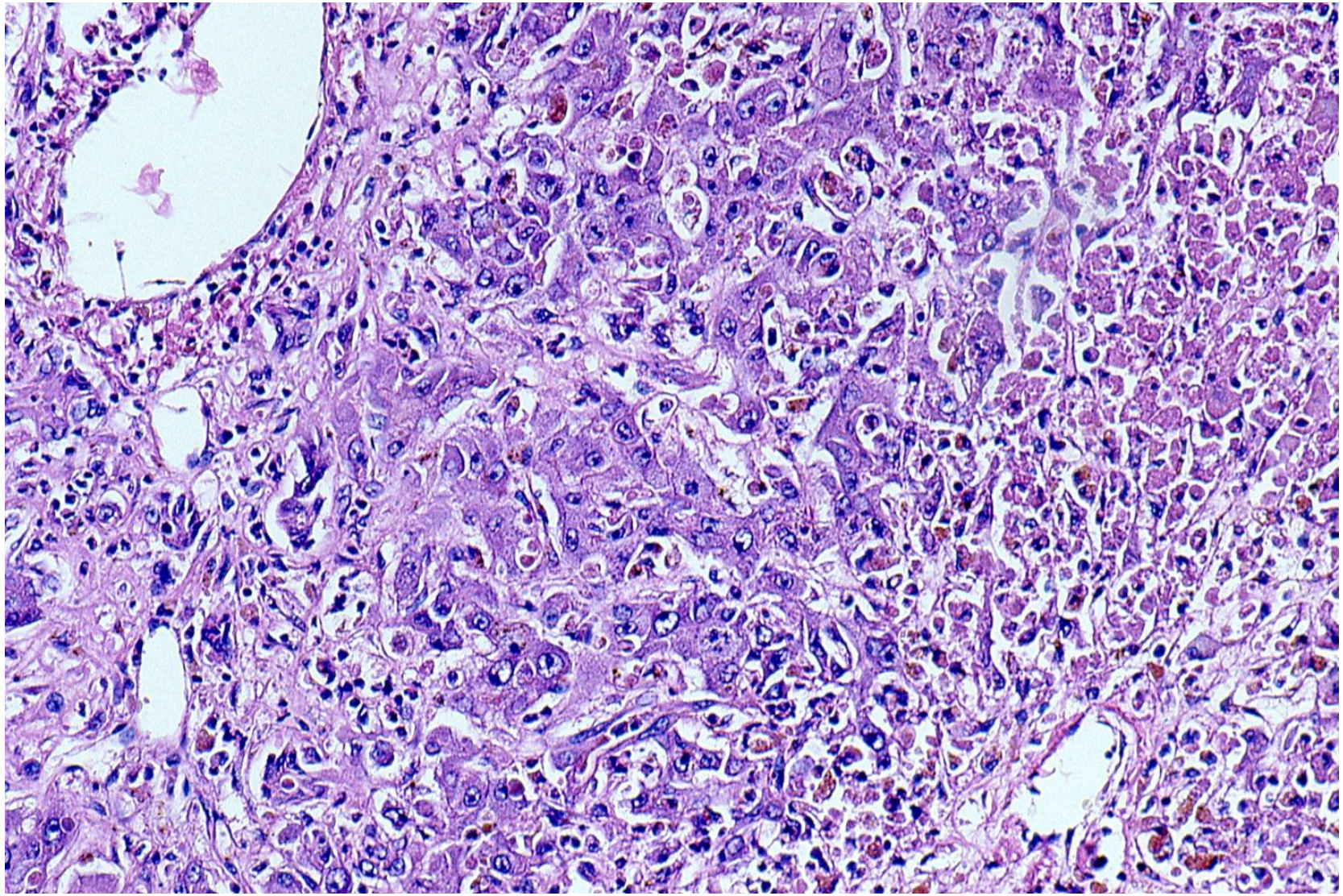
Naegleria fowleri, a free-living amoeba known as the “brain-eating amoeba”, invades the central nervous system, causing primary amoebic meningoencephalitis (an acute and fulminating infection). The protozoa reaches the nasal cavity by diving to the water pool in the tropical and substropical zone. The pathogens mainly grow in Virchow-Robin’ space. The presence of karyosome (round-shaped basophilic material) in the center of the nucleus is characteristic. H&E



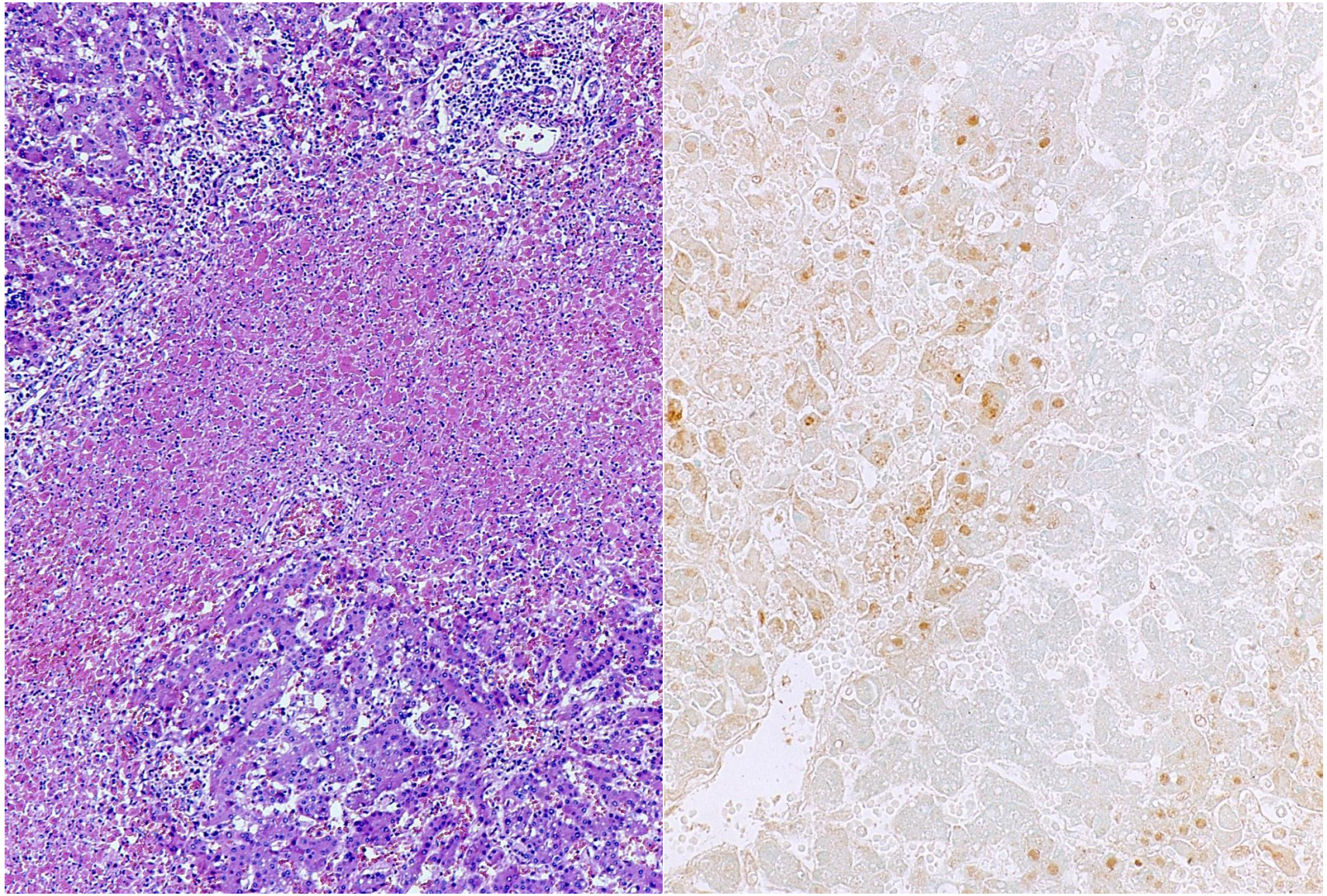
Gross appearance of lethal enterohemorrhagic *E. coli* O-157 infection in a 4-year-old girl. Shigatoxin has provoked bacillary dysentery-like diffuse hemorrhagic inflammation in the colorectum.



Lethal enterohemorrhagic *E. coli* O-157 infection in a 4-year-old girl (H&E). The colonic mucosa (left) reveals acute hemorrhagic necrosis. Hemorrhage is also noted in the submucosa. Shigatoxin has provoked hemolytic uremic syndrome (HUS) in the kidney (right). Microthrombotic obstruction of the glomerular capillary lumina is evident.



Fulminant hepatiis B. Acute HBV infection and acute exacerbation (flare-up or reactivation) of chronic HBV infection can cause fulminant hepatitis. Cytolytic CD8-positive T-cells infiltrate to destroy the HBV-infected hepatocytes. Severe hepatocyte loss causes acute hepatic failure. Of note is that immunostaining for HBs antigen is negative. H&E



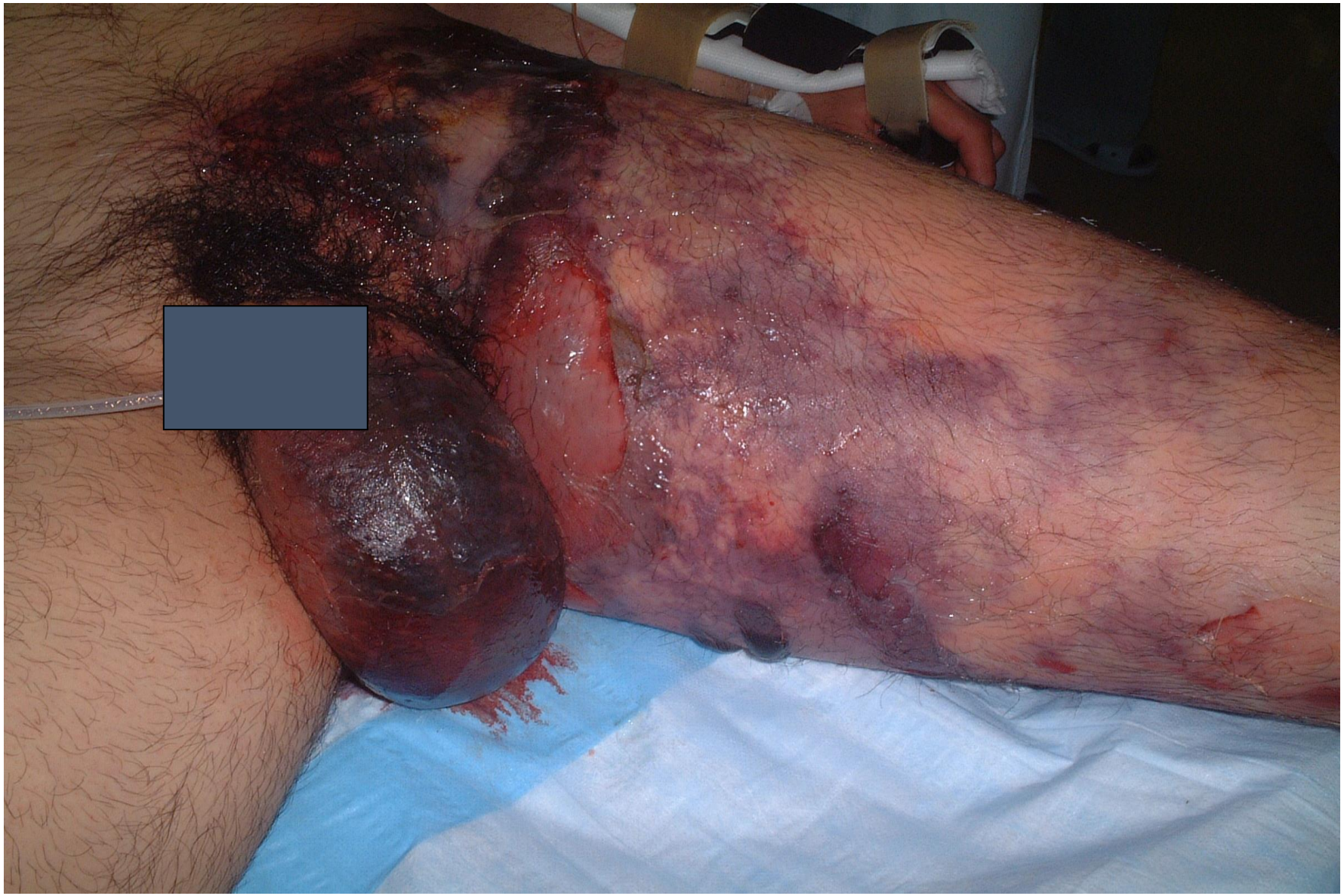
Neonatal HSV hepatitis (left: H&E, right: immunostaining for HSV-2 antigen). Disseminated neonatal HSV infection is featured by progressive multiple organ failure and a high mortality rate. Neonatal HSV infections are mostly acquired during delivery. Either HSV-1 or HSV-2 causes the fulminant infection, particularly fulminant hepatitis. Nuclear localization of HSV-2 is observed.

Flesh-eating bacterial infections

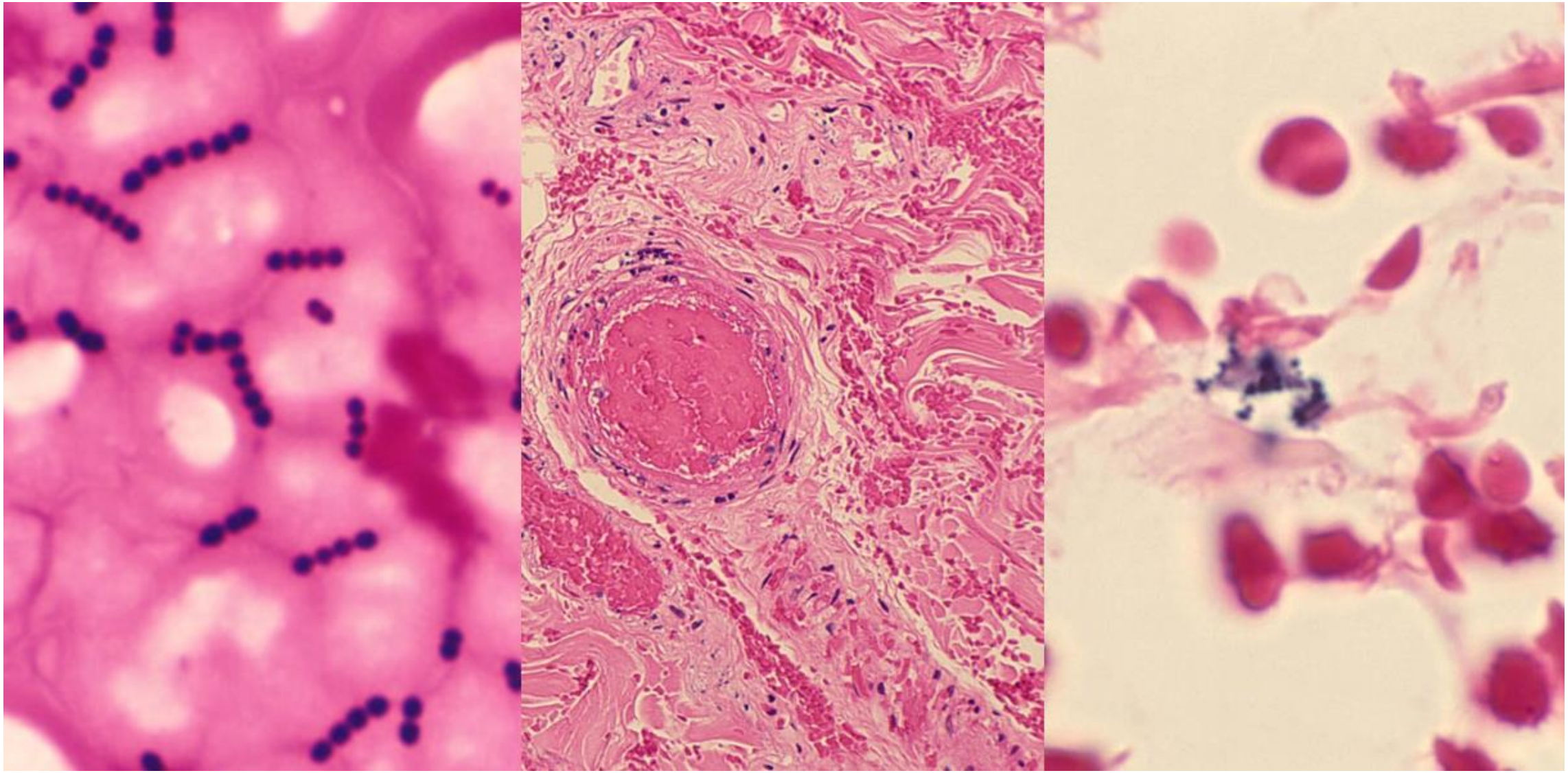
A variety of microbes cause progressive and often lethal gangrenous lesions in the soft tissue, particularly on the extremities. The mass media often call this frightening condition as “flesh-eating bacteria infection”. Three representative forms are included in this fulminant infection.

1) fulminant streptococcal infection in a healthy individual
2) *Vibrio vulnificus* infection in a cirrhotic patient
3) *Aeromonas hydrophila* infection in a diabetic patient

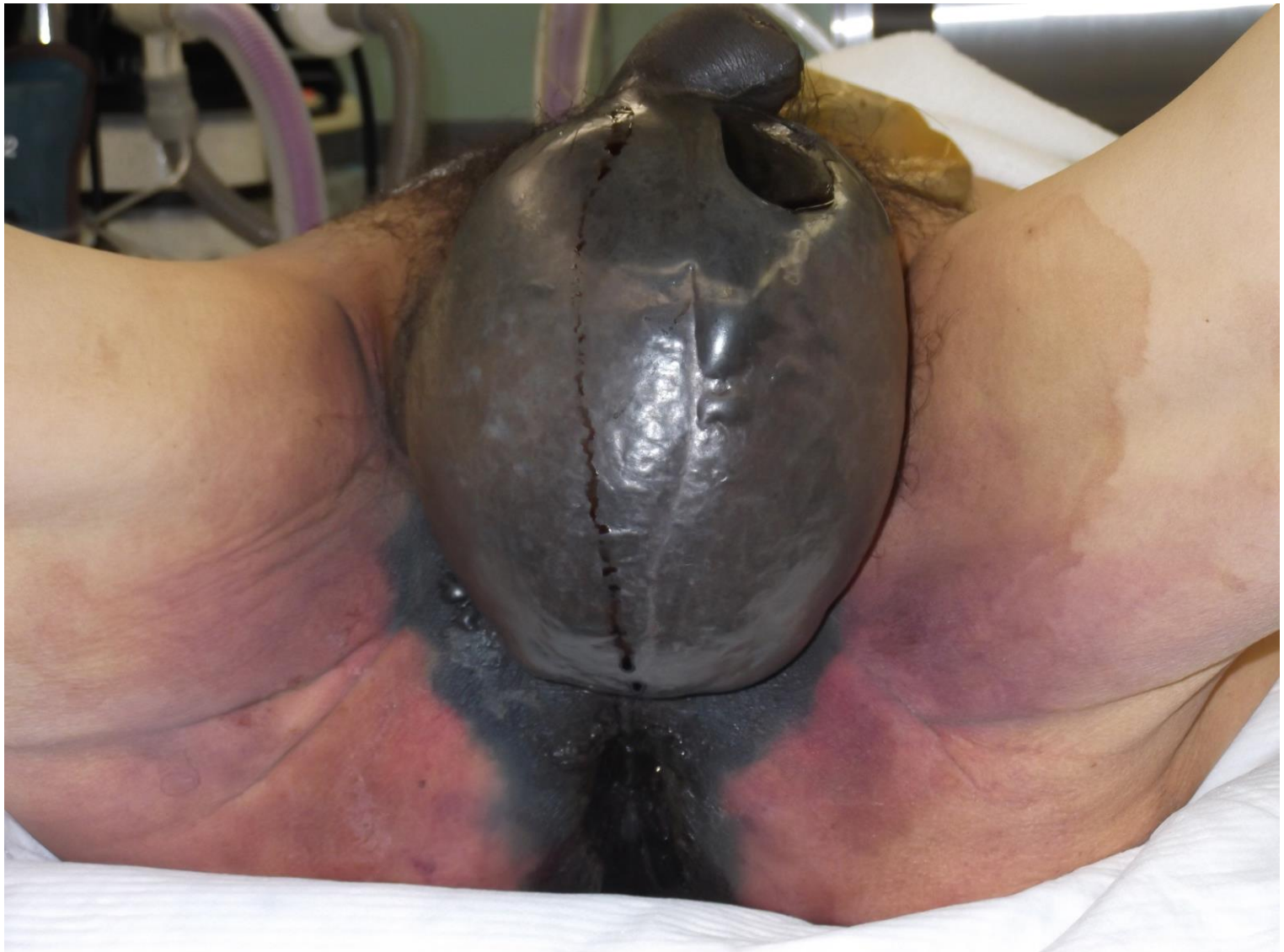
*A special form of fulminant infection is seen in the male scrotum, called Fournier’ gangrene. Fournier’s gangrene is often seen in diabetic patients.



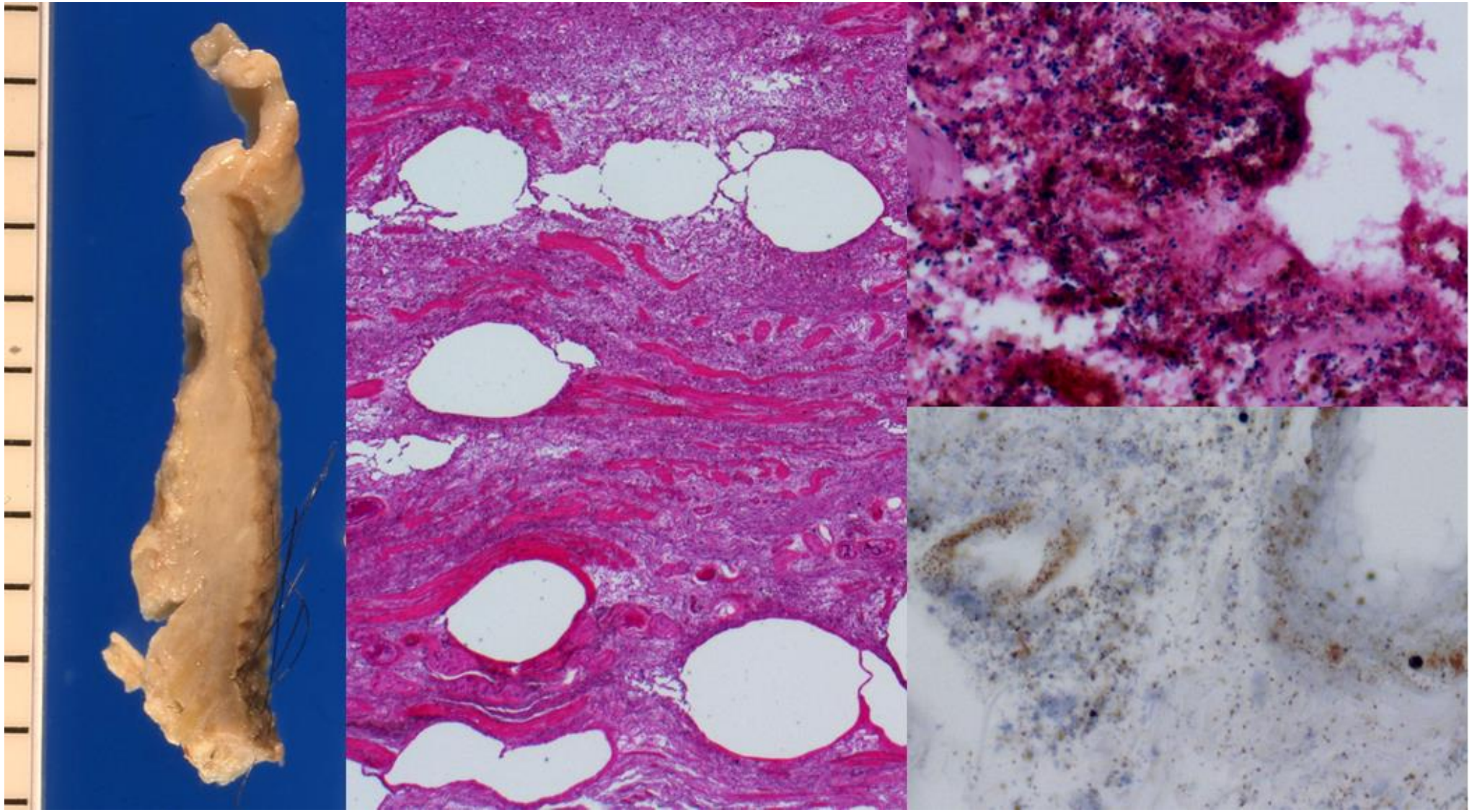
Gross appearance of fulminant streptococcal infection (streptococcal myonecrosis: so-called flesh-eating bacteria infection). The scrotum reveals Fournier's gangrene-type hemorrhagic necrosis (the penis spared), and the gangrenous lesion extends to the left groin and thigh.



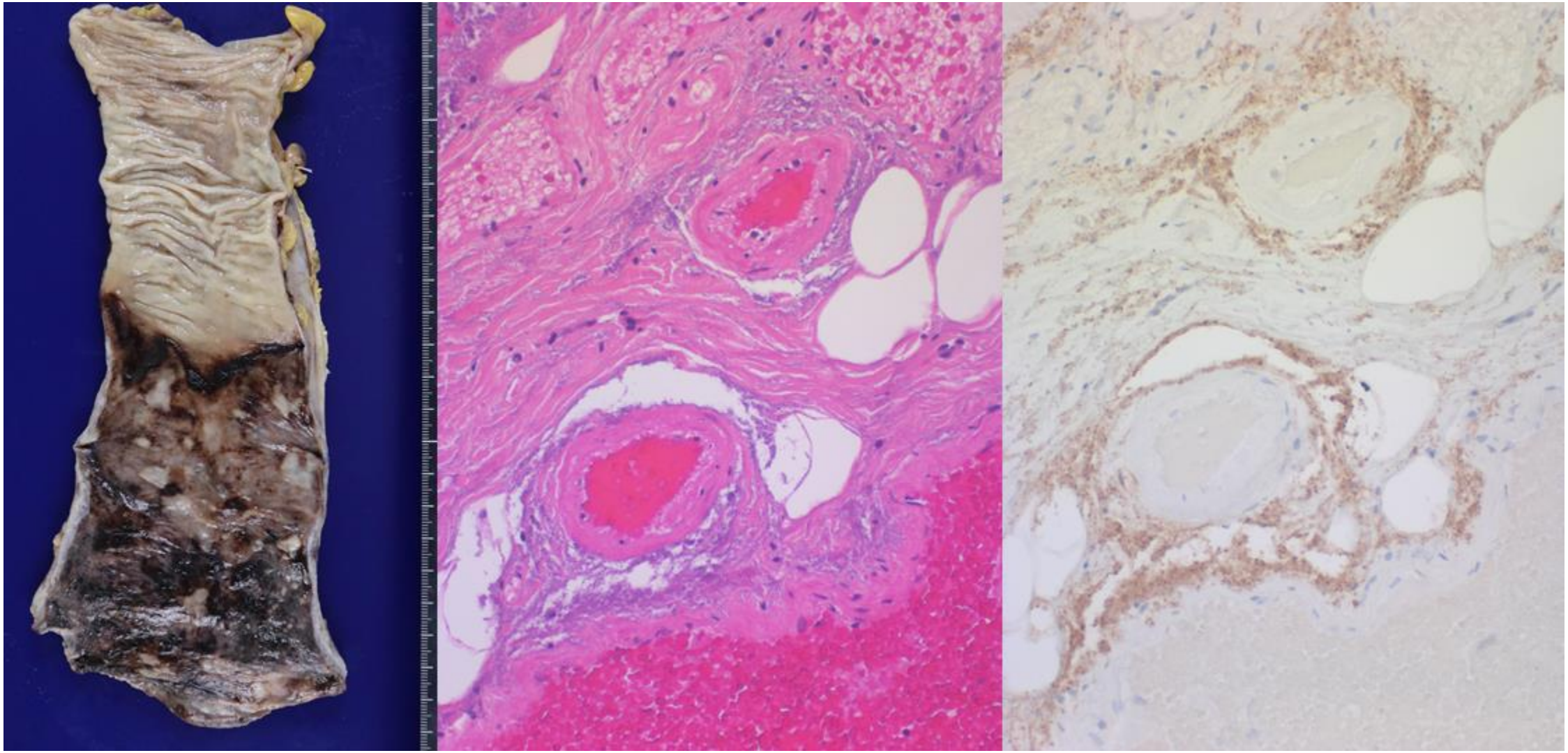
Fulminant streptococcal infection (streptococcal myonecrosis) (Giemsa, H&E and Gram). Numerous chained cocci are demonstrated in the cultured blood. In the emergency-amputated left leg reveals fresh thrombosis in small arteries, and the striated muscle fibers show coagulation necrosis. Colonies of Gram-positive cocci are scattered in the ischemic muscle tissue.



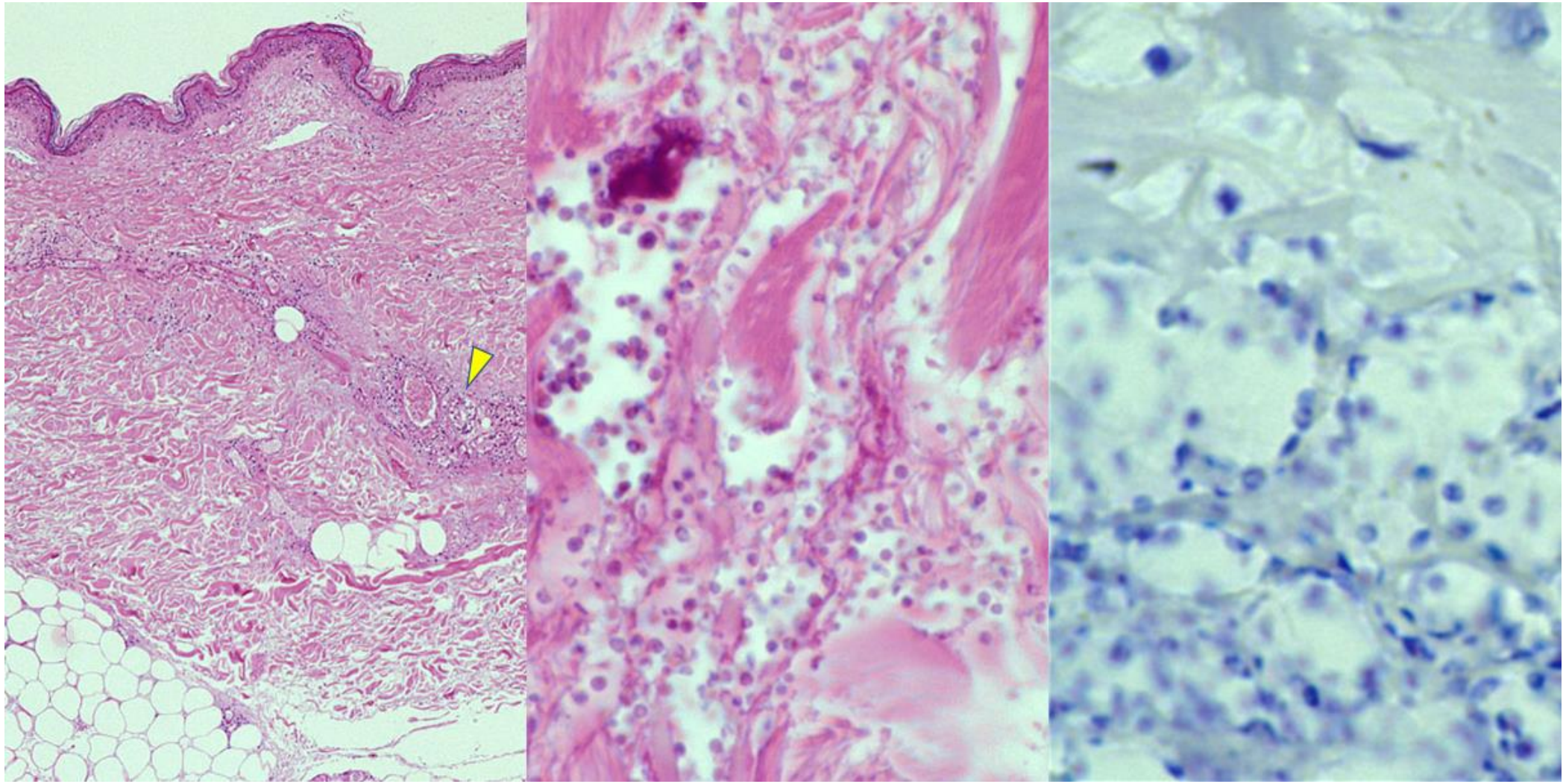
Gross appearance of Fournier's gangrene in a 64-year-old diabetic male patient. Massive hemorrhagic necrosis started from the scrotum and extended to the anus and penis. Marked black swelling of the scrotum is serious. The rapidly progressive gangrene caused death in the present case. Diabetes mellitus may accelerate the fulminant scrotal infection.



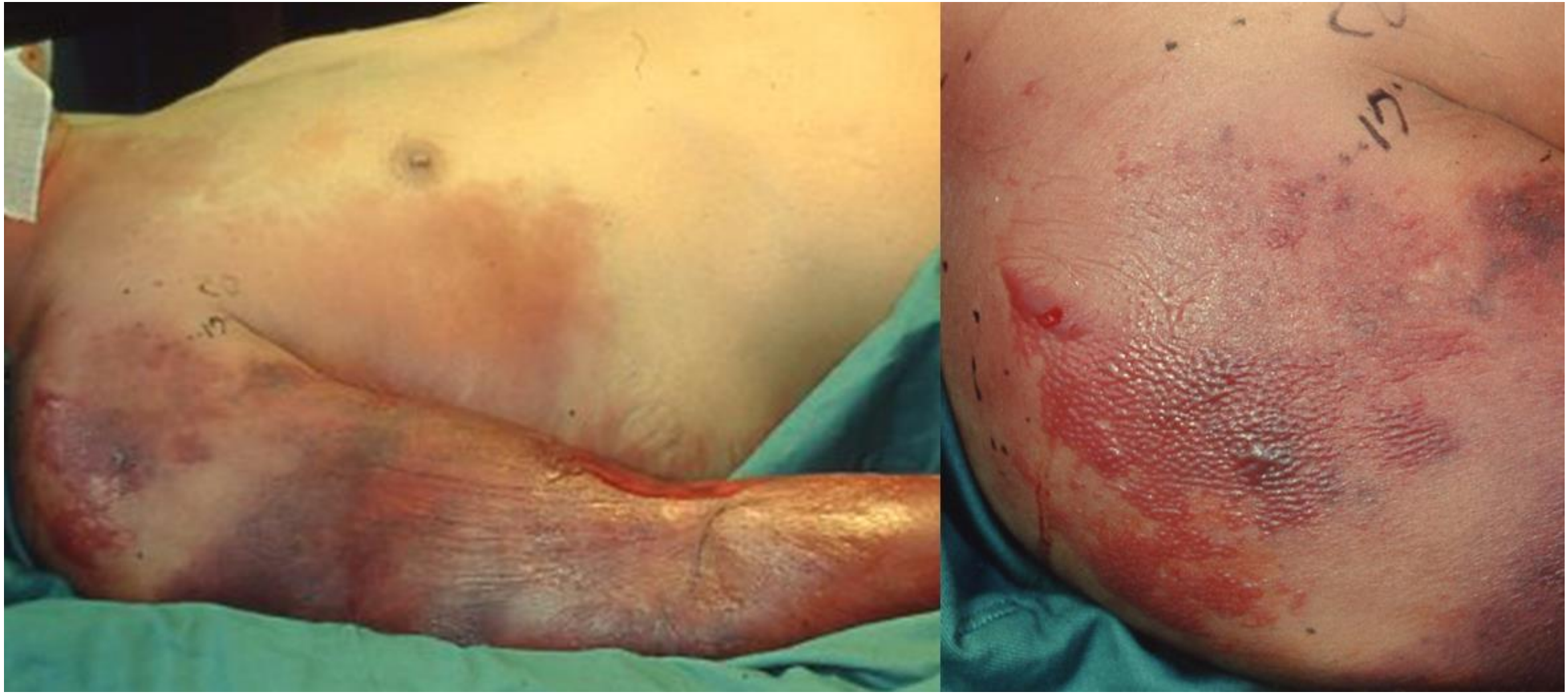
Fournier's gangrene (gross, H&E, Gram and immunostain). A debridement specimen discloses massive transmural necrosis of the scrotal tissue. Gas bubbles are scattered in the heavily infected necrotic tissue. Gram-positive cocci are immunoreactive for streptococcal antigens. This case represents fulminant streptococcal infection with gas formation (non-clostridial gas gangrene).



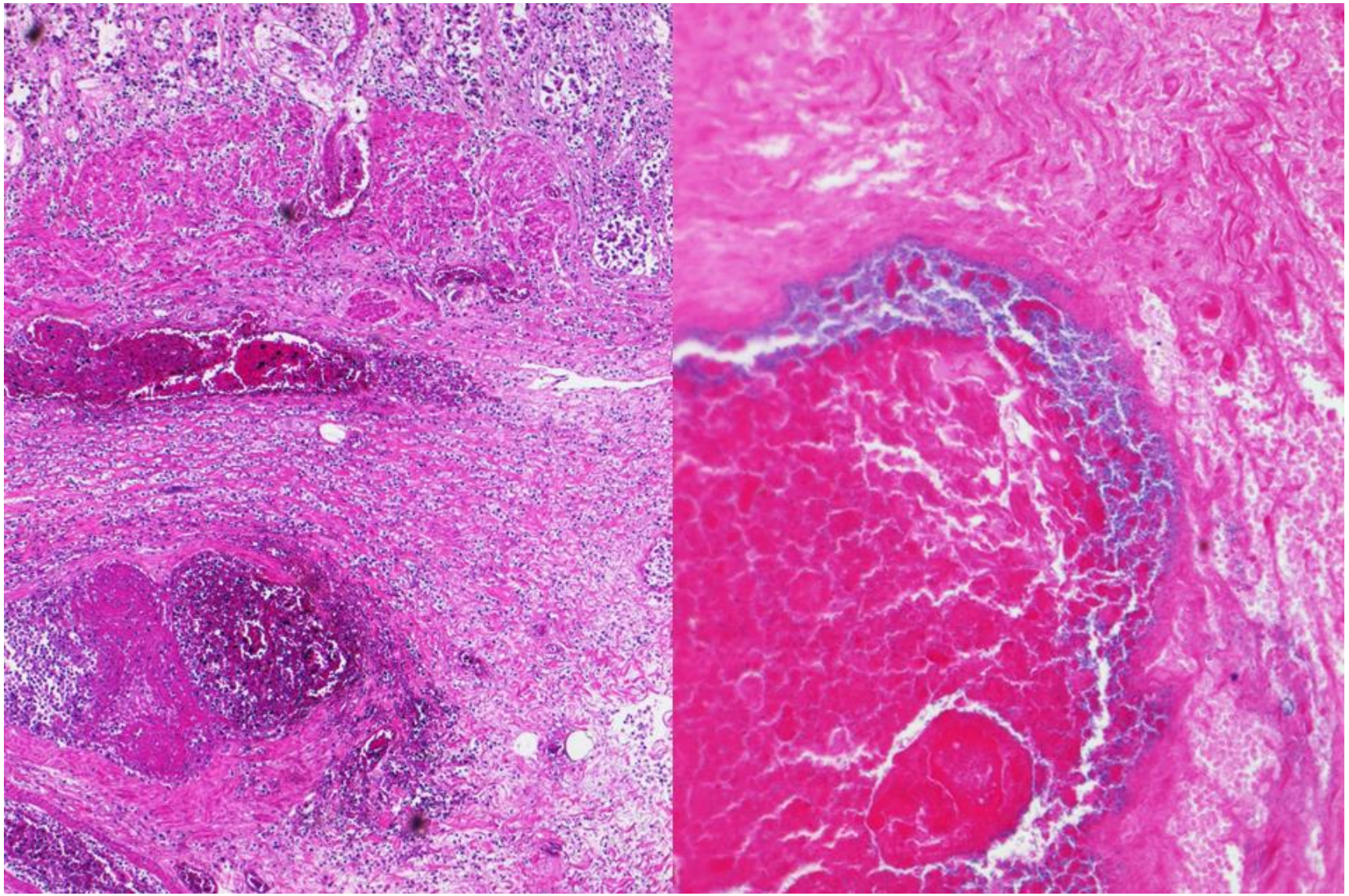
Fournier's gangrene of the rectum (gross, H&E and immunostain). Transmural necrotic and gas-forming gangrenous inflammation is seen in the lower part of the rectum in a 61-year-old female, suffering from myelodysplastic syndrome. Gram-negative rods are immunoreactive for *E. coli*-related lipopolysaccharide.



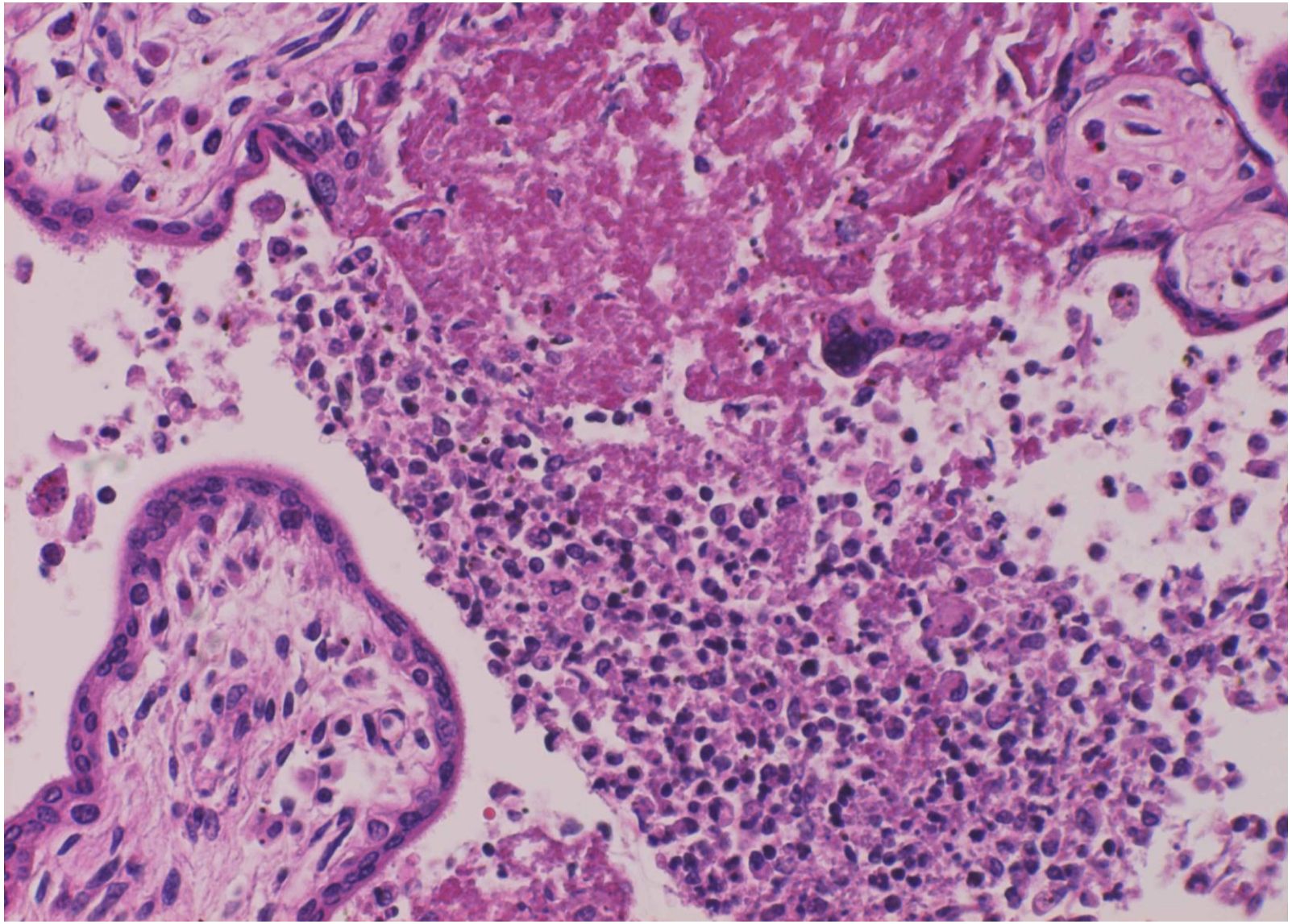
Vibrio vulnificus infection in a cirrhotic male patient (H&E and Giemsa). In a biopsy specimen taken in an emergency suite, perivascular cuffing by infected microbes is observed around small vessels and sweat glands (arrowhead) in the deep dermis through subcutis. Coccoid transformation is recognized in H&E and Giemsa stained preparations. Inflammatory reaction is sparse. Gram stain showed negativity.



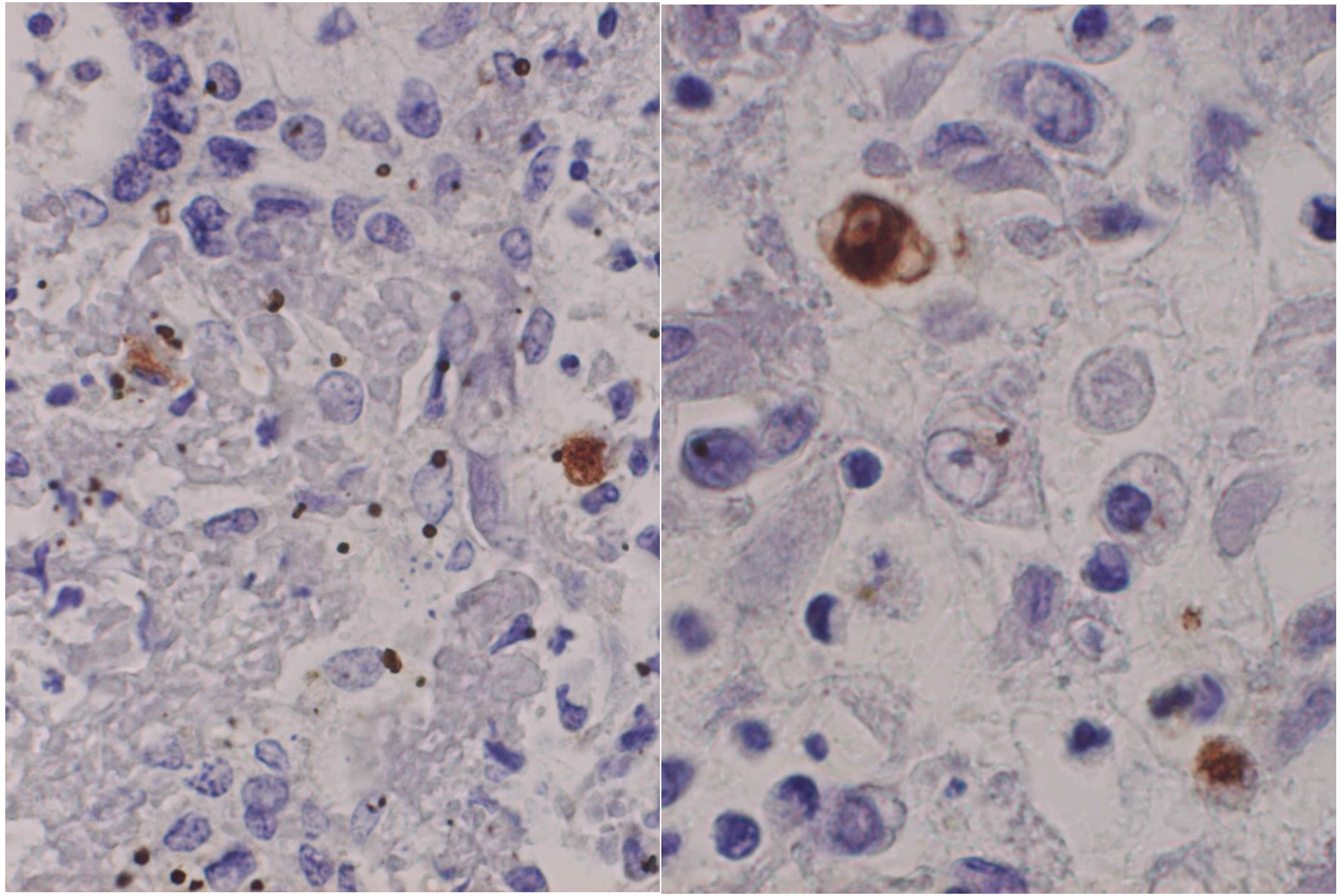
Gross appearance of *Aeromonas hydrophila* infection in a diabetic male patient. Lethal gangrene is observed on the right upper arm. Vesicular skin change is evident. Autopsy confirmed that septicemia caused abscess formation in multiple organs.



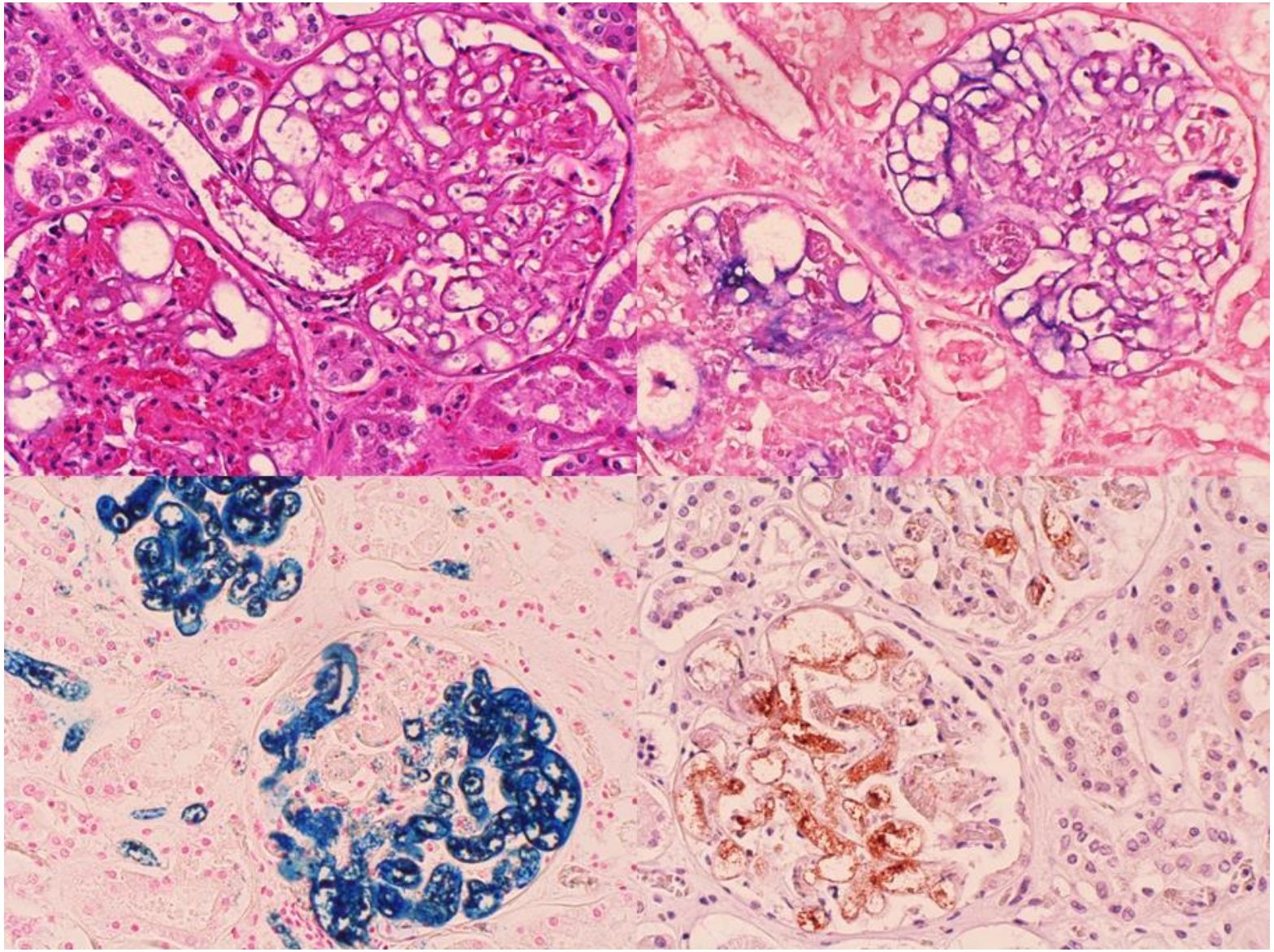
Aeromonas hydrophila infection (H&E). Septic and necrotic/hemorrhagic lesions are seen in the rectal submucosa (left) and epididymis (right). Septic embolism is noted in the rectum, while Gram-negative rods are clustered around the dilated and thrombosed vascular structure in the epididymis, where inflammatory reaction is sparse.



Lethal and fulminant pneumococcal infection (H&E). In this pregnant young female patient with a history of splenectomy, the placenta was the entry of Gram-positive cocci. Small abscesses are scattered among the placental villi. Of note is that splenectomy accelerates fulminant pneumococcal infection.



Lethal and fulminant pneumococcal infection (immunostain for pneumococcal antigens). In this young pregnant female with a history of splenectomy, the cocci with immunoreactivity of pneumococcal antigens are identified in the cytoplasm of neutrophils in the small abscess among placental villi.

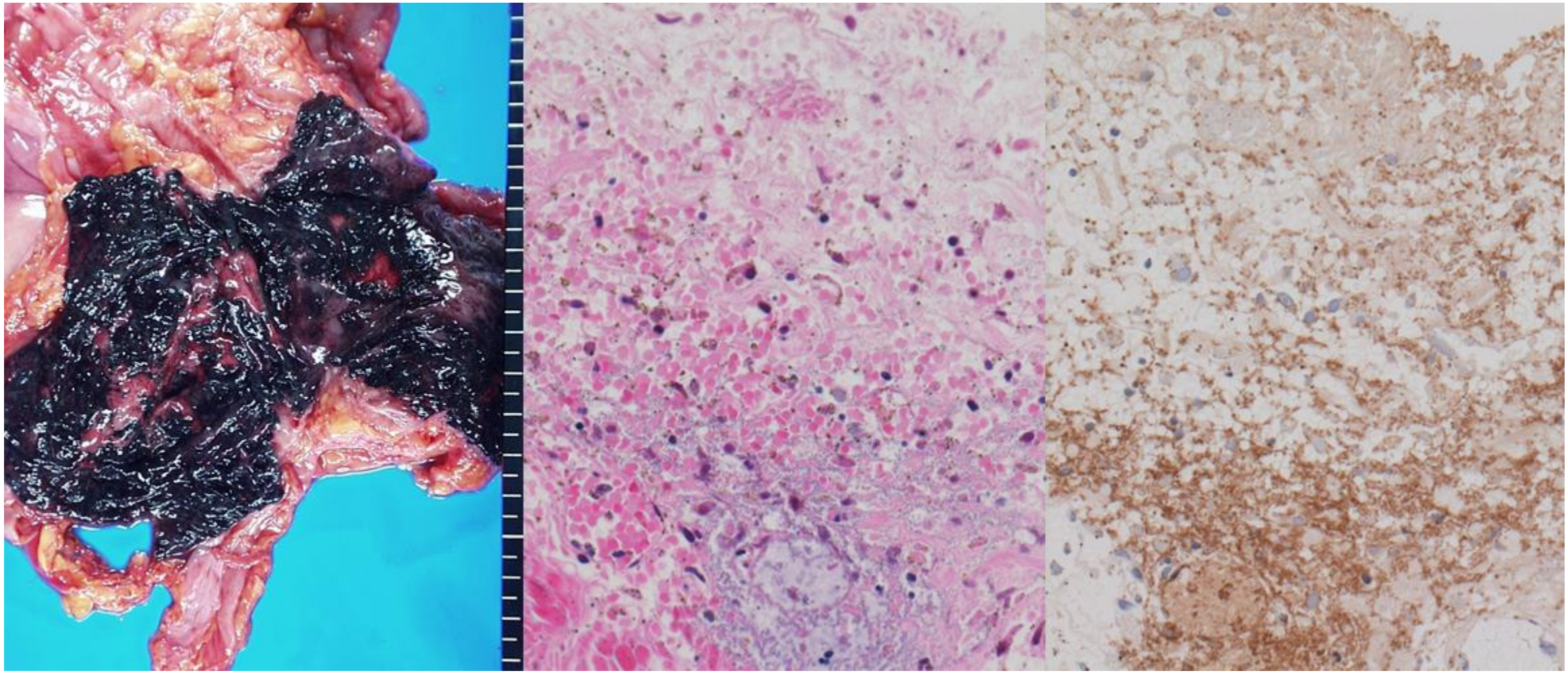


Fulminant pneumococcal infection (H&E, Gram, colloidal iron and immunostain). Systemic spread of capsule-forming Gram-positive cocci drastically killed the patient. The glomeruli show septic embolism by Gram-positive cocci with colloidal iron-positivity (stained blue) and pneumolysin immunoreactivity (stained brown).

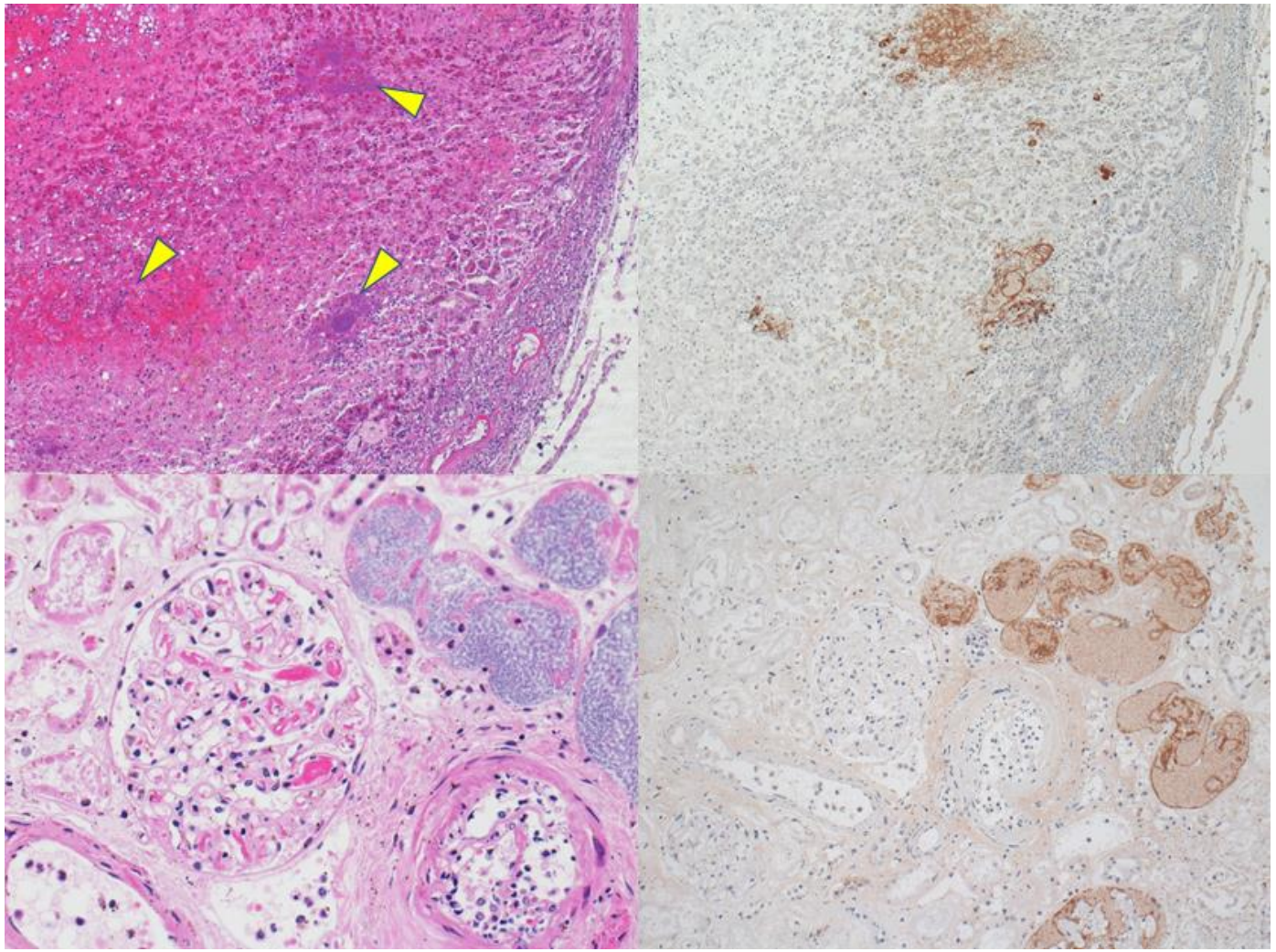
Fulminant group A streptococcal infection without gangrene in the extremities

Five autopsy cases of fulminant group A streptococcal infection without gangrene in the extremities are presented. The clinical course of the fulminant illness was short (2-4 days). One pathological autopsy case was aged (86-years-old), and hemorrhagic cystitis was observed. The other four forensic autopsy cases were young (24-38 years-old) with the mean age of 32, and the primary infective lesions were located in the postpartum endometrium, tonsil and bronchus (2 cases). Systemic coccal dissemination with poor neutrophilic reaction was seen in two of five cases. Bilateral renal cortical necrosis was noted in three cases (including two with bacterial embolism). Hemophagocytosis, probably resulting from hypercytokinemia, was characteristic in three cases without bacterial embolism. Gram-positive cocci colonizing the hemorrhagic and necrotizing lesions were consistently immunoreactive for streptococcal antigens and Strep A (a carbohydrate antigen on group A streptococci). Neutrophilic reaction was mild in the primary infected foci. Clinicians should note that fulminant streptococcal infection (streptococcal toxic shock syndrome) in young and immunocompetent patients may not be associated with gangrene in the extremities. Autopsy prosecutors (diagnostic and forensic pathologists) must recognize the difficulty in making an appropriate autopsy diagnosis, particularly when bacterial embolism is not associated.

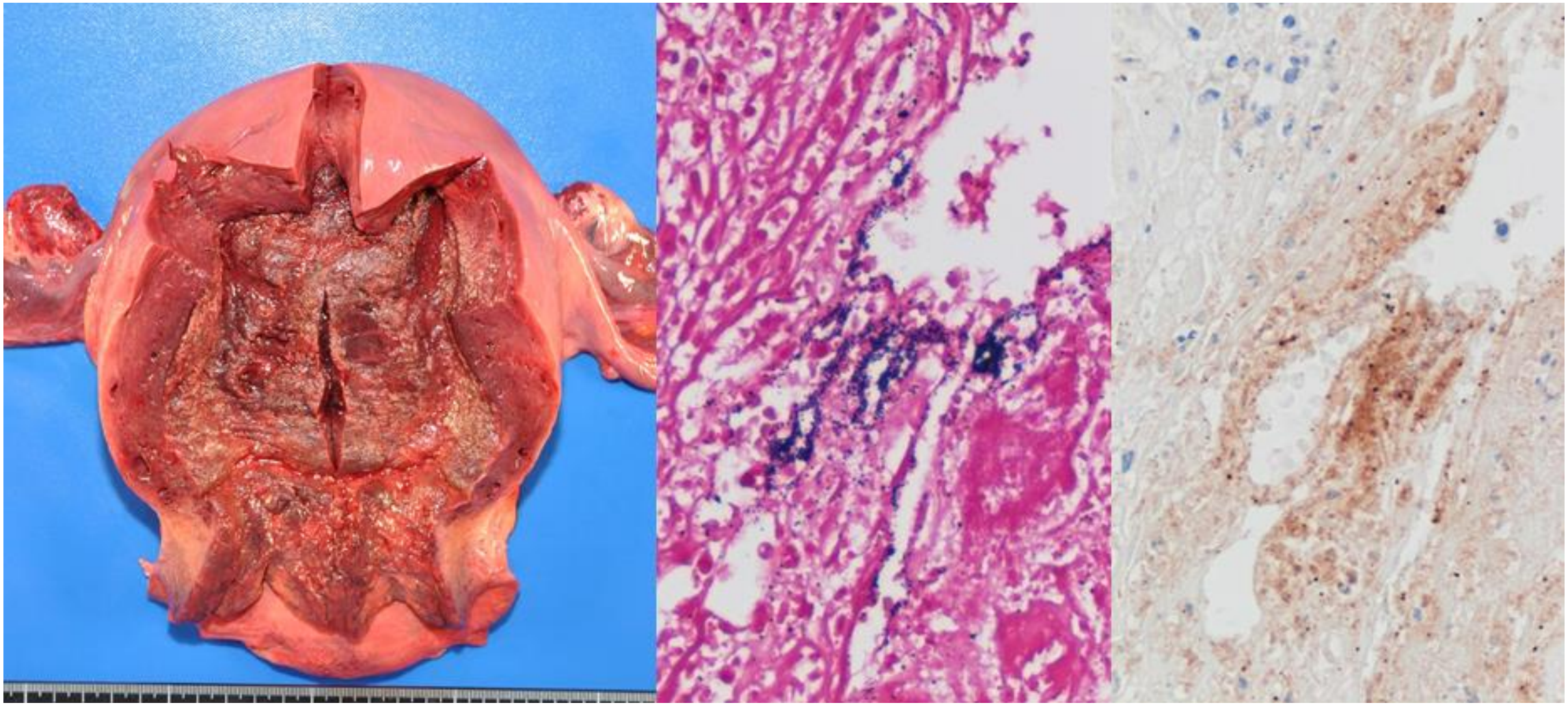
Ref.: Kato S, et al. Fulminant group A streptococcal infection without gangrene in the extremities: analysis of five autopsy cases. Pathol Int 2018; 68: 419-424. doi: 10.1111/pin.12678



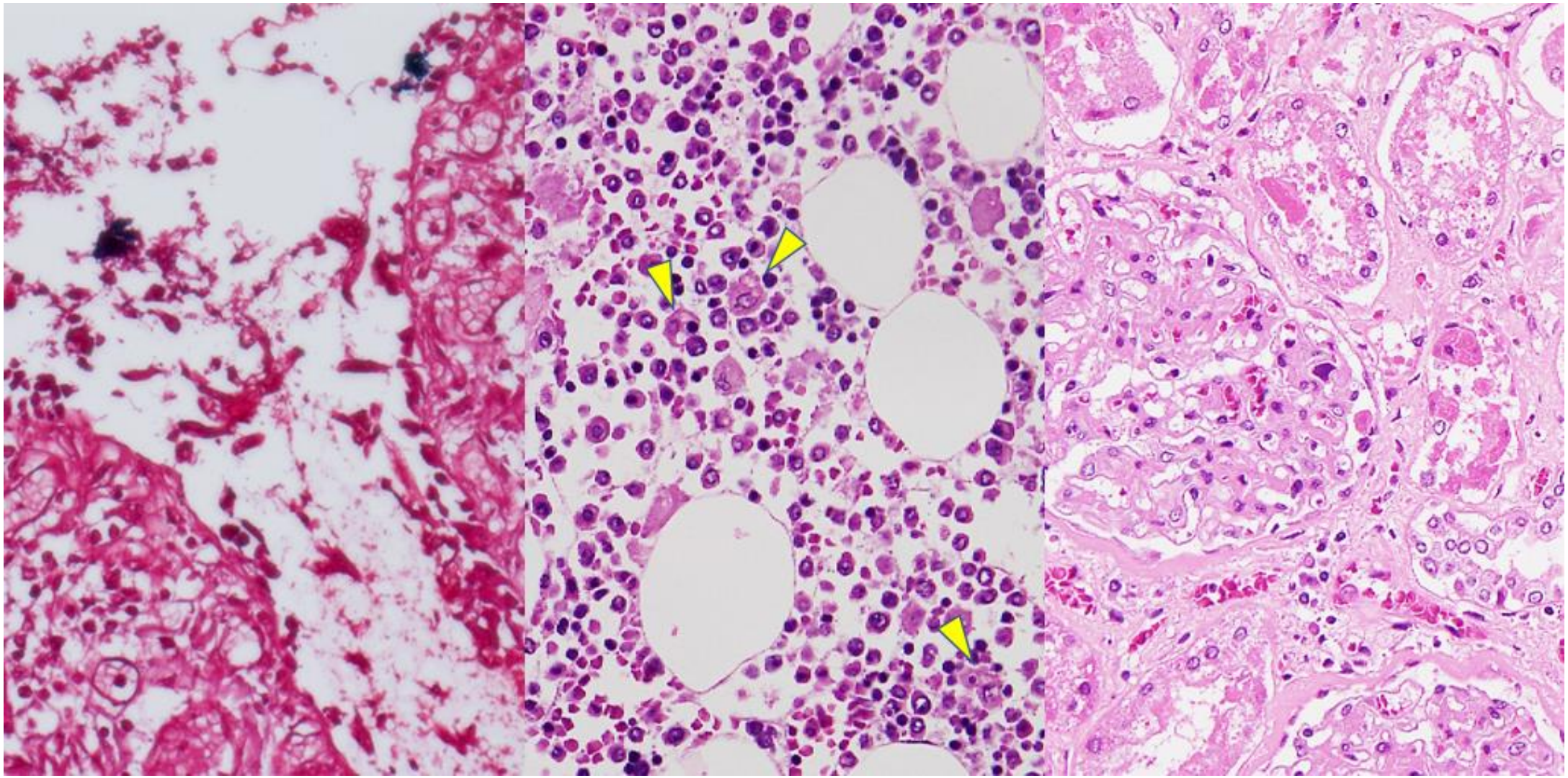
Fulminant streptococcal infection without gangrene of the extremities (1). Massive hemorrhagic cystitis in an 86-year-old female (gross, H&E and immunostain). The cocci infected in the eroded bladder wall are clearly immunoreactive for streptococcal antigens. Systemic streptococcal spread with Waterhouse-Fridrichsen's syndrome and bilateral renal cortical necrosis killed the patient.



Fulminant streptococcal infection without gangrene of the extremities (1). Waterhouse-Friderichsen's syndrome and bilateral renal cortical necrosis are observed in the case of hemorrhagic cystitis (adrenal and kidney; H&E and immunostain). The adrenal glands show massive hemorrhagic necrosis. Septic streptococcal emboli (arrowheads) are seen in capillary vessels of the adrenal cortex. The kidney shows bilateral cortical necrosis with marked fibrin thrombosis in the glomeruli and streptococcal colonization in the renal tubules (streptococcal antigen-positive).



Fulminant streptococcal infection without gangrene of the extremities (2). Necrotizing endometritis is seen in the autopsied puerperal uterus of a 38-year-old female (gross, Gram, immunostain). The eroded postpartum endometrium four days after delivery is colonized by Gram-positive cocci with positive immunoreactivity for Strep A, a carbohydrate antigen of group A Streptococcus. Neutrophilic reaction is limited to the endometrium. This condition can be categorized in puerperal fever.



Fulminant streptococcal infection without gangrene of the extremities (3) (bronchus: Gram, bone marrow and kidney: H&E). Local infection of Gram-positive cocci on the bronchus (streptococcal erosive bronchitis) has provoked hypercytokinemia and disseminated intravascular coagulopathy. Activated hemophagocytic macrophages (arrowheads) are noted in the bone marrow. The kidney shows acute tubular necrosis. No septic embolism is seen in the present case.

Septicemic zoonotic infections

1) *Capnocytophaga canimorsus* septicemia

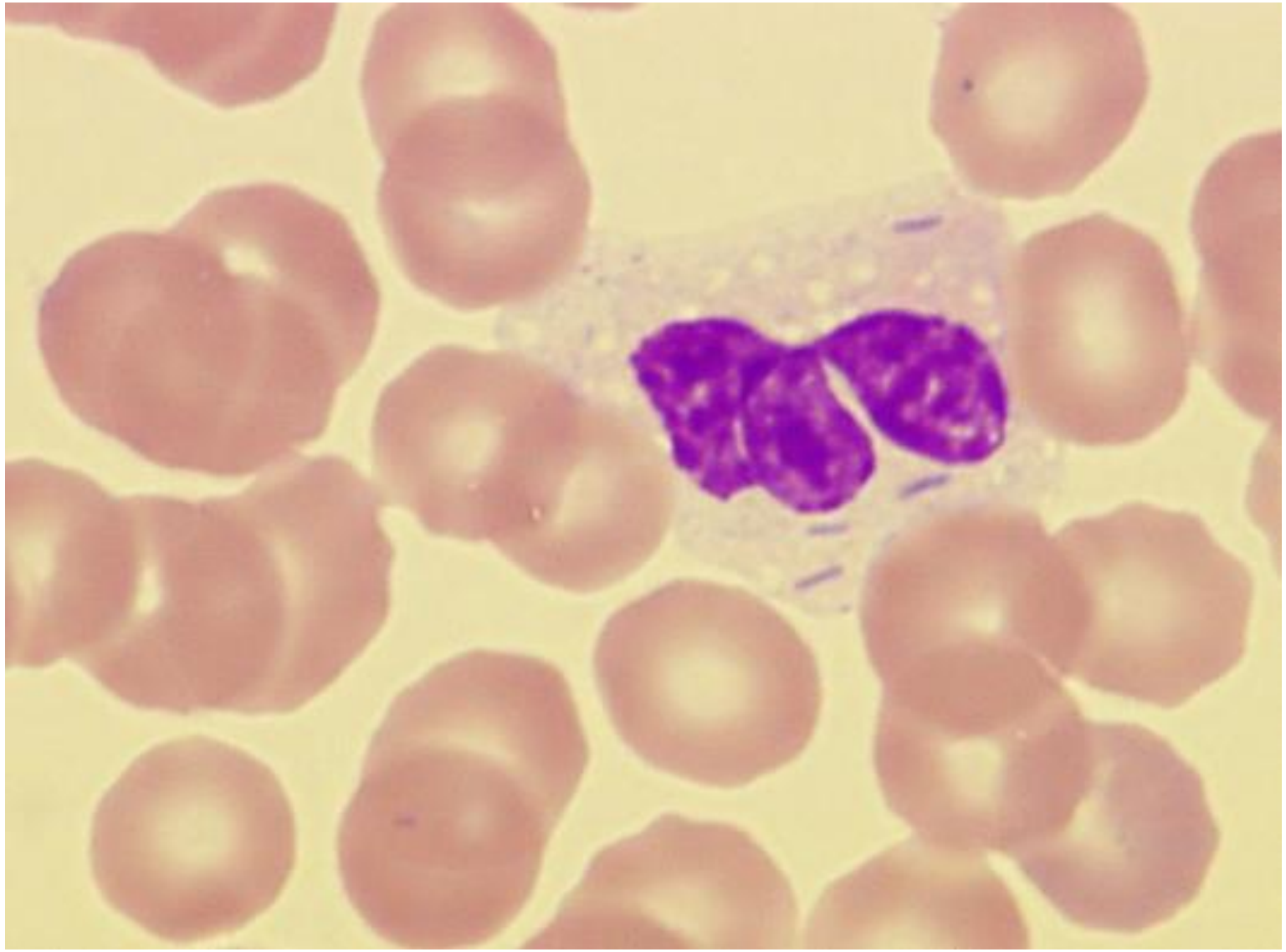
Capnocytophaga canimorsus, Gram-negative rod, is a normal commensal bacterium of the oral cavity of the dog and cat. Five days after pet dog bite, the immunocompetent male patient aged at 60 complained of numbness, vomiting and gait disturbance. The infection rapidly progressed to septic shock, and the patient died six hours after hospitalization. Neutrophils in the peripheral blood smear were infected with rods. At autopsy, bilateral renal cortical necrosis, bilateral adrenocortical hemorrhage and hemophagocytosis were observed, together with bacterial dissemination.

Ref.: Nakayama R, et al. *Capnocytophaga canimorsus* infection led to progressively fatal septic shock in an immunocompetent patient. Acute Med Surg. 2022; 9(1): e738. doi: 10.1002/ams2.738

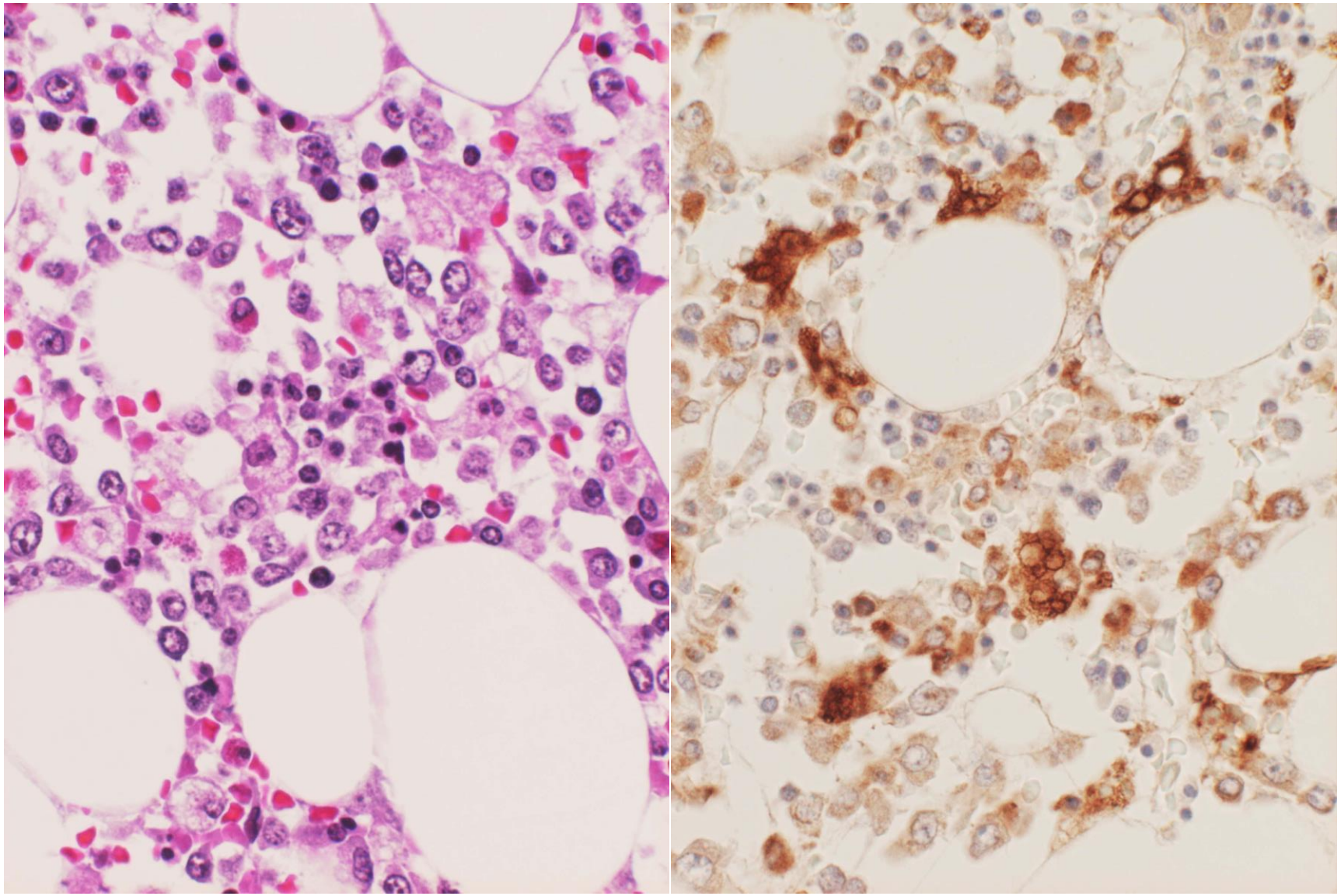
2) *Streptococcus suis* septicemia

Streptococus suis, Gram-positive coccus, is a commensal bacterium of healthy pigs. The pigs carry *S. suis* in the nasal cavity, tonsils, and upper respiratory, genital and alimentary tracts. Fulminant human infection of *S. suis* such as septicemia, arthritis and meningitis may occur mainly in pig farmers/rearers. Numbers of cases have been recorded mainly in Southeastern Asia. A Japanese immunocompetent male pig farmer aged at 30's complained of sudden fever, vomiting, consciousness disturbance and septicemic shock. The disease rapidly progressed to kill the patient in two days. The peripheral blood smear showed a few Gram-positive diplococci. At autopsy, bilateral adrenocortical hemorrhage, hemophagocytosis and acute tubular necrosis of the kidney were observed.

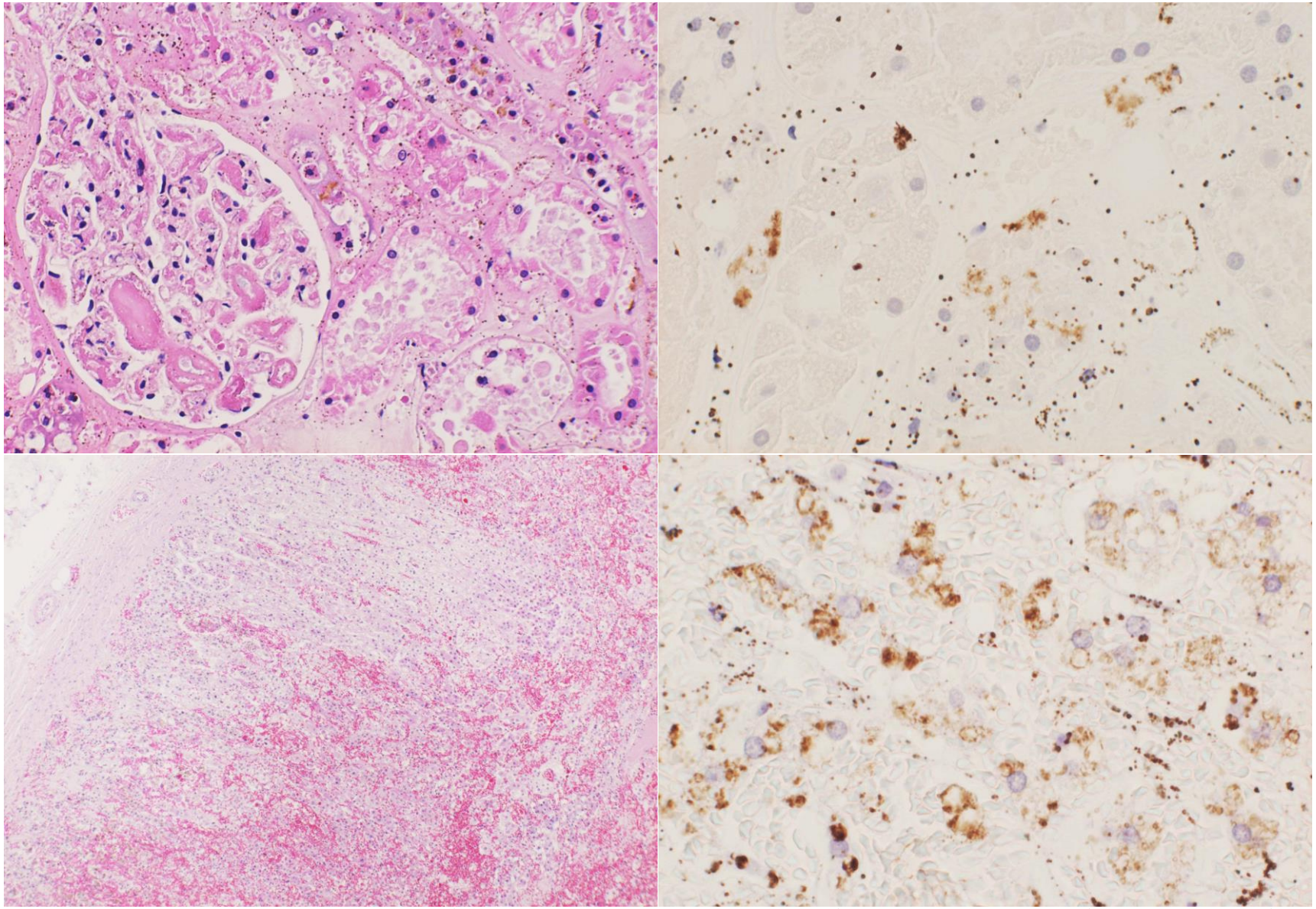
Ref. Hughes JM, et al. Streptococcus suis: an emerging human pathogen. Clin Infect Dis 2009; 48(5): 617–625. doi: 10.1086/596763



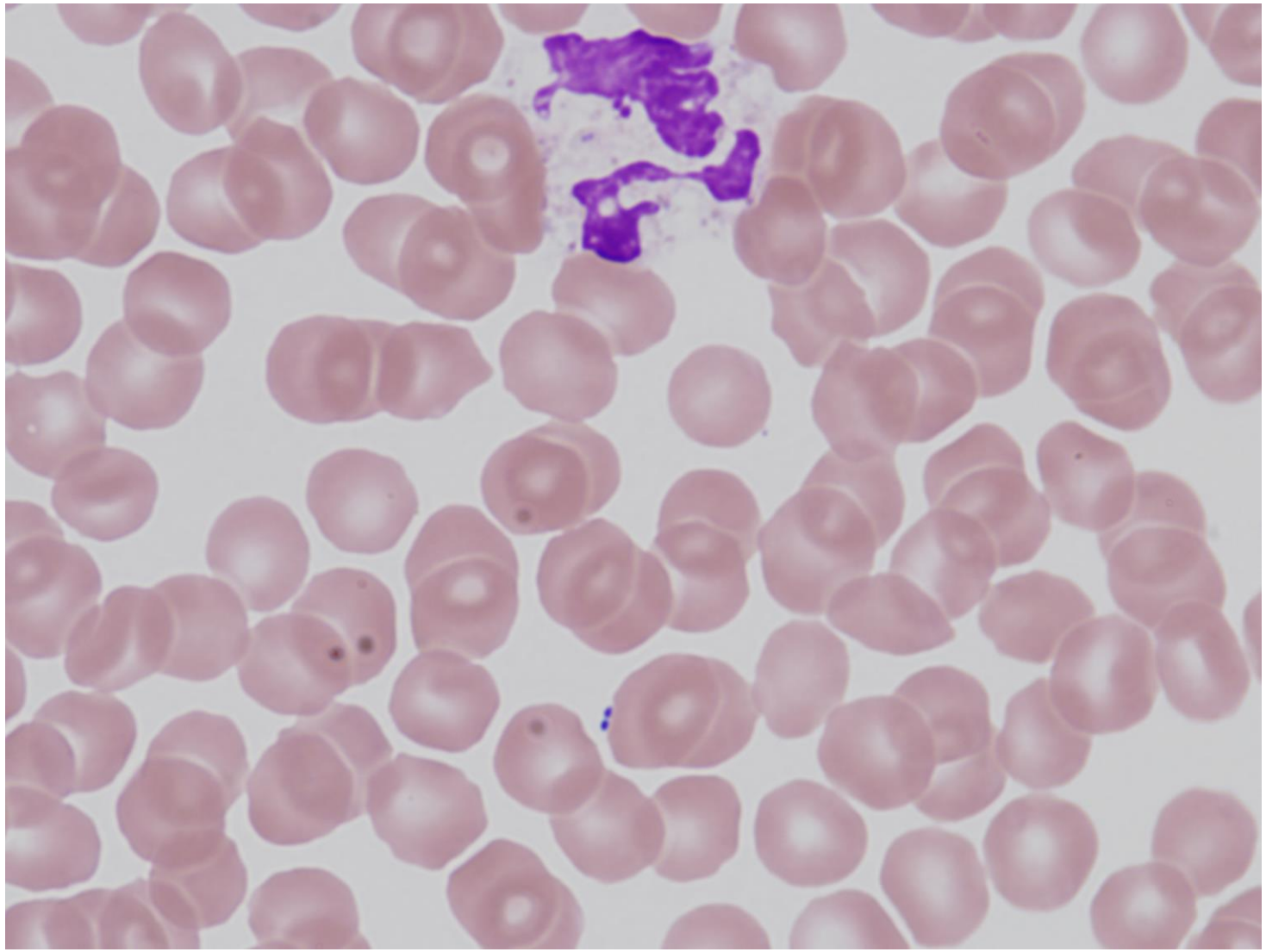
Peripheral blood smear in *Capnocytophaga canimorsus* septicemia caused by pet dog bite (May-Giemsa). A neutrophil phagocytizes large-sized rods in the cytoplasm.



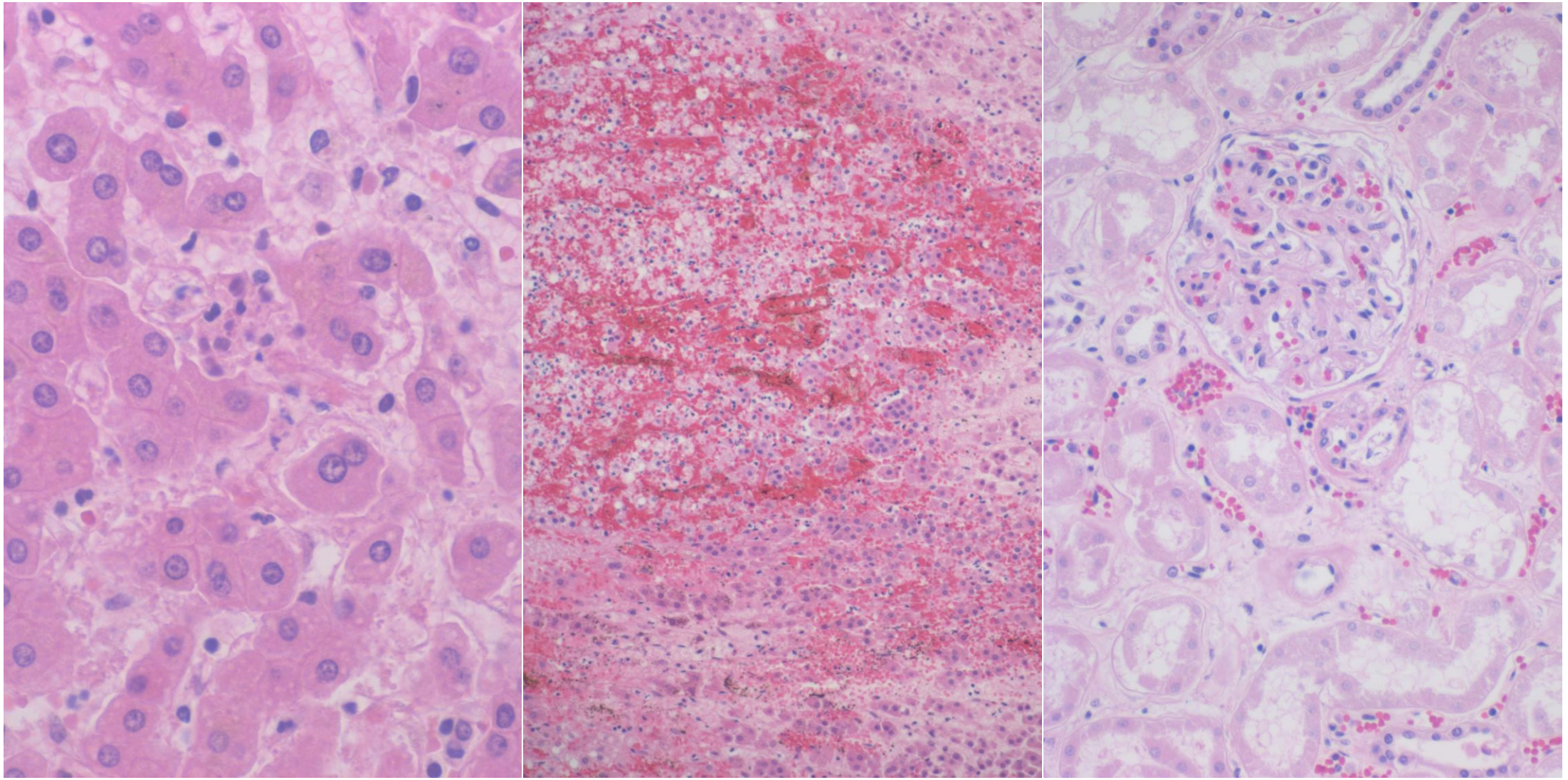
Capnocytophaga canimorsus septicemia. At autopsy, hemophagocytic macrophages are seen in the bone marrow (left: H&E). CD68 immunostaining demonstrates the hemophagocytic macrophages (right).



Capnocytophaga canimorsus septicemia (H&E and immunostain). The kidney (top panels) reveals bilateral cortical necrosis with fibrin thrombosis in the glomeruli. The adrenal (bottom panels) discloses bilateral cortical hemorrhage with Waterhouse-Friderichsen's syndrome. Immunostaining using antisera against *Treponema pallidum* (top) and *E. coli* (bottom) cross-reactively identifies the infective pathogens.



Peripheral blood smear in *Streptococcus suis* septicemia occupationally infected from the pig (May-Giemsa). Diplococci are not phagocytized by neutrophils.



Streptococcus suis septicemia occupationally infected from the pig. At autopsy, Kupffer cells are activated to show hemophagocytosis (left). The adrenal gland reveals bilateral cortical hemorrhage (Waterhouse Friderichsen's syndrome) (center). The kidney demonstrates acute tubular necrosis (right). H&E