

Exudative tuberculosis complicated with molecularly targeted therapy by Gleevec for metastatic gastrointestinal stromal tumor

Gastrointestinal stromal tumor (GIST) is consistently treated with Gleevec (Imatinib mesylate), an inhibitor of c-kit tyrosine kinase. Imatinib inhibits multiple tyrosine kinases, including M-CSF receptor. The inhibitory effect of Imatinib on the macrophage growth/function actually accelerates the susceptibility to tuberculosis. It must be recognized that this can be a lethal adverse effect of this molecularly targeted medicine. An adult male case of metastatic GIST of the duodenal origin treated with Imatinib is complicated with lethal exudative and miliary tuberculosis. The phagocytes were diffusely immunoreactive for BCG antigens. Autopsy findings are demonstrated. It must be noted with caution that the autopsy gives a dangerous biohazard for the autopsy executors (pathologists) and assistants in the autopsy suite.

Ref.-1: Senn L, et al. Peritoneal tuberculosis after Imatinib therapy. Arch Intern Med 2009; 169(3): 312-316. doi: 10.1001/archinternmed.2008.581

Ref.-2: Dewar AL, et al. Macrophage colony-stimulating factor receptor c-fms is a novel target of imatinib. Blood 2005; 105(8): 3127-3132. doi: 10.1182/blood-2004-10-3967

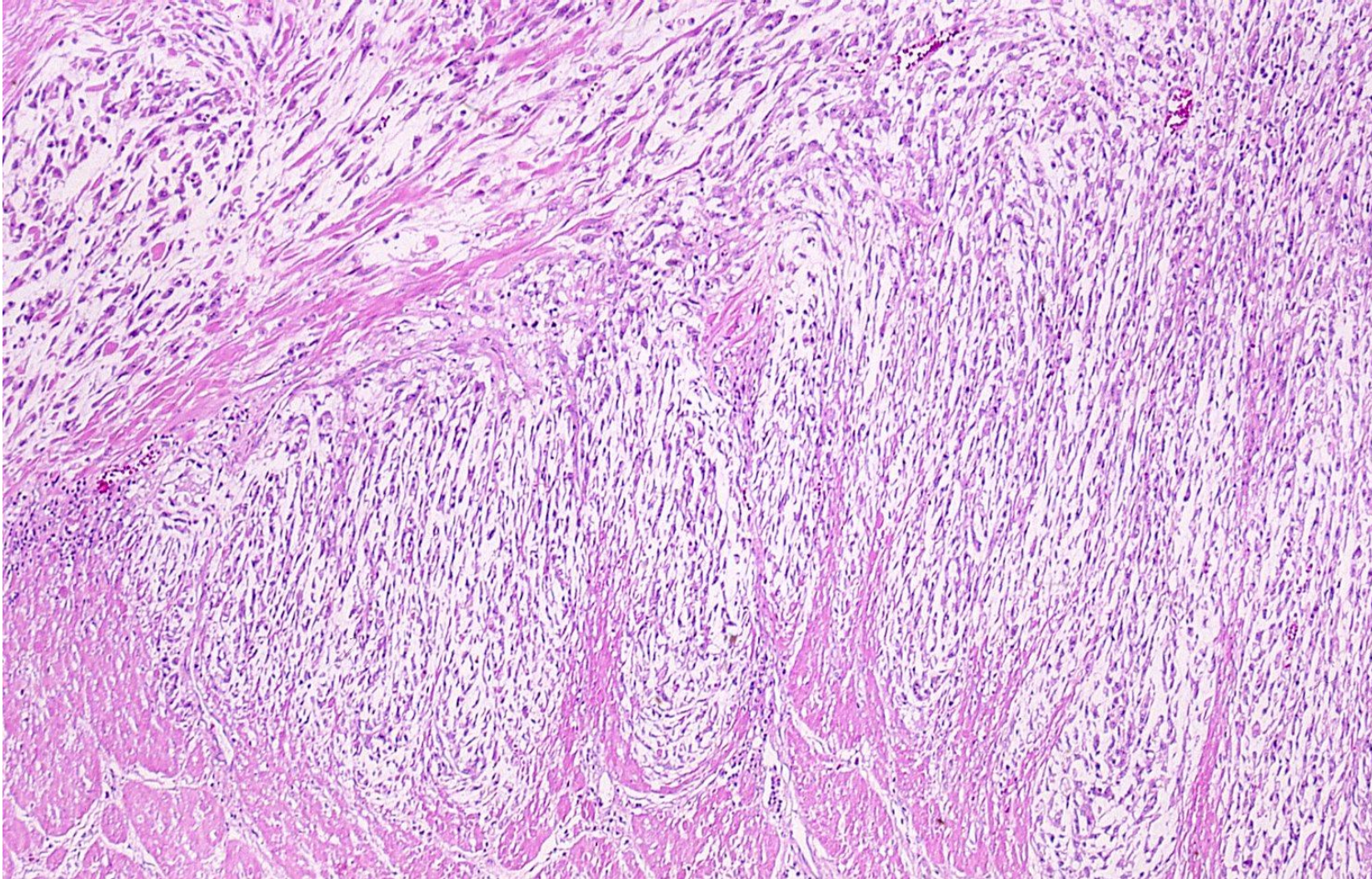
Case presentation

A 61 y-o male patient manifested anemia, and systemic evaluations disclosed a 6 x 6 cm-sized ulcerating duodenal tumor with liver and lymph nodal metastases. Biopsy confirmed c-kit-positive gastrointestinal stromal tumor (GIST), high-grade. Pylorus-preserving pancreatoduodenectomy was then performed. Soon, peroral administration of Gleevec (Imatinib mesylate), an inhibitor of the c-kit tyrosine kinase, started. Five months after surgery, he complained of persistent appetite loss. Ten months after surgery, multiple pulmonary nodules and ascites were pointed out. Appetite loss and general malaise were accelerated. His general conditions deteriorated with high fever. The patient died 9 months after surgery. The total clinical course was 14 months. Autopsy was performed four hours after death.

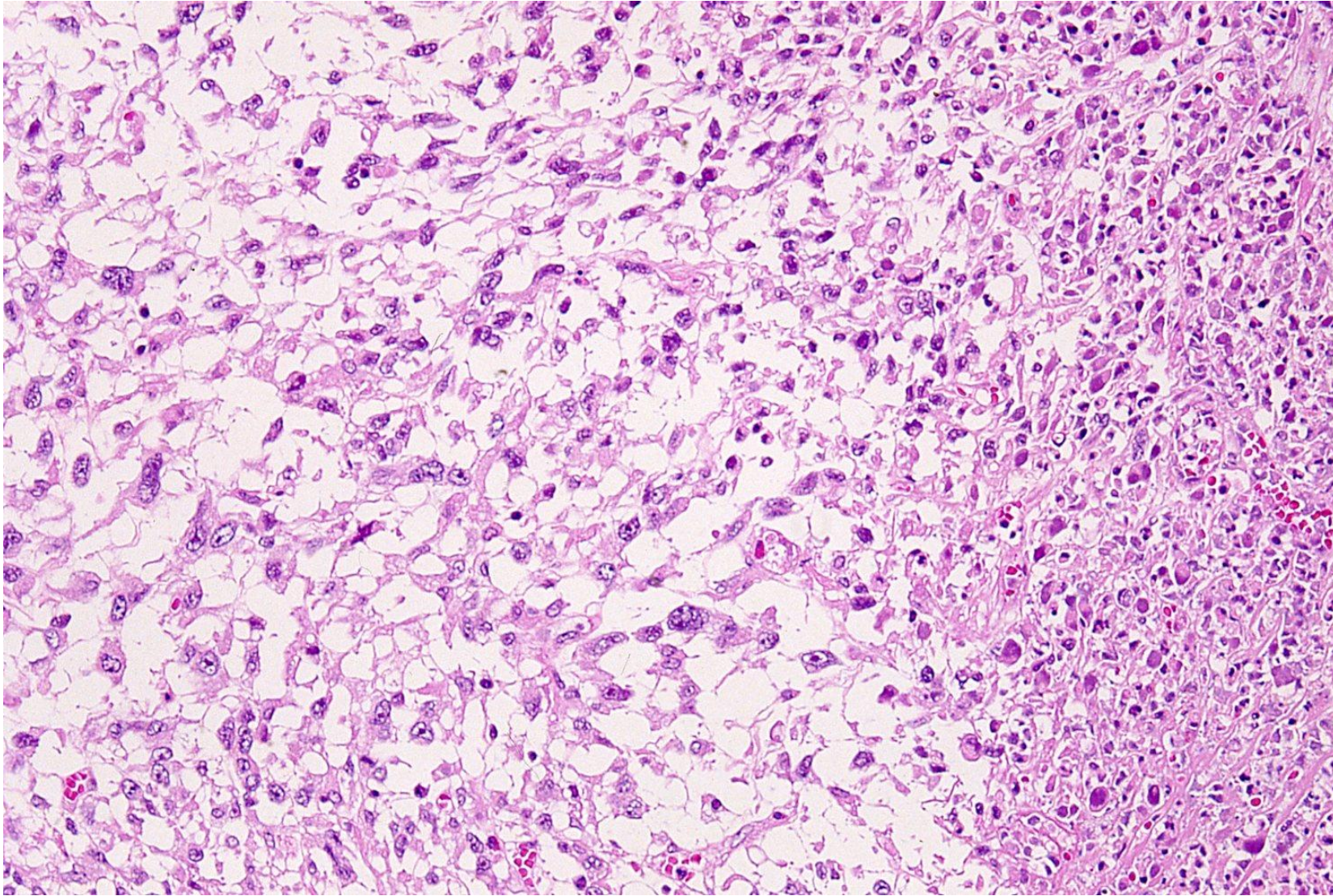
Gleevec (Imatinib Mesylate)

Gleevec (Imatinib mesylate) is a targeted therapy medication as an inhibitor targeting multiple tyrosine kinases such as CSF1R, Bcr-Abl, c-Kit, FLT3, and PDGFR- β . This small molecule oral medicine can be quite effective to treat chronic myeloid leukemia (CML), Ph1-positive acute lymphoblastic leukemia (ALL), chronic eosinophilic leukemia, systemic mastocytosis, hypereosinophilic syndrome, myelodysplastic syndrome, dermatofibrosarcoma protuberans, and gastrointestinal stromal tumor (GIST). The tumor cells result in programmed cell death. Patients may need to continue taking Imatinib for an extended period of time to maintain remission. The patient should avoid pregnancy, since the risk of embryo-fetal toxicity is high. The risk of growth stunting in children or adolescents must also be commented.

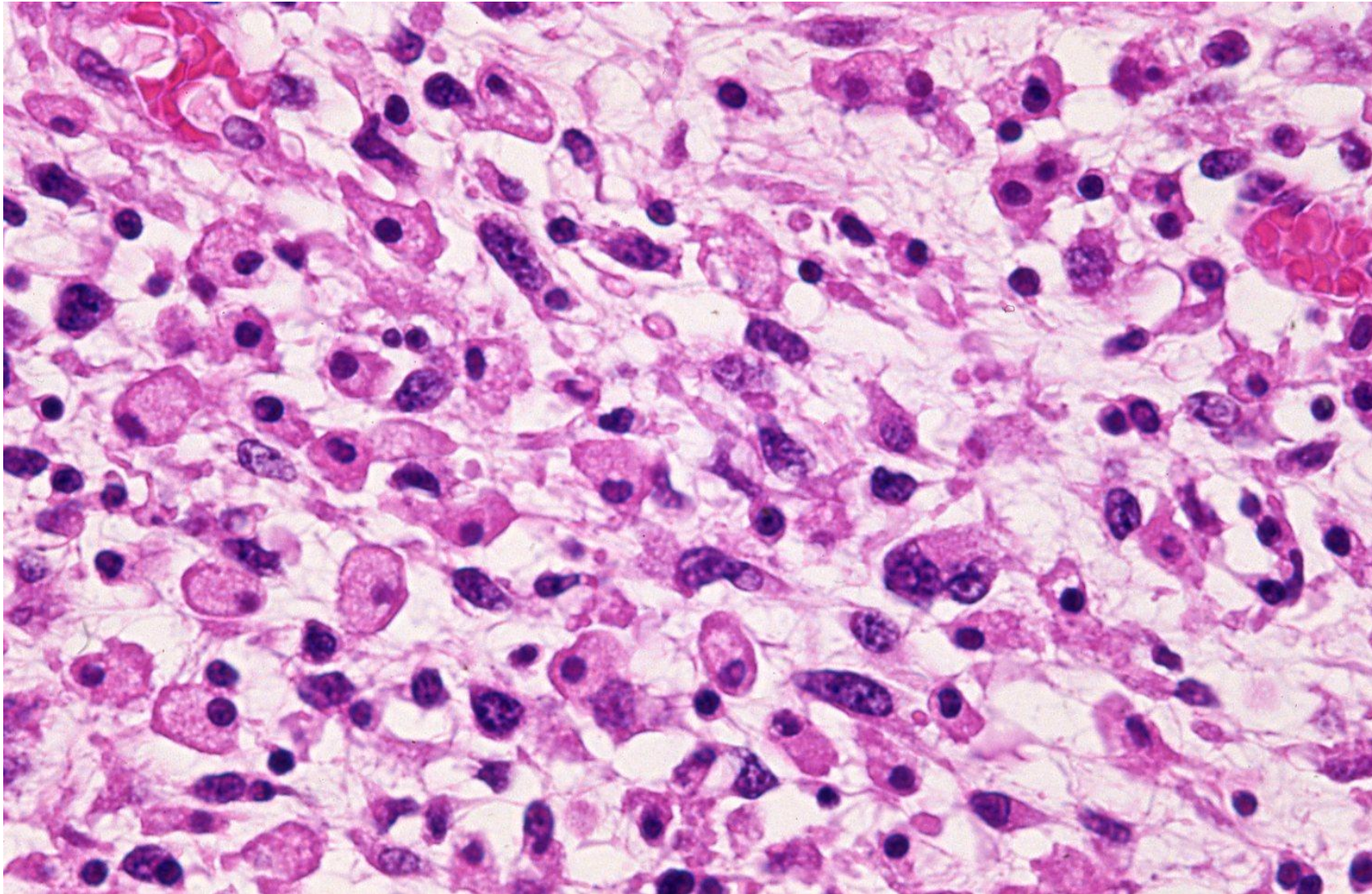
It should be noted that Imatinib inhibits the growth and function of non-neoplastic monocytes and macrophages, because phosphorylation of macrophage colony-stimulating factor (M-CSF) receptor c-fms is inhibited by therapeutic concentrations of Imatinib. The receptor c-fms is expressed at low levels on monocytes, and its expression markedly increases during M-CSF-mediated differentiation to macrophages. The inhibitory effect of Imatinib on the macrophage growth/function can actually accelerate the susceptibility to tuberculosis. In the present 61 y-o male case of GIST, Imatinib administration provoked lethal systemic exudative and miliary tuberculosis. Granulomatous reaction was limited, while phagocytic activity of macrophages was activated. At autopsy, pathologists and assistants are exposed onto the high-degree biohazard. In fact, occupational infection of tuberculosis happened in the pathologist on duty, who was culturally positive for *Mycobacterium tuberculosis* In his sputum.



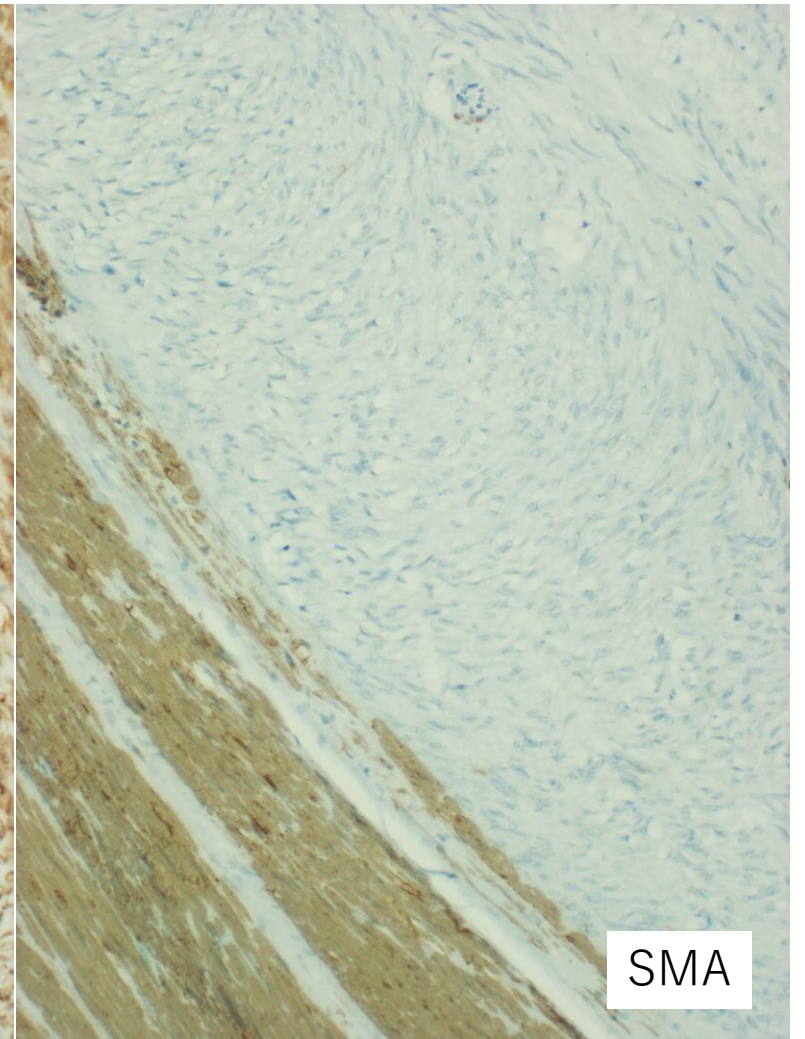
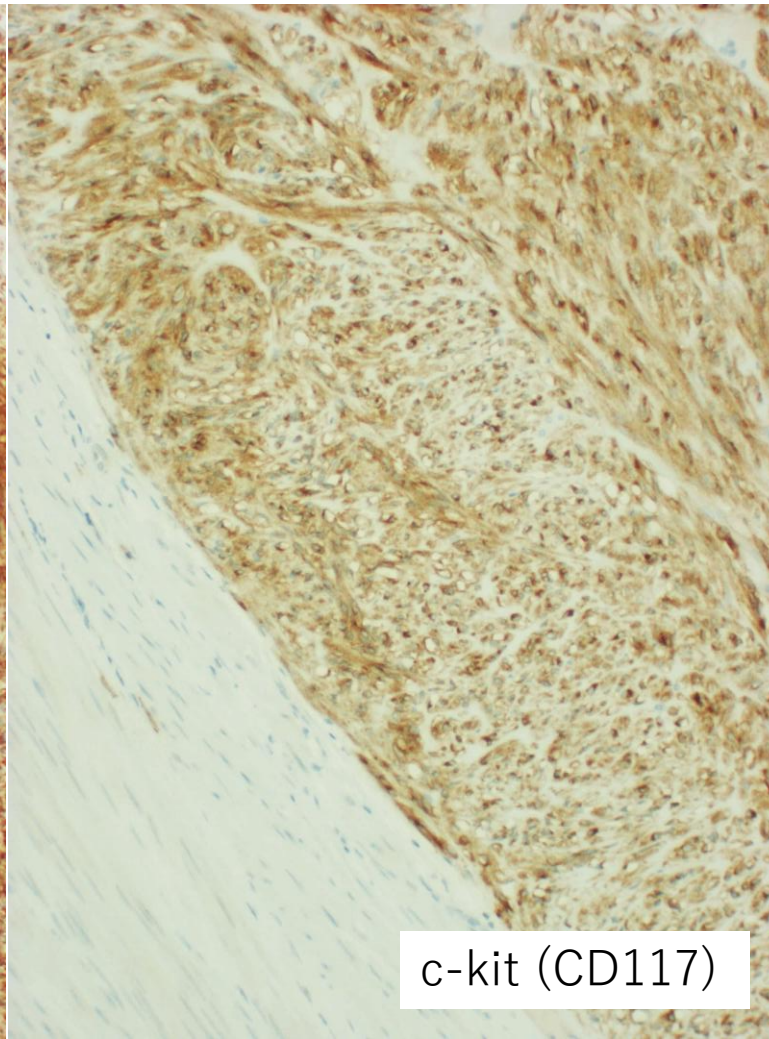
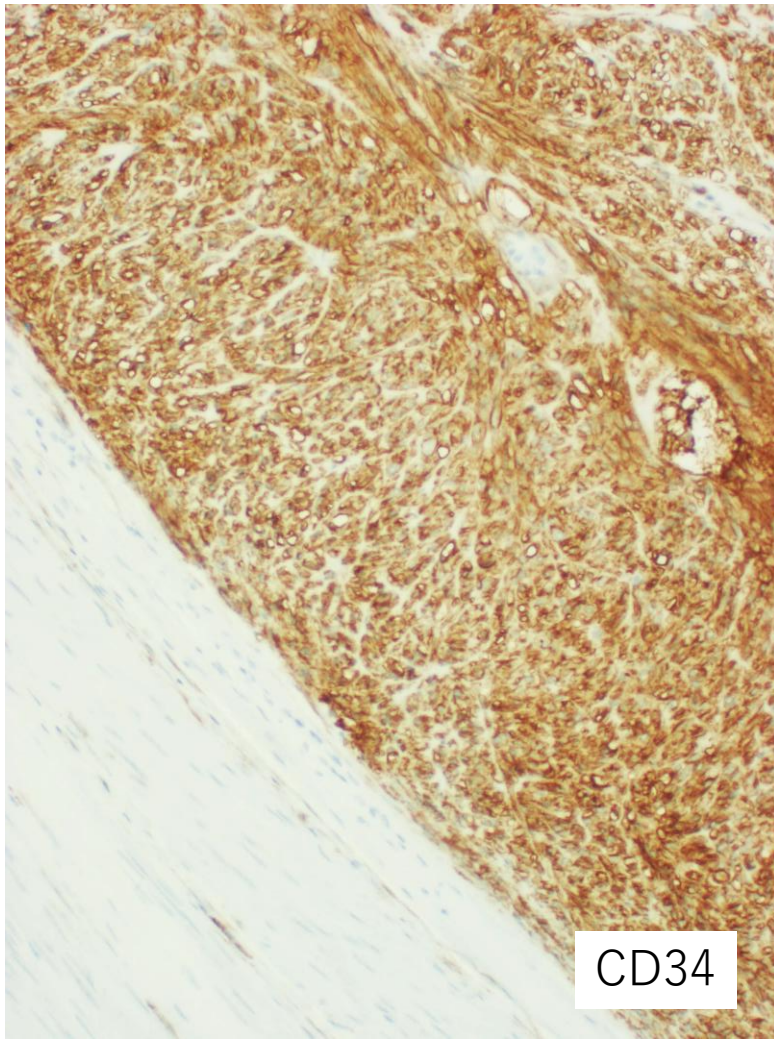
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient (H&E-1). The surgical specimen reveals invasive growth of spindled tumor cells with myxoid stroma in the proper muscle layer.



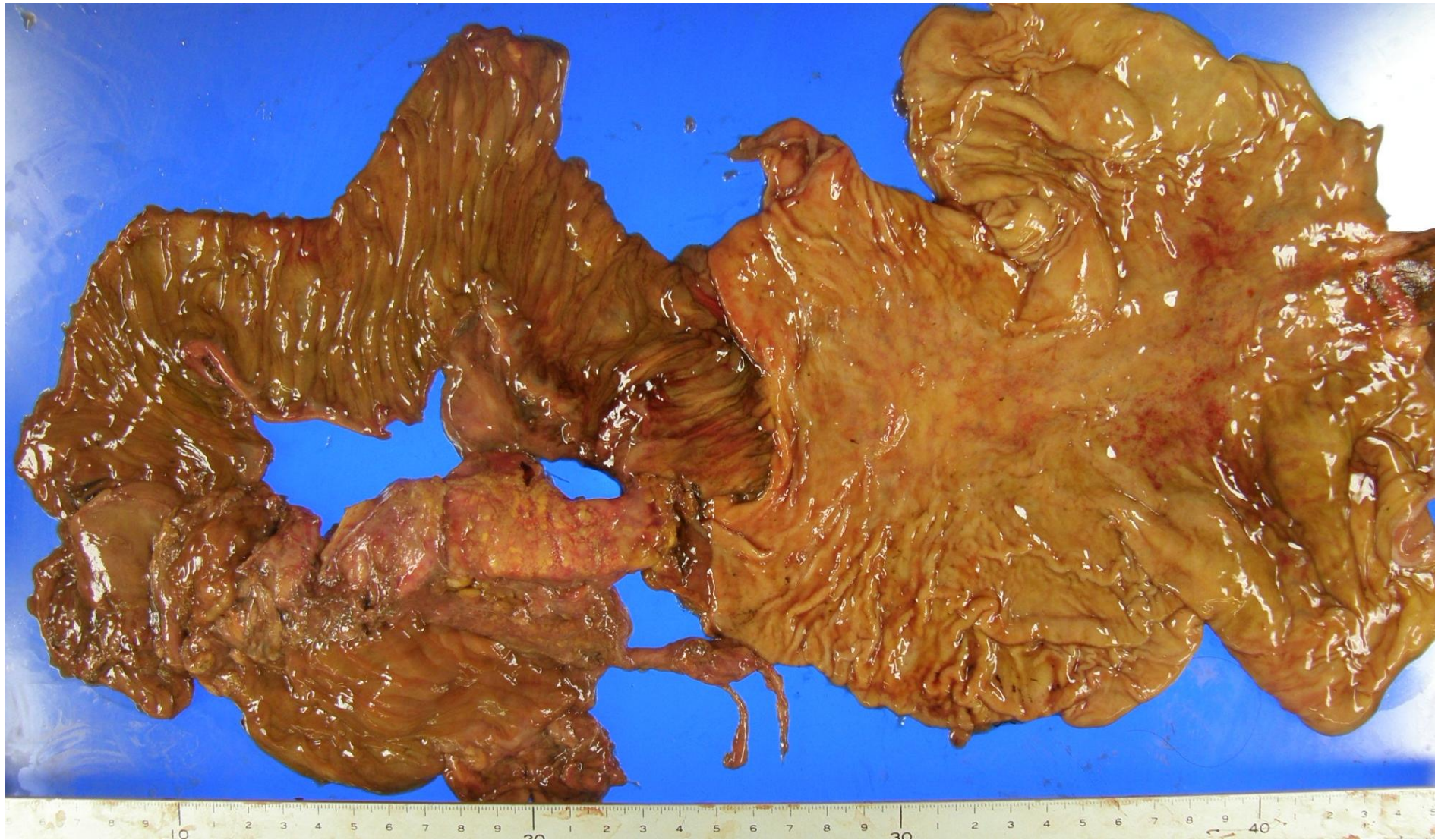
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient (H&E-2). The surgical specimen reveals invasive growth of spindled and polygonal tumor cells with myxoid stroma. Nuclear pleomorphism is evident, indicating a high-grade neoplasm.



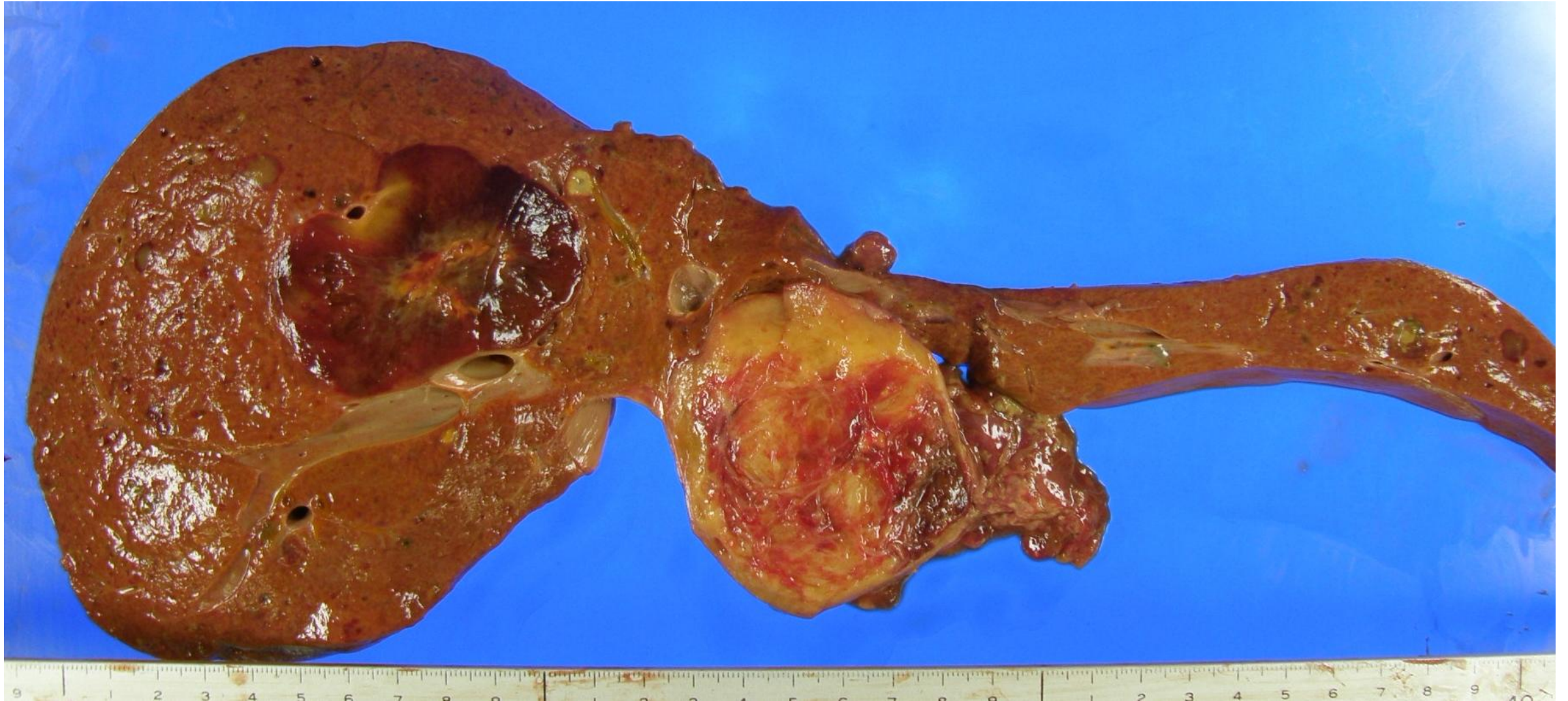
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient (H&E-3). The surgical specimen reveals invasive growth of spindled and polygonal tumor cells with myxoid stroma. Nuclear pleomorphism is evident, indicating a high-grade neoplasm.



Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient (immunostaining). The spindled and polygonal tumor cells are strongly immunoreactive for CD34 (left) and c-kit (CD117) (center). SMA is expressed in the non-neoplastic proper smooth muscle layer, while the tumor cells are negative for SMA (right). The c-kit expression on the tumor cells predicts the effectiveness of Imatinib administration.



Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy, no tumor recurrence was grossly seen in the gastrointestinal tract.



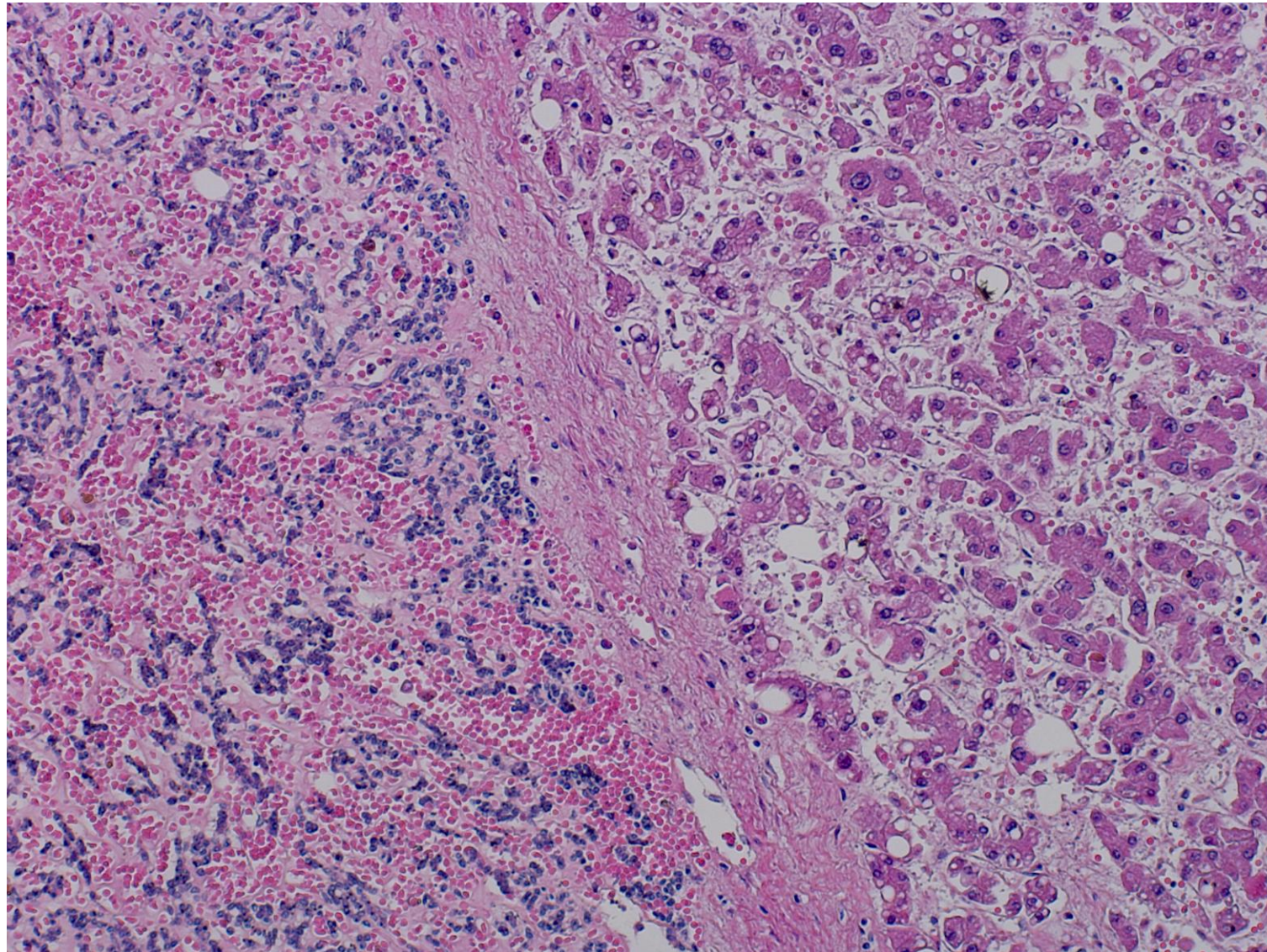
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy, multiple liver metastases (max. 9 cm in size) grossly show evident therapeutic effects of Imatinib (administered for 10 months) with hemosiderin deposition and focal necrosis. The liver weight: 1,580 g.



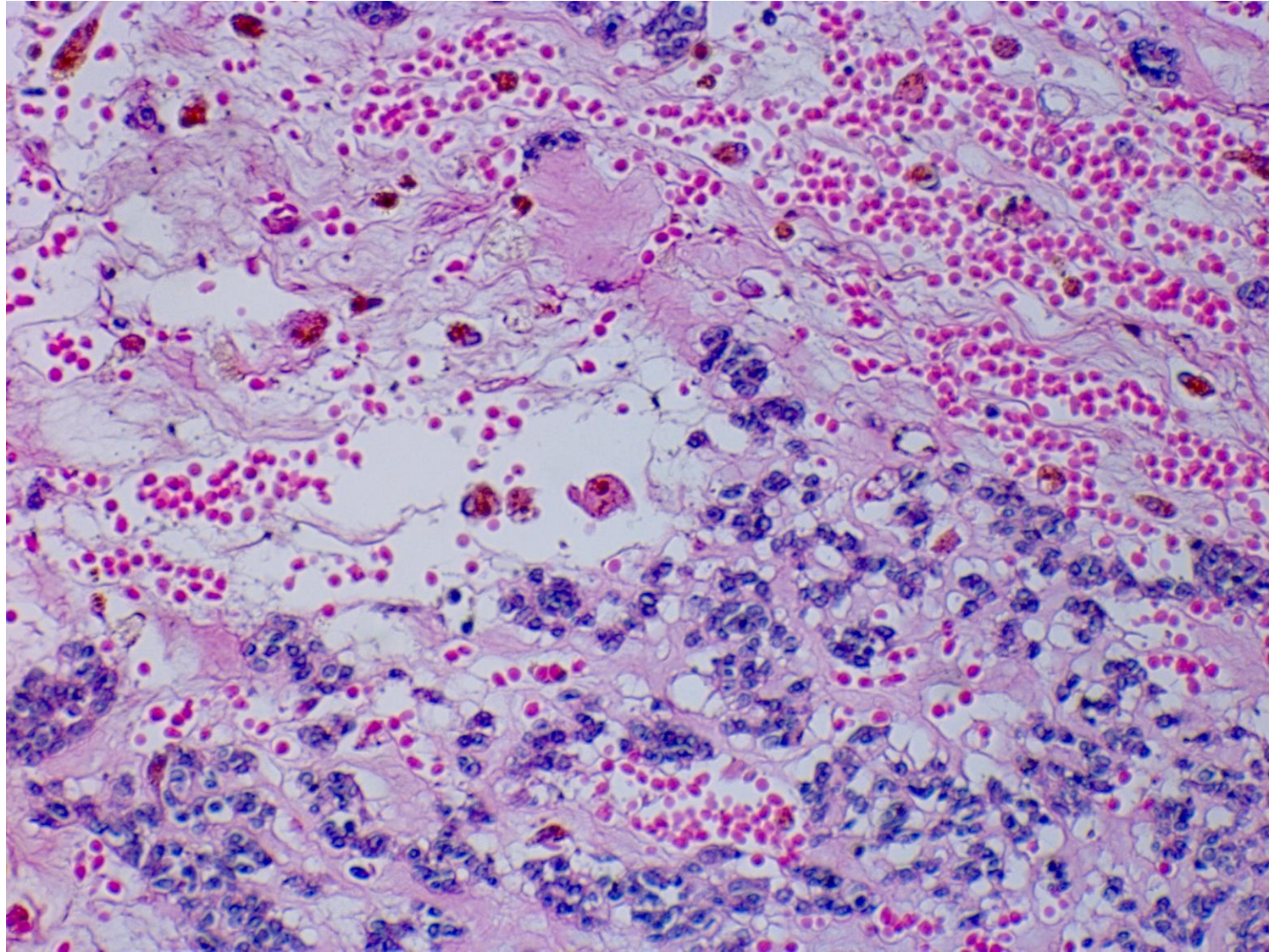
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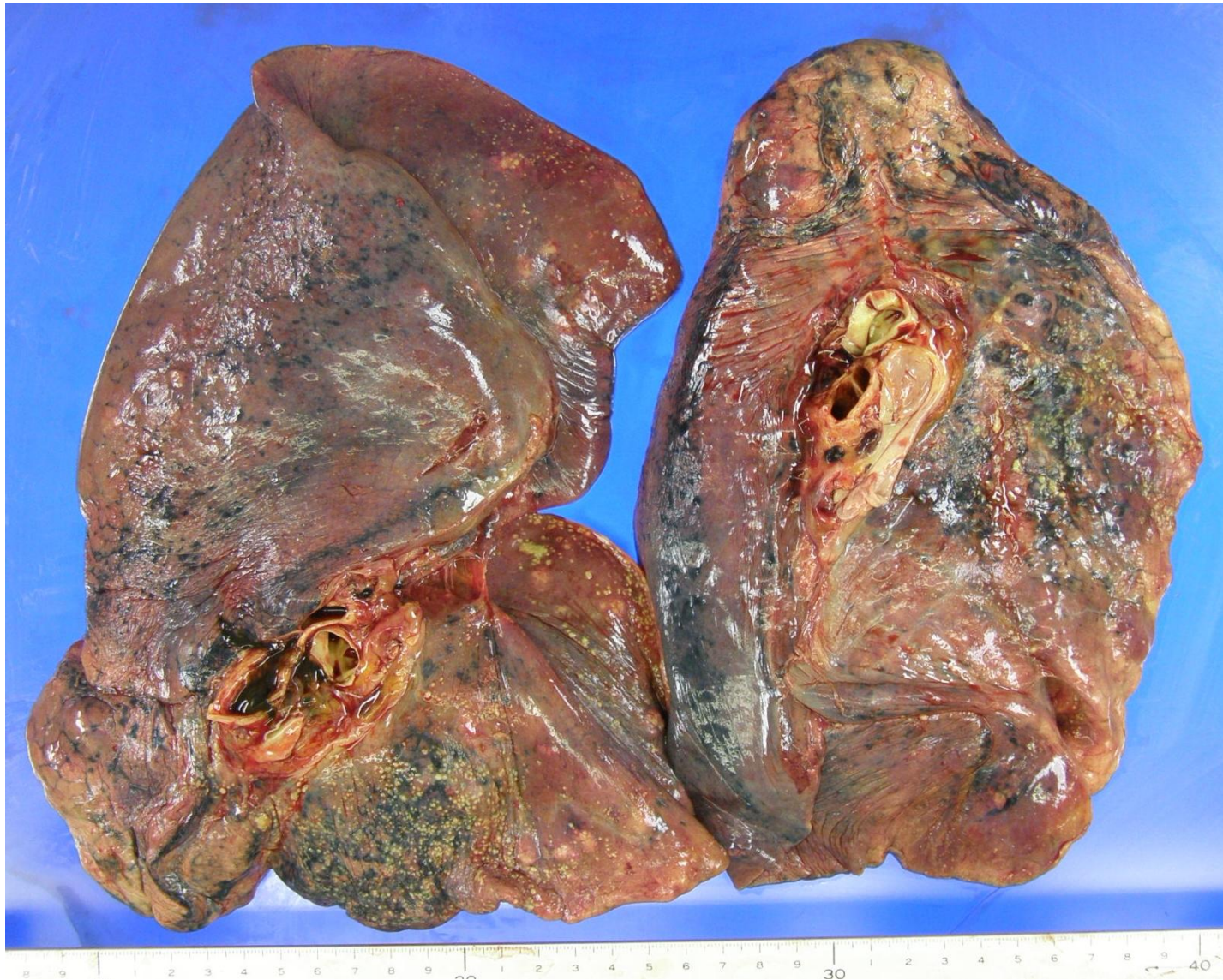
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy, the liver metastasis grossly shows evident therapeutic effects of Imatinib (administered for 10 months) with myxoid shrinkage. Disseminated miliary tuberculous nodules are seen on the peritoneum.



Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib, the liver metastasis microscopically shows evident shrinkage effect of the tumor cells with stromal hemorrhage (H&E-a).



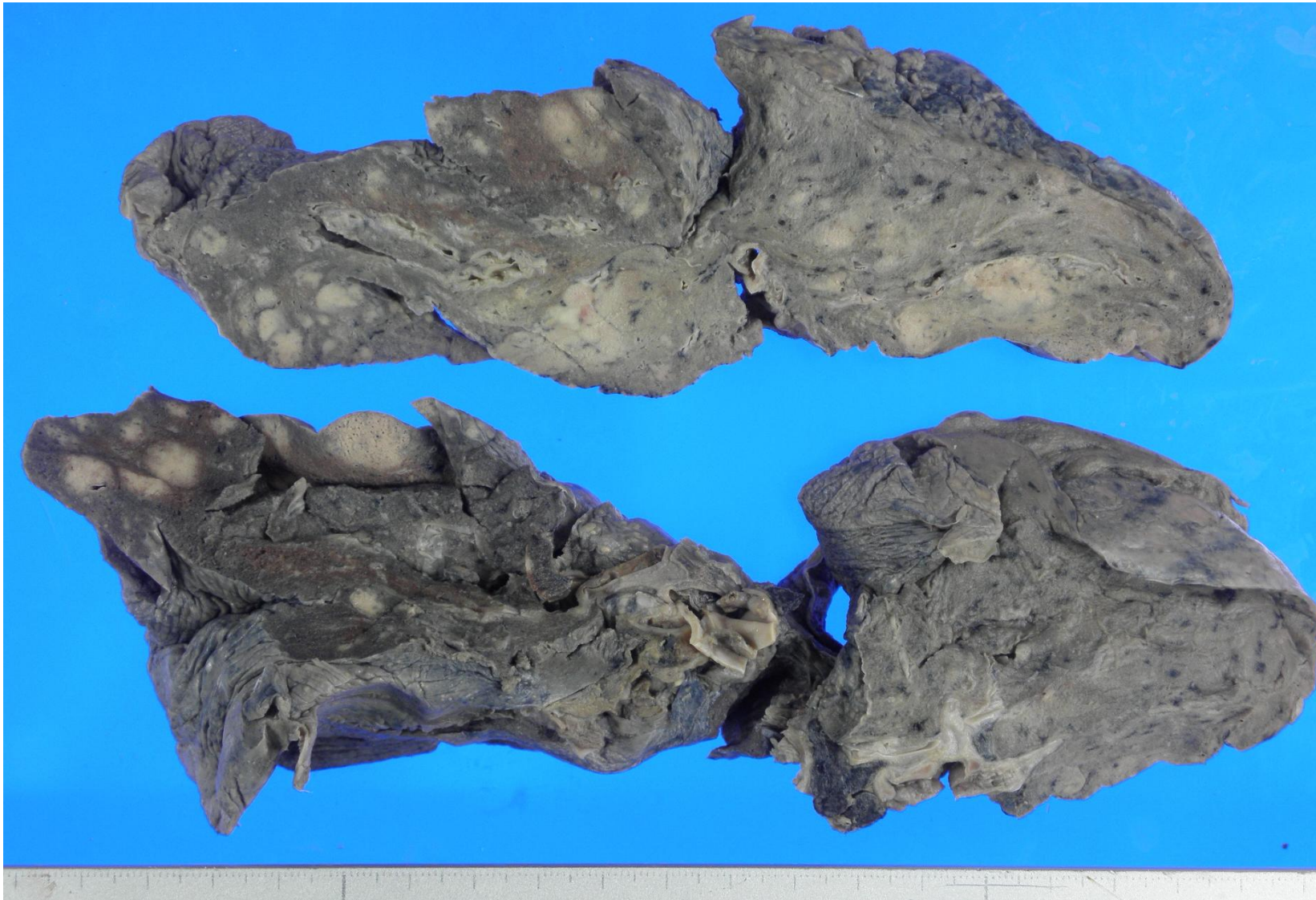
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib, the liver metastasis microscopically shows evident shrinkage effect of the tumor cells with stromal hemosiderin deposition (H&E-b).



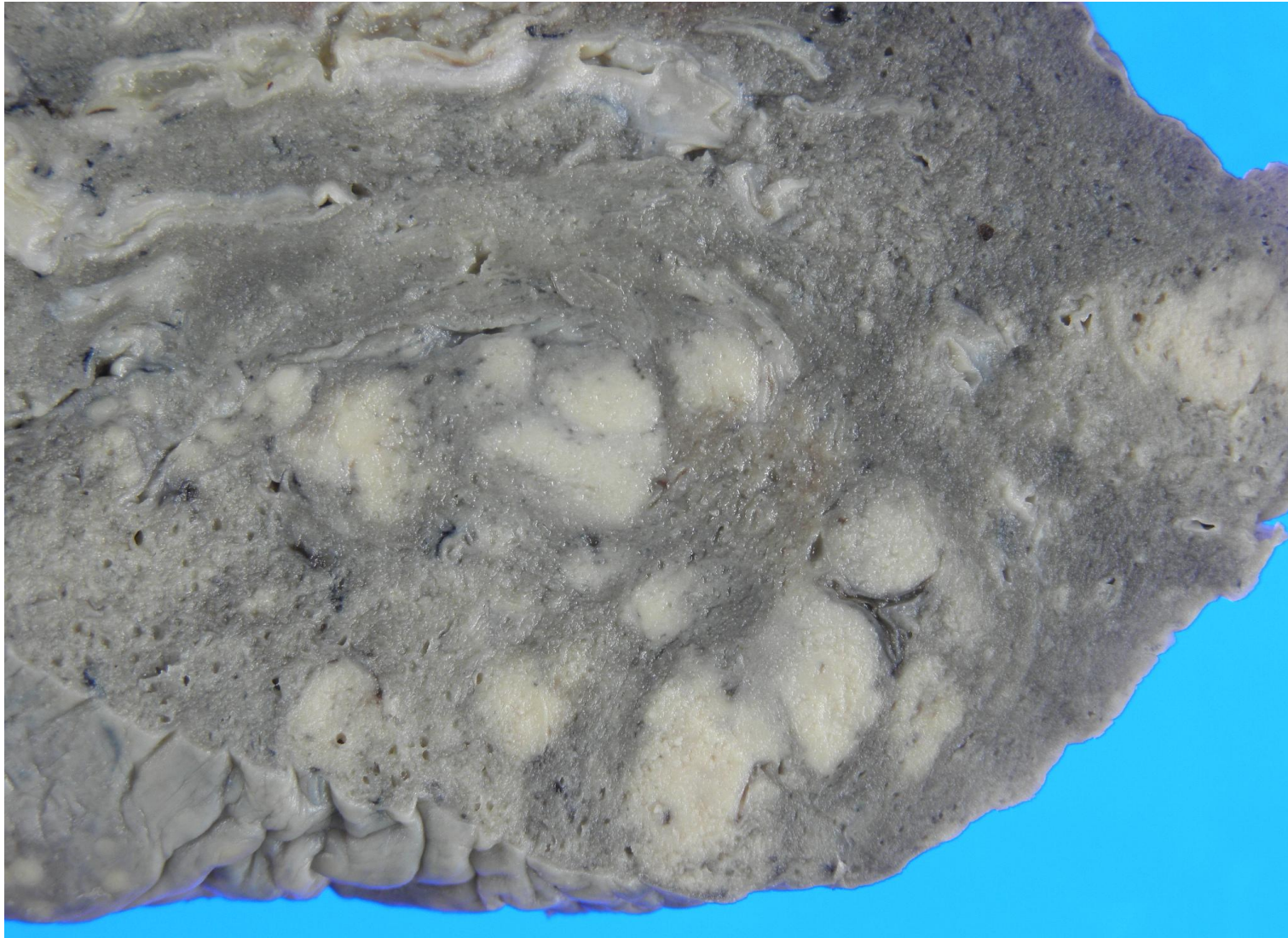
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib, the both lungs grossly show congestion and multiple small nodule formation. Pleural dissemination of tuberculosis is noted. The lung weight: left 540 g, right: 780 g.



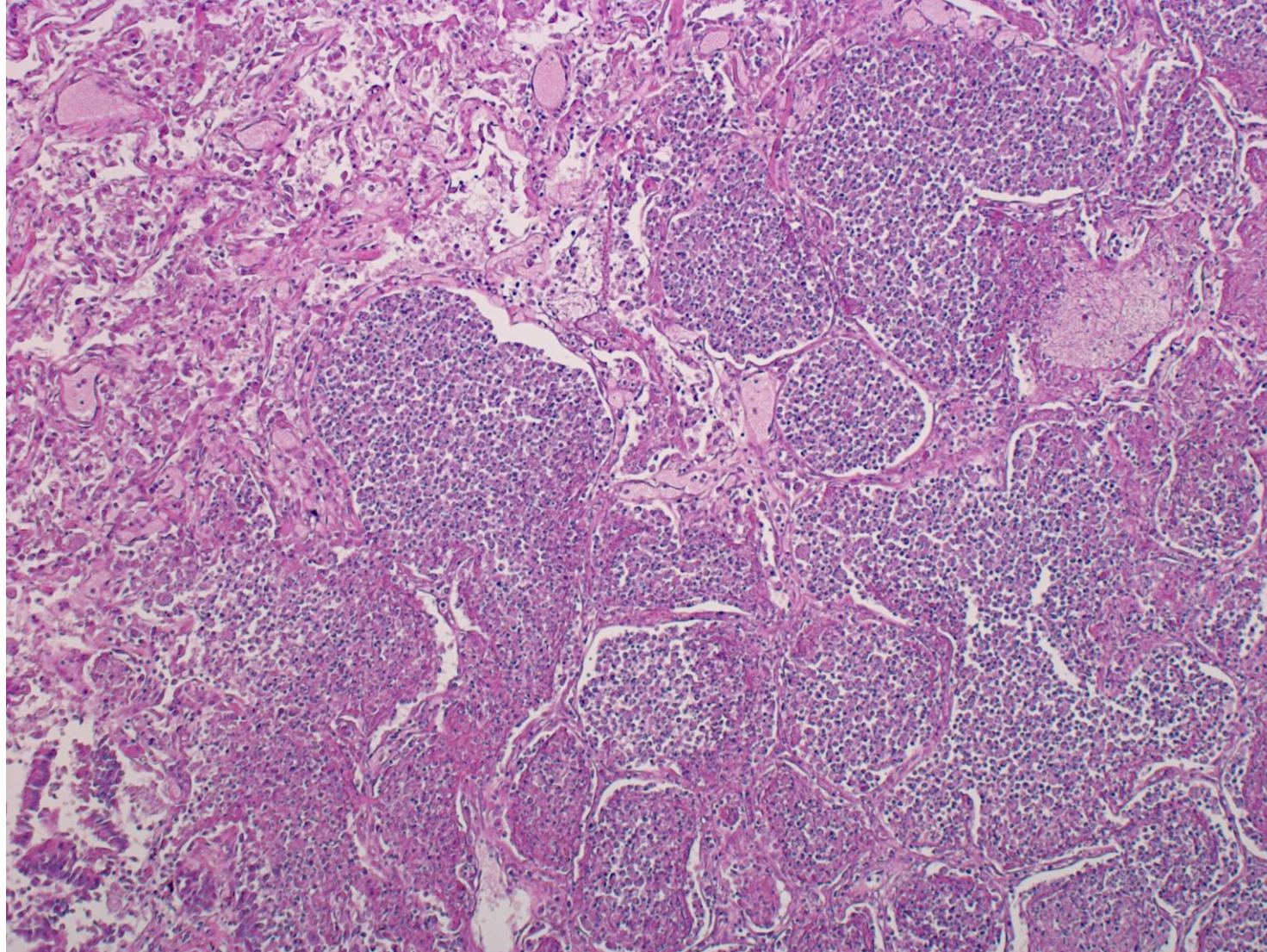
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient. At autopsy 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib, the cut surface of the lung grossly show congestion and multiple small nodule formation. Pleural dissemination of miliary tuberculosis is noted. Taking photographs of the unfixed lung with exudative tuberculosis is highly biohazardous.



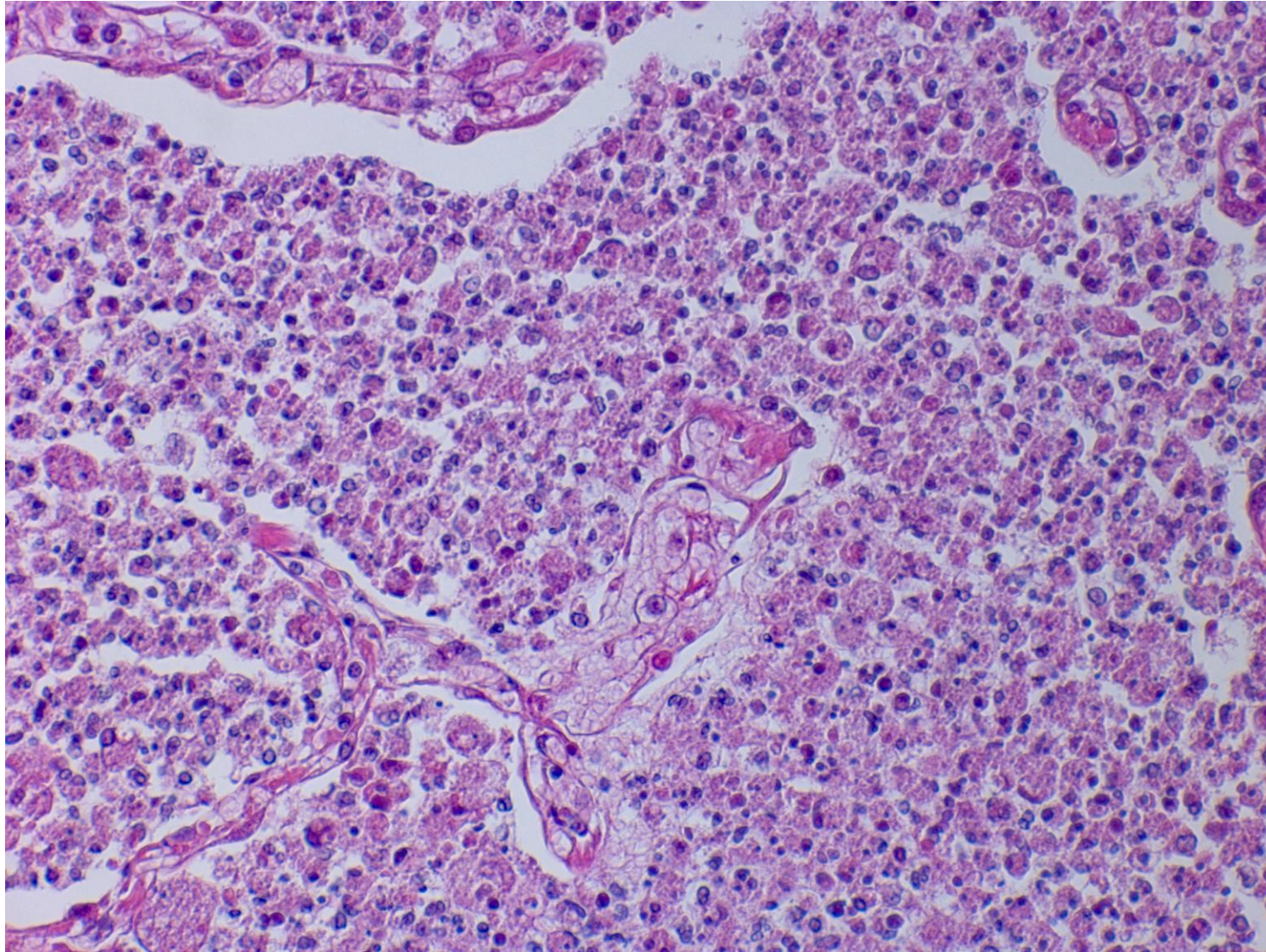
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The cut surfaces of the lung after formalin fixation grossly reveal multiple coalesced exudative nodules throughout the lung.



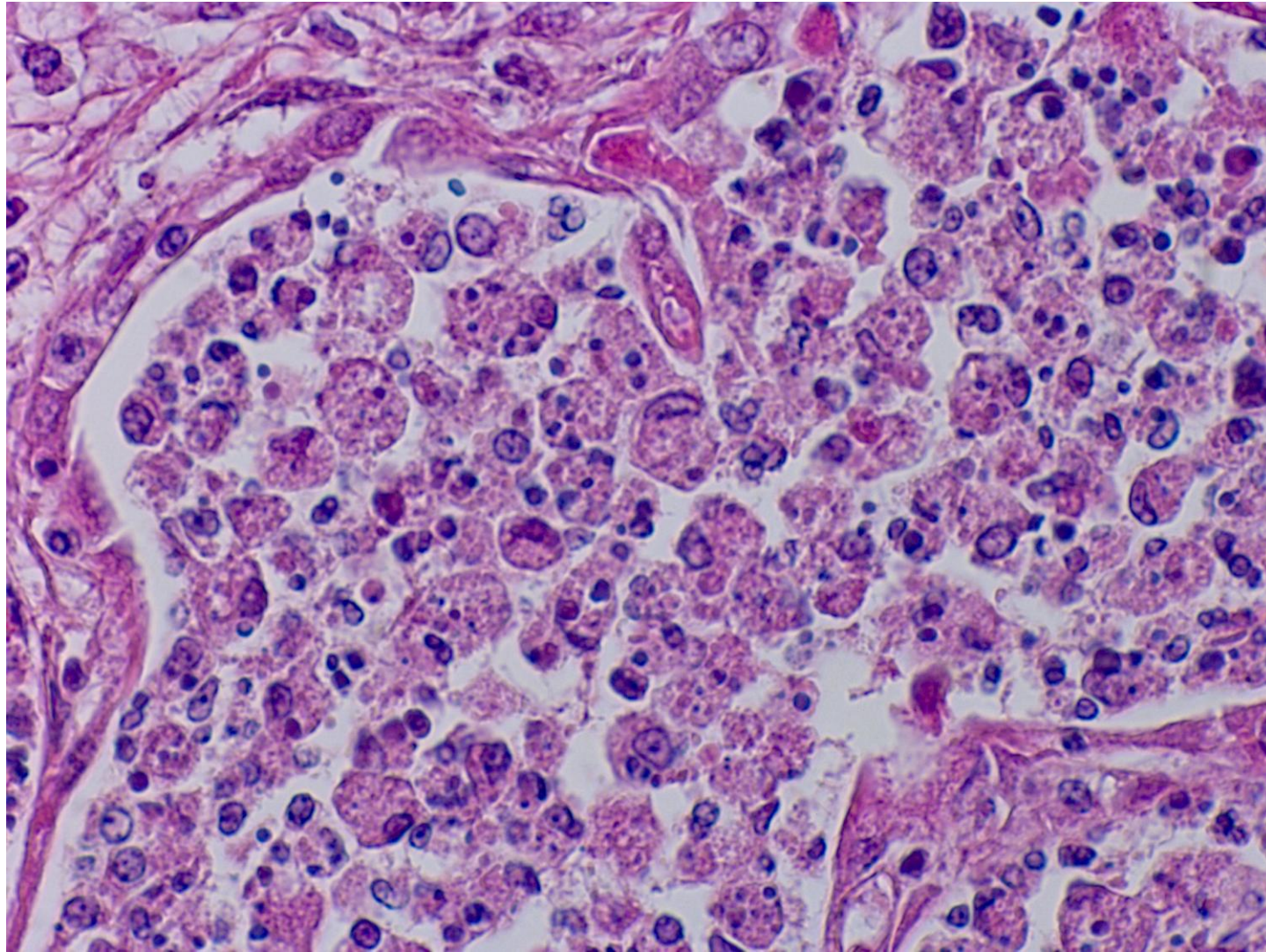
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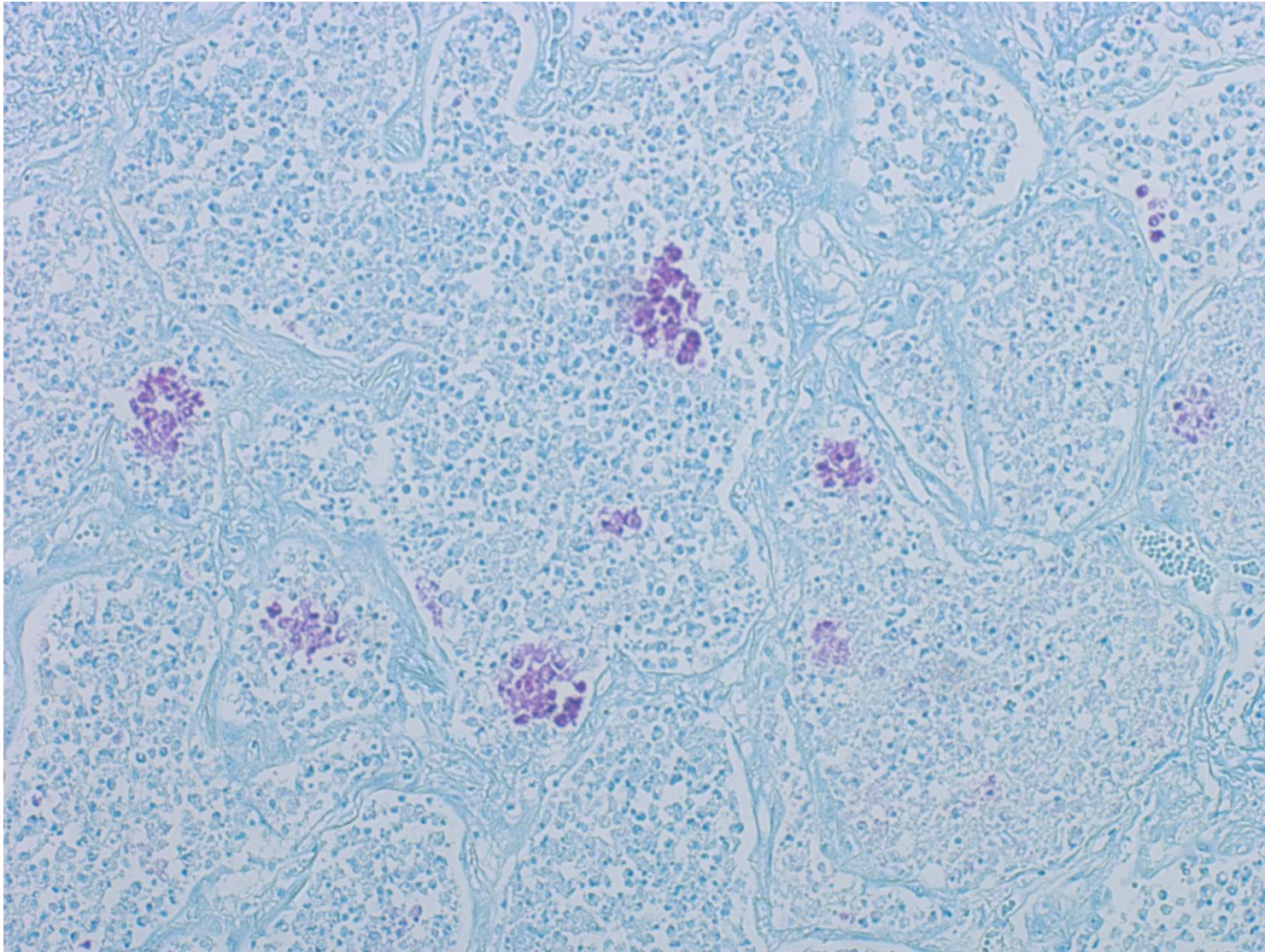
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. Microscopically, the coalesced lung nodule consists of exudation of neutrophils and macrophages without destruction of the pre-existing lung structure (H&E-c).



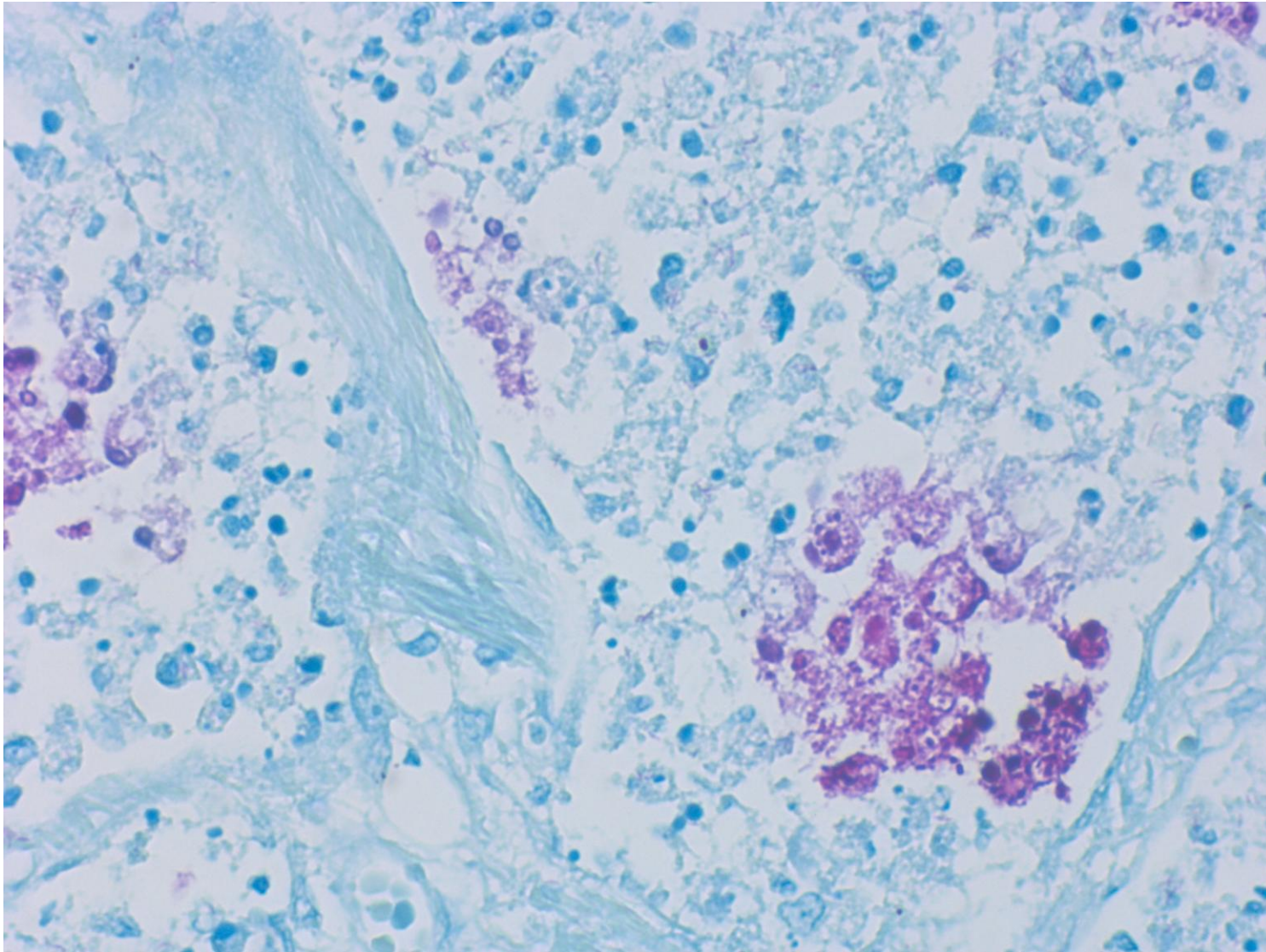
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. Microscopically, the coalesced lung nodule consists of exudation of neutrophils and activated macrophages without destruction of the pre-existing lung structure (H&E-d).



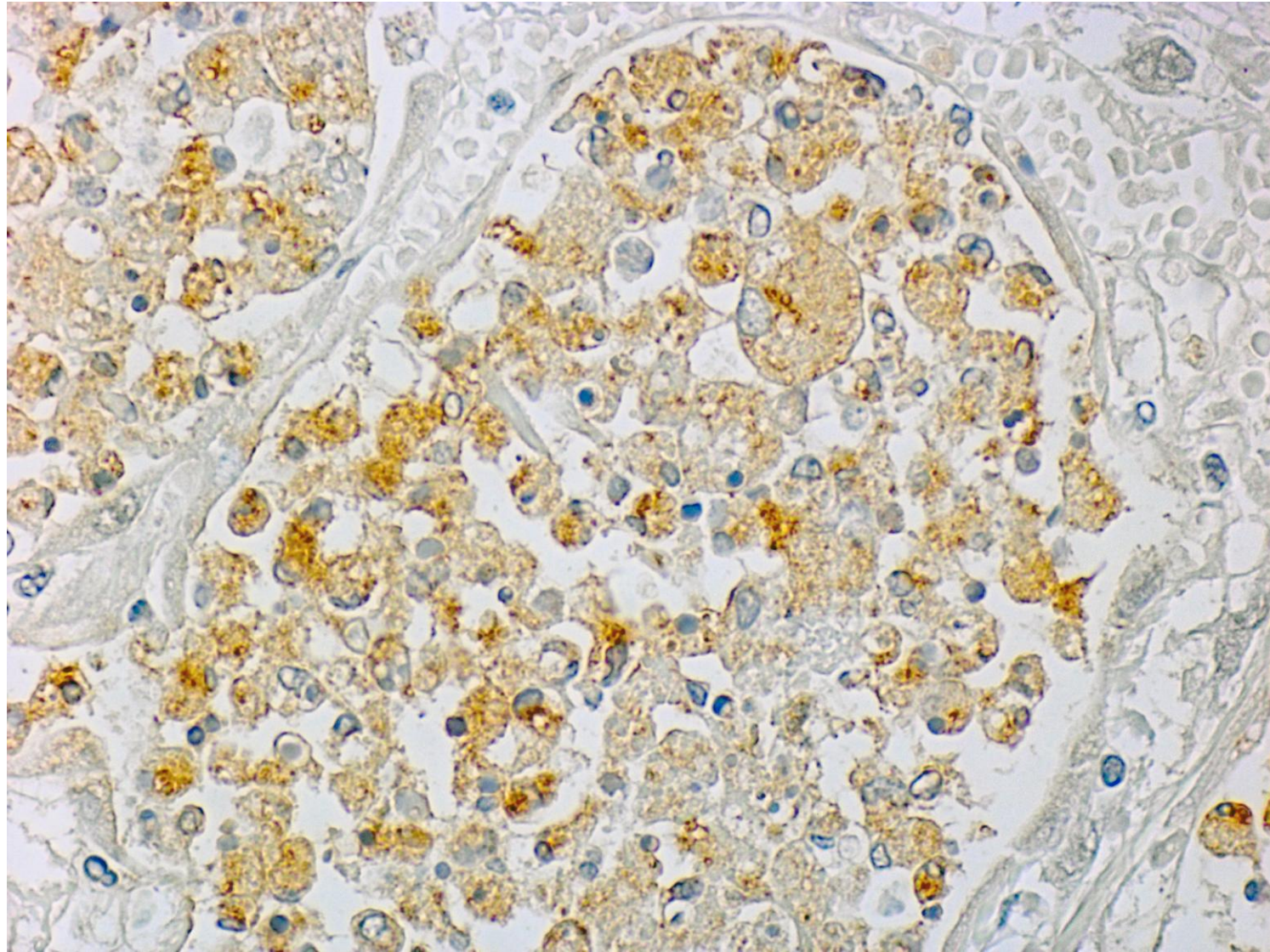
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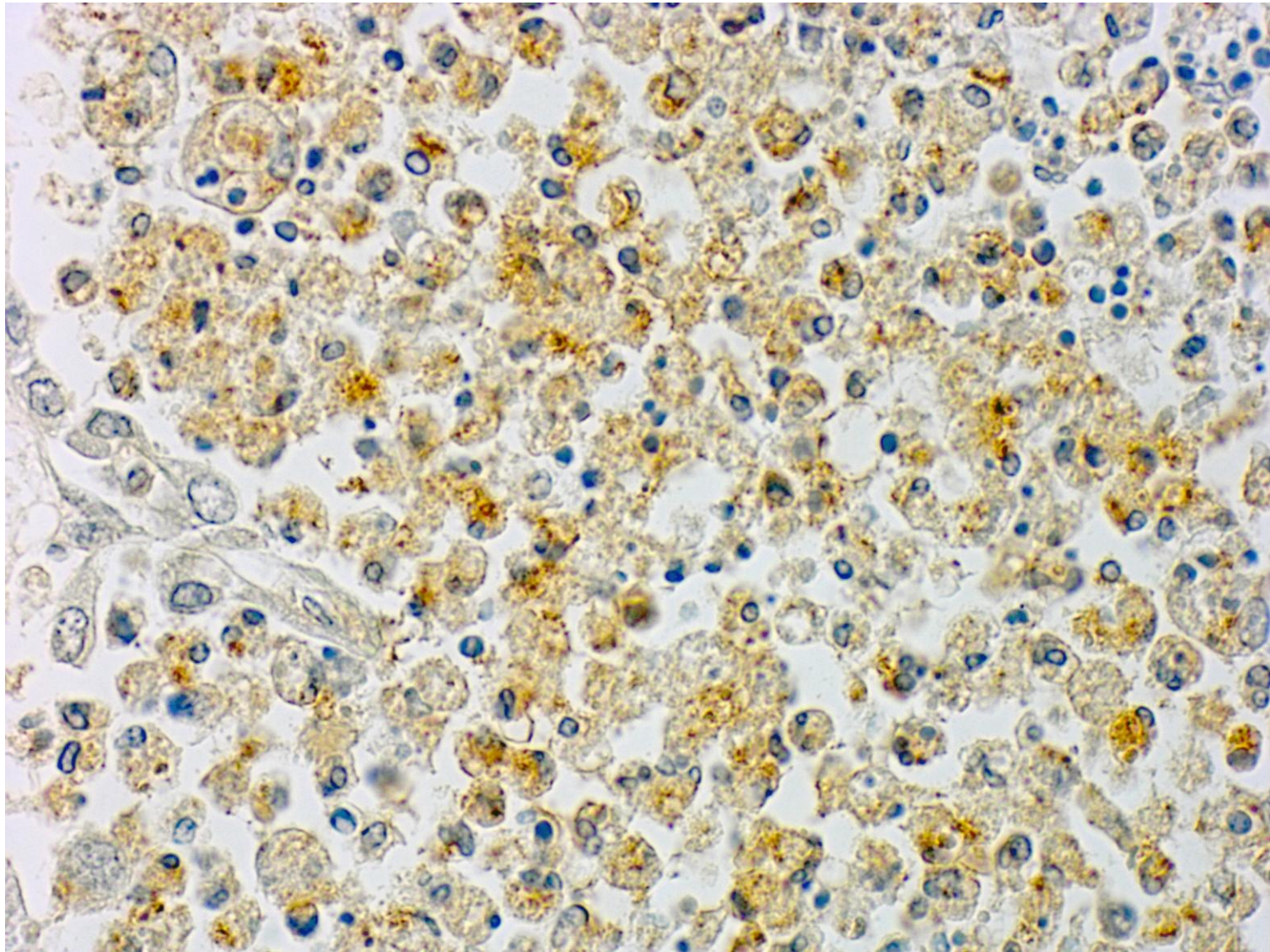
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. Microscopically, the coalesced lung nodule consists of exudation of neutrophils and activated macrophages. Ziehl-Neelsen stain reveals numerous acid-fast bacilli in the cytoplasm of the macrophages.



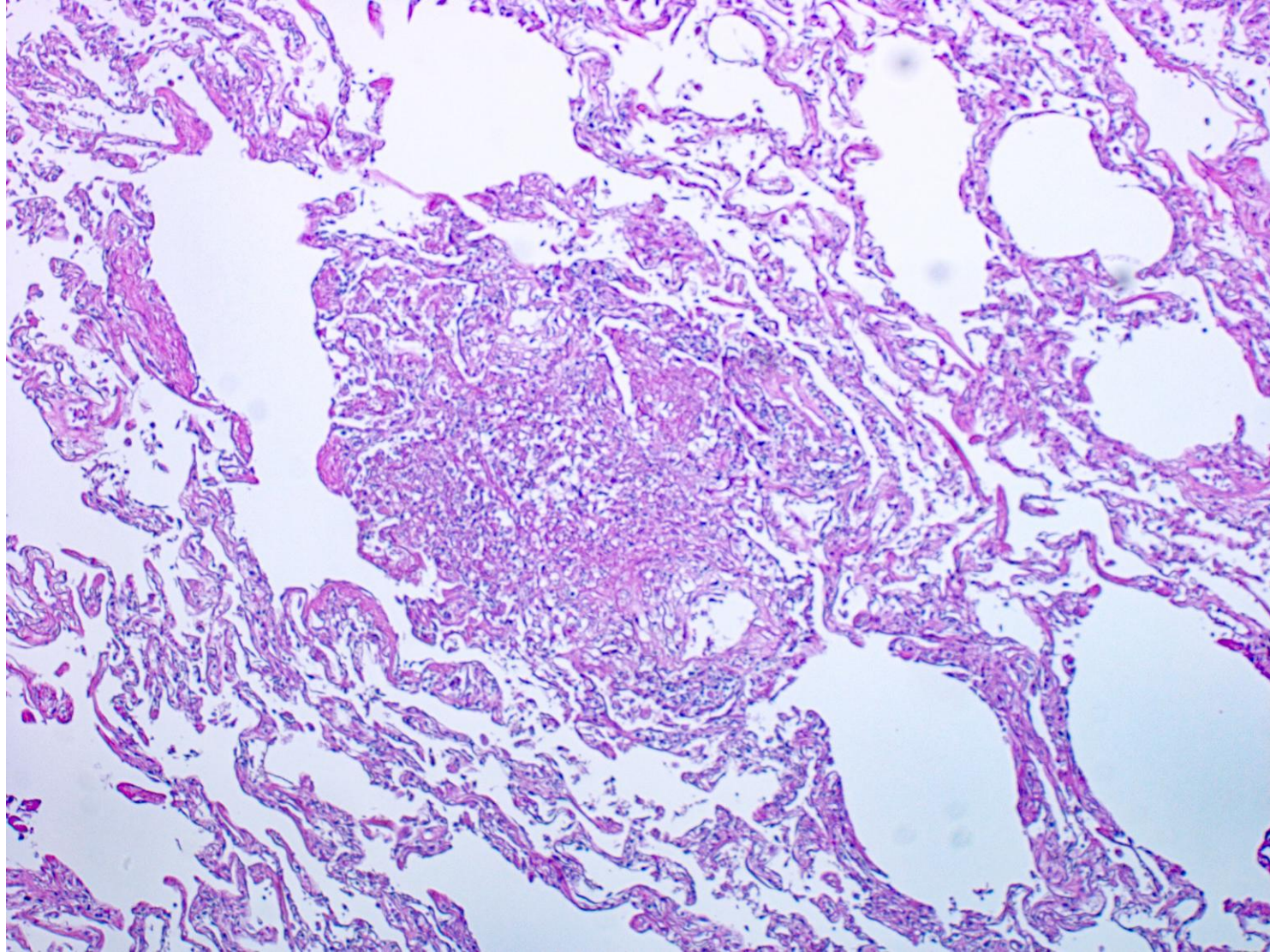
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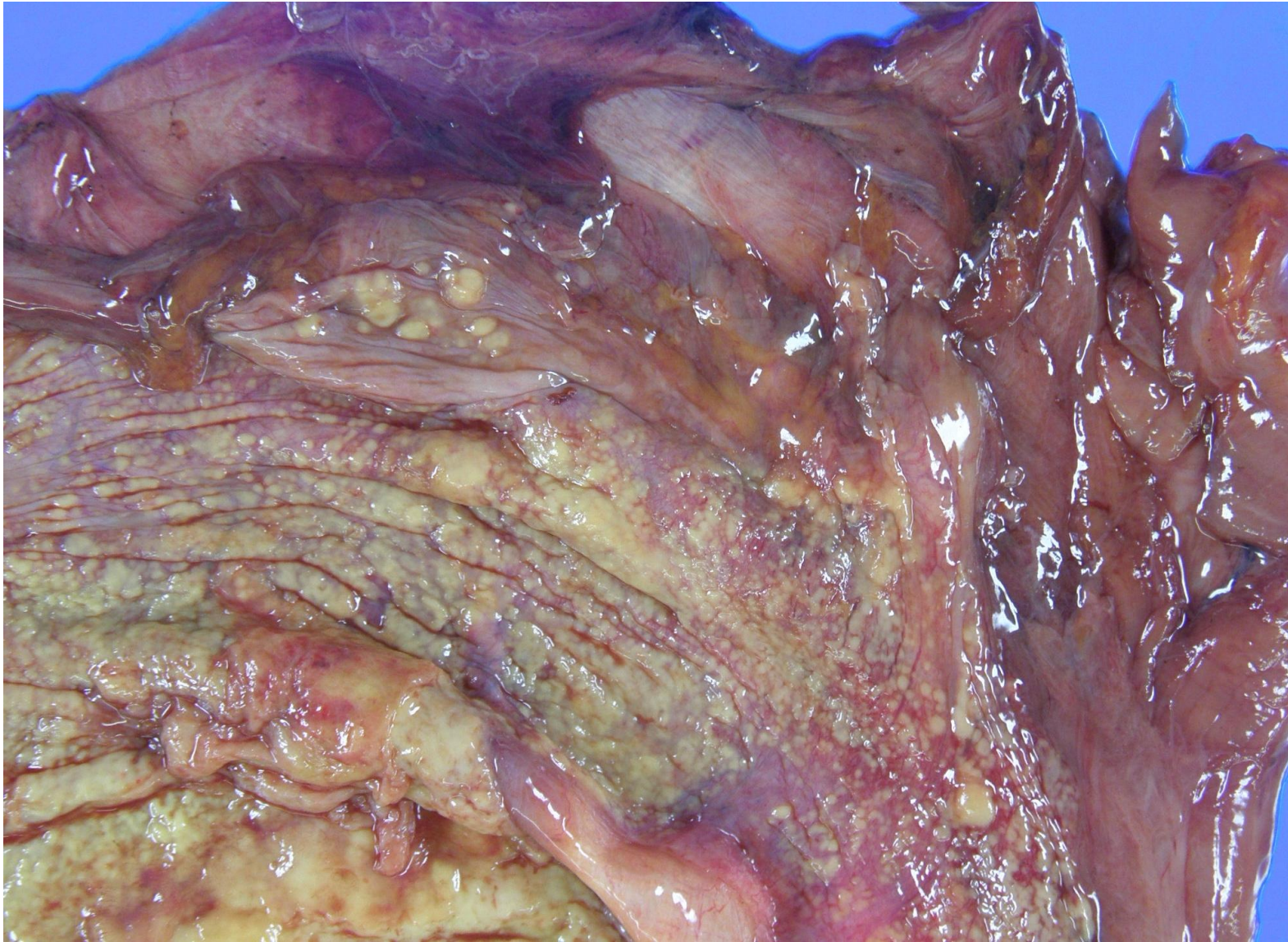
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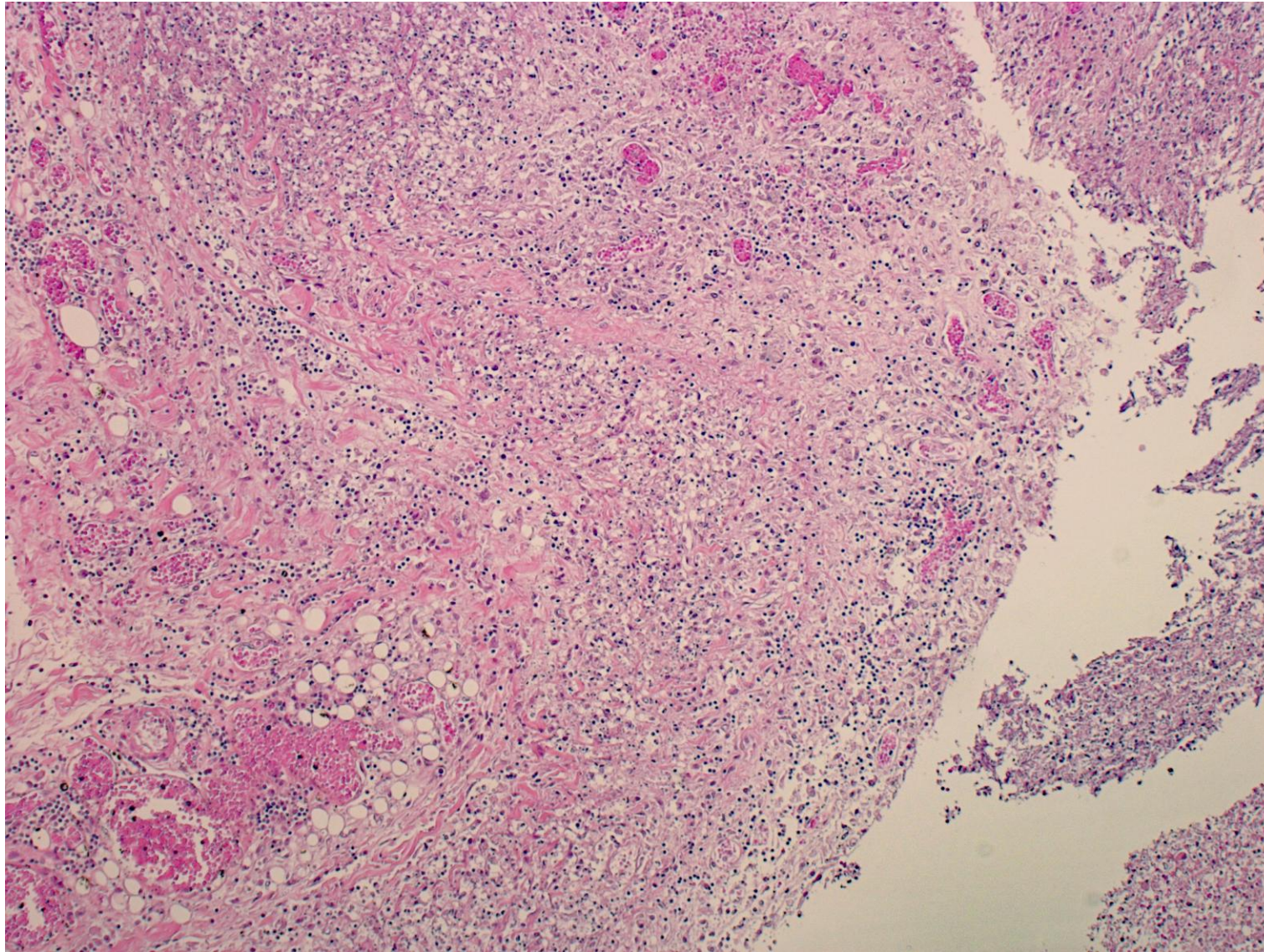
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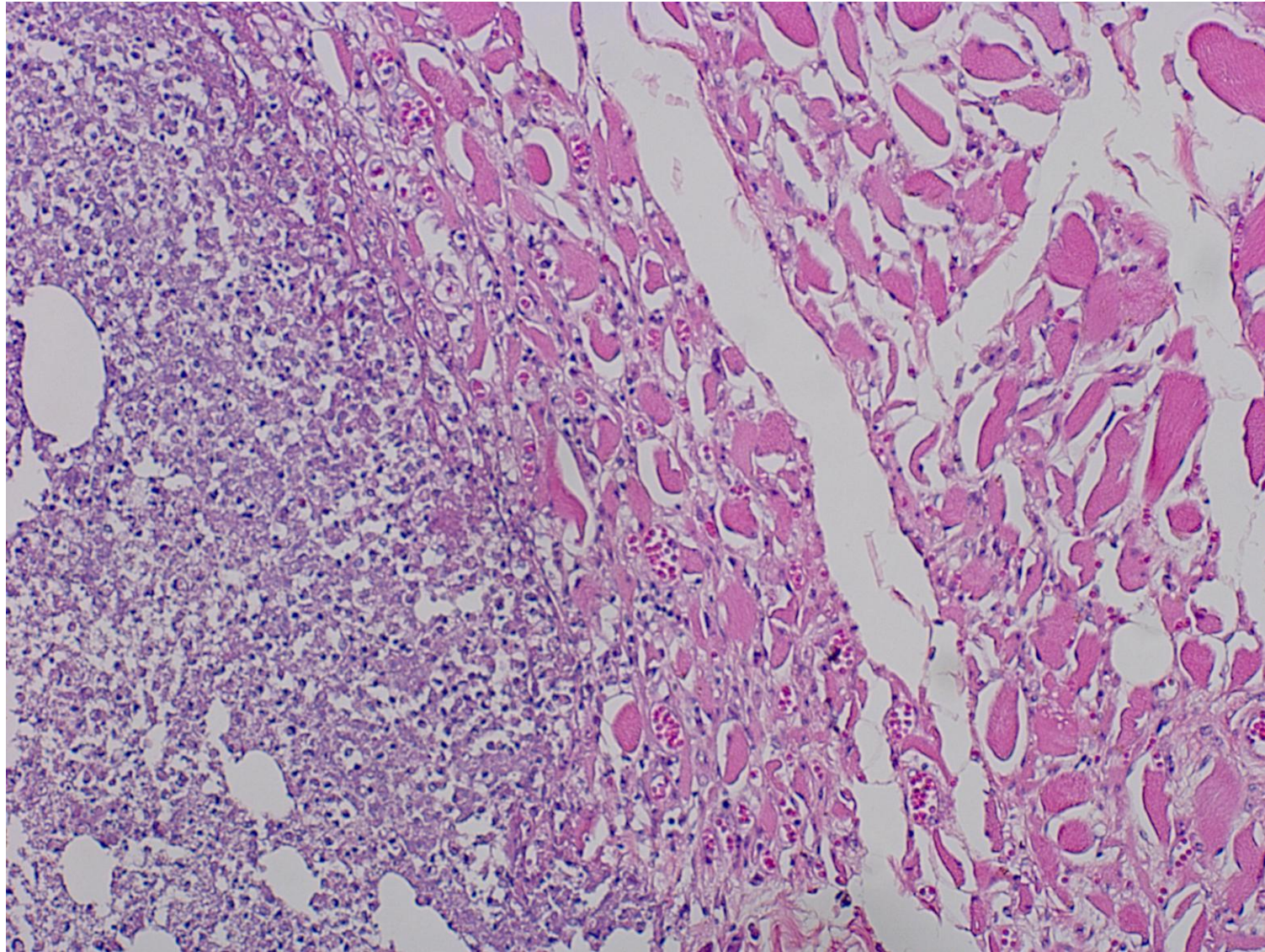
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The lung shows miliary dissemination of tuberculosis (H&E-f).



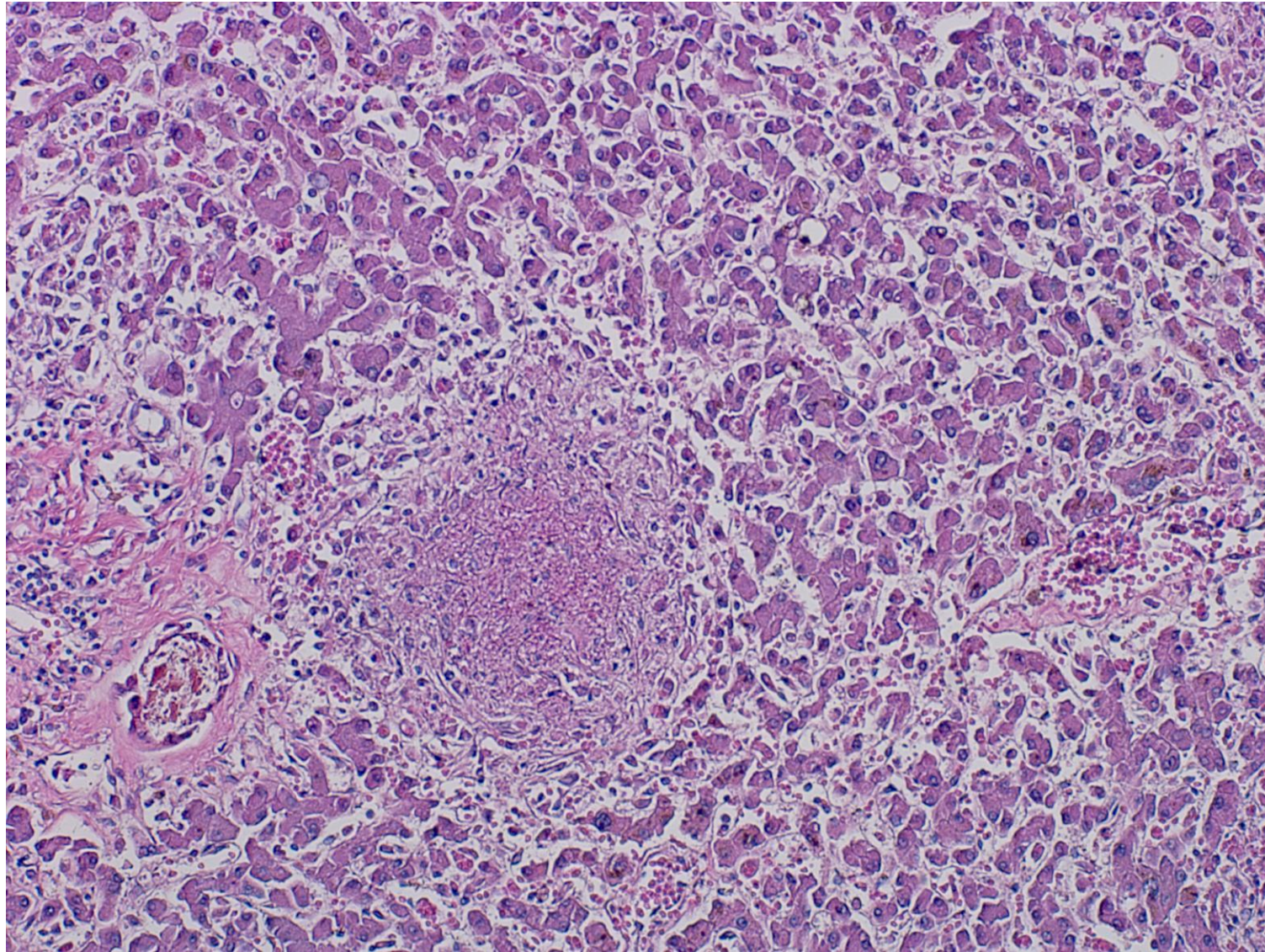
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. Douglass fossa (the rectal serosa) grossly reveals coalesced yellowish-colored exudation on the peritoneum.



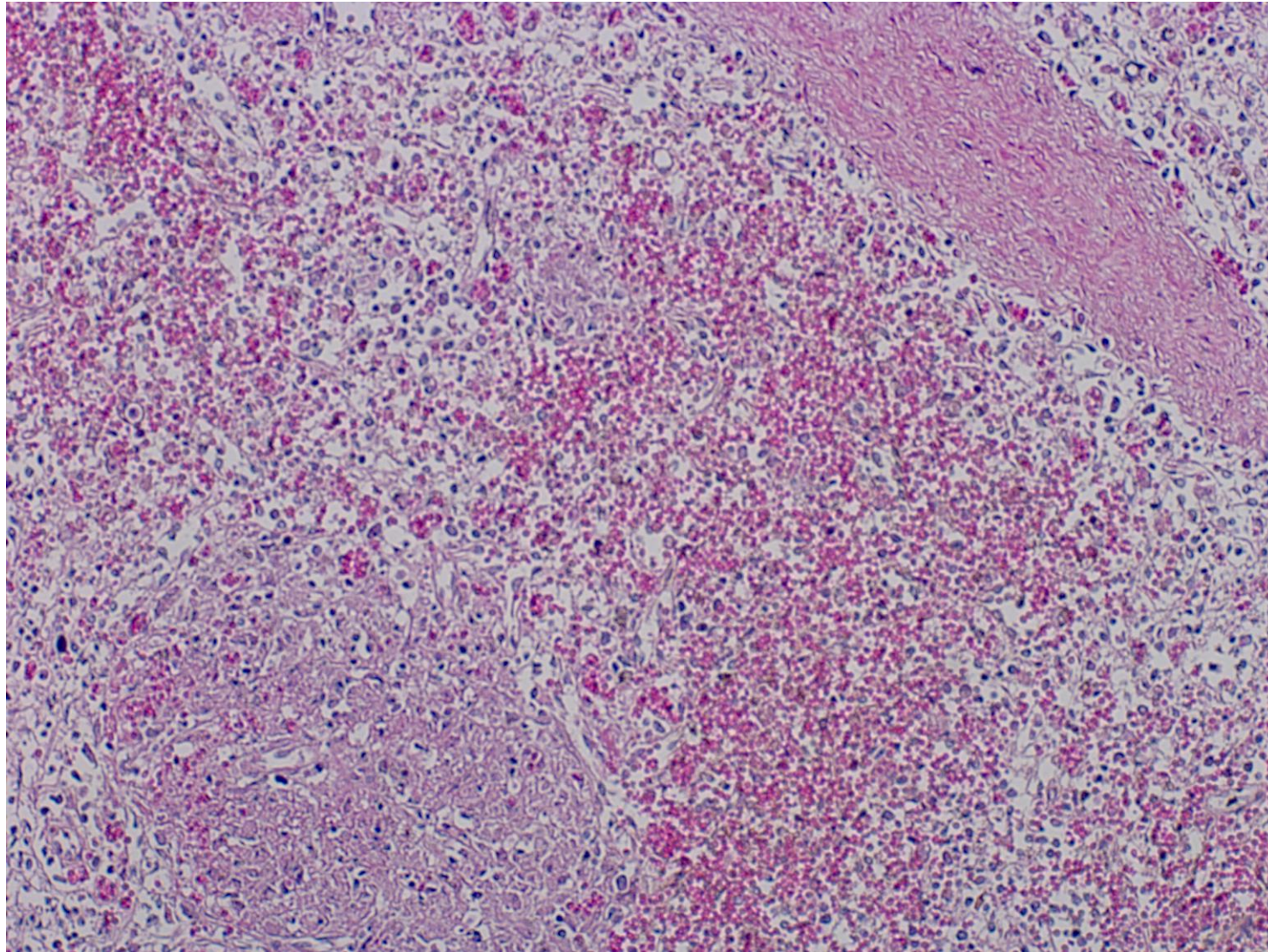
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. Douglass fossa (the rectal serosa) microscopically reveals actively exudative inflammation consisting of neutrophils and activated macrophages (H&E-f). Ziehl-Neelsen stain identifies numerous acid-fast bacilli.



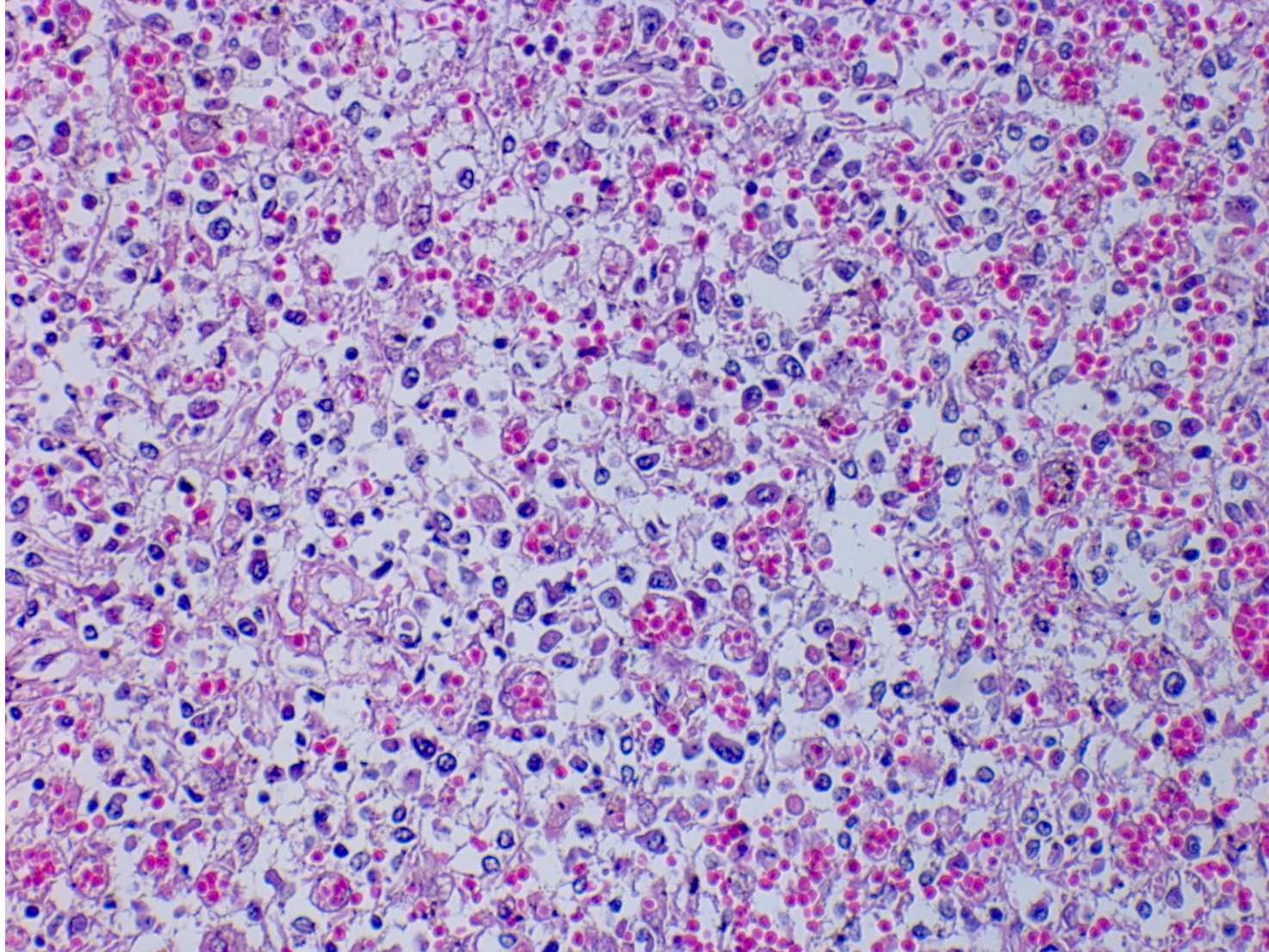
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The diaphragmatic surface reveals actively exudative inflammation consisting of neutrophils and activated macrophages. The diaphragmatic striated muscle layer is deranged and regenerative (H&E-g).



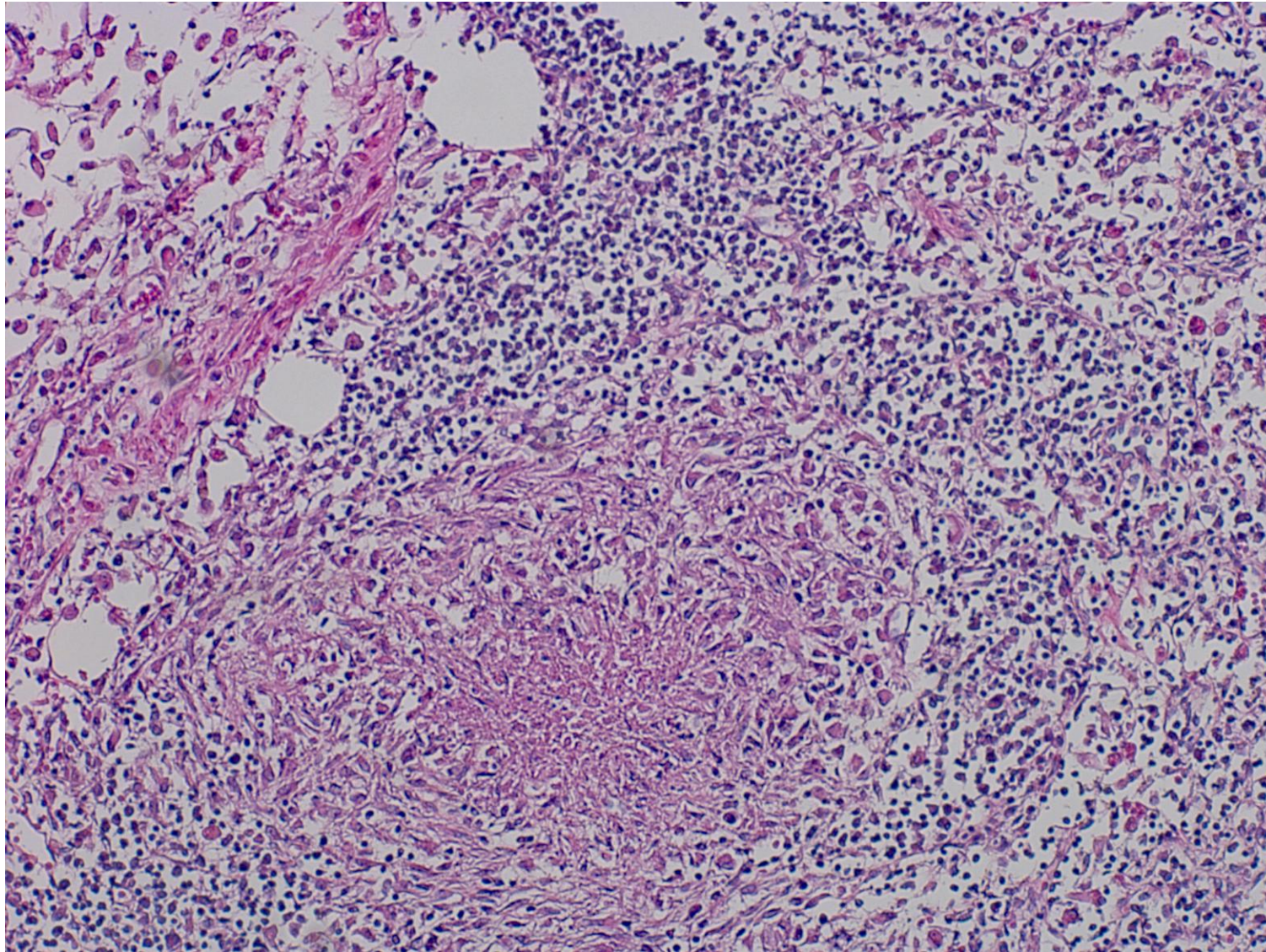
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The liver microscopically reveals miliary tuberculosis of exudative type in the liver parenchyma (H&E-h).



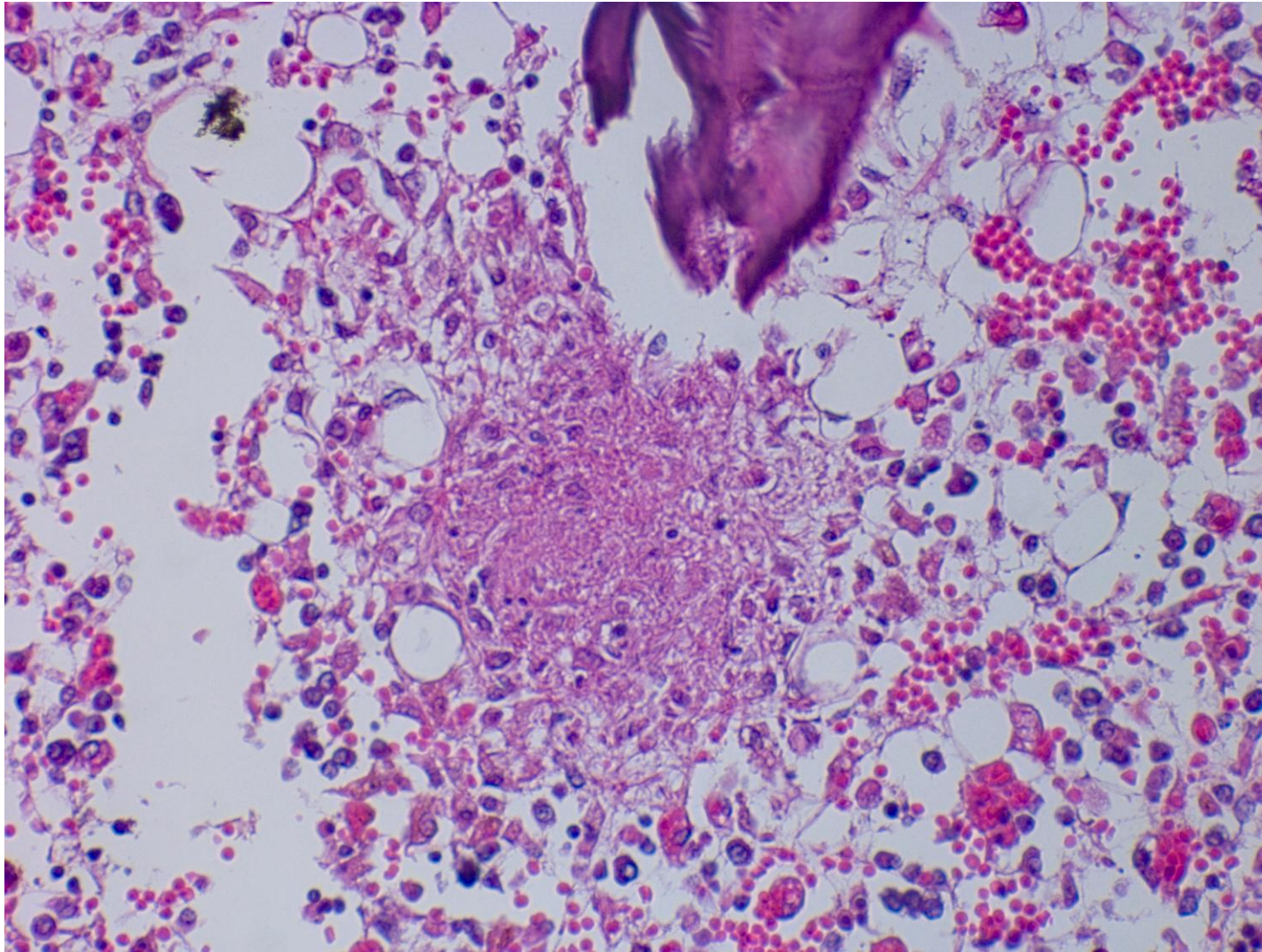
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The spleen microscopically reveals miliary tuberculosis of exudative type in the red pulp. Hemophagocytosis is associated (H&E-i).



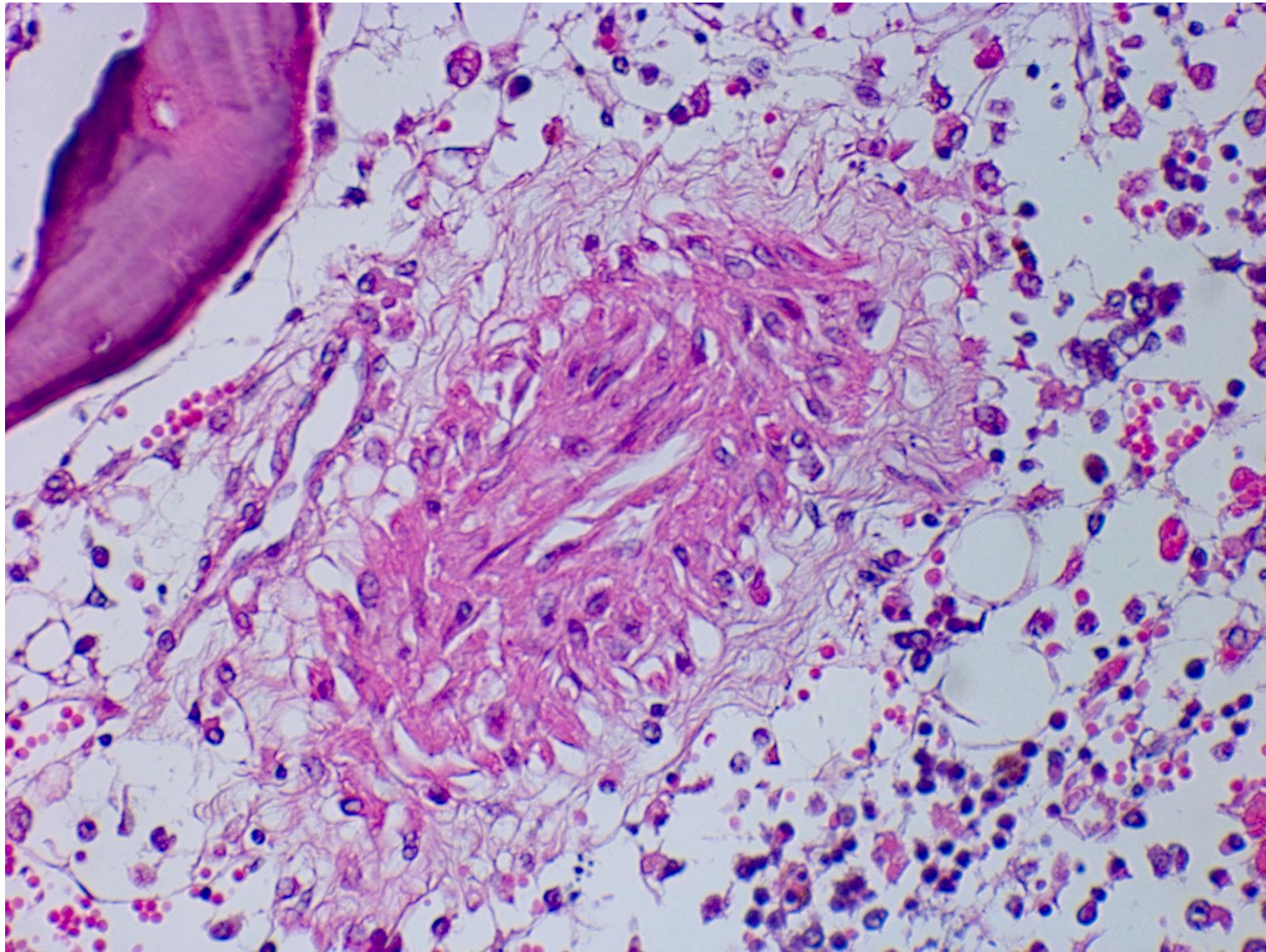
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The splenic red pulp microscopically reveals active erythrophagocytosis by activated macrophages (H&E-j).



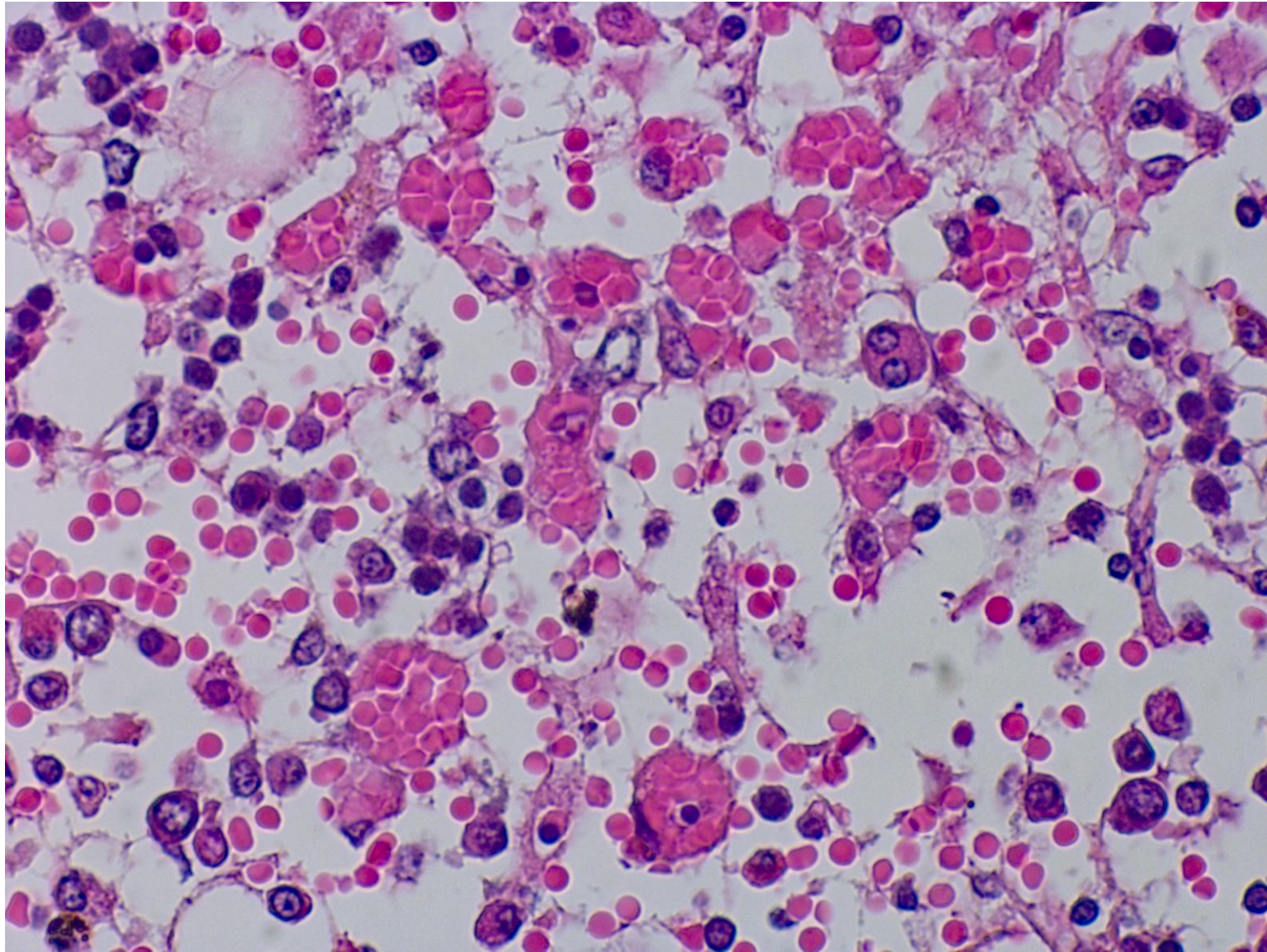
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The lymph node microscopically reveals miliary tuberculosis of exudative type in nodal parenchyma. Hemophagocytosis is associated (H&E-k).



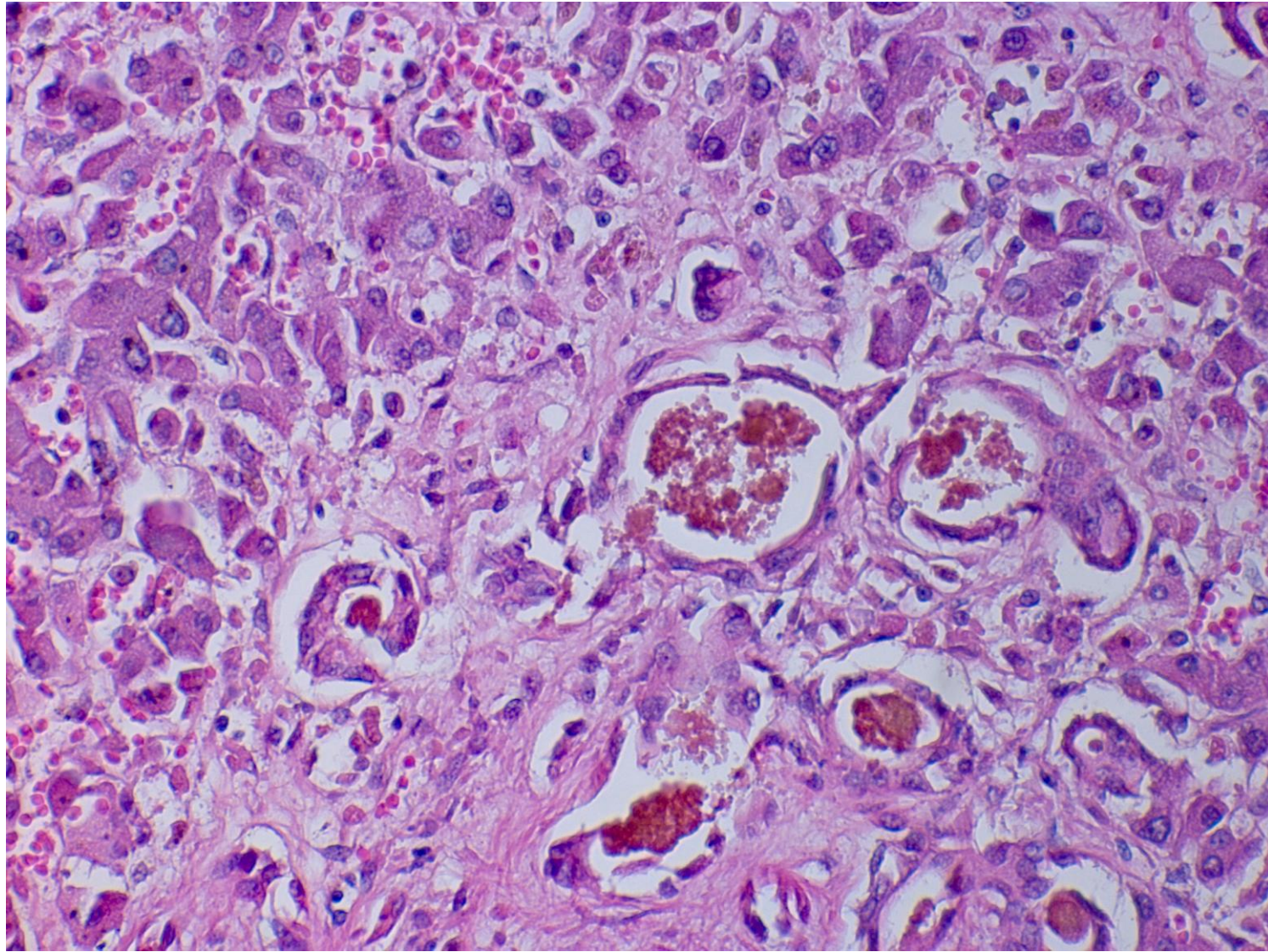
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The bone marrow microscopically reveals miliary tuberculosis of exudative type. Hemophagocytosis is associated (H&E-I).



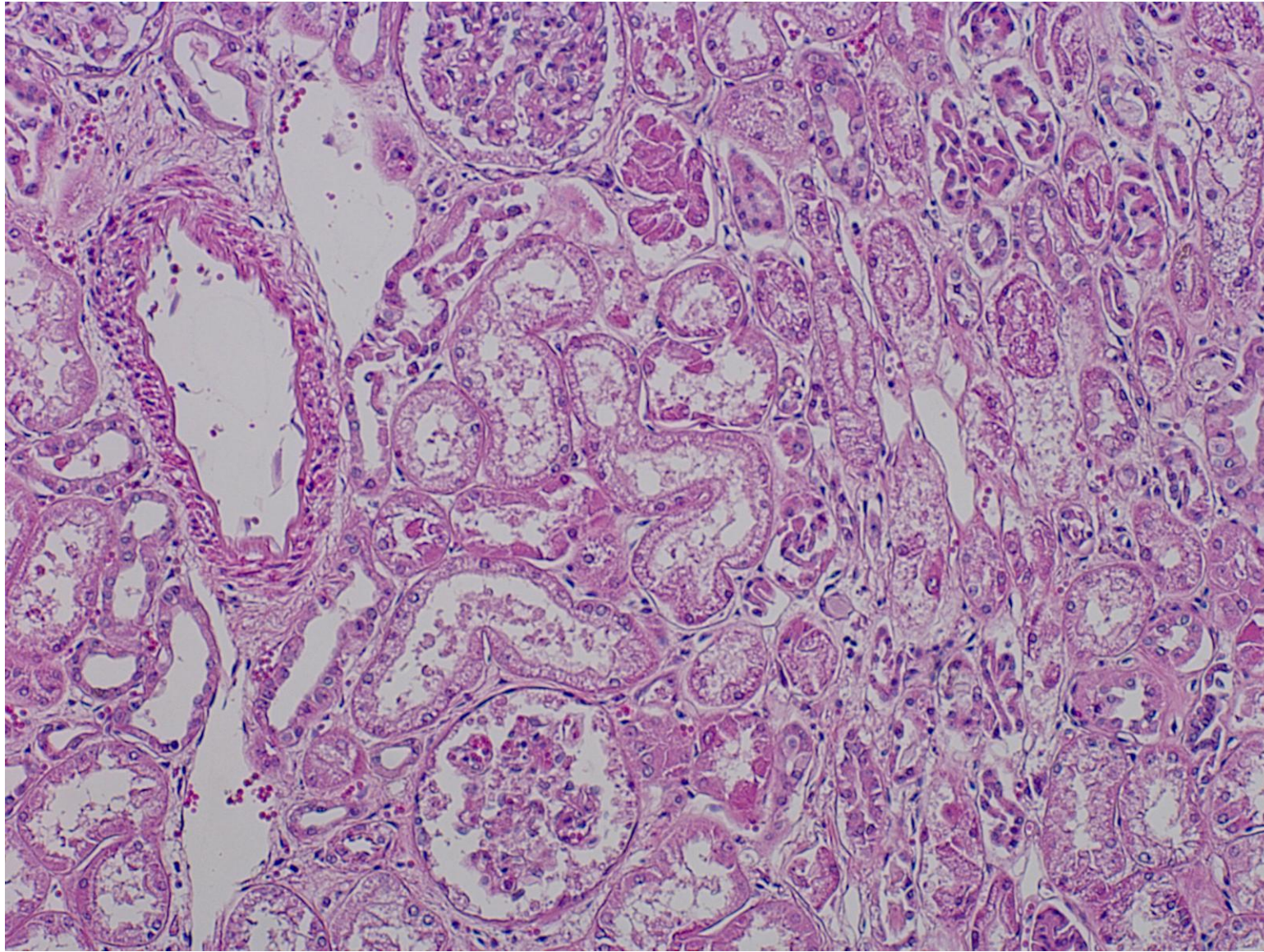
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The bone marrow microscopically reveals miliary tuberculosis of epithelioid granuloma type, an exceptional host reaction in the present case. Hemophagocytosis is associated (H&E-m).



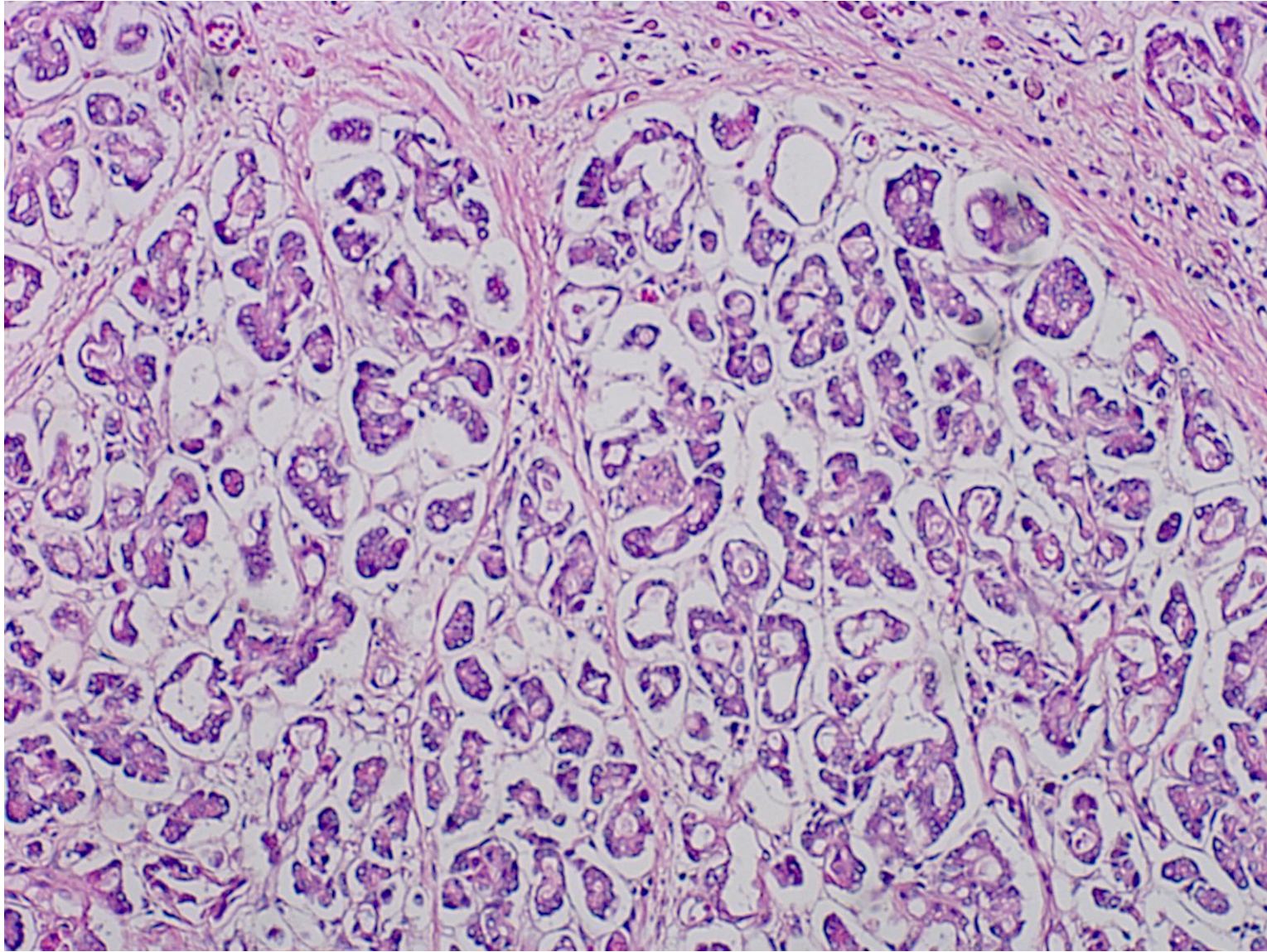
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The bone marrow microscopically reveals active erythrophagocytosis by activated macrophages (H&E-n).



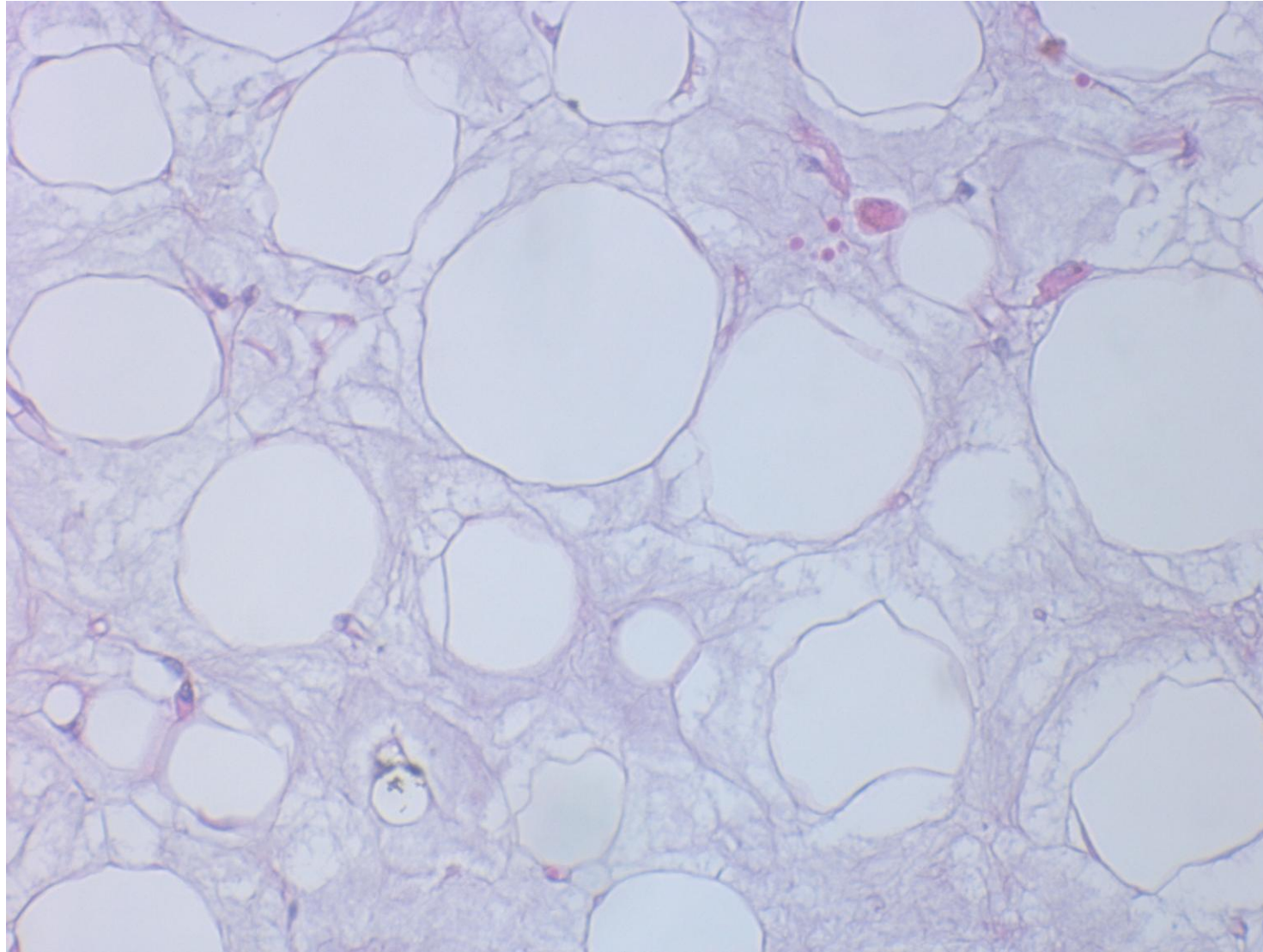
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The liver reveals cholestasis in the bile ductules in the portal triad (H&E-o).



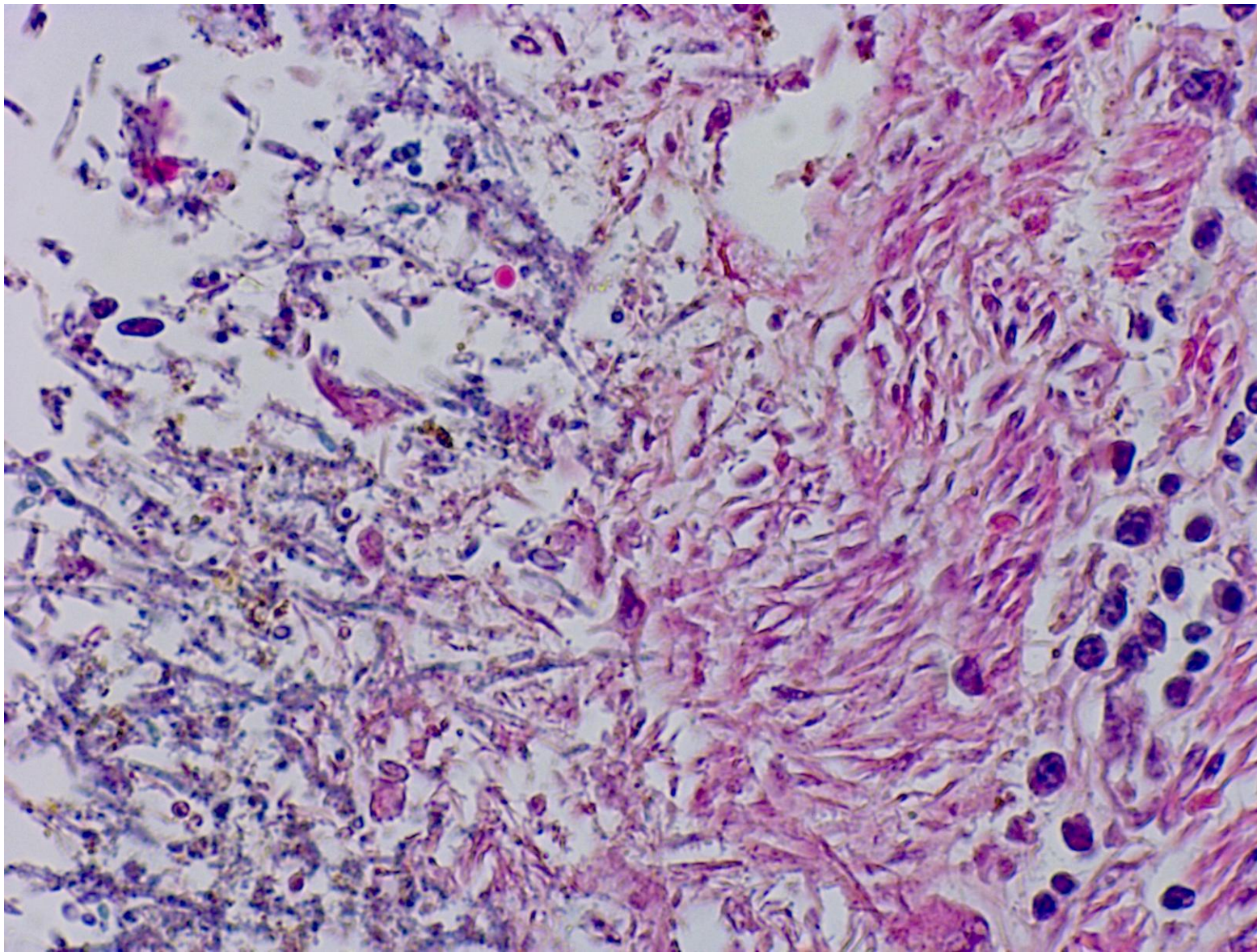
Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The kidney (weighing 160 g) microscopically reveals features of acute tubular necrosis (shock kidney) (H&E-p).



Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The pancreas microscopically reveals acinar ectasia (H&E-q).



Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The renal hilus microscopically reveals serous atrophy of fat tissue (H&E-r).



Gastrointestinal stromal tumor (GIST) of the duodenum seen in a 61 y-o male patient, 11 months after pylorus-preserving pancreatoduodenectomy with 10 months administration of Imatinib. The esophagus reveals candida infection (H&E-s).

Final anatomical diagnosis

1. Gastrointestinal stromal tumor of the duodenum, high-grade, 6 x 6 cm
 - a) S/P: pancreatoduodenectomy (11 months earlier)
without local recurrence
 - b) S/P: Gleevec (Imatinib mesylate) administration for 10 months
 - c) Liver metastasis, multifocal, max 9 cm
with Imatinib-related therapeutic effect
2. Exudative tuberculosis (both lungs, pleura and peritoneum)
with numerous acid-fast bacilli
 - a) Ascites (1,000 mL) and pleural effusions (left: 550 mL, right: 600 mL)
 - b) Systemic miliary tuberculosis (exudative type)
epithelioid cell granuloma seen focally in the bone marrow miliary nodule
 - c) Hemophagocytosis
 - d) Multiorgan failure
(jaundice/cholestasis, renal acute tubular necrosis, pancreatic acinar ectasia, DIC)
3. Emaciation (cachexia)
 - a) Decubitus (sacral region)
 - b) Serous atrophy of fat tissue
4. Esophageal candidosis