Paraneoplastic pemphigus caused by mantle cell lymphoma

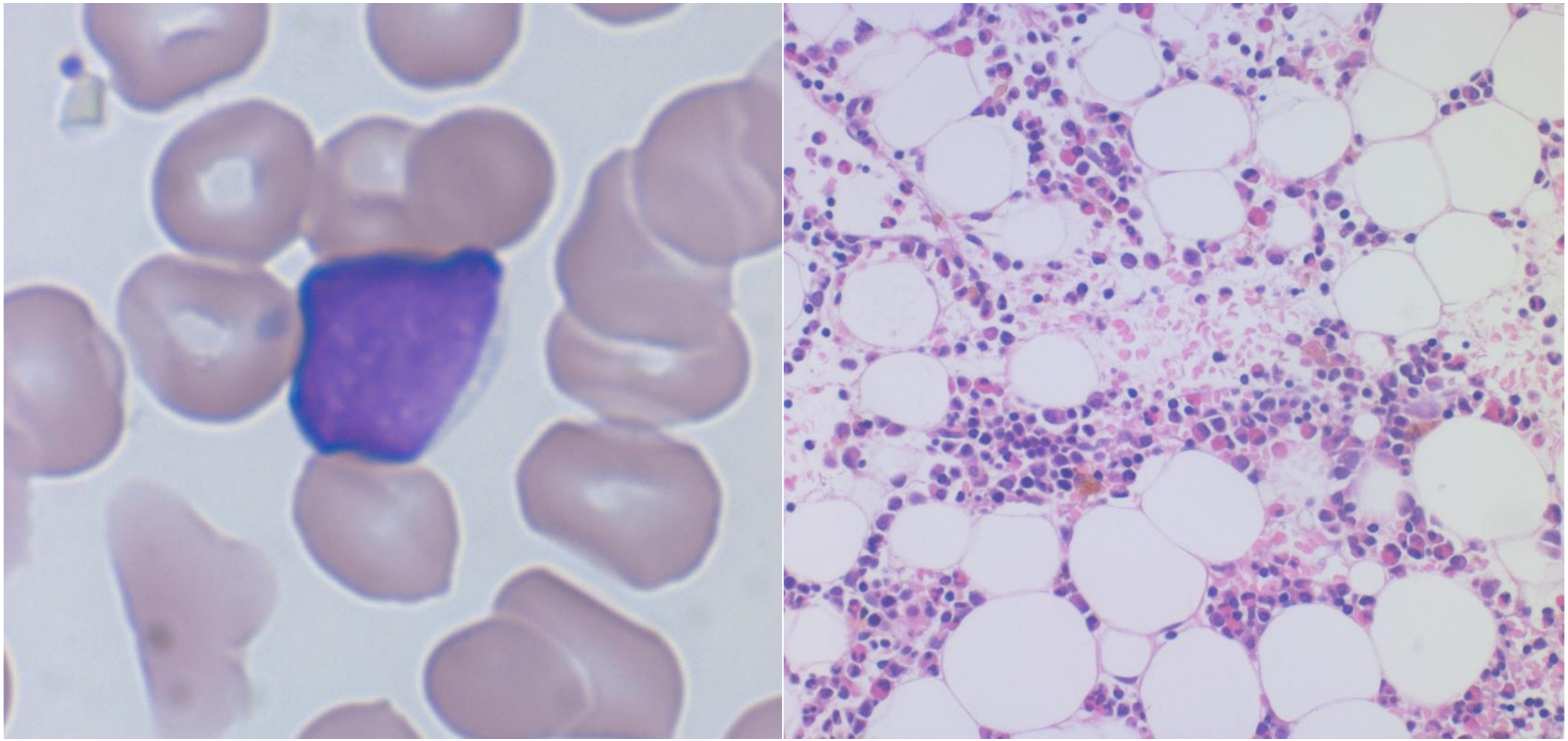
Paraneoplastic pemphigus (PNP), an autoimmunity-mediated, blister-forming mucocutaneous disorder, is a rare complication of malignancy. PNP shows a poor prognosis: most of the patients die within a year after diagnosis. Immunosuppressive therapy may provoke opportunistic infections, and progression of the underlying malignancy may cause death.

PNP is frequently associated with hematologic neoplasms, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia. PNP-related mucocutaneous lesions may manifest prior to tumor identification. PNP affects the lung together with the skin and oral mucosa: bronchiolitis obliterans is a unique form of PNP-related lung lesions. PNP may damage the gastrointestinal tract.

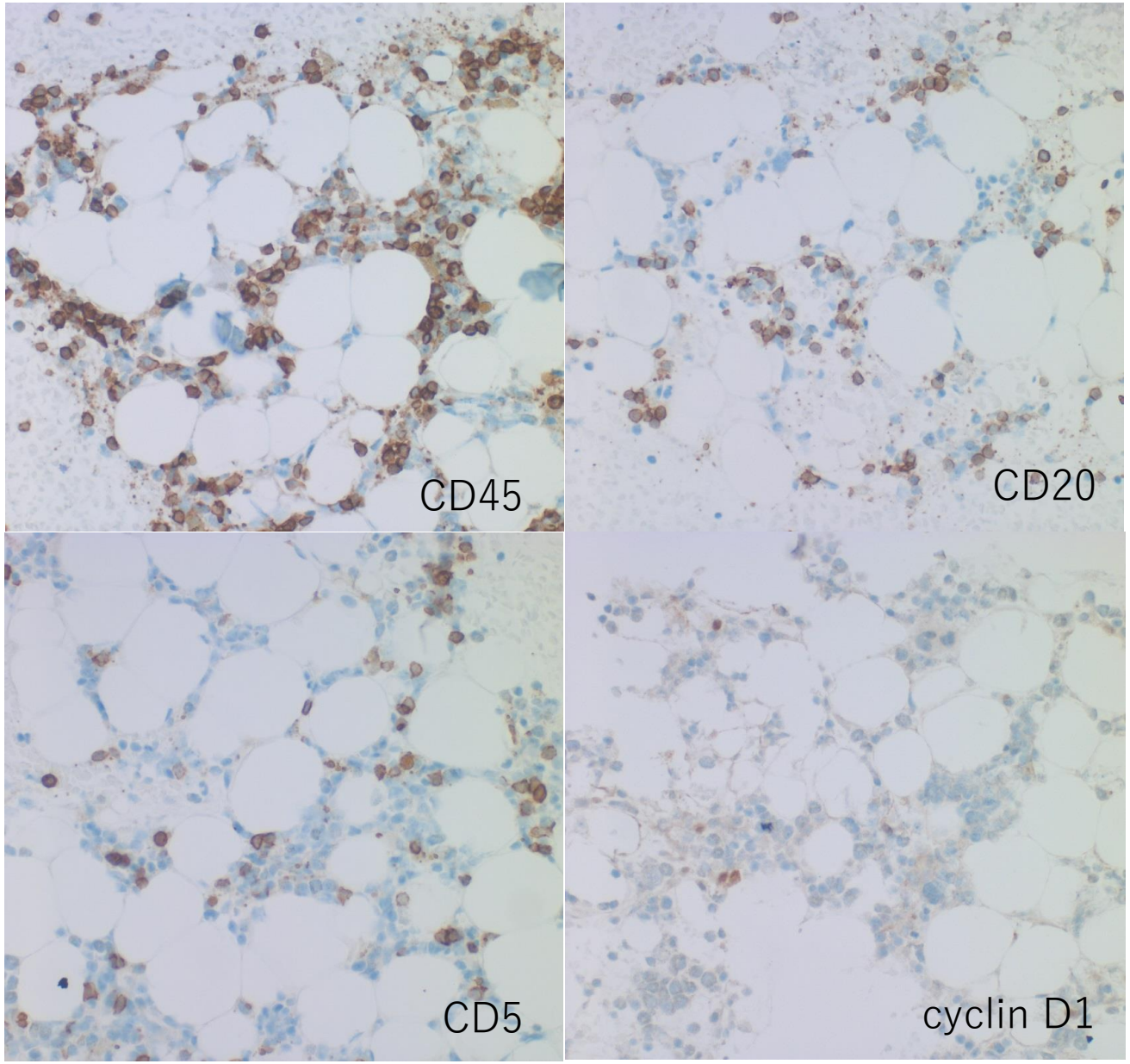
PNP is serologically featured by autoantibodies to varied keratinocyte-associated proteins, commonly belonging to IgG-type. The autoantibodies are targeted at desmosome-related cadherin-like molecules and plakin proteins that connect the cadherin-like molecules and cytokeratin filaments. The lung lesions are closely related to anti-epiplakin antibody and desmoglein-3 antibody.

Ref.: Odani K, et al. Paraneoplastic pemphigus involving the respiratory and gastrointestinal mucosae. Case Rep Pathol 2020; 2020: 7350759. doi: 10.1155/2020/7350759

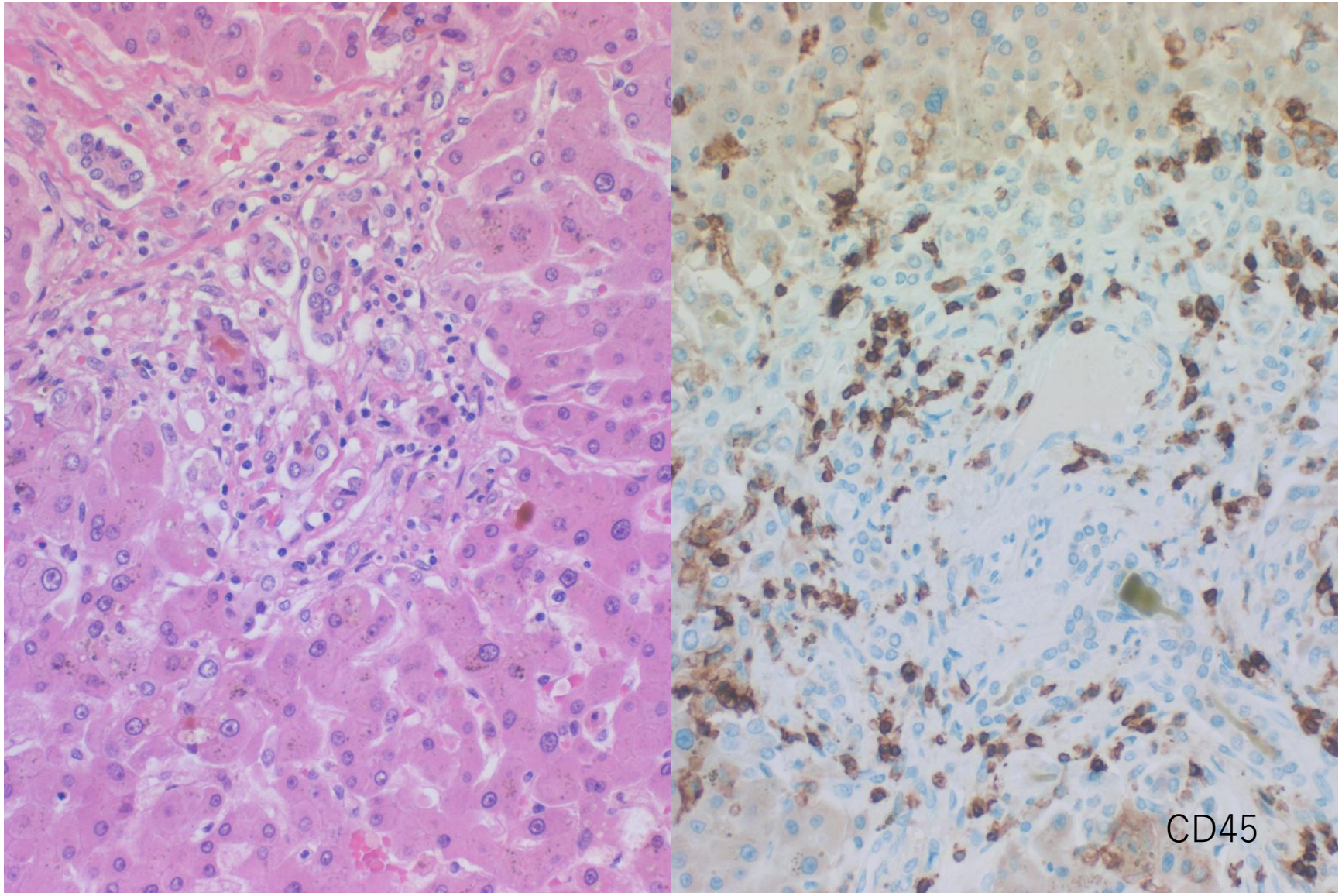
A 70-year-old male complained of dry cough, stomatitis and sore throat. The lips and oral mucosa were severely eroded and skin eruptions were seen on the chest and abdomen. Serum autoantibodies to desmoglein-3, desmocollin-2 and -3, bullous pemphigoid antigen-1, envoplakin and periplakin were proven. Systemic evaluation disclosed mantle cell lymphoma, stage 4B. Chemotherapy led the lymphoma to partial remission. PNP was treated with methylprednisolone and intravenous immunoglobulins, and the oral lesion temporarily responded to the immunoglobulin therapy. He died of respiratory failure two months after onset. Autopsy revealed residual lymphoma and systemic opportunistic infections. Aspergillus colonized the eroded bronchial/bronchiolar mucosa, with extensive vascular invasions. Co-infection of cytomegalovirus (CMV) and *Pneumocystis jirovecii* was noted. The oropharyngeal, esophageal and gastrointestinal mucosae were multifocally infected by CMV. Bronchiolitis obliterans was observed in the peripheral lung. Furthermore, PNP-related acantholytic mucosal lesions were microscopically identified in the lung and gastrointestinal mucosa. IgG deposited on the involved mucosal columnar cells, accompanying cleaved caspase-3-immunoreactive apoptotic cell death.



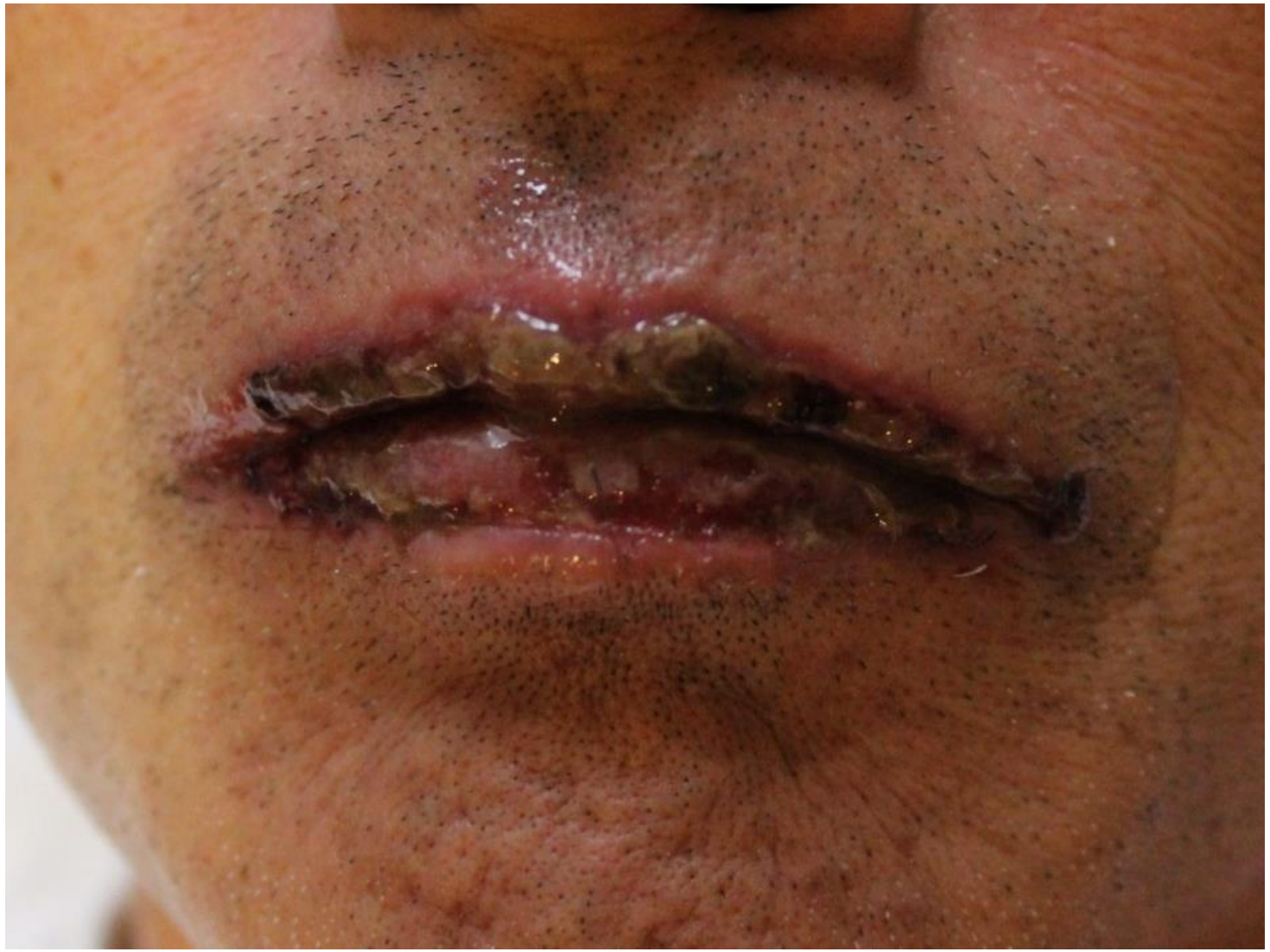
Bone marrow involvement of mantle cell lymphoma. Aspiration specimens show infiltration of mantle cell lymphoma. Small-sized lymphoid cells infiltrate the marrow space. The lymphomatous infiltration is not massive. (left: May-Giemsa, right: H&E)



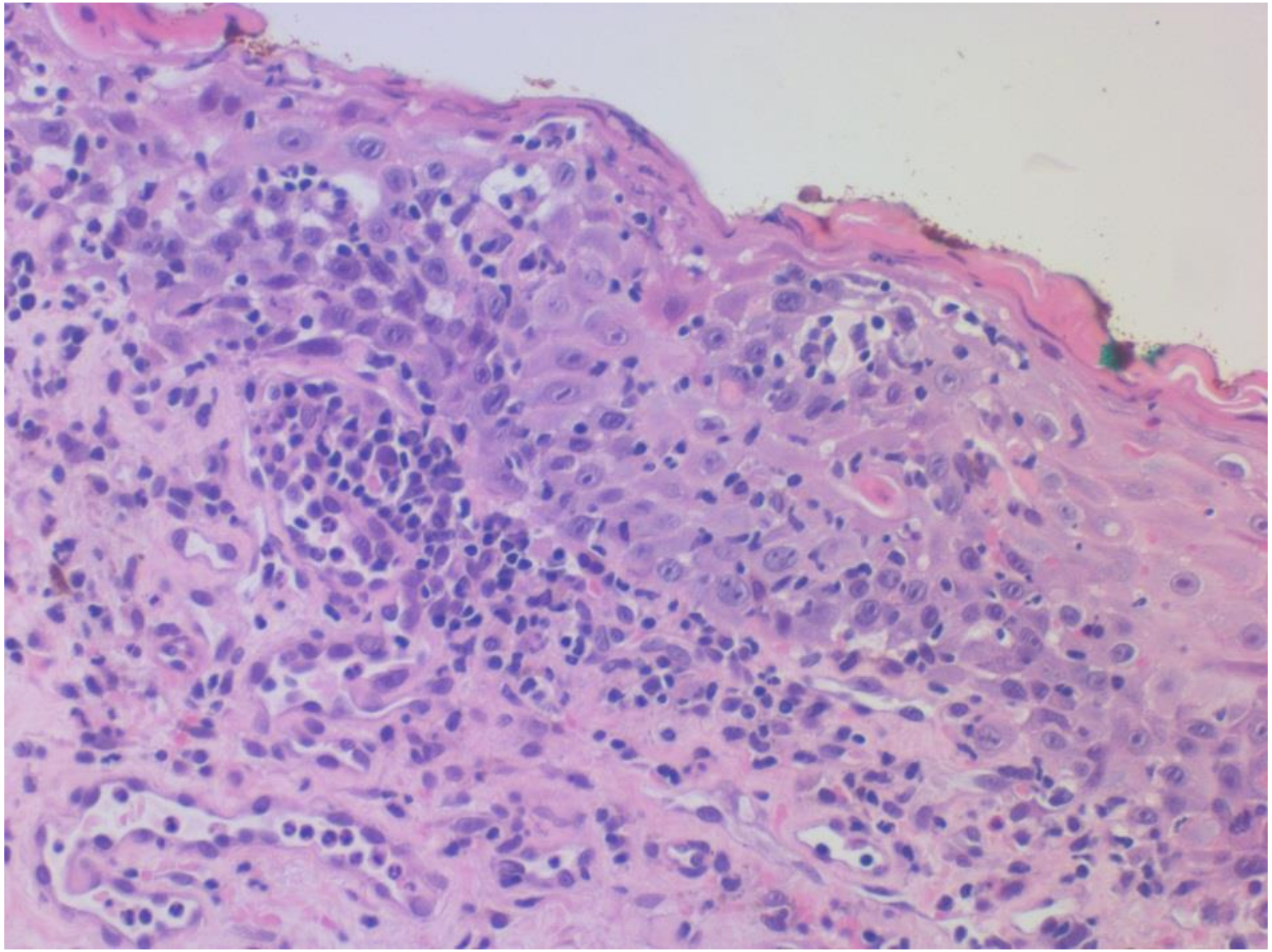
Bone marrow involvement of mantle cell lymphoma. Atypical small lymphocytes are immunoreactive for CD45, CD20 and CD5. Some cells express cyclin D1 in the nuclei.



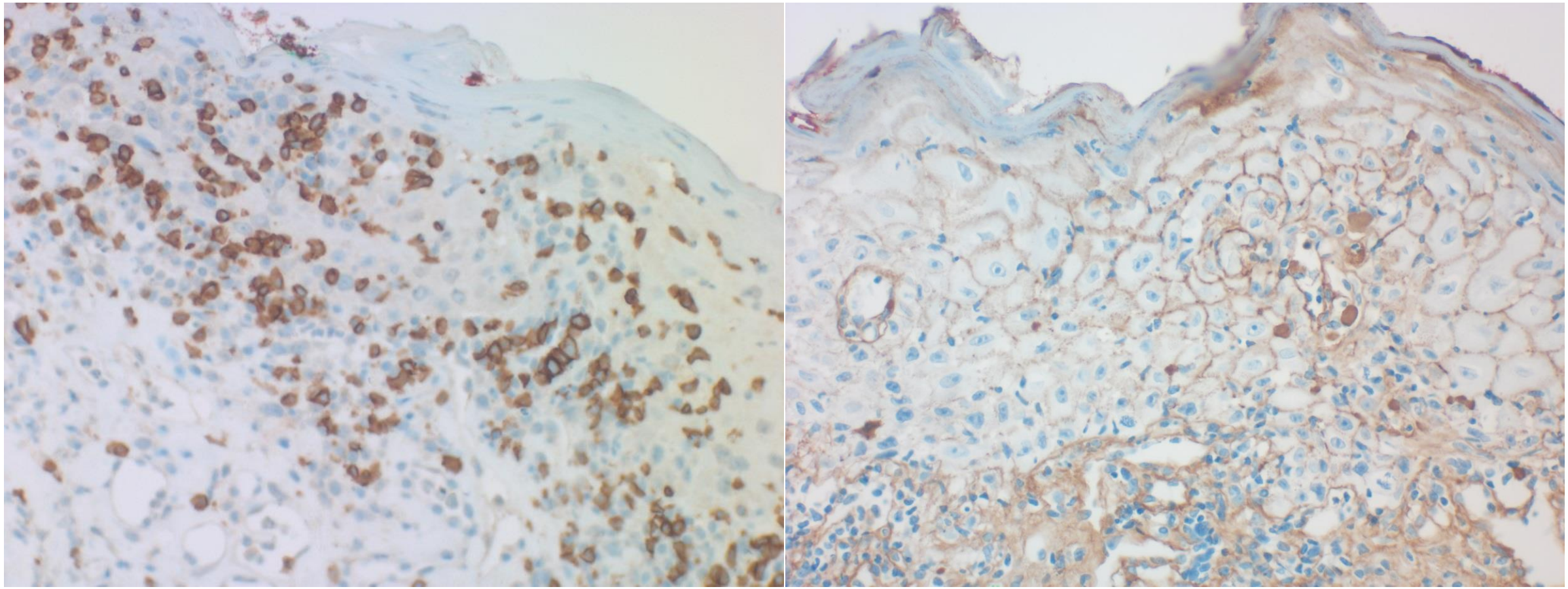
Liver involvement of mantle cell lymphoma at autopsy. Atypical small lymphocytes immunoreactive for CD45 mildly remain in the portal triad.



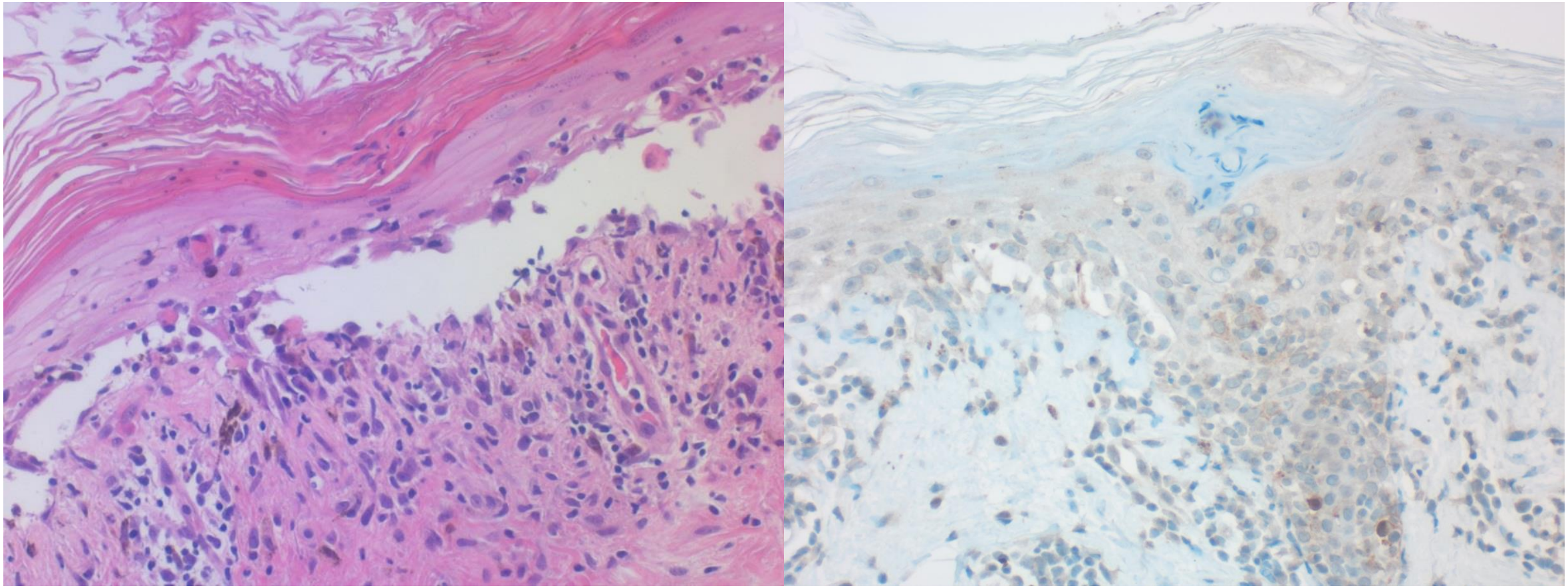
Paraneoplastic pemphigus in a 70-year-old male patient. The lips grossly reveal extensive erosions.



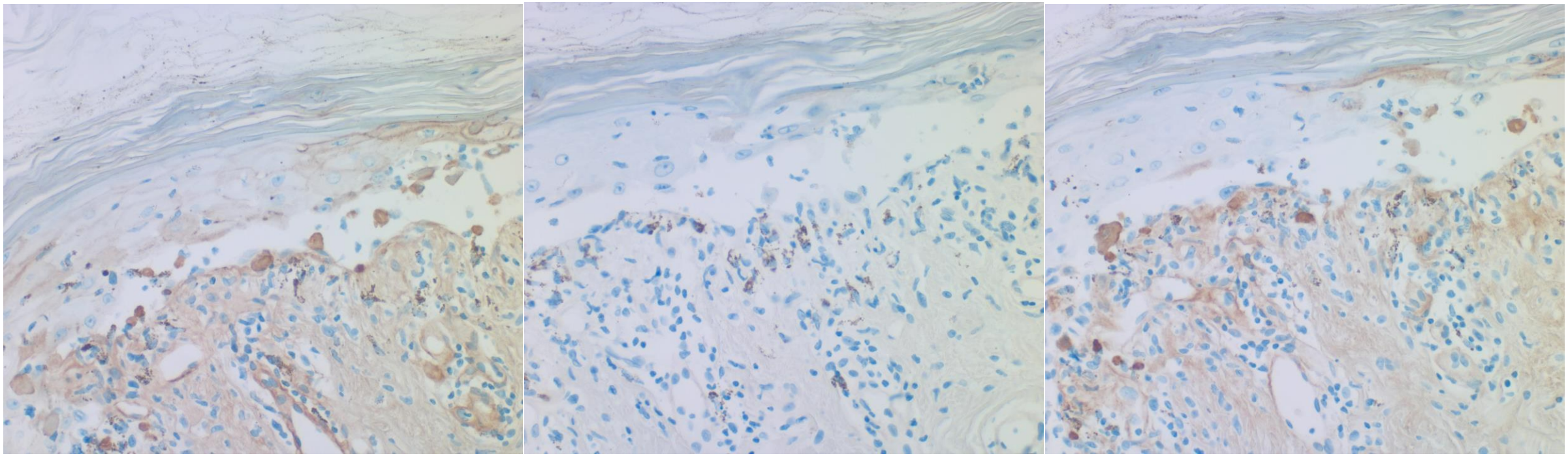
Paraneoplastic pemphigus in a 70-year-old male patient. Lip biopsy reveals infiltration of small lymphocytes in both the spongiotic epidermis with graft-versus-host disease-like appearance and upper dermis. H&E



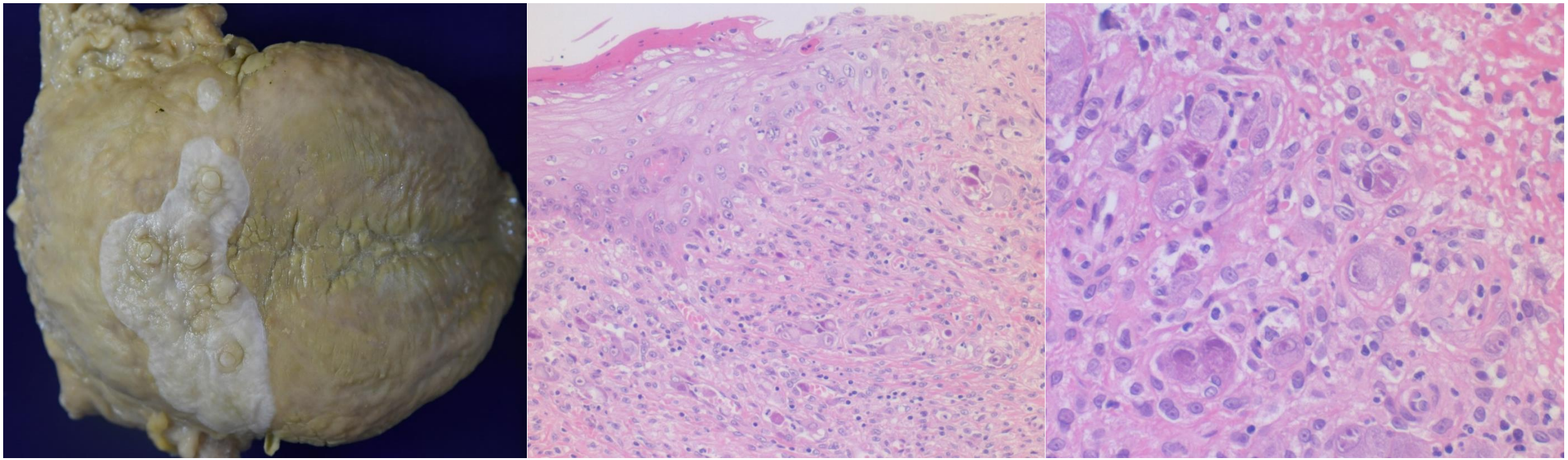
Paraneoplastic pemphigus in a 70-year-old male patient. In the lip, lymphocytes are predominantly immunoreactive for CD8 (left). After proteinase-1 digestion of the paraffin section, IgG deposition along the plasma membrane of the involved keratinocytes is proven (right).



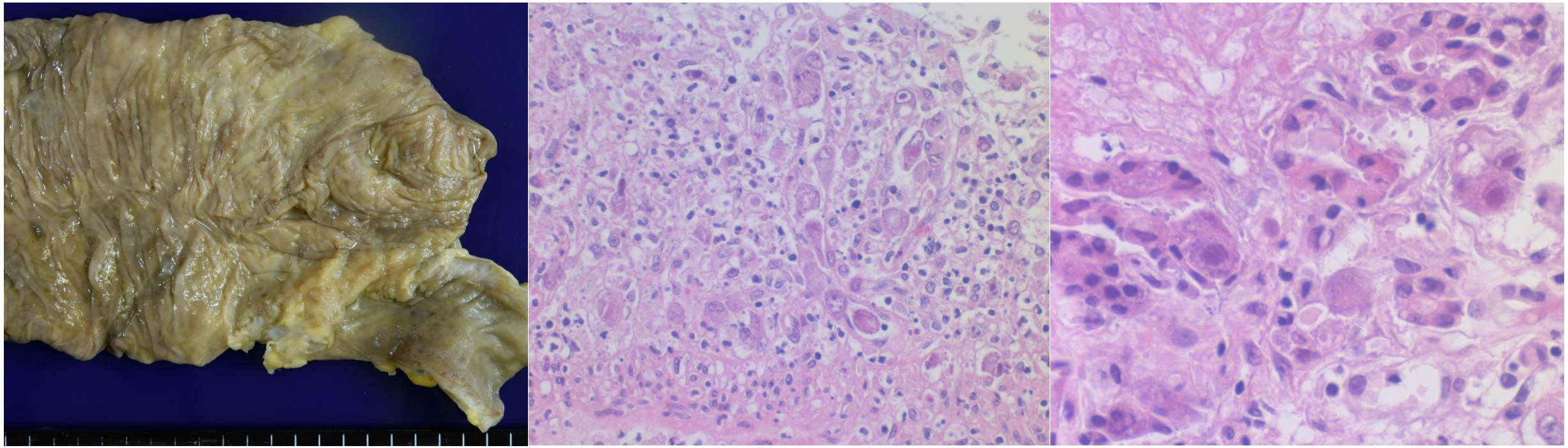
Paraneoplastic pemphigus in a 70-year-old male patient. Biopsy from the abdominal skin exhibits pemphigus vulgaris-like interface blister formation. Acantholytic keratinocytes and Civatte bodies are scattered (left: H&E). Cleaved caspase-3 immunoreactivity is seen in apoptotic keratinocytes (right).



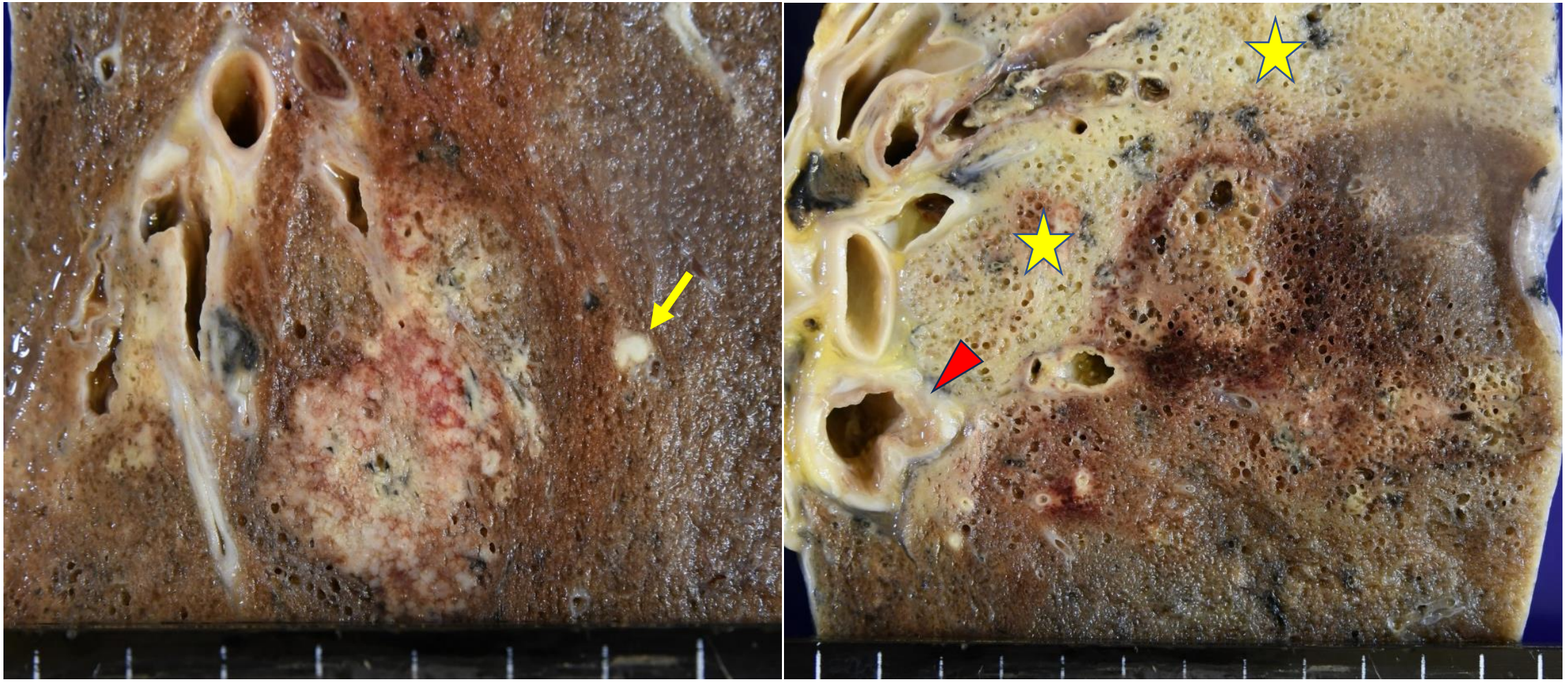
Paraneoplastic pemphigus in a 70-year-old male patient. Biopsy from the abdominal skin with pemphigus vulgaris-like interface blister formation. Acantholytic keratinocytes are labeled for IgG (left), but not for IgA (center) and IgM (right). Immunostaining using formalin-fixed, paraffin-embedded sections was performed after prolonged proteinase-1 digestion



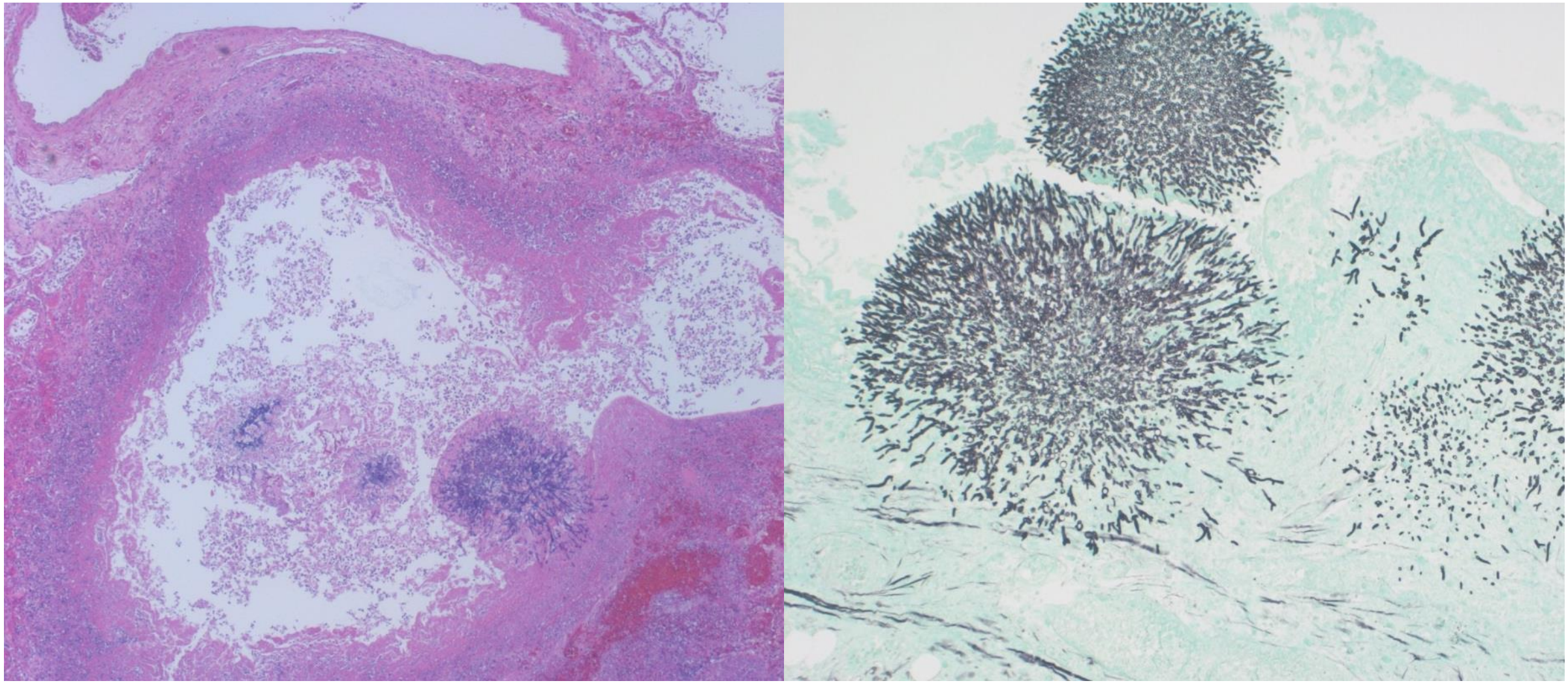
Paraneoplastic pemphigus in a 70-year-old male patient. Opportunistic CMV infection in the tongue mucosa. The tongue is extensively eroded: the white-colored mucosa around the vallate papillae remains intact (left: gross appearance). Glossal erosion adjacent to intact squamous mucosa reveals infection of CMV (center, HE), and the high-powered view clarifies CMV infection in the endothelial cells (right, HE).



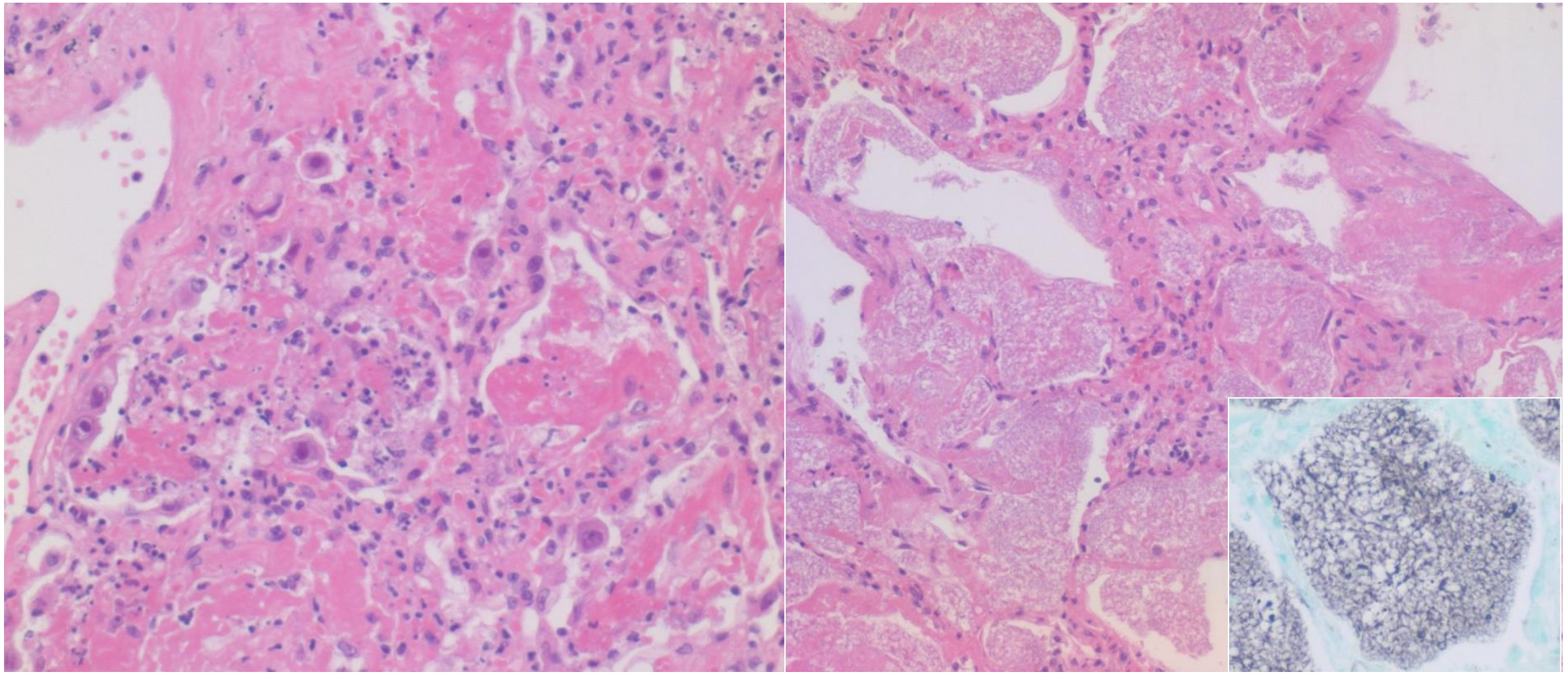
Paraneoplastic pemphigus in a 70-year-old male patient. Multifocal erosions are formed in the mucosae of the terminal ileum and cecum (left: gross appearance). The endothelial cells of the eroded cecal mucosa are heavily infected by CMV, and crypt epithelial cells are lost (center: H&E). CMV infection in the pancreas has provoked fat necrosis (right: H&E).



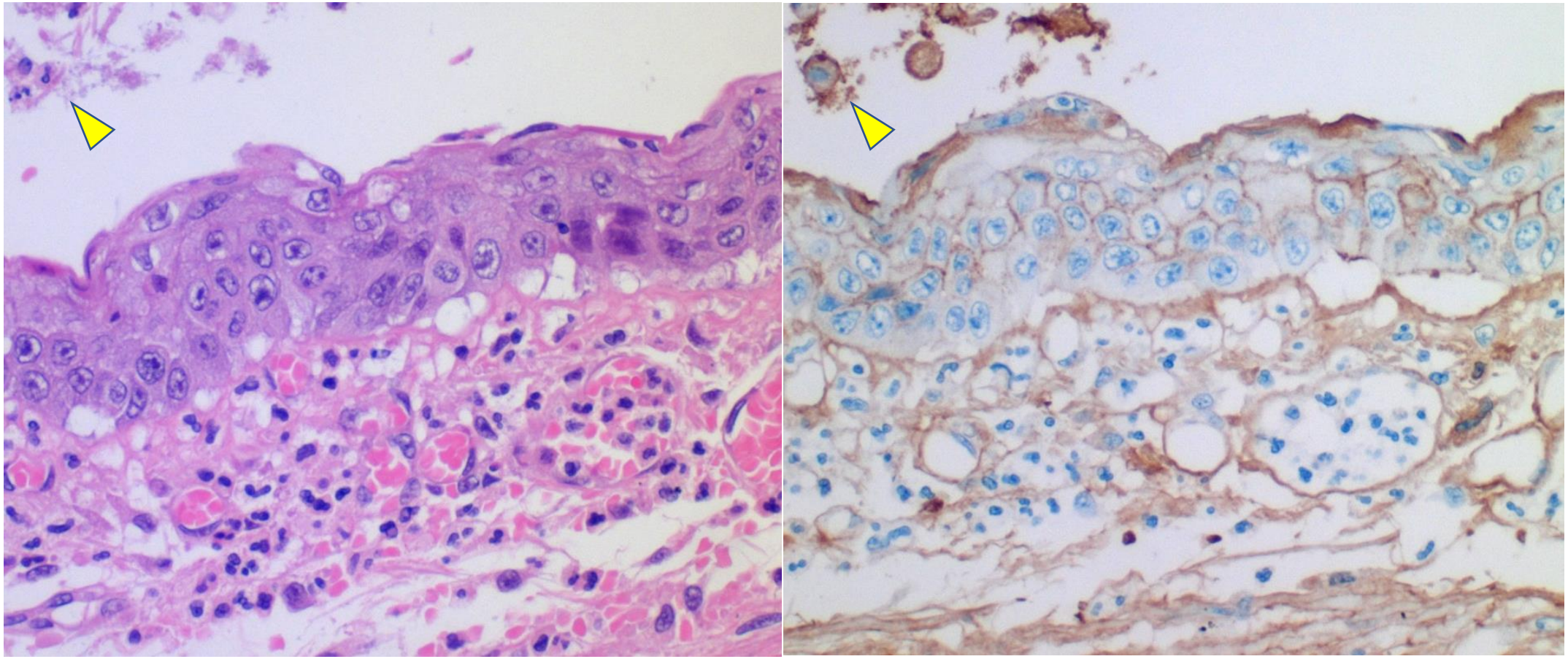
Paraneoplastic pemphigus in a 70-year-old male patient. Opportunistic infections in the lung. Gross appearance of aspergillosis reveals irregular-shaped foci of infarction rimmed with hemorrhage (left and right). Arrow indicates mycotic vascular invasion. Interstitial reactions with fibrinous exudation are seen segmentally (asterisks). Mycosis-induced bronchial mucosal erosion is indicated by arrowhead.



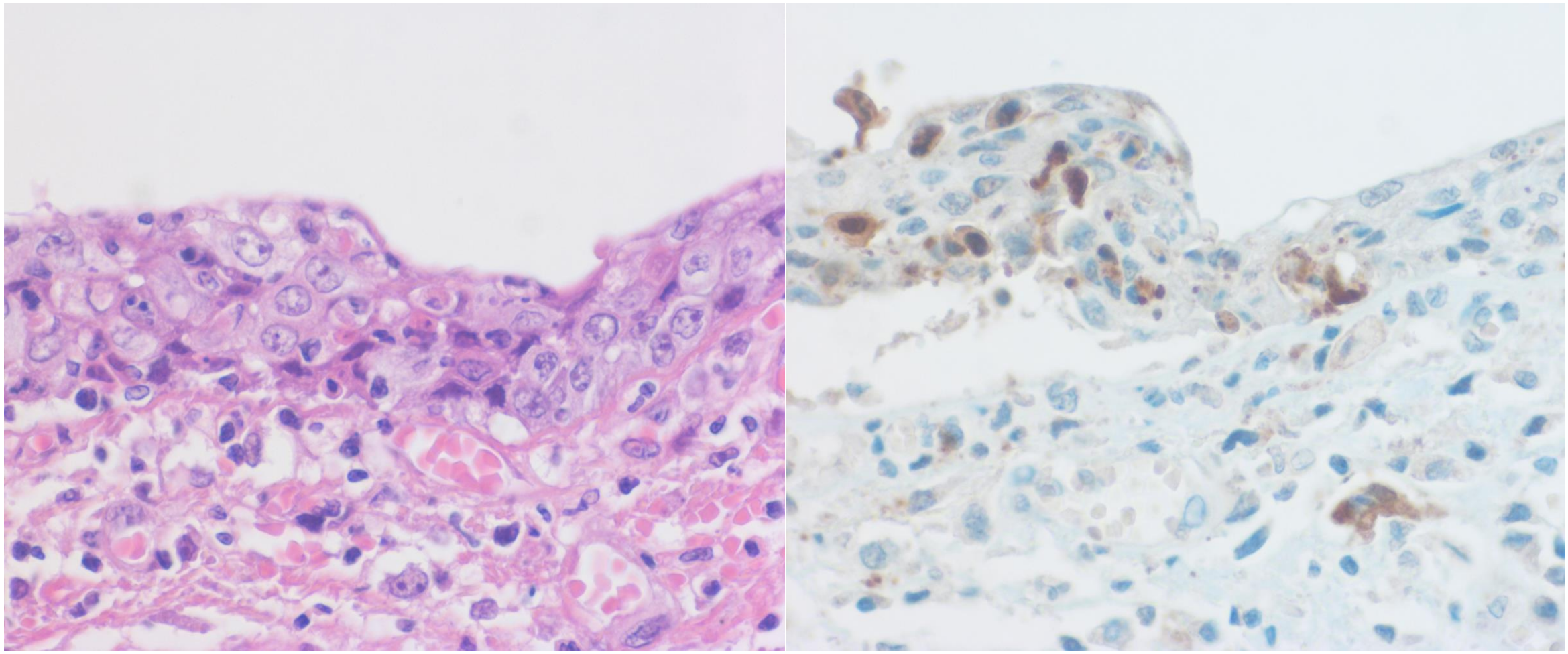
Paraneoplastic pemphigus in a 70-year-old male patient. Hypha-forming Aspergillus colonizes the eroded bronchiolar mucosa (left, H&E). Grocott silver stain clearly reveals hypha-forming colonies on the bronchial mucosa.



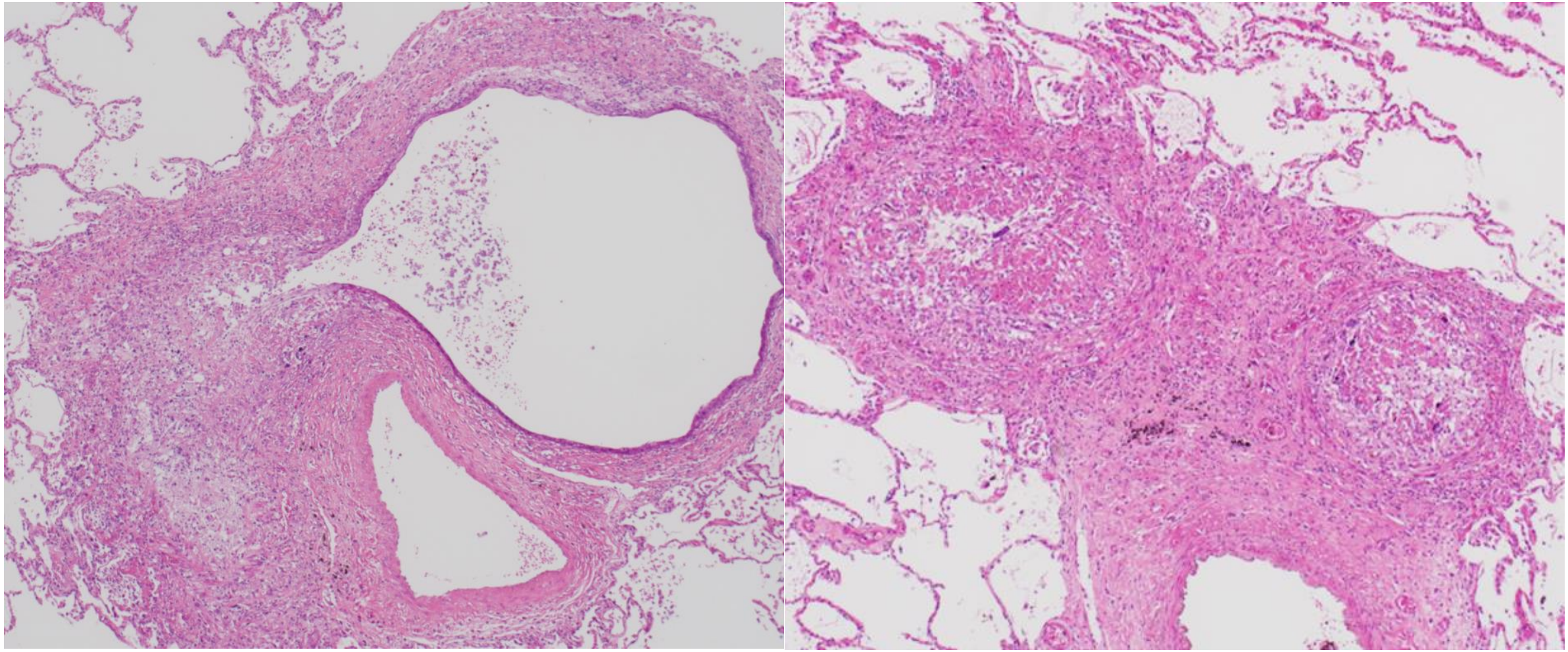
Paraneoplastic pemphigus in a 70-year-old male patient. CMV infection has provoked interstitial pneumonia with intra-alveolar fibrinous exudation (left, HE). Frothy intra-alveolar exudation represents infection of *Pneumocystis jirovecii* (right, HE). Inset demonstrates Grocott-reactive cyst walls of *P. jirovecii*.



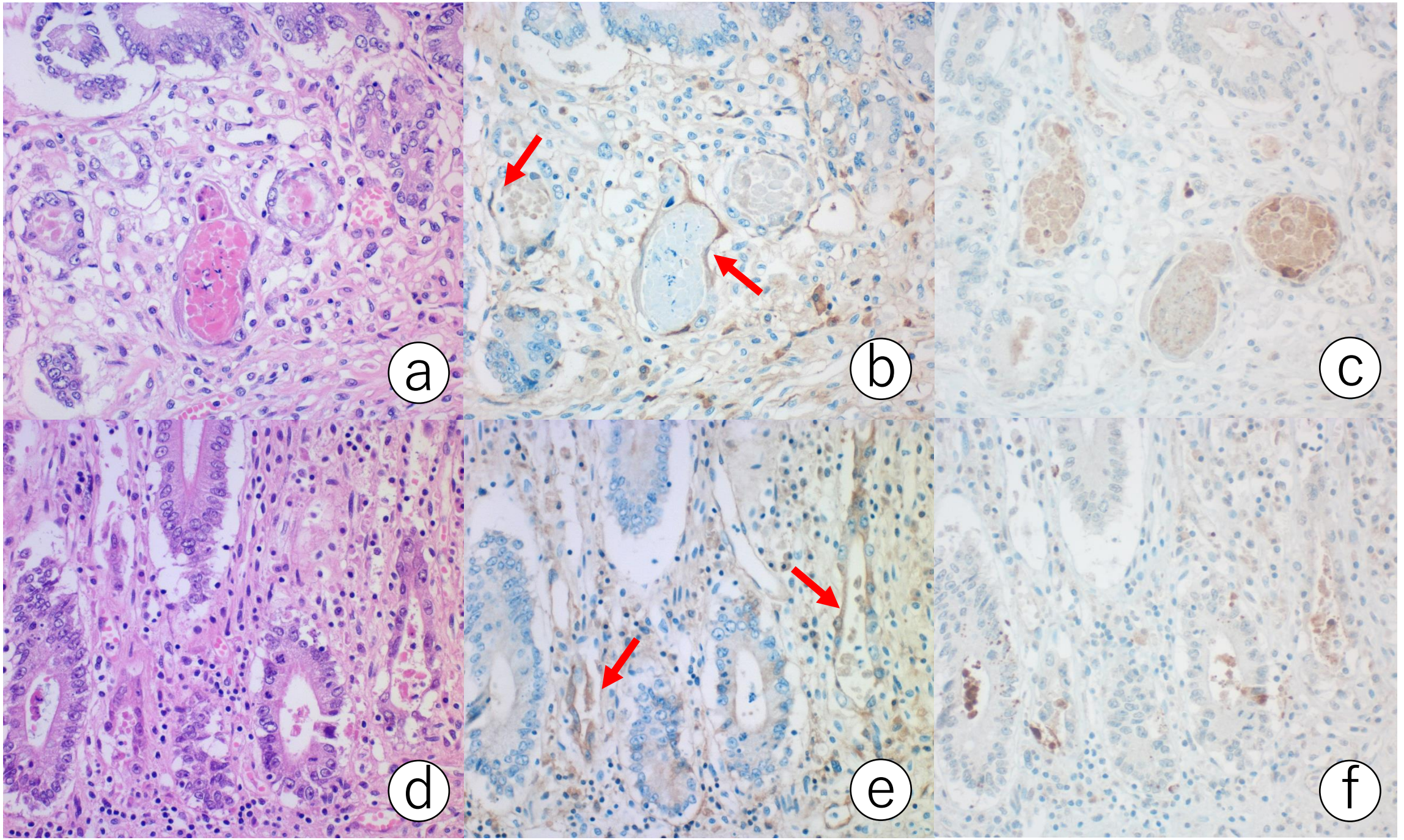
Paraneoplastic pemphigus in a 70-year-old male patient. PNP-related bronchial/bronchiolar lesions. The regenerative bronchial mucosa focally with basal intercellular vesicle formation is associated with IgG deposition on the plasma membrane (left: HE, right: IgG immunostaining after proteinase-1 digestion). Intraluminal cellular debris is also labeled for IgG (yellow arrowheads). The stromal labeling represents endogenous IgG distributed in the tissue fluid.

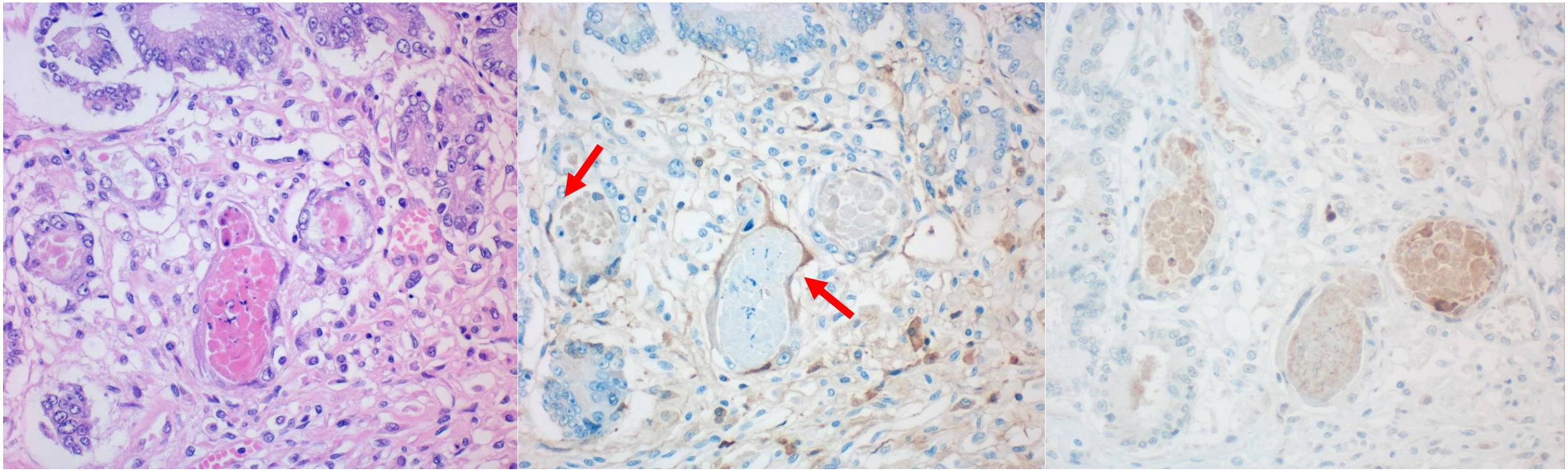


Paraneoplastic pemphigus in a 70-year-old male patient. PNP-related bronchial/bronchiolar lesions. Another part of the disorganized bronchial mucosa shows clustering of apoptotic cells immunoreactive for cleaved caspase-3 (left: HE, right: cleaved caspase-3).

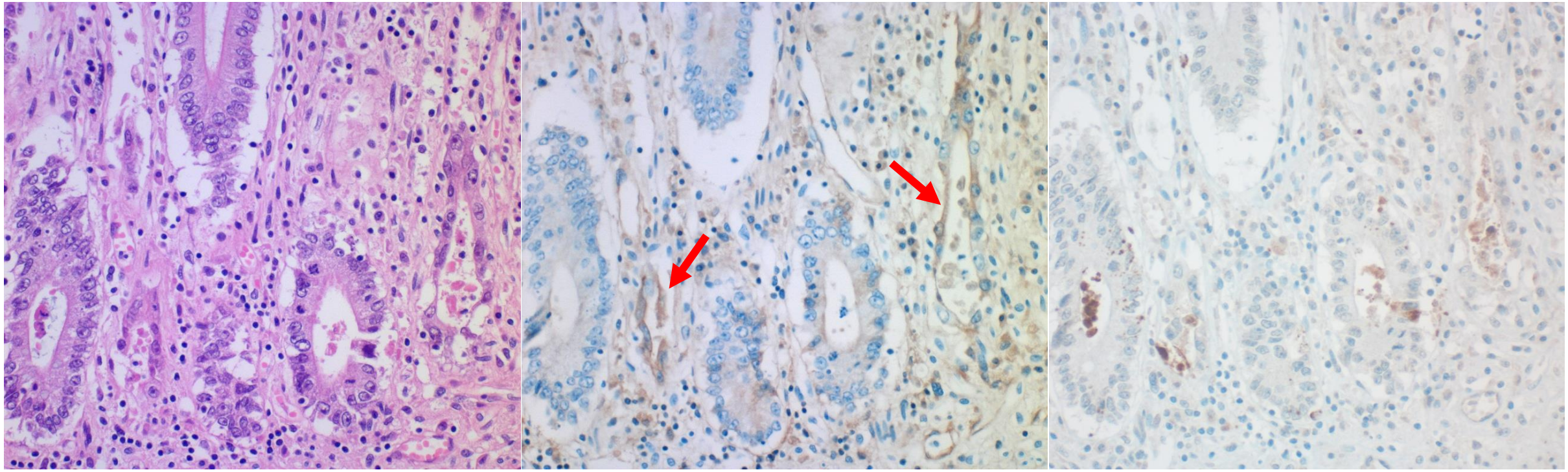


Paraneoplastic pemphigus in a 70-year-old male patient. PNP-related bronchial/bronchiolar lesions. Microscopic features of bronchiolitis obliterans are observed in the peripheral lung. Mucosal erosion-associated exudation has provoked secondary luminal dilatation (left, HE) and luminal obstruction (right, HE). Peribronchiolar fibrosis is noted.


a
b
c
d
e
f



Paraneoplastic pemphigus in a 70-year-old male patient. PNP-related gastric antral mucosal lesions. Distorted pyloric glands in the CMV-uninfected islands seen among extensively CMV-infected mucosae exhibit apoptotic cellular debris in the lumen (left: HE). As indicated by red arrows, IgG deposition is proven on the plasma membrane and in the cytoplasm of the involved antral epithelial cells (center: IgG immunostaining after proteinase-1 digestion). Cleaved caspase-3-immunoreactive apoptotic cells are clustered in the lumen of the diseased glands (right).



Paraneoplastic pemphigus in a 70-year-old male patient. PNP-related colonic mucosal lesions: Distorted colonic crypts in the CMV-uninfected islands seen among extensively CMV-infected mucosae exhibit apoptotic cellular debris in the lumen (left: HE). Intraepithelial lymphocytes are increased in the colonic mucosa. As indicated by red arrows, IgG deposition is proven on the plasma membrane and in the cytoplasm of the involved epithelial cells (center: IgG immunostaining after proteinase-1 digestion). Cleaved caspase-3-immunoreactive apoptotic cells are clustered in the lumen of the diseased glands/crypts (right).