

Pathology of plasma cells

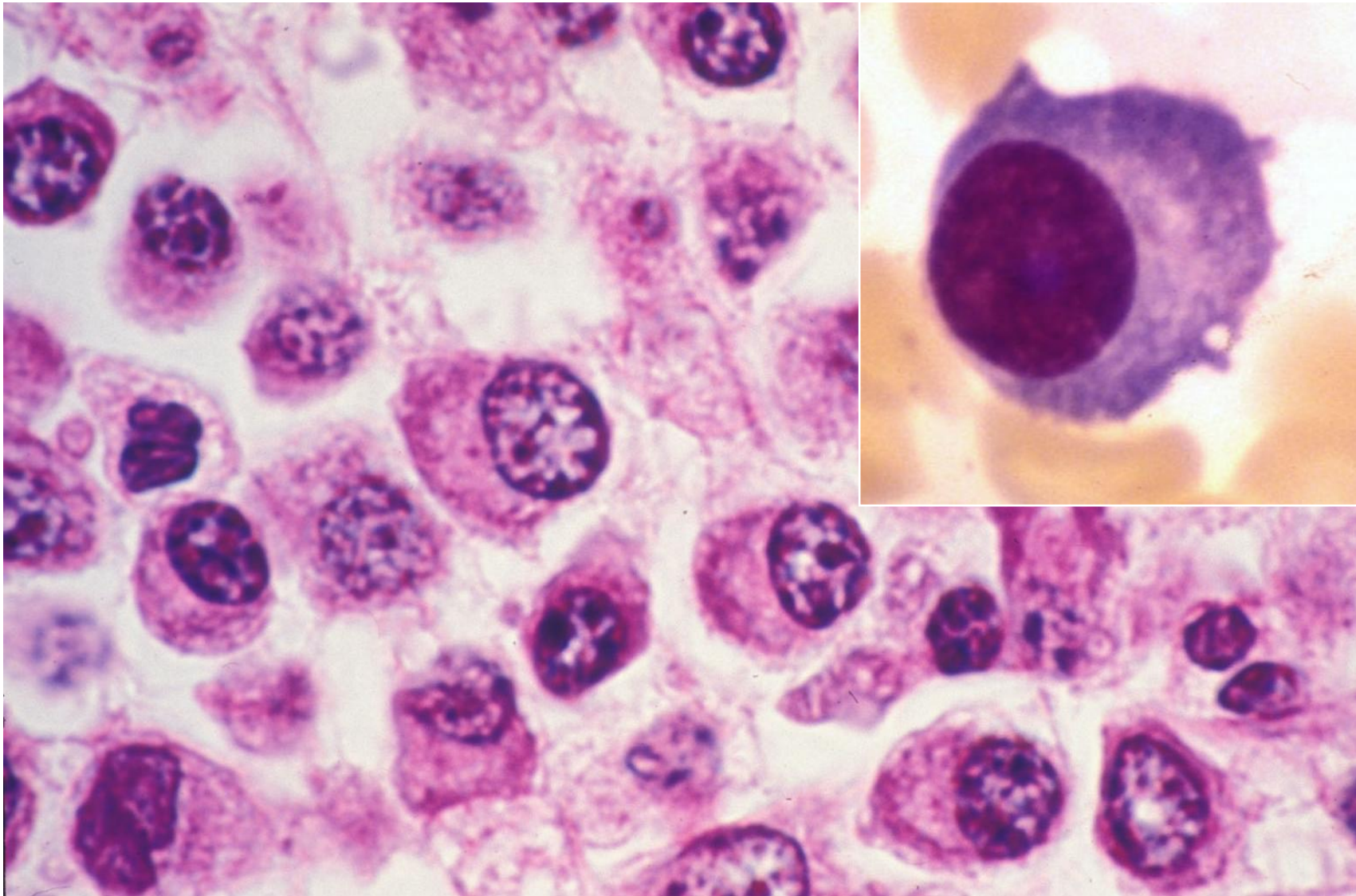
Plasma cells are the final effectors of the B-cell lineage, with proliferative activity lost. After activation by antigen, in the presence of T-cell help when required, naive B cells in the marginal zone and follicles rapidly develop into short-lived plasma cells. Follicular B cells can also undergo a germinal-center reaction, and after proliferation, affinity maturation and class-switch recombination, both memory B cells and plasma cells are formed. It has been described that post-germinal-center plasma cells migrate to the bone marrow, survive and continue to secrete immunoglobulin for prolonged periods as long-lived plasma cells. The chemokines, integrins, selectins and cytokines may be required for plasma cell survival. Plasma cells also derive from non-germinal center pathway. Under physiological conditions, plasma cells are diffusely distributed in the gut mucosa without lymphoid follicle formation, and many pathological lesions such as syphilis and multiple myeloma show the presence of plasma cells without lymphoid follicle formation. A variety of chronic inflammatory disease shows active plasma cell infiltration. Some chronic inflammatory lesions are rich in IgG4-type plasma cells, and categorized in IgG4-related disorders. Russell bodies may be seen in some lesions. In congenital immunodeficient disorders such as X-linked immunodeficiency of Bruton type and severe combined immunodeficiency, plasma cells are scarcely seen in the gut mucosa. Neoplastic growth of plasma cells and lymphoplasmacytic cells are presented. The mystery of plasma cells is summarized herein.

Ref.-1: Shapiro-Shelef M, Calame K. Regulation of plasma-cell development. Nat Rev Immunol 2005; 5: 230-242.
<https://doi.org/10.1038/nri1572>

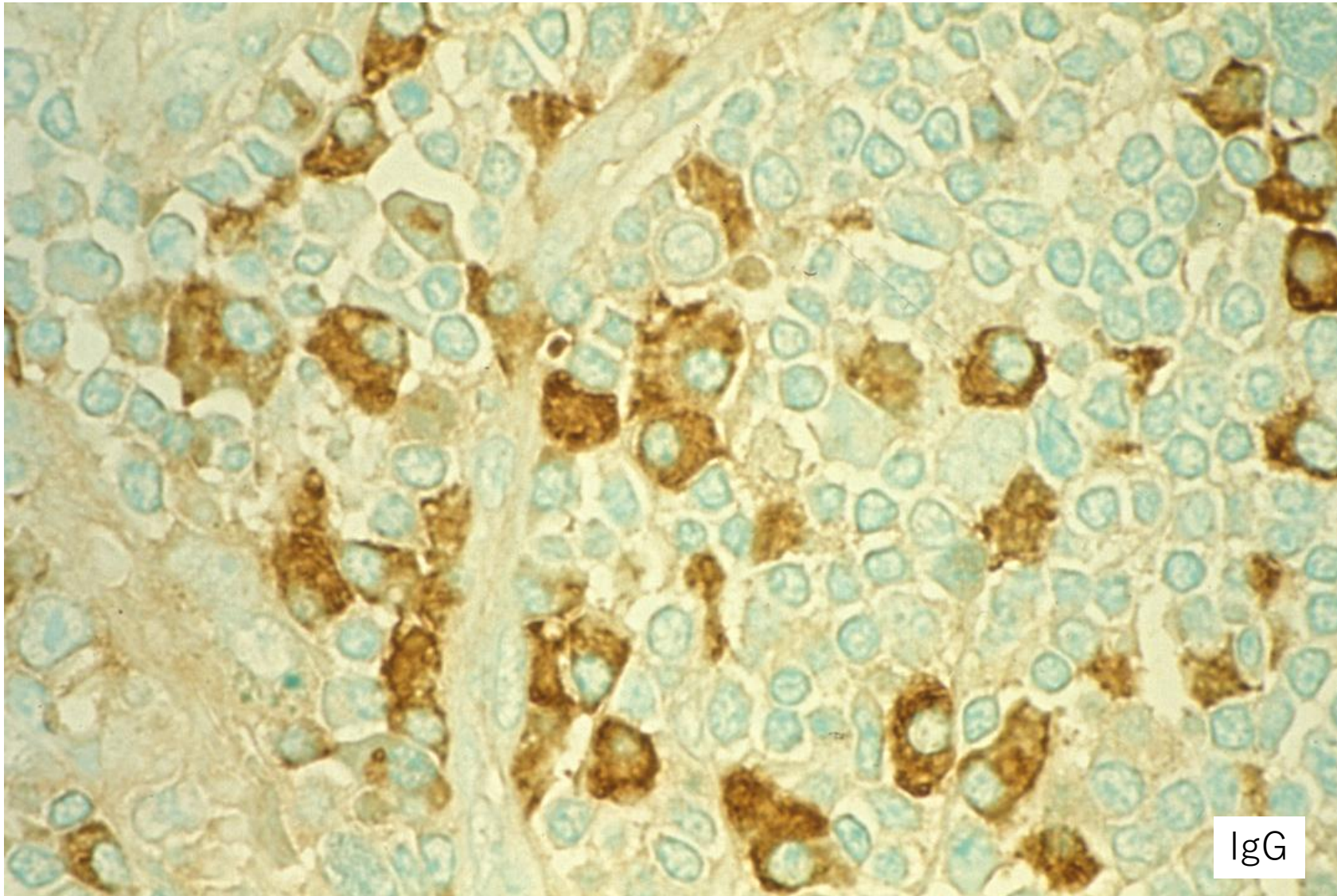
Ref.-2: Tsutsumi Y. Plasma cells. Who are you? Microscopia 1995; 12(3): 170-177 (in Japanese).
<https://pathos223.com/essay/keisitsusaibou.html>

Mystery of plasma cells

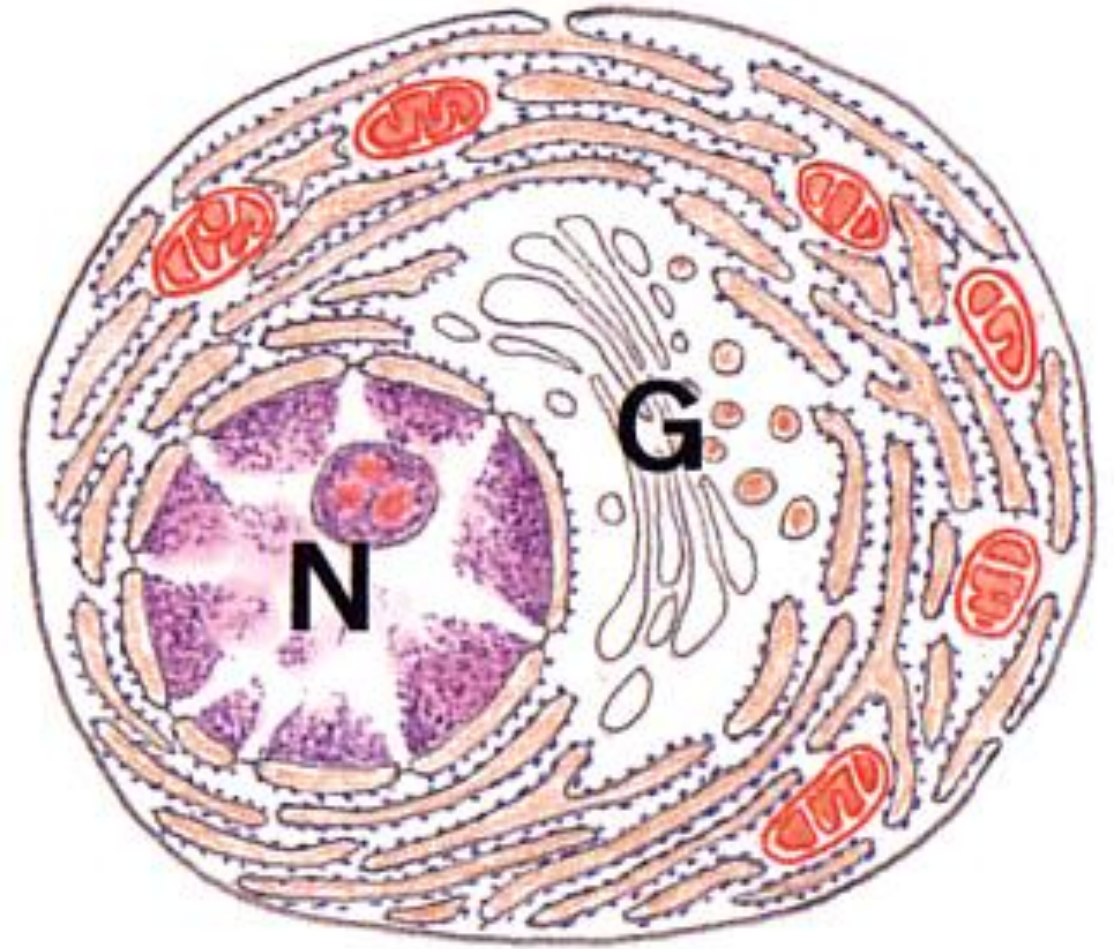
- 1) Plasma cells are known as non-proliferative terminally differentiated B-cells producing immunoglobulins, but plasma cell neoplasm occurs mainly in the bone marrow.
- 2) Does all IgG function as antibodies? The Fc portion of IgG is the source (precursor) of migratory factors of inflammatory cells. Neutrophilic proteases break down IgG molecules into the migratory factors.
- 3) Plasma cell neoplasm (plasmacytoma) occurs in the bone marrow as multiple myeloma. Normally, plasma cells are few in number in the bone marrow. Plasma cells are rich in the lymph node, spleen, tonsil and intestinal mucosa, but plasmacytoma is rare in these sites. The total volume of plasma cells may reach 100 to 1,000 times in comparison with the normal state. The level of serum immunoglobulins in the serum of multiple myeloma as much as 10 g/dL (10 times than the normal state). This means that the immunoglobulin secretion from the myeloma cells are markedly suppressed. In fact, the Golgi apparatus is often positive for immunoglobulin in the neoplastic plasma cells (in the normal state, the Golgi apparatus is negatively labeled).
- 4) How is the secretion of immunoglobulin from the plasma cell controlled? Lymphokines and monokines secreted from the lymphocytes and macrophages may control the secretion. The life span of the plasma cells may be short or very long. What is the mechanism of longevity of the life span of the plasma cells?
- 5) In the immunology textbooks, plasma cells differentiate from the immunoblasts in the germinal center of the lymphoid tissue. This should be the pathway for antibody production against exogenous antigens. Plasma cells producing antibodies against endogenous antigens may differentiated directly from plasmablasts without the mediation of the germinal center, known as B-1 cell lineage (old B-cell category). In fact, in the intestinal mucosa, IgA plasma cells are diffusely distributed in the lamina propria mucosae without lymphoid follicle formation. The myeloma cells may belong to the B-1 cell lineage. Milky spots in the peritoneum (omentum) may be the source of B-1 cells, and IgA-mediated mucosal immunity is closely related to the old-type B-cell lineage. In the lymph node of the nude mouse lacking T-cells, there is no lymphoid follicle formation, but plasma cells are easily observed. In the myeloma tissue, no germinal centers are observed at all. In MALT lymphoma, plasma cell differentiation is common, and Sjogren's syndrome may be complicated. MALT lymphoma results from chronic organitis such as Helicobacter-related chronic active gastritis, chronic thyroiditis and chronic sialadenitis.
- 6) Immunity may have started as the recognition of self cells or endogenous (auto)antigens. The recognition of the "non-self" should be a byproduct of the recognition of the self. When normal peripheral B-cells are transformed by EB virus, the lymphoblastoid cell line can produce autoantibodies against the nucleus, smooth muscle cells, etc. In immunofluorescence study using normal human serum and fresh frozen sections of various organs, not only the nuclei and smooth muscle cells, but also thyroid tissue, insular islets of the pancreas and pituitary gland demonstrates positive signals, indicating the presence of low-titer autoantibody. In the laboratory study for antinuclear antibodies, normal human serum stains the nuclei of cultured cells up to 1:20 dilution. The antinuclear antibodies can be judged positive when the 1:40 diluted serum stains the nuclei. Most of the non-functioning IgG molecules in the serum (the precursor proteins for migratory factors) can be IgG against endogenous antigens, and the activity of the antigen-binding Fab portion is masked by unknown mechanism.
- 7) The plasma cells appear and disappear like a phantom.
 - a) Plasma cells survive in tissues after radiation therapy against esophageal and uterine cervical cancer, where the cancer cells are lost and lymphoid cells became sparse.
 - b) In the deep adrenal cortex (with high concentration of steroid hormones), lymphoid cells are physiologically clustered as chronic adrenalitis, and numbers of plasma cells are intermingled.
 - c) Plasma cells lack migratory activity. In chronic pleuritis or peritonitis, inflammatory cells including plasma cells are seen, but almost no plasma cells can be seen in the effusion fluid. Plasma cell leukemia is a rare occasion in case of multiple myeloma. It should be clarified how the plasma cells are diffusely distributed in the normal gut mucosa.
 - d) Syphilitic lesions are characterized by the appearance of mature plasma cells, and this can be a clue for the histopathological diagnosis of syphilis. It is unclear whether IgG secreted from the locally infiltrating plasma cells may be directed against *Treponema pallidum* or not. Lymphoid follicle formation is scarcely seen in the syphilitic lesion.



Plasma cells in granulation tissue (H&E, inset: May-Giemsa). An eccentric nucleus with a cartwheel pattern, basophilic cytoplasm and prominent Golgi area are characteristic of the plasma cells. The plasma cells are terminally differentiated B-lymphoid cells and do not proliferate any longer.



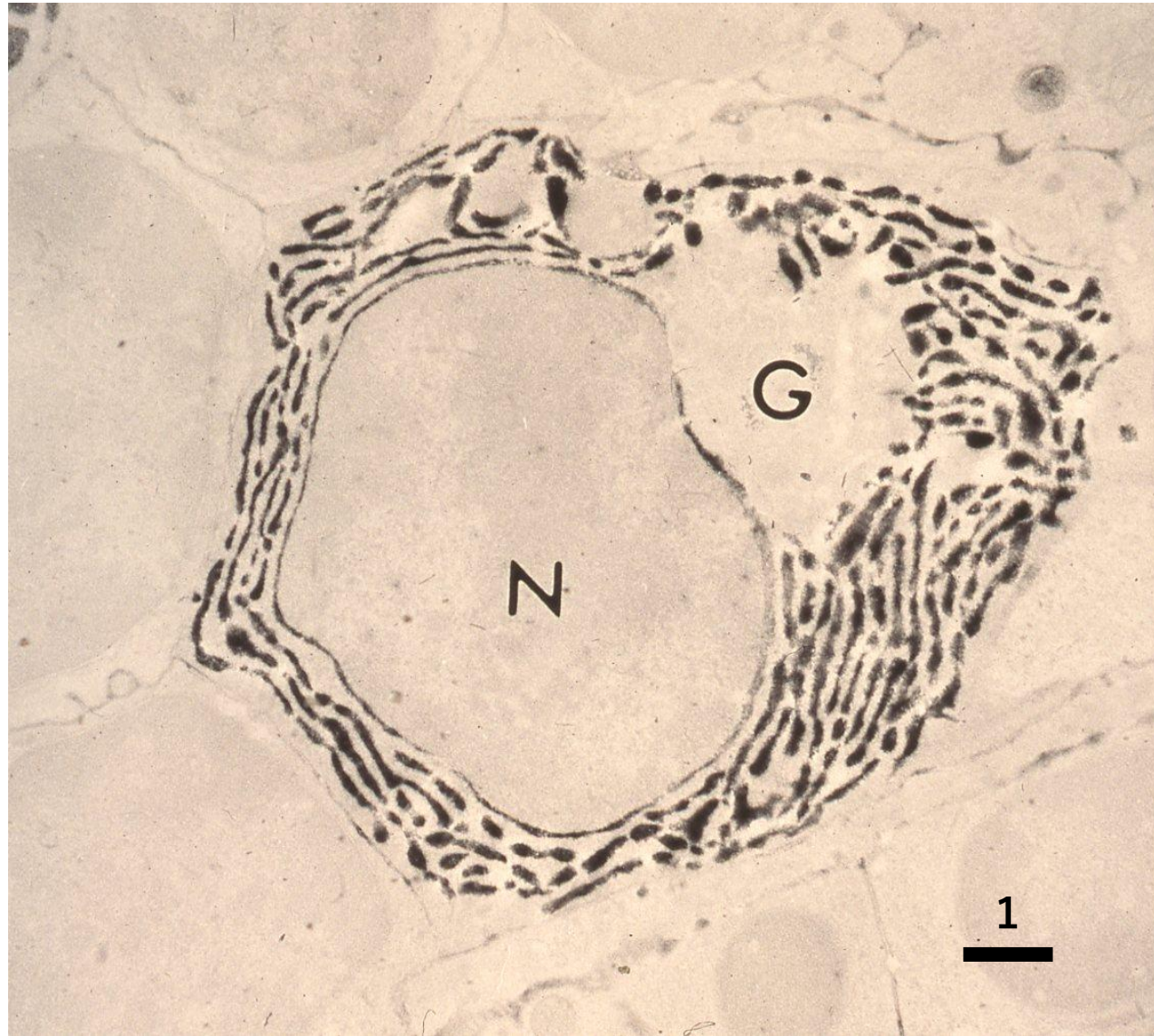
Immunostaining for IgG in **plasma cells** in the lymph node. The cytoplasm is immunoreactive for IgG. The Golgi area may or may not be labeled with IgG.



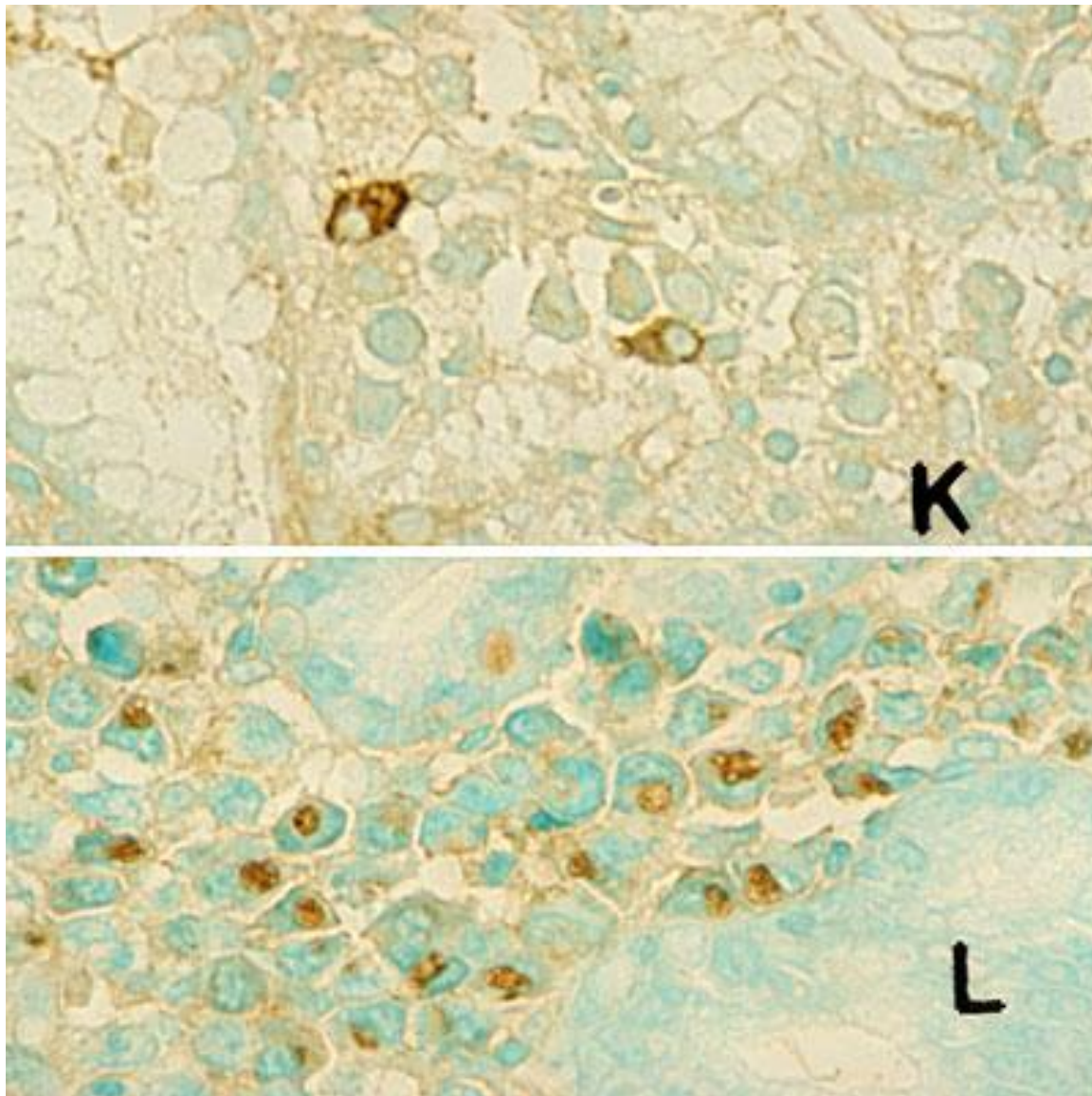
Ultrastructure of **plasma cell** (left) and its schematic representation (right). The eccentric nucleus (N) possesses condensed chromatin along the nuclear membrane (with a cartwheel pattern). Rough endoplasmic reticulum and Golgi apparatus (G) are well developed in the cytoplasm. Mitochondria are dispersed.



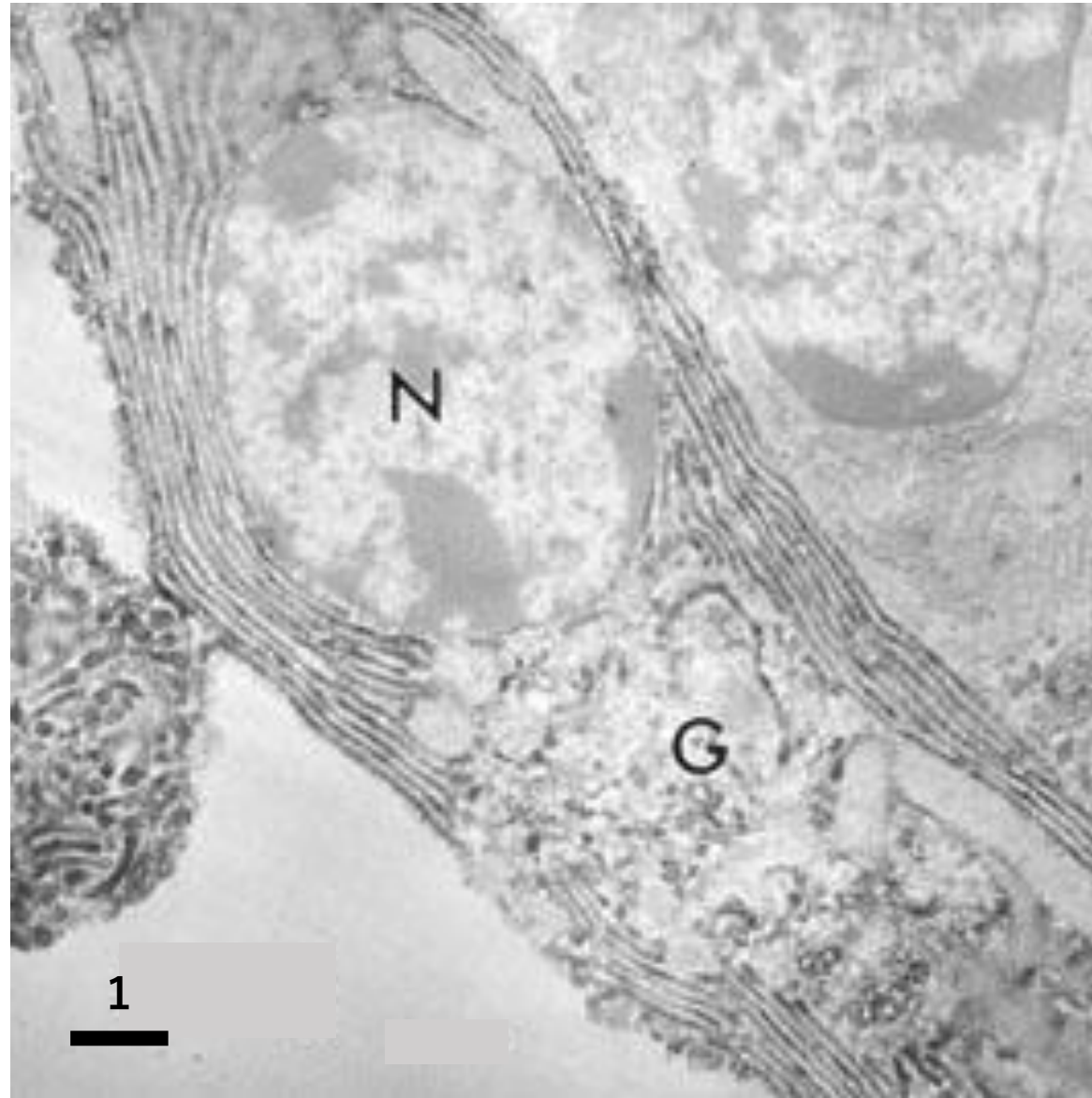
Pre-embedding immunoelectron microscopy for IgG in **plasma cells**. The cisterna of rough endoplasmic reticulum and nuclear membrane are positively labeled. The Golgi apparatus is not labeled.



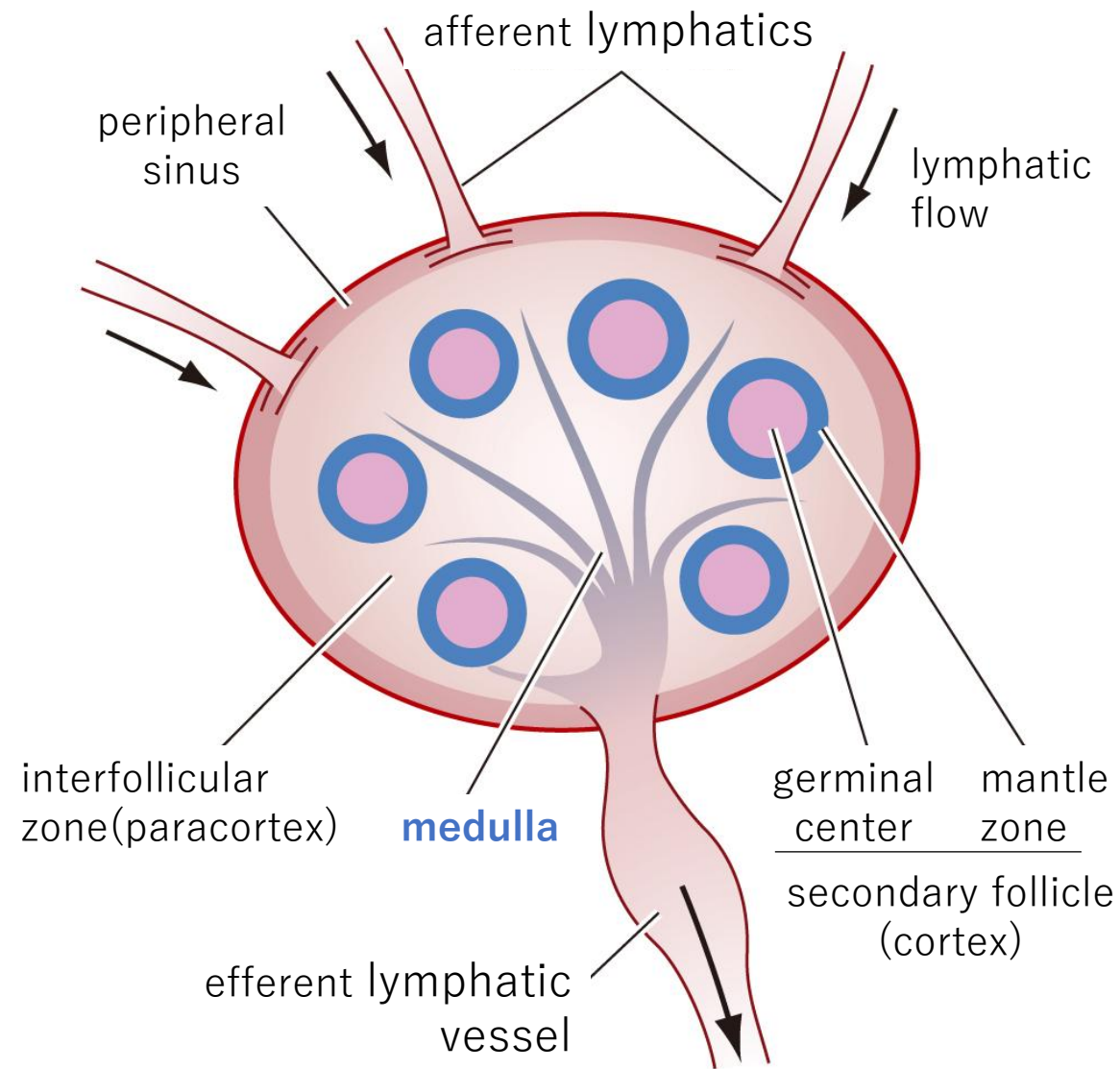
Pre-embedding immunoelectron microscopy for IgM in the **plasma cell**. The cisterna of rough endoplasmic reticula and nuclear membrane are positively labeled. The Golgi apparatus is negative. N=nucleus, G= Golgi apparatus



Immunostaining for kappa and lambda chains of immunoglobulin in **plasmacytoma** of the gastric mucosa with lambda chain monoclonality. The monoclonal lambda chain (L) is characteristically localized in the Golgi zone, while kappa chain (K) seen in a reactive plasma cell component is localized diffusely in the cytoplasm with poorly stained Golgi zone.

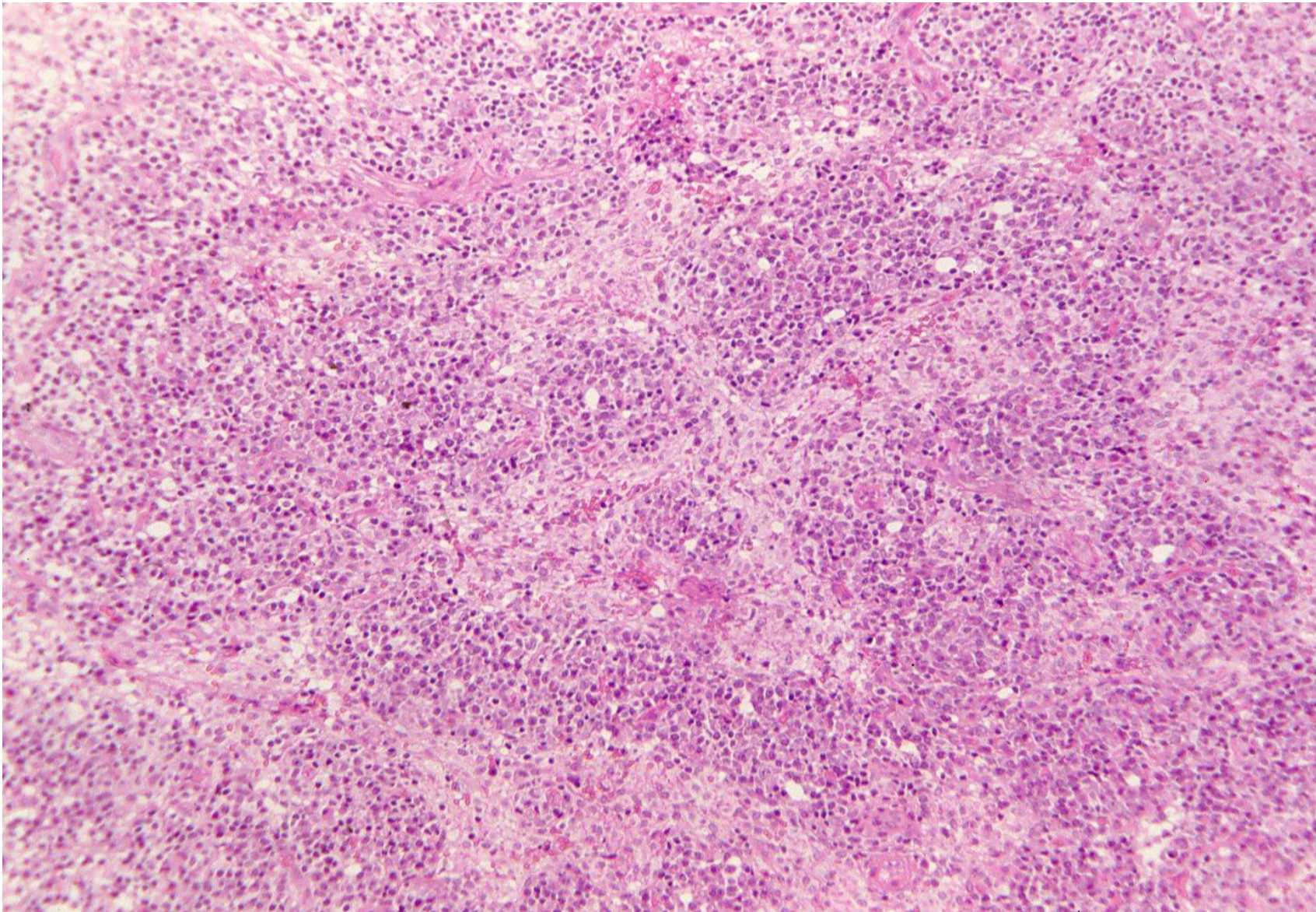


Pre-embedding immunoelectron microscopy for kappa chain in the **multiple myeloma** cell. Not only the cisterna of rough endoplasmic reticula but also the Golgi apparatus (G) are positively labeled. N= nucleus.

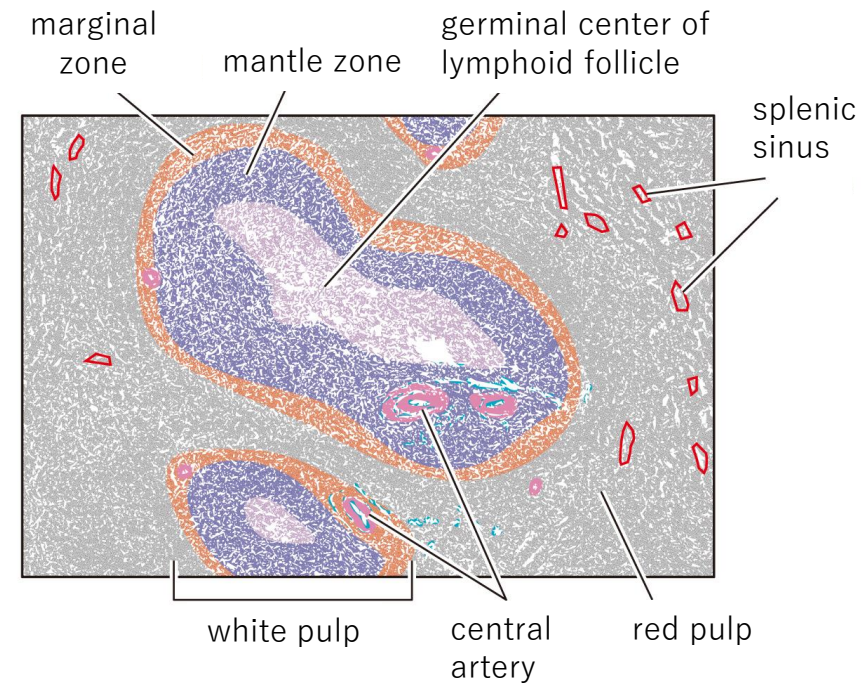
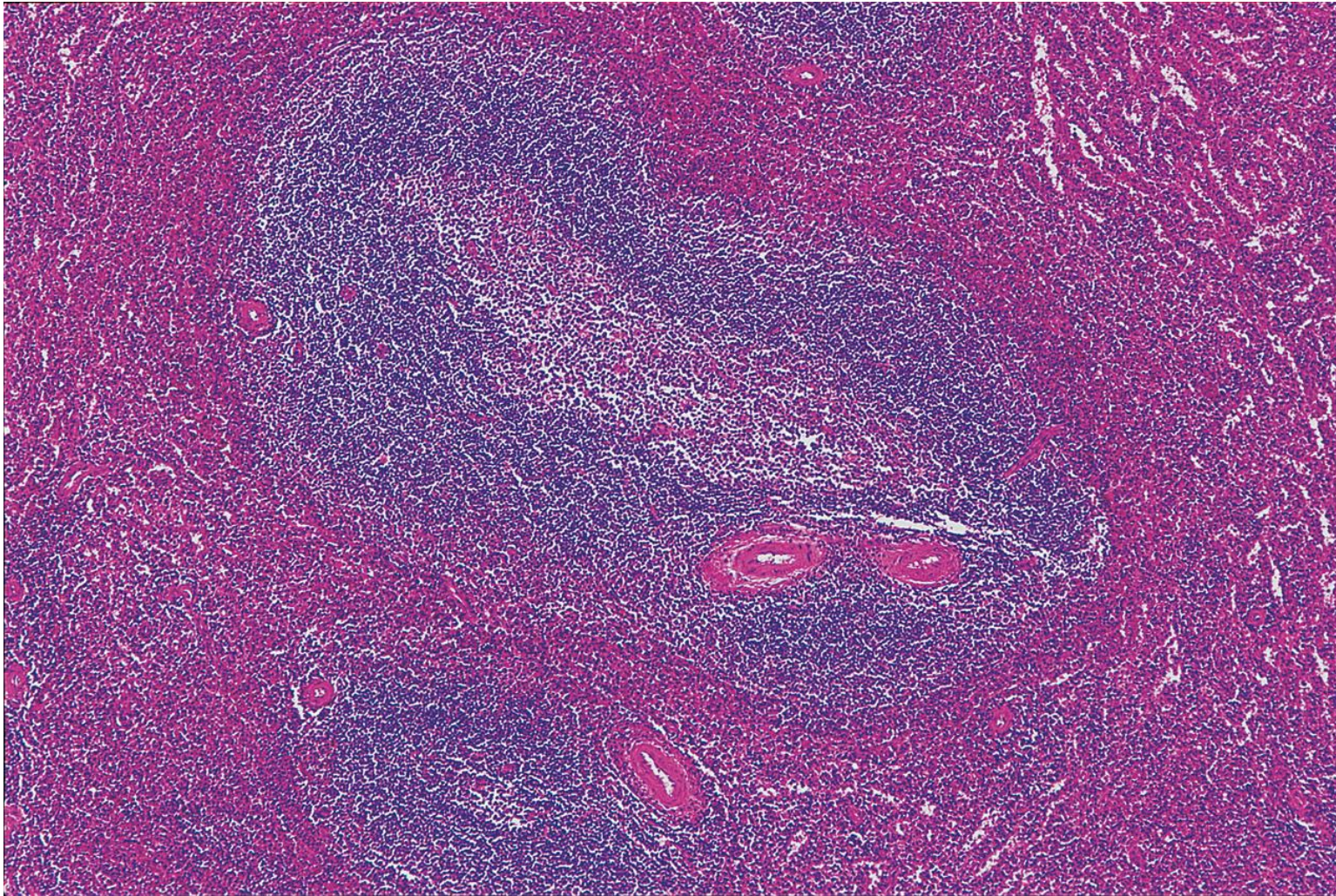


Schema of the structure of normal lymph node

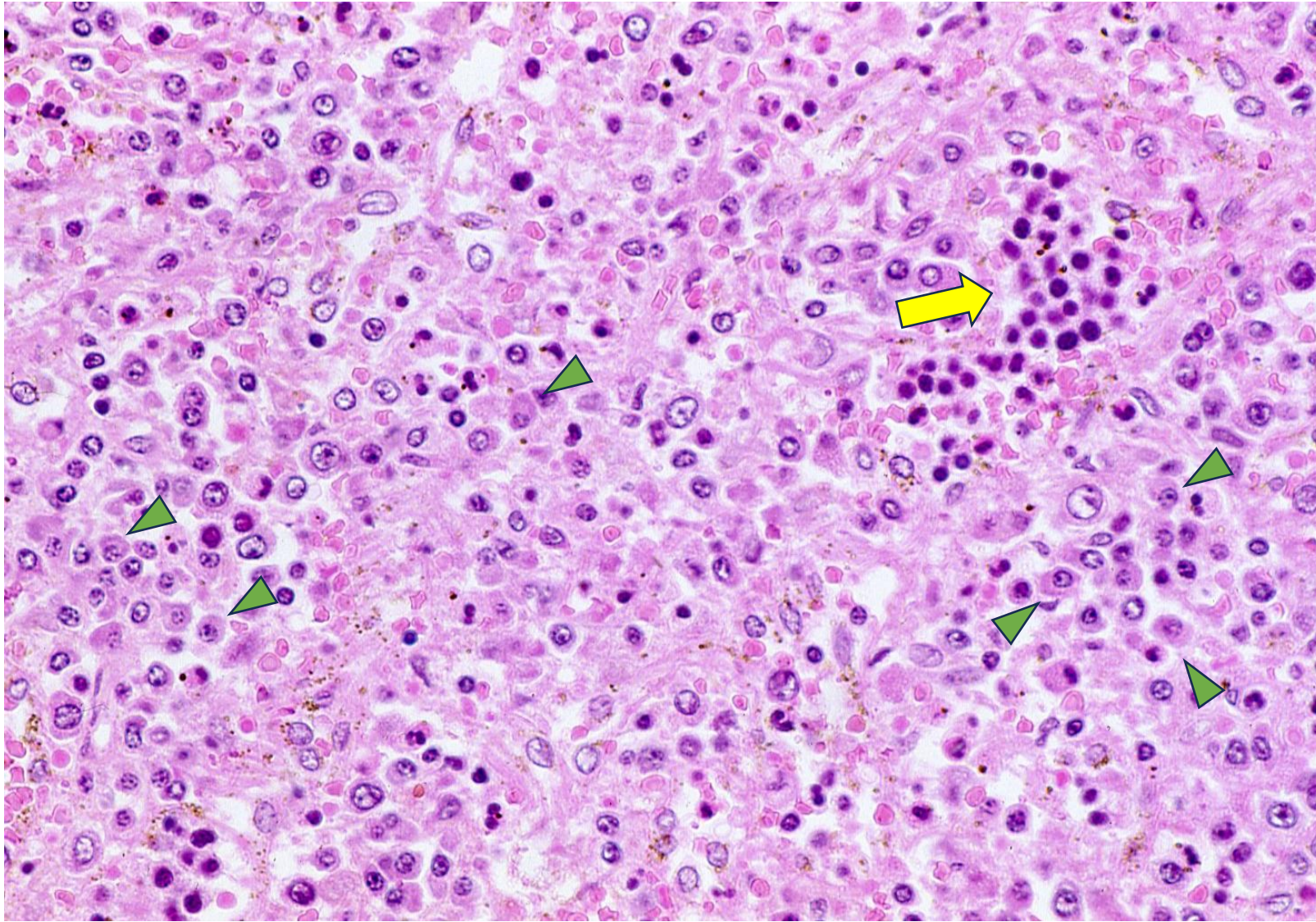
Plasma cells are mainly distributed in the medulla.



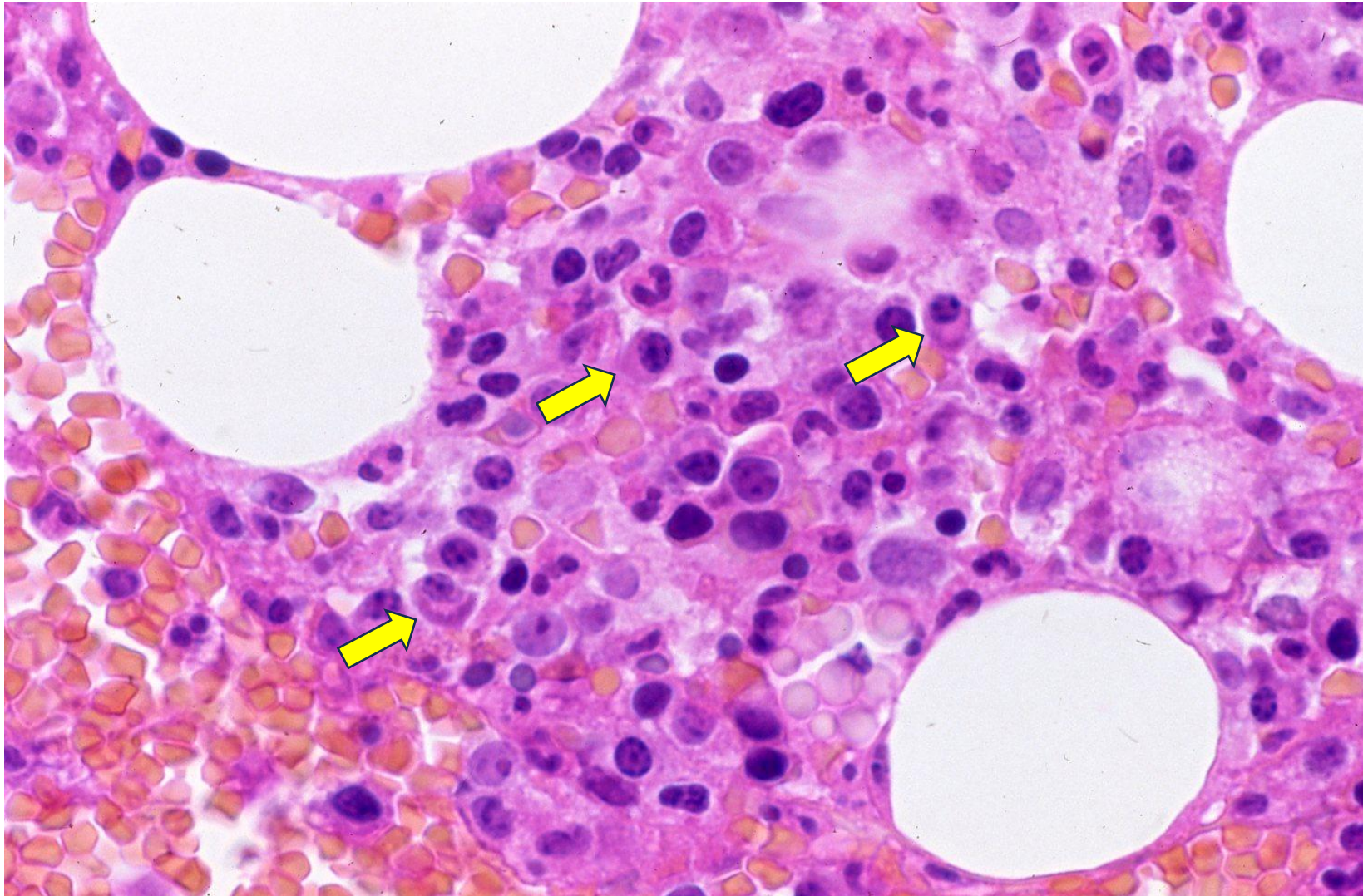
The **medulla** of the reactive lymph node (H&E). Plasma cells are mainly distributed in the medulla of the lymph node, separated by the medullary sinus.



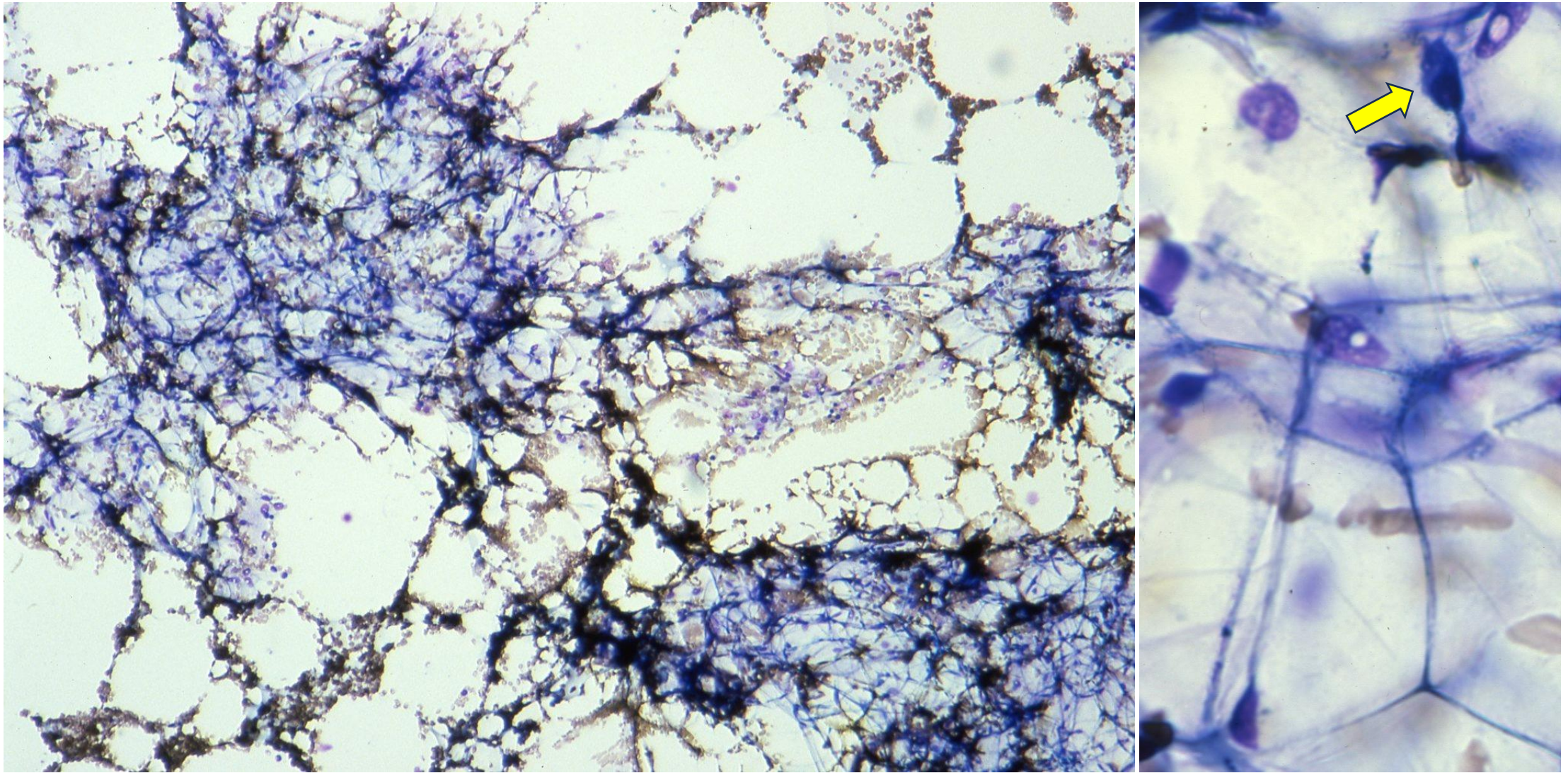
The **white pulp of the spleen** contains a well-developed lymphoid follicle and T-cell zone around the central arteriole (H&E). The association of the marginal zone is characteristic of the lymphoid follicle of the spleen. In the sinus of the red pulp, numbers of macrophages are located. Plasma cells are predominantly distributed in the red pulp (not in the white pulp).



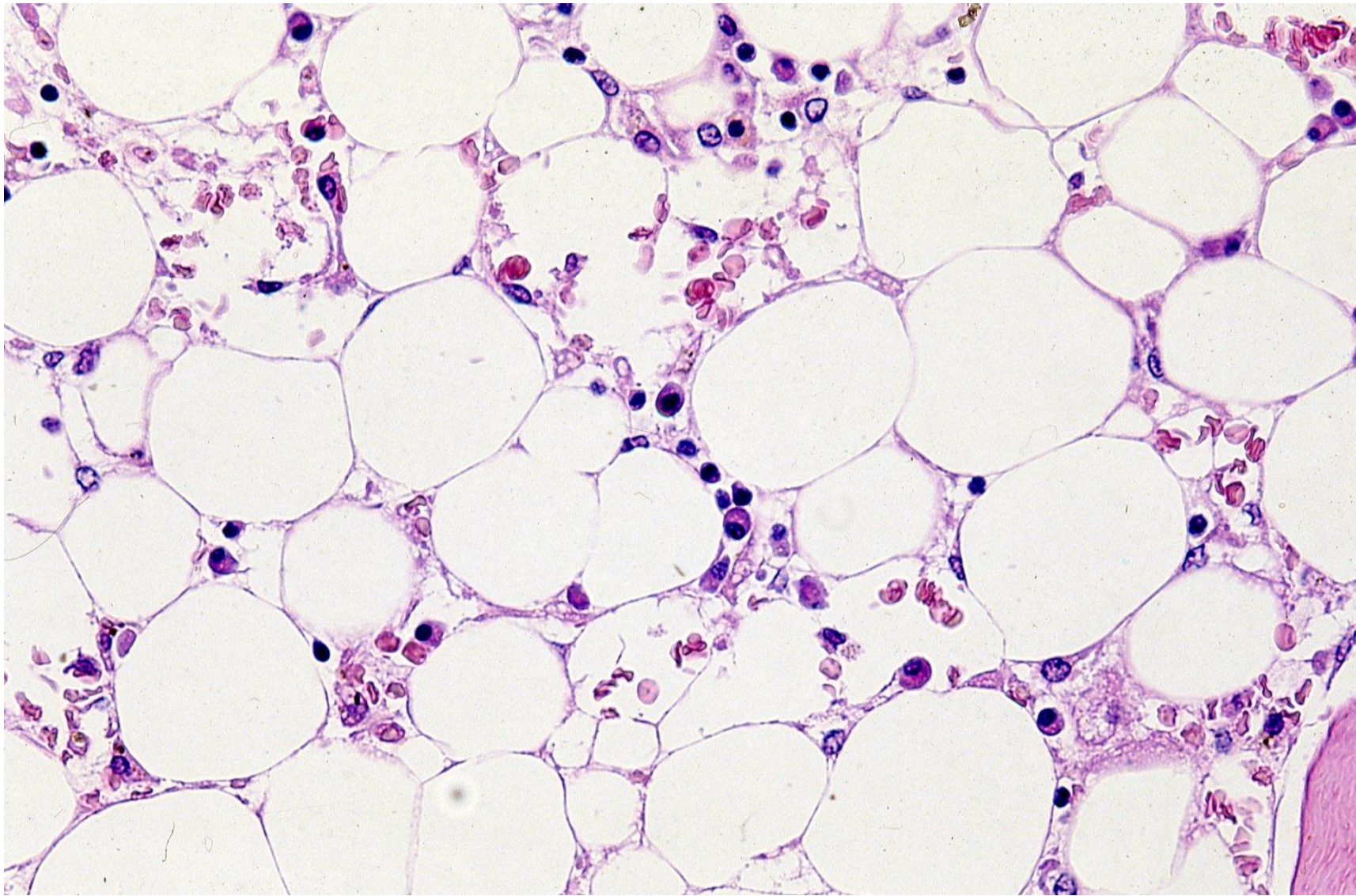
The **red pulp of the spleen** (H&E). Plasma cells are dispersed in the splenic cord (the cord of Billroth), as arrowheads indicate. Extramedullary erythropoiesis is also noted in the present case (arrow).



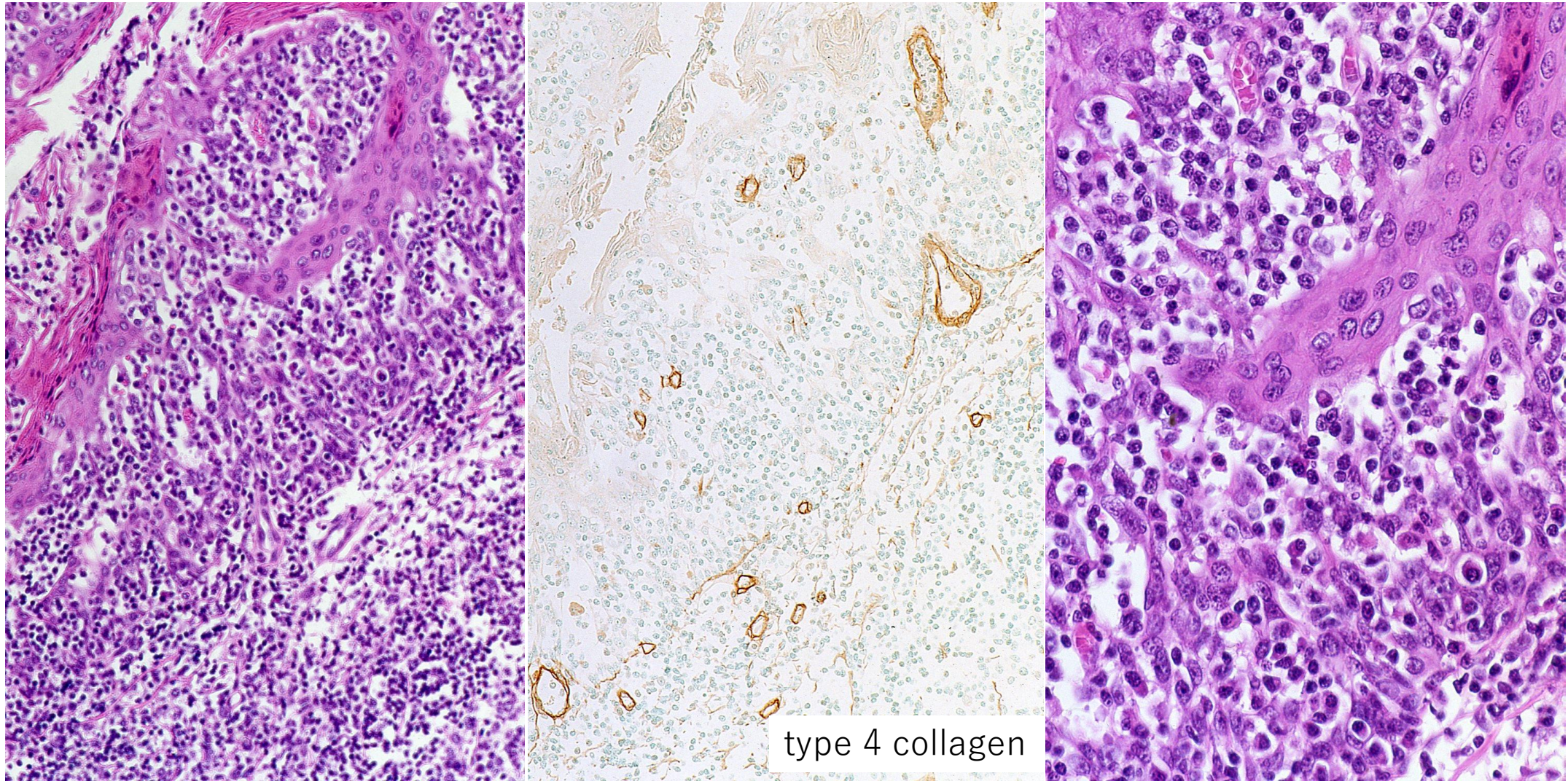
In the normal **bone marrow** with normocellularity (H&E), a few plasma cells are scattered, with the percentage of **plasma cells**/nucleated cells being around 1% (range: 0.4-4%). Arrows indicate mature plasma cells with a prominent Golgi zone in the normal bone marrow space.



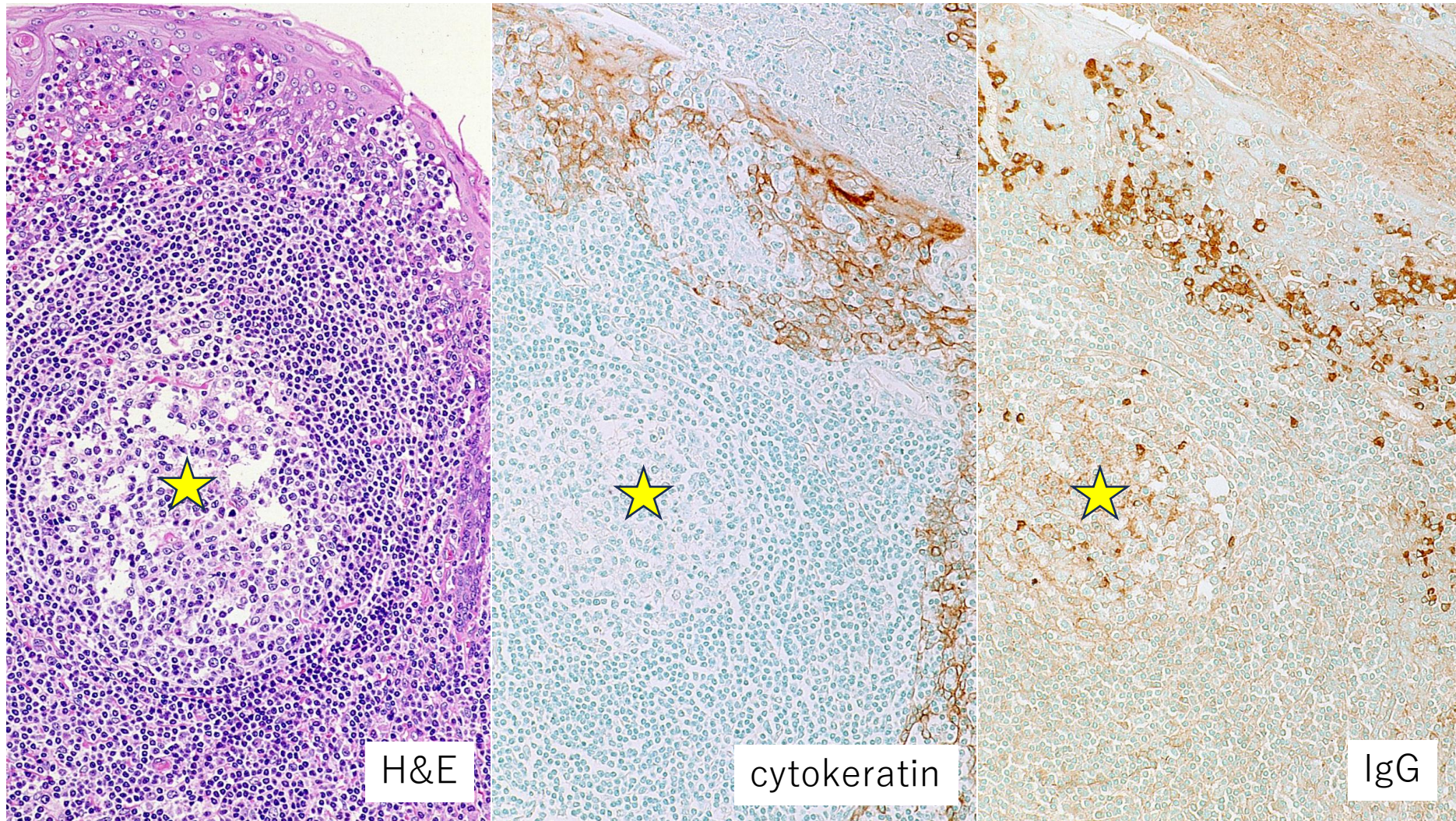
Aplastic anemia with markedly hypocellular (fatty) marrow (May-Giemsa). Plasma cells are observed among the fat cell background (arrow).



Aplastic anemia with markedly hypocellular (fatty) marrow (H&E). In the biopsied bone marrow tissue, plasma cells remain, and a relatively increased number of plasma cells is observed.



Unique structure of the **reticular mucosa of the pharyngeal tonsil**. Numbers of lymphoid cells are seen among the squamous mucosa (left: H&E). Of note is that capillary vessels are distributed in the reticular mucosa evidenced by immunostaining for type 4 collagen (center). High-powered view reveals numbers of plasma cells are seen in the reticular mucosa (right: H&E).



Unique structure of the **reticular mucosa of the pharyngeal tonsil**. Numbers of lymphoid cells are seen among the squamous mucosa above the lymphoid follicle (asterisks) (left: H&E). The epithelial cells are labeled with cytokeratin immunostaining (center). Numbers of plasma cells immunoreactive for IgG are observed within the reticular mucosa (right).

“Immunity” started with the recognition of self! Plasma cells can be produced without the mediation of the germinal center

Two types of antigens

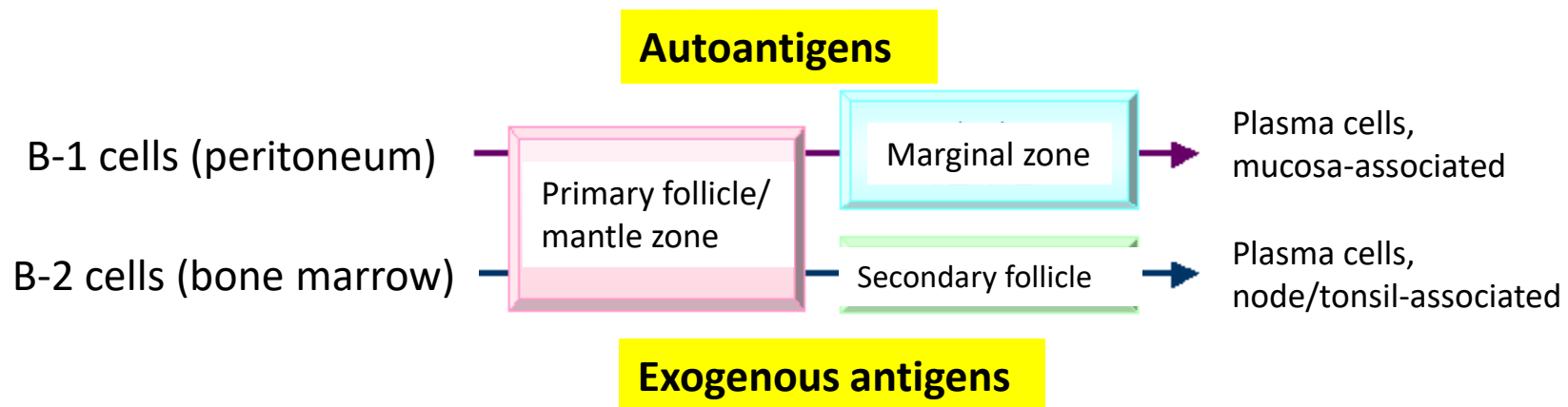
- ① Exogenous antigens: defense ② Endogenous (auto)antigens: homeostasis

Two types of T-cells

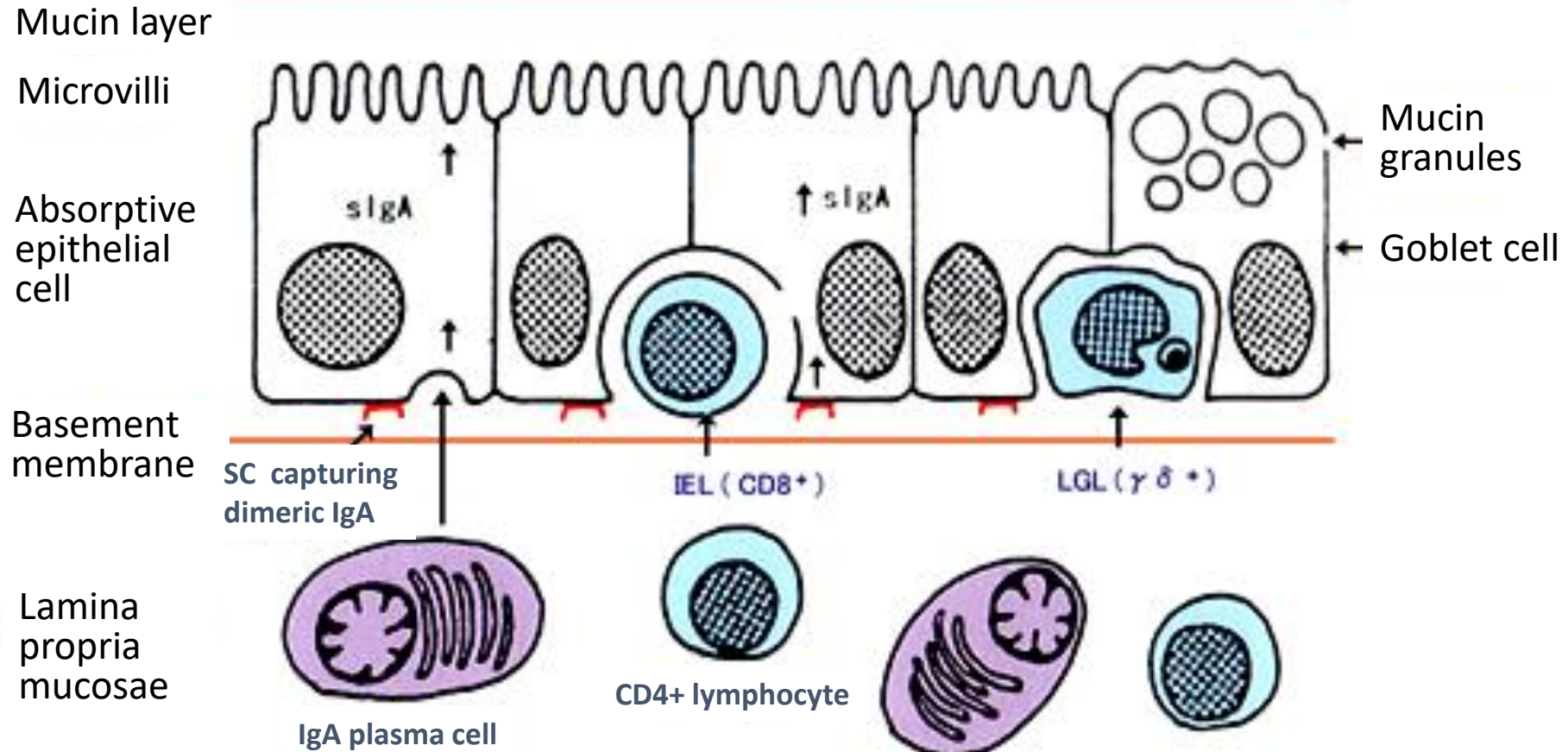
- ① Thymus-educated T-cells ② Extrathymic T-cells (old system T-cells)
(inducing apoptosis)

Two types of B-cells

- ① Germinal center-educated B-cells ② B-1 cells (old system B-cells)
(reactive with enterobacteria and blood groups)

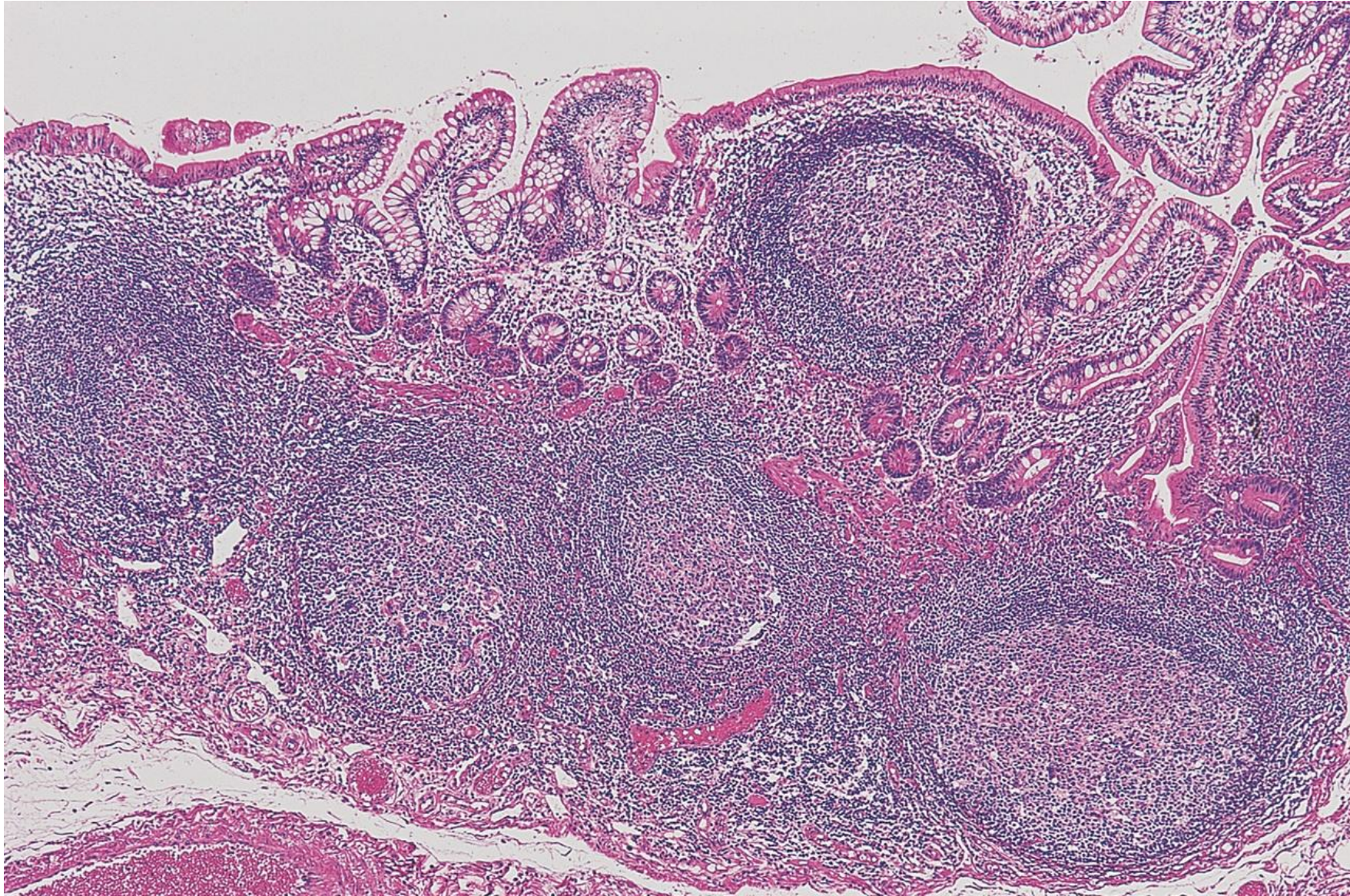


Enterobacteria in the gut lumen

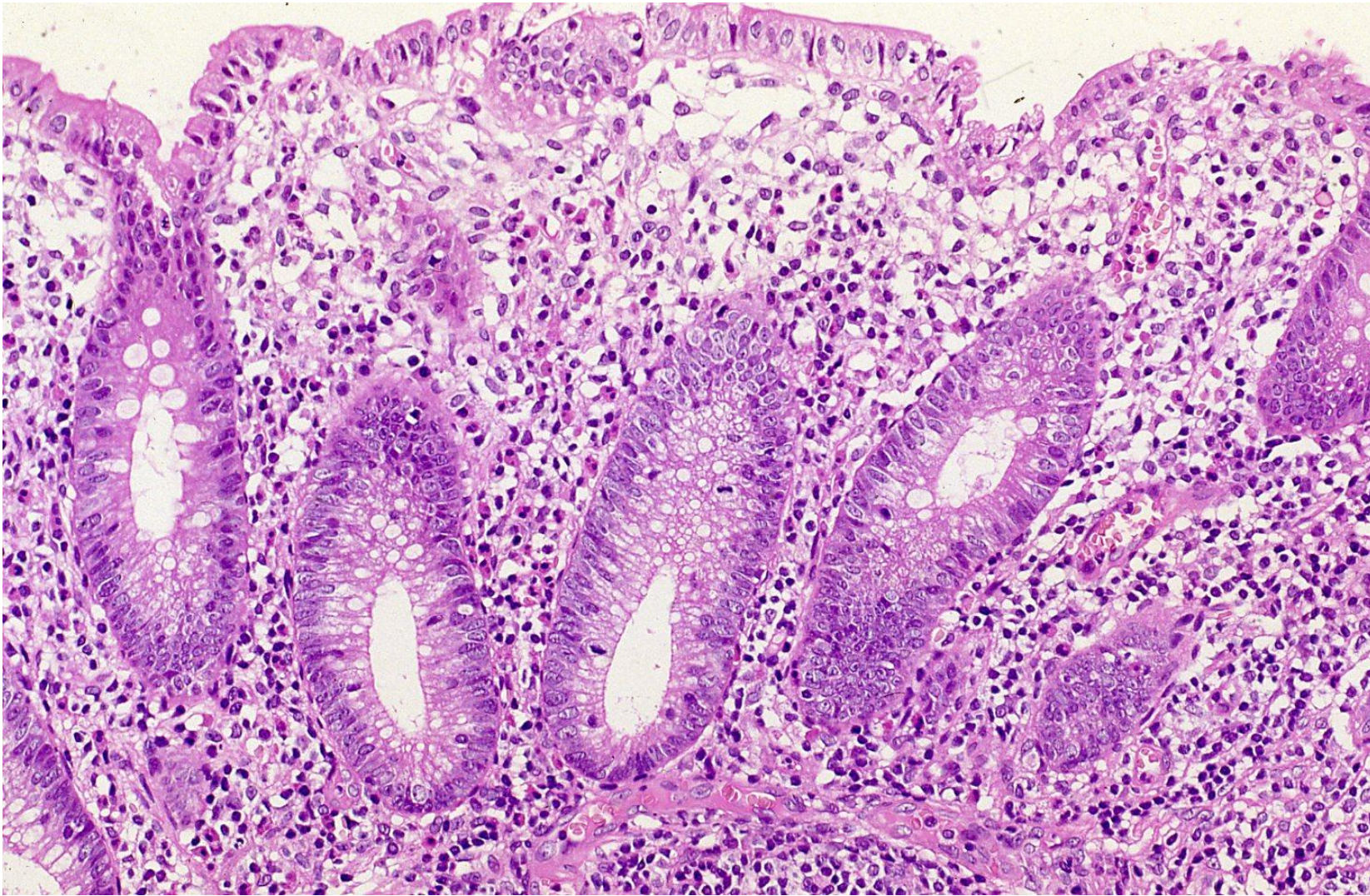


Schematic presentation of secretory IgA through the intestinal columnar epithelial cells and CD8-positive intraepithelial lymphocytes (IEL)

SC: secretory component, LGL: large granular lymphocyte



Peyer's patch in the terminal ileum with well-developed lymphoid follicles (H&E)



Normal mucosa of the **vermiform appendix** (H&E). Number of small lymphocytes (T-cells, mainly CD4+) and plasma cells are distributed in the lamina propria mucosae. Intraepithelial lymphocytes (CD8+) are also recognized. Plasma cells in normal gut mucosa predominantly secrete dimeric IgA, and secretory IgA is transported through the epithelial cells into the lumen. The normal appendiceal mucosa apart from the lymphoid follicle is shown.

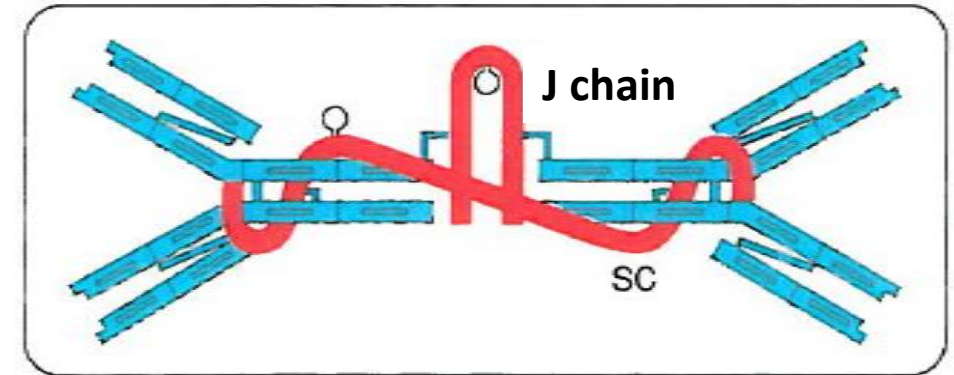
Mucosal immunity: protecting invasion of pathogens at the mucosal surface by secretory IgA

Secretory IgA = dimeric IgA + secretory component (SC)

(SC is produced by mucosal columnar cells)

Enterohepatic circulation of IgA

Dimeric IgA with linker J chains produced in the intestinal mucosa enters the portal vein, and combines with secretory component produced by the bile duct epithelial cells to secrete into the bile.

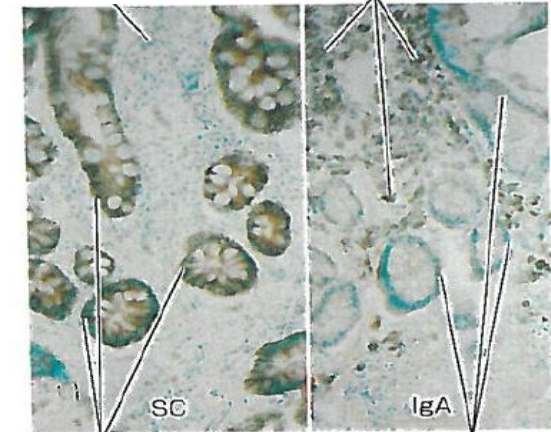


Features of IgA-related kidney lesions

- 1) Intestinal symptoms (such as diarrhea) precede in IgA nephropathy.
- 2) Dimeric IgA deposits in the glomeruli
- 3) The renal lesion in Henoch-Schönlein purpura nephritis is identical to IgA nephropathy. IgA deposition is also seen in the skin purpura.
- 4) Hepatic glomerulosclerosis reveals deposition of dimeric IgA in the glomeruli.

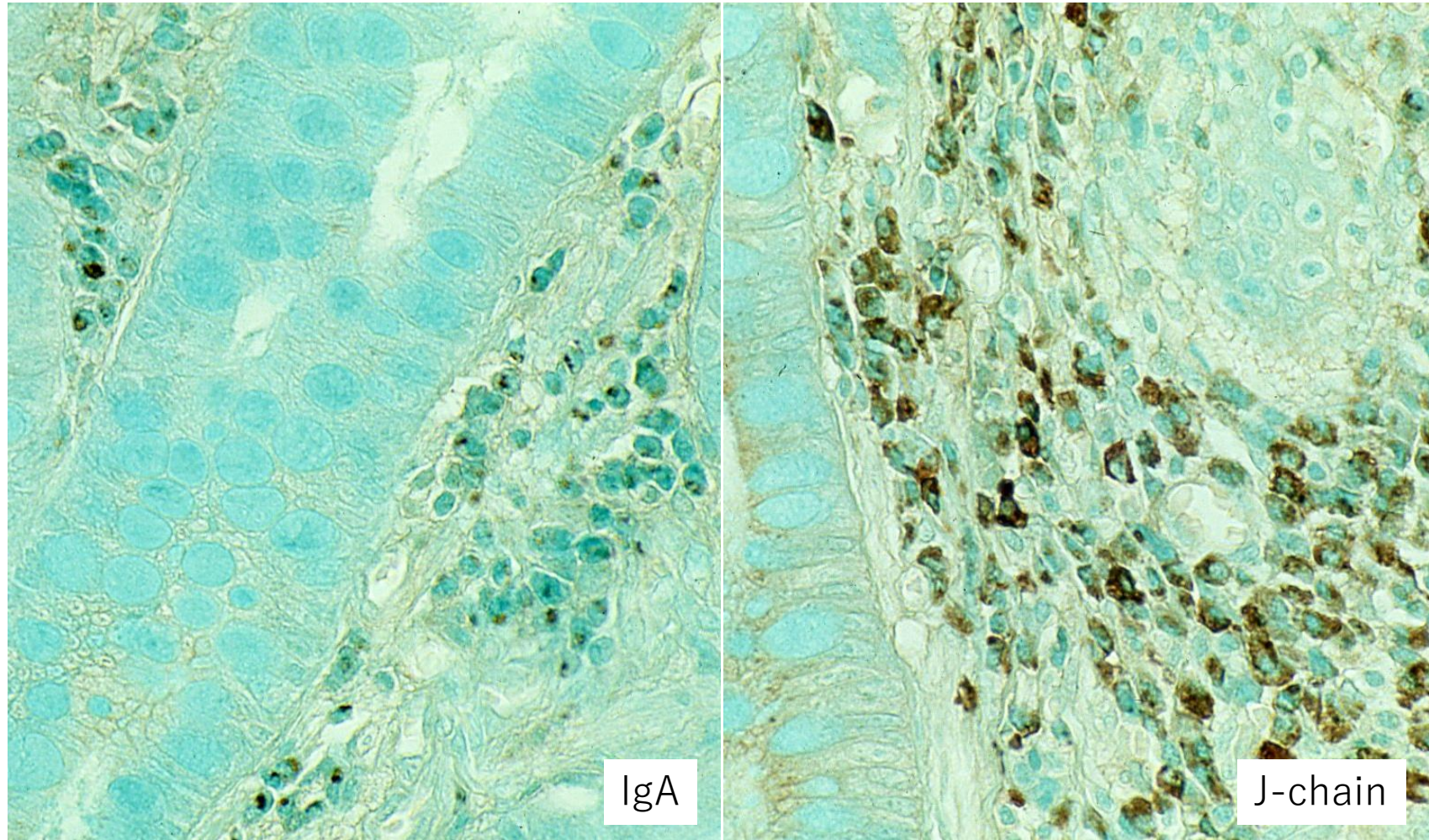
SC is negative in the stromal plasma cells

IgA-producing plasma cells in the lamina propria mucosae.



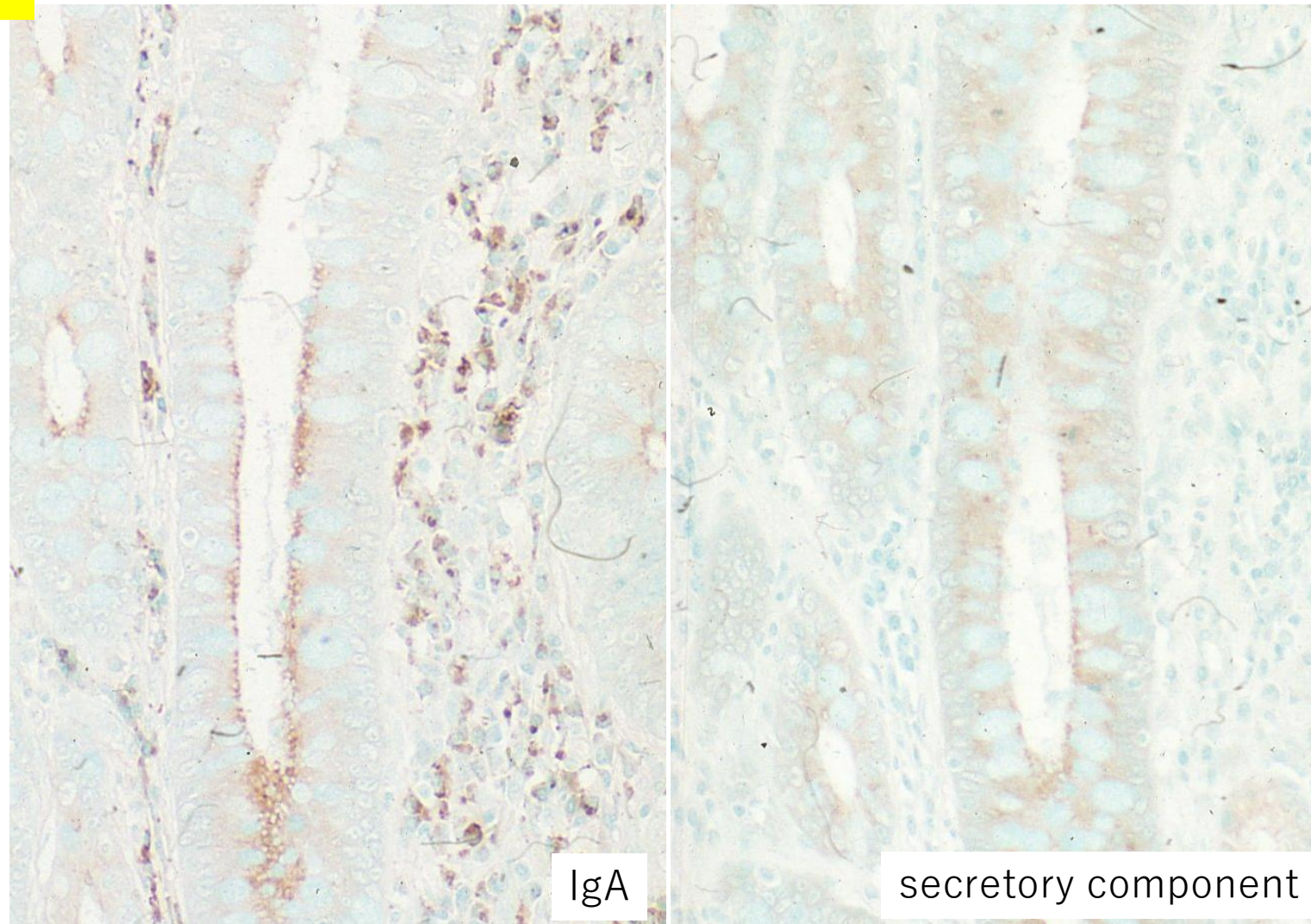
SC is produced by the intestinal columnar cells.

Secretory IgA is secreted through the intestinal columnar epithelial cells.



Production of dimeric IgA in the appendiceal mucosa. The plasma cells located in the lamina propria mucosae are immunoreactive for both IgA (left) and J-chain (right). The dimeric IgA contains J-chain within the molecules.

Intestinal metaplasia



Production of IgA and transepithelial transport of secretory IgA in the **intestinal metaplasia** of the gastric mucosa (immunostaining for IgA, left, and secretory component (SC), right). The lamina propria mucosae is rich in IgA plasma cells, and dimeric IgA is combined with SC produced by the intestinal-type epithelial cells to secrete into the lumen as **secretory IgA**. The apical cytoplasm of the epithelial cells is labeled for both IgA and SC. SC functions as receptors for dimeric IgA on the basolateral plasma membrane of the columnar epithelial cells.

Mucosal immunity vs. systemic immunity

B-cell system

	Site	Secretion	Serum	Roles	Specificity	Memorization
Mucosal	mucosa	sIgA	monomer IgA	defense on mucosal surface	low	difficult
Systemic	serum	Fcγbp	IgG	killing of invaded pathogens	high	easy

	Feature	Site of Ig production	Cell of production	Cell supply source
Mucosal	enterohepatic circulation	lamina propria mucosae	B-1 cells (GC-skipped)	milky spots (omentum)
Systemic	booster effect	lymph node	B-2 cells (GC-needed)	Peyer's patch, appendix

Fcγbp: IgG Fc-binding protein (Kobayashi K, et al: Mucosal Immunity 2021; 27(6): 423-436), GC: germinal center

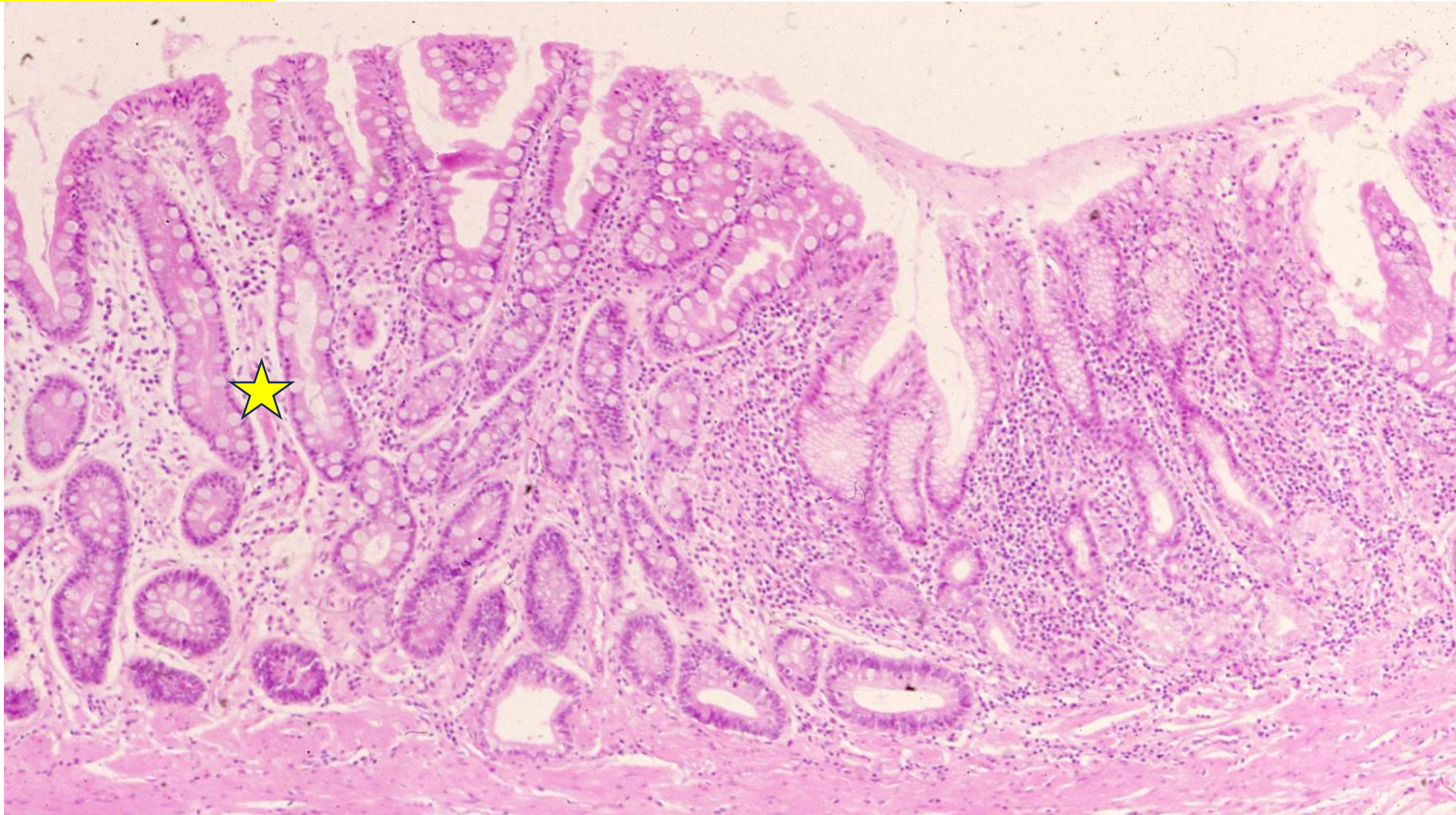
T-cell system

	Site	Functioning cell	Morphology	Markers
Mucosal	mucosa	extrathymic T-cell	large granular lymphocyte	CD8 ⁺ , CD56 ⁺ , TCRγδ
Systemic	systemic	thymus-educated T-cell	small lymphocyte	CD4 ⁺ >CD8 ⁺ , TCRαβ

	Autoimmunity	Site of production	Distribution
Mucosal	present	lamina propria crypt patch	gut mucosa (IELs), epidermis, liver sinusoid, decidua
Systemic	absent	paracortex of lymph nodes	systemic

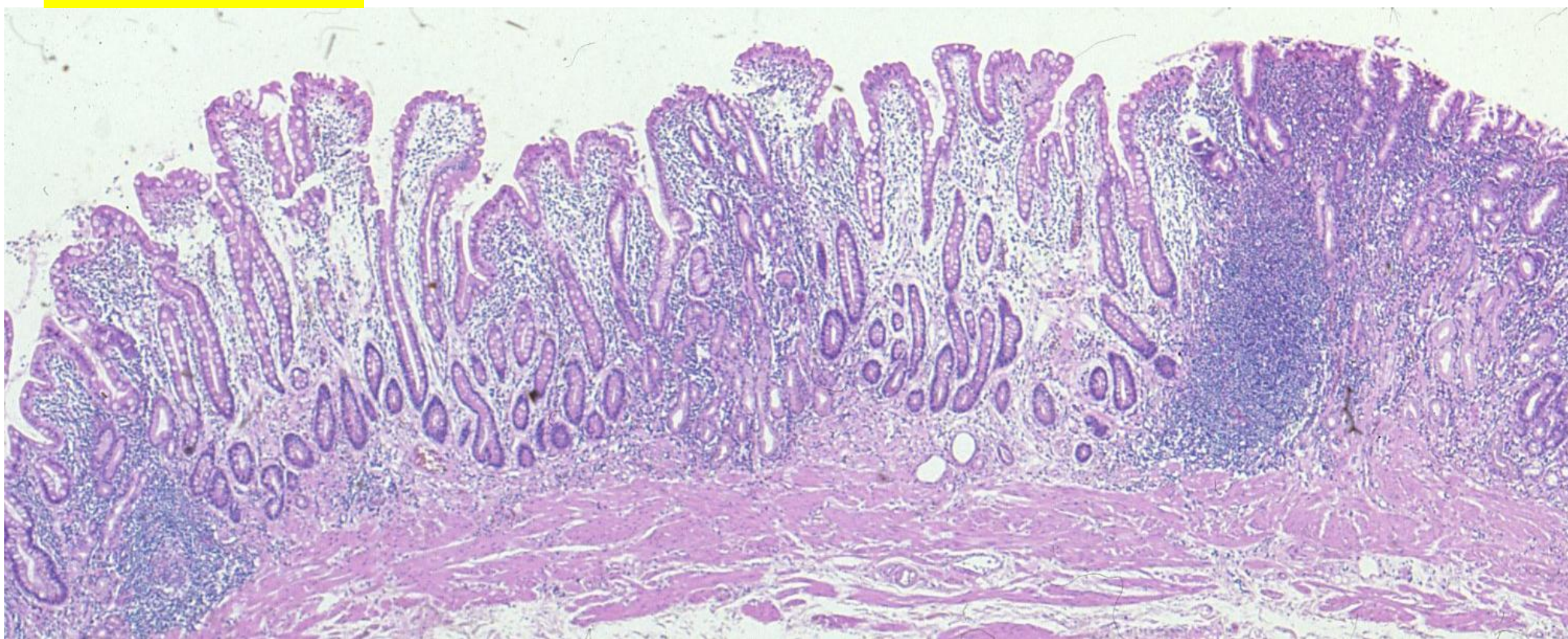
IELs: intraepithelial lymphocytes

Intestinal metaplasia



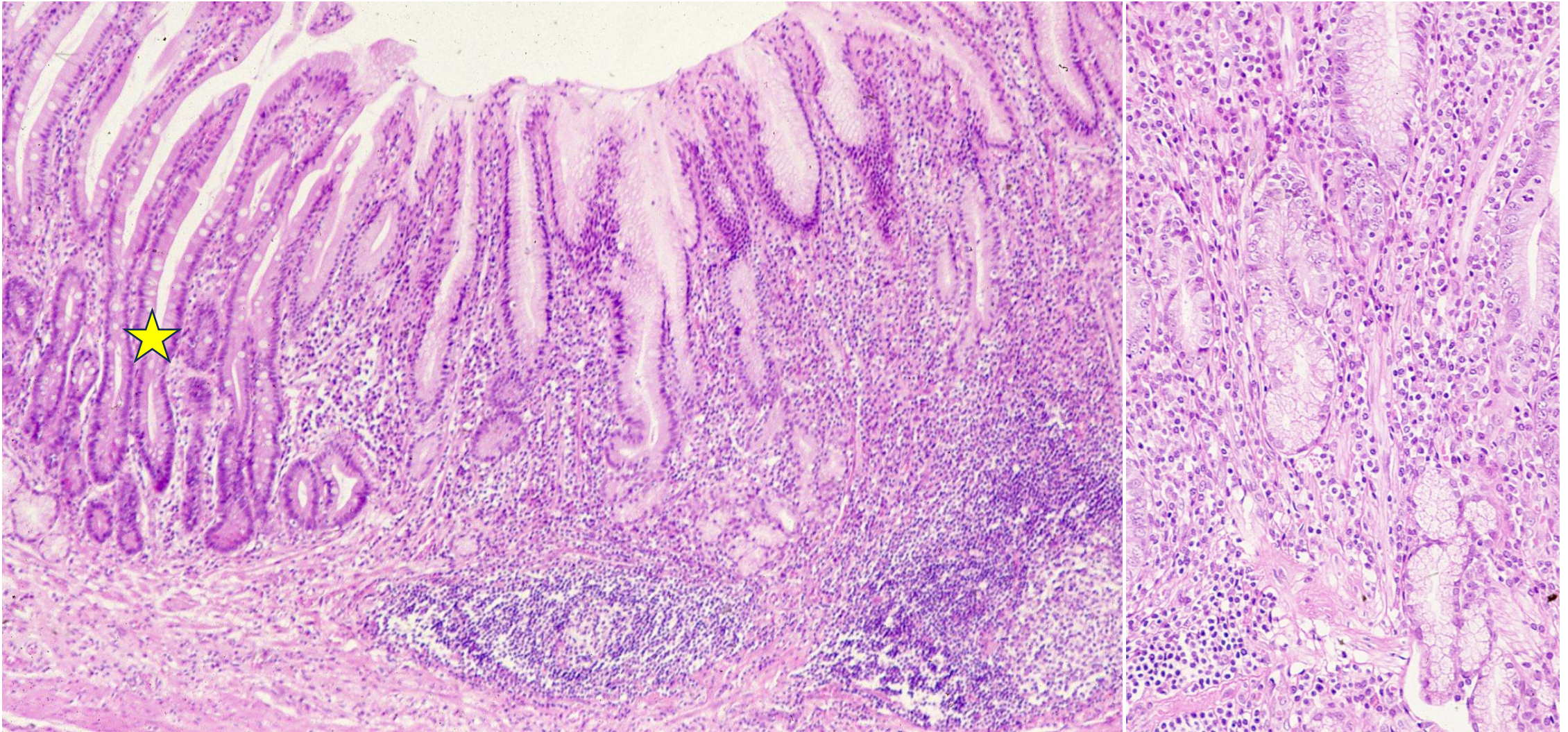
The degree of chronic inflammation in **intestinal metaplasia** (asterisk) is milder than non-metaplastic gastritic mucosa. **Ref.:** Tsutsumi Y, et al. Immune aspects of intestinal metaplasia of the stomach: an immunohistochemical study. *Virchows Arch A Pathol Anat Histopathol* 1984; 403(4): 345-359. doi: 10.1007/BF00737285

Intestinal metaplasia



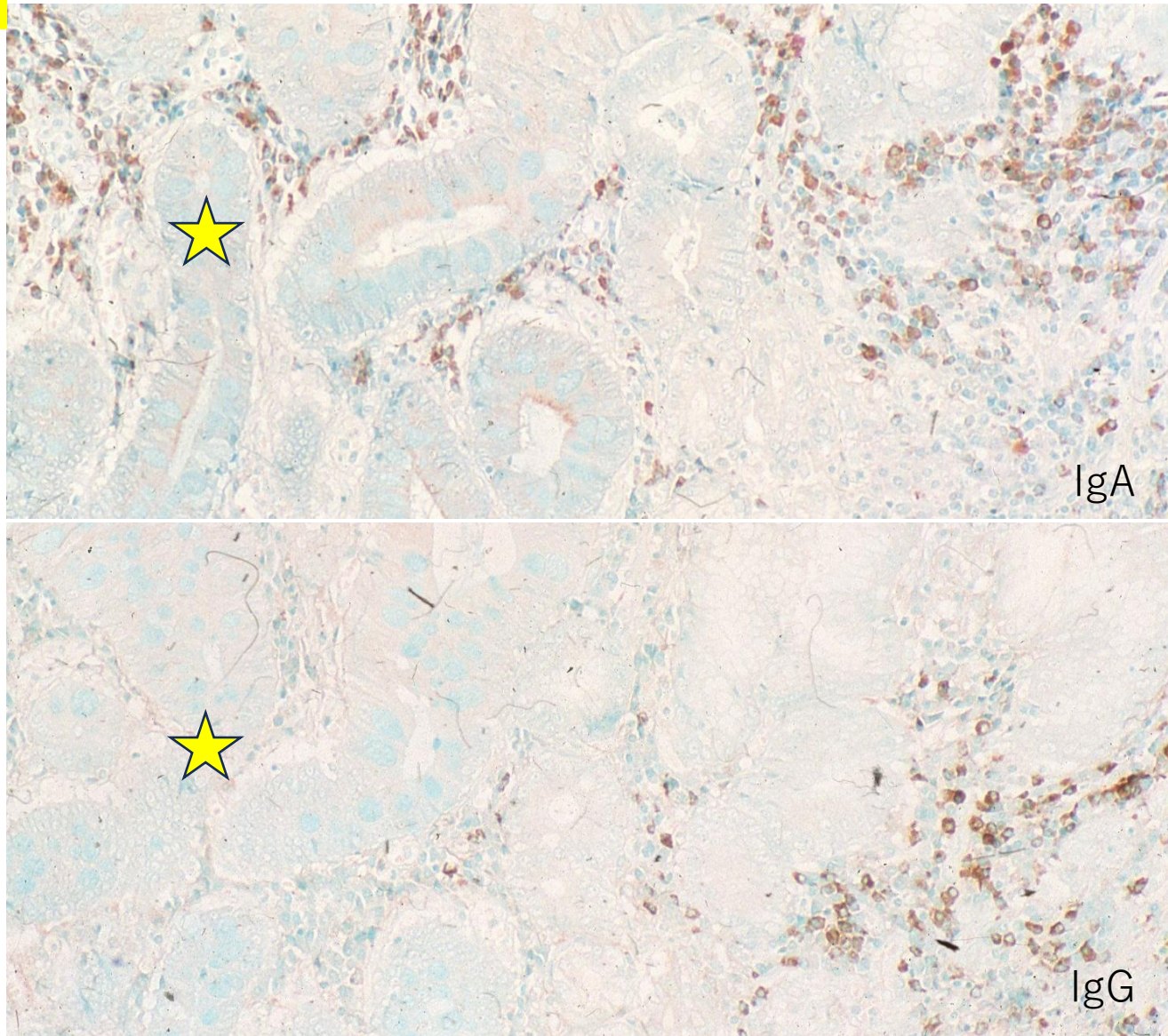
The degree of chronic inflammation in **intestinal metaplasia** is milder than non-metaplastic gastritic mucosa. Lymphoid follicle formation is often seen in the non-metaplastic mucosa. **Ref.:** Tsutsumi Y, et al. Immune aspects of intestinal metaplasia of the stomach: an immunohistochemical study. *Virchows Arch A Pathol Anat Histopathol* 1984; 403(4): 345-359. doi: 10.1007/BF00737285

Intestinal metaplasia

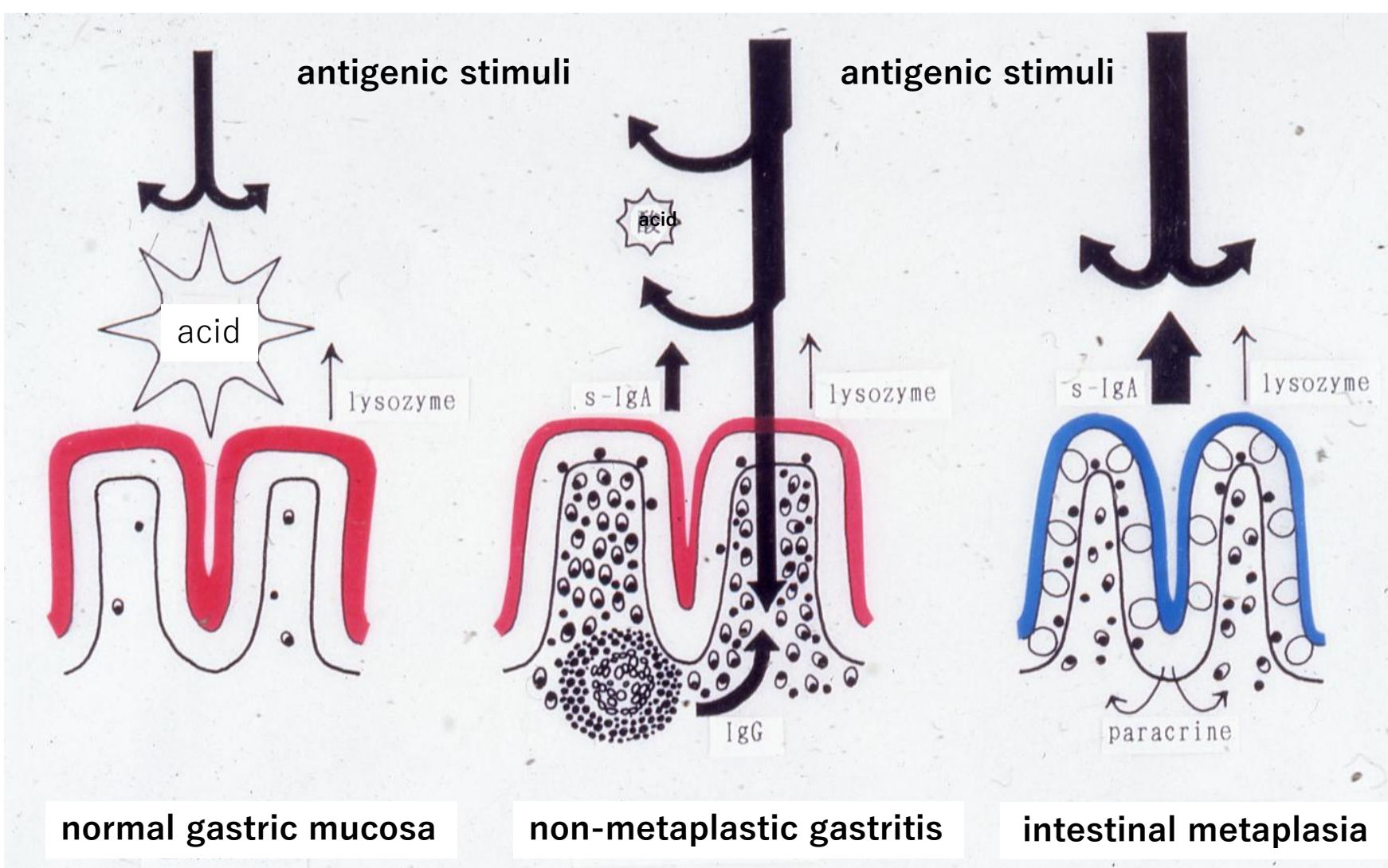


Chronic gastritis and intestinal metaplasia (H&E). Non-metaplastic gastritis shows chronic active inflammation with lymphoid follicle formation. Intestinal metaplasia (asterisk) is associated with milder inflammation without lymphoid follicles. Plasma cells are richly distributed in the lamina propria mucosae.

Intestinal metaplasia

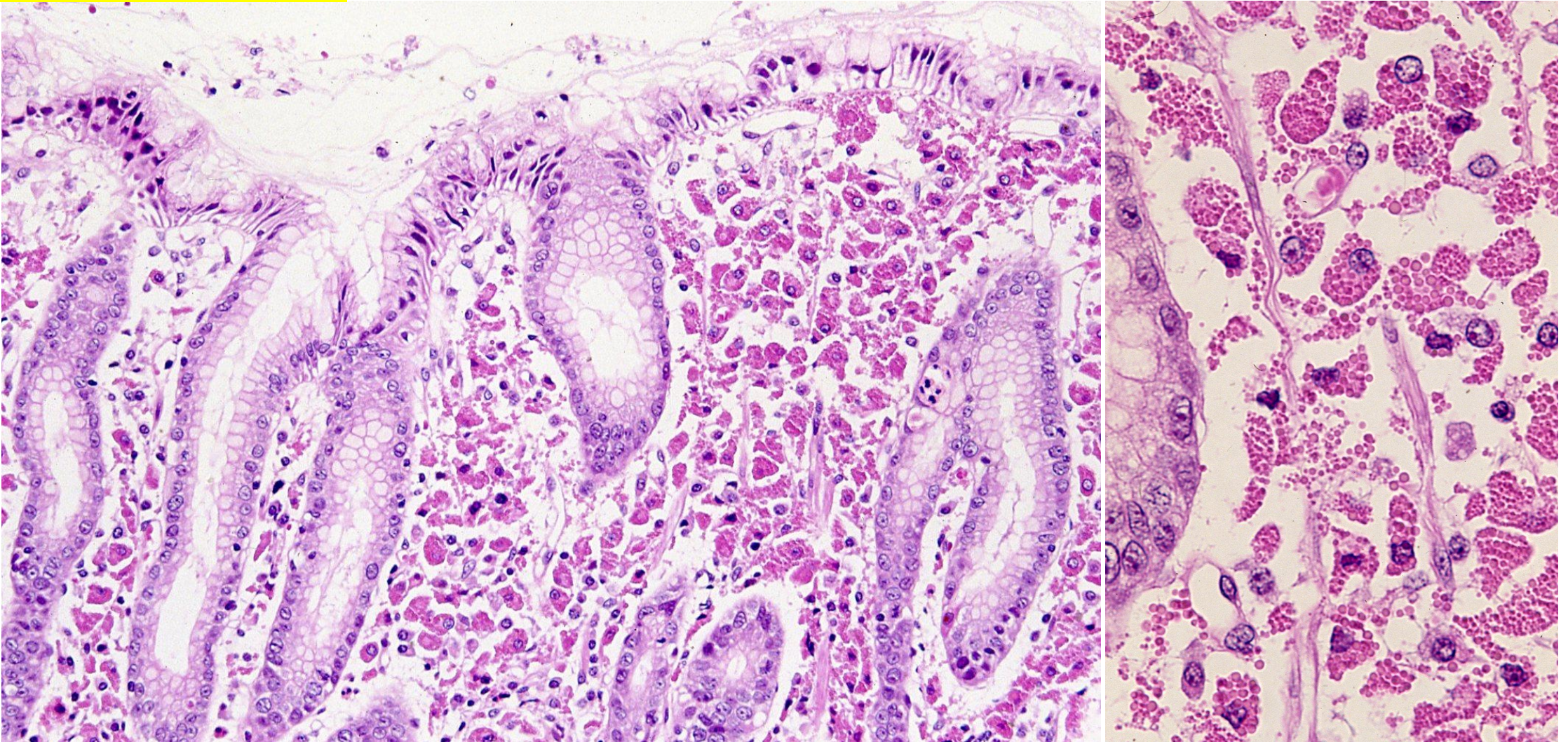


IgA plasma cells are distributed in both **intestinal metaplasia** (asterisks) and non-metaplastic gastritic mucosa (top). In contrast, IgG plasma cells are scarcely seen in the intestinal metaplasia (bottom). IgA plasma cells are evenly distributed in both metaplastic and non-metaplastic gastric mucosae.



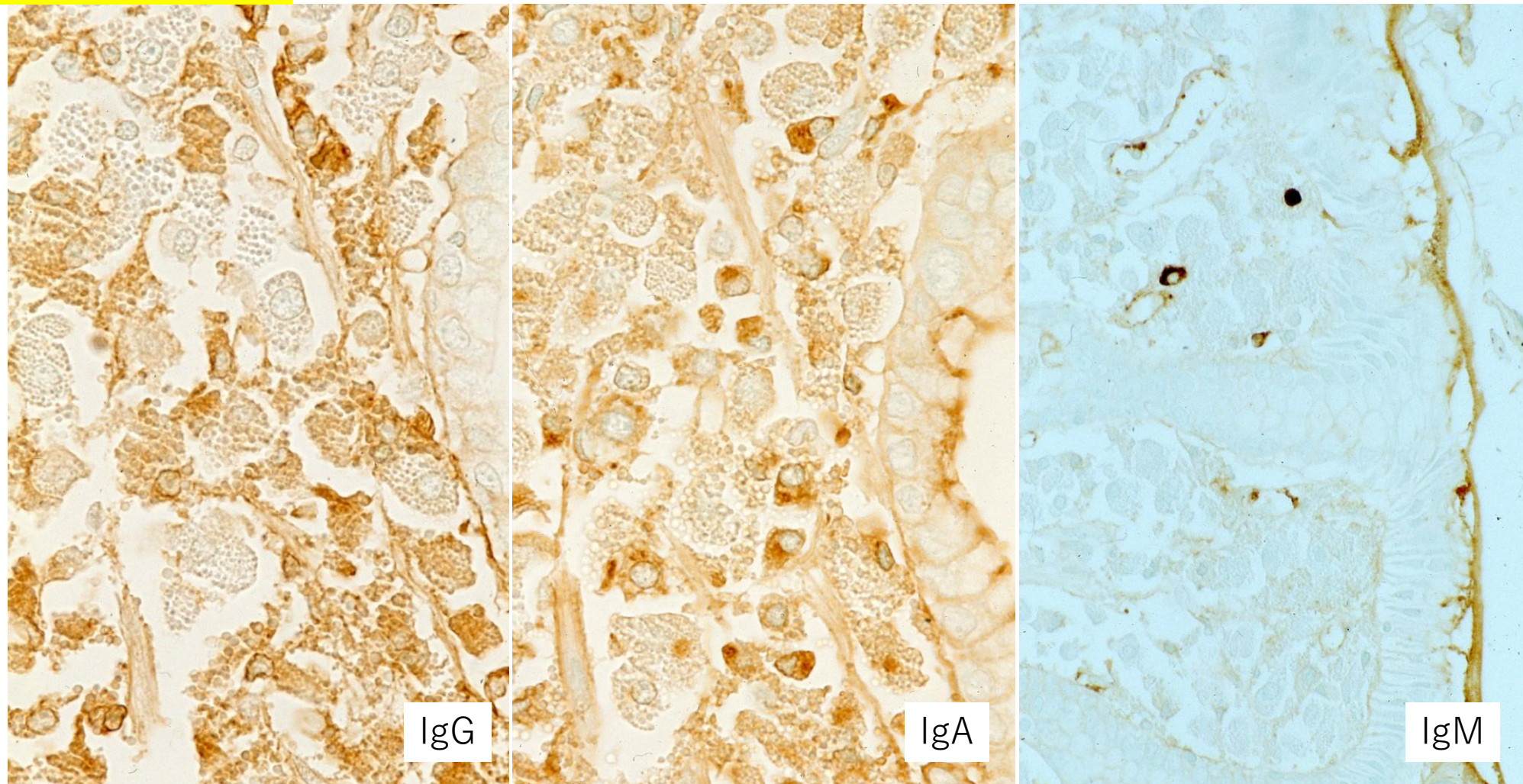
Mucosal immunity in the gastric mucosa. In normal gastric mucosa with neutrophilic mucin production and under high acidity, almost no inflammatory cells are seen in the lamina propria. In the inflamed gastric mucosa, principally with *Helicobacter pylori* infection, plasma cells producing either IgA or IgG are heavily distributed together with lymphoid follicle formation. The acidity is decreased, and secretion of sIgA starts. In intestinal metaplasia with alcianophilic mucin production, the transportation of sIgA is quite effective to protect antigenic stimuli. As a result, the number of inflammatory cells is decreased, and IgG plasma cells disappear, with IgA plasma cells predominant. Secretion of lysozyme is retained in all three phases.

Russell body gastritis



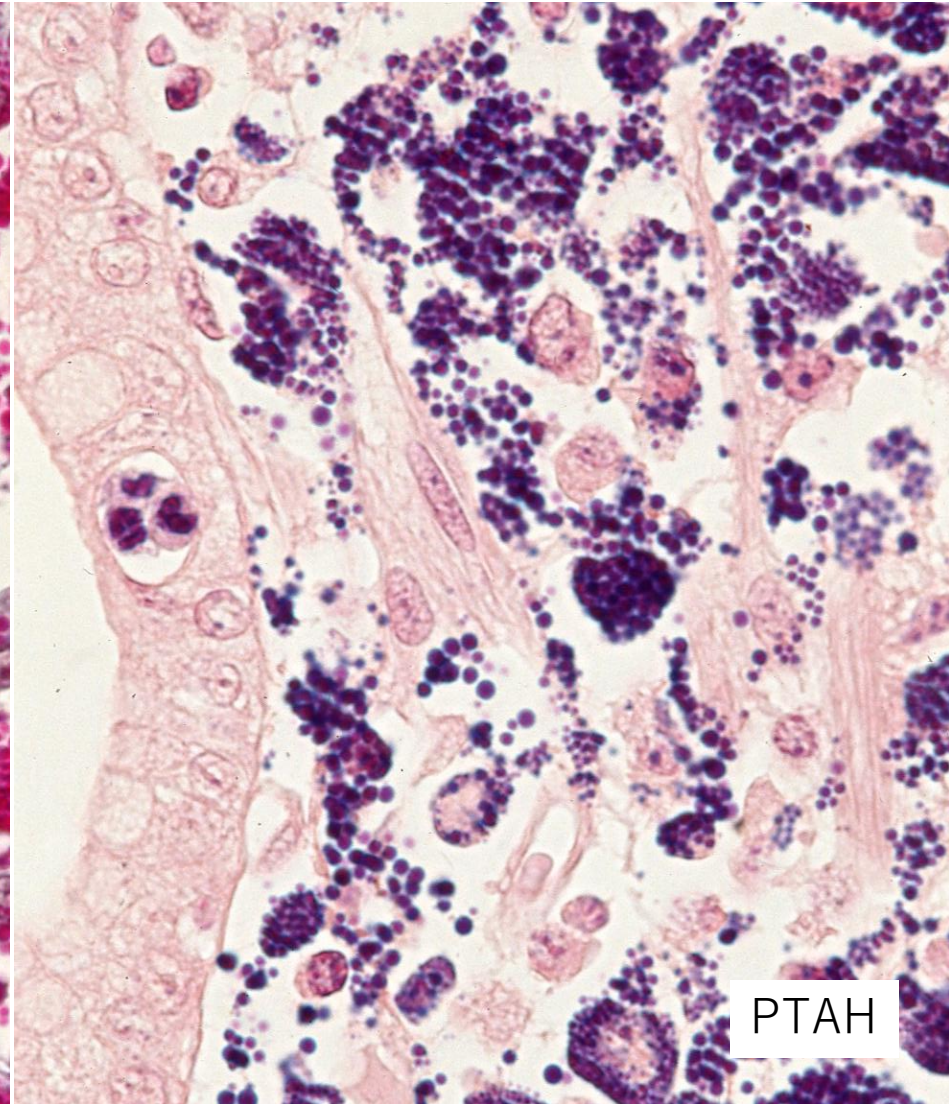
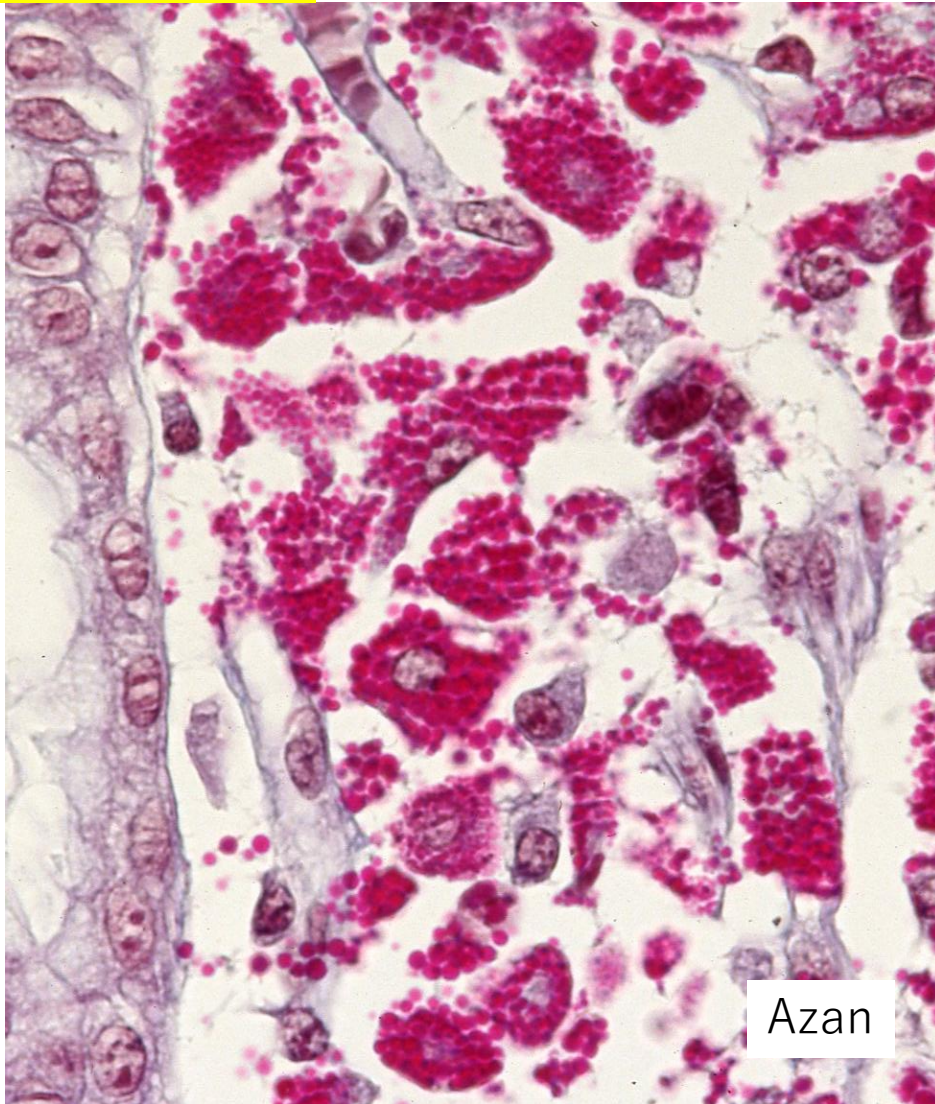
Russell body gastritis (H&E). The plasma cells in the gastric mucosa possess Russell bodies (eosinophilic globular inclusions) in the cytoplasm. **Ref.:** Tazawa K, Tsutsumi Y. Localized accumulation of Russell body-containing plasma cells in gastric mucosa with *Helicobacter pylori* infection: 'Russell body gastritis'. *Pathol Int* 1998; 48(3): 242-244. doi: 10.1111/j.1440-1827.1998.tb03901.x

Russell body gastritis



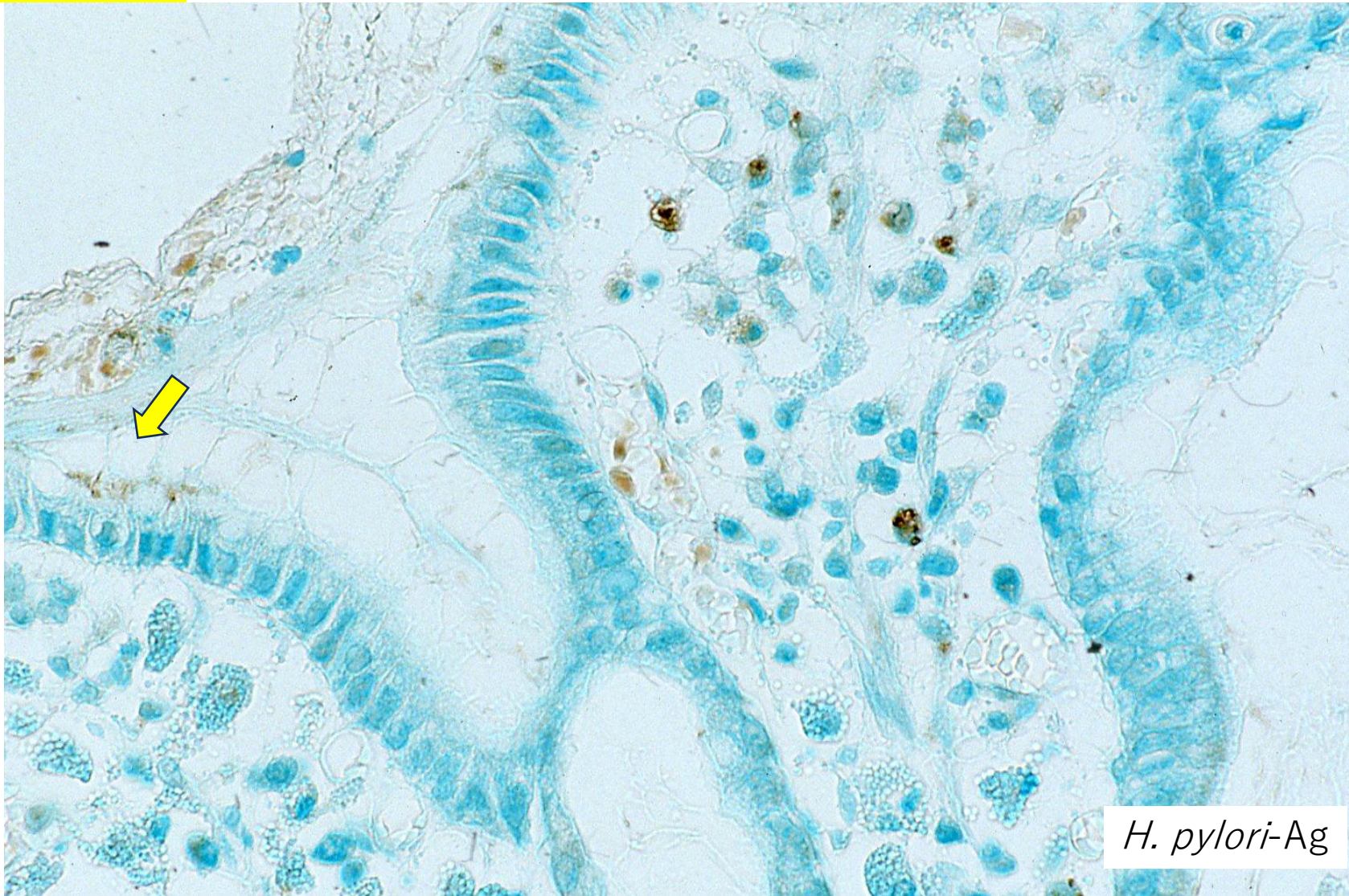
Russell body gastritis. The plasma cells containing Russell bodies in the cytoplasm are immunoreactive for IgG (left) and less frequently for IgA (center). A few plasma cells with IgM immunoreactivity lack Russell body formation (right). It should be noted that the plasma cells with Russell bodies may show monoclonality (an example of monoclonality in benign lesions). **Ref.:** Araki D, et al. Russell body gastritis showing IgM kappa-type monoclonality. *Pathol Int* 2013; 63(11): 565-567. doi: 10.1111/pin.12105

Russell body gastritis



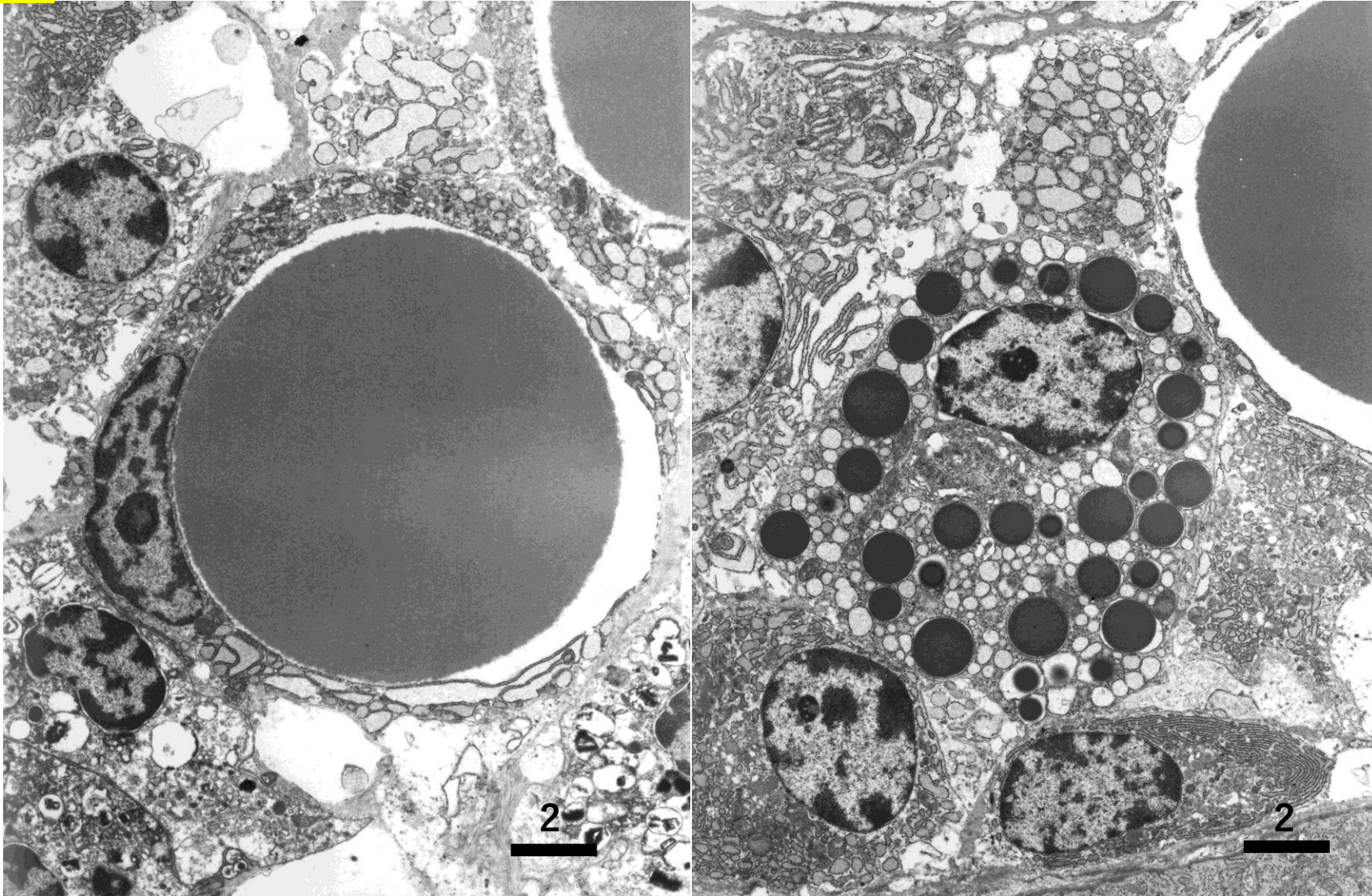
Russell body gastritis. Russell bodies formed in the plasma cell cytoplasm are stained red with Azan stain (left) and dark blue with PTAH stain (right), indicating the content of concentrated proteins, namely immunoglobulins.

Russell body gastritis



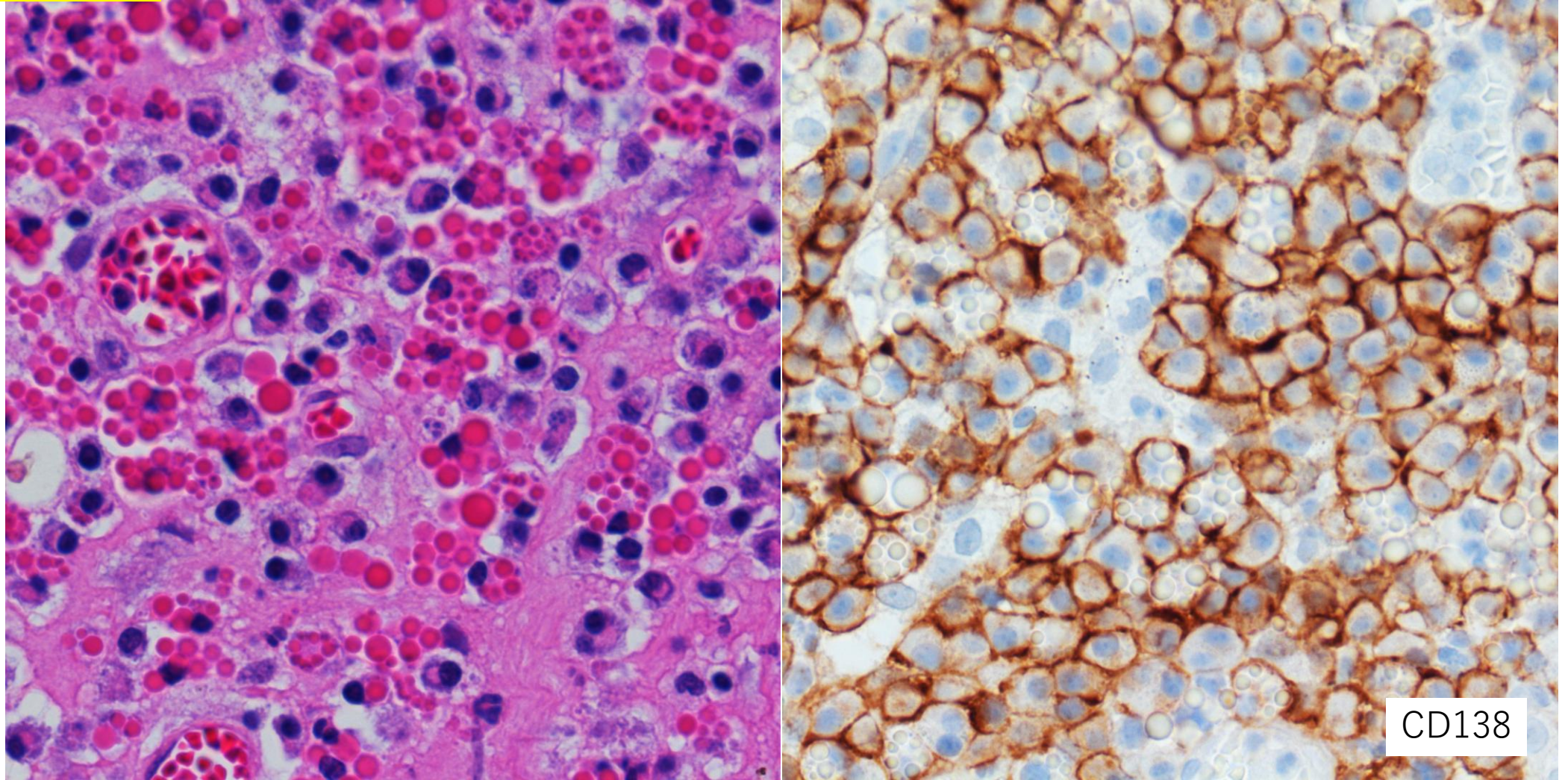
Russell body gastritis. *Helicobacter pylori* antigens are localized in the cytoplasm of macrophages adjacent to plasma cells with Russell bodies. Surface-infected *H. pylori* is indicated by the arrow. Russell body gastritis may be related to *H. pylori* infection.

Russell bodies



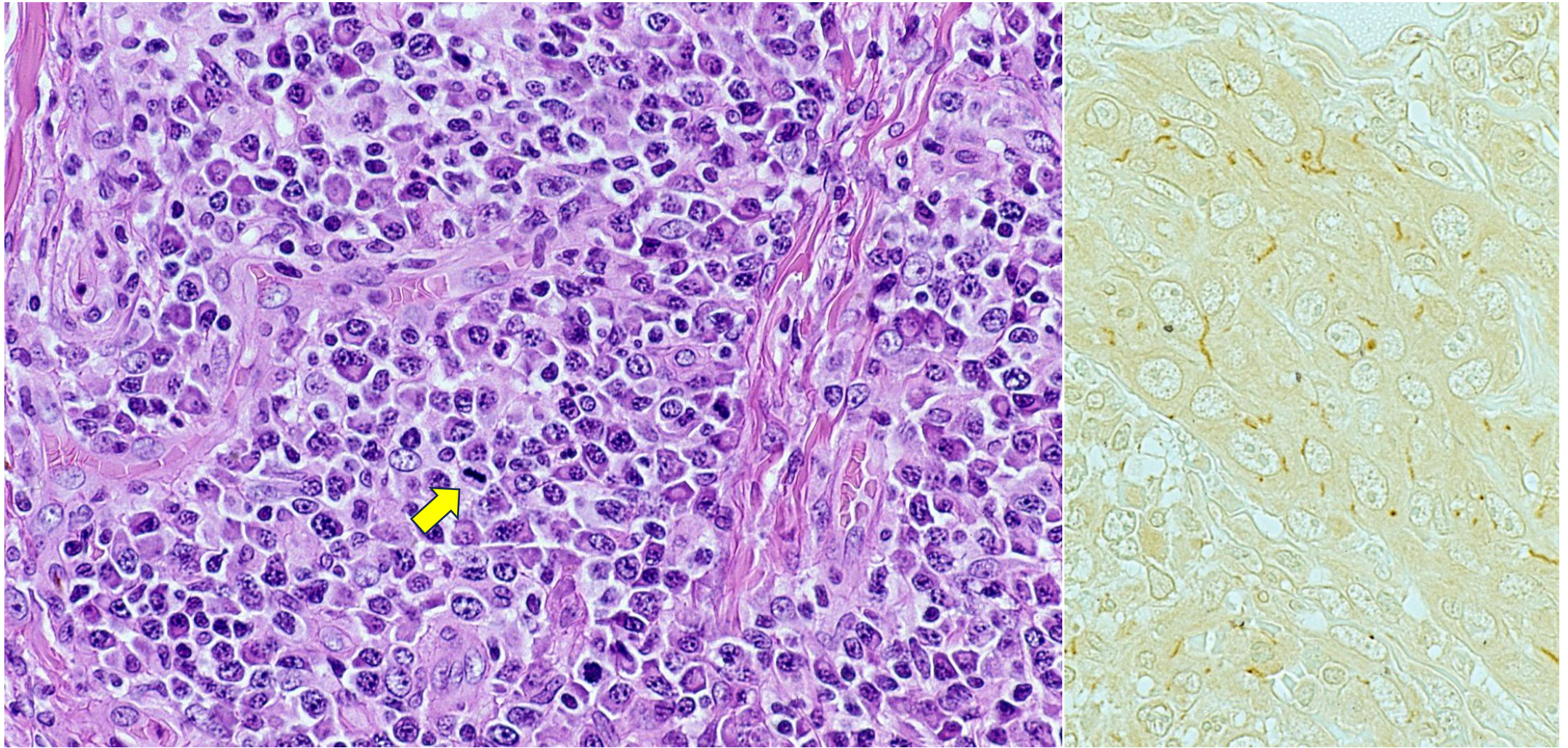
Ultrastructure of **Russell bodies** in plasma cells in the gastric mucosa (a 57 y-o female patient). Electron-dense globular inclusions, measuring 1-10 μm , are formed within the cisterna of rough endoplasmic reticulum. The inclusions represent the secretory disturbance of immunoglobulin.

Russell bodies



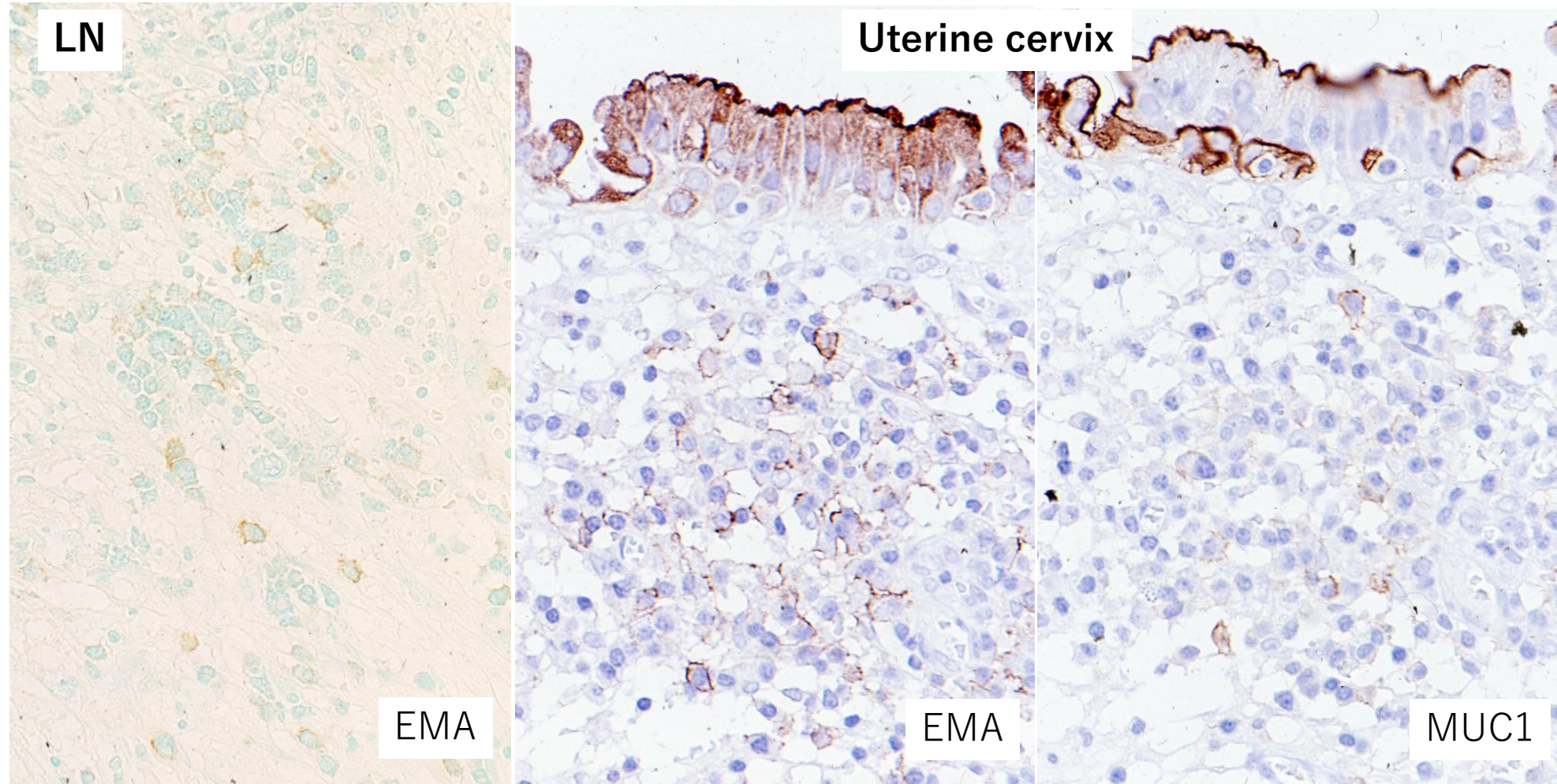
Dental caries-associated **radicular cyst** with numbers of plasma cells containing **Russell's bodies** (left: H&E, right: CD138). Russell bodies are clustered in the cytoplasm of CD138-positive plasma cells. It is known that the radicular cyst reveals dense accumulation of mature plasma cells.

Plasma cells in syphilitic lesions



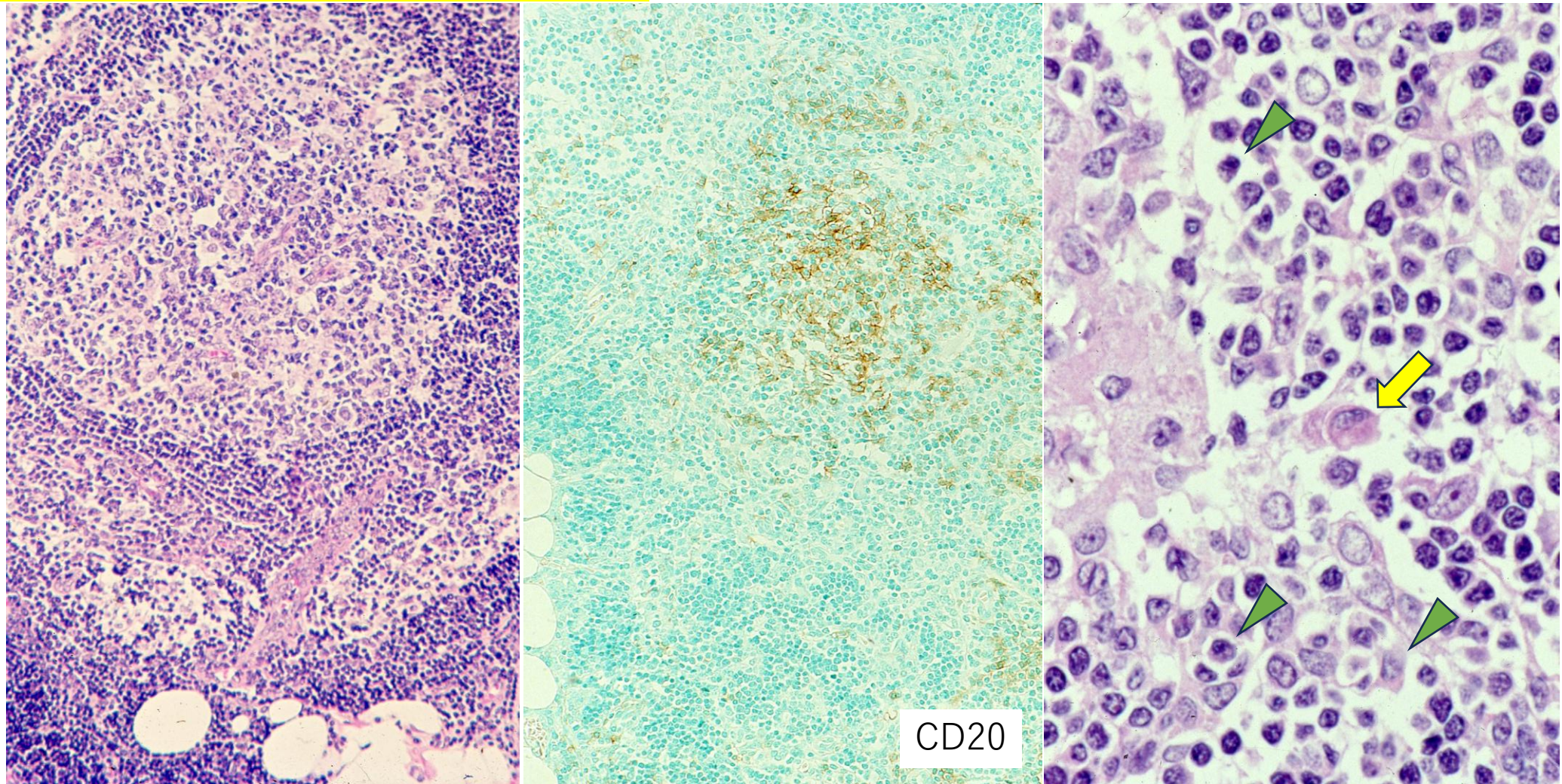
Secondary syphilis. Skin biopsy reveals marked infiltration of mature **plasma cells** in the dermis. Some plasma cells are binucleated. Swelling of the endothelial cells is also noted (left: H&E). The possibility of syphilitic lesion was microscopically suspected, and immunostaining with antiserum against *Treponema pallidum* identified spiral pathogens among the epidermal keratinocytes (right). Note that a mitotic activity is seen in the infiltrating plasma cell (arrow).

Plasma cells in chronic inflammatory lesions



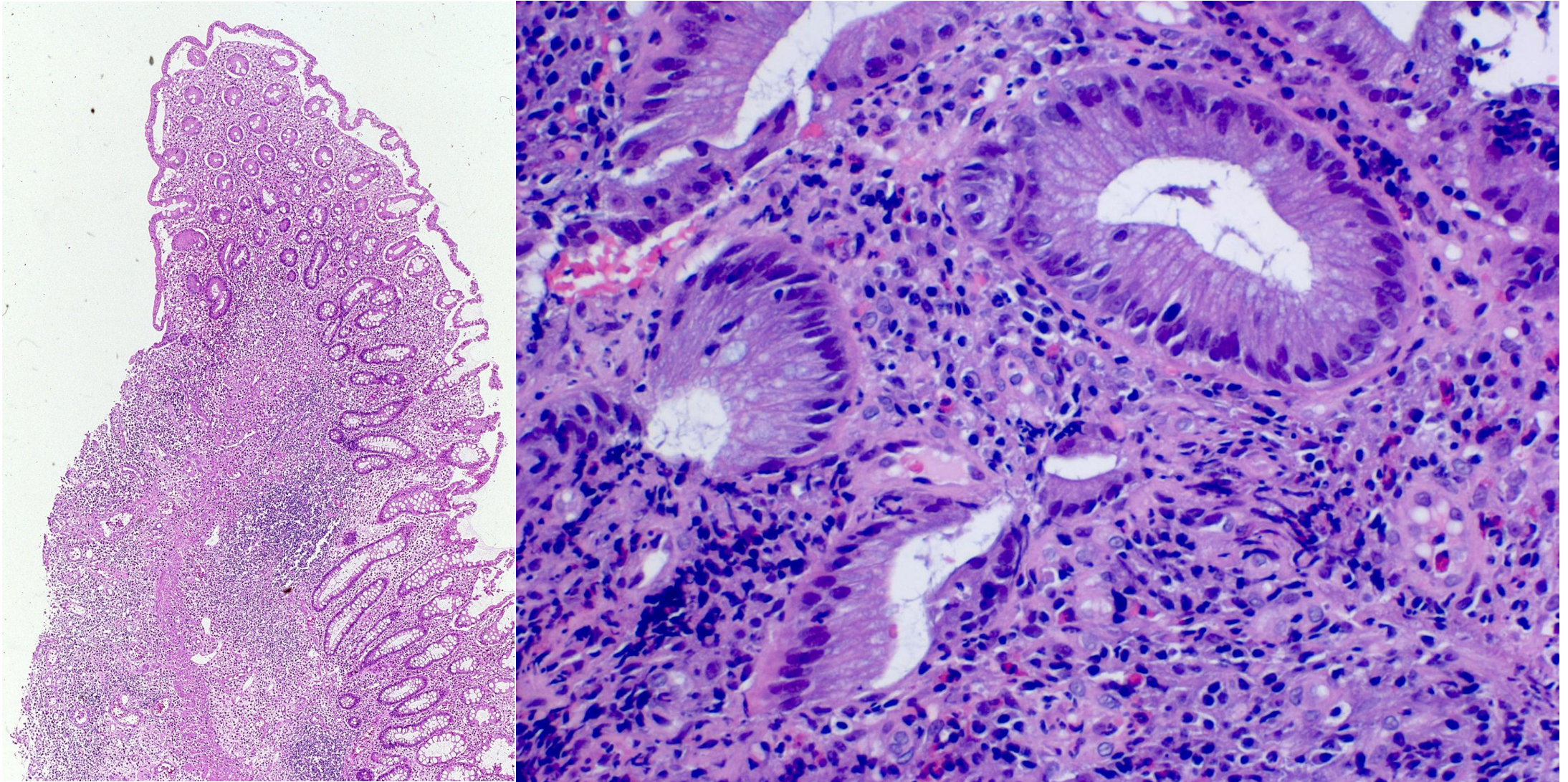
Expression of EMA and MUC1 on the plasma membrane of **plasma cells** (left: EMA in the medulla of the normal lymph node, center: EMA (E29) in **chronic cervicitis**, right: MUC1 (115D8) in chronic cervicitis). Note that epithelial markers are expressed on the plasma cells. EMA (a MUC1-related molecule) and MUC1 are positive in the mucous epithelial cells covering the uterine cervix.

Plasma cells in chronic inflammatory lesions



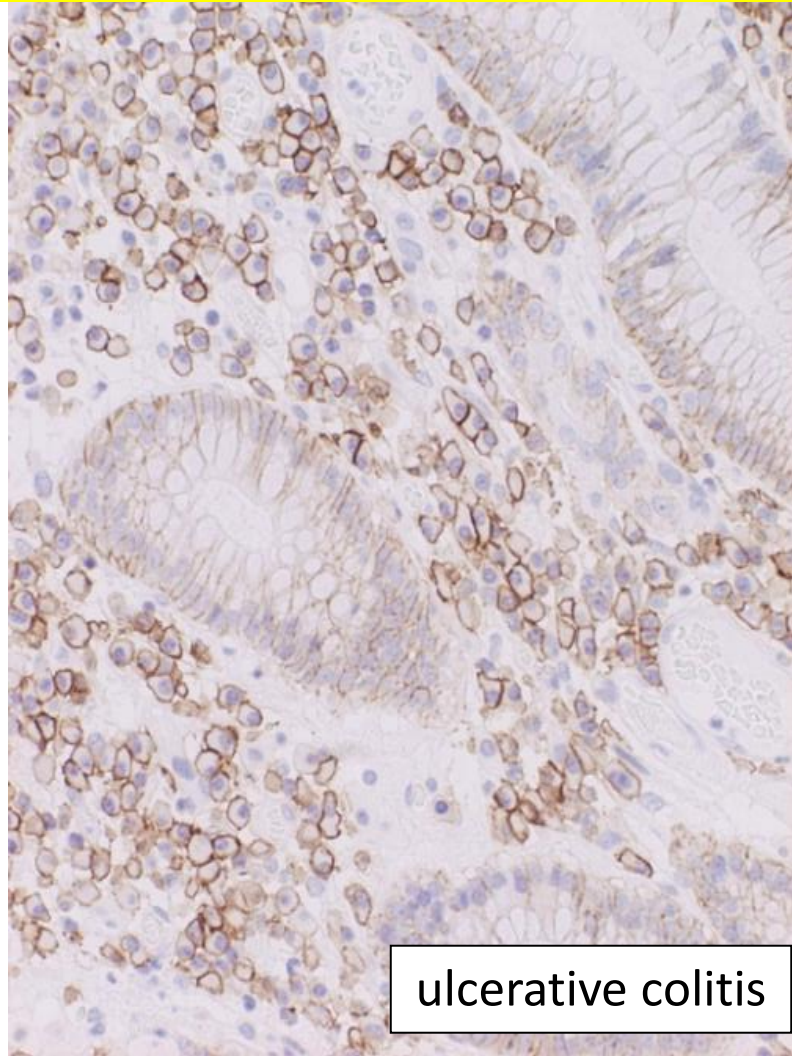
Thymic hyperplasia complicated with **myasthenia gravis** in a male patient aged 40's. In the thymic medulla, lymphoid follicles with enlarged germinal centers are formed (left: H&E), where CD20-positive B-lymphocytes are clustered (center: immunostaining for CD20). Around the myoid cell (arrow), plasma cells are scattered (arrowheads) (right: H&E).

Plasma cells in chronic inflammatory lesions

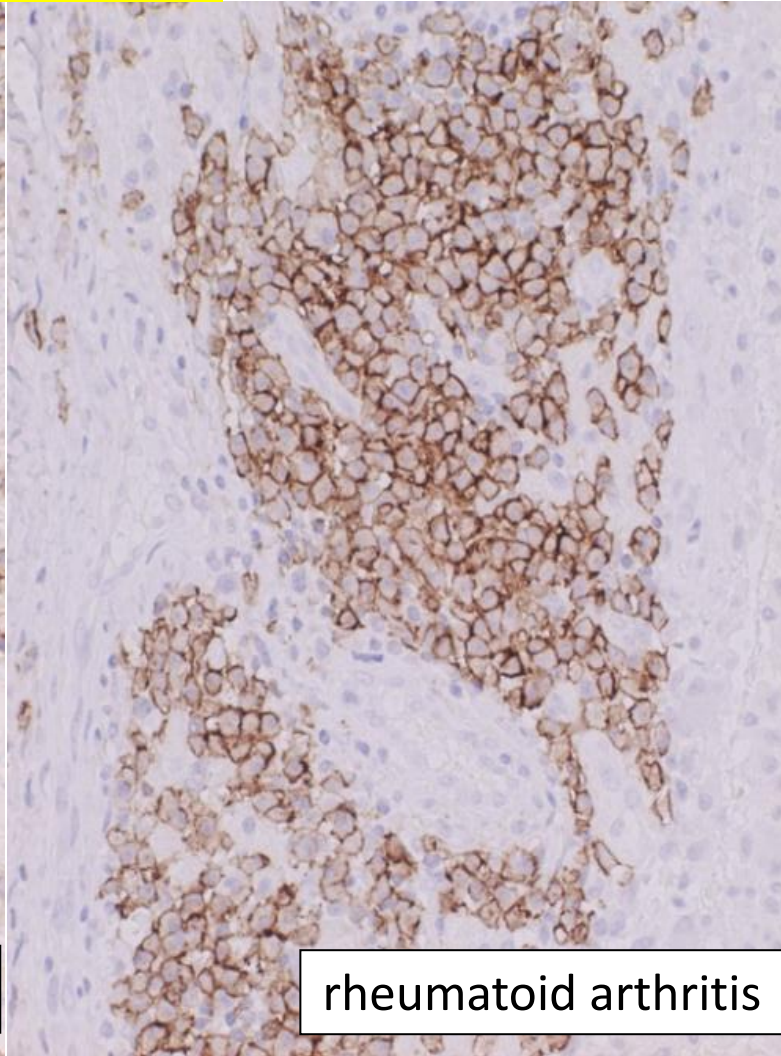


Ulcerative colitis reveals chronic active inflammation with features of cryptitis (crypt abscess formation) (H&E). **Basal plasmacytosis** is one of the diagnostic criteria of active ulcerative colitis. Eosinophils are also increased in the lamina propria mucosae.

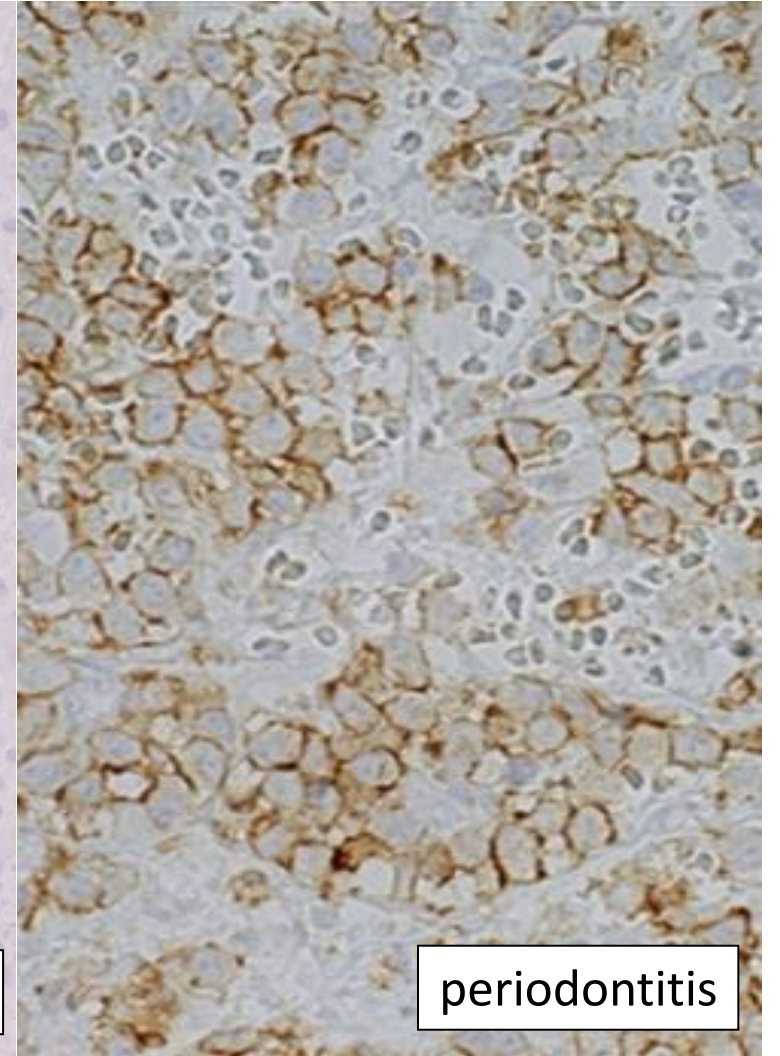
Plasma cells in chronic inflammatory lesions



ulcerative colitis



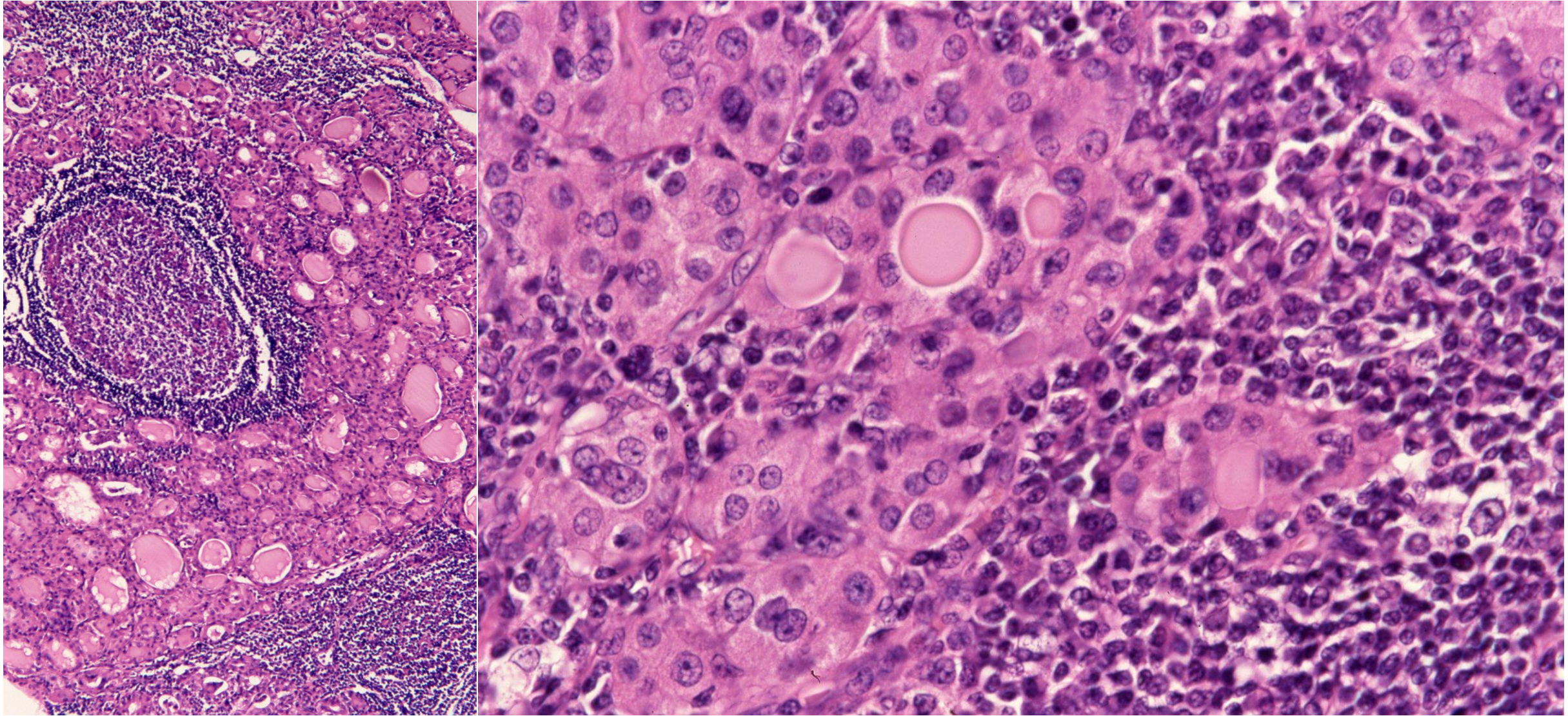
rheumatoid arthritis



periodontitis

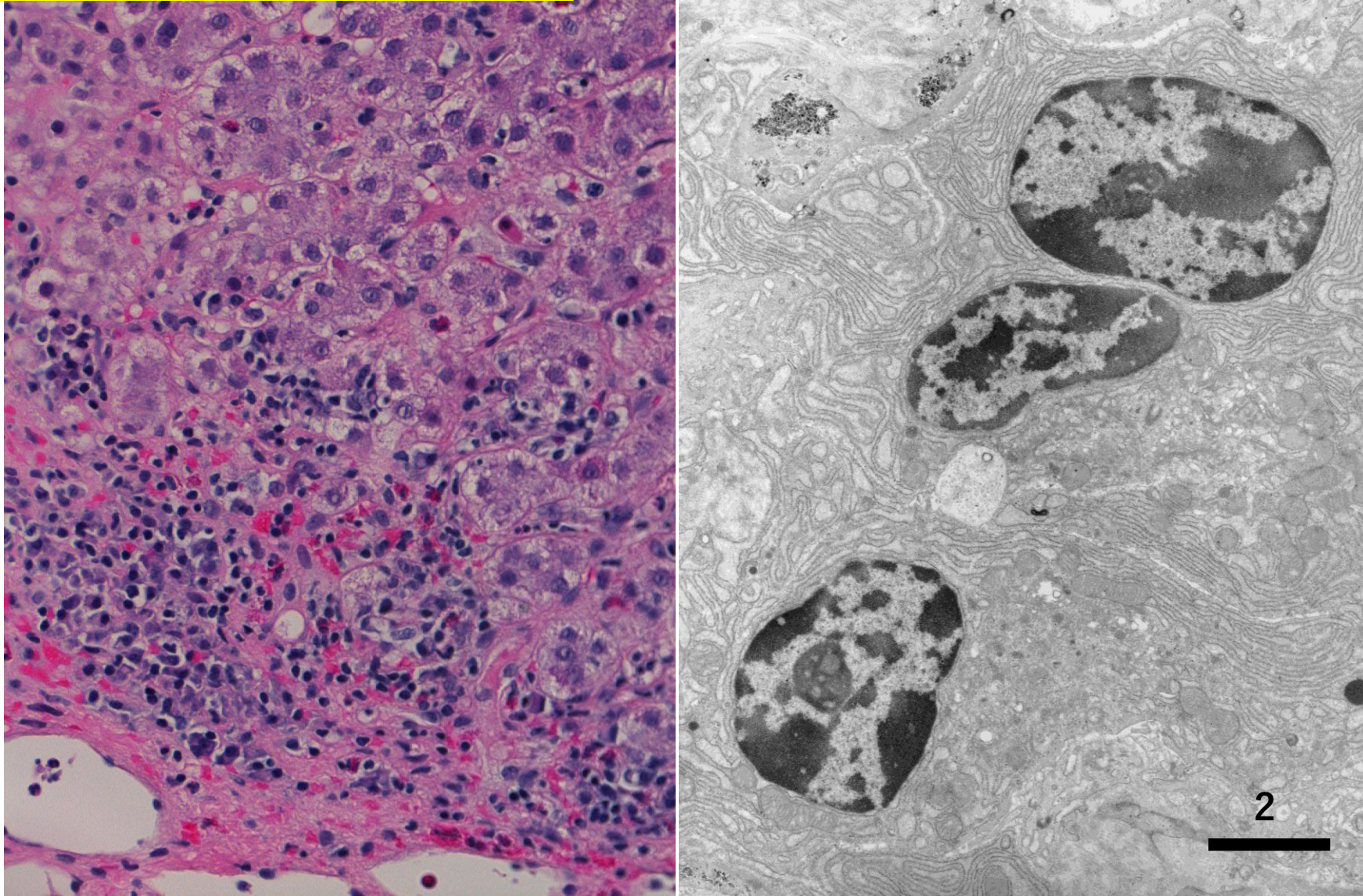
CD138-immunoreactive plasma cells in chronic organitis, such as **ulcerative colitis** (left), **rheumatoid arthritis** (center) and **periodontitis** (right). CD138 is an excellent marker of normal and neoplastic plasma cells.

Plasma cells in chronic inflammatory lesions



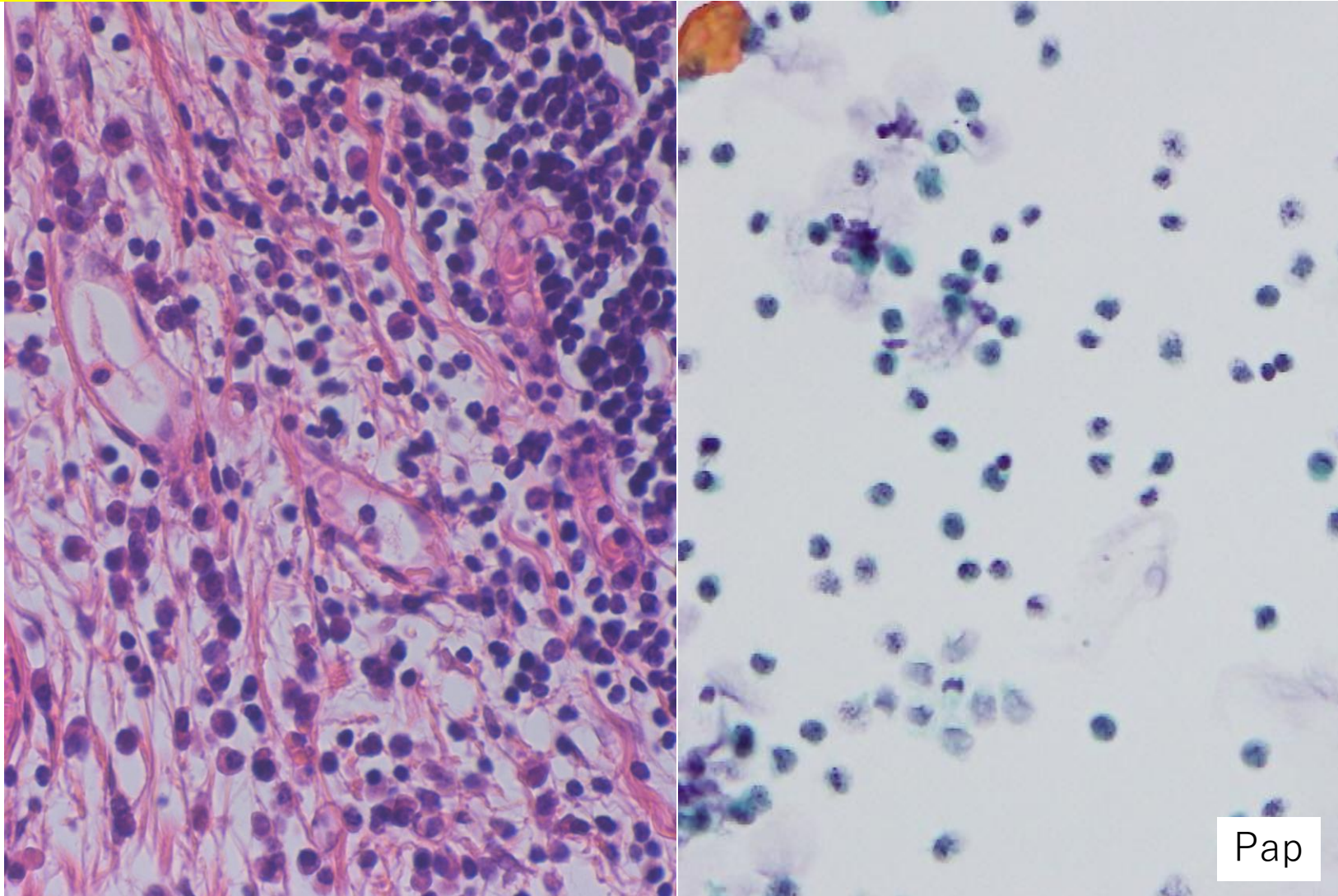
Hashimoto thyroiditis shows chronic inflammation with lymphoid follicle formation (left: low-power H&E). A good number of plasma cells are seen among the lymphoid infiltration. Oncocytic change is associated in the follicular epithelial cells (right: high power H&E).

Plasma cells in chronic inflammatory lesions

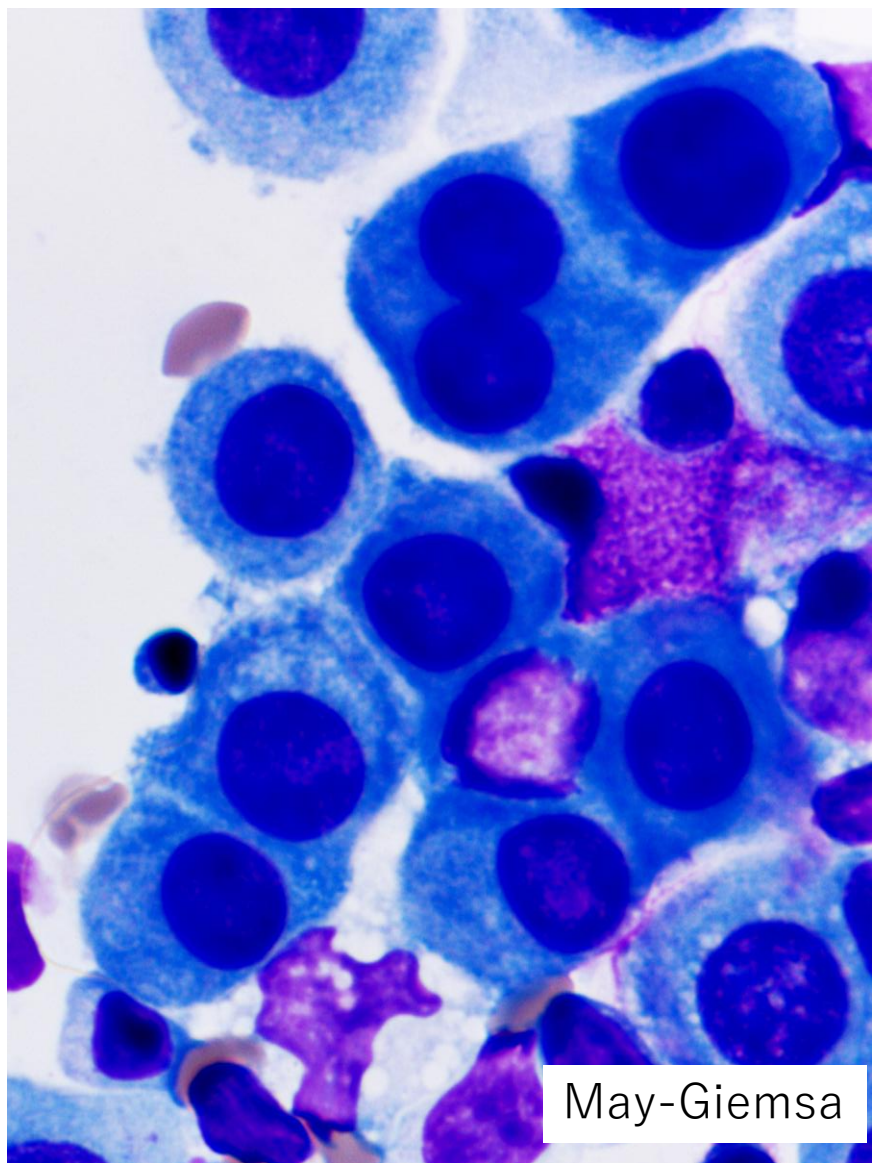


Autoimmune hepatitis (liver biopsy). Left: H&E, right: EM. Infiltration of mononuclear cells and some eosinophils is seen in the portal triad. Plasma cells are intermingled. Mature plasma cells with well-developed rough endoplasmic reticula are observed ultrastructurally.

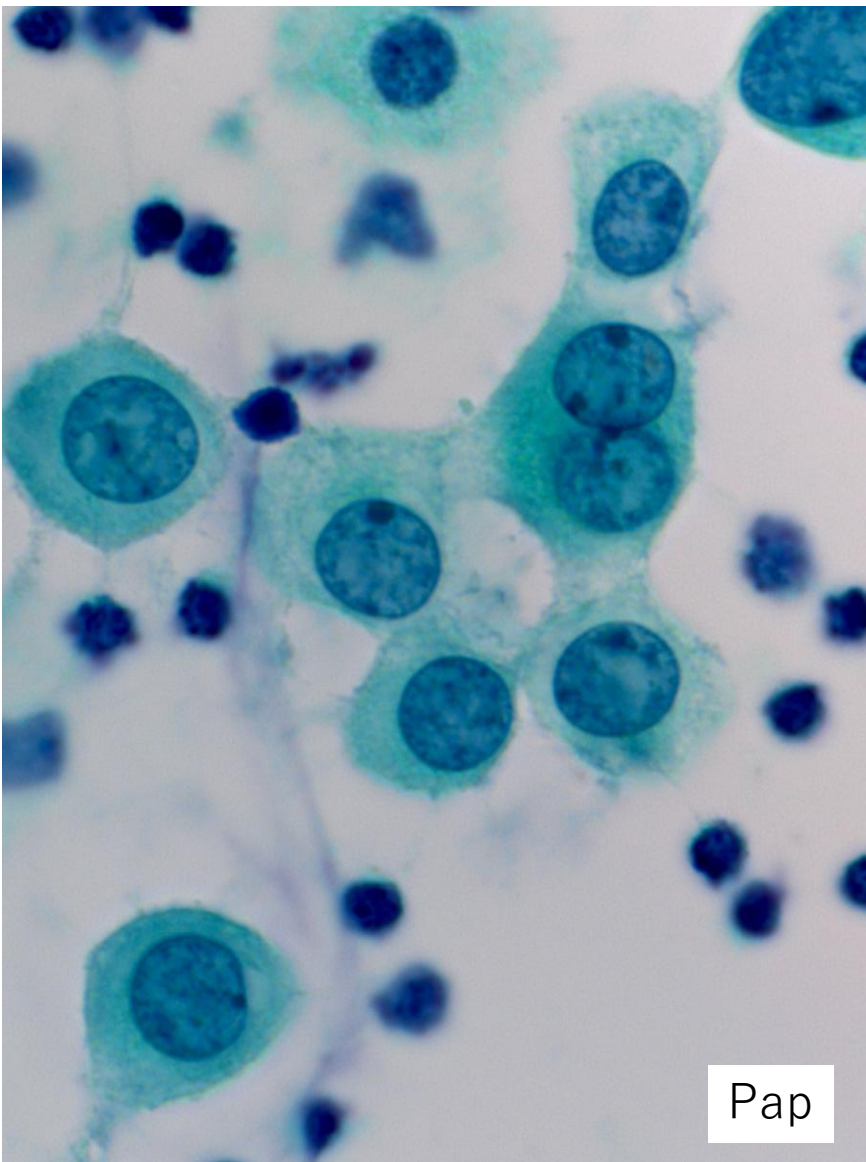
Plasma cells without migratory activity



Chronic pleuritis (left: H&E, right: pleural effusion, Pap). In chronically inflamed pleura, a good number of mature plasma cells are seen together with small lymphocytes. In pleural effusion, small lymphocytes and some neutrophils are noted, but with almost no plasma cells exudated. It seems plasma cells lack migratory activity.

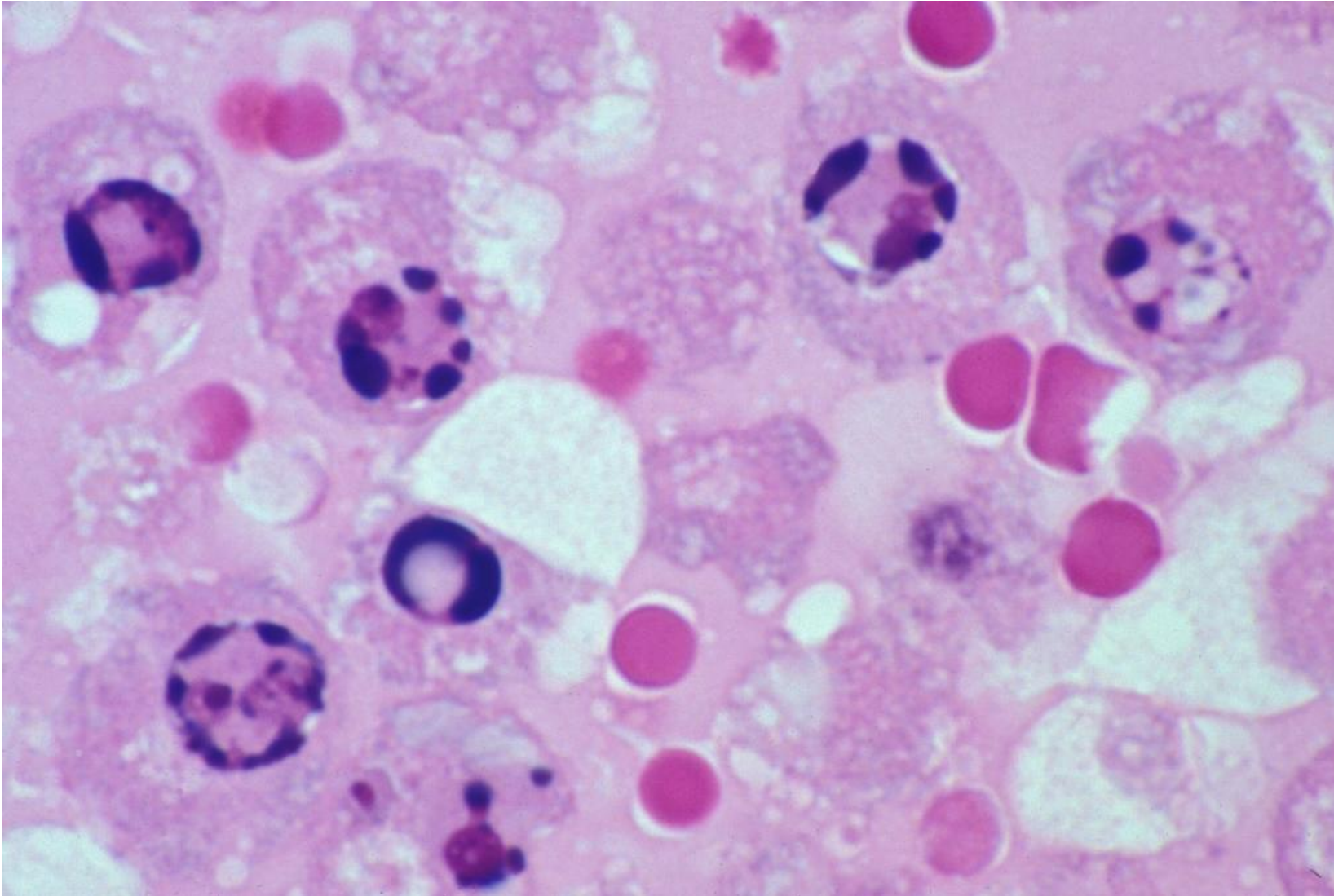


May-Giemsa



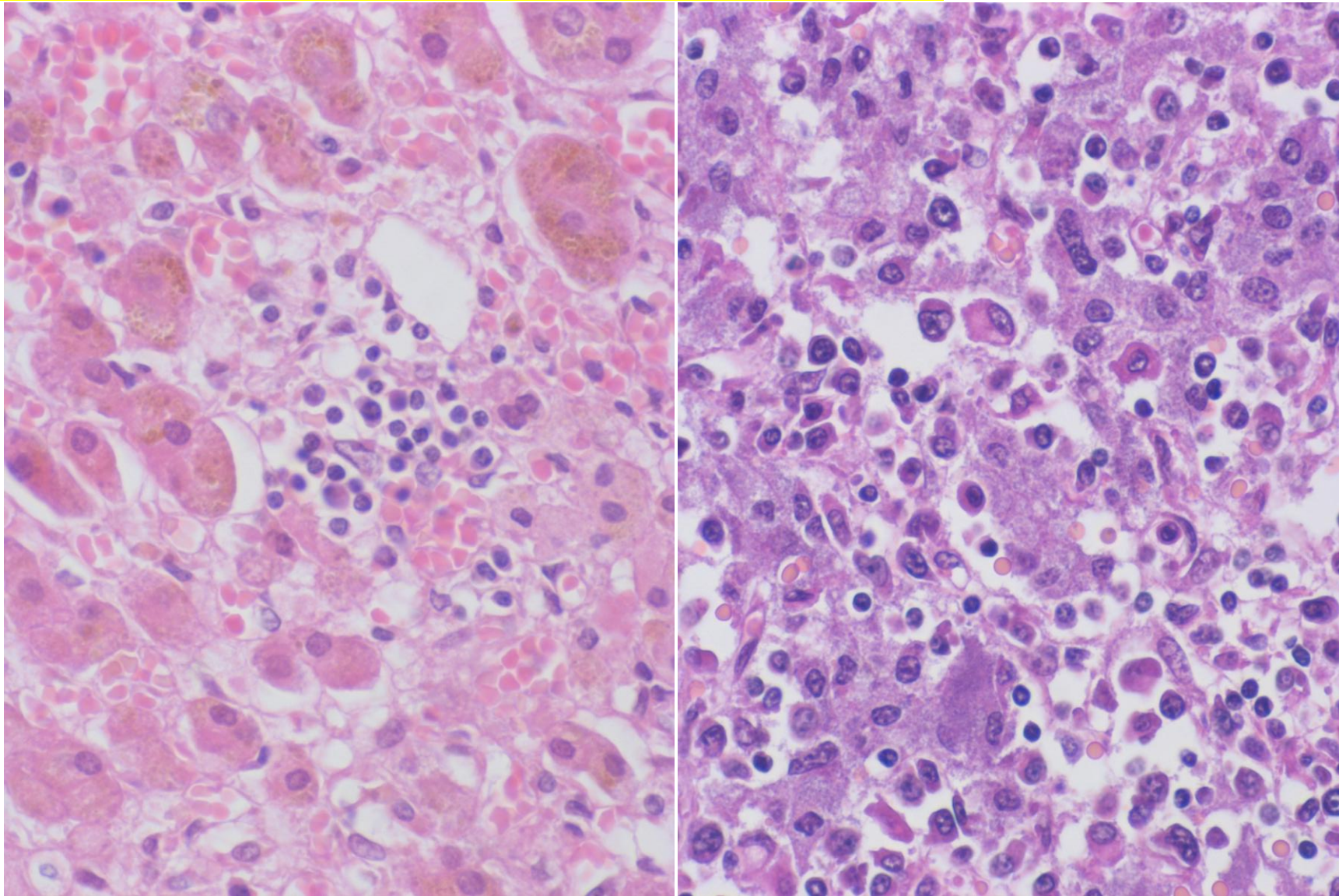
Pap

Pleural effusion with **multiple myeloma** (left: May-Giemsa, right: Pap). A 57 y-o female patient manifested massive pleural effusion, and cytological diagnosis was positive for multiple myeloma cells. Bone marrow aspiration disclosed IgG, kappa-type plasmacytoma. In sharp contrast to normal plasma cells, the neoplastic plasma cells may migrate into the pleural effusion.



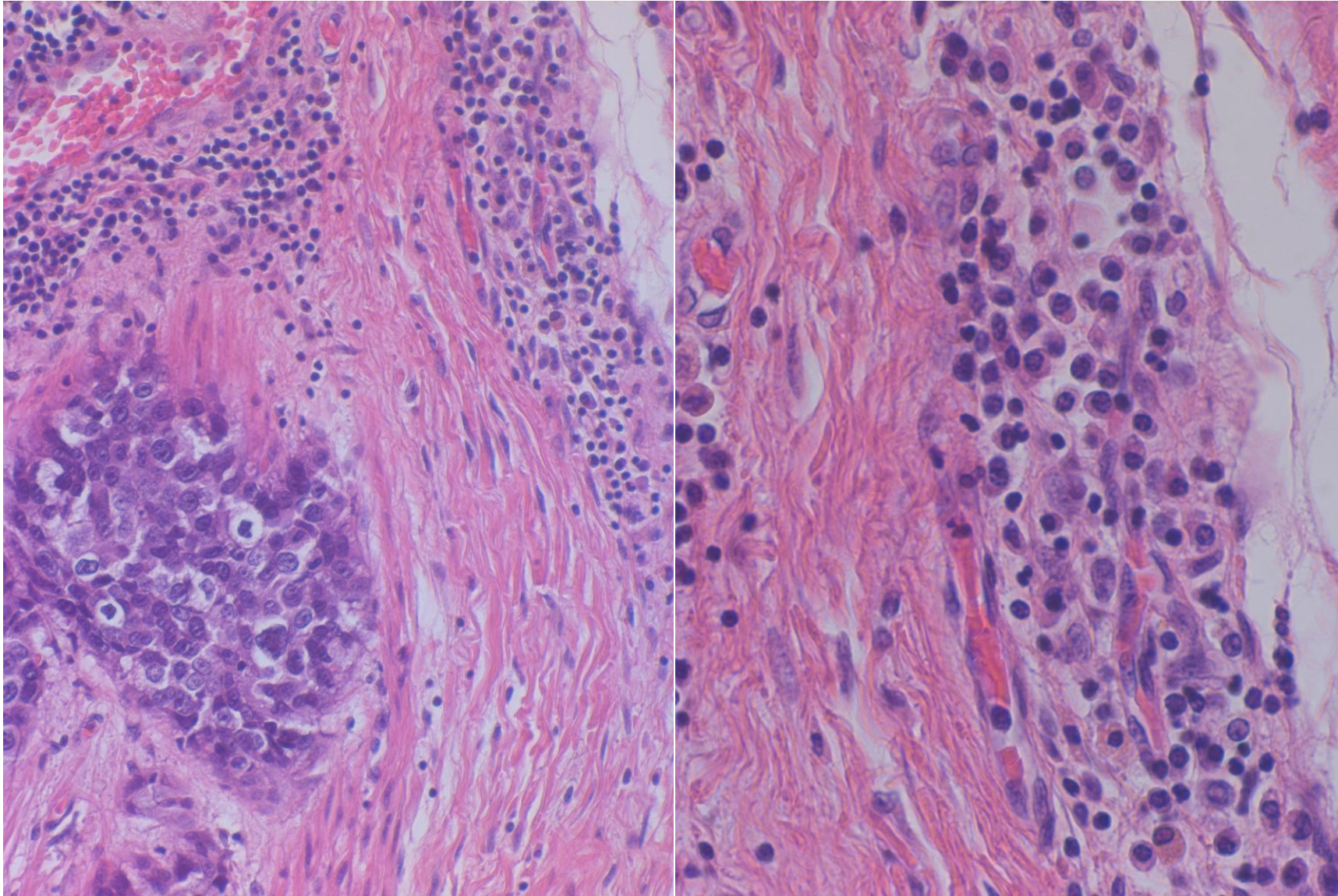
Apoptosis of **multiple myeloma** cells in pleural effusion (cell block, H&E). A male patient of multiple myeloma aged 70's manifested bilateral pleural effusions. The tapped hemorrhagic effusion left on the table overnight. The myeloma cells in the cell block preparation show features of apoptosis with coarse chromatin condensations along the nuclear membrane.

Plasma cells with the resistance to steroid hormones and irradiation



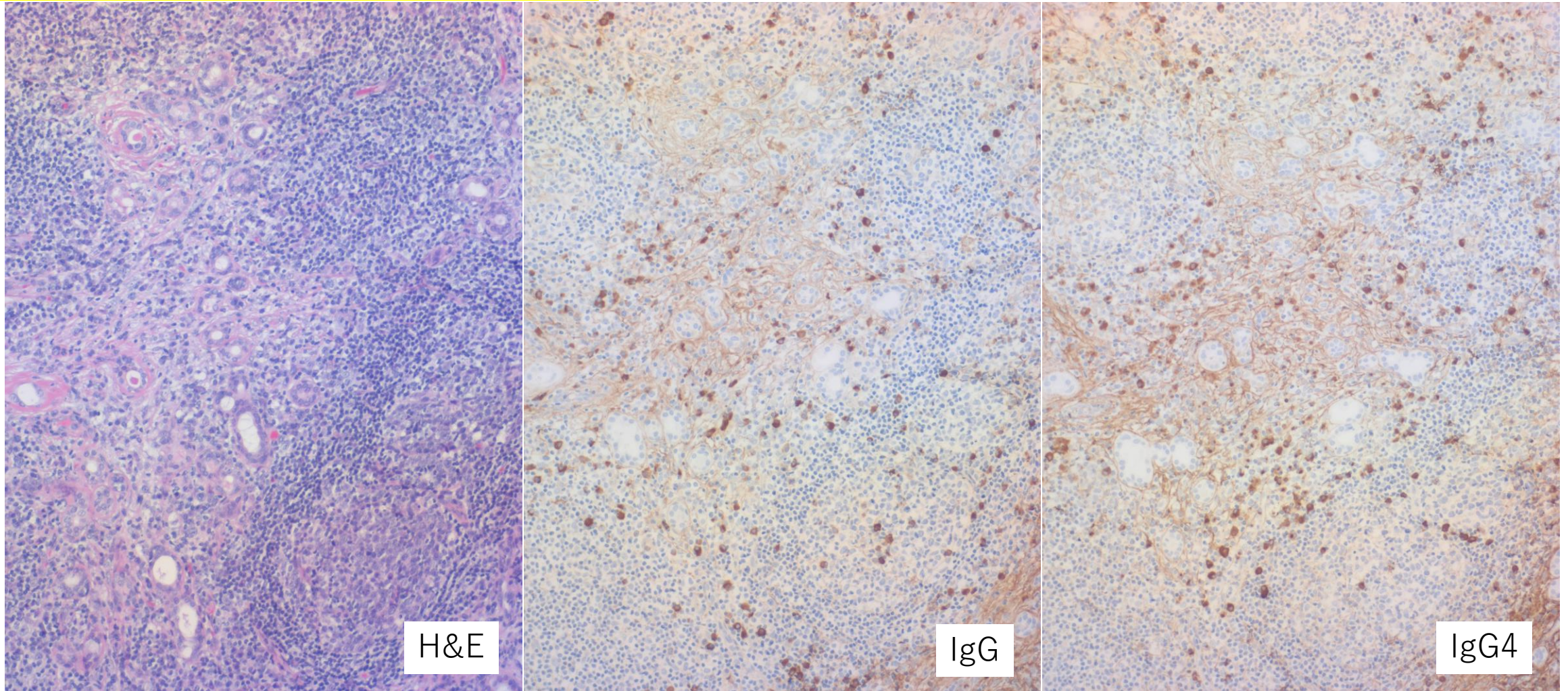
So-called **chronic adrenalitis** (H&E). **Physiologically**, the deep adrenal cortex shows multifocal clusters of lymphoid cells (two cases shown). A good number of plasma cells are noted. It is known that the plasma cells are resistant to steroid hormones. The deep adrenal cortex and the medulla reveal high concentration of adrenocortical hormones.

Plasma cells with the resistance to steroid hormones and irradiation

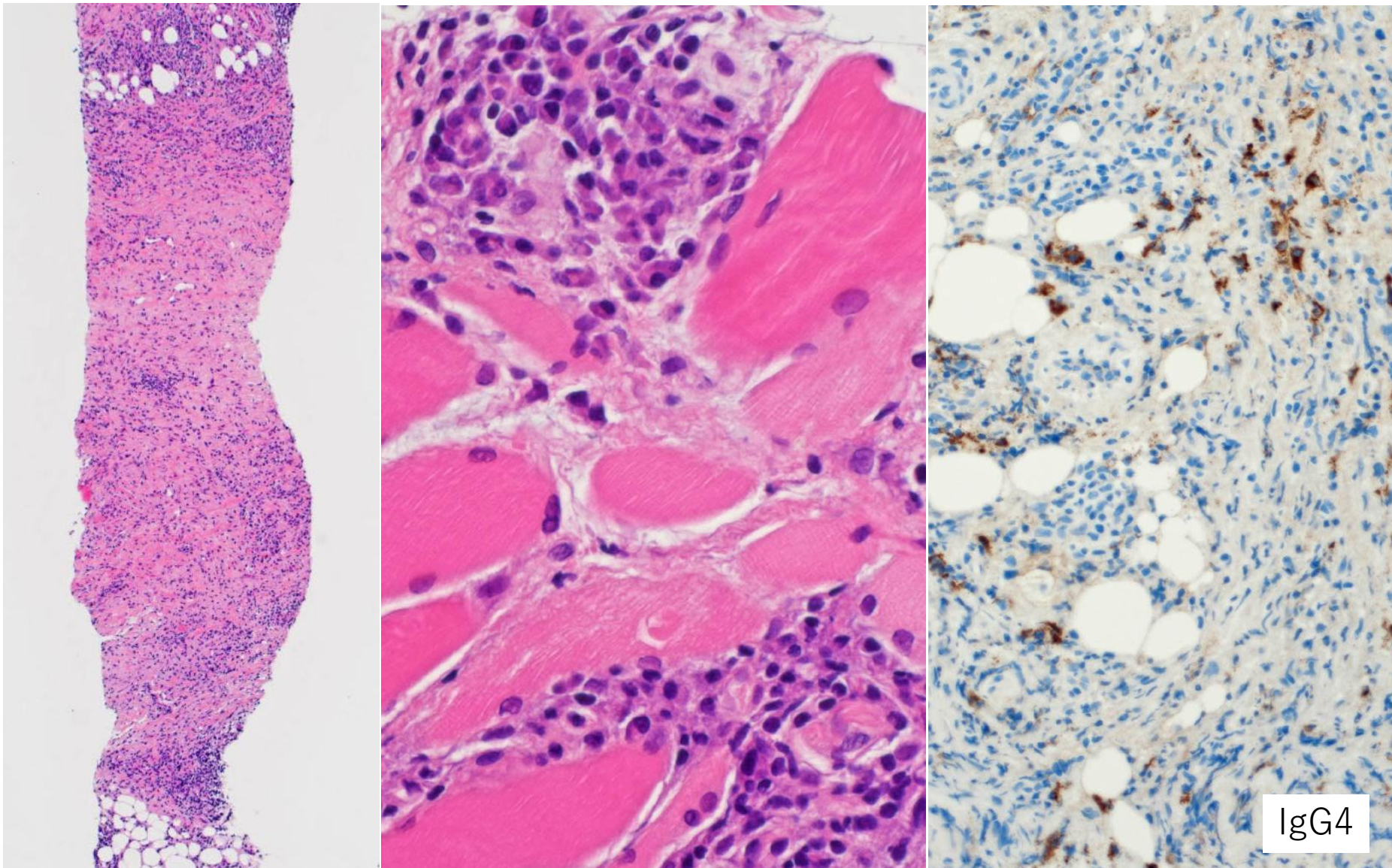


Surgical specimen of esophageal **squamous cell carcinoma after radiotherapy** (H&E). A small volume of viable non-keratinizing squamous cell carcinoma remains (left). Mononuclear cells are seen in the fibrotic connective tissue in the submucosa. A considerable number of mature plasma cells can be observed (right).

Plasma cells and IgG4-related disorders

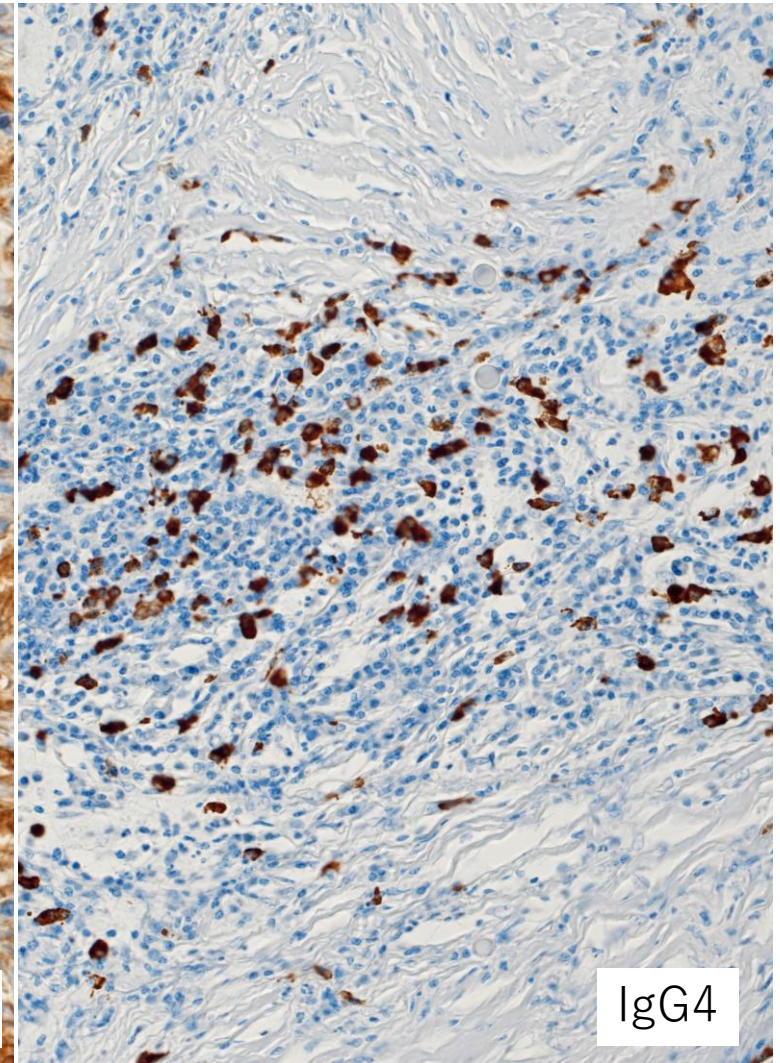
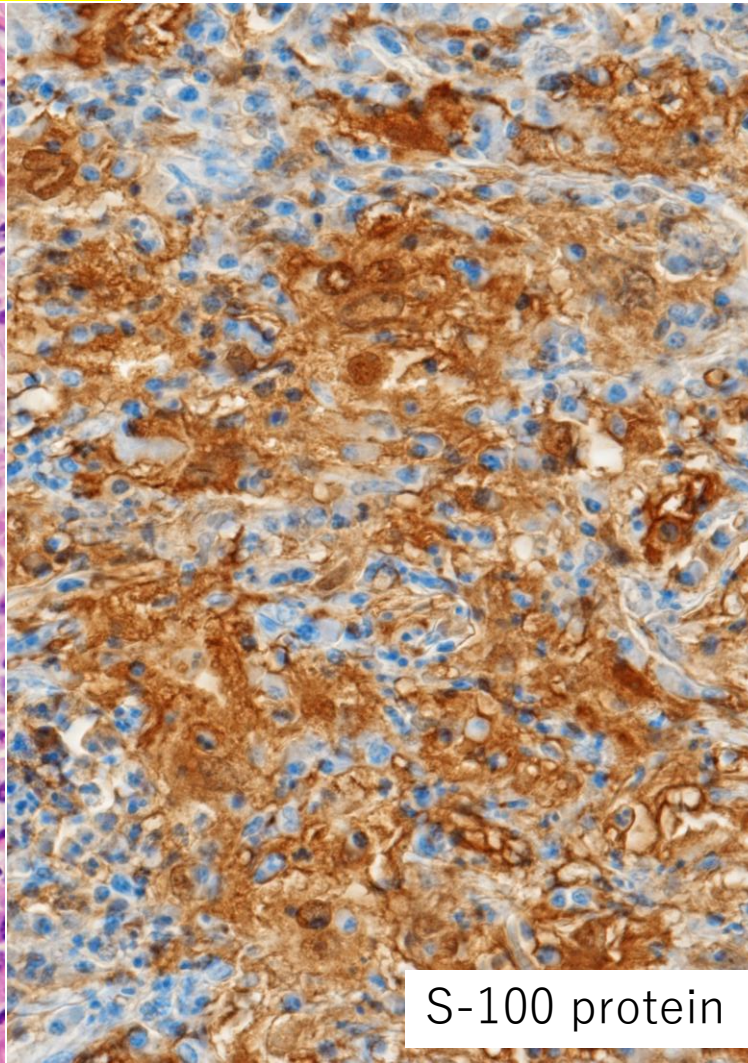
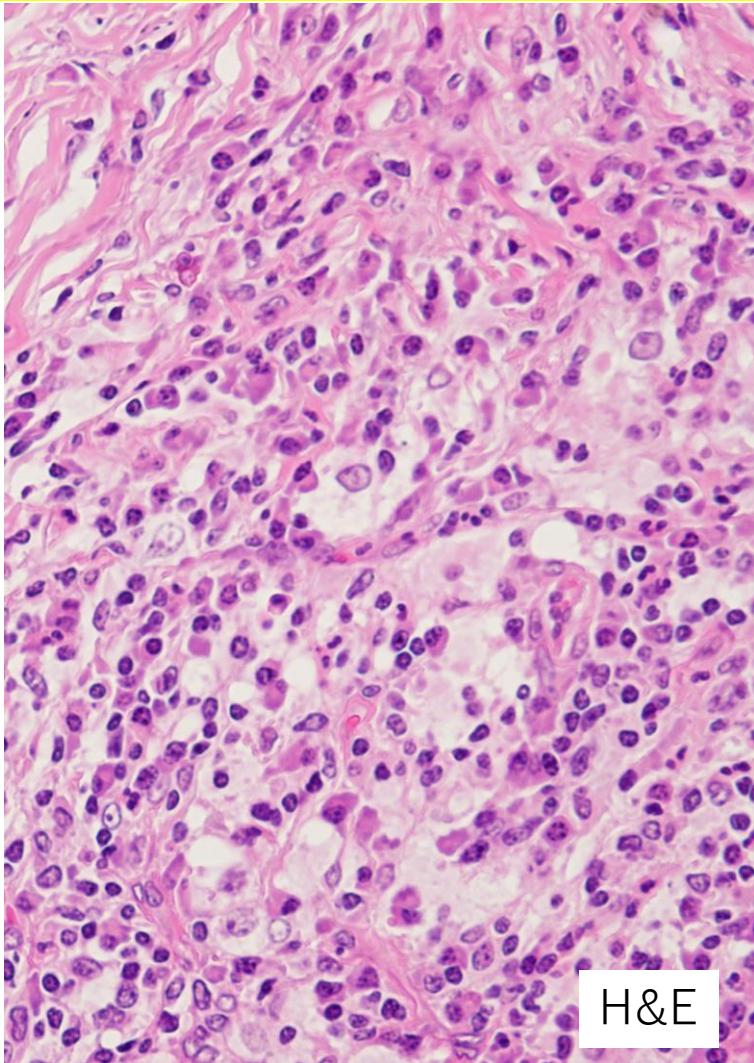


IgG4-related disorders (1): **Mikulicz disease** of the salivary gland. The swollen salivary gland reveals dense infiltration of mononuclear cells including a good number of plasma cells, in addition to lymphoid follicle formation (left: H&E). Plasma cells are immunoreactive for IgG (center), and most of the plasma cells produce IgG4 (right).



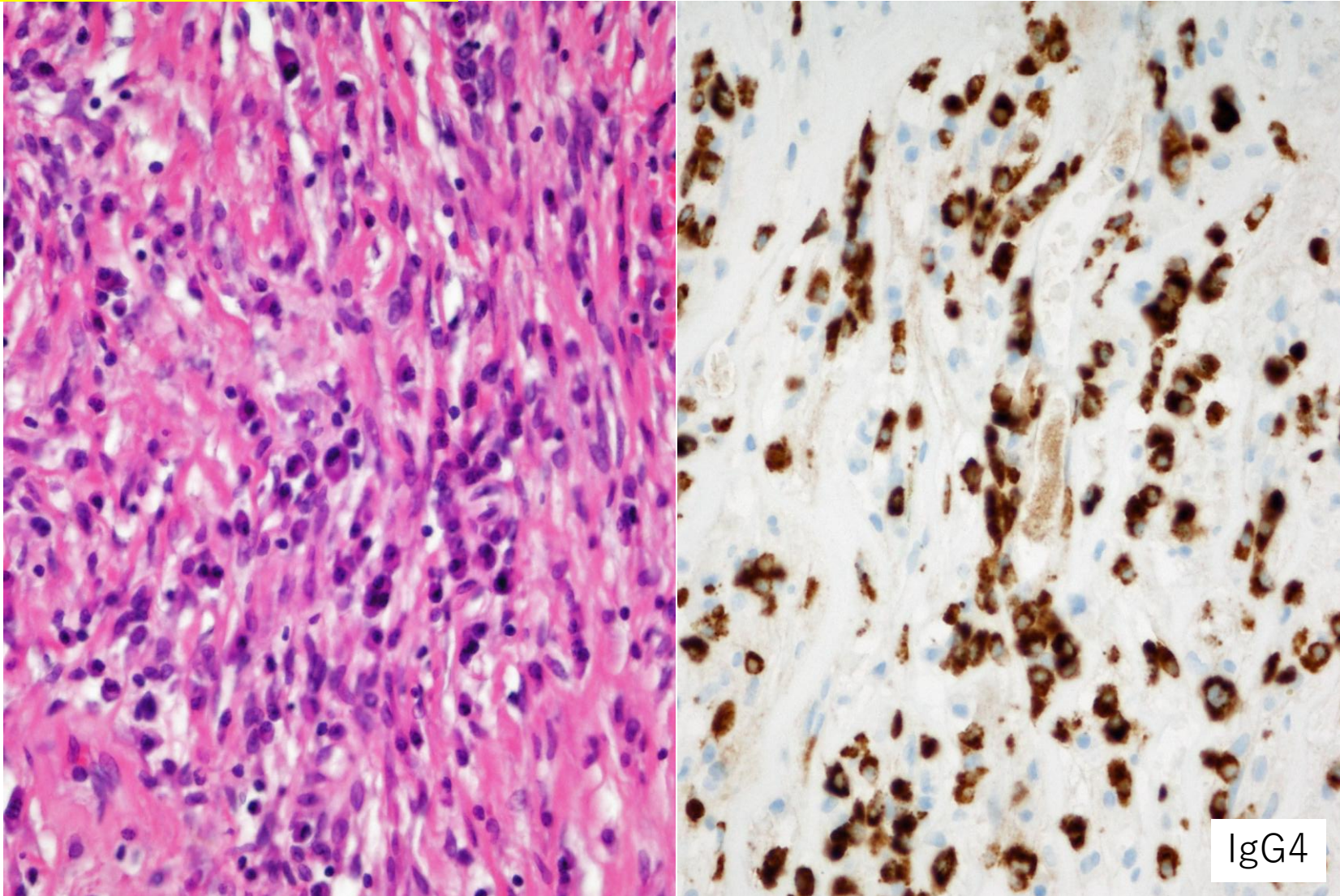
IgG4-related disorders (2): **Retroperitoneal fibrosis**. Needle biopsy from a 70 y-o male patient presenting with bilateral hydronephrosis. In the lesion of inflammatory fibrosis (left: H&E), a good number of mature plasma cells are seen (center: H&E). IgG4 immunoreactivity is identified in the plasma cells (right: IgG4).

Plasma cells and IgG4-related disorders



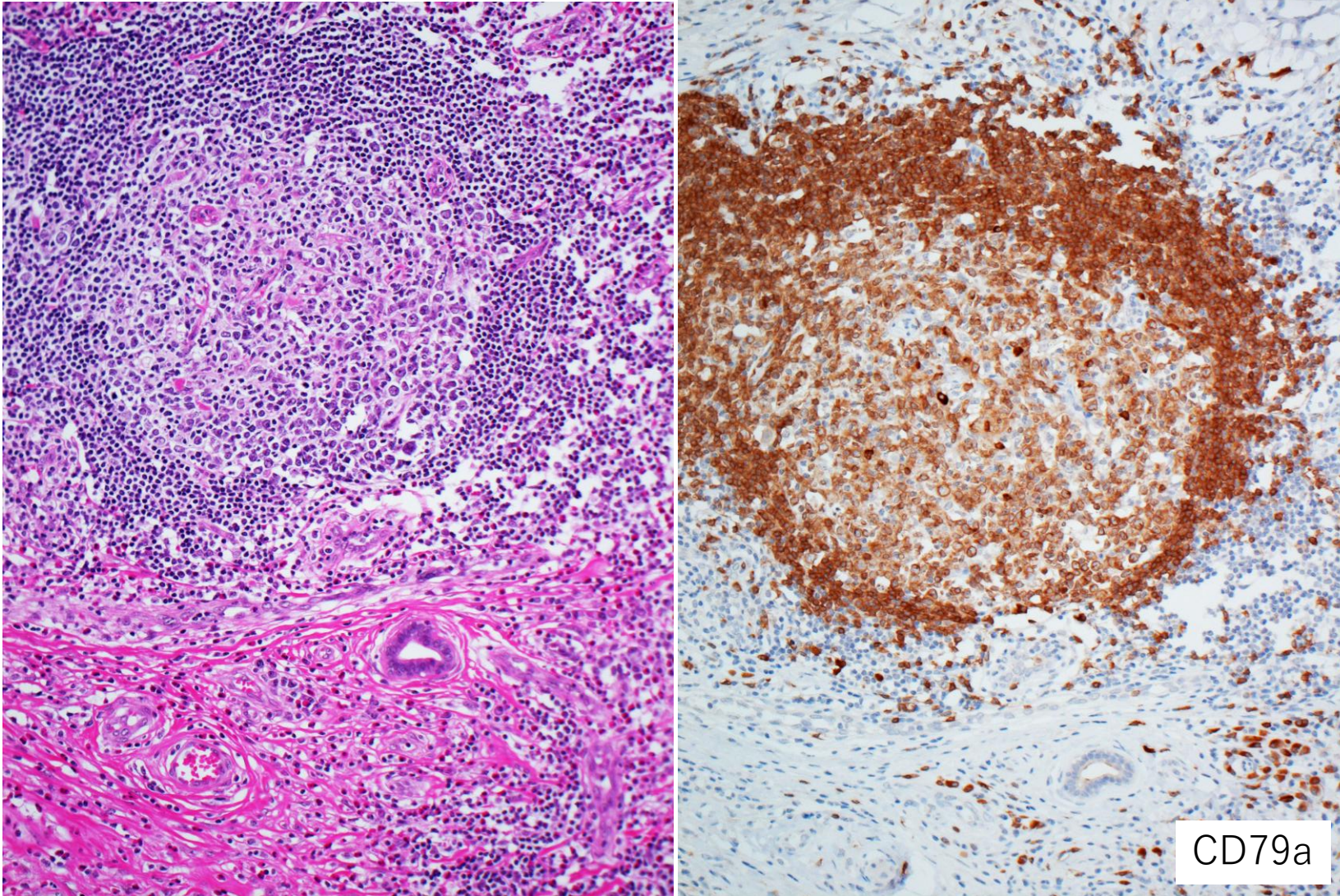
IgG4-related disorders (3): **Rosai-Dorman's disease** of the meninges seen in a male patient aged 70's. The meningeal nodule shows infiltration of foamy macrophages with lymphocytic emperipolesis and a good number of mature plasma cells (left: H&E). The macrophages are strongly immunoreactive for S-100 protein (center). IgG4-positive plasma cells are richly distributed (right).

Plasma cells and IgG4-related disorders



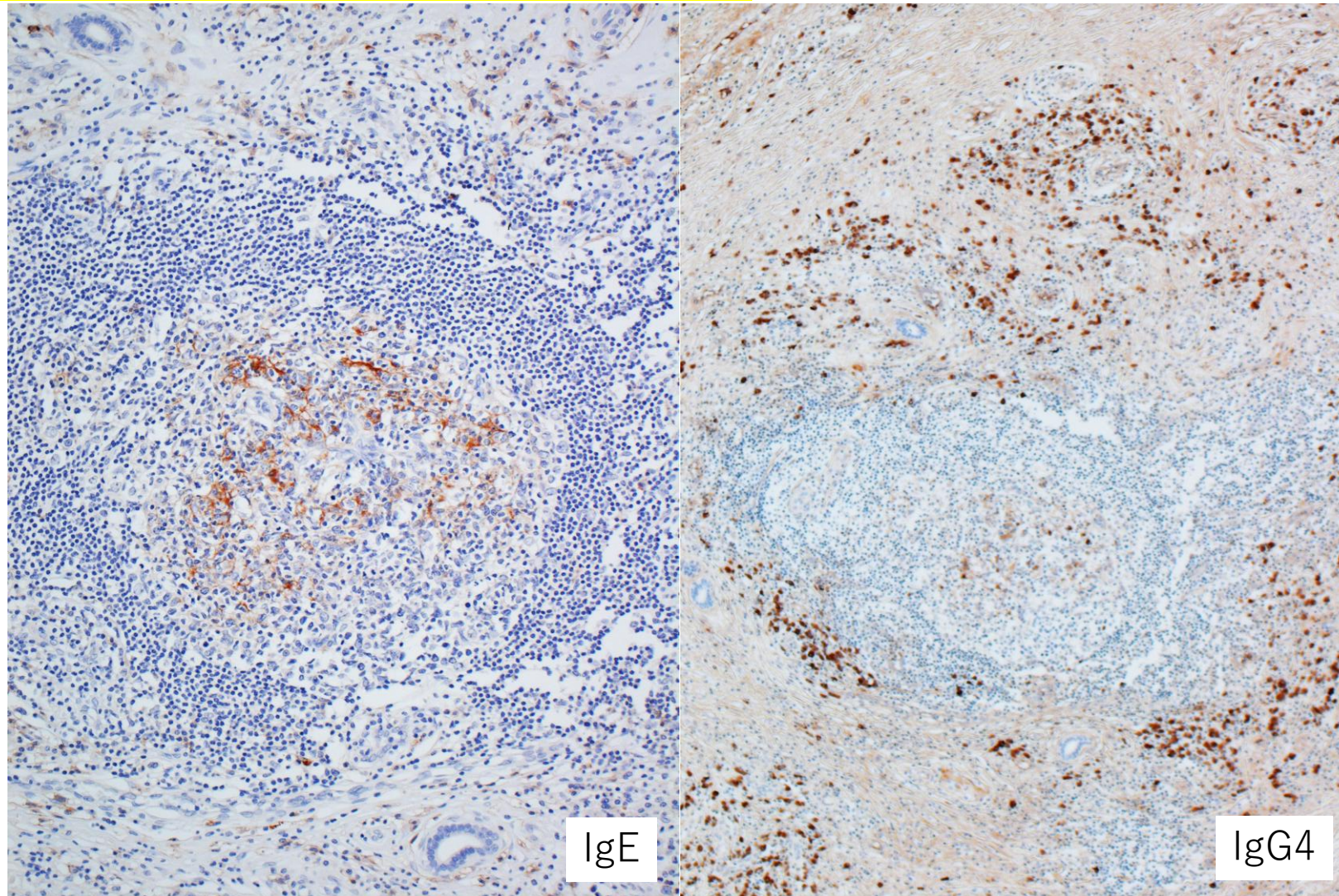
IgG4-related disorders (4): **IgG4-related pericarditis** seen in a 68 y-o male patient. The biopsied pericardial nodule shows infiltration of mononuclear cells with a good number of mature plasma cells (left: H&E). IgG4-positive plasma cells are richly distributed in the lesion (right).

Plasma cells and IgG4-related disorders: Kimura's disease



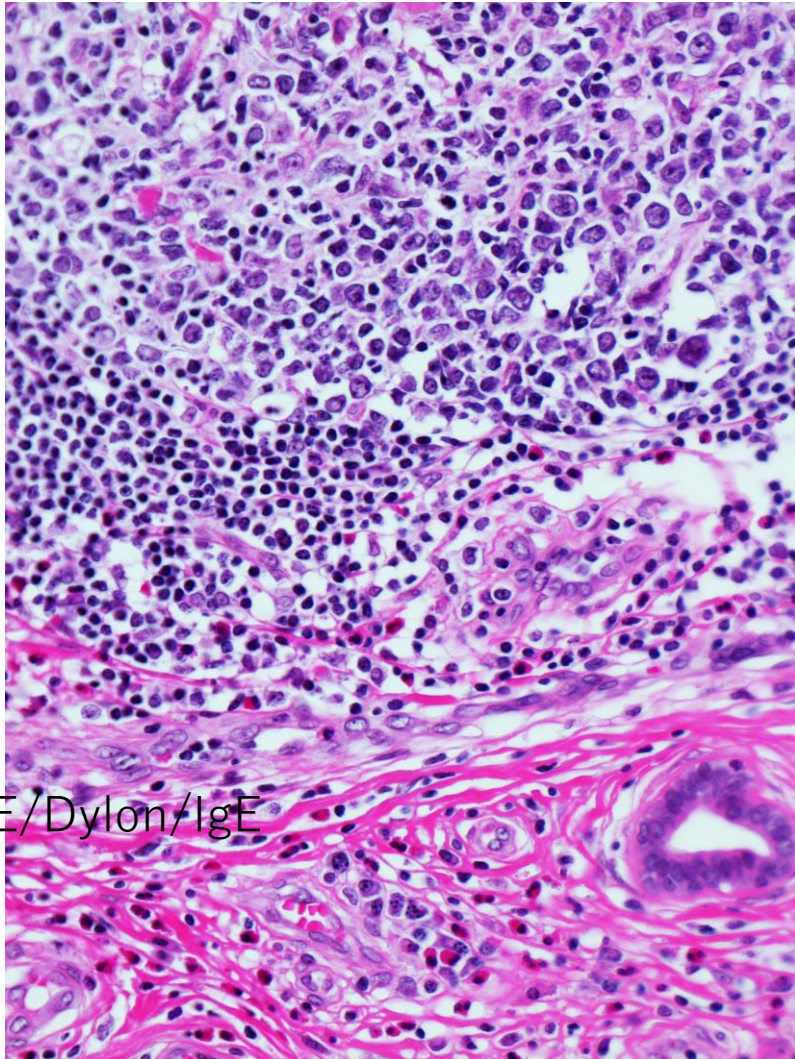
IgG4-related disorders (5): **Kimura's disease** is included in IgG4-related disorders. A 41 y-o male patient presented with a subcutaneous nodule in the neck (left: H&E, right: CD79a). Lymphoid follicles with enlarged germinal centers are seen, together with infiltration of eosinophils and mature plasma cells. Immunostaining for CD79a demonstrates B-cells in the lymphoid follicles and mature plasma cells in the perfollicular area.

Plasma cells and IgG4-related disorders: Kimura's disease

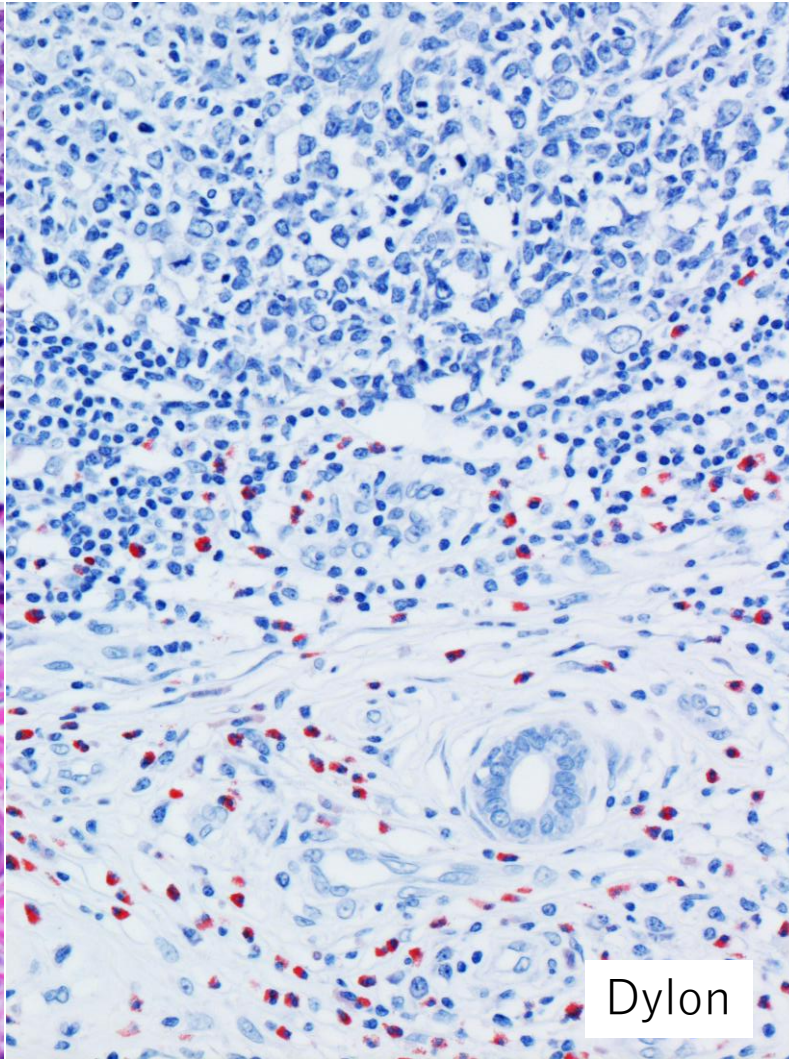


IgG4-related disorders (5): **Kimura's disease** is included in IgG4-related disorders. A 41 y-o male patient presented with a subcutaneous nodule in the neck (immunostaining for IgE, left, and IgG4, right). The deposition of IgE on the follicular dendritic cells is characteristic of Kimura's disease. Numbers of IgG4-positive plasma cells are seen around the lymphoid follicle.

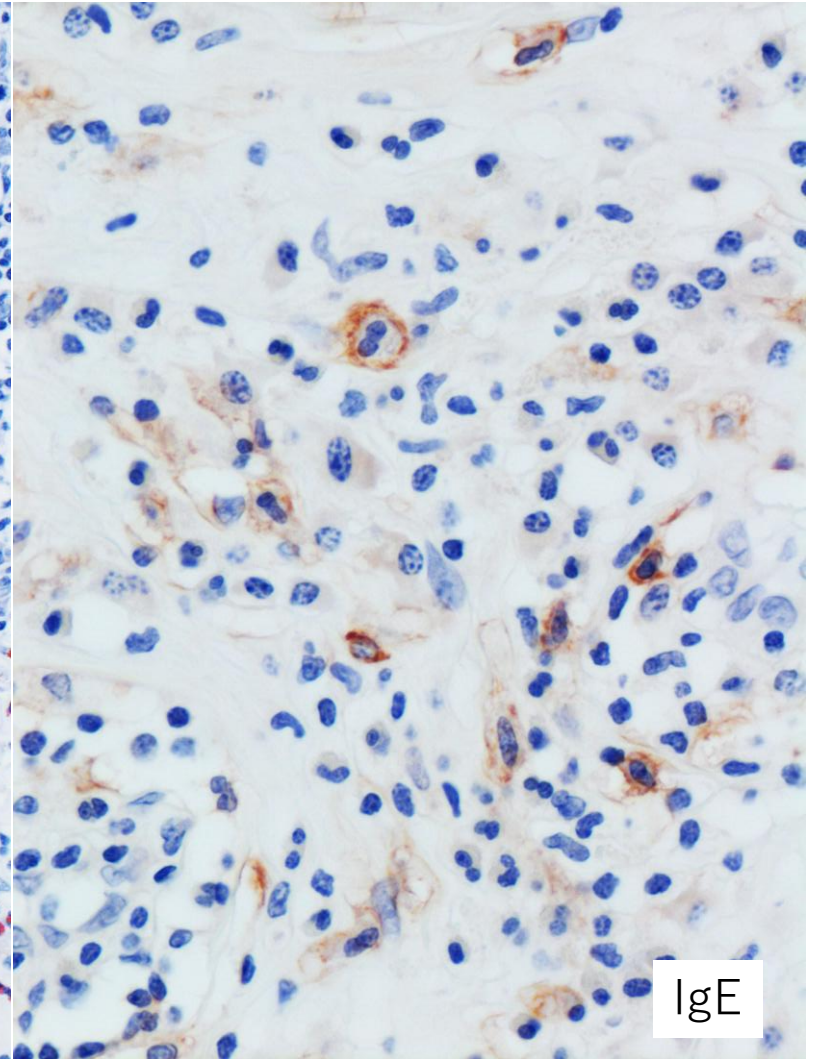
Plasma cells and IgG4-related disorders: Kimura's disease



HE/Dylon/IgE



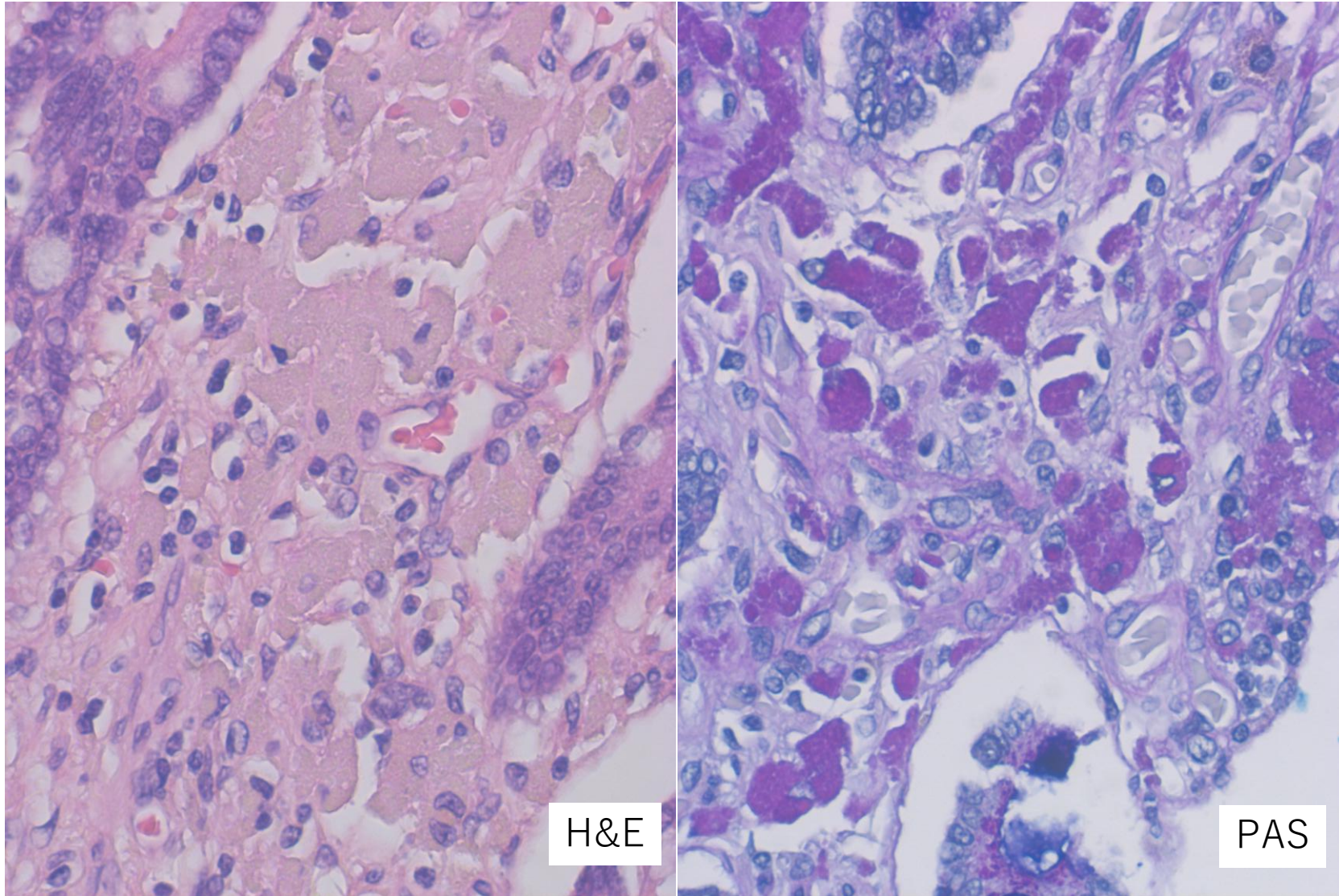
Dylon



IgE

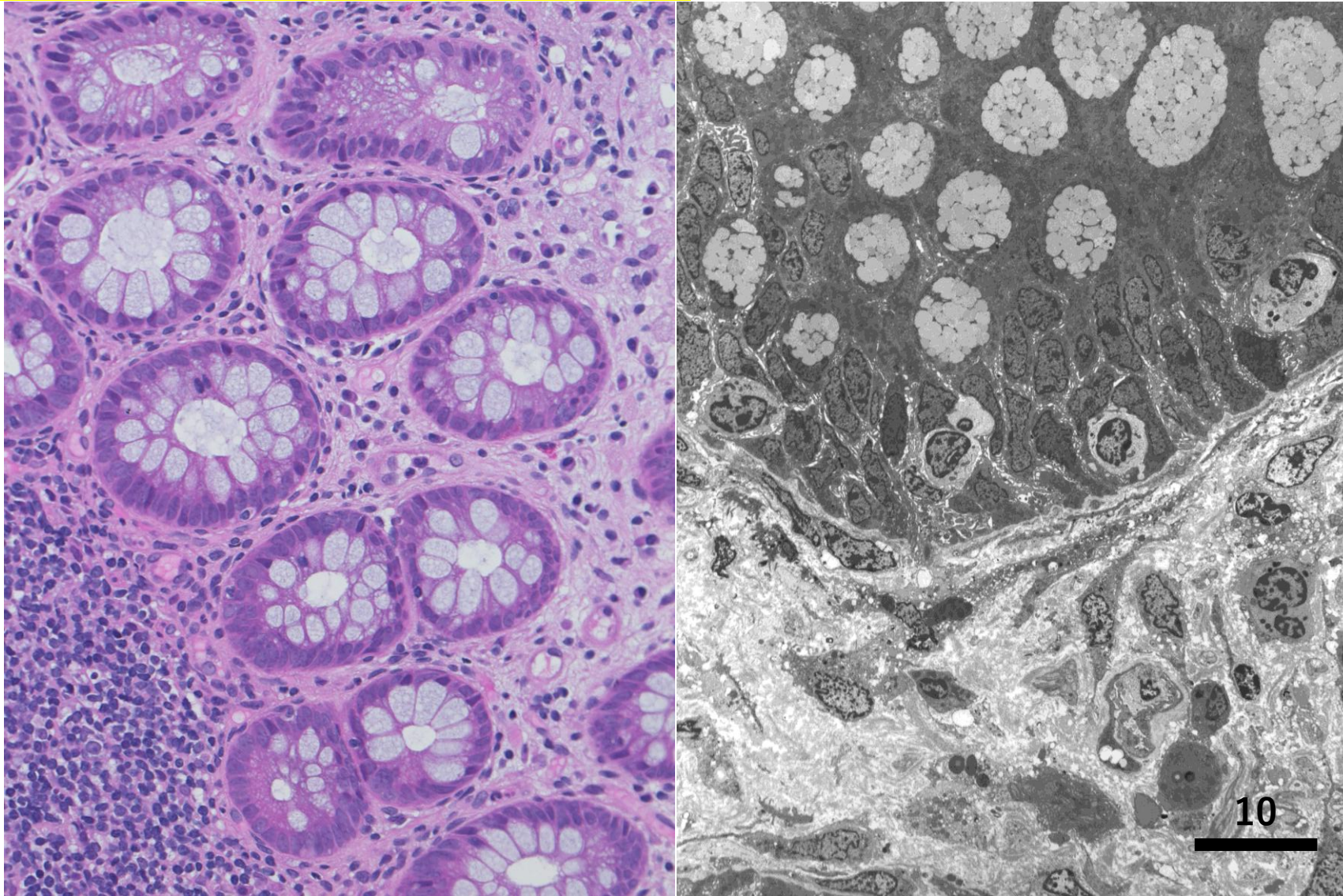
IgG4-related disorders (5): **Kimura's disease** is included in IgG4-related disorders. A 41 y-o male patient presented with a subcutaneous nodule in the neck (left: H&E, center: Dylon, right immunostaining for IgE). In the perifollicular area, numbers of Dylon-positive eosinophils are discerned. Mast cells with membrane-bound IgE and a small number of IgE-producing plasma cells are observed.

Lack of plasma cells in congenital immune deficiency



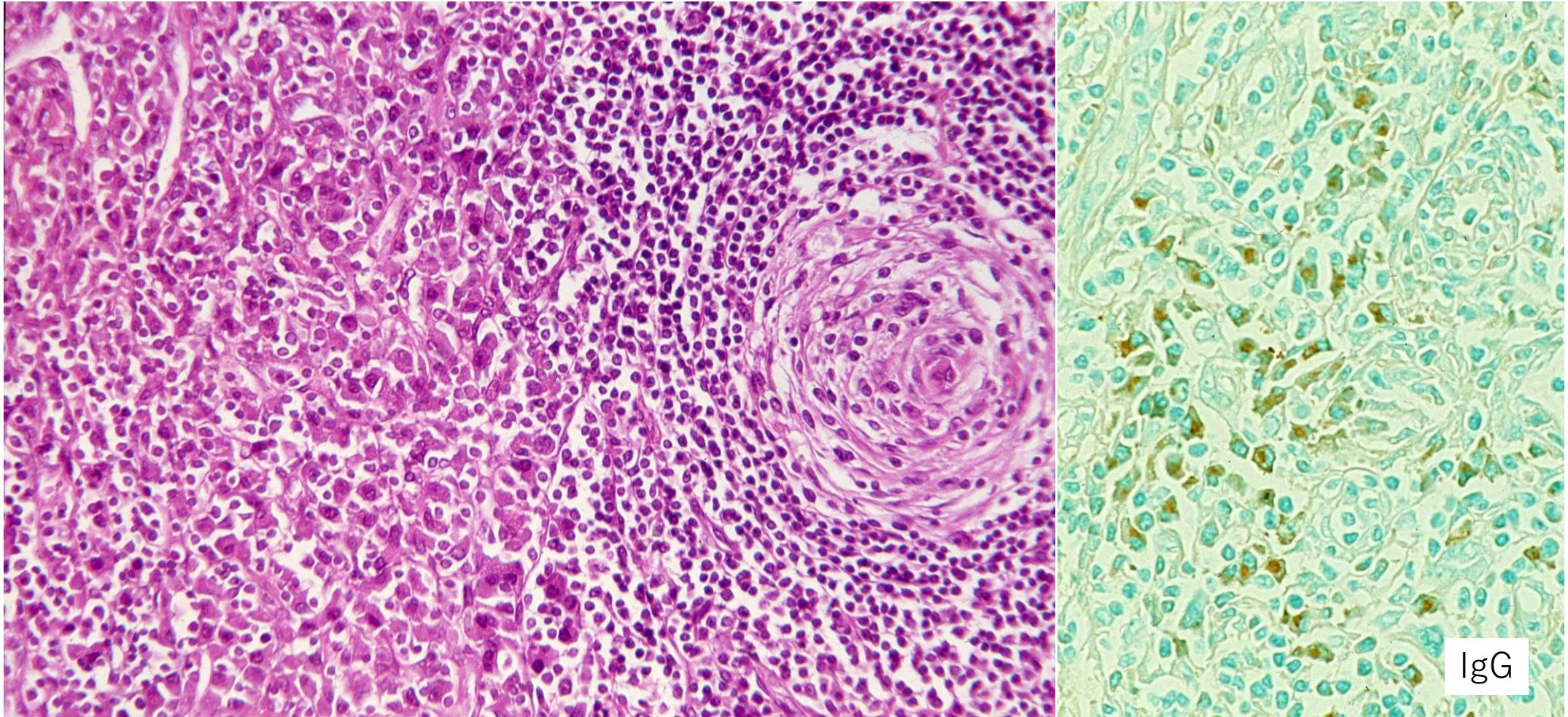
X-linked immunodeficiency of Bruton type seen in a 44 y-o male patient (left: H&E, right: PAS). Duodenal biopsy reveals marked deposition of PAS-reactive ceroid pigment in macrophages. No plasma cells are seen in the lamina propria mucosae.

Lack of plasma cells in congenital immune deficiency



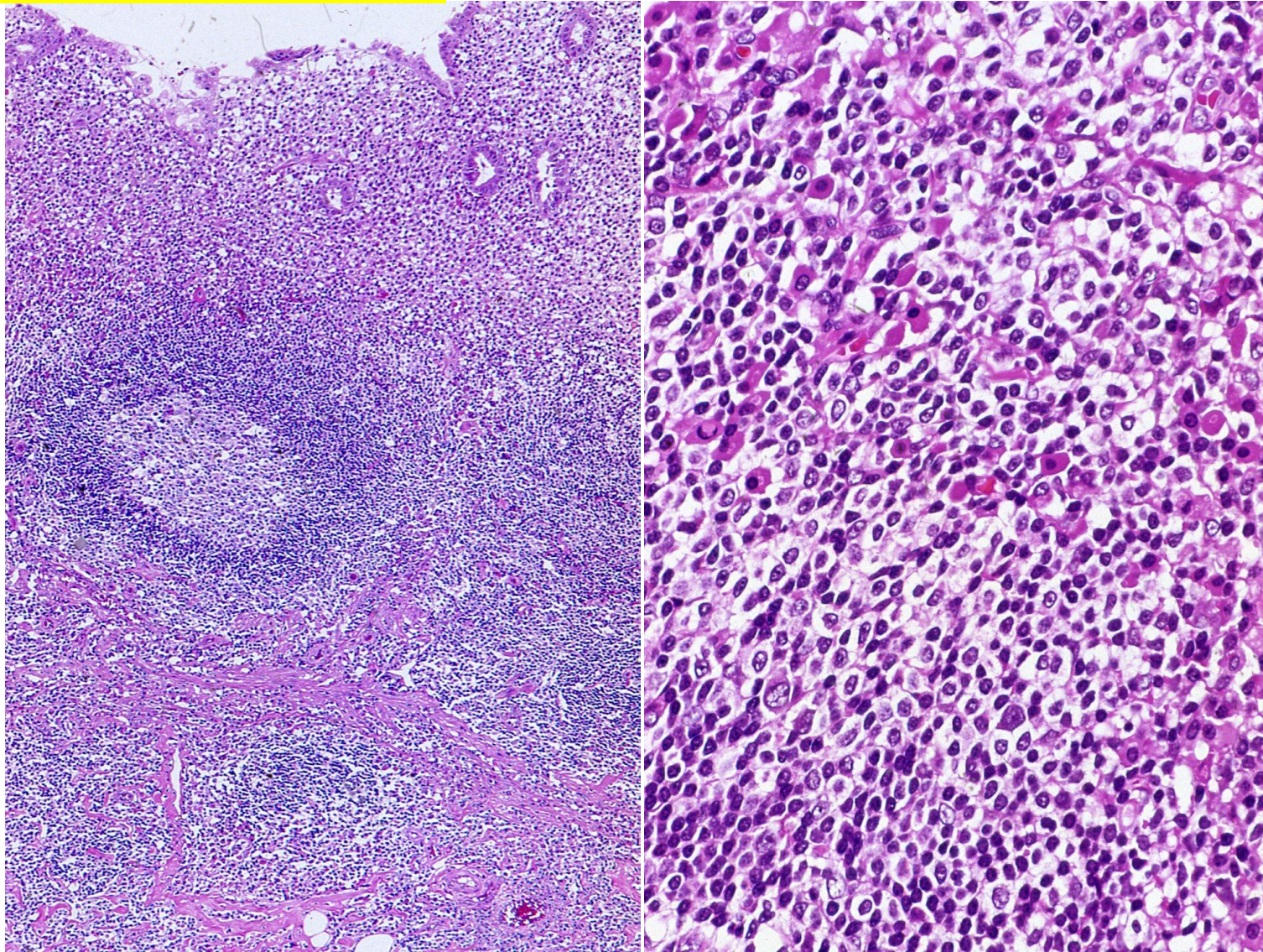
Chronic colitis in **severe combined immunodeficiency** seen in a 6 y-o boy (left: H&E, right: EM). Lymphoid follicles are scattered in the colonic mucosa. Differentiation toward plasma cells is poor (only a few plasma cells are seen). Ultrastructurally, plasma cells are few in number in the lamina propria mucosae.

Plasma cells in lymphoproliferative lesions



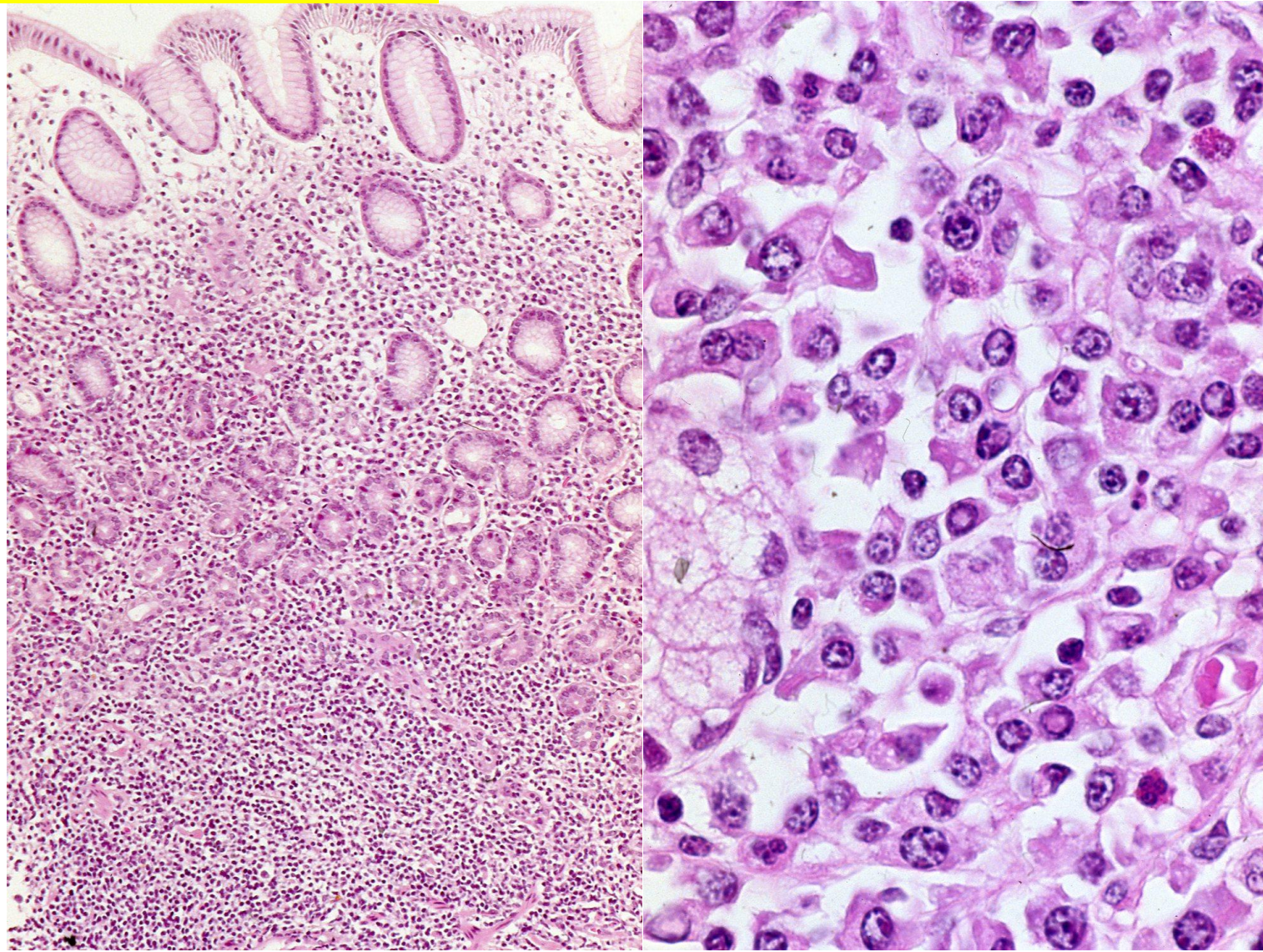
Castleman's disease, plasma cell type, seen in the retroperitoneal lymph node of a male patient aged 50's (left: H&E, right: immunostaining for IgG). Fever, night sweat, hypergammaglobulinemia and splenomegaly are associated. Around the unique germinal center with a concentric arrangement (in the interfollicular area), mature plasma cells are clustered. Many of them are positive for IgG. The disease should be distinguished from IgG4-related disease.

Plasma cells in lymphoproliferative lesions



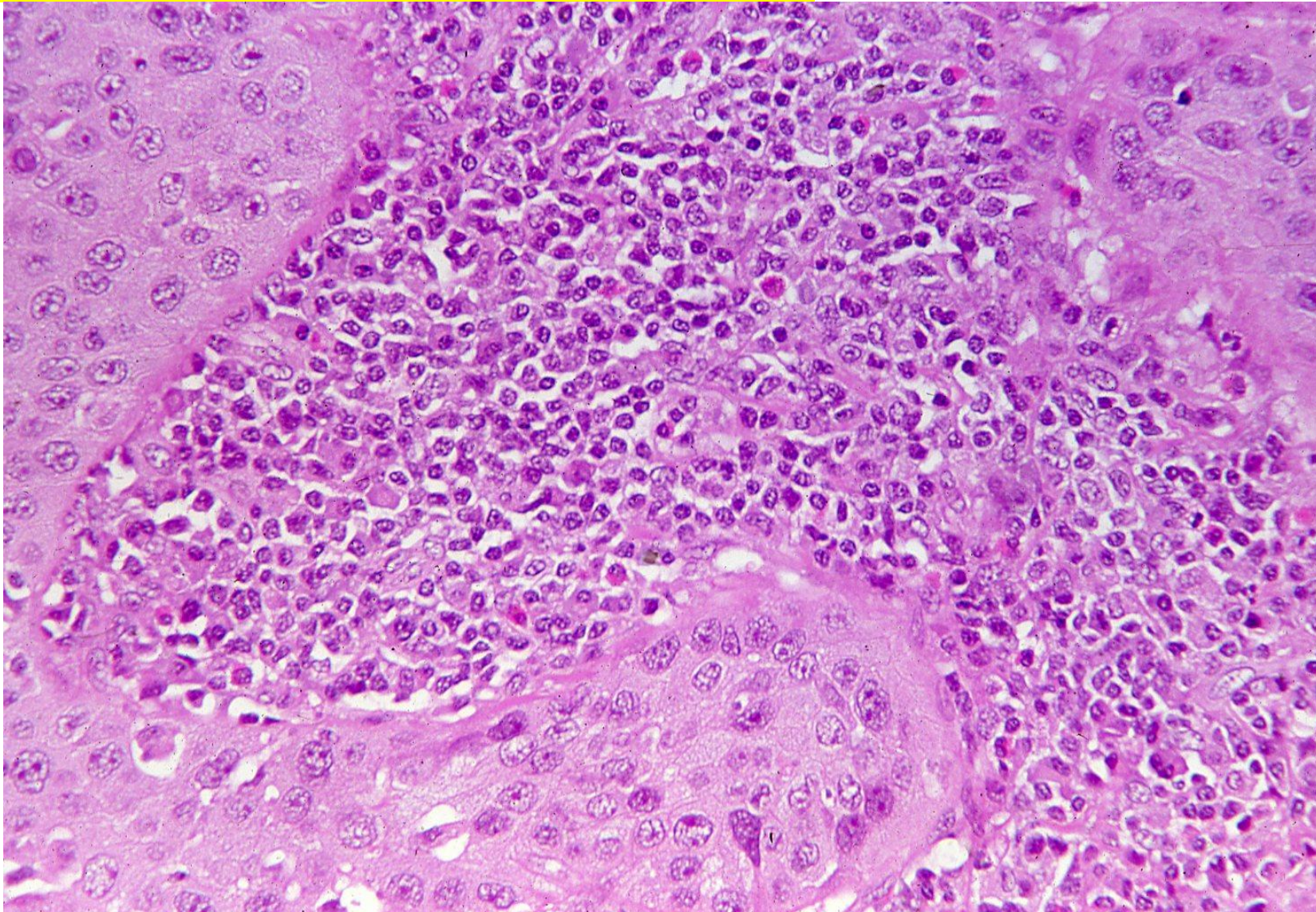
MALT lymphoma of the stomach (H&E). Low-grade B-cell lymphoma of marginal zone origin shows dense lymphoid infiltration with lymphoid follicle formation (left) and clustering of centrocyte-like cells (monocytoid B-cells) in the gastric mucosa(right).

Plasma cells in lymphoproliferative lesions



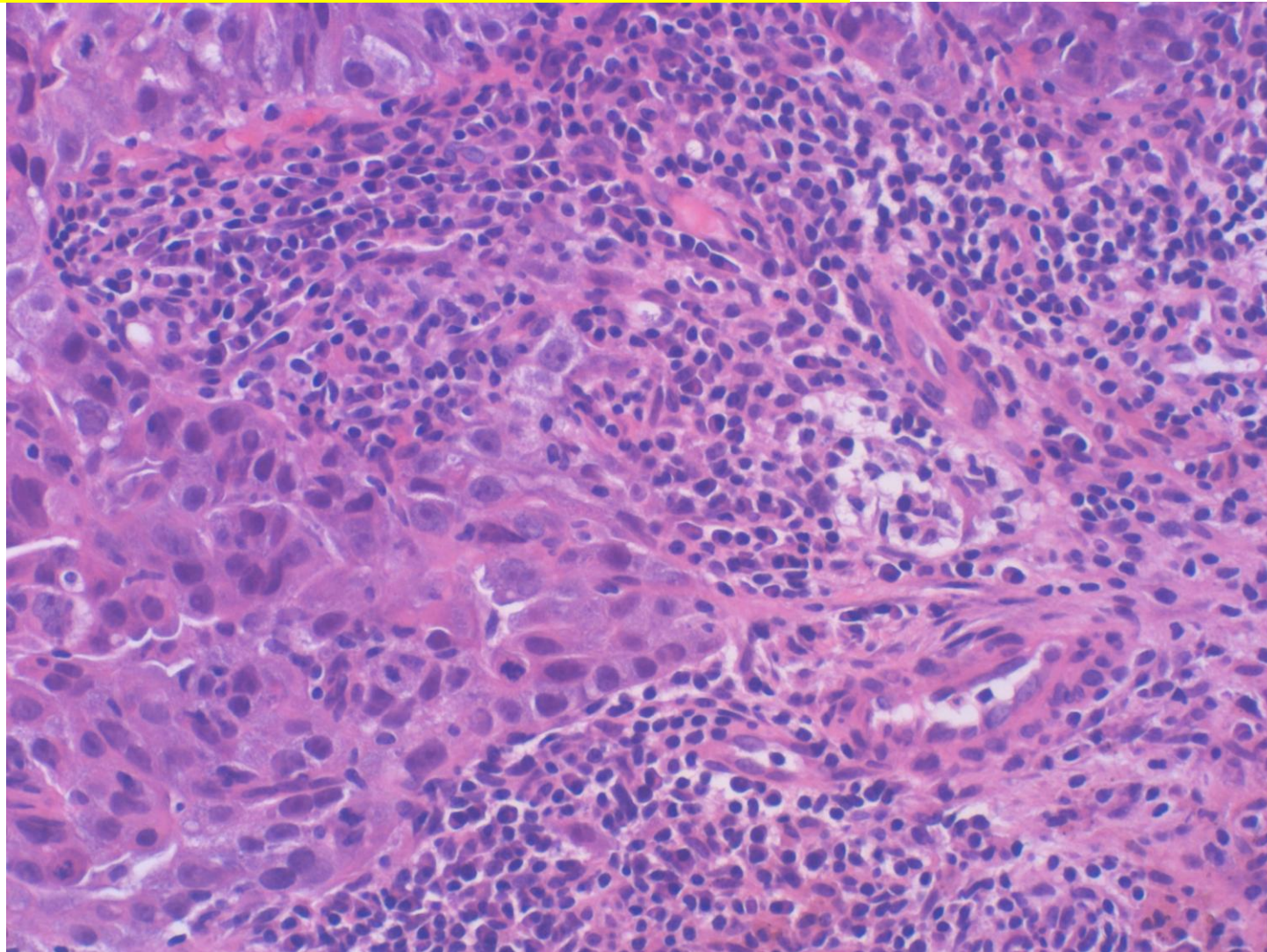
MALT lymphoma of the stomach with plasmacytic differentiation (H&E).
Low-grade B-cell lymphoma of marginal zone origin often shows differentiation toward mature plasma cells (of either monoclonal or polyclonal).

Plasma cells in epithelial malignancy with lymphoid stroma



Non-keratinizing **squamous cell carcinoma of the uterine cervix** with **lymphoid stroma** (H&E). Lymphoplasmacytic infiltration is often seen in HPV-induced cervical cancer.

Plasma cells in epithelial malignancy with lymphoid stroma



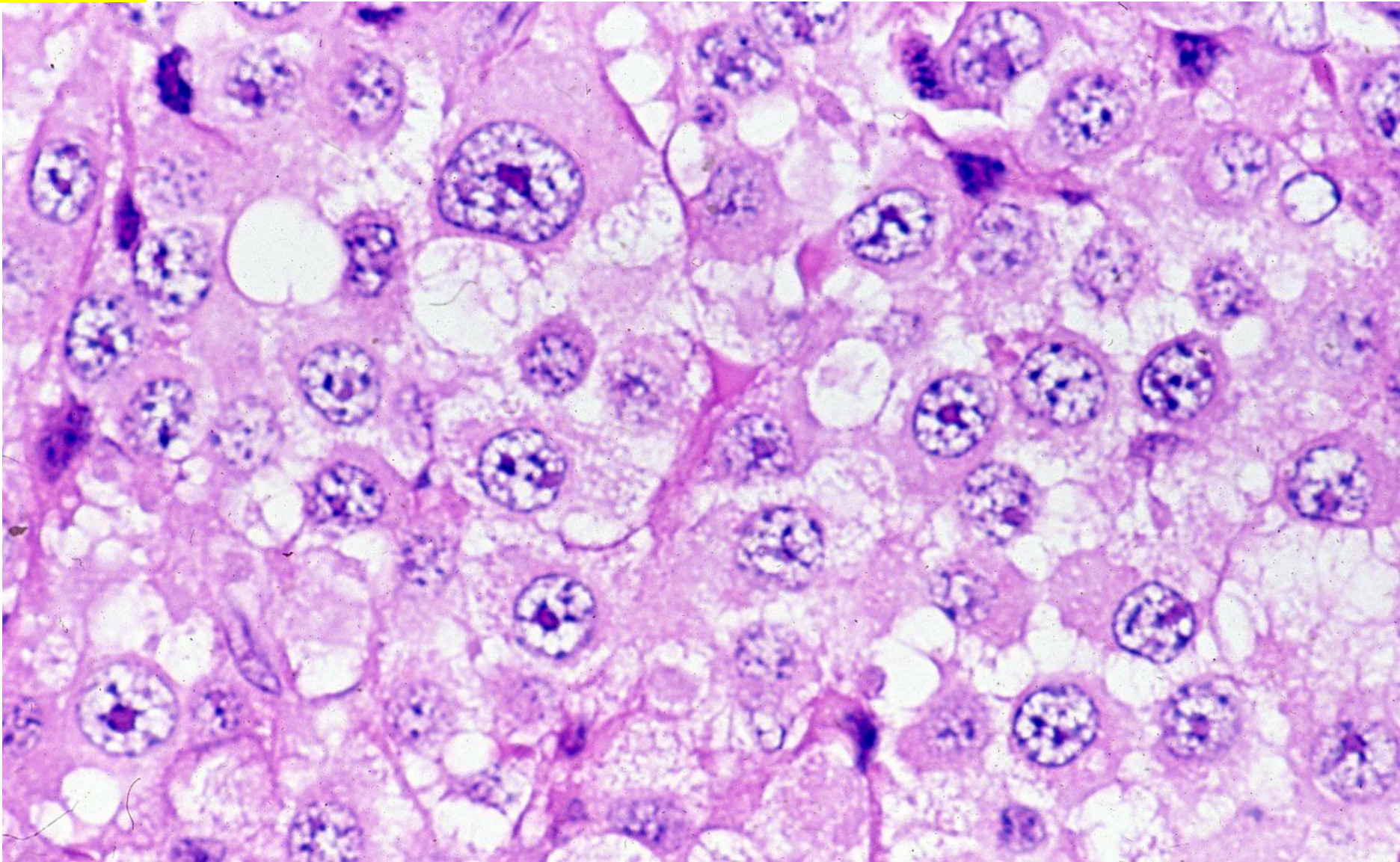
Triple-negative breast carcinoma (TNBC) with high-grade nuclear atypia is featured by the association with **lymphoid stroma**. Numbers of small lymphocytes and mature plasma cells infiltrate in this high-grade malignancy. It should be noted that The TNBC cells often overexpress p53 protein, and in the serum antibodies against p53 protein are detected. The antibodies may locally be secreted from the cancer stroma.

Multiple myeloma



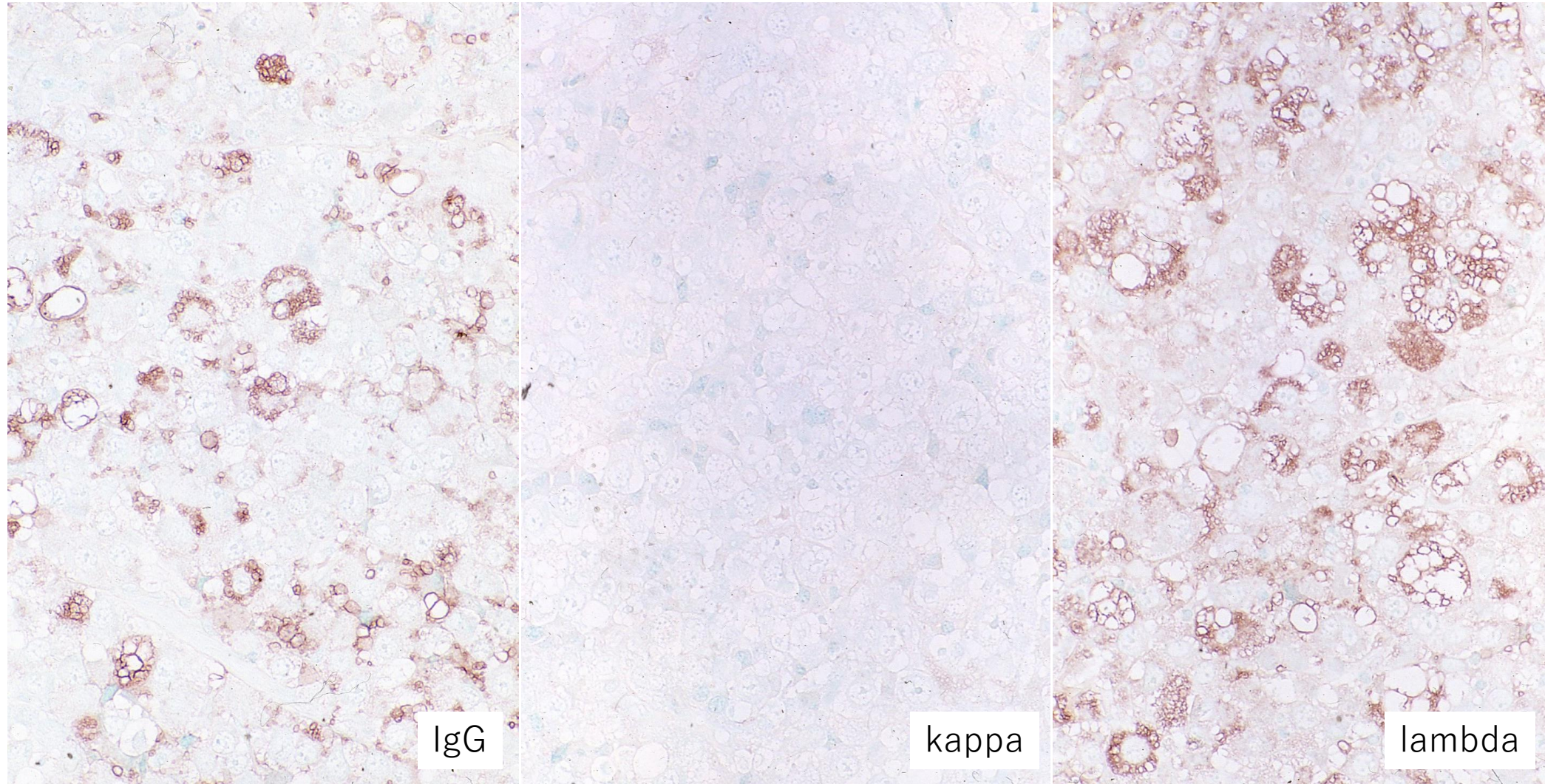
Gross appearance of the spine with **multiple myeloma**, IgG lambda type, after formalin fixation. Punched-out lesions (irregular cystic osteolysis) are evident.

Multiple myeloma



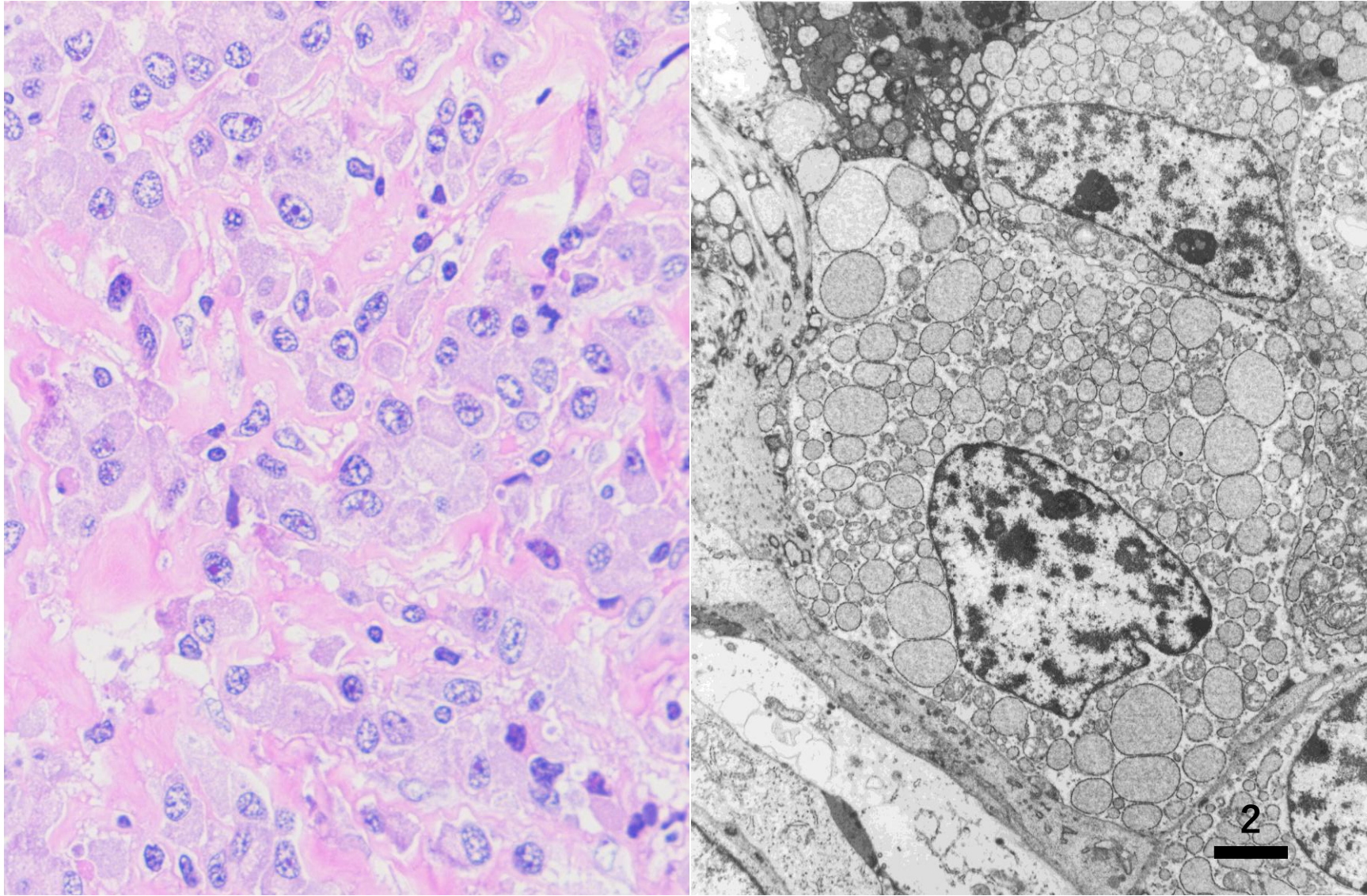
Multiple myeloma, IgG, lambda type (H&E). Atypical plasma cells with enlarged nuclei and prominent nucleoli massively occupy the marrow space.

Multiple myeloma



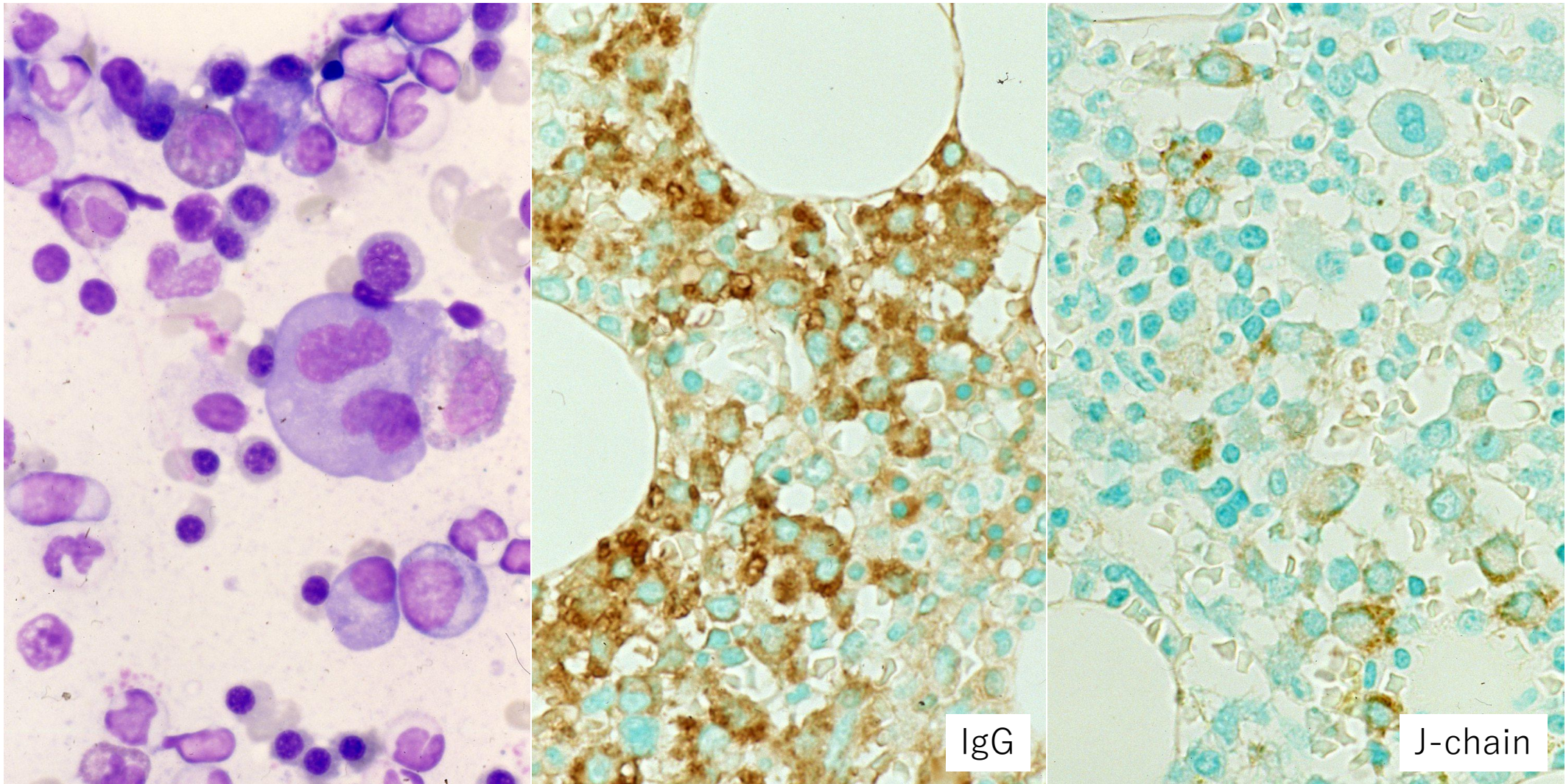
Multiple myeloma, IgG, lambda type (immunostaining, left: IgG, center: kappa chain, right: lambda chain). The growing plasma cells show IgG, lambda-type monoclonality.

Multiple myeloma



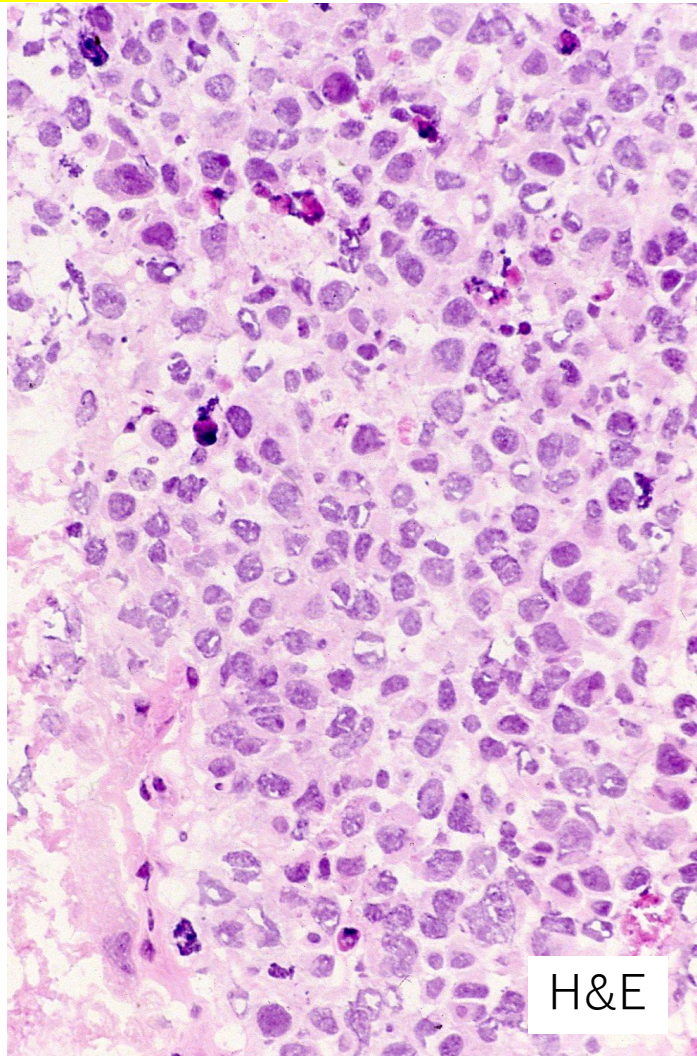
Multiple myeloma. A biopsied scalp mass seen in a 56 y-o female patient (left: H&E, right: EM study). Infiltration of atypical plasma cells is noted in the subcutaneous layer of the scalp. Ultrastructurally, globular/vesicular dilatation of the cisterna of rough endoplasmic reticula is observed.

Multiple myeloma

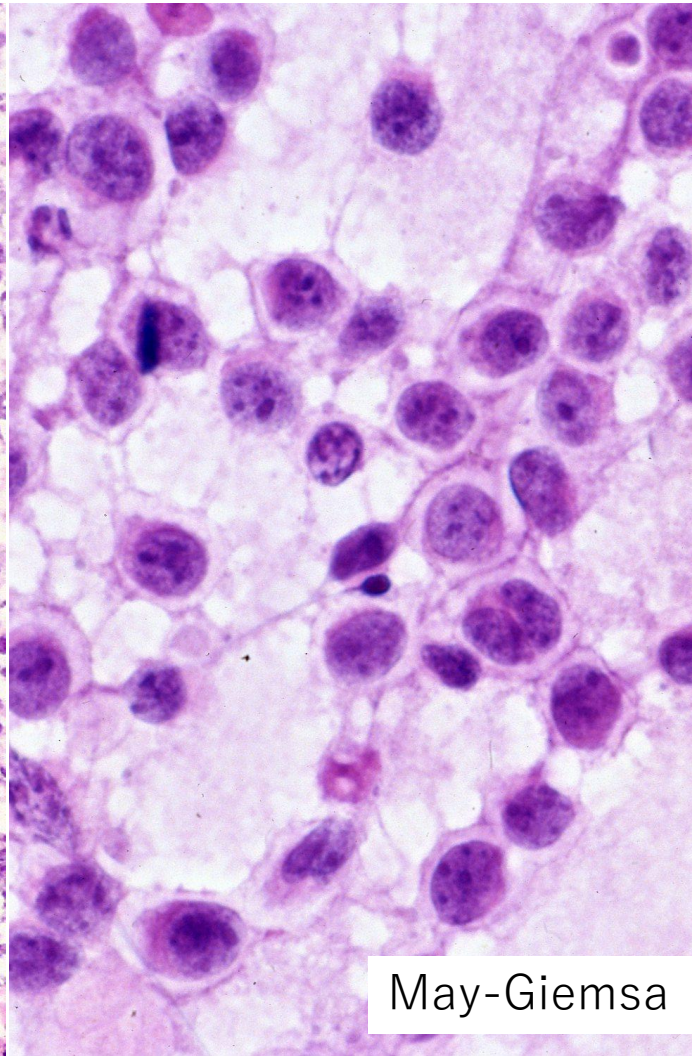


J-chain expression in **multiple myeloma**, IgG, lambda type (left: May-Giemsa, center: IgG, right: J-chain). The myeloma cells express IgG in the cytoplasm. J-chain is also expressed in some myeloma cells. In the normal state, IgG plasma cells lack J-chain expression. It is well known that J-chain is a linker protein of dimeric IgA and pentameric IgM.

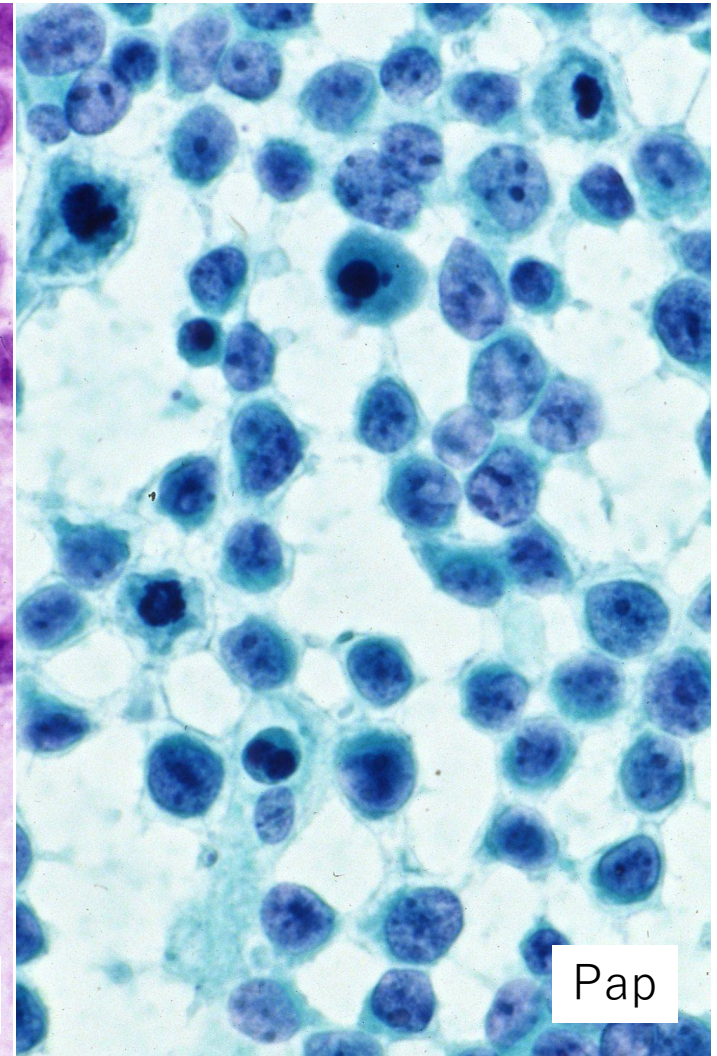
Multiple myeloma



H&E



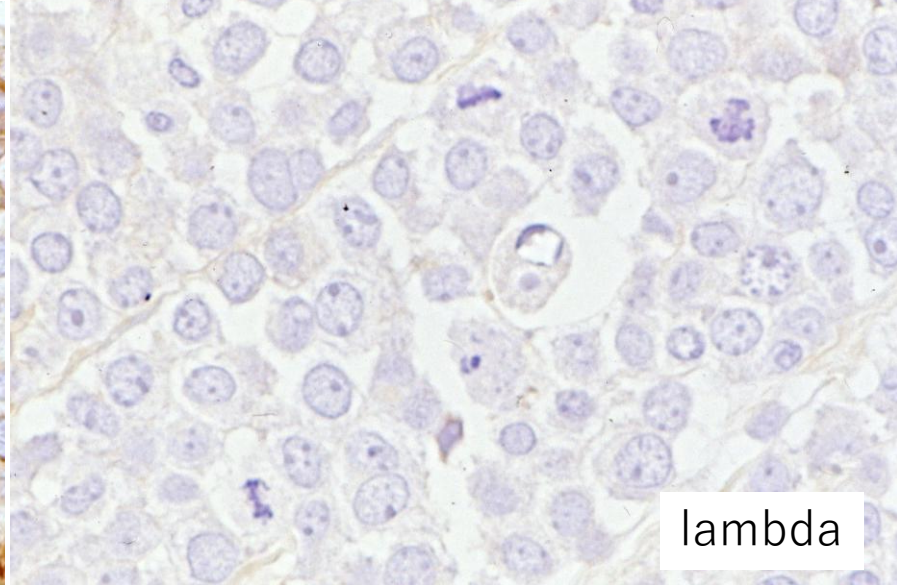
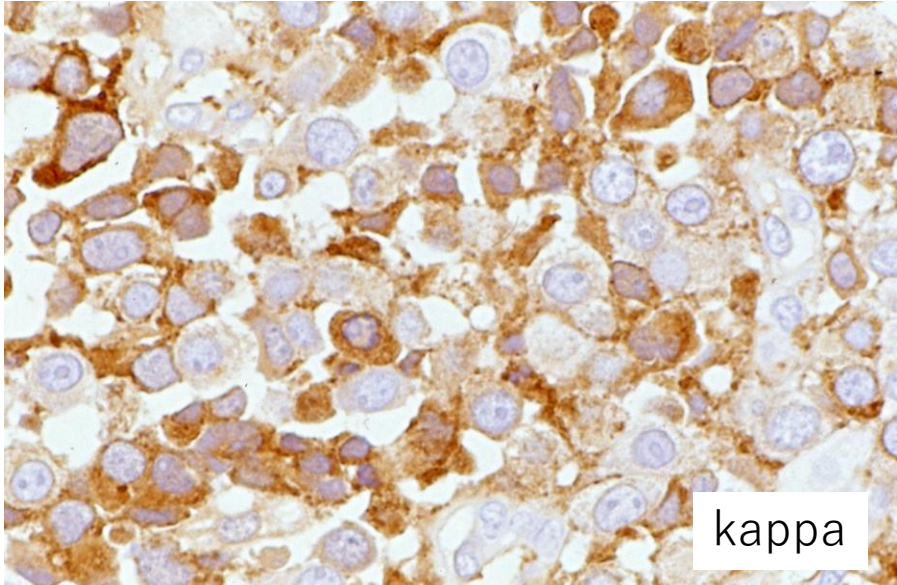
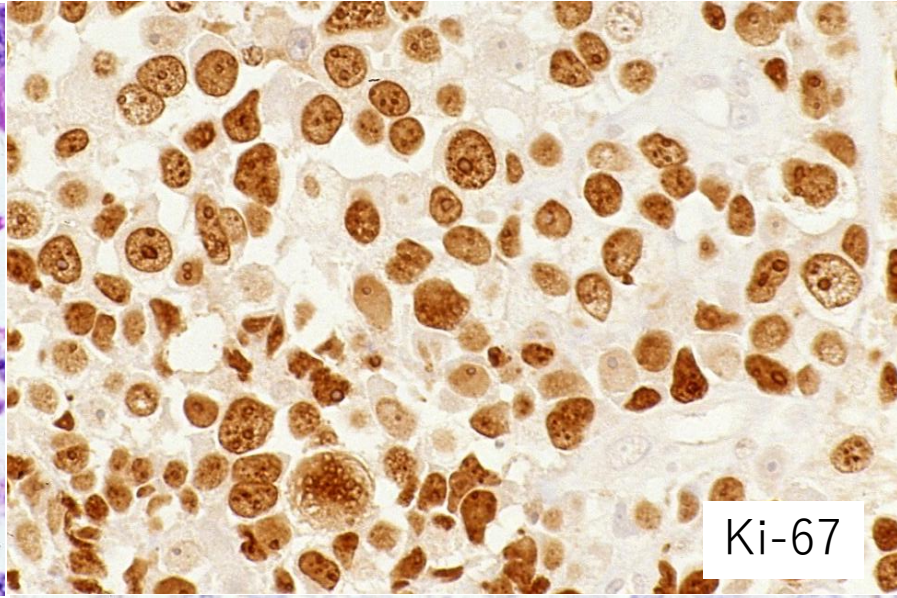
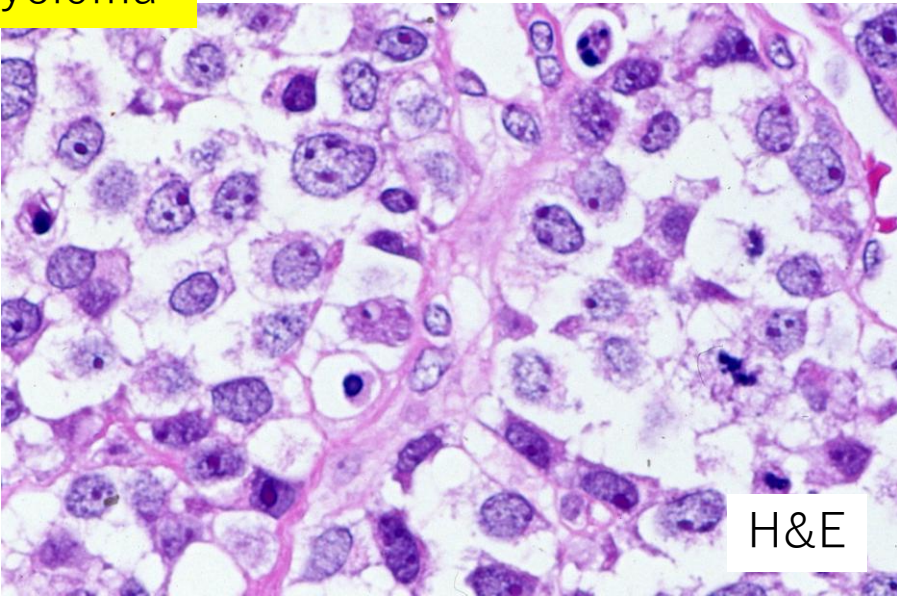
May-Giemsa



Pap

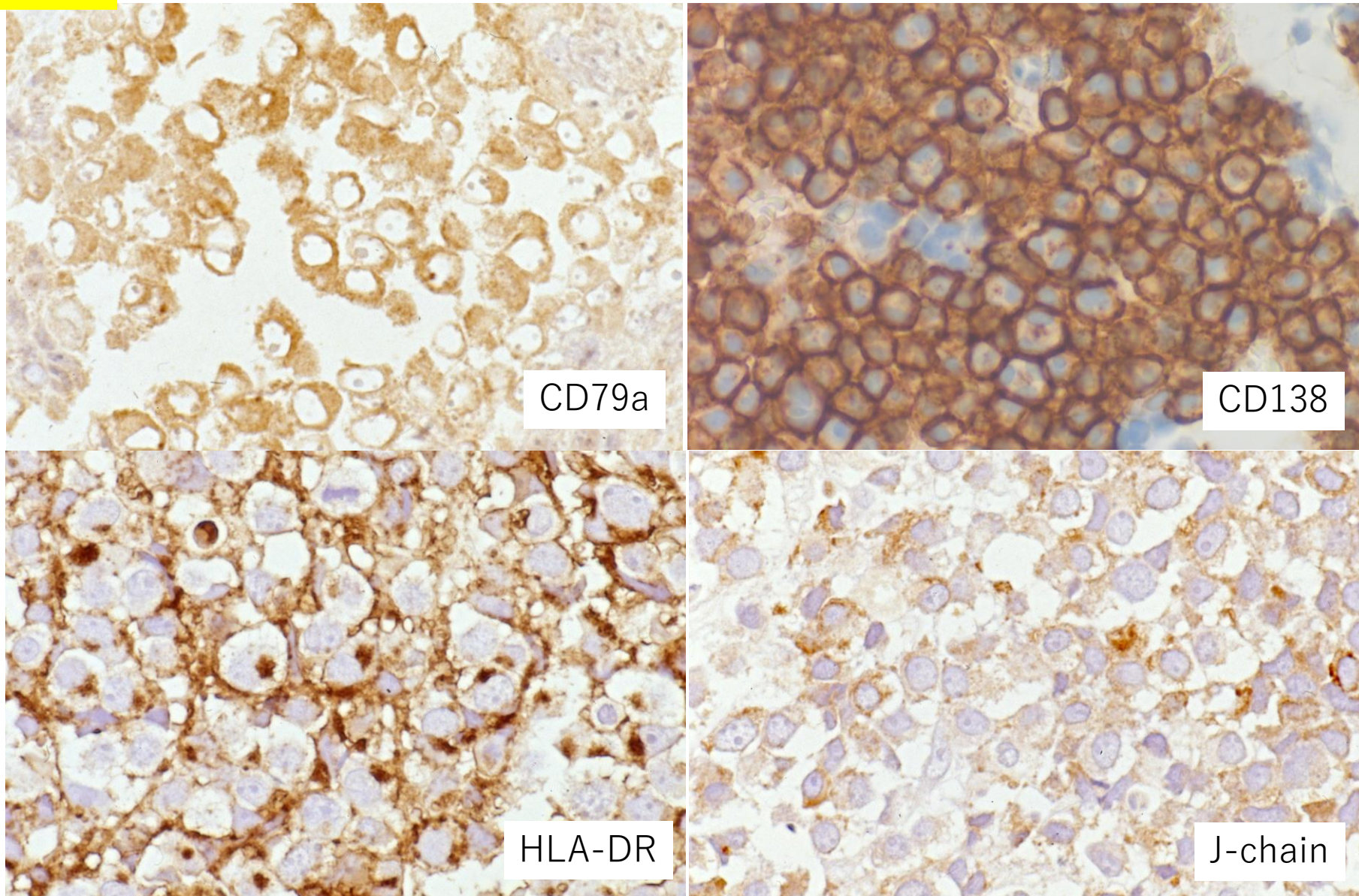
Multiple myeloma. Intraoperative consultation for a paravertebral tumor sampled from a female patient aged 60's (left: H&E, frozen section, center: stamp cytology, May-Giemsa, right: Pap). Because of the immature cytological features, the diagnosis of malignant lymphoma was suspected.

Multiple myeloma



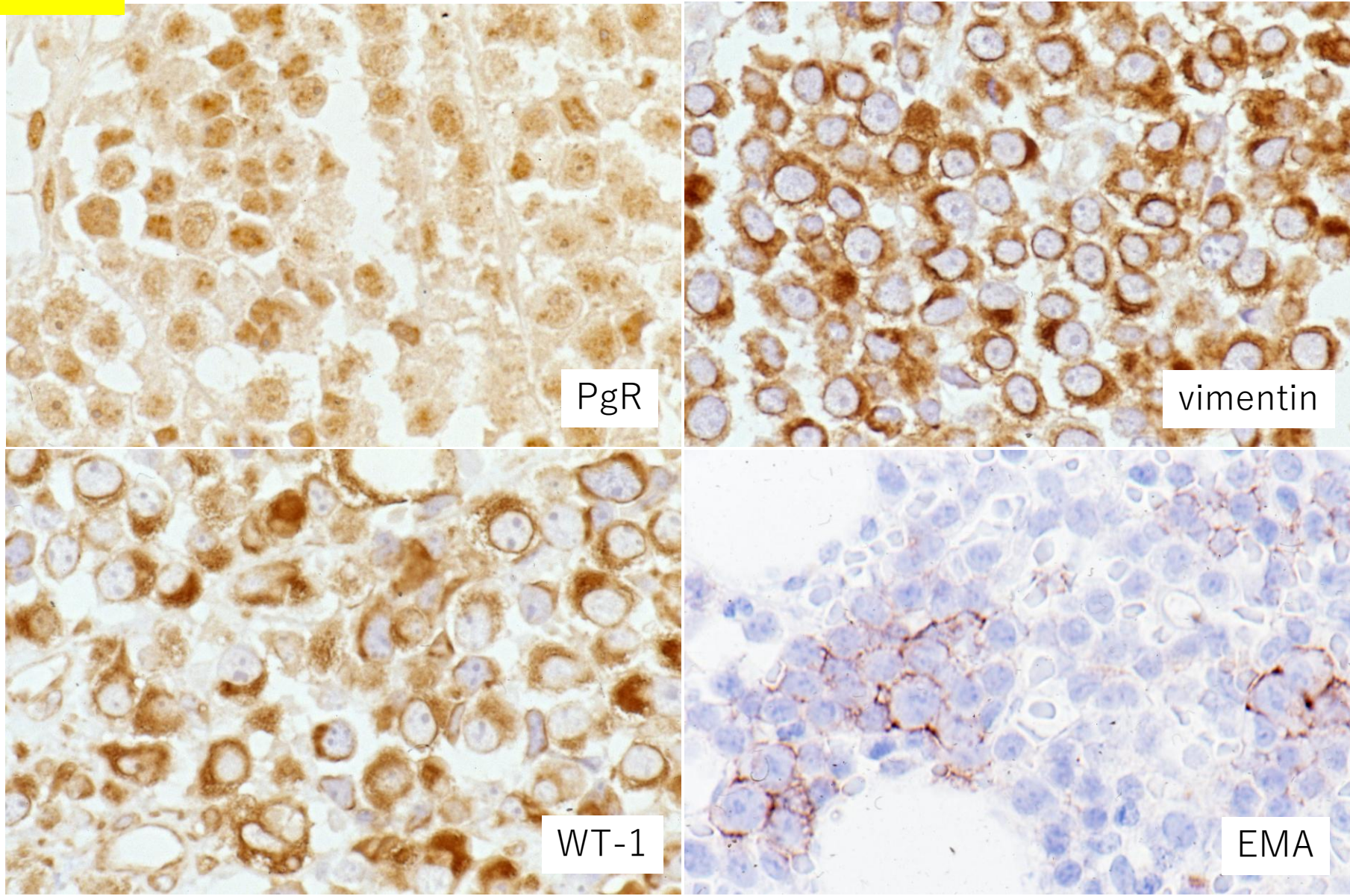
A paravertebral tumor seen in a female patient aged 60's (left: H&E, center: kappa chain, right: lambda chain, in paraffin sections). The tumor cells with frequent mitotic activity are highly proliferative with high Ki-67 labeling, and show kappa chain monoclonality, confirming the diagnosis of **multiple myeloma**.

Multiple myeloma



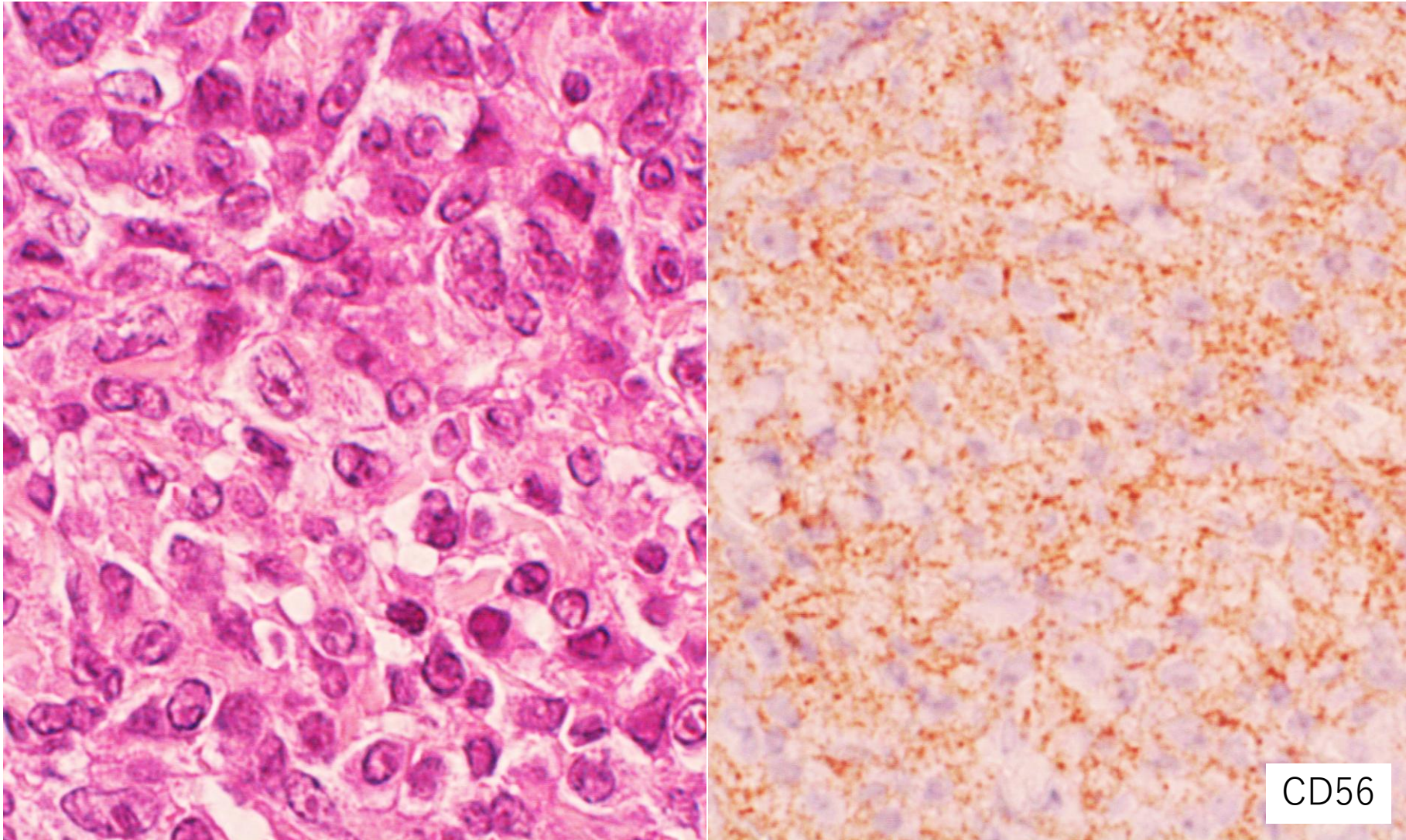
Marker expression of paravertebral **multiple myeloma** seen in a female patient aged 60's. The myeloma cells express CD79a, CD138, HLA-DR and J-chain.

Multiple myeloma



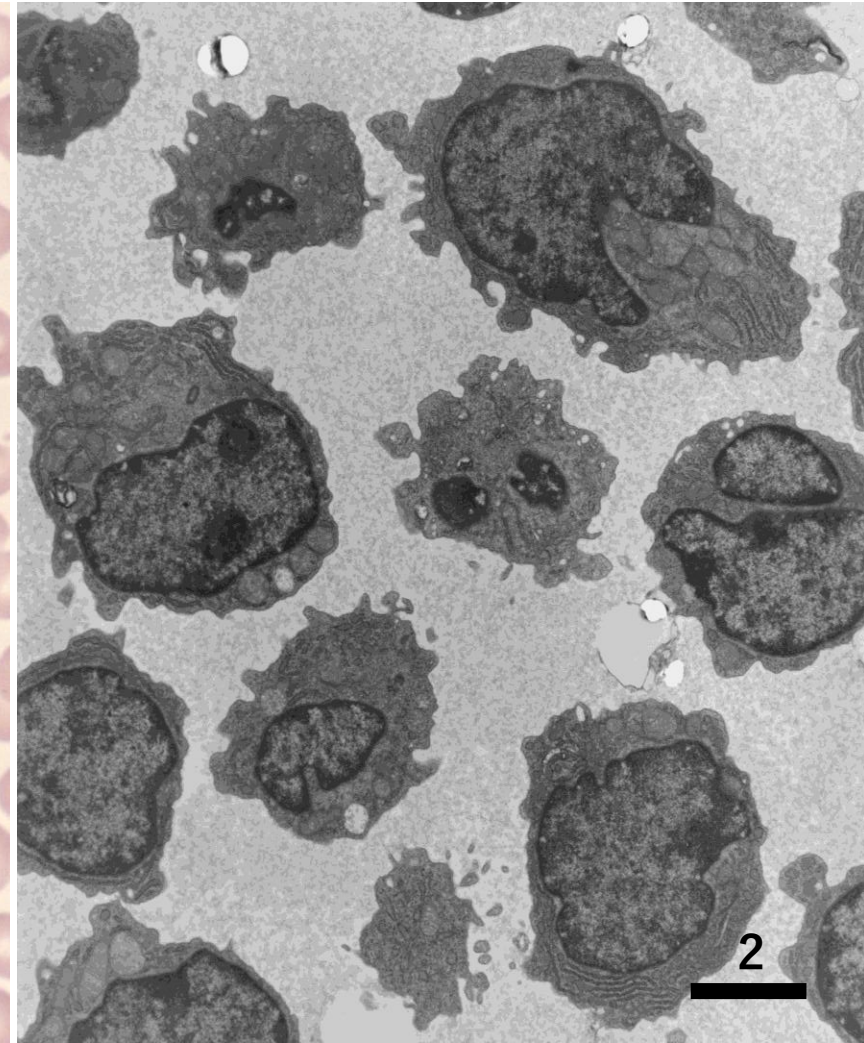
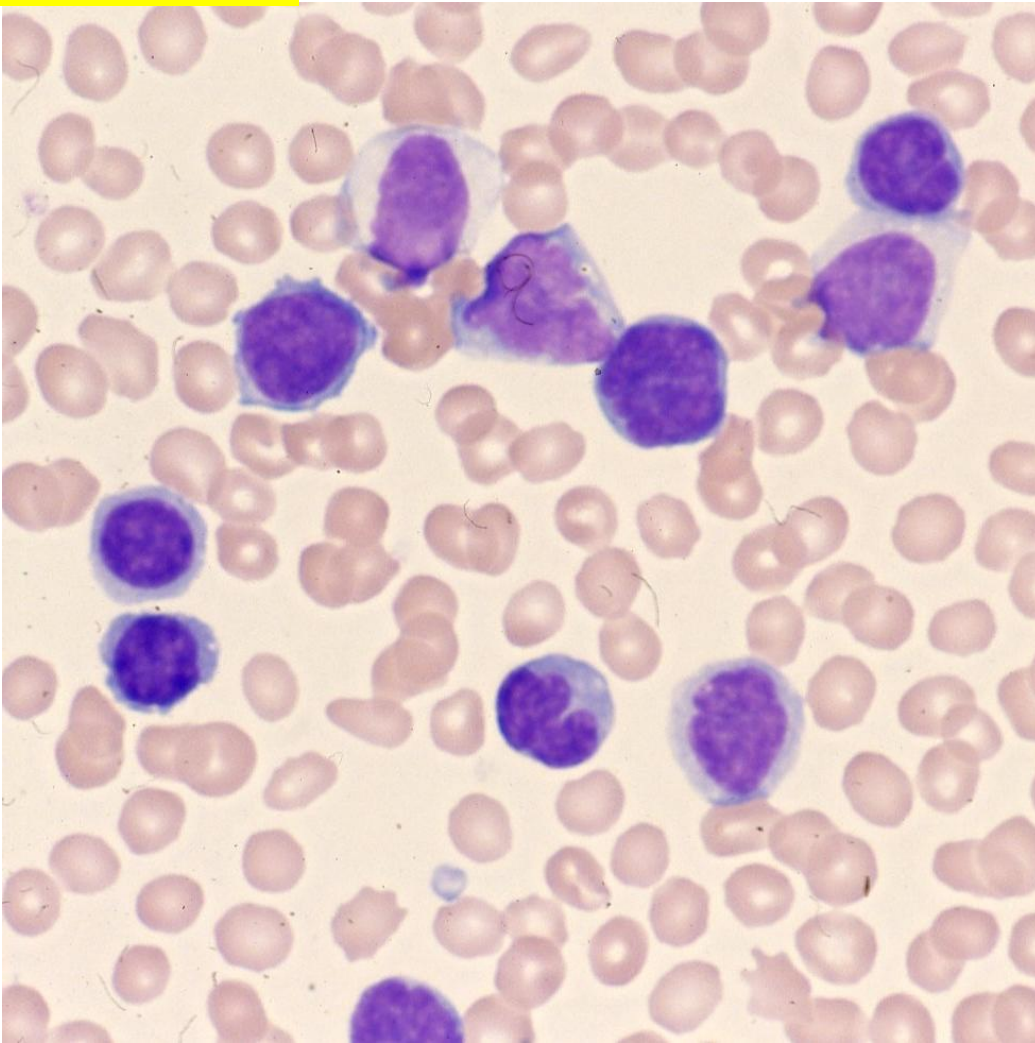
Marker expression of paravertebral **multiple myeloma** seen in a female patient aged 60's. The myeloma cells diffusely express PgR, vimentin and WT-1. EMA immunoreactivity detected by DF3 monoclonal antibody is also focally expressed.

Multiple myeloma



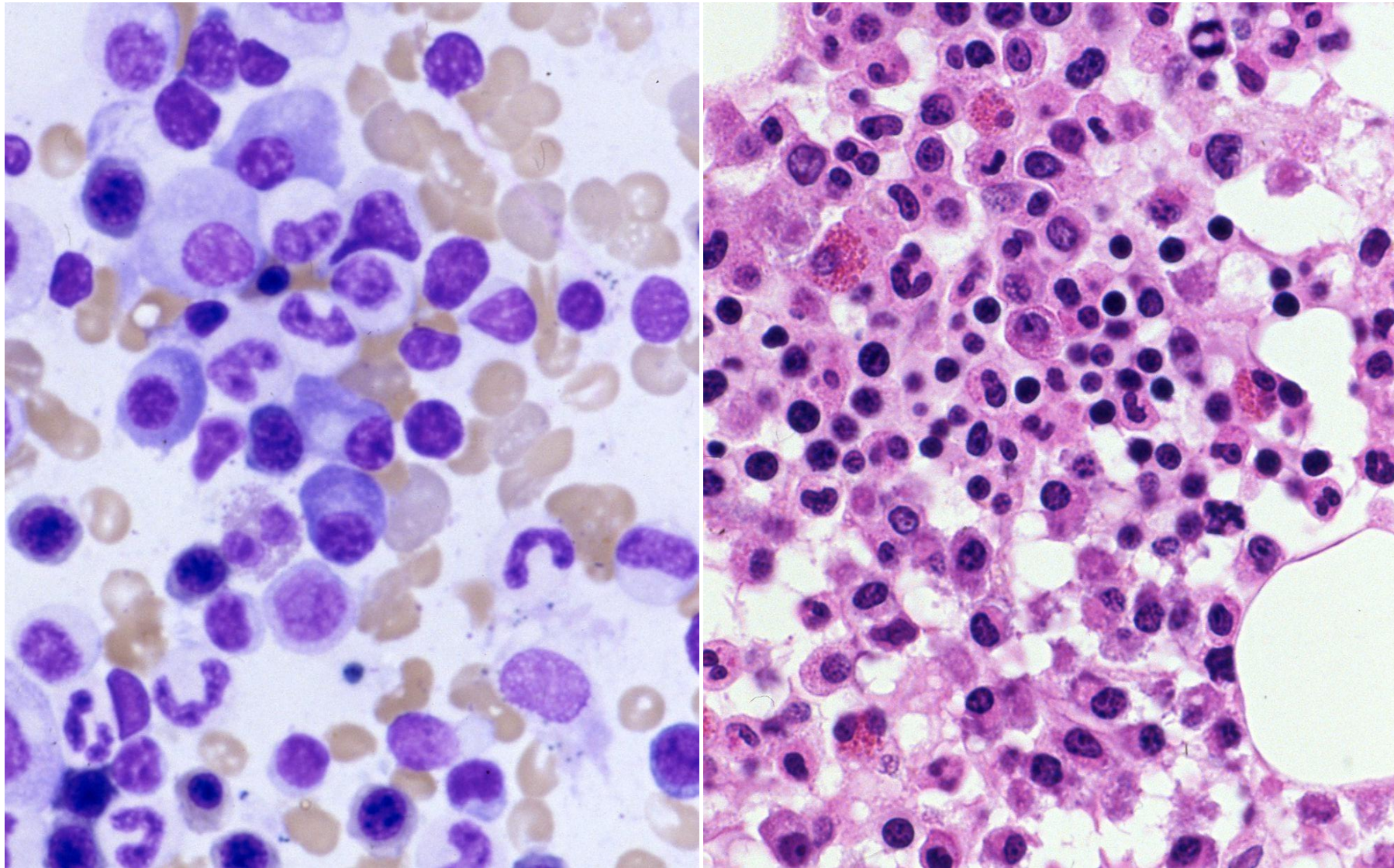
Multiple myeloma. Aberrant expression of **CD56 (NCAM)** on myeloma cells in a 72 y-o male patient. CD56 is a marker of NK cells and neuroendocrine cells. The neoplastic plasma cells often express CD56, while normal plasma cells lack the expression.

Plasma cell leukemia



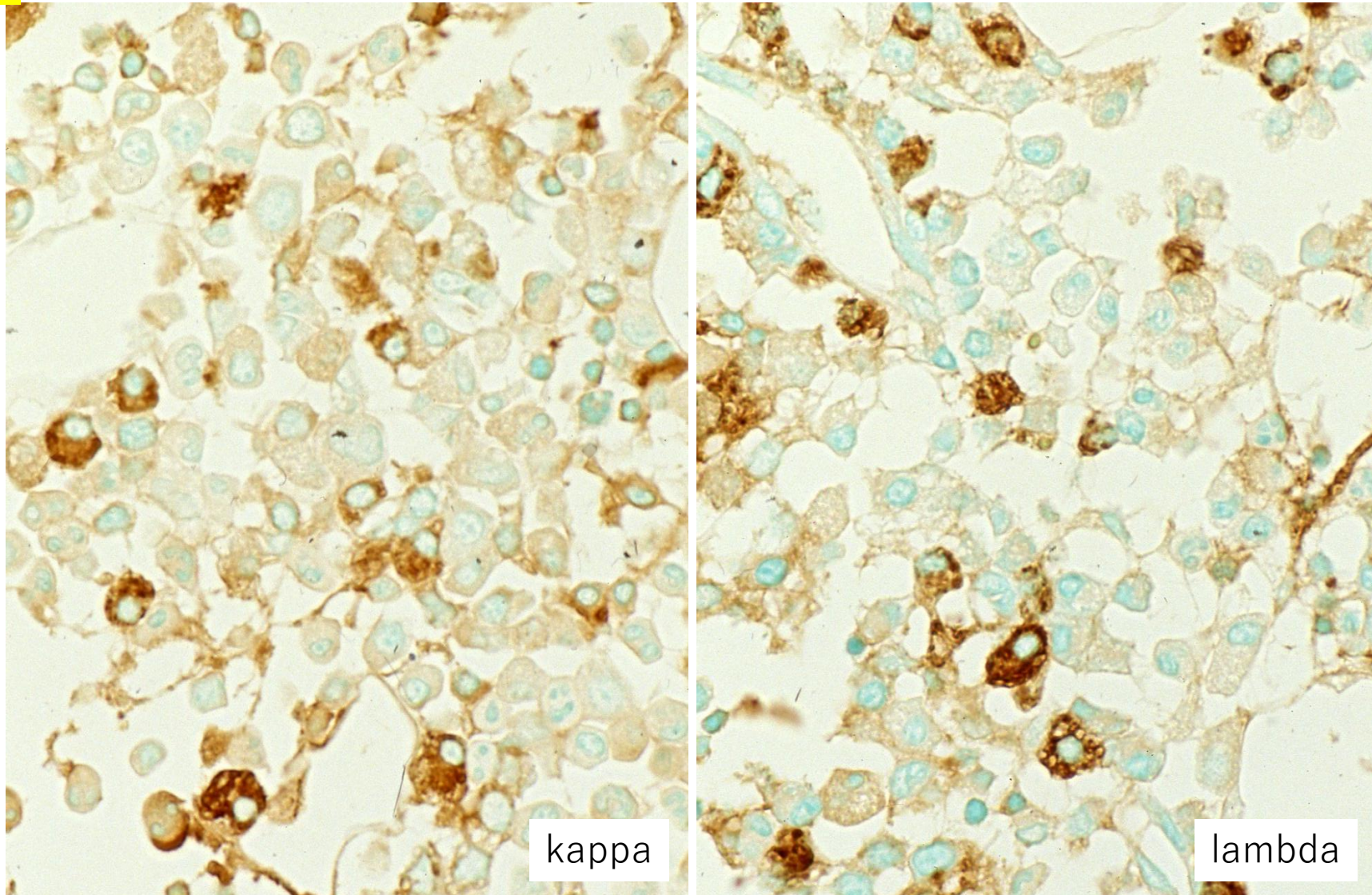
Plasma cell (plasmablastic) leukemia in the peripheral blood of a 63 y-o female patient (left: May-Giemsa, right: EM). The white blood cell count is 130,000/ μ L. Immature-looking plasma cells (plasmablasts) with nucleoli and rough endoplasmic reticula are seen in the peripheral blood, a rare phenomenon in plasma cell neoplasias. Non-secretory type is common. Leukemic manifestation (>20% circulating plasma cells) of may or may not follow the pre-existing multiple myeloma.

Plasmacytosis



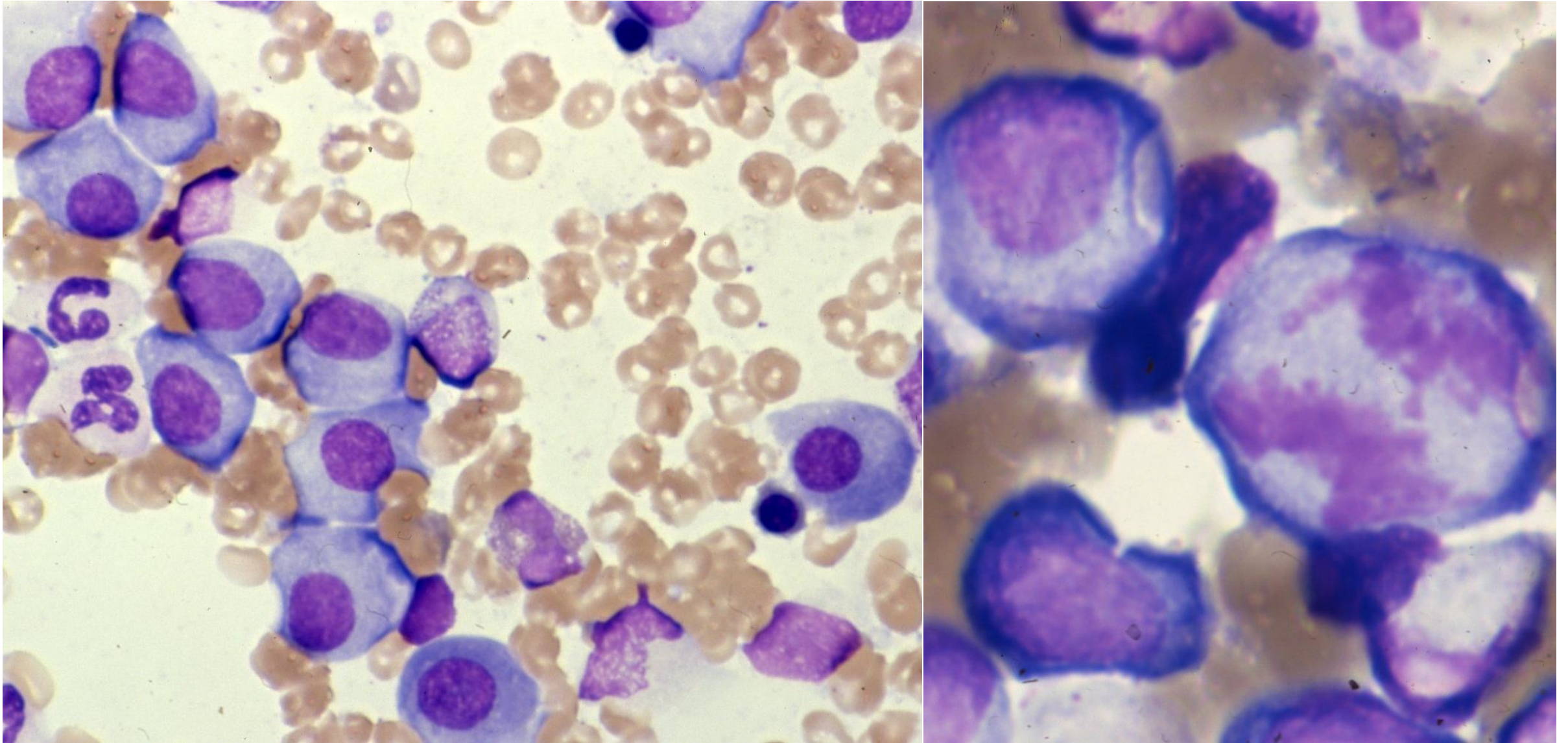
Plasmacytosis in the bone marrow (left: May-Giemsa, right: H&E). Mature-looking plasma cells evidently increase in the marrow space. It is difficult to distinguish from multiple myeloma in routine morphology.

Plasmacytosis



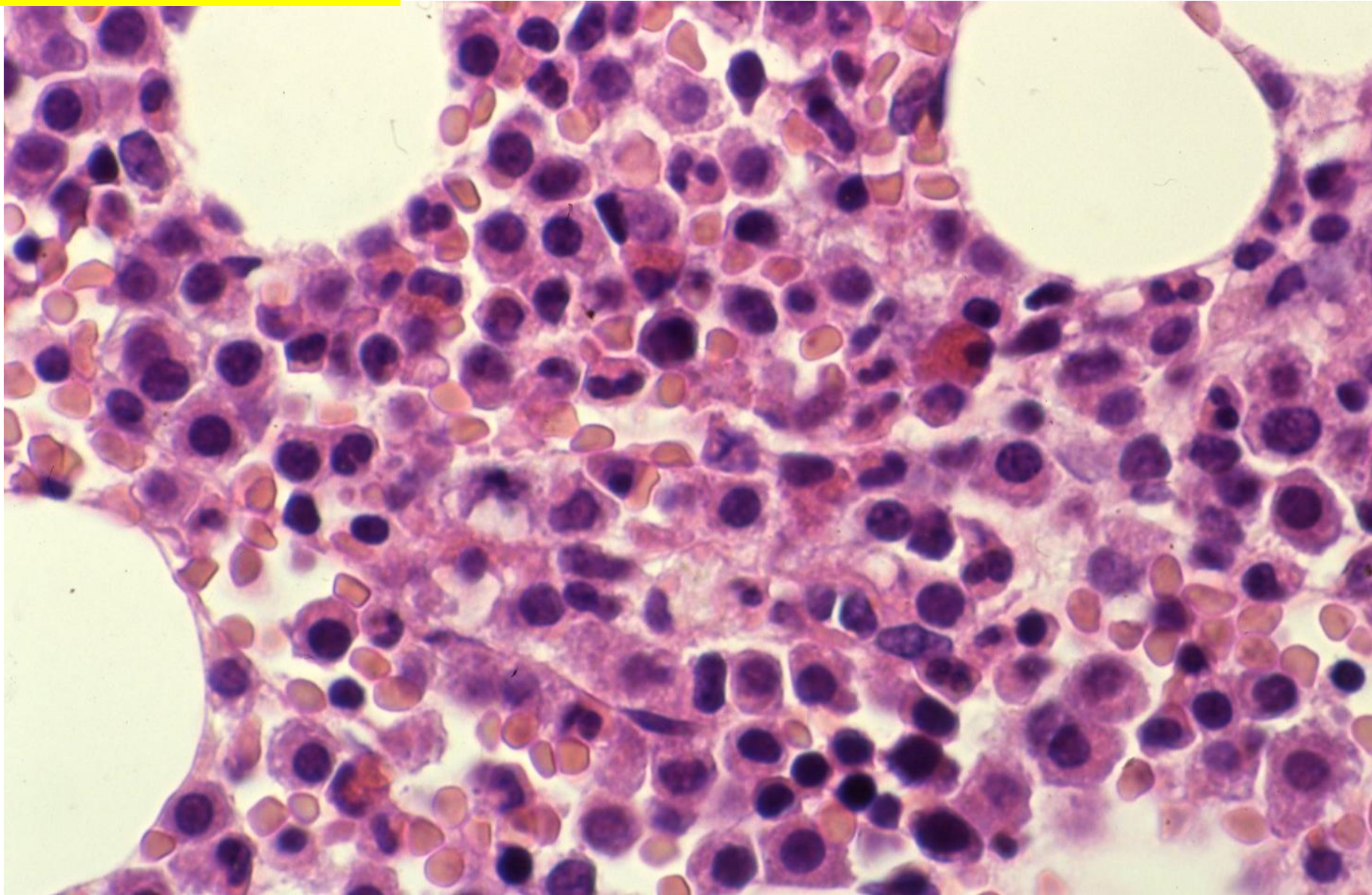
Plasmacytosis in the bone marrow (immunostaining, left: kappa chain, right: lambda chain). Mature-looking plasma cells increased in the marrow space show polyclonality, indicating a benign, reactive process. Immunostaining is quite useful to exclude the possibility of multiple myeloma.

Special type of multiple myeloma



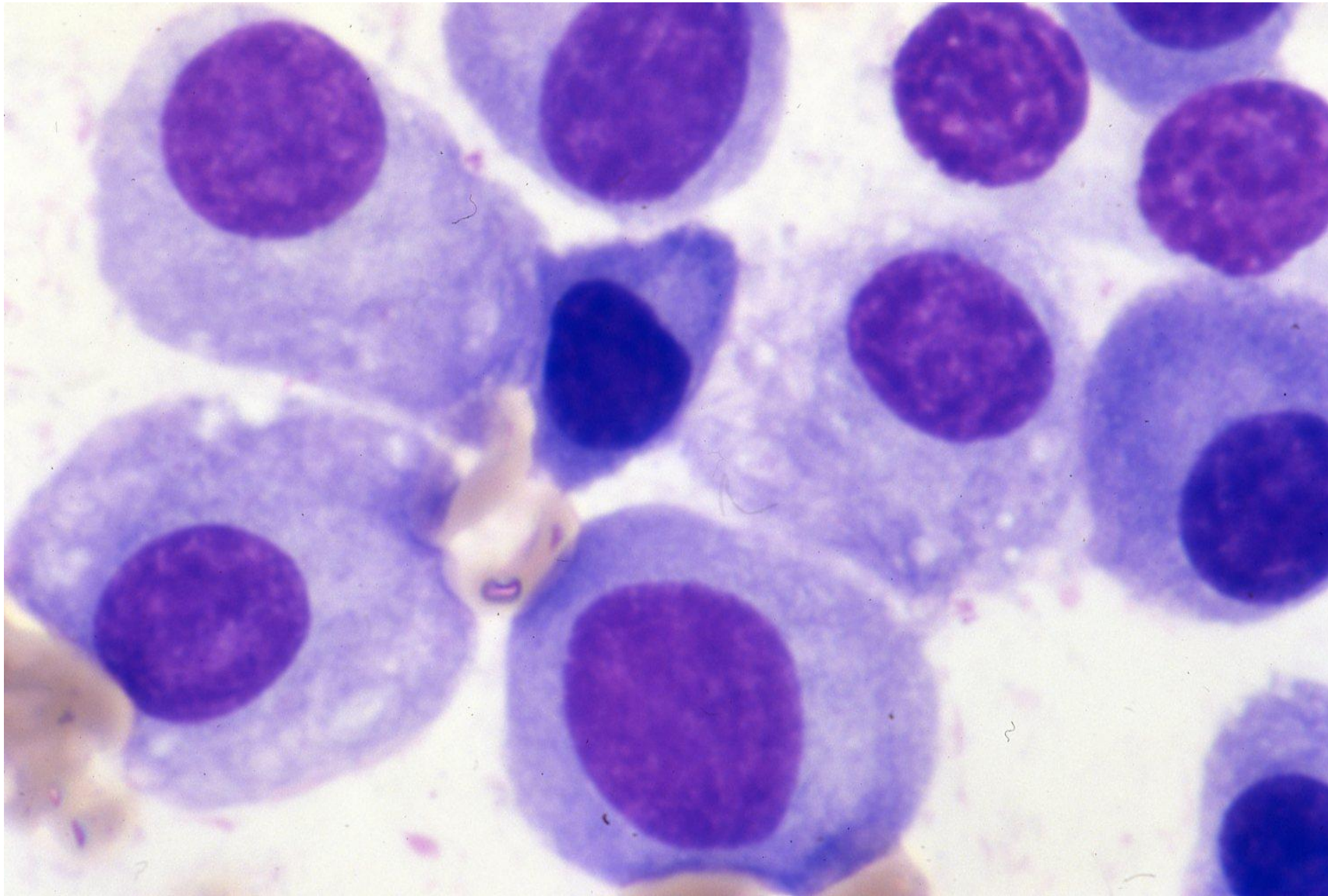
Multiple myeloma, IgA, kappa type (May-Giemsa). Monomorphous growth of plasma cells with eccentric enlarged nuclei and occasional mitosis is observed. The plump cytoplasm is basophilic.

Special type of multiple myeloma



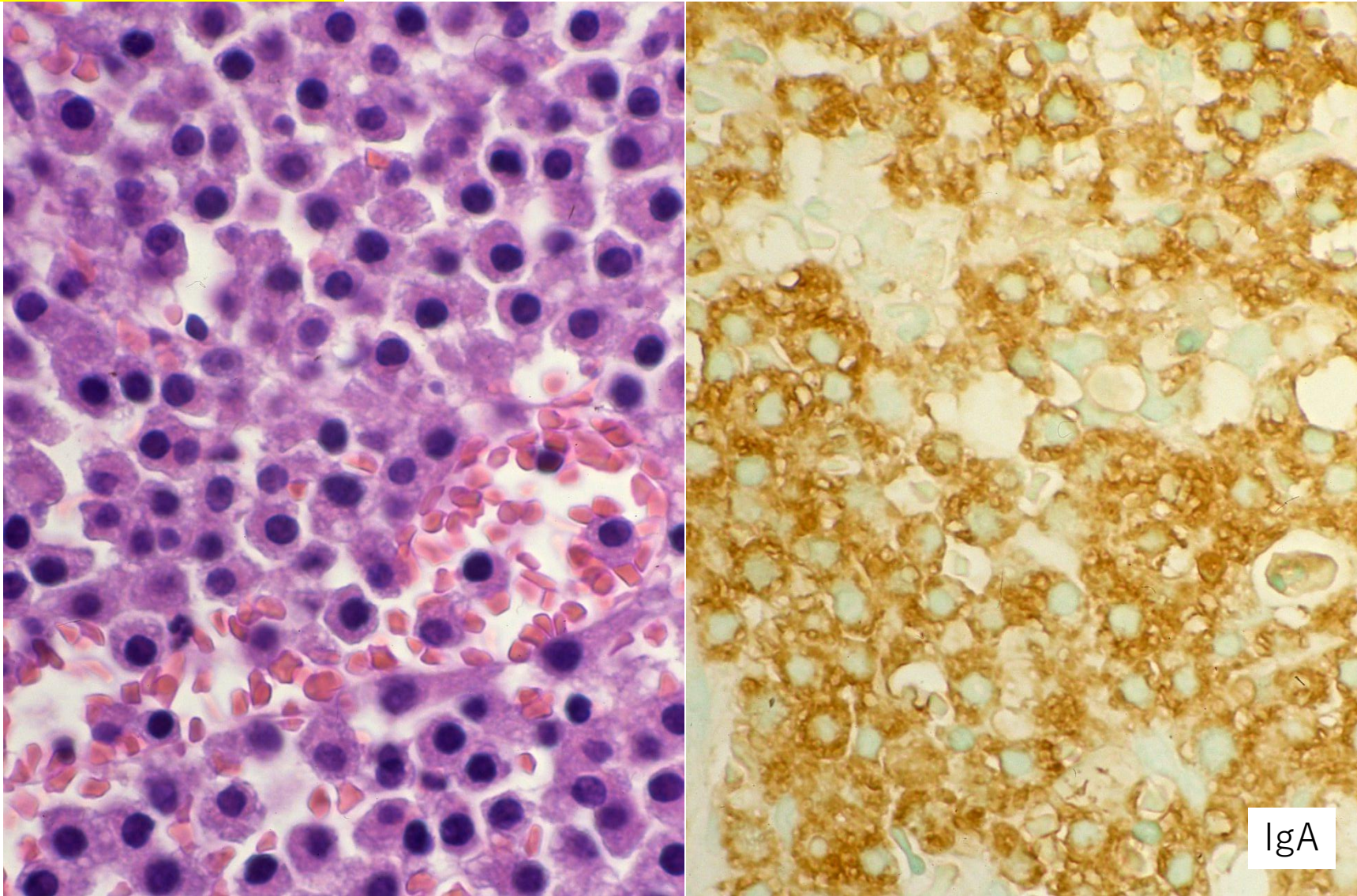
Multiple myeloma, IgA, kappa type (H&E). The marrow space is occupied by atypical plasma cells. Hyperchromatic eccentric nuclei and basophilic cytoplasm are observed.

Special type of multiple myeloma



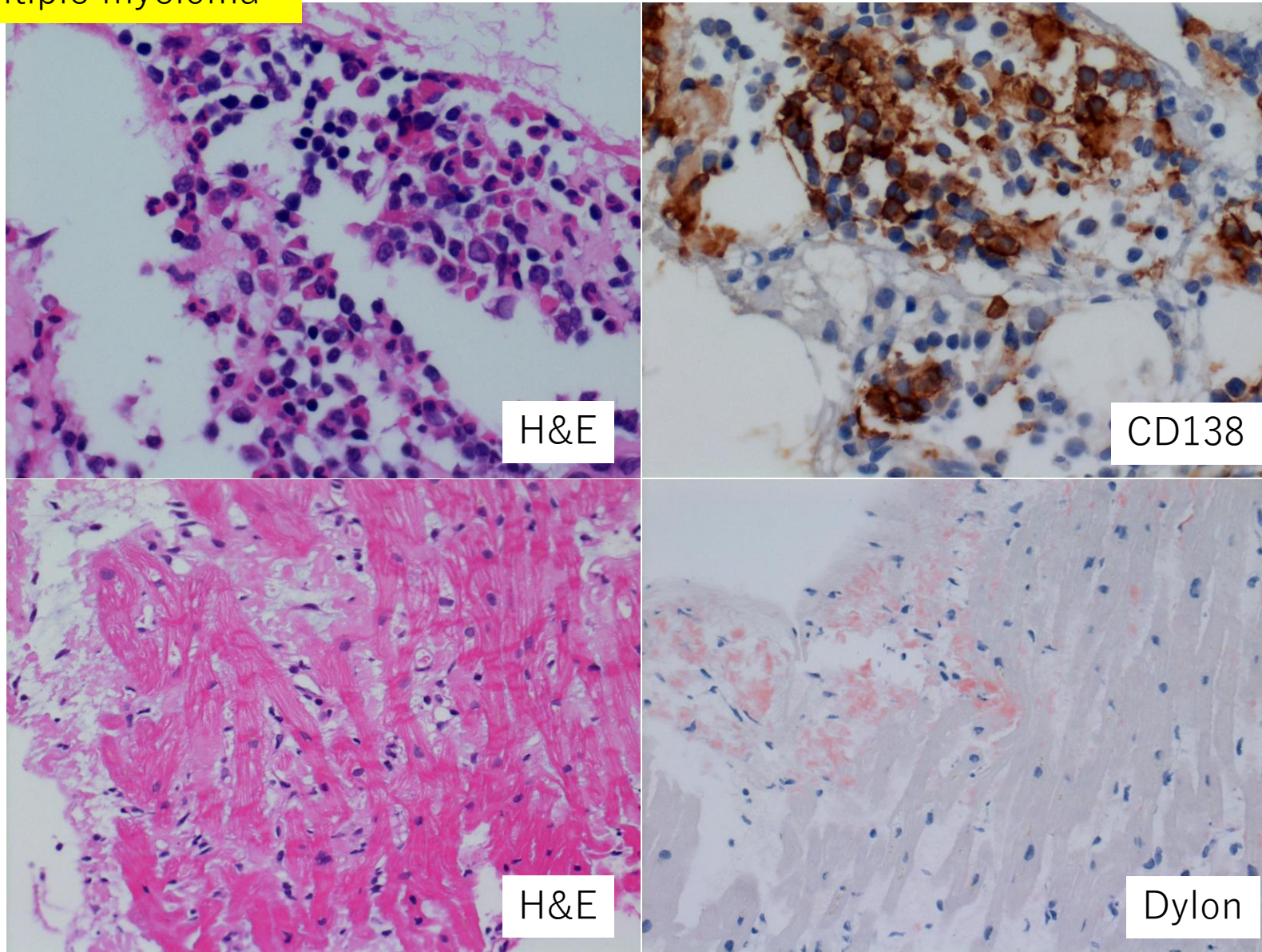
Multiple myeloma with **alpha chain disease** (May-Giemsa).
Atypical plasma cells with distinct Golgi area are noted.

Special type of multiple myeloma



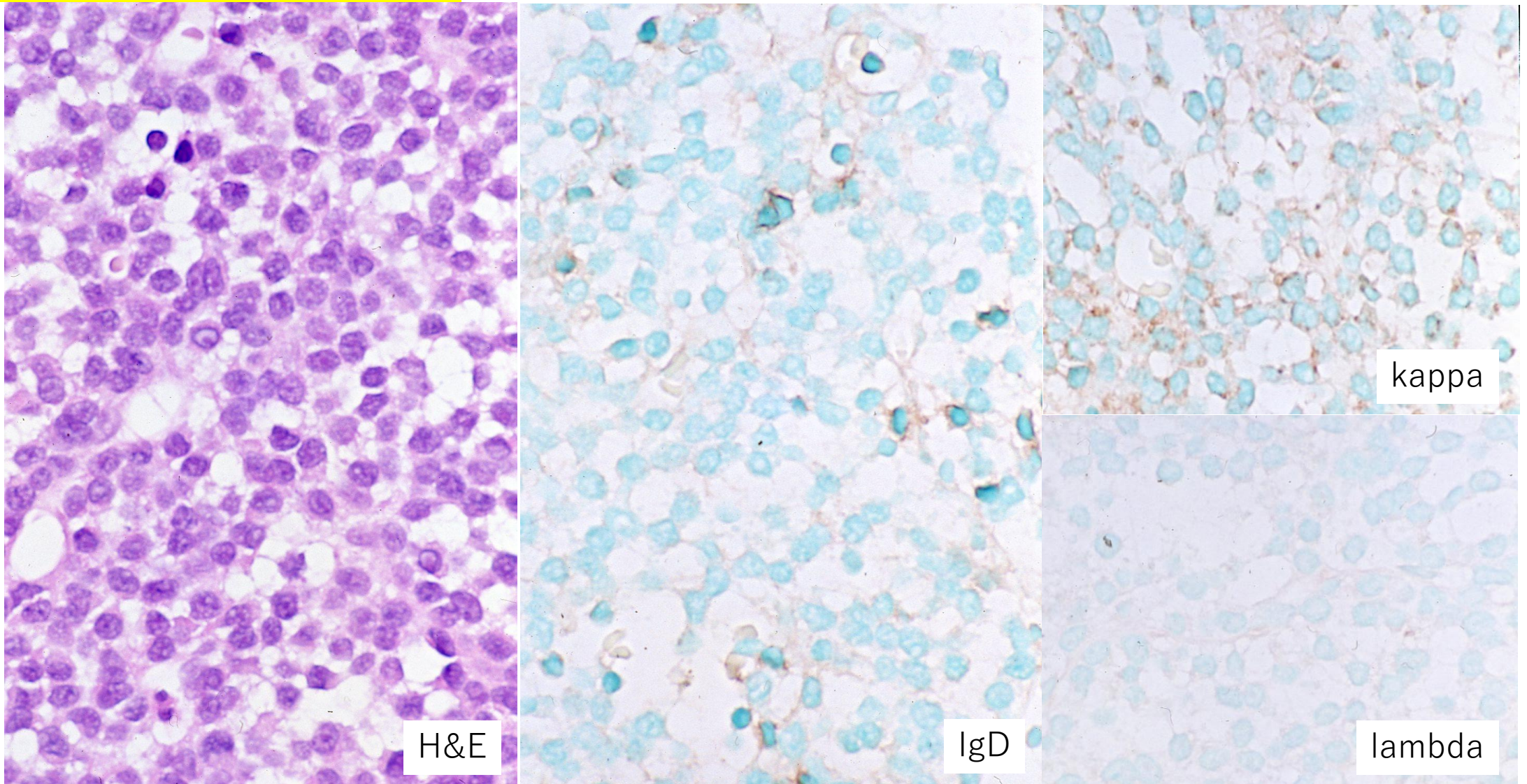
Multiple myeloma with **alpha chain disease** (left: H&E, right: immunostaining for IgA). Atypical plasma cells with hyperchromatic eccentric nuclei and basophilic cytoplasm are noted. The myeloma cells are diffusely positive for alpha-chain, but negative for light chains.

Special type of multiple myeloma



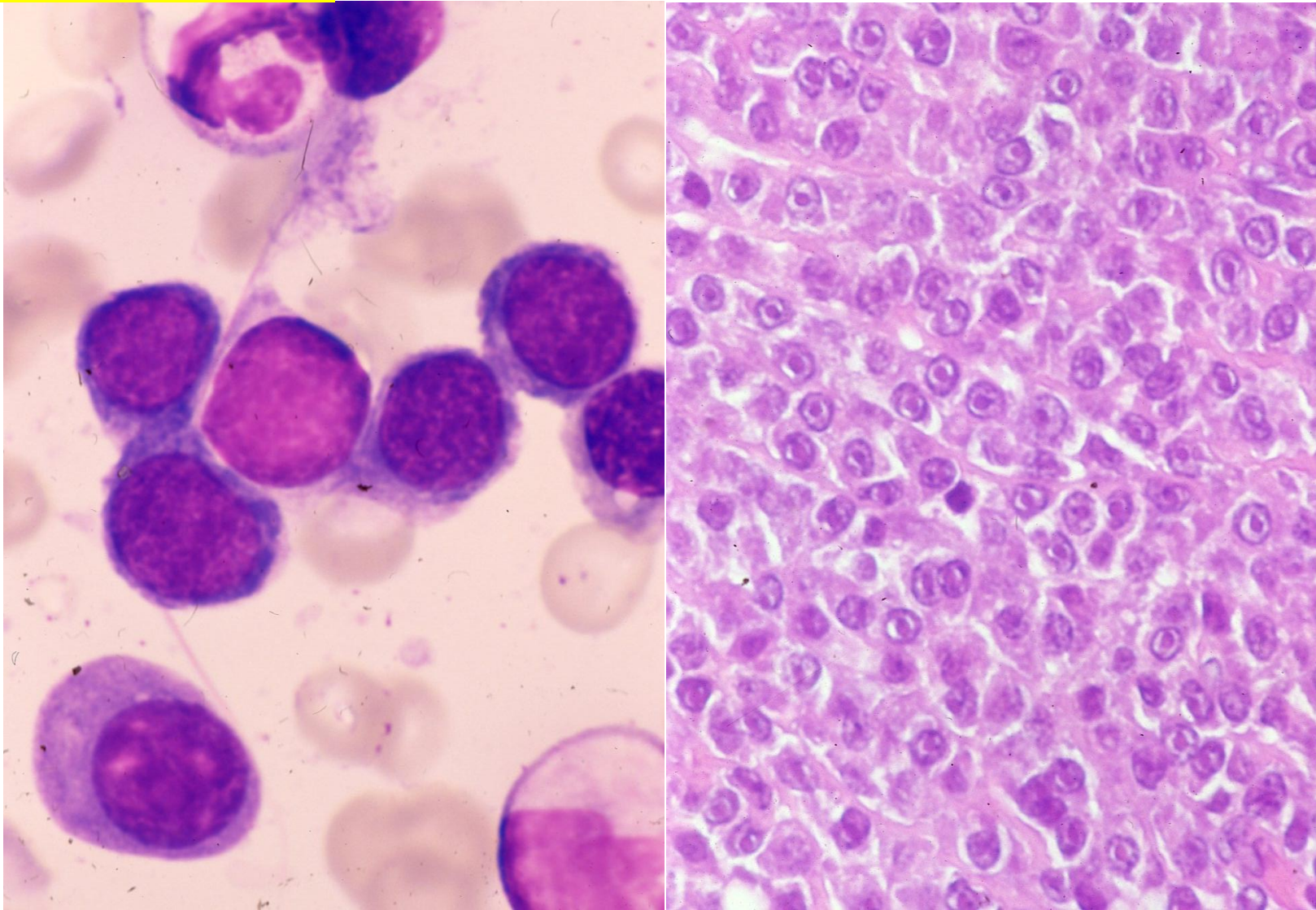
Multiple myeloma, IgG, kappa type, associated with **cardiac amyloidosis** in a male patient aged 40's (top panels). The myeloma cells express CD138. Cardiac biopsy (bottom panels) reveals Dylon-positive amyloid deposition of light chain (AL) type, which caused lethal heart failure.

Special type of multiple myeloma



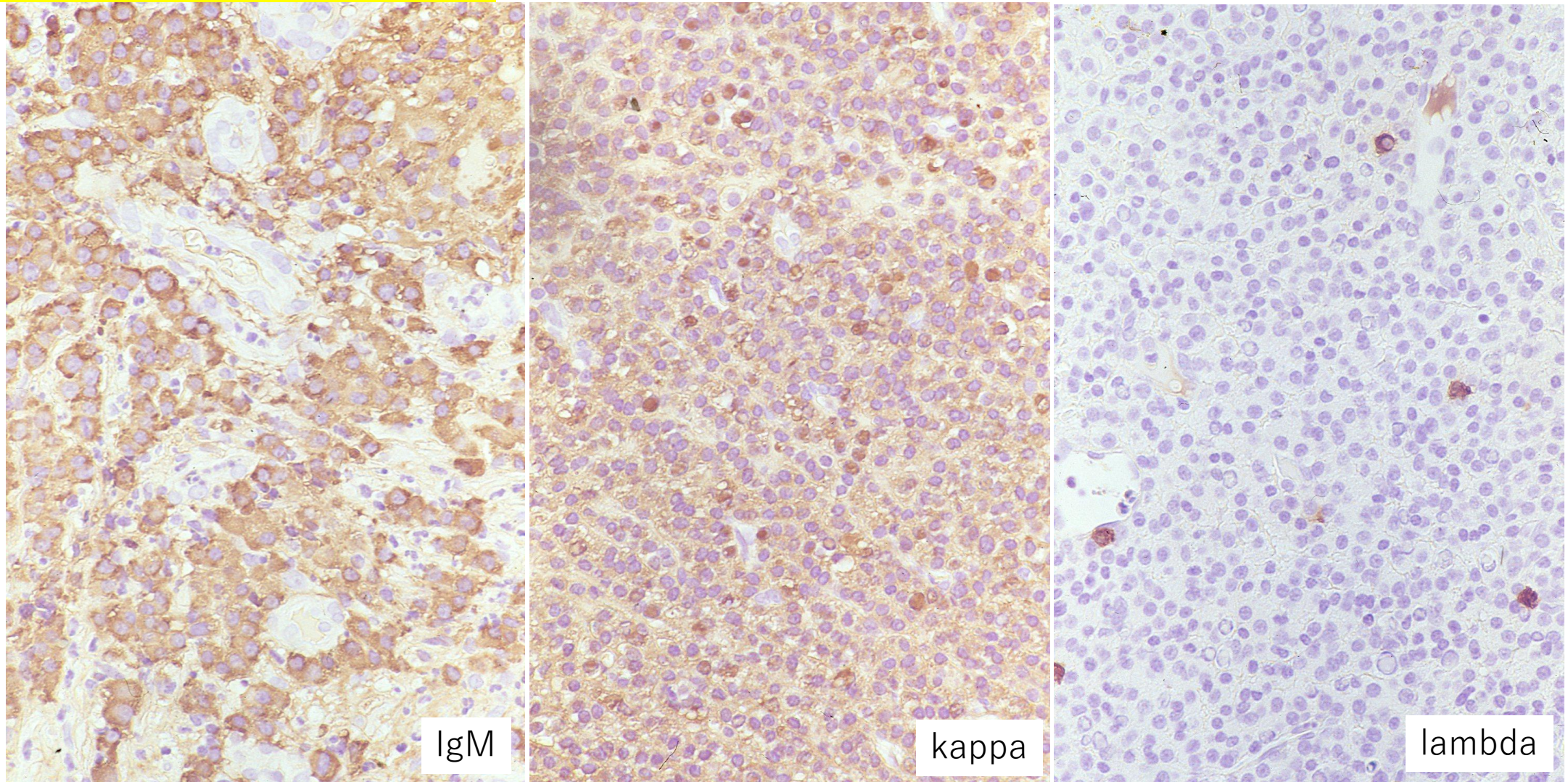
Multiple myeloma, IgD, kappa type (bone marrow aspiration, left: H&E, center: IgD, right top: kappa, right bottom: lambda). IgD, kappa-type myeloma is shown. The expression of delta chain in the myeloma cells is not diffuse, while kappa chain monoclonality is diffusely observed.

Special type of multiple myeloma



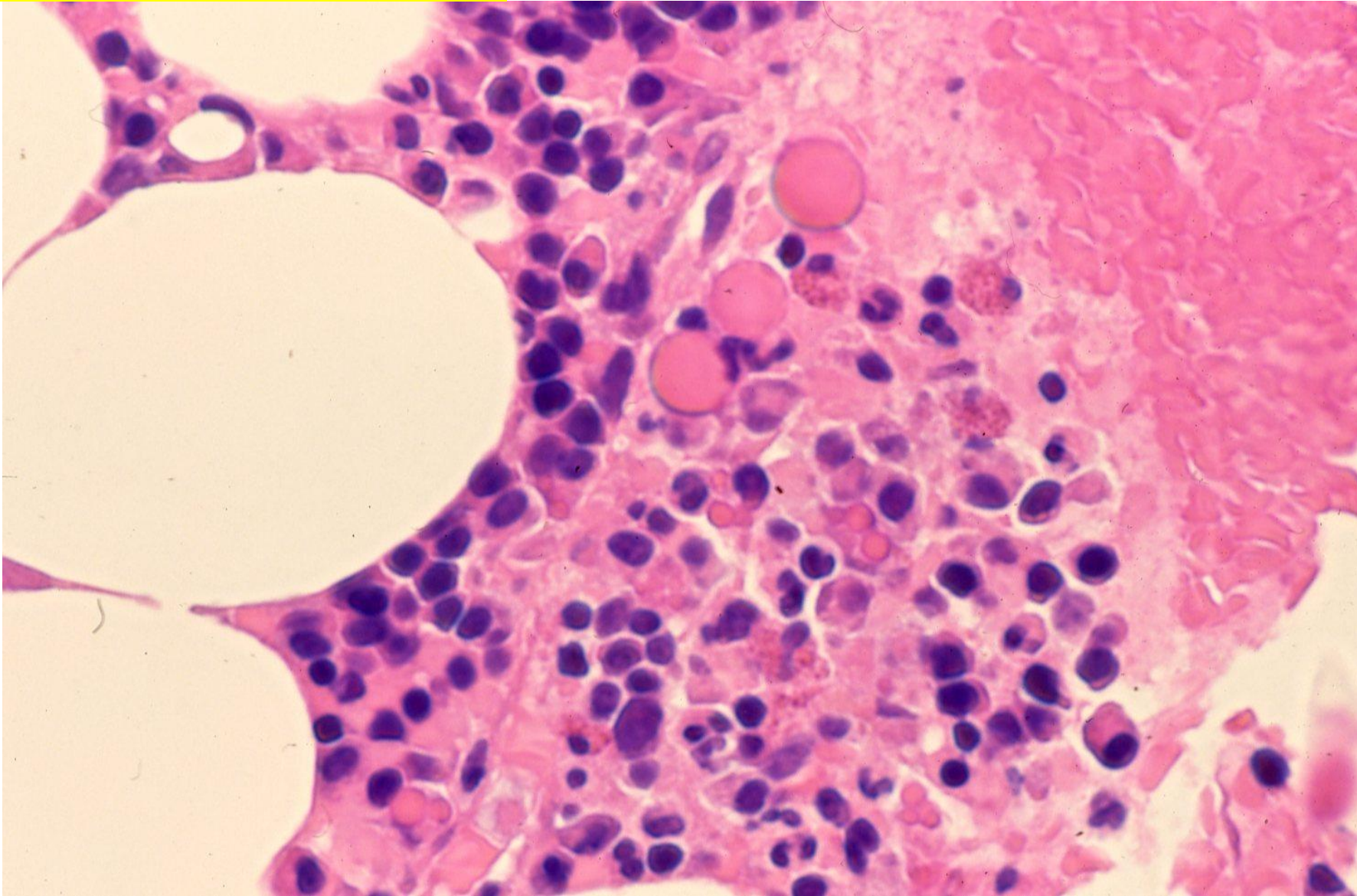
Multiple myeloma, IgM, kappa type monoclonality seen in a 72 y-o male patient (bone marrow aspirate, left: May-Giemsa, right: H&E). Punched-out lesions and a neoplastic nasal polyp are complicated. Lymphoplasmacytoid features are characteristic.

Special type of multiple myeloma



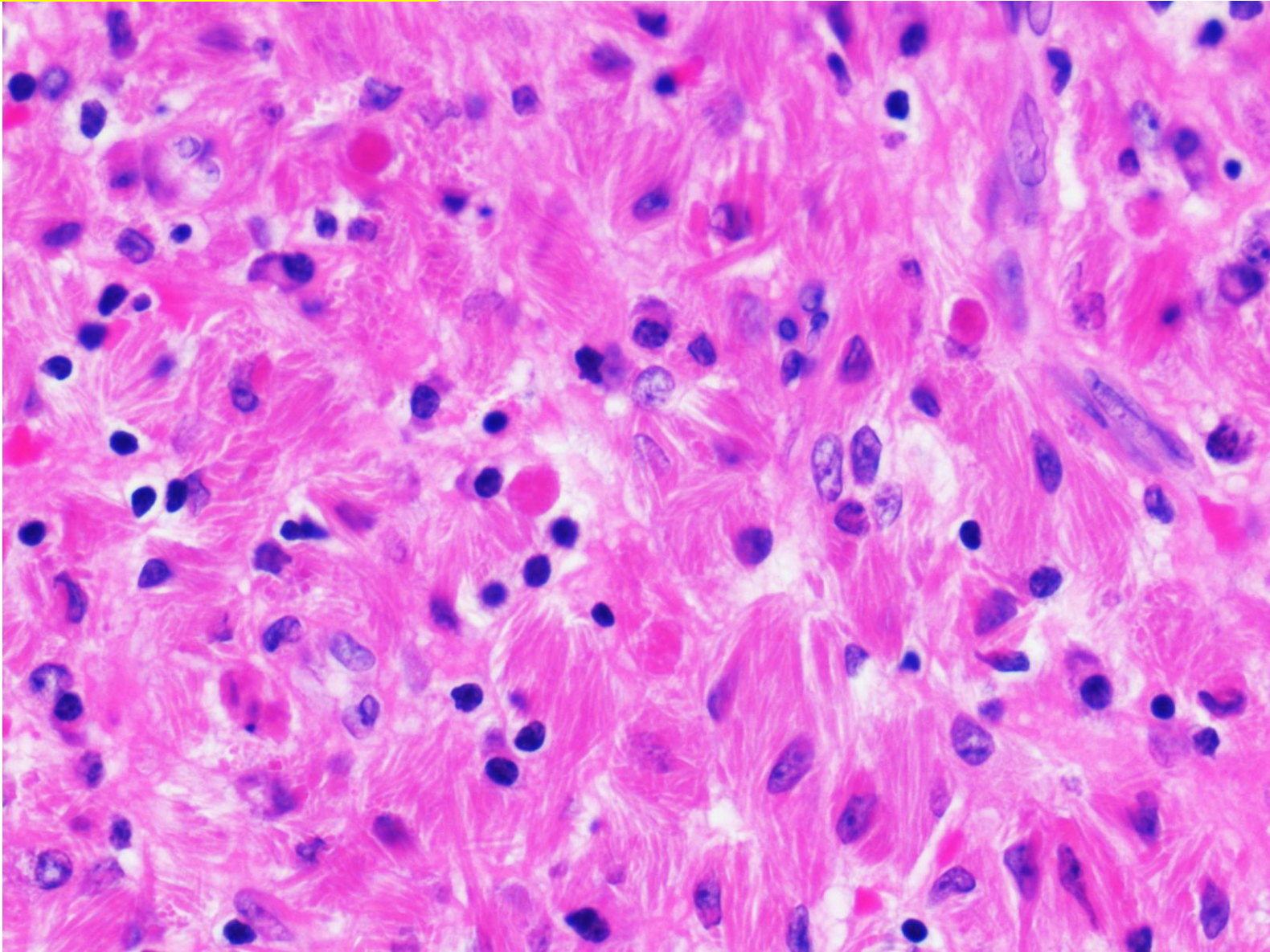
Multiple myeloma, IgM, kappa type monoclonality seen in a 72 y-o male patient (immunostaining, left: IgM, center: kappa chain, right: lambda chain). The bone destructive lymphoplasmacytoid cells express IgM, kappa chain monoclonality. Ref.: Tsutsumi Y, et al. A case of IgM(k)-type myeloma with pyroglobulinemia. Nihon Monaikei Gakkai Zasshi 1981; 21(3): 271-280 (in Japanese). doi: 10.3960/jslrrt1961.21.271

Multiple myeloma with inclusion bodies



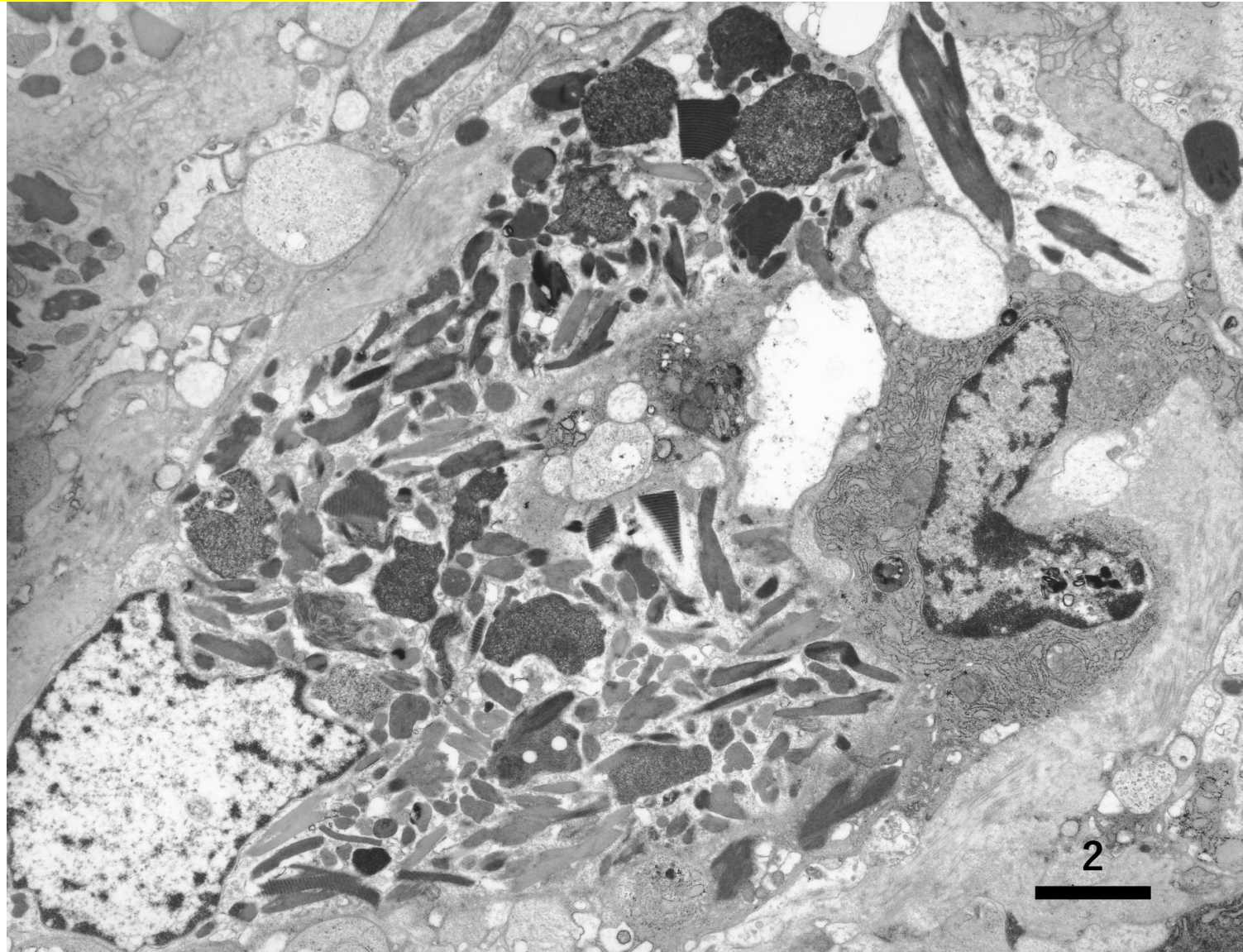
Russell bodies in **multiple myeloma** cells (H&E). Some myeloma cells contain eosinophilic globular cytoplasmic inclusions (Russell bodies).

Multiple myeloma with inclusion bodies



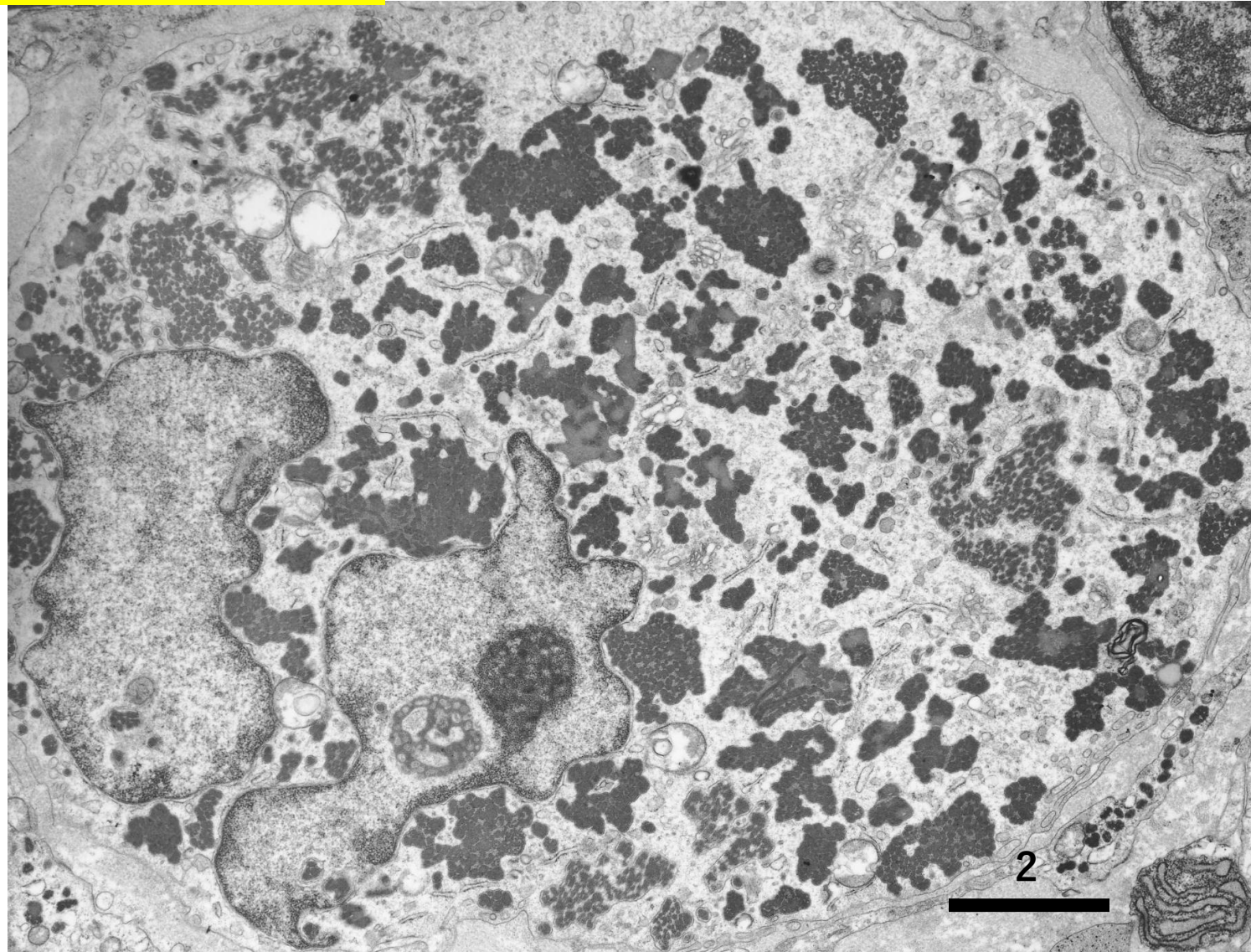
Plasmacytoma of the nasal cavity seen in a 65 y-o female patient (H&E). Crystallized cytoplasmic inclusions are noted in the neoplastic plasma cells.

Multiple myeloma with inclusion bodies



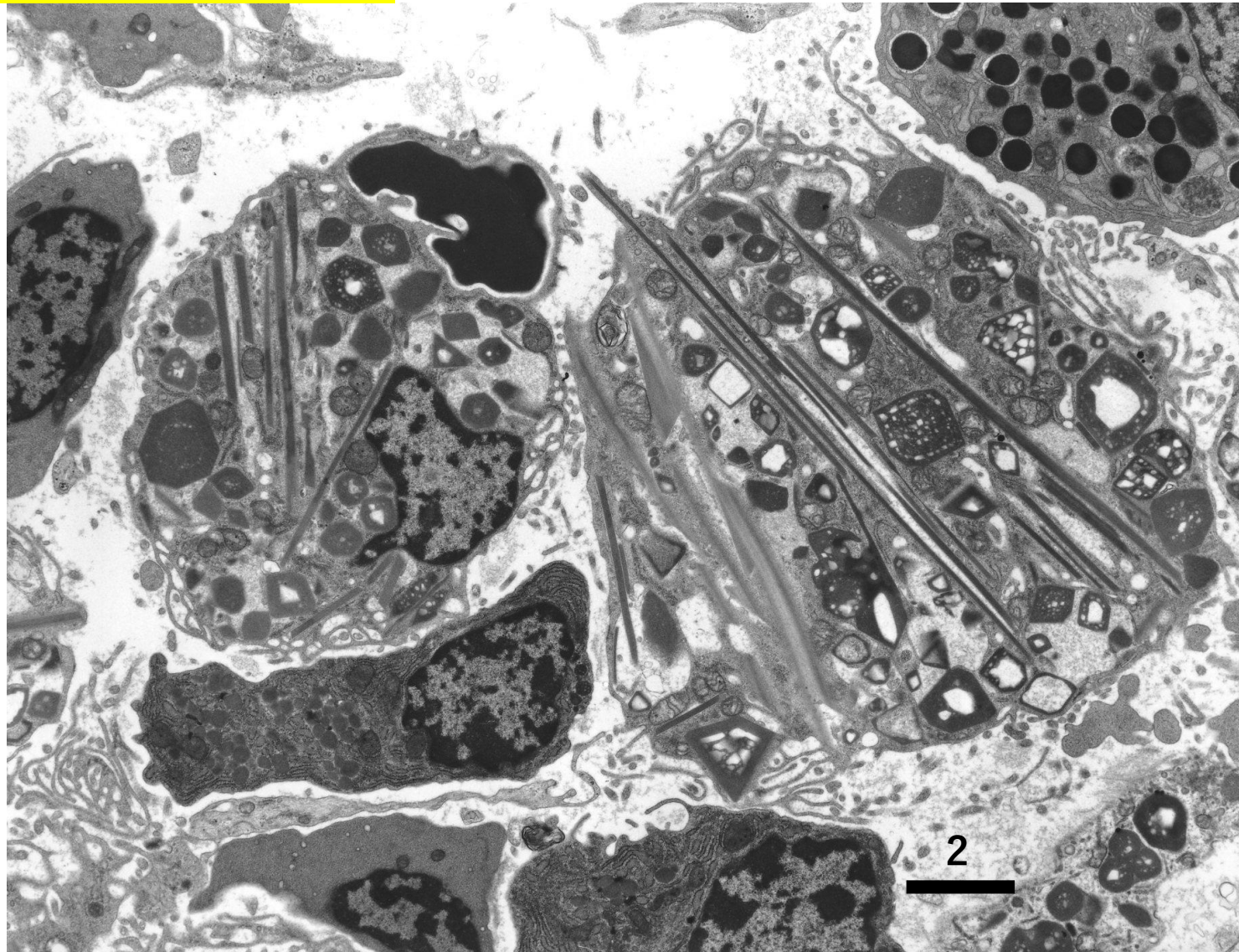
Ultrastructure of **plasmacytoma** of the nasal cavity seen in a 65 y-o female patient (1). The neoplastic plasma cell has electron-dense needle-like or irregular-shaped crystalline inclusions in the cisterna of the rough endoplasmic reticula.

Multiple myeloma with inclusion bodies



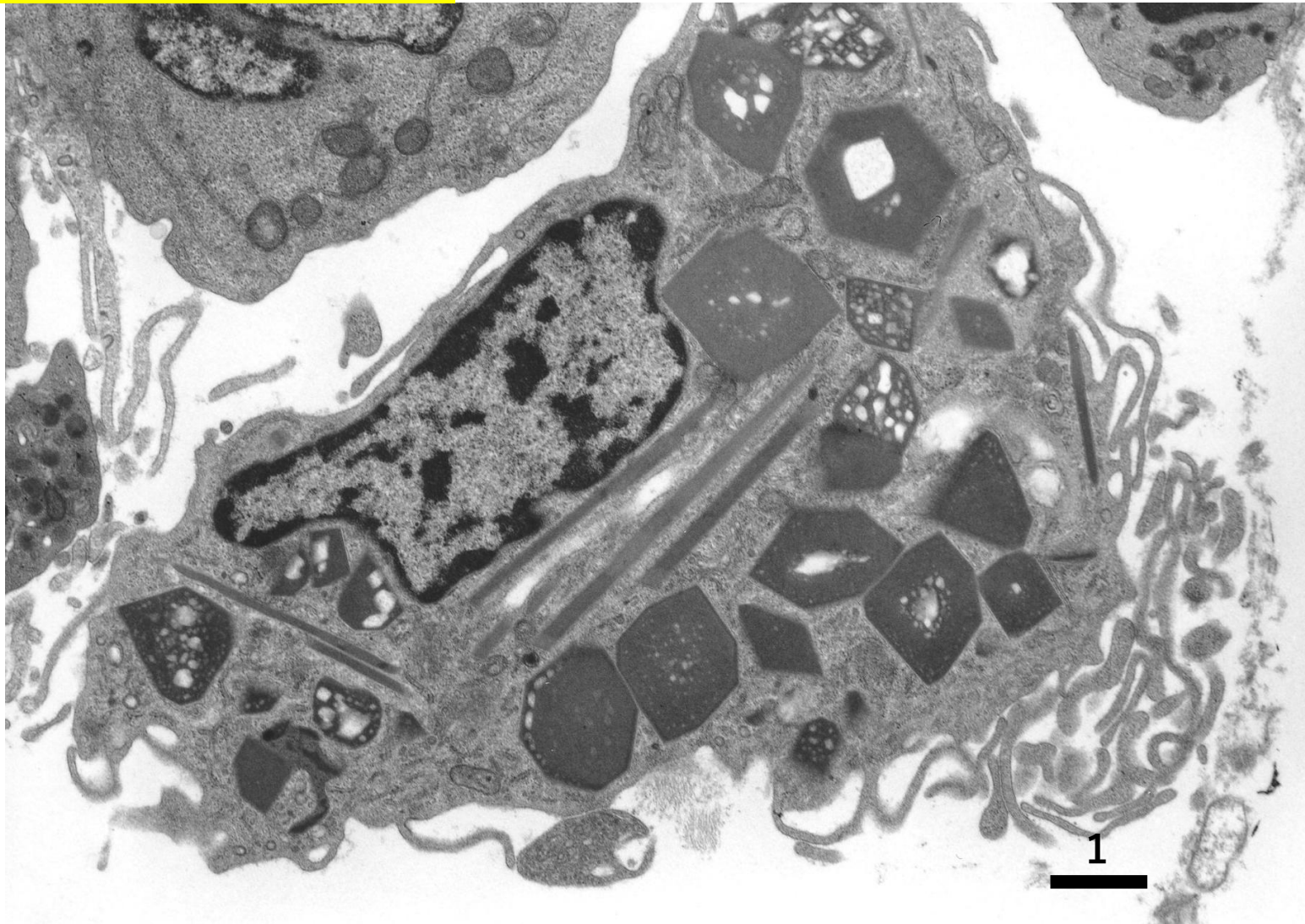
Ultrastructure of **plasmacytoma** of the nasal cavity seen in a 65 y-o female patient (2). The neoplastic plasma cell has electron-dense irregular-shaped crystalline inclusions in the cisterna of the rough endoplasmic reticula.

Multiple myeloma with inclusion bodies



Ultrastructure of **multiple myeloma, kappa-light chain type**, seen in an 85 y-o male patient (a). The neoplastic plasma cells growing the bone marrow are filled with needle-like crystalline inclusion bodies.

Multiple myeloma with inclusion bodies



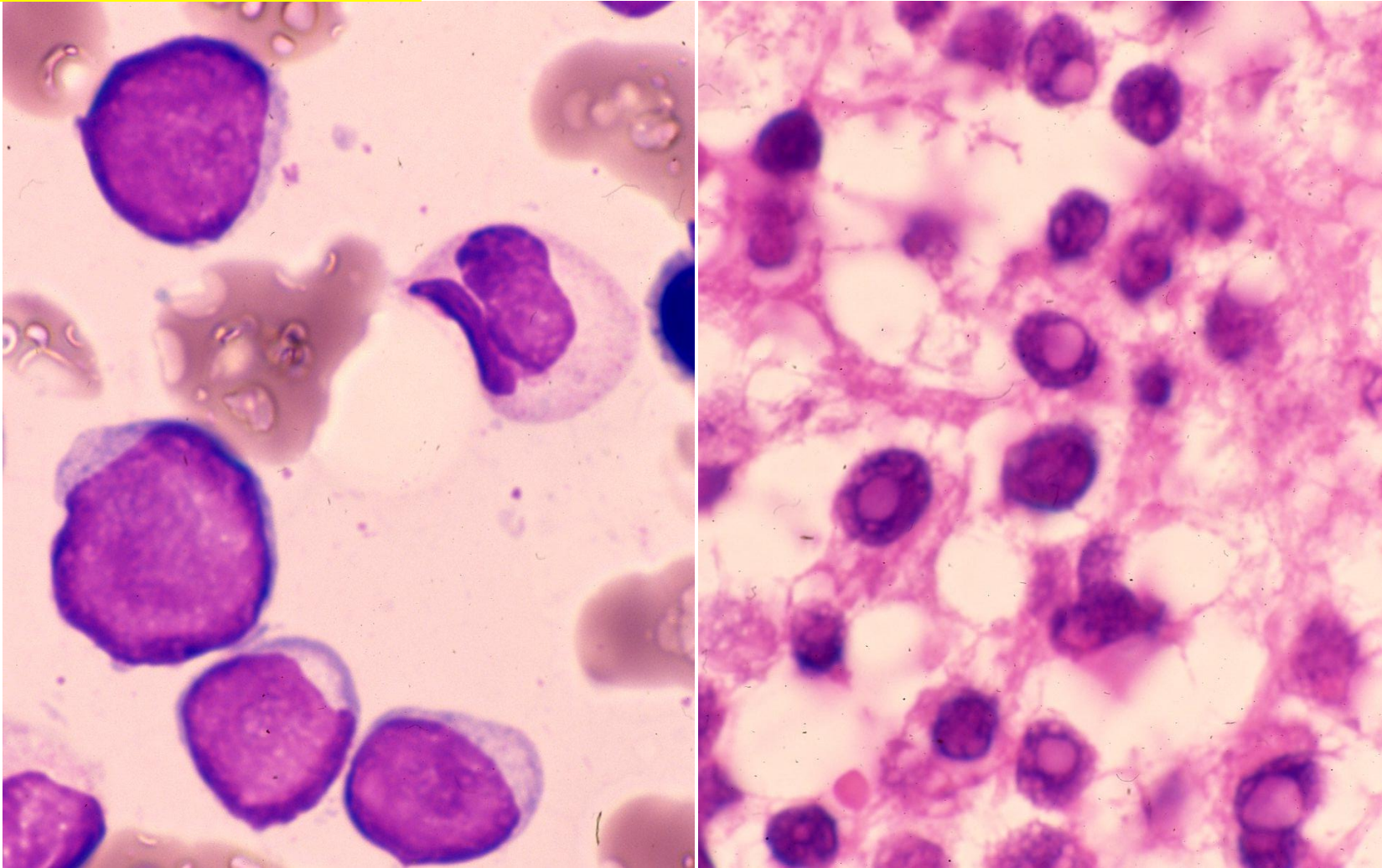
Ultrastructure of **multiple myeloma, kappa-light chain type**, seen in an 85 y-o male patient (b). The neoplastic plasma cells growing the bone marrow are filled with needle-like and cuboidal/pentagonal-shaped crystalline inclusion bodies.

MALT lymphoma with plasmacytic differentiation



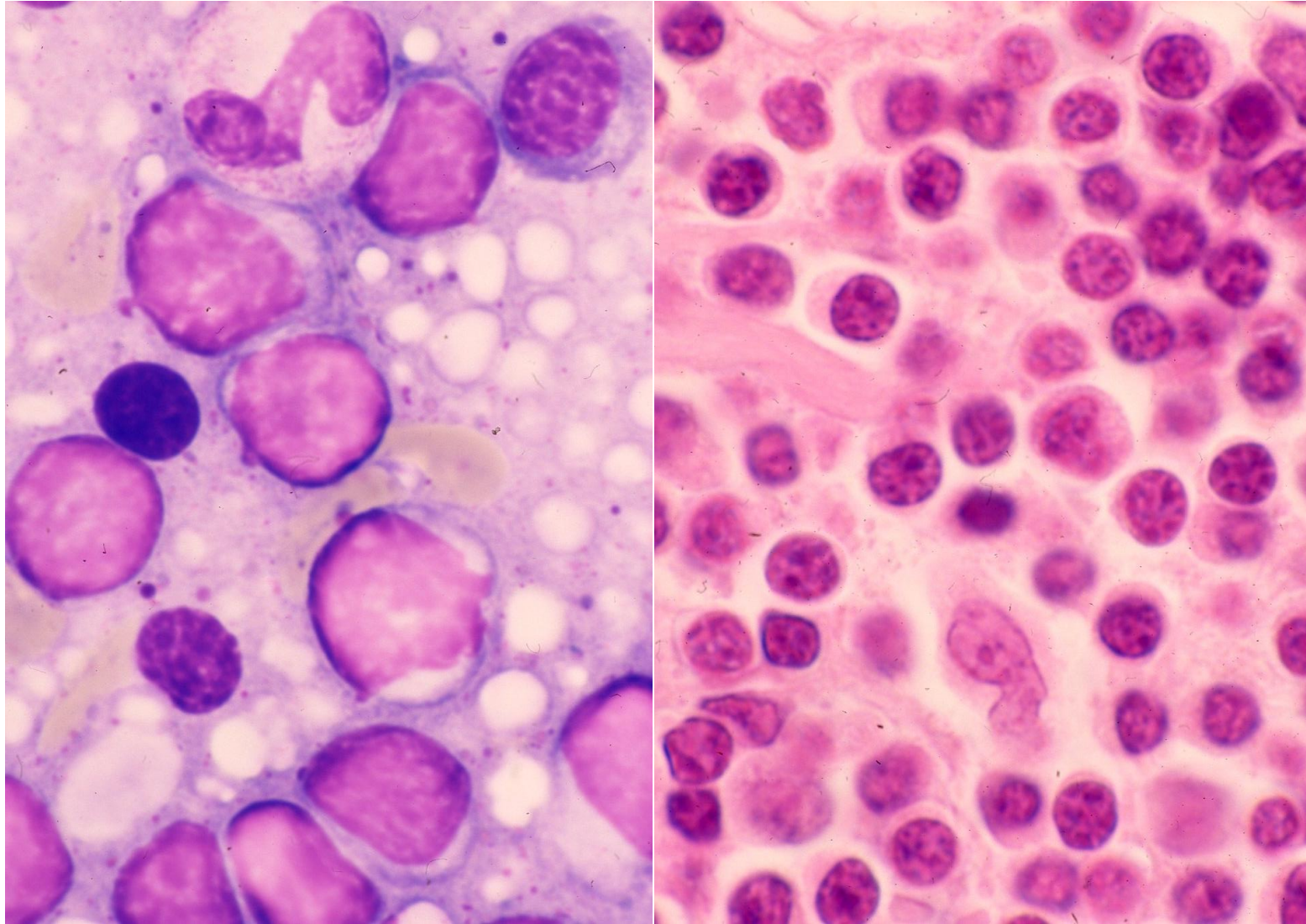
Ultrastructure of **MALT lymphoma of the stomach with plasmacytic differentiation**, seen in a male patient aged 60's. Electron-dense crystalline inclusions are formed in the cisterna of rER, suggesting the secretory disturbance.

Waldenström's macroglobulinemia



Waldenström's macroglobulinemia seen in a 50 y-o male patient (bone marrow aspiration, left: May-Giemsa, right: H&E). Lymphoplasmacytoid features are characteristic of Waldenström's macroglobulinemia. **Dutcher bodies** (intranuclear cytoplasmic inclusions) are observed in H&E preparation. Punched out bone lesions are not seen clinically. Elevation of monoclonal IgM in the serum are common between IgM myeloma and Waldenström's macroglobulinemia.

Waldenström's macroglobulinemia



Waldenström's macroglobulinemia seen in a 50 y-o male patient (lymph node biopsy, left: stamp, May-Giemsa, right: H&E). The lymph nodal lesion of Waldenström's macroglobulinemia represents lymphoplasmacytic lymphoma. Punched out bone lesions are not seen clinically. Elevation of monoclonal IgM in the serum are common between IgM myeloma and Waldenström's macroglobulinemia.

Two types of lymphoplasmaeytic lymphoproliferative lesions

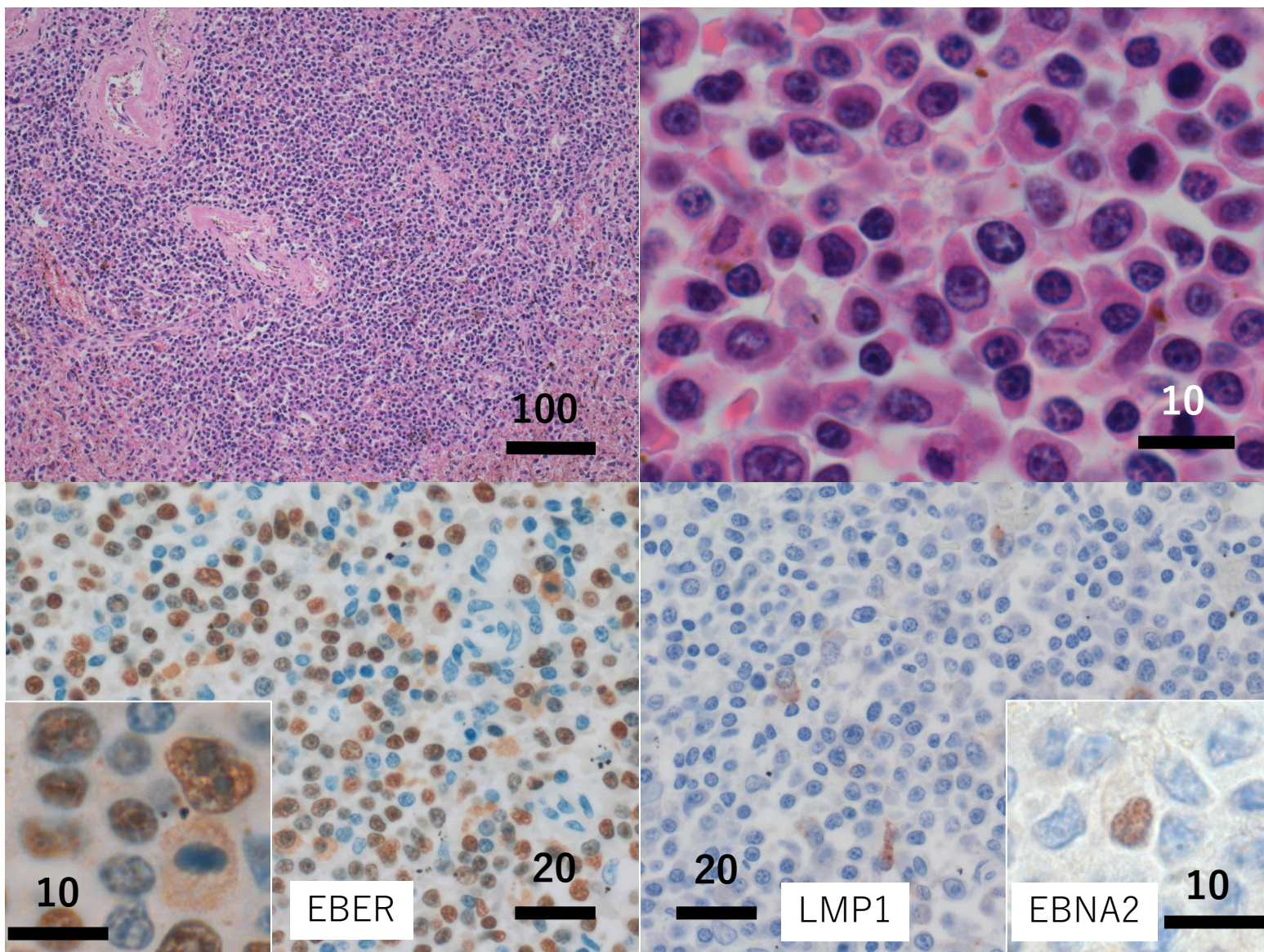
1) Low-proliferative type

Lymphoplasmaeytic lymphoma or Waldenström's macroglobulinemia is a low-grade B-cell malignancy with elevated monoclonal IgM in the serum. Proliferative activity is low, and EBV infection is not observed.

2) High-proliferative type

The following lymphoproliferative lesions show highly proliferative lymphoplasmaeytic cells induced by EBV infection. Clonality of immunoglobulin is not proven.

- a) Polyclonal lymphoplasmaeytic growth after the repeated use of anti-thymocyte globulin
- b) Lymphomatoid granulomatosis involving the skin, lung and brain
- c) EBV-positive mucocutaneous ulcer of plasmablastic type

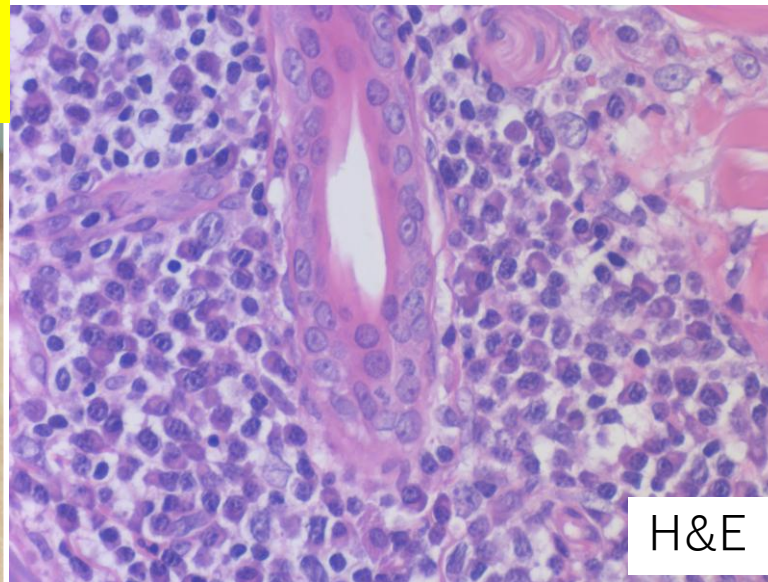


EBV-related lymphoproliferation with lymphoplasmacytoid features

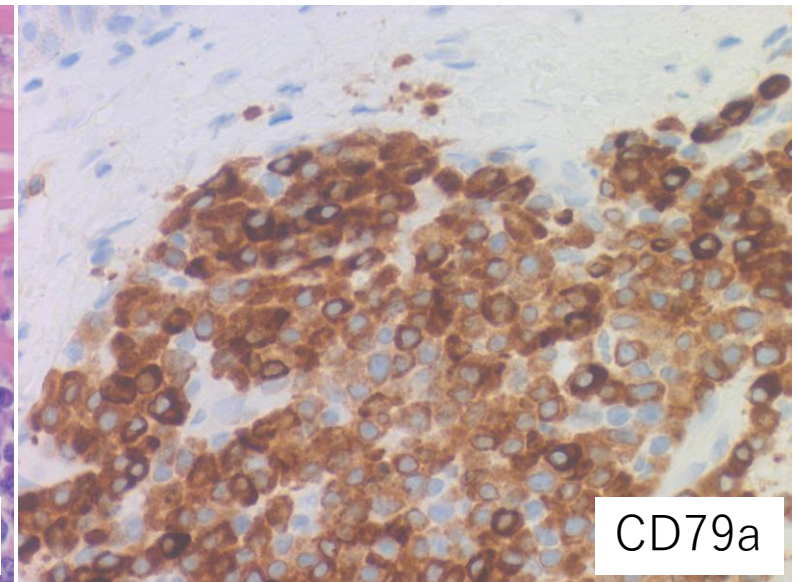
Ref.: Okada E, et al. Epstein-Barr virus-induced polyclonal lymphoproliferative disorder of lymphoplasmacytic type in an autopsy case of aplastic anemia treated twice with anti-thymocyte globulin therapy. Pathol Int 2015; 65(5): 274-276. doi: 10.1111/pin.12258

Polyclonal lymphoproliferative disorder of lymphoplasmacytic type of the spleen in an autopsy case of aplastic anemia treated with anti-thymocyte globulin therapy twice. Top: H&E, bottom: EBER and LMP1. The white pulp is replaced by lymphoplasmacytic cells. Some proliferative cells accompany enlarged nuclei with prominent nucleoli with mitotic activity. Most of the lymphoplasmacytic cells express EBER1 in the nuclei, including the cells with enlarged nuclei and mitotic cells. LMP1 is expressed along the plasma membrane and in the cytoplasm of some proliferating cells, and EBNA2 expression in the nuclei is focally observed.

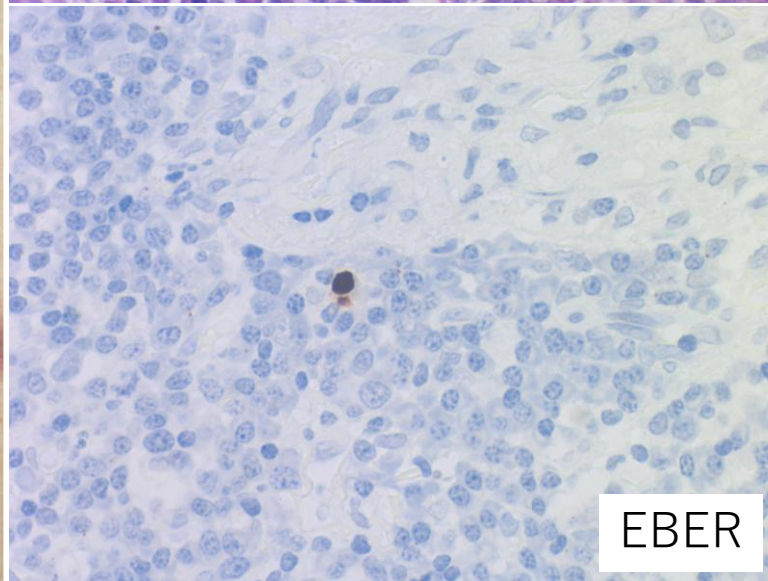
EBV-related lymphoproliferation with lymphoplasmacytoid features



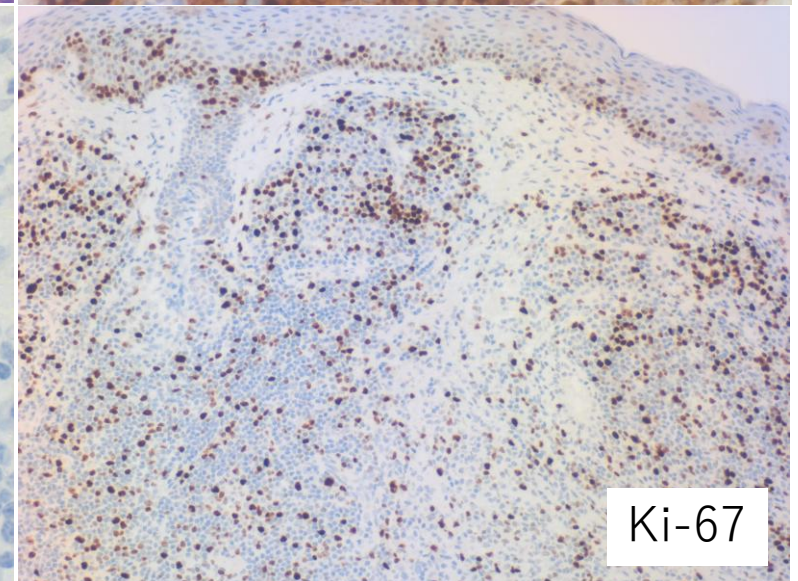
H&E



CD79a



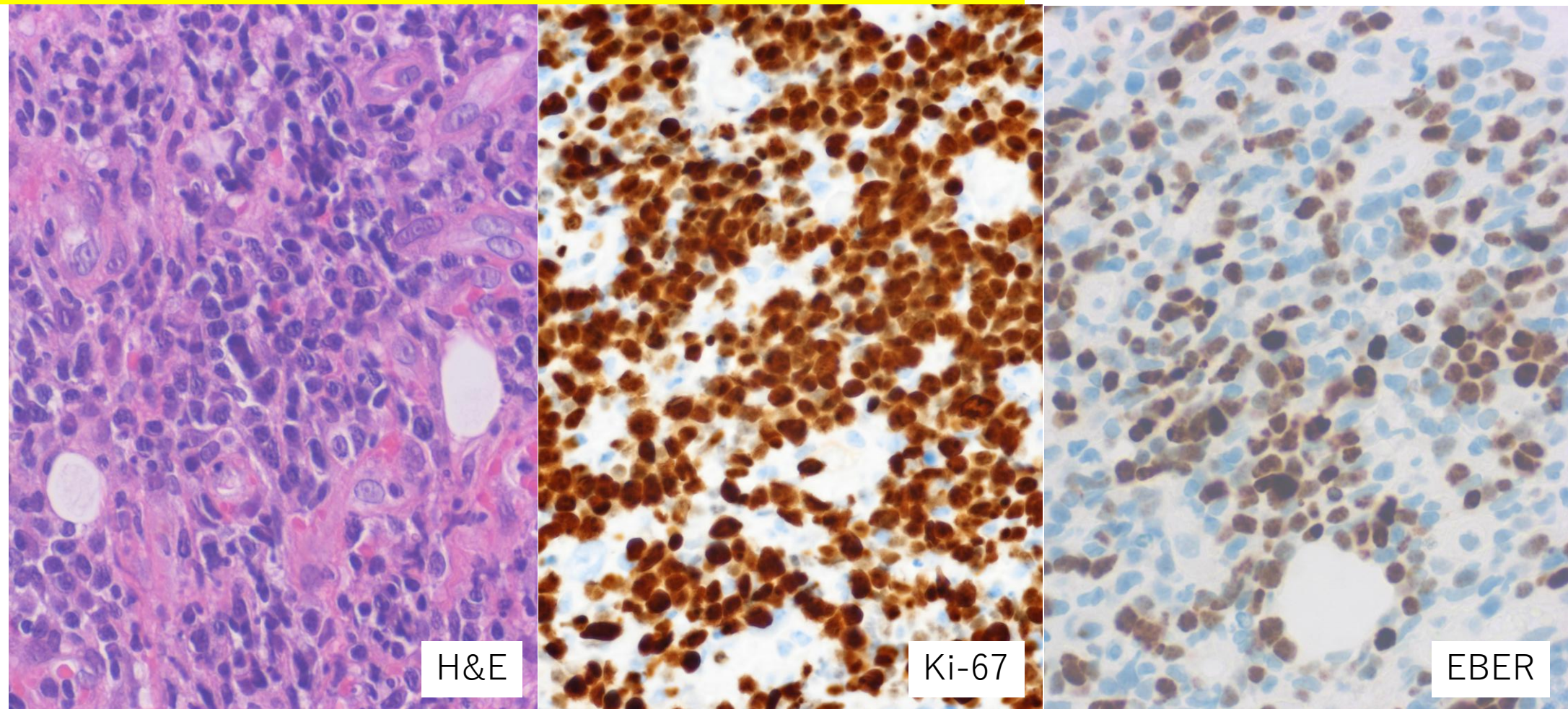
EBER



Ki-67

Lymphomatoid granulomatosis of the back skin of an 80 y-o male patient. The infiltrative skin lesion microscopically shows proliferation of lymphoplasmacytoid cells expressing CD79a and CD138. A few nuclei are labeled for EBER. The lymphoma cells are moderately proliferative (Ki-67 labeling). Nodular lesions are also seen in the lung and brain. **Ref.:** Saito Y, et al. Central nervous system lymphomatoid granulomatosis with polyclonal plasmacytoid cell proliferation: a case report and review of the literature. *Interdiscip Neurosurg* 2020; 22: 100840. doi: 10.1016/j.inat.2020.100840

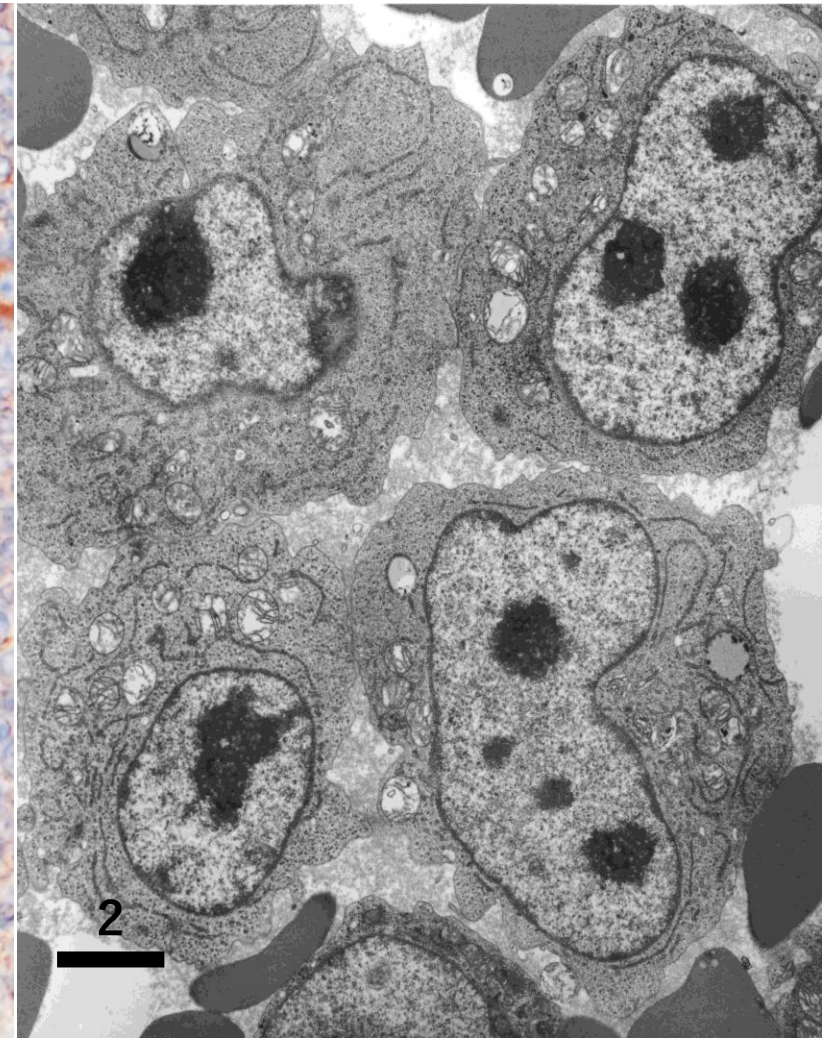
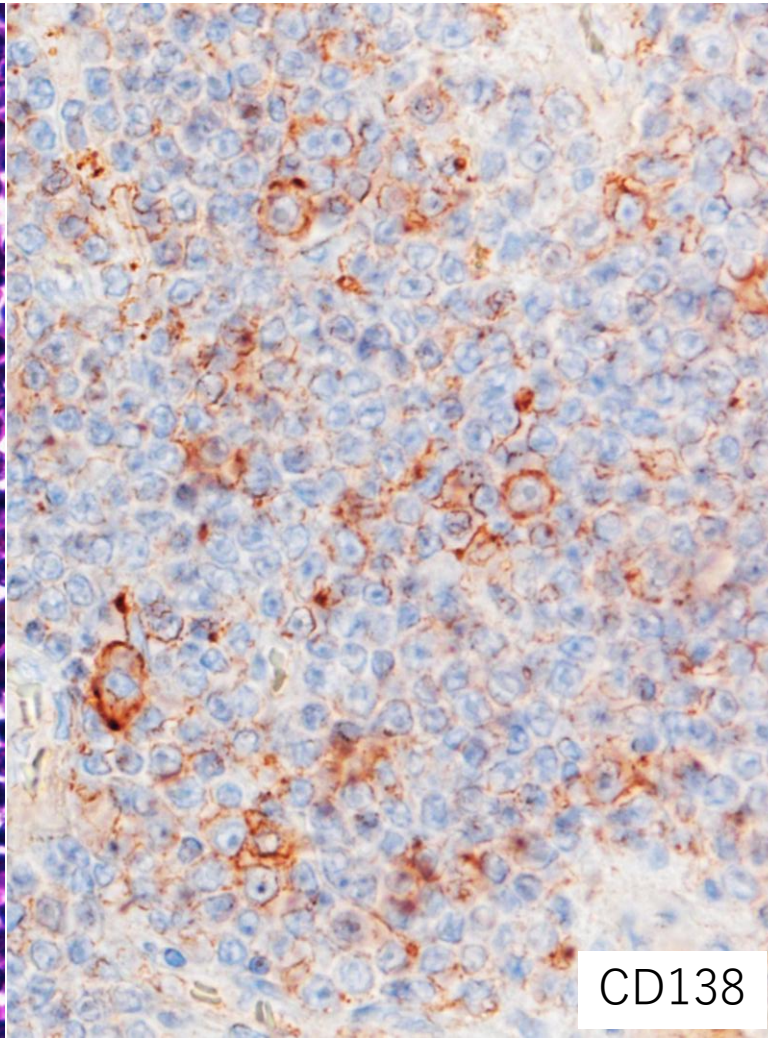
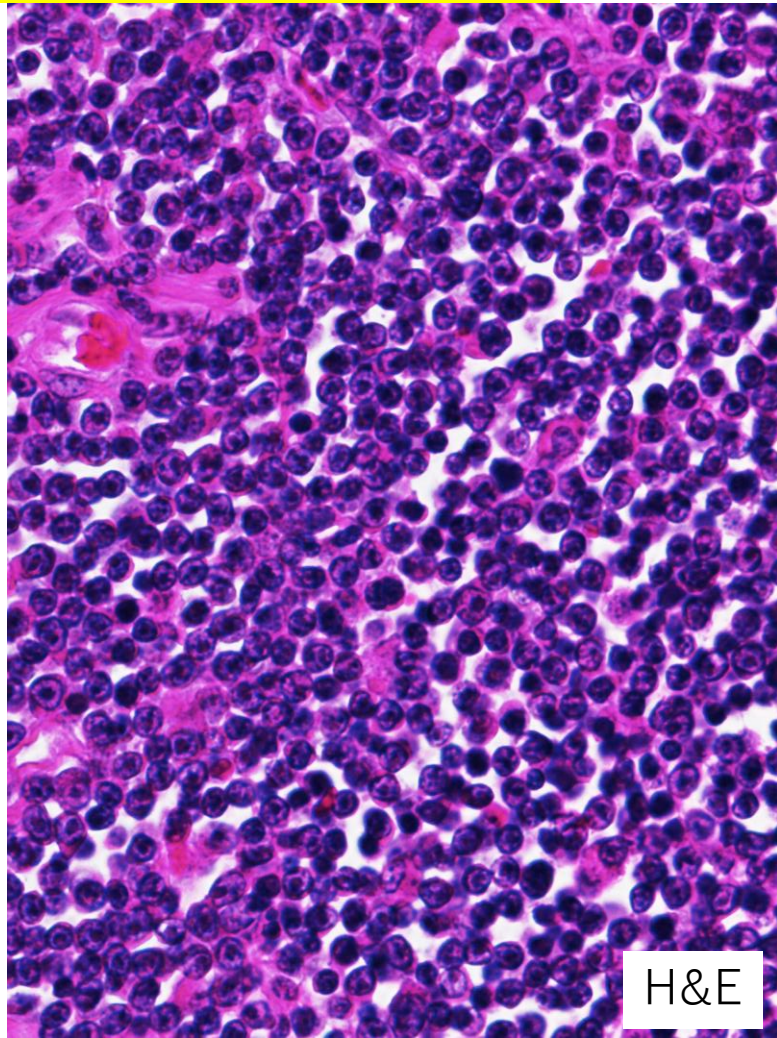
EBV-related lymphoproliferation with lymphoplasmacytoid features



EBV-positive mucocutaneous ulcer seen in the leg skin of an HIV-negative 86 y-o female patient (left: H&E, center: Ki-67, right: EBER). Subcutaneous infiltration of plasmablastic cells show extremely high Ki-67 labeling index and diffuse infection of EBV in the nuclei (EBER-positive). The microscopic features are indistinguishable from plasmablastic lymphoma, but the lesion was spontaneously regressed after cessation of steroid administration.

Ref.: Tsutsumi Y, et al. Epstein-Barr virus-positive mucocutaneous ulcer, plasmablastic type, associated with nodal CD4+ angioimmunoblastic T-cell lymphoma and generalised pruritus: a self-limiting lymphoproliferative disorder resembling cutaneous plasmablastic lymphoma. *BMJ Case Rep* 2022; 15(5): e247430. doi: 10.1136/bcr-2021-247430

Plasmablastic lymphoma



Plasmablastic lymphoma of the pleura seen in an HIV-negative 84 y-o male patient (left: H&E, center: CD138, right: EM). The monomorphous plasmablasts are highly proliferative and EBER-positive. CD138 is expressed. Ultrastructurally, prominent nucleoli and mildly developed rough endoplasmic reticula are characteristic. This type of lymphoma, often seen in AIDS patients, shows a very poor prognosis. **Ref.:** Ramirez-Gamero A, et al. Plasmablastic lymphoma: 2024 update on diagnosis, risk stratification, and management. Am J Hematol 2024; 99(8): 1586-1594. doi: 10.1002/ajh.27376