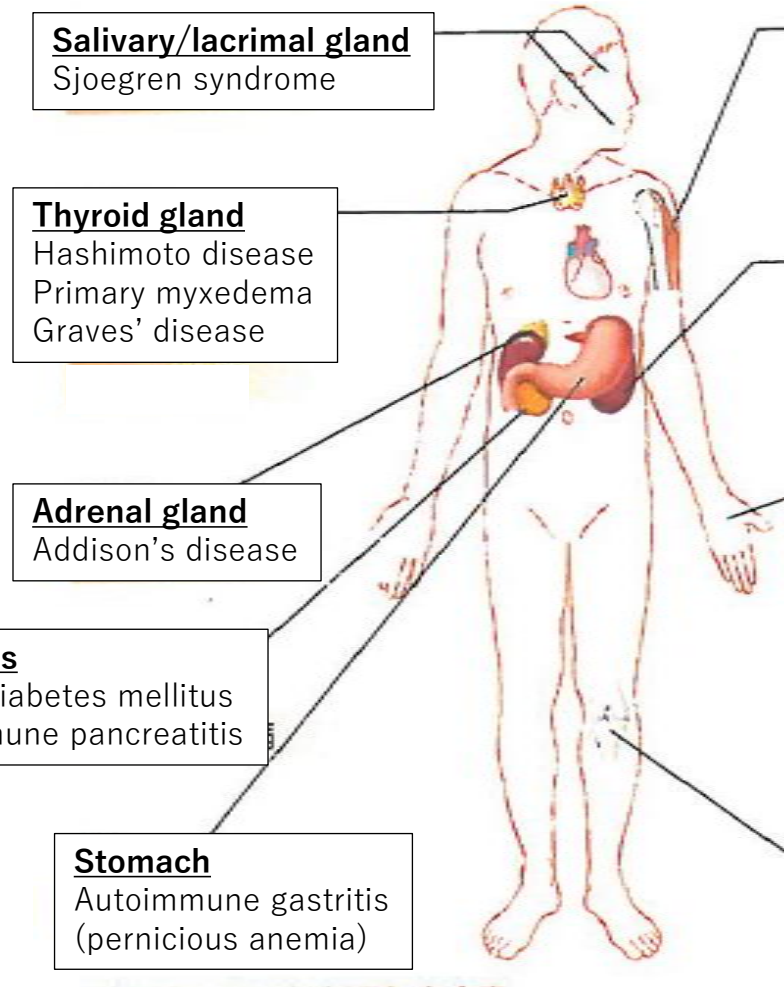
Autoimmune disorders

Autoimmune disorders, characterized by the occurrence of autoantibodies to a variety of cellular components, are categorized into organ nonspecific collagen disease and organ-specific autoimmunity. They may manifest as vasculitis syndrome of varying types. Based upon the etiology, autoimmune disorders can be divided into 5 types: type I: immediate-type hypersensitivity (anaphylaxis), type II: cell injury-type hypersensitivity, type III: immune complex-type hypersensitivity, type IV: delayed hypersensitivity and type V: anti-receptor-type hypersensitivity. Representative features of a variety of autoimmune disorders are briefly summarized herein.

Ref. Pisetsky DS. Pathogenesis of autoimmune disease. Nature Rev Nephrol 2023; 19: 509-524. doi: 10.1038/s41581-023-00720-1



Salivary/lacrimal gland
Sjoegren syndrome

Thyroid gland
Hashimoto disease
Primary myxedema
Graves' disease

Adrenal gland
Addison's disease

Pancreas
Type 1 diabetes mellitus
Autoimmune pancreatitis

Stomach
Autoimmune gastritis
(pernicious anemia)

Striated muscle
Dermatomyositis
Myasthenia gravis

Kidney
SLE
Goodpasture syndrome

Skin
SLE
Scleroderma
Pemphigus vulgaris
Bullous pemphigoid

Joint
Rheumatoid arthritis

Nervous system
Guillain-Barre syndrome
Multiple sclerosis

Vessel
Polyarteritis nodosa
Churg-Strauss syndrome
Wegener's granulomatosis

Blood
Autoimmune hemolytic anemia
Idiopathic thrombocytopenic purpura

Organ-nonspecific autoimmune disorders belong to collagen disease.
Organ-specific autoimmune disorders are clinically varied, depending on the organs involved. Sjoegren's syndrome has an aspect of organ-nonspecific disease, involving the skin and kidney. Wegener's granulomatosis especially involves the nasal cavity, lung and kidney.

Autoimmune disorders

Organ-nonspecific autoimmune disorders (collagen disease)

SLE, RA, RF, DM/PM, SSc, PN +(MCTD)

In 1942, Paul Klemperer (1887-1964) defined 6 kinds of collagen disease based upon the histopathological features.

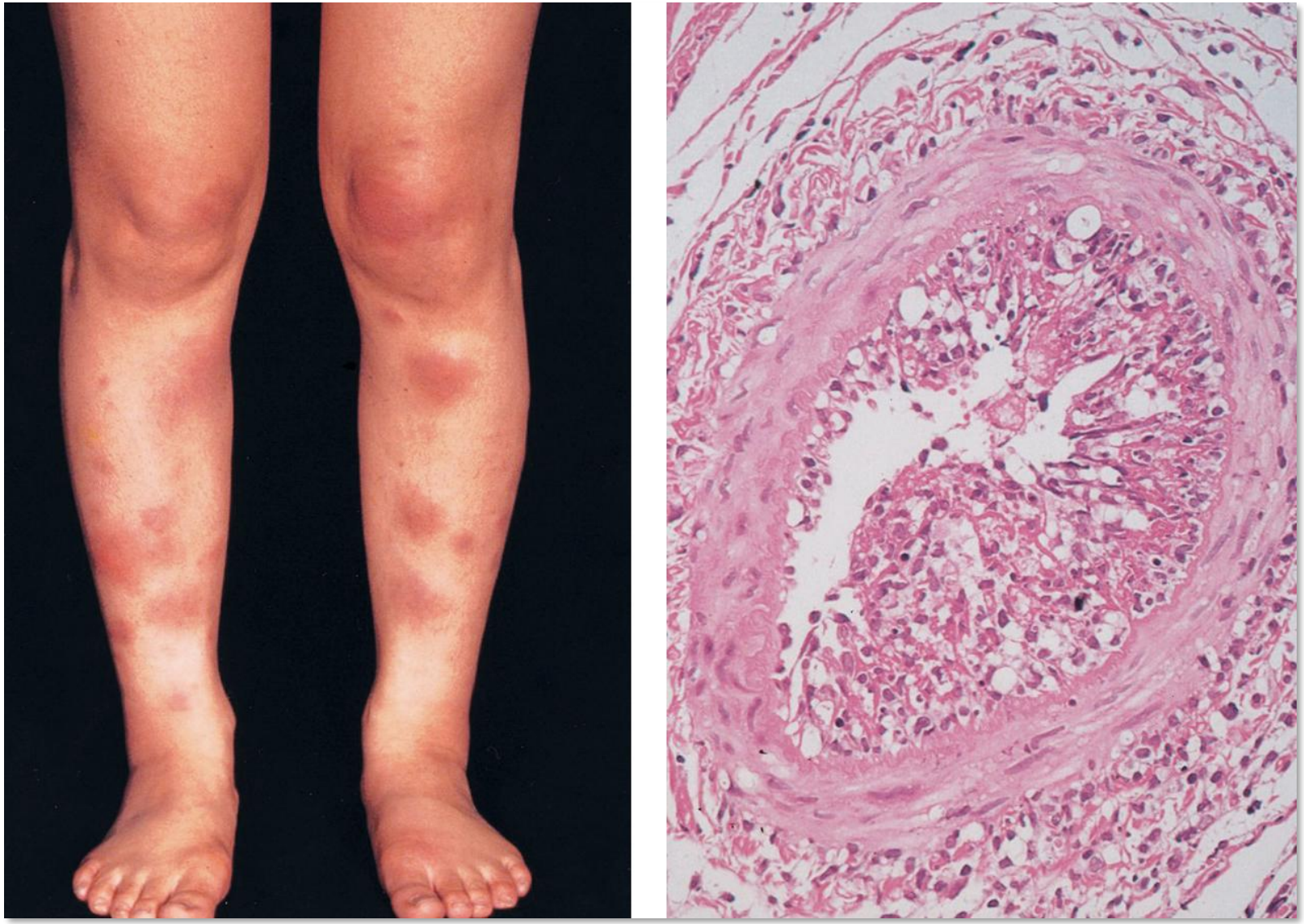
Fibrinoid necrosis of collagen fibers is the common microscopic features of collagen disease. Collagen disease is categorized in “rheumatoid diseases”.

Vasculitis syndrome

Necrotizing angiitis group
Classical polyarteritis nodosa (PN)
Microscopic polyarteritis (pANCA-positive)
Churg-Strauss syndrome (eosinophilic granulomatosis with polyangiitis) (pANCA-positive)
Wegener's granulomatosis (granulomatosis with polyangiitis) (cANCA-positive)
Hypersensitivity angiitis
Henoch-Schönlein purpura
Cryoglobulinemia
Collagen disease-associated necrotizing angiitis (SLE, DM, SSc and RA)

Other angiitis

Takayasu disease (aortitis syndrome)	aorta and pulmonary artery
Behcet disease	aorta (vascular Behcet)
Temporal arteritis	temporal artery and ophthalmic artery
Kawasaki disease	coronary artery
Bürger disease	arteries of extremities

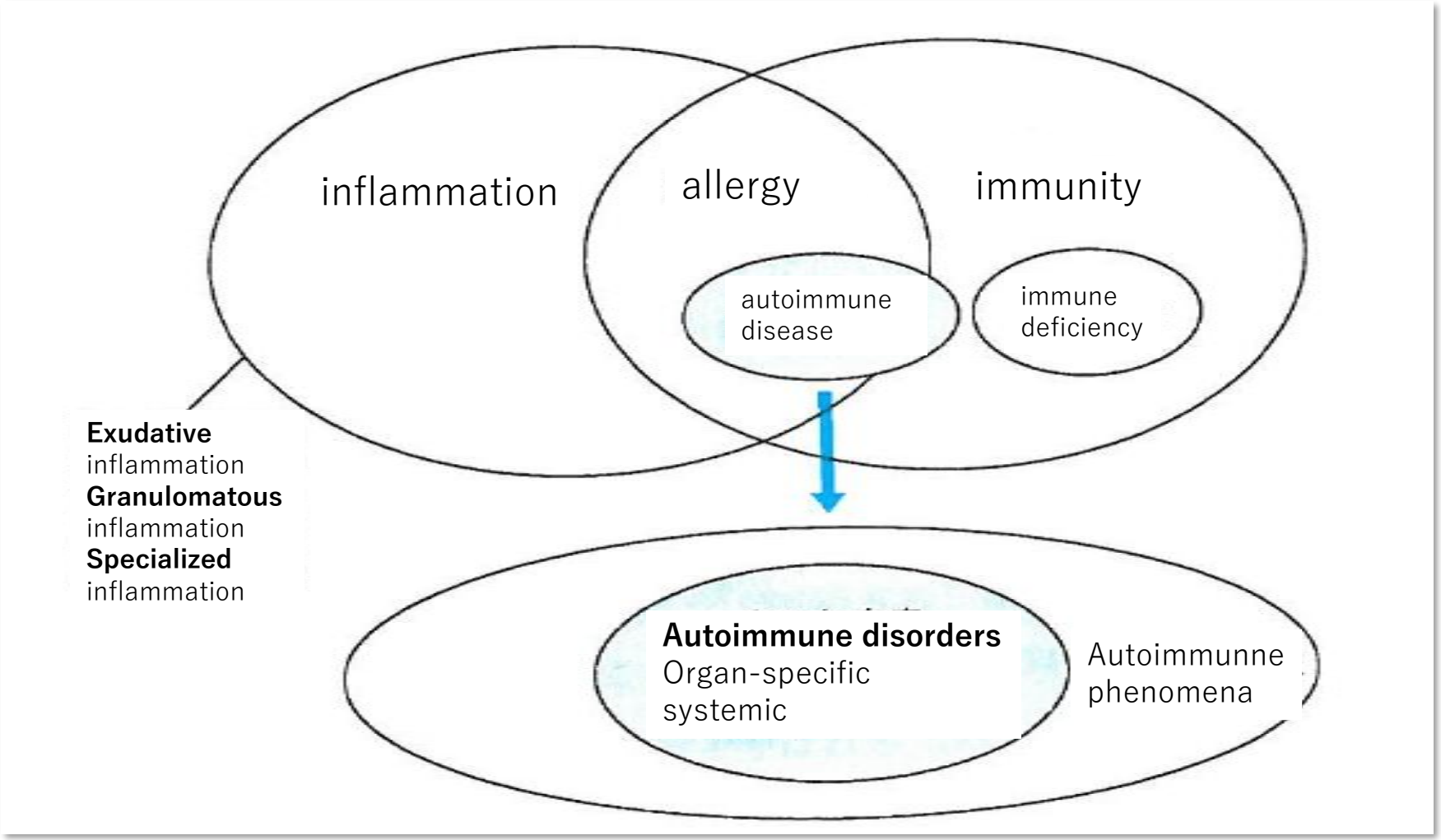


Erythema nodosum (left: gross features, right: endophlebitis, H&E)
Erythema nodosum shows cutaneous vasculitis seen in cases of SLE, sarcoidosis, tuberculosis, Behcet disease.

Organ-specific autoimmune disorders

Vogt-Koyanagi-Harada disease	retinal melanocyte
Vitiligo vulgaris	skin melanocyte
Sjögren syndrome	SS-A, SS-B
Wegener's granulomatosis	c-ANCA (PR3-ANCA)
Microscopic PN/Churg-Strauss syndrome	p-ANCA (MPO-ANCA)
Dermatomyositis	TIF1 γ, MDA5, Mi2, SRP, NXP2, Jo1, PL7, PL12, OJ
Hashimoto disease	microsome (thyroid peroxidase)
Graves disease	TSH receptor
Myasthenia gravis	acetylcholine receptor
Type A gastritis/pernicious anemia	proton pump (H^+-K^+ ATPase)
Type 1 diabetes mellitus	beta-islet cell
Goodpasture syndrome	glomerular basement membrane
Addison disease	adrenocortical cell
Primary biliary cirrhosis	mitochondria
Autoimmune (lupoid) hepatitis	smooth muscle cell
Pemphigus vulgaris	desmosome (desmoglein-3, desmocollin)
Bullous pemphigoid	hemidesmosome (collagen XVII: BP180 and plakin: BP230)
Autoimmune hemolytic anemia	red blood cell plasma membrane
Idiopathic thrombocytopenic purpura	platelet plasma membrane
Guillain-Barre syndrome	peripheral nerve myelin glycolipid (GM1)
Multiple sclerosis	central nervous system myelin glycolipid

Places of autoimmune disorders



Serum immunoglobulin was quantitated with two methods in the same patient.

Which values of serum immunoglobulin levels represent the real value?

i) Total protein in the serum 9.0 g/dL

γ-globulin on electrophoresis 30%

—— 2.7 g/dL

ii) Immunoglobulin immunoassay testing

IgG 5,100 mg/dl

IgA 200 mg/dl

IgM 100 mg/dl

—— 5.4 g/dl

Antinuclear antibody: positive x80

How to examine the antinuclear antibody?

Indirect immunofluorescent antibody (IFA) method

The serum is stepwise-doubling diluted from x20.

x20 should be regarded as negative.

(Ethanol-fixed HEp-2 culture cells used)

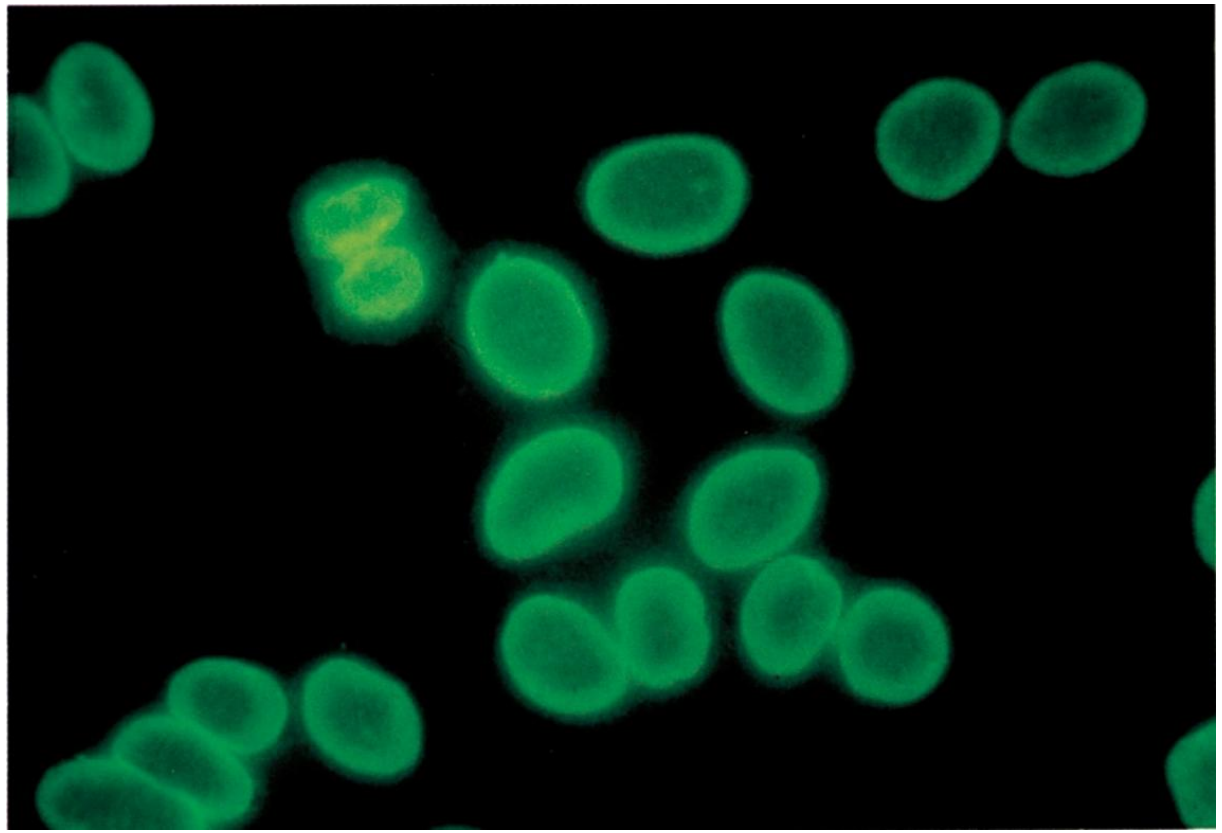
① shaggy pattern: DNA antibody

② homogeneous pattern:
DNA+histone

③ speckled pattern:
extractable nuclear antigen

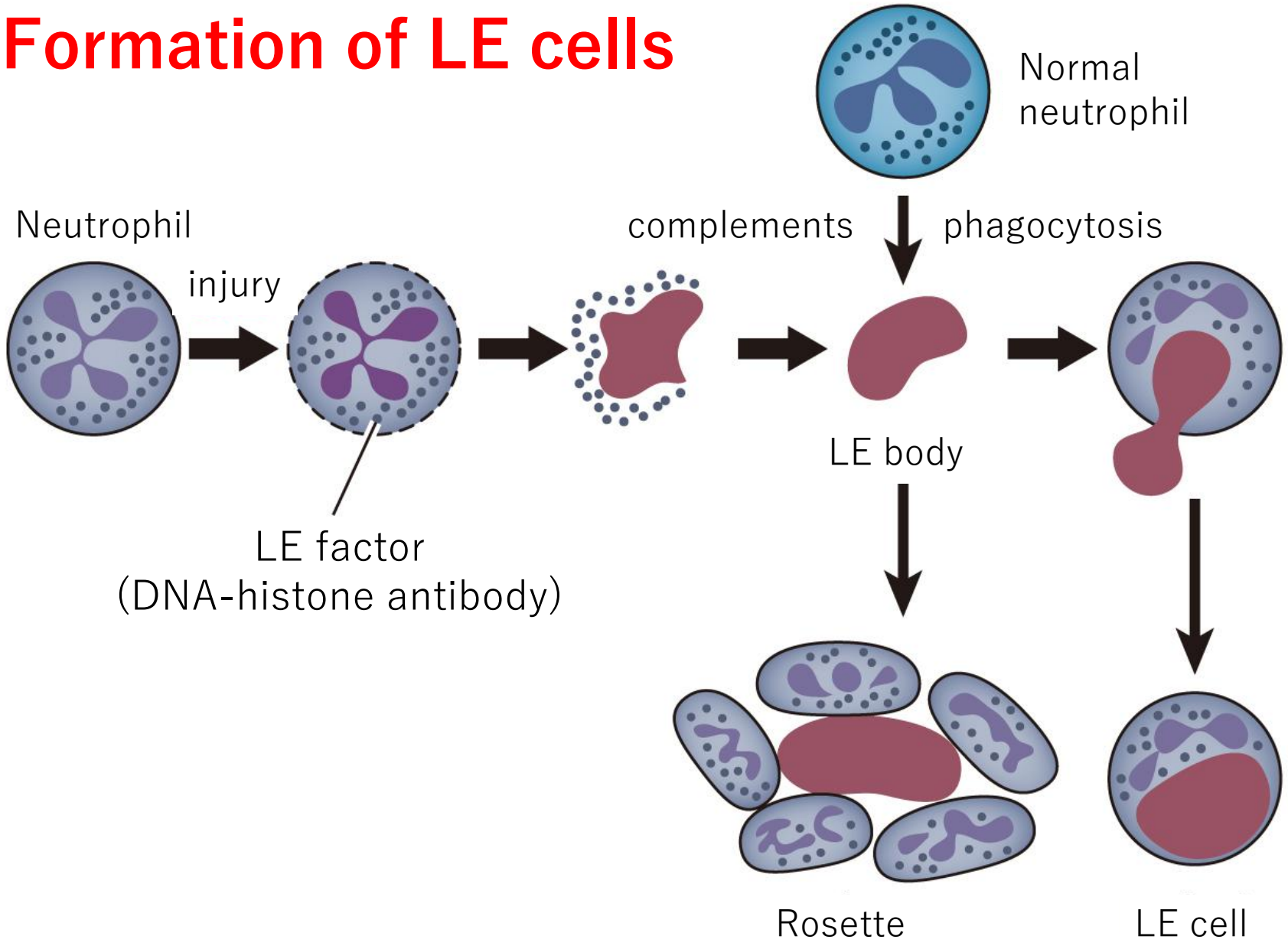
④ nucleolar pattern: nucleolus

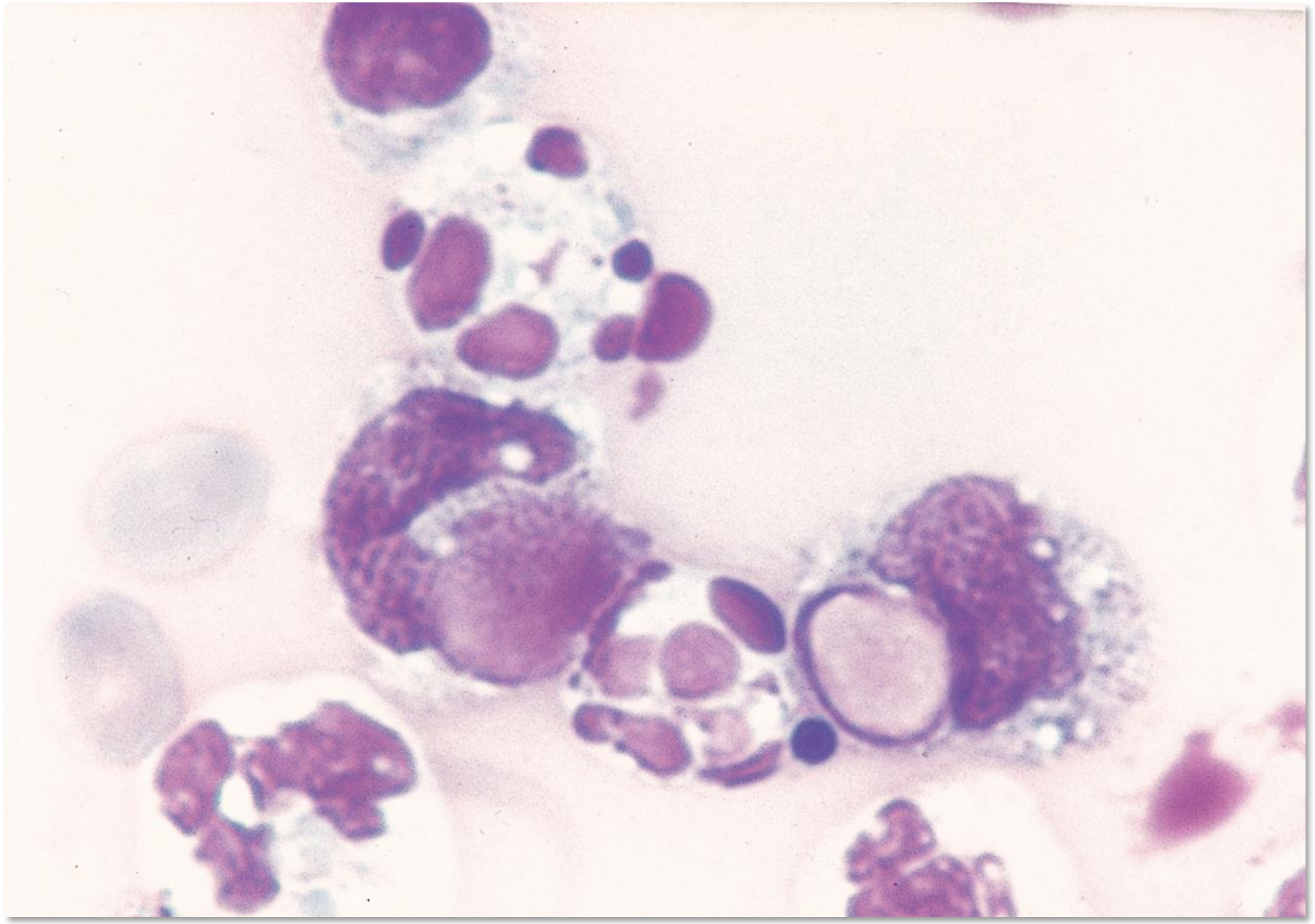
⑤ discrete speckled pattern: centromere



(shaggy pattern)

Formation of LE cells





LE cells (May-Giemsa staining)

Allergic (hypersensitivity) reaction

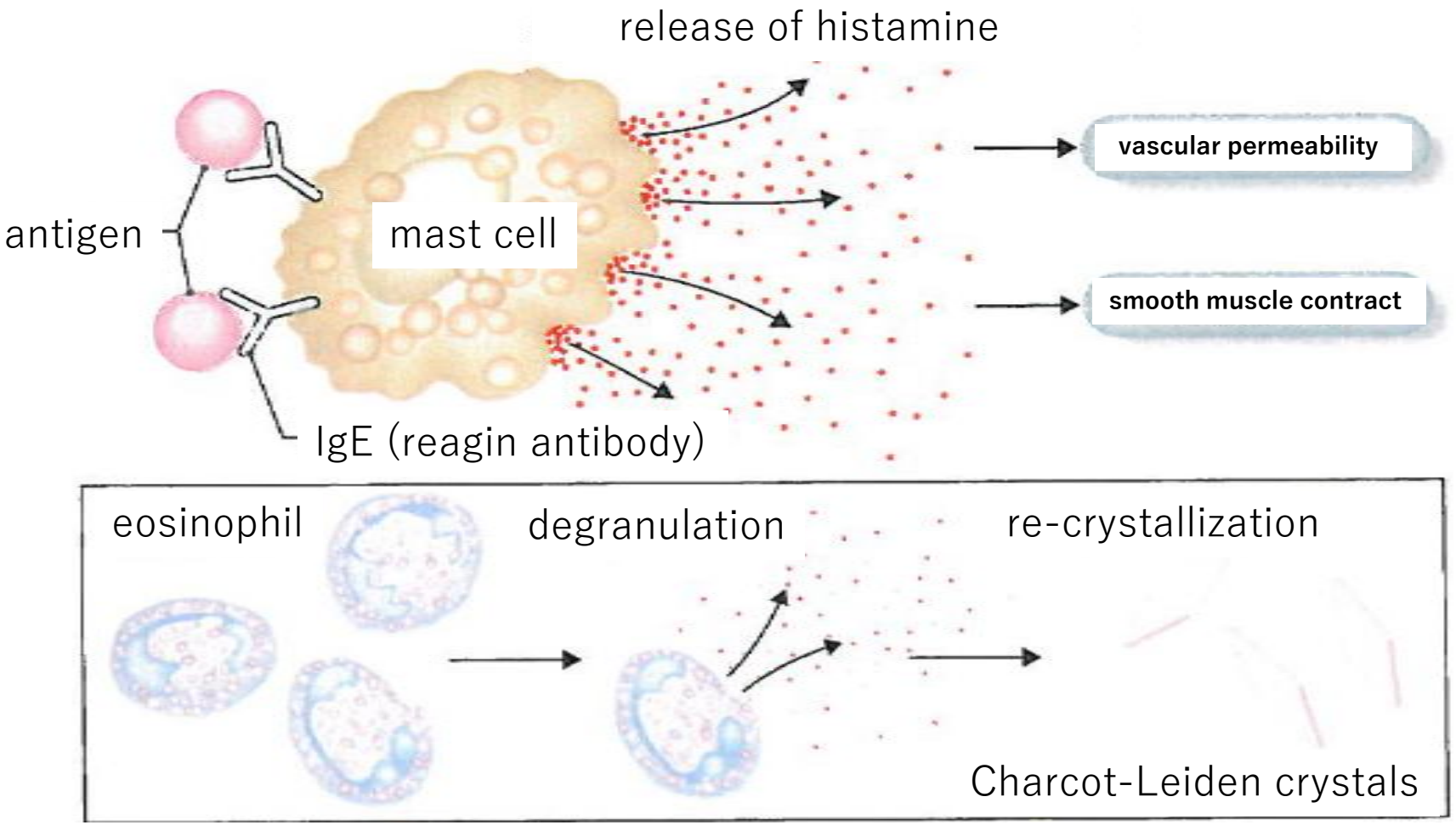
Type I: immediate-type hypersensitivity (Anaphylaxis)
mosquito bite, urticaria, bronchial asthma,
pollen allergy, soba (buckwheat noodles) allergy

Type II: cell injury-type hypersensitivity
autoimmune hemolytic anemia, pemphigus vulgaris
rheumatic fever

Type III: immune complex-type hypersensitivity
glomerulonephritis, SLE, serum sickness

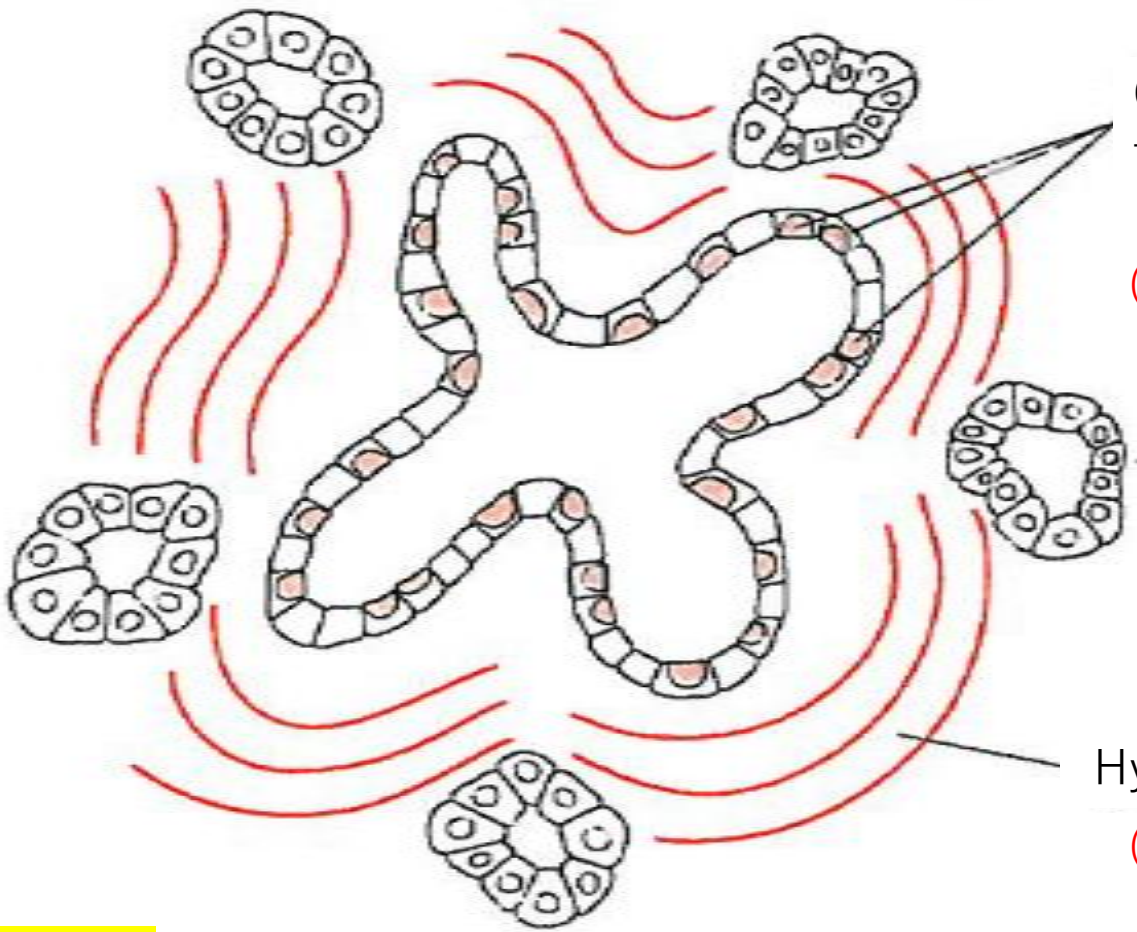
Type IV: delayed hypersensitivity
contact/atopic dermatitis, tuberculin reaction, tuberculosis

Type V: anti-receptor-type hypersensitivity
Graves' disease, myasthenia gravis



Type I hypersensitivity reaction

Schematic pathogenesis of bronchial asthma



Goblet cell metaplasia of the bronchial mucosa

(activated viscous mucin secretion)

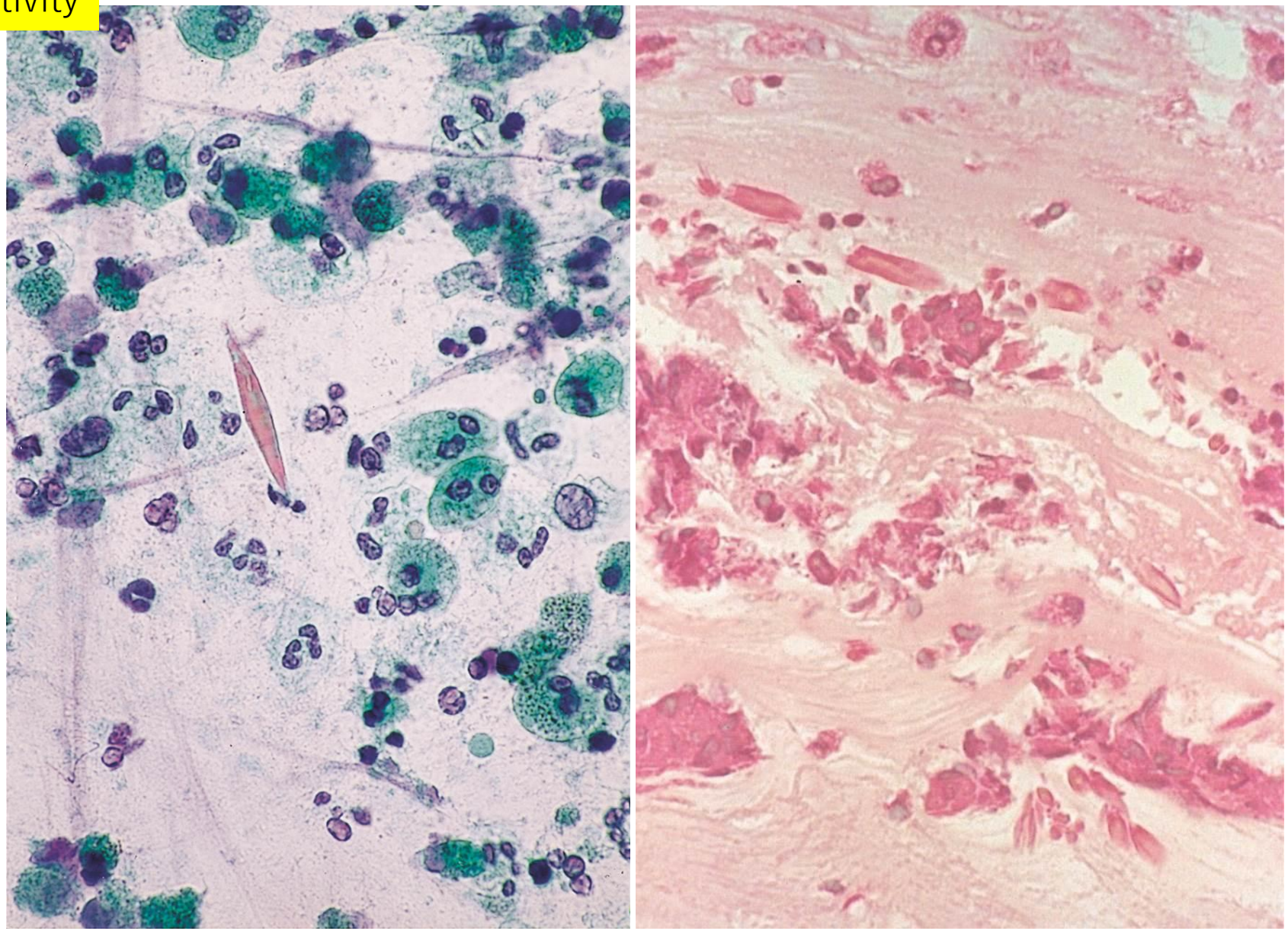
Hyperplasia of the bronchial accessory glands

Hyperplasia of smooth muscle cells

(spastic stenosis of the bronchi)

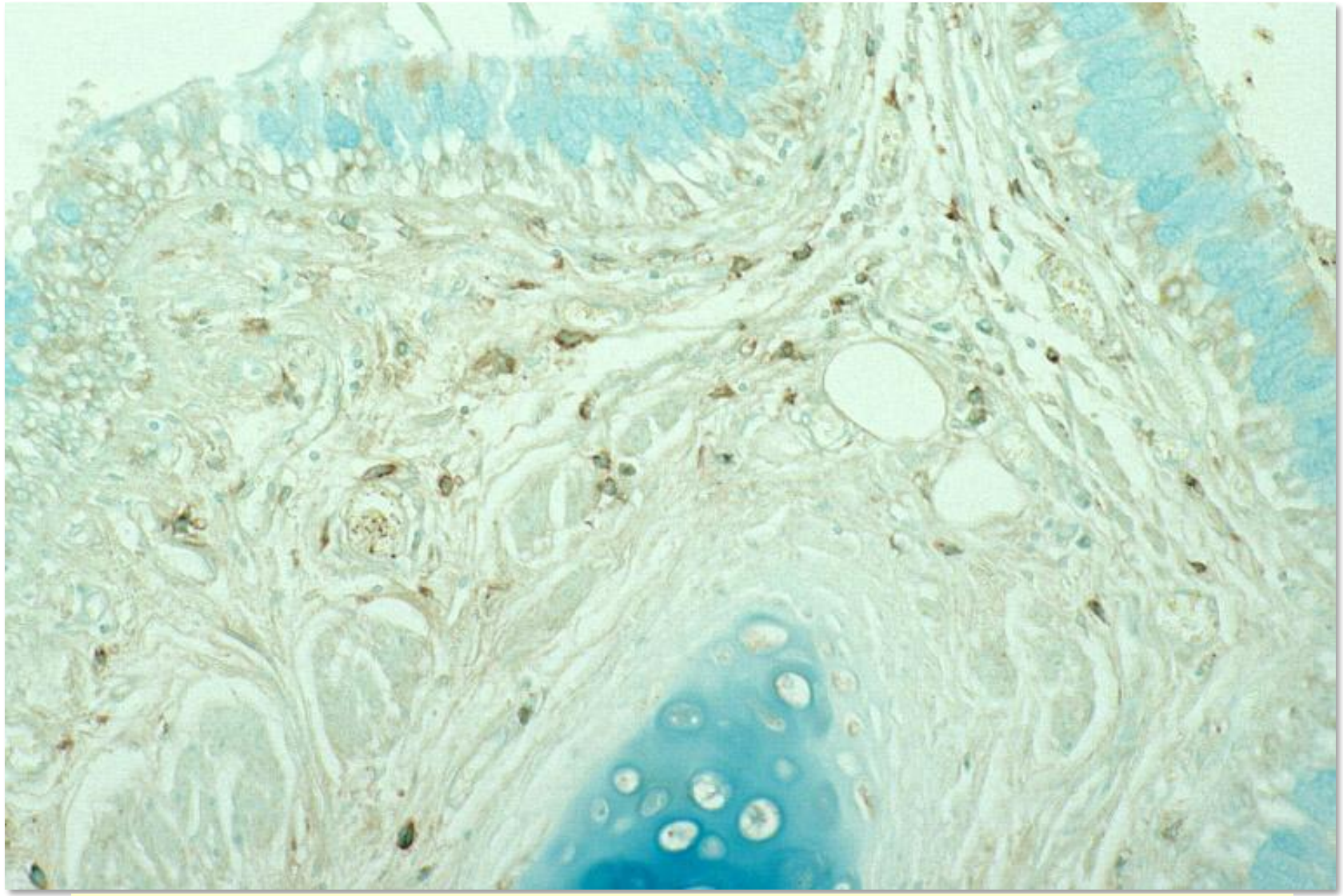
Type I hypersensitivity

Type I hypersensitivity



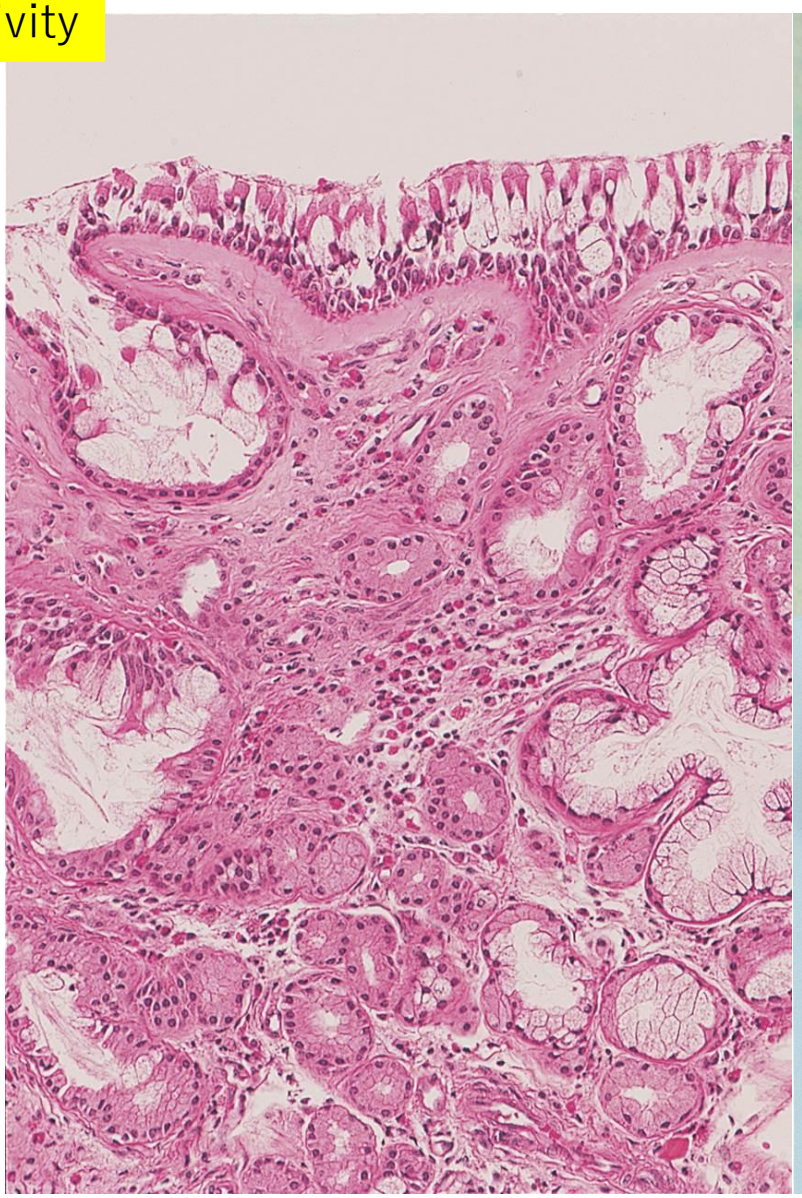
Eosinophilic infiltration and deposition of Charcot-Leiden's crystals in bronchial asthma (left: Pap, right: H&E)

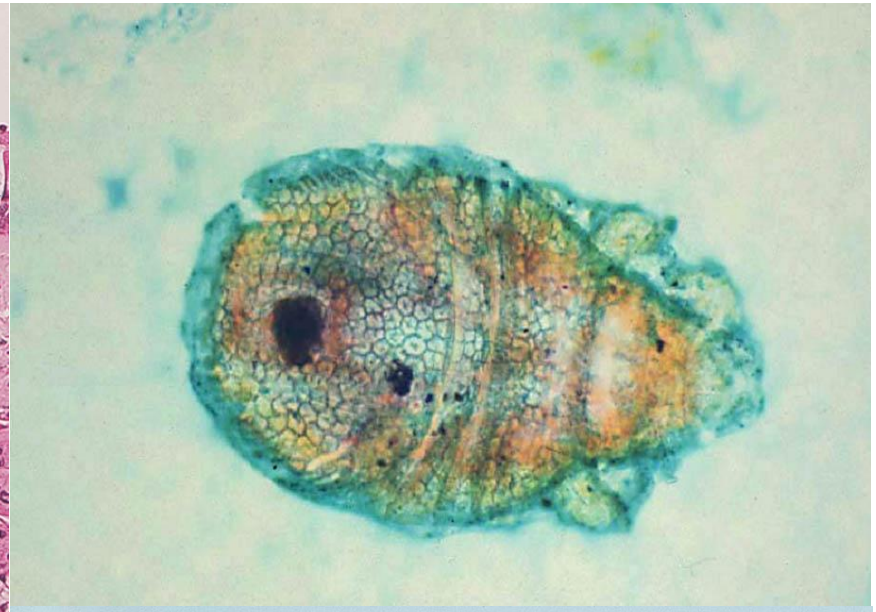
Type I hypersensitivity

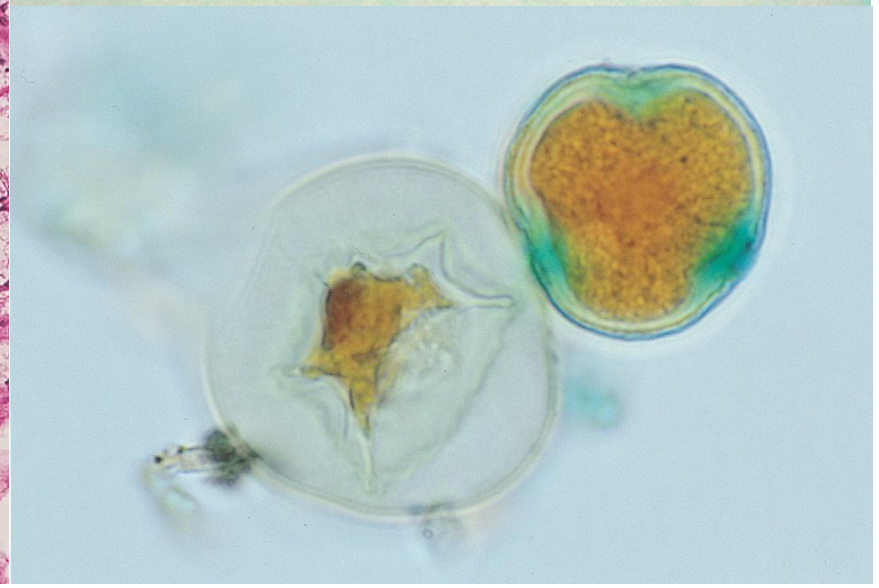


IgE-bound mast cells in the bronchial wall of a patient with bronchial asthma (immunostaining for IgE)

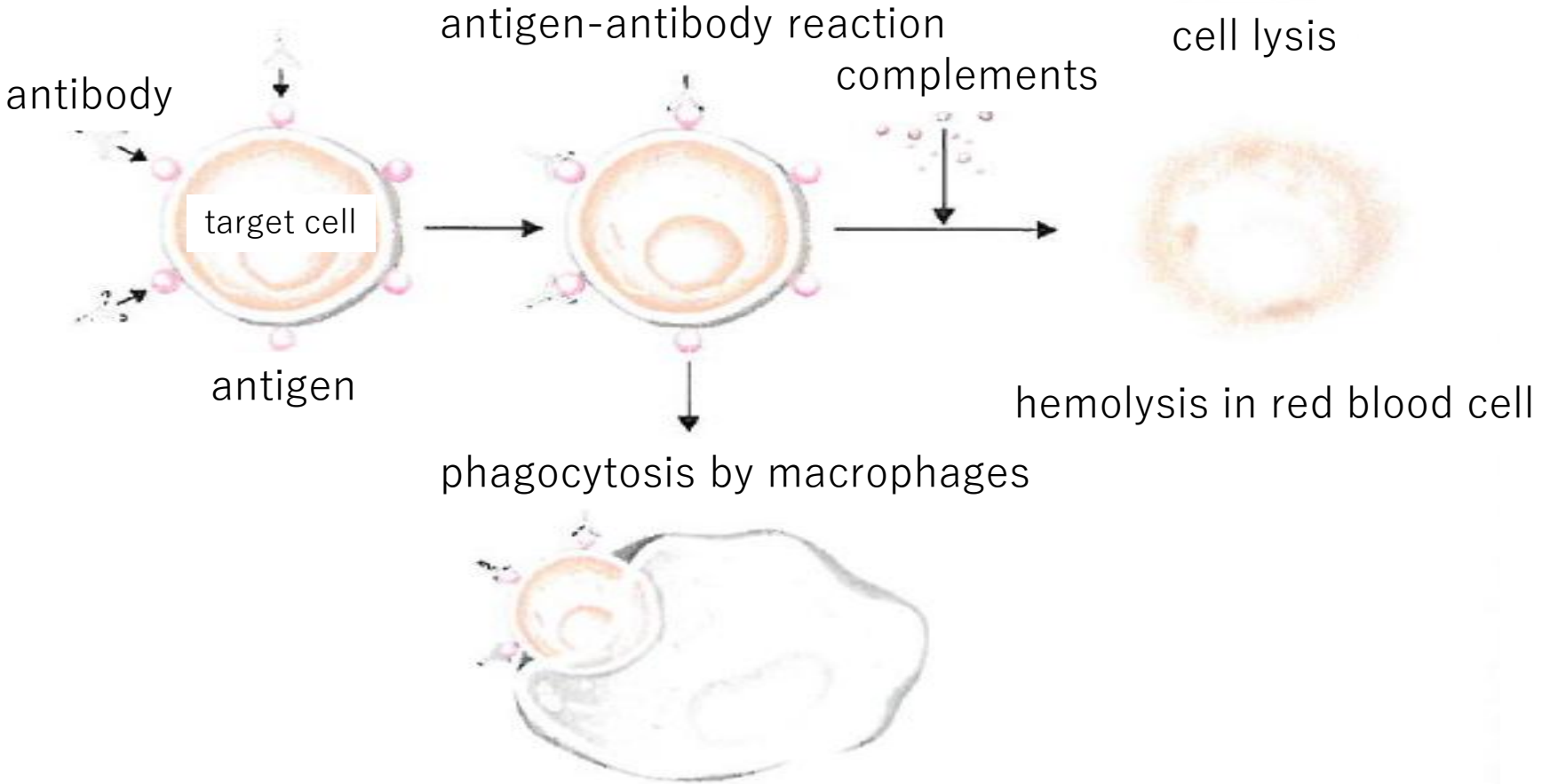
Type I hypersensitivity







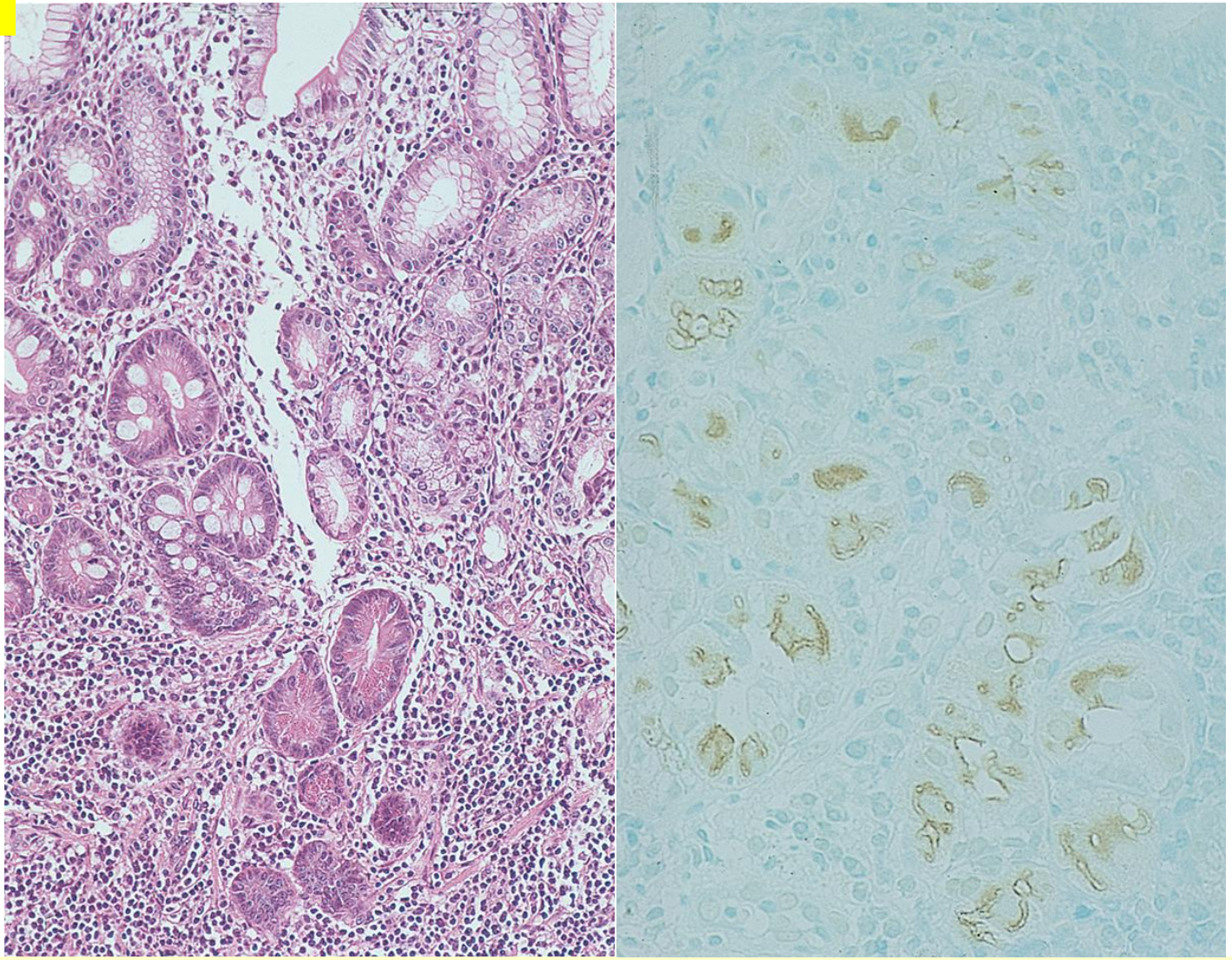
Allergic rhinitis: histology of the nasal mucosa (H&E) and causative agents (dust mite and Cedar pollen, Pap staining). The nasal mucosa reveals eosinophilic infiltration and thickening of the basement membrane.



Antibodies react with surface antigens on the target cells. Cell lysis is mediated by the complements, or the target cells are phagocytized by macrophages.

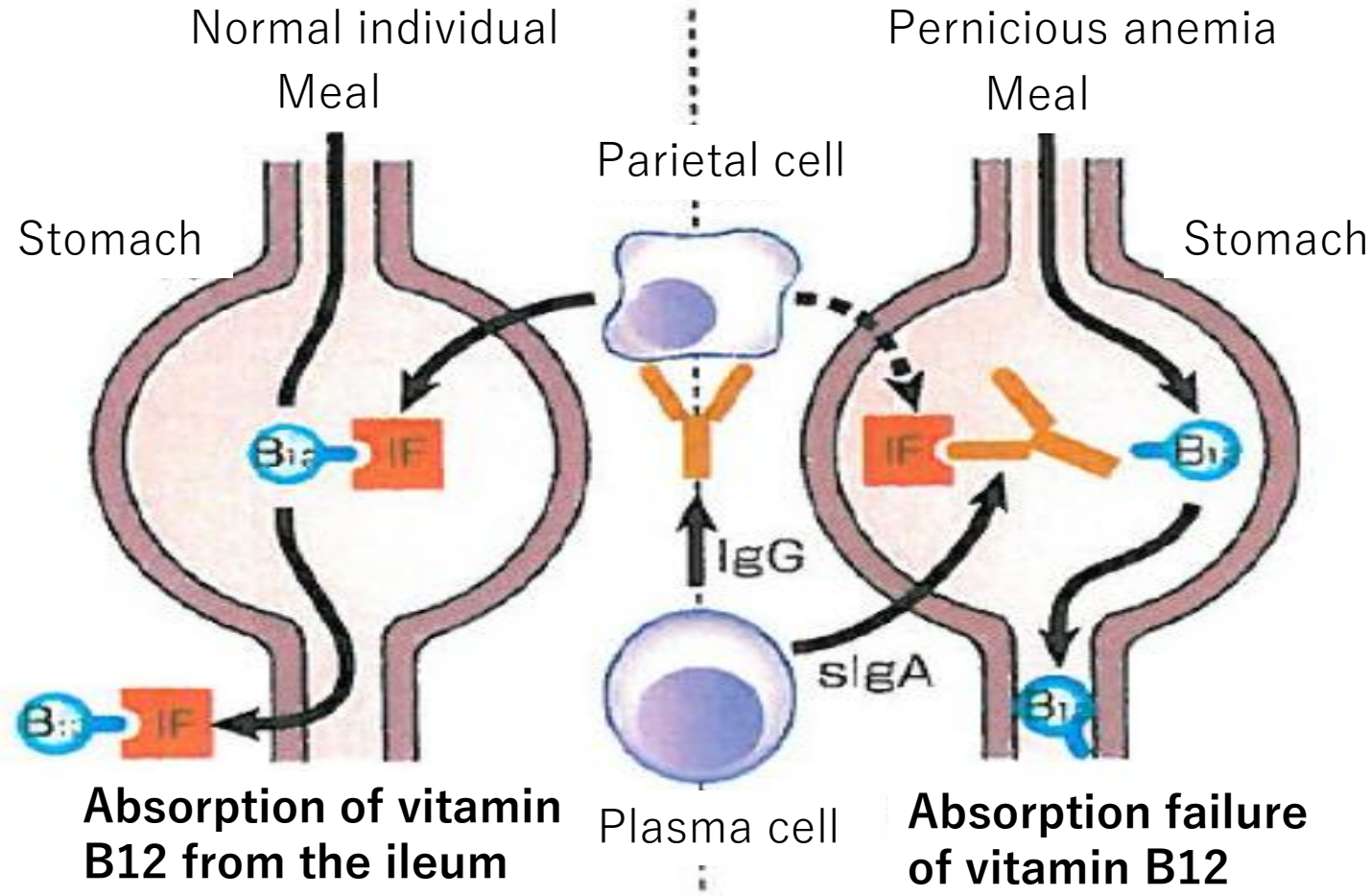
Type II hypersensitivity reaction (cell injury type)

Type II hypersensitivity



Autoimmune (type A) gastritis reveals chronic atrophic gastritis with intestinal metaplasia in the gastric body mucosa (left: H&E), and the presence of parietal cell antibody (H^+K^+ATPase antibody) can be proven by immunostaining with the diluted patient's serum (right). The intracytoplamic secretory canaliculi in normal parietal cells in paraffin sections are positively stained with the autoantibodies.

Absorption of vitamin B12 in the ileal mucosa

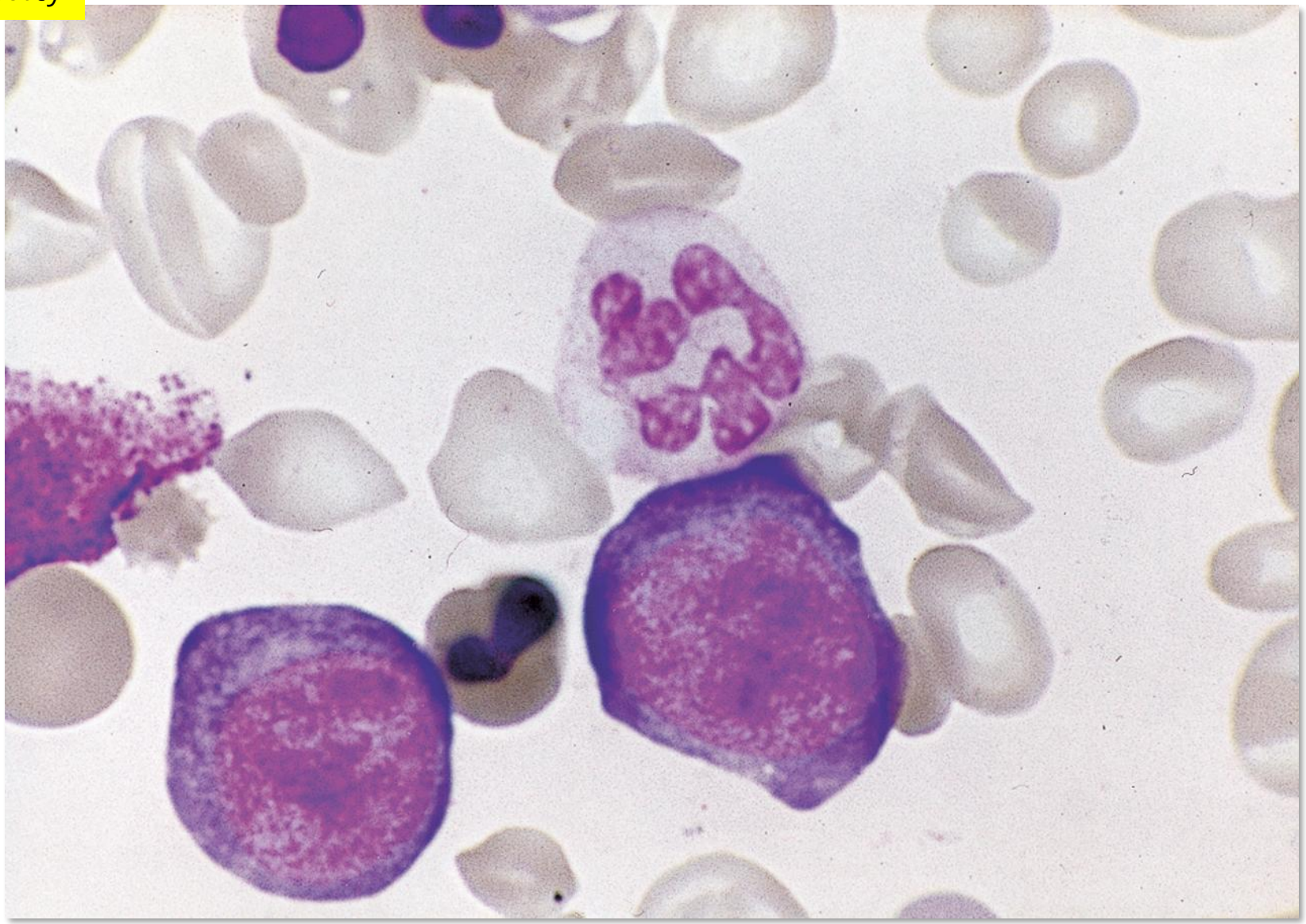


Intrinsic factor (IF) is secreted from the normal parietal cell in the oxyntic gastric mucosa. In type A gastritis, the parietal cells are destroyed by the action of IgG autoantibodies to proton pump. Secretory IgA-type autoantibody to IF inactivates secreted IF in the gut lumen.

IF: intrinsic factor

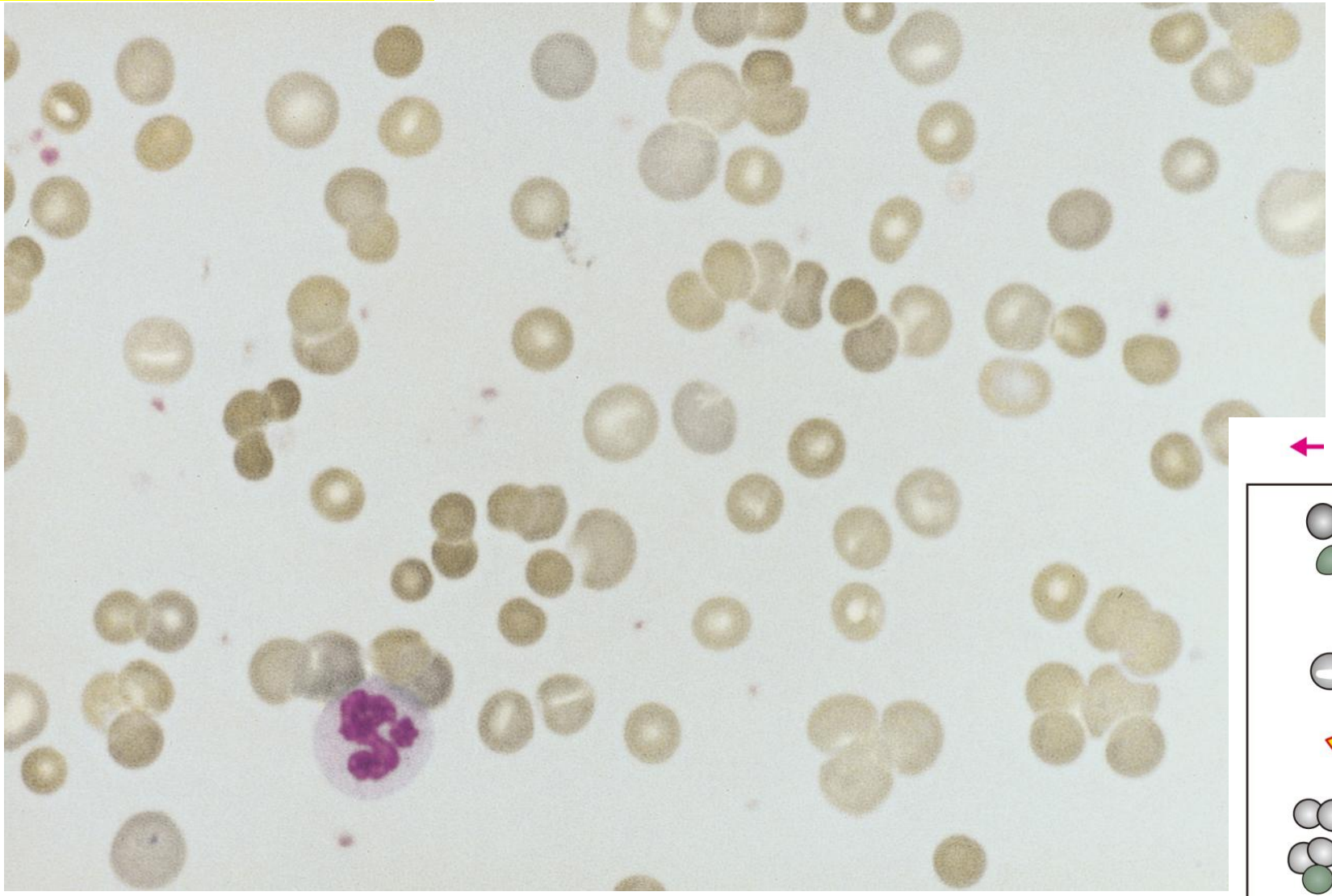
Type II hypersensitivity

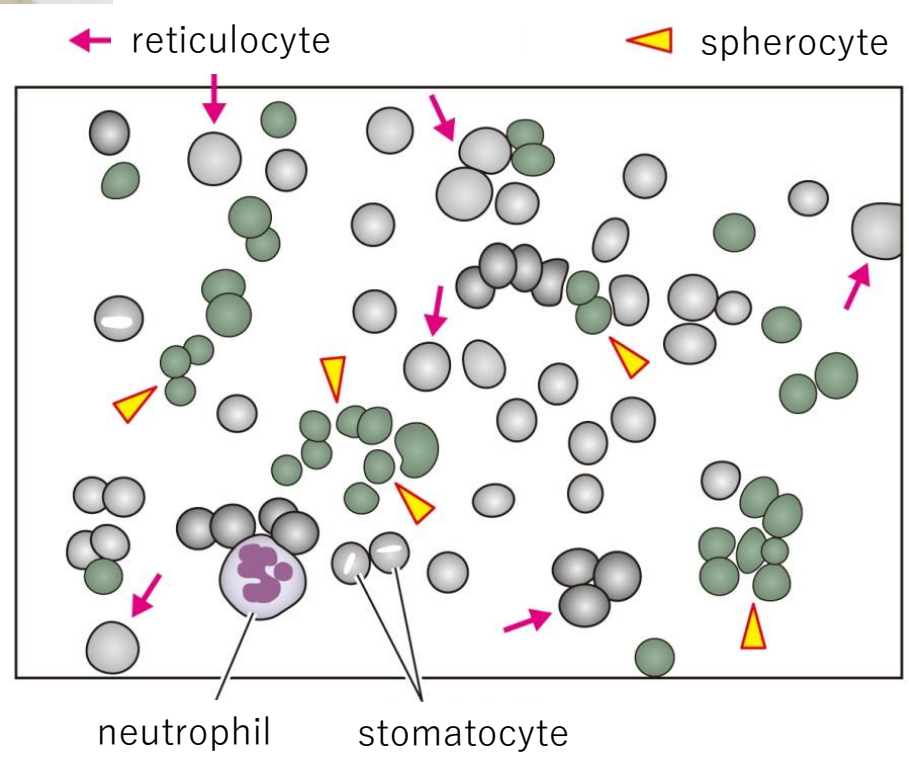
Type II hypersensitivity



Pernicious anemia (vitamin B12 deficiency) associated with autoimmune (type A) gastritis: Megaloblasts and a hypersegmented neutrophil in the bone marrow smear (May-Giemsa)

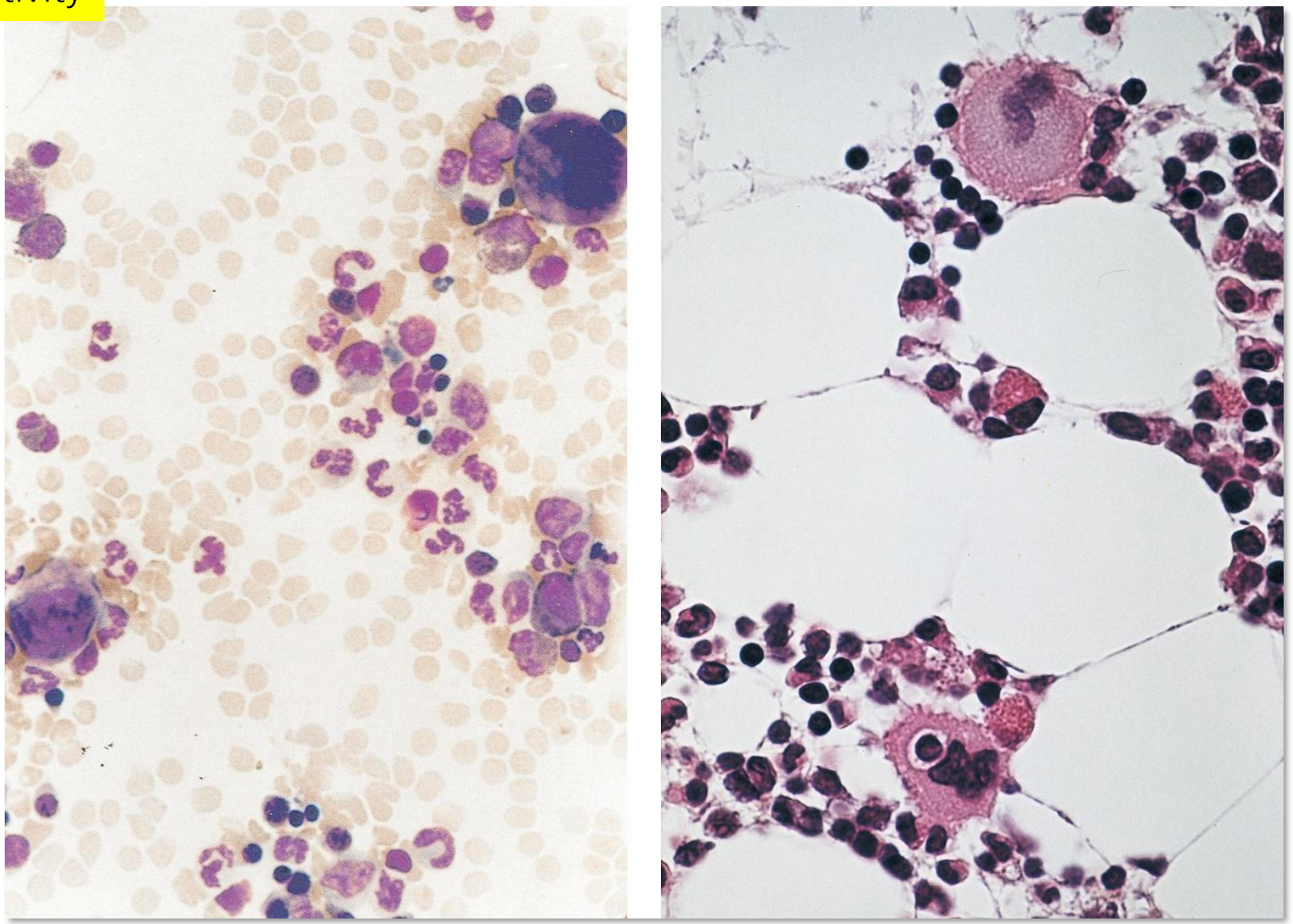
Type II hypersensitivity





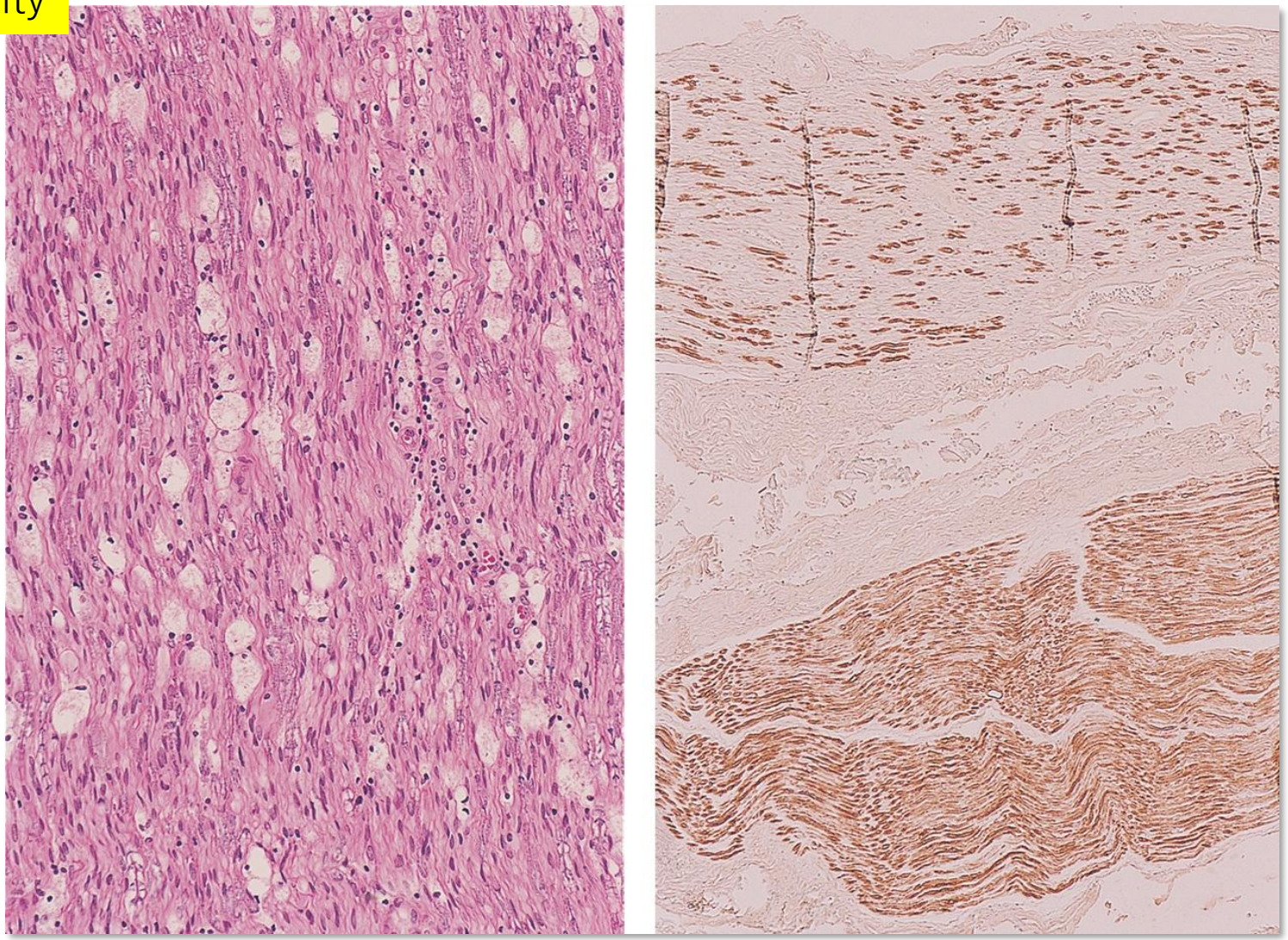
Autoimmune hemolytic anemia
(peripheral blood smear, May-Giemsa)

Type II hypersensitivity



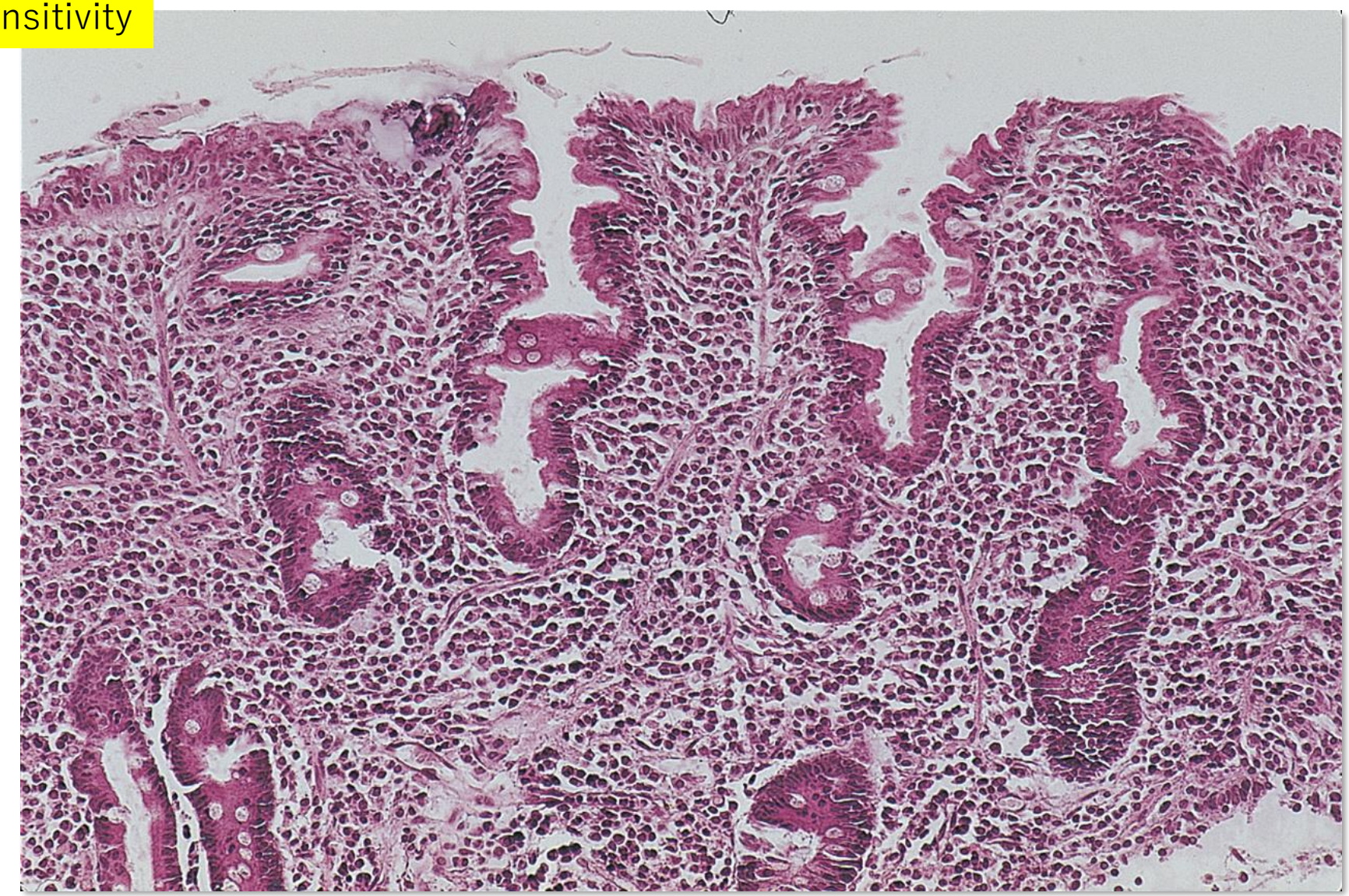
Idiopathic thrombocytopenic purpura (bone marrow aspiration, left: May-Giemsa, right: H&E). Small-sized megakaryocytes without platelet production are seen.

Type II hypersensitivity



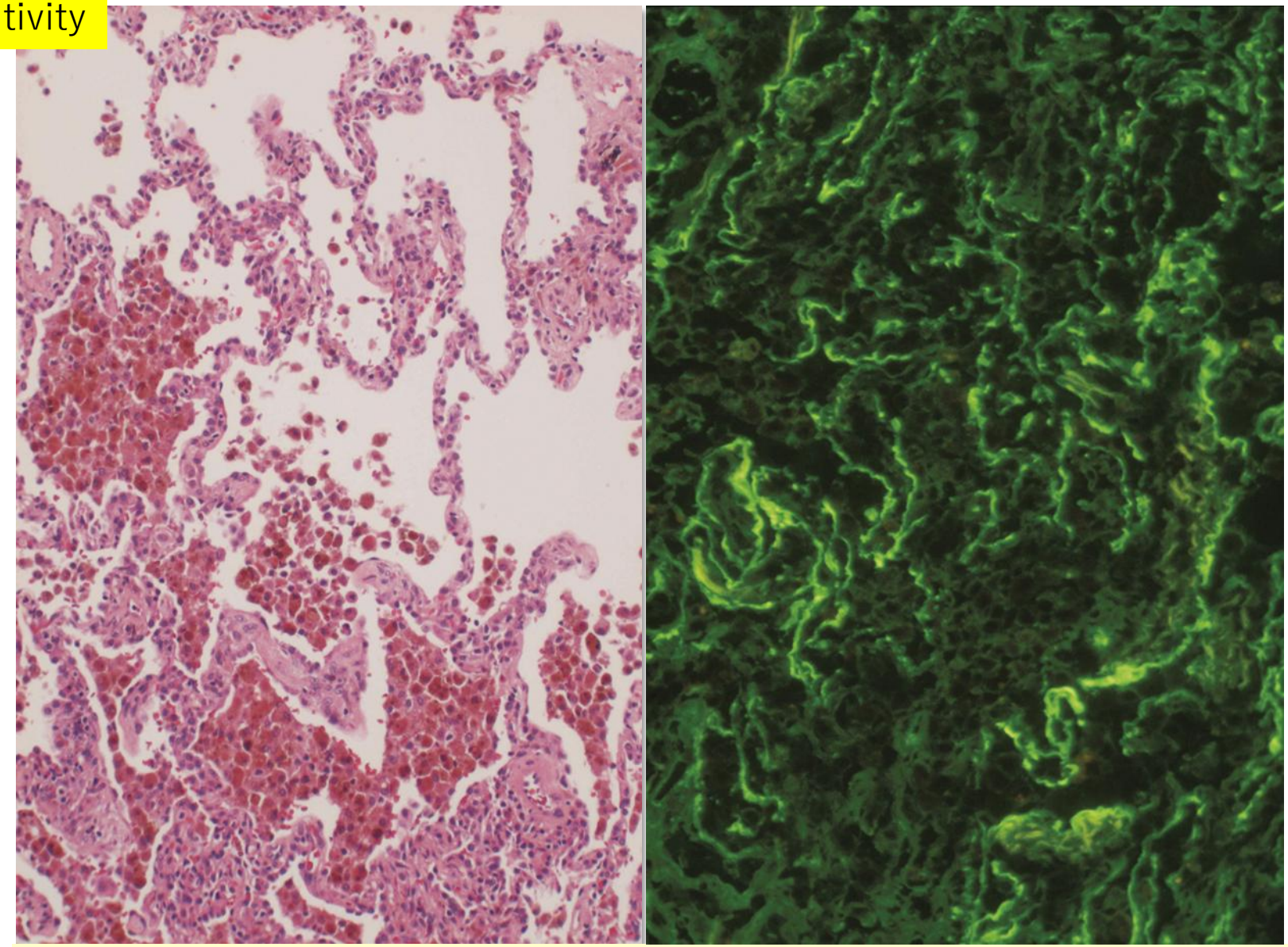
Guillain-Barre syndrome (left: H&E, right: immunostaining for MBP: myelin basic protein). Small lymphocytes and foamy macrophages infiltrate in the motor nerve fascicle. MBP immunostaining in the cauda equina discloses that motor nerves (the upper fascicle) are more severely demyelinated than sensory nerves (the lower fascicle).

Type II hypersensitivity

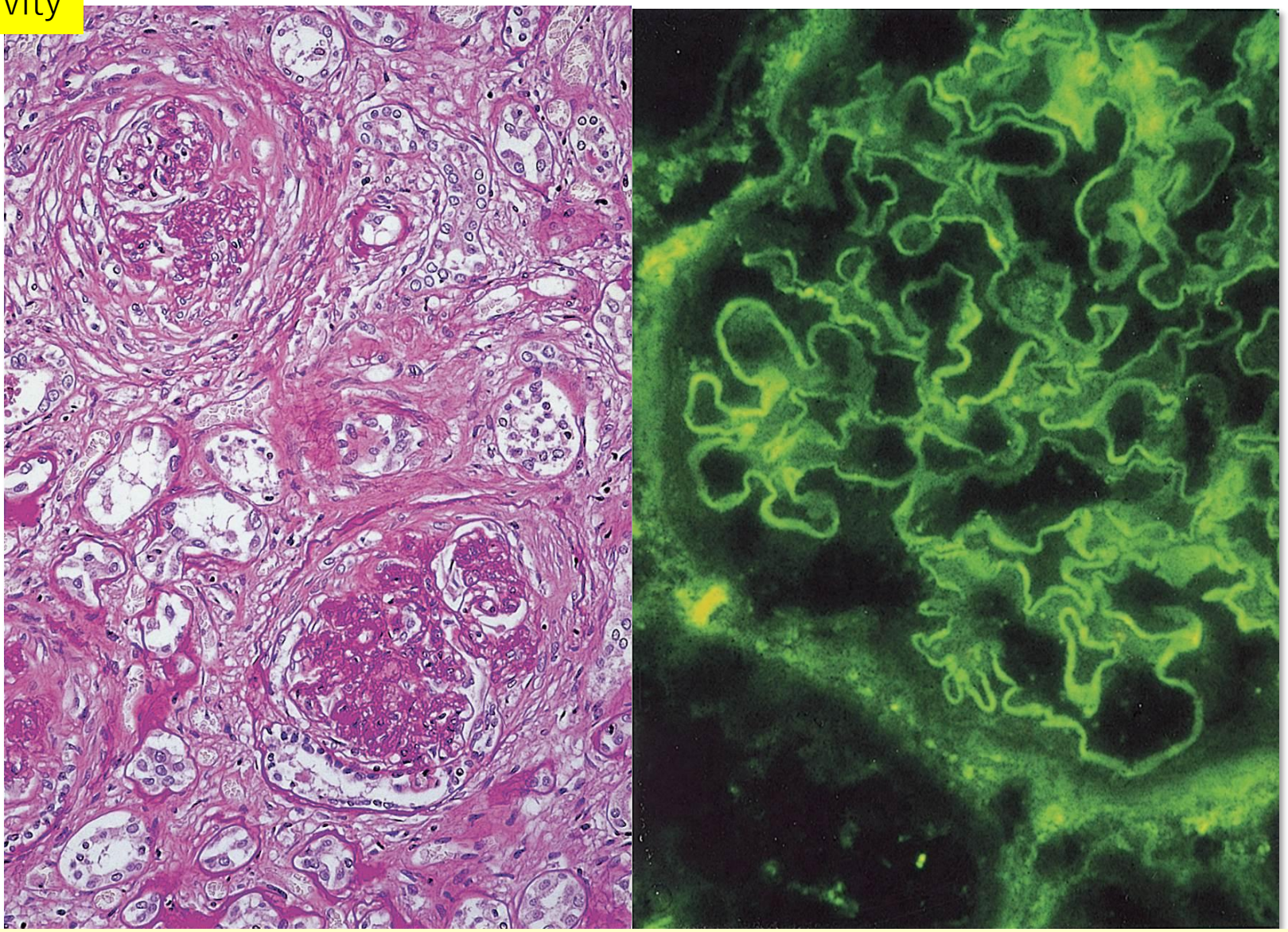


Celiac sprue (gluten enteropathy, duodenal biopsy, H&E). The patient has wheat allergy with gliadin antibodies in the serum. The duodenal villi are shortened with marked chronic inflammatory infiltration in the lamina propria mucosae. Intraepithelial lymphocytes are increased.

Type II hypersensitivity

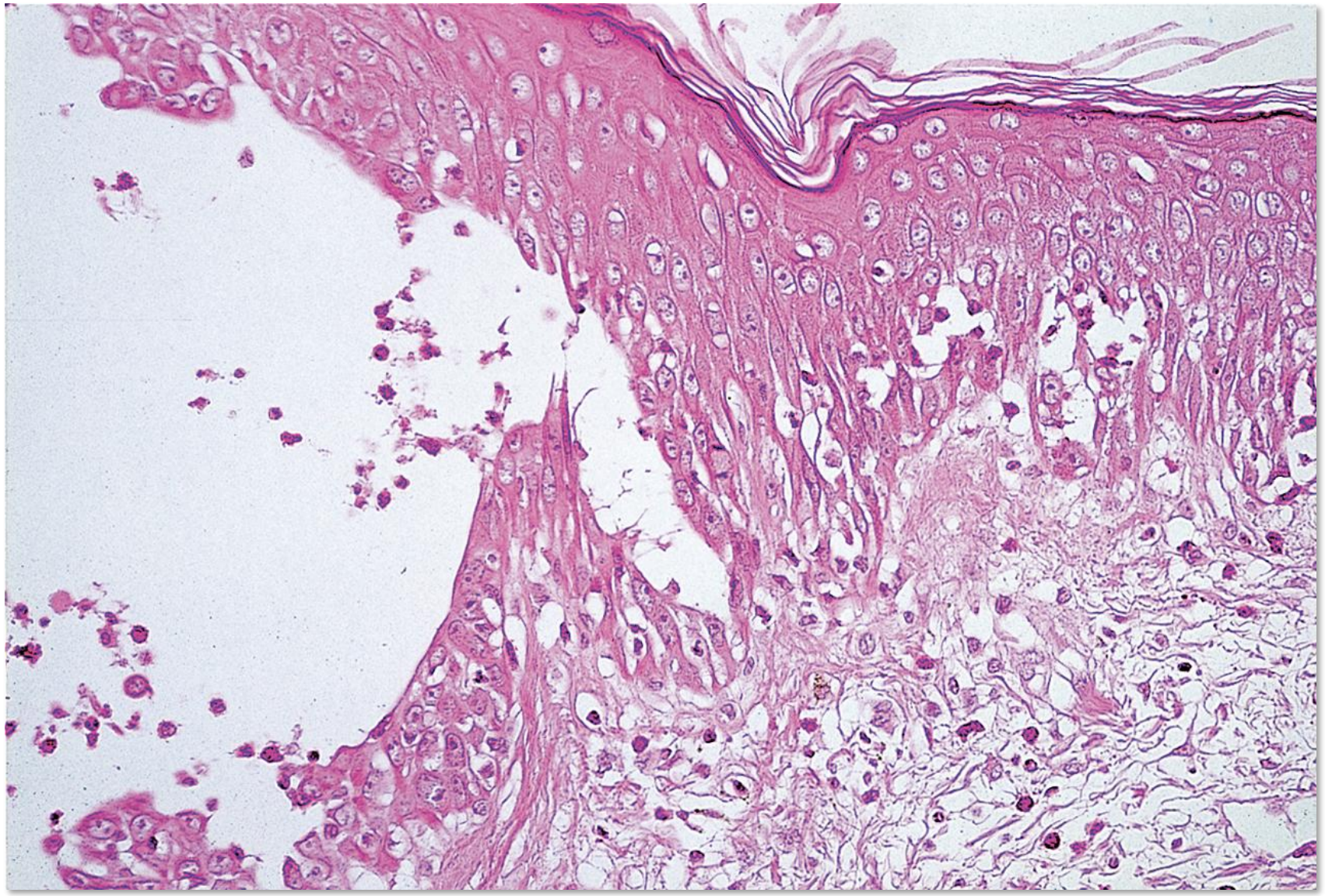


Goodpasture syndrome-1 (left: hemosiderin deposition in the lung, H&E, right: IgG deposition along the alveolar lining, indirect immunofluorescence for basement membrane antibody).



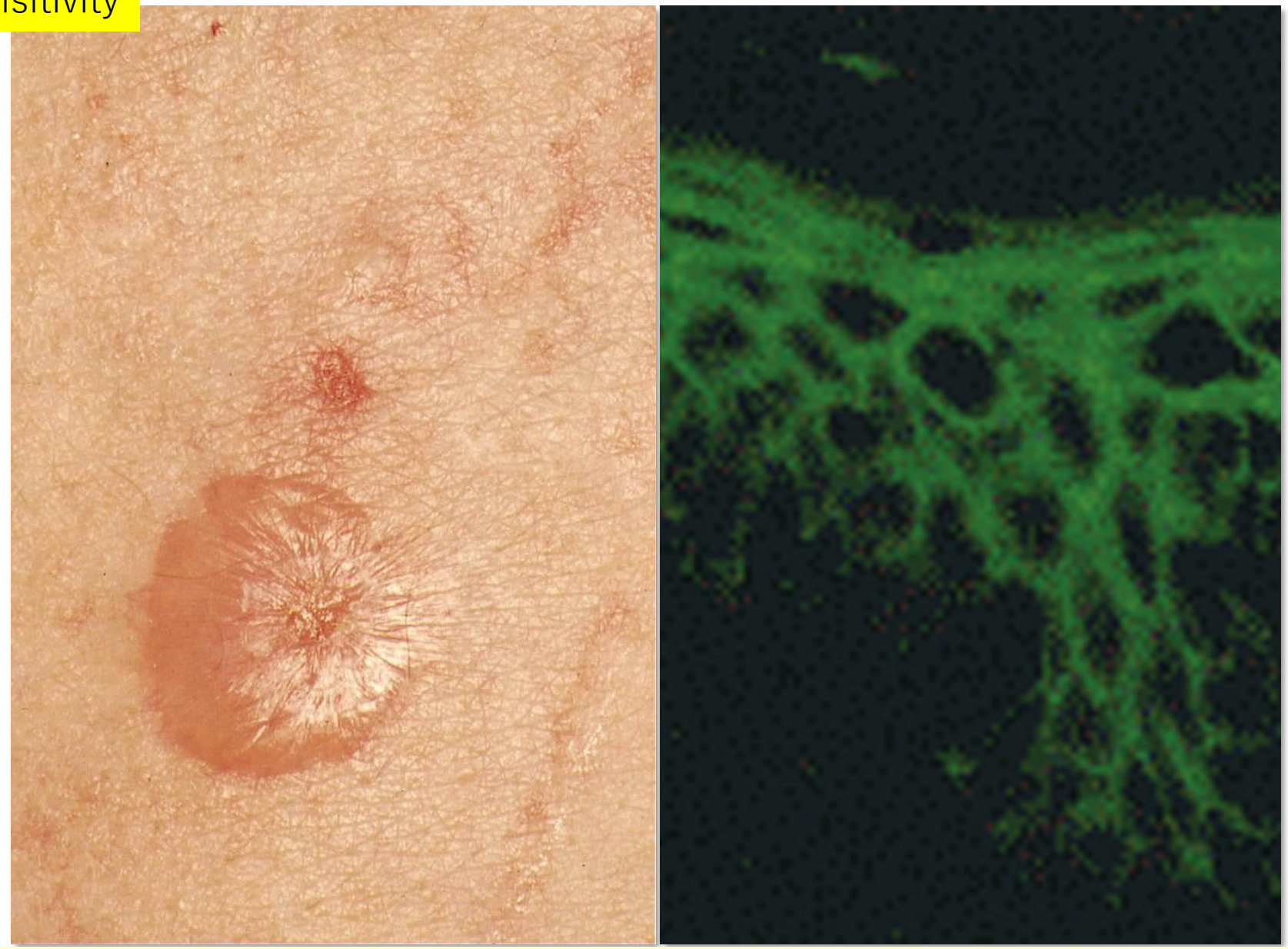
Goodpasture syndrome-2 (left: crescentic glomerulonephritis, PAS, right: linear IgG deposition along the capillary tuft caused by glomerular basement membrane antibody, indirect immunofluorescence).

Type II hypersensitivity



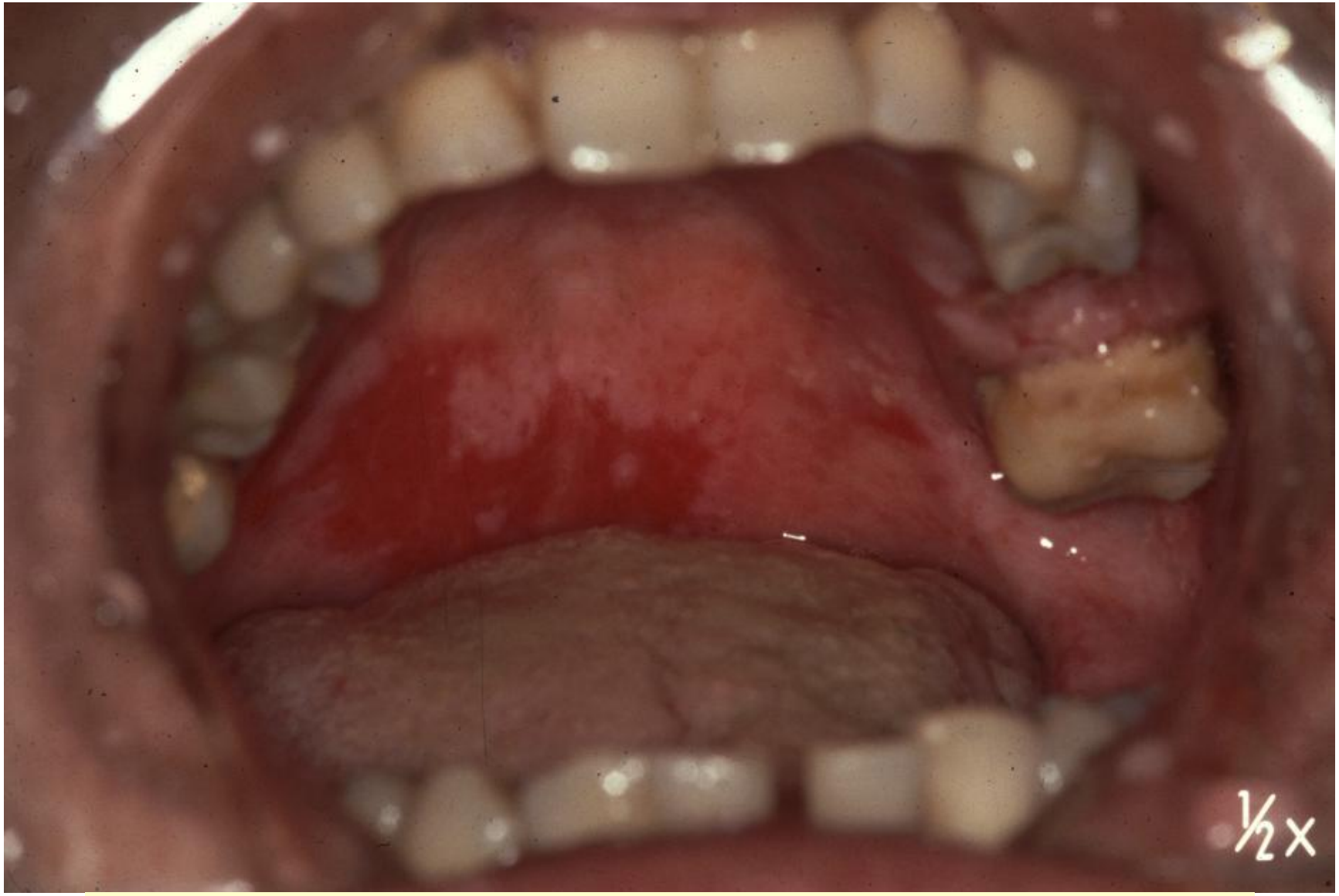
Pemphigus vulgaris-1 （skin biopsy, H&E). Intraepidermal bulla formation with acantholytic cells is observed.

Type II hypersensitivity



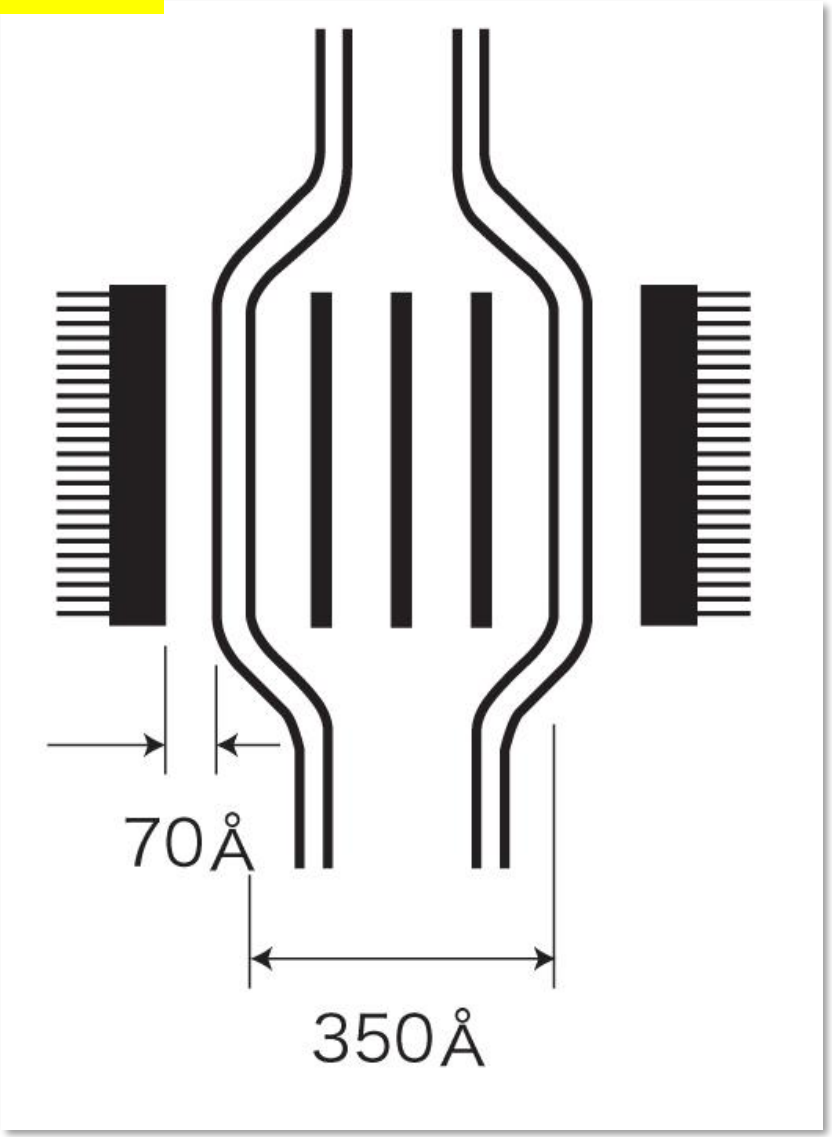
Pemphigus vulgaris-2 (left: gross appearance of the cutaneous bulla, right: indirect immunofluorescence for IgG, demonstrating intercellular IgG deposition in the epidermis)

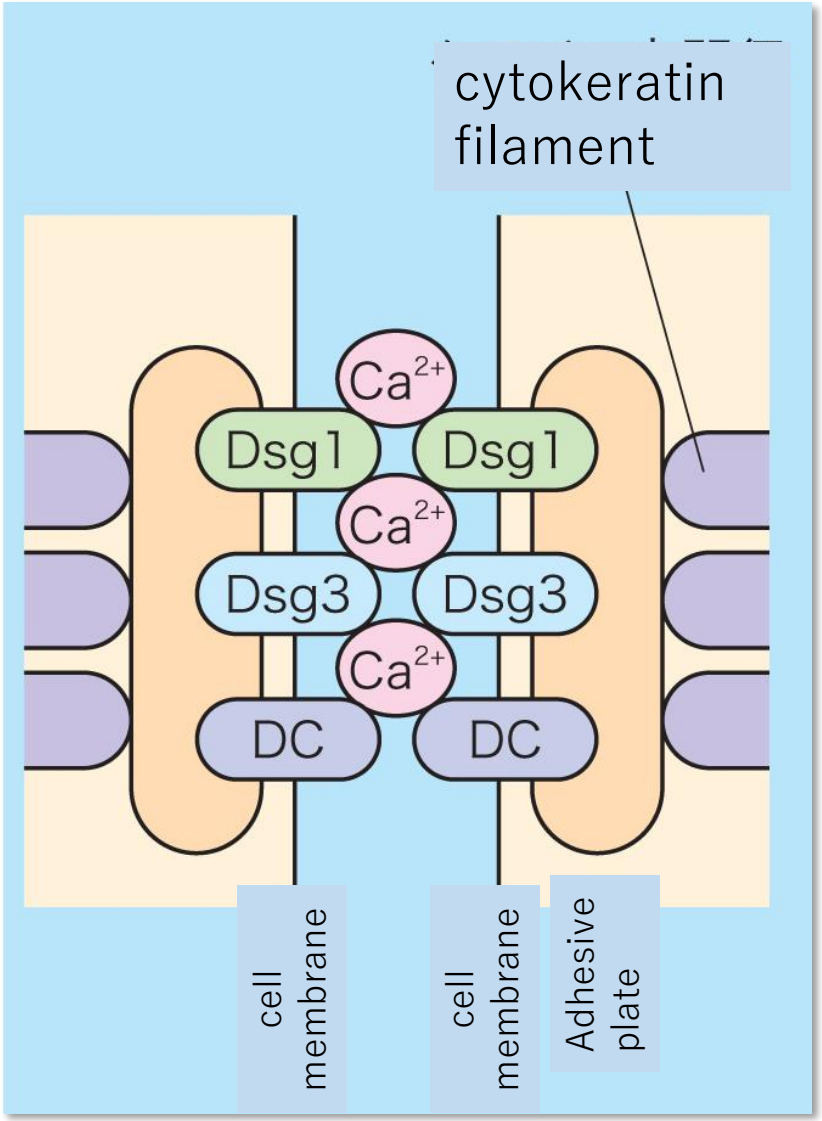
Type II hypersensitivity



Pemphigus vulgaris-3 (bulla formation on the oral mucosa: initial clnical presentation)

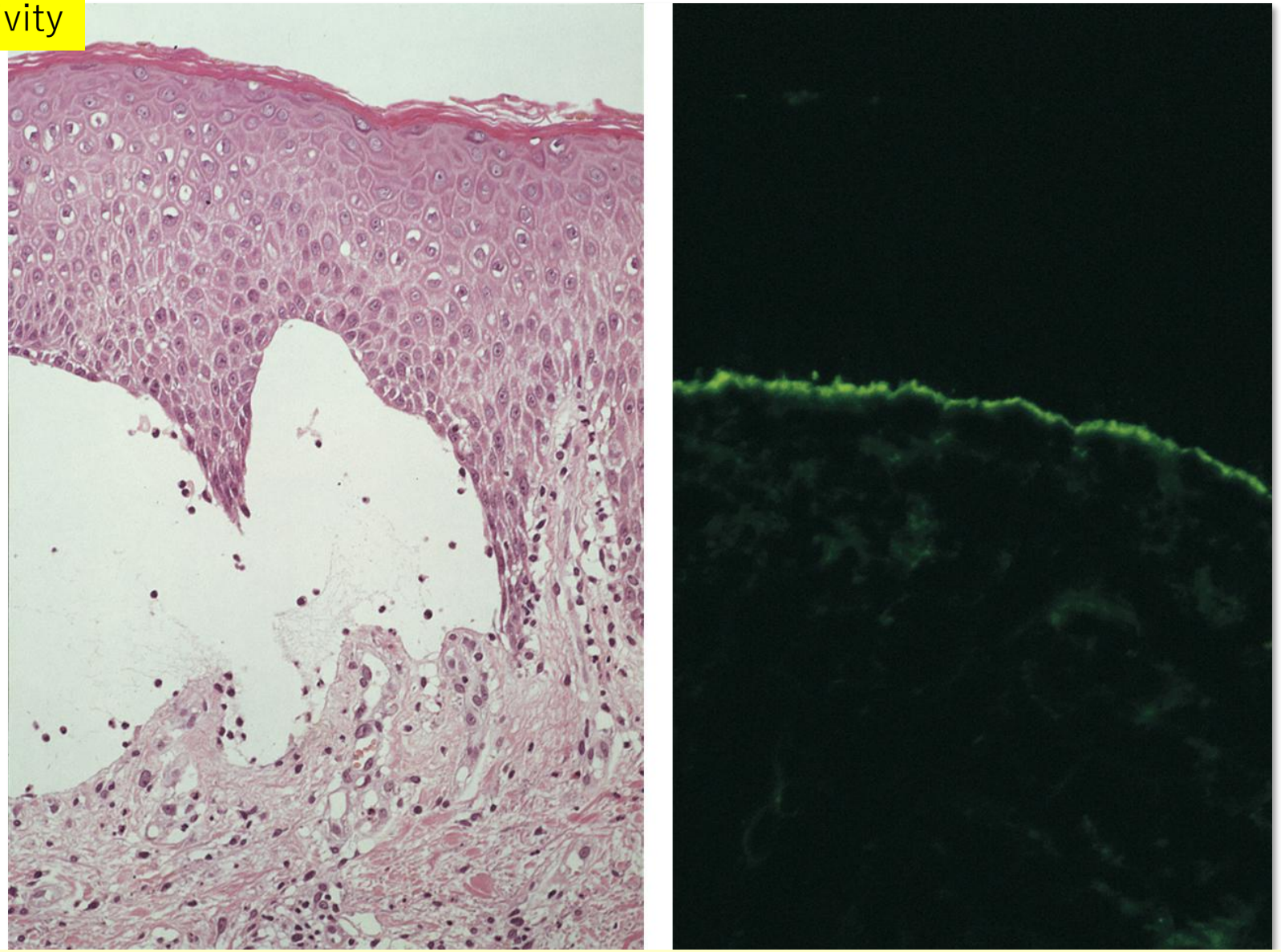
Type II hypersensitivity





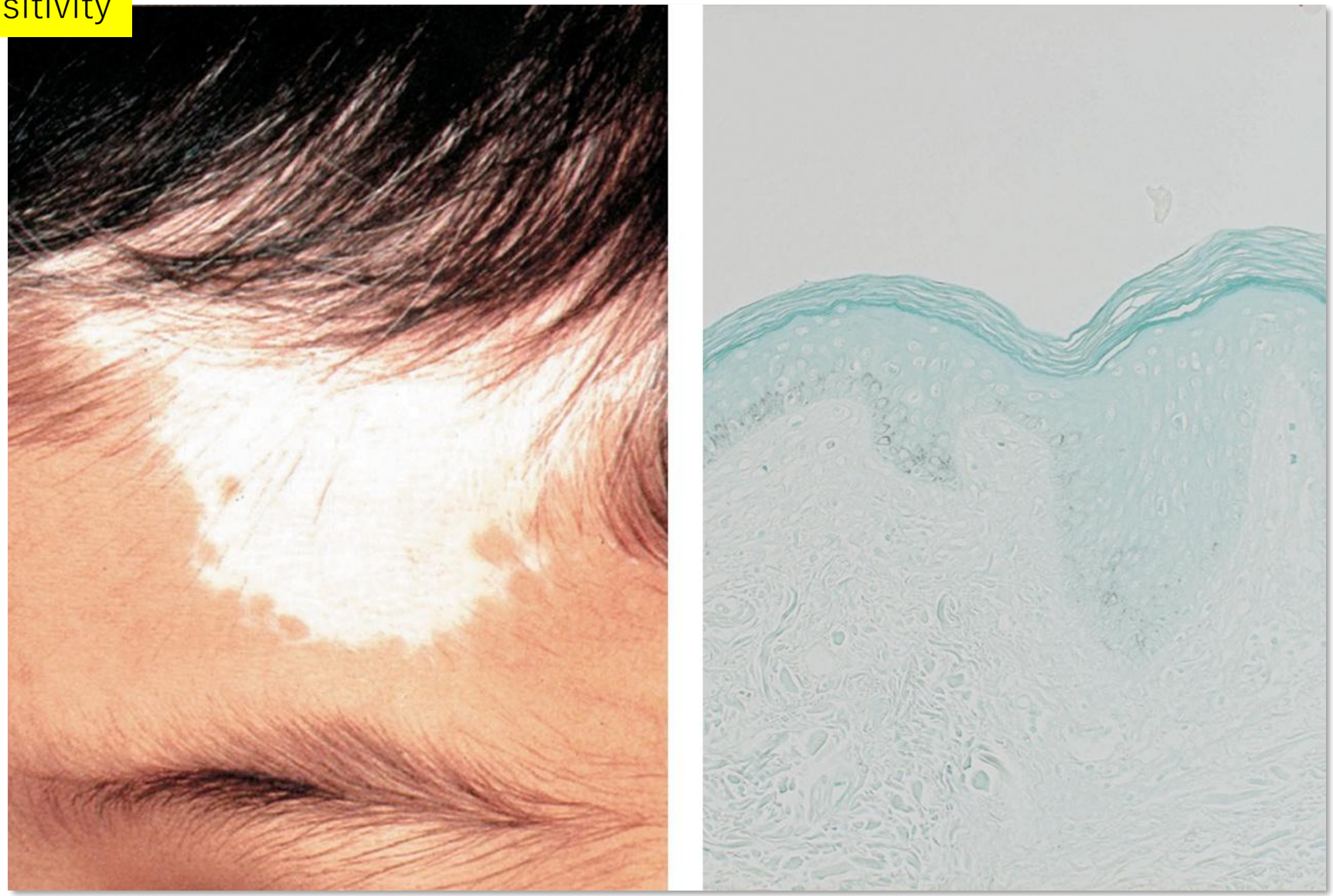
Molecular structure of desmosome (Dsg: desmoglein, DC: desmocollin): Dsg3 is the target antigen of pemphigus vulgaris.

Type II hypersensitivity



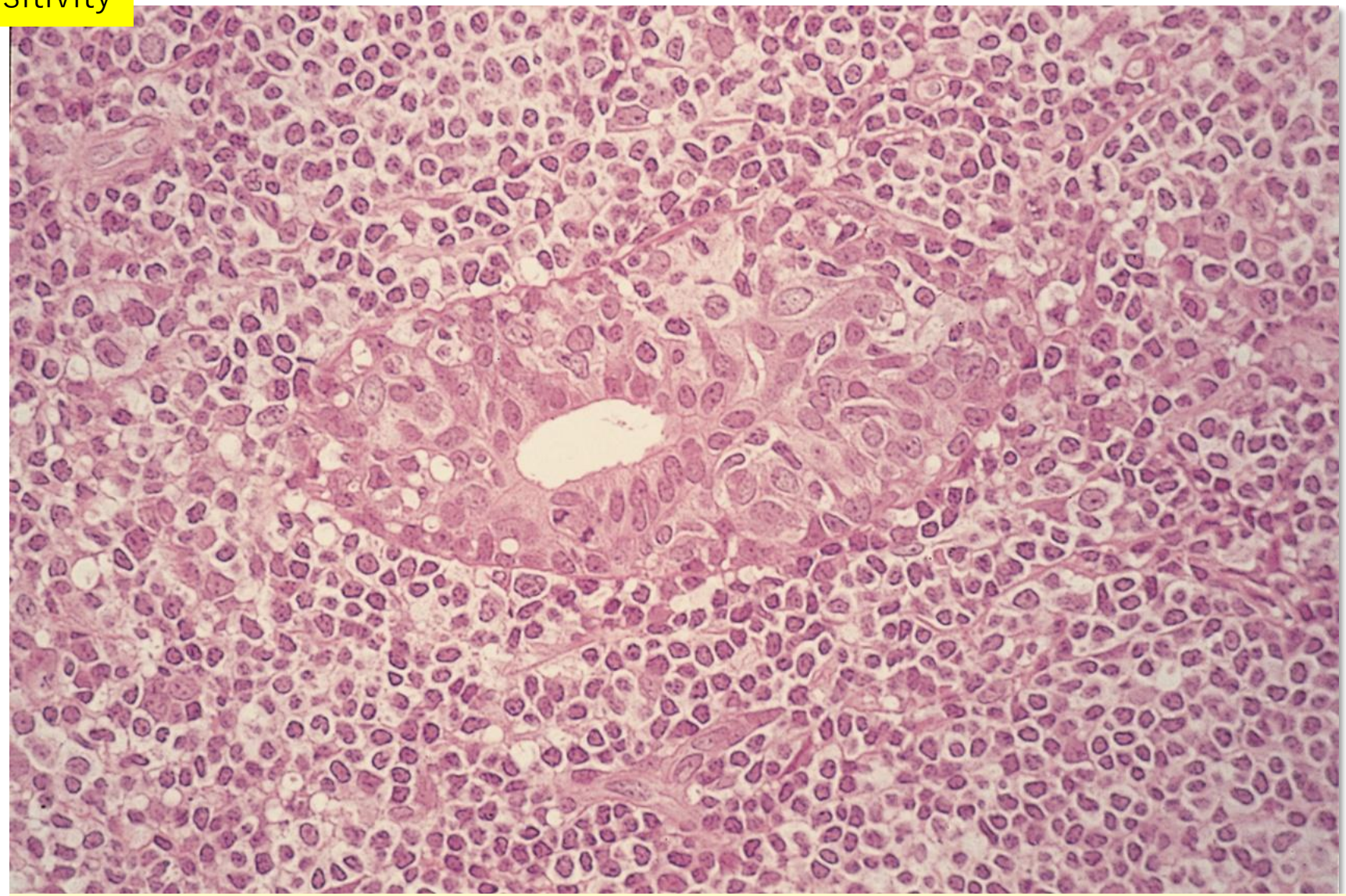
Bullous pemphigoid (left: subepidermal bulla, H&E, right: indirect immunofluorescence for IgG): Linear deposition of IgG is seen along the epidermal basement membrane. The autoantigen of bullous pemphigoid is collagen XVII (BP180) on the hemidesmosome.

Type II hypersensitivity



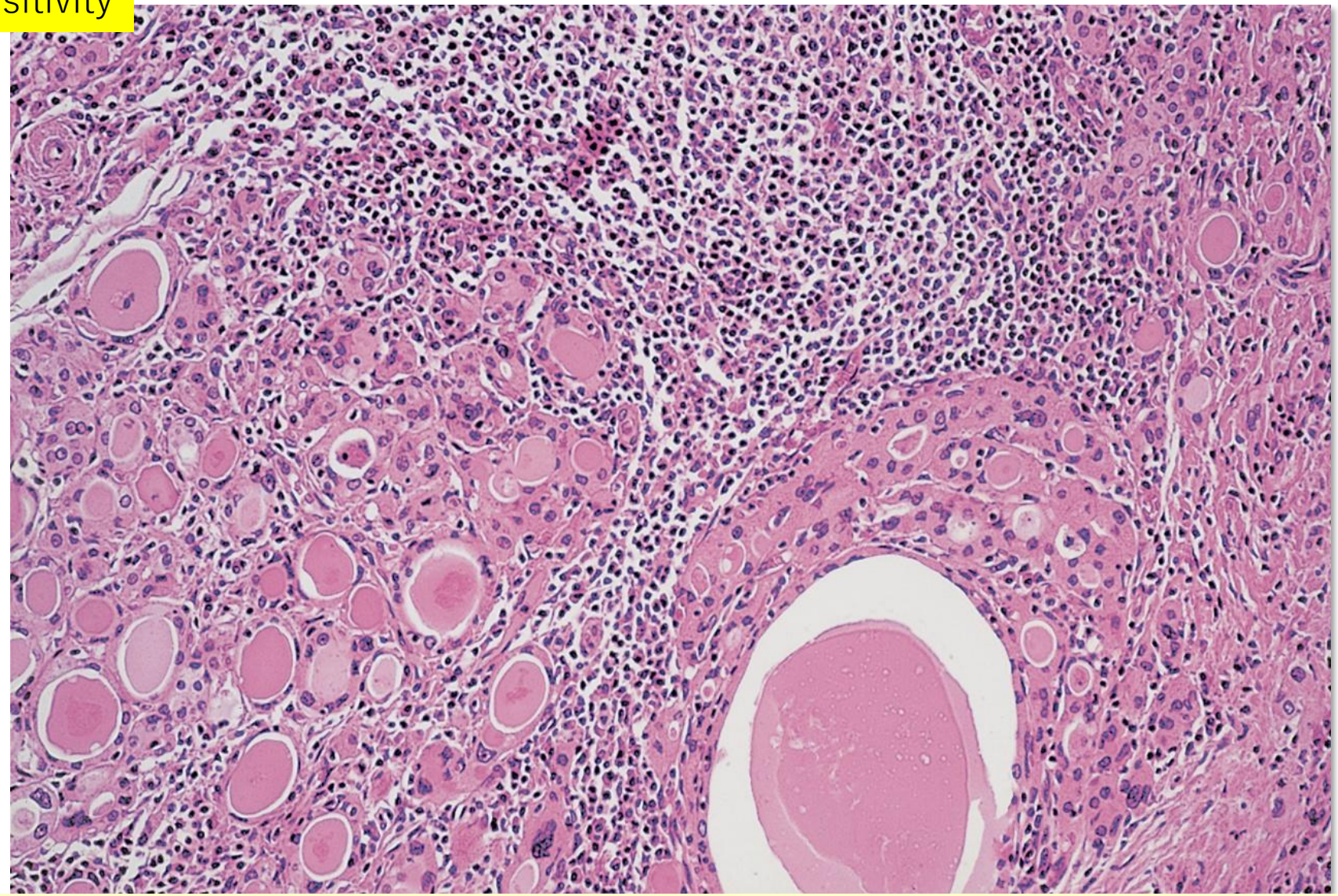
Vitiligo vulgaris, an autoimmunity against skin melanocytes (left: gross appearance of the forehead, right: Fontana-Masson argentaffin reaction). In the right-sided vitiligo area, Fontana-Masson-reactive melanin pigment is lost from the basal layer.

Type II hypersensitivity

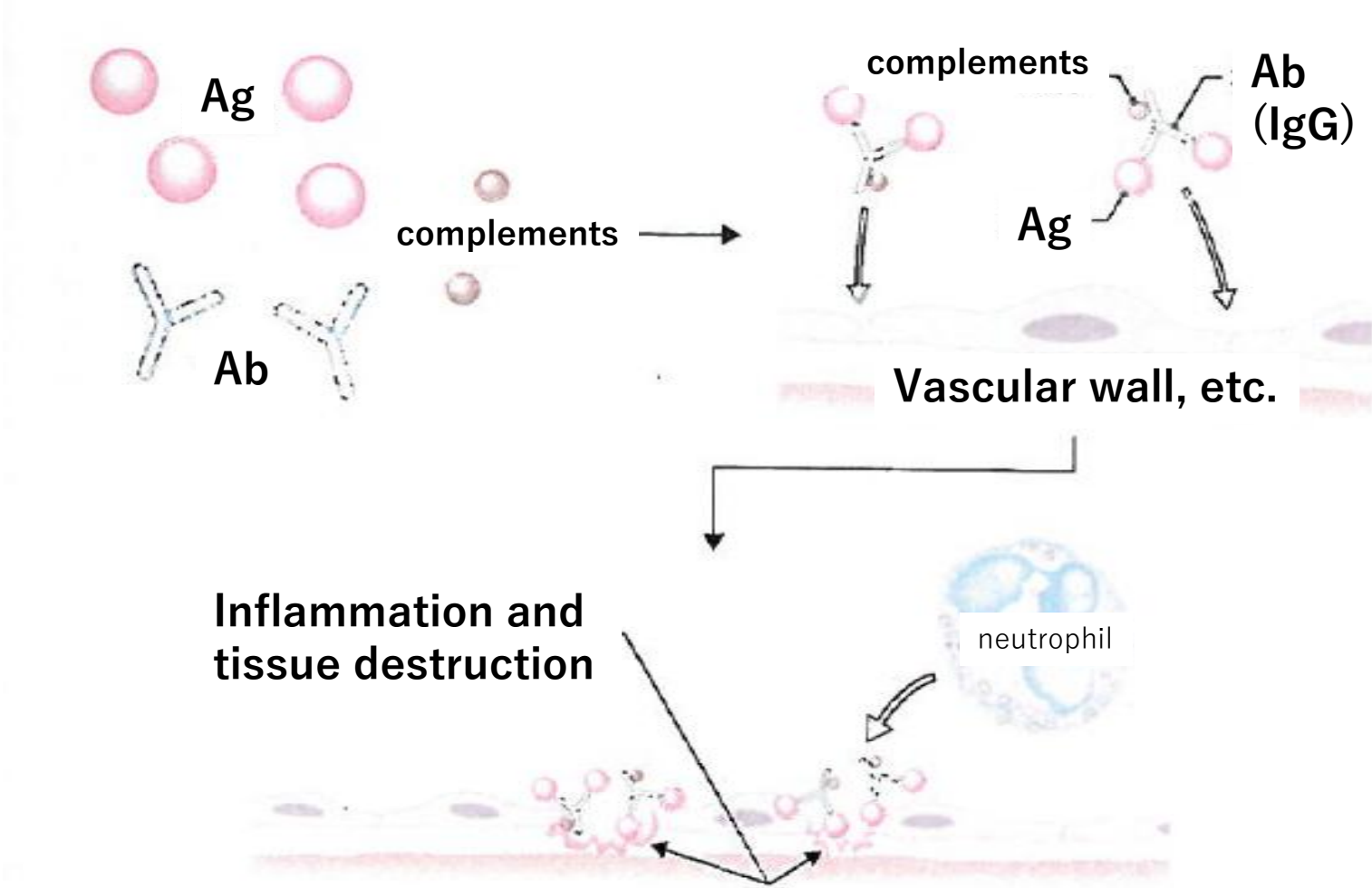


Sjoegren syndrome (salivary gland biopsy, H&E). Marked lymphocytic infiltration with a lymphoepithelial lesion (lymphocytic involvement among the ductal cells) is seen.

Type II hypersensitivity



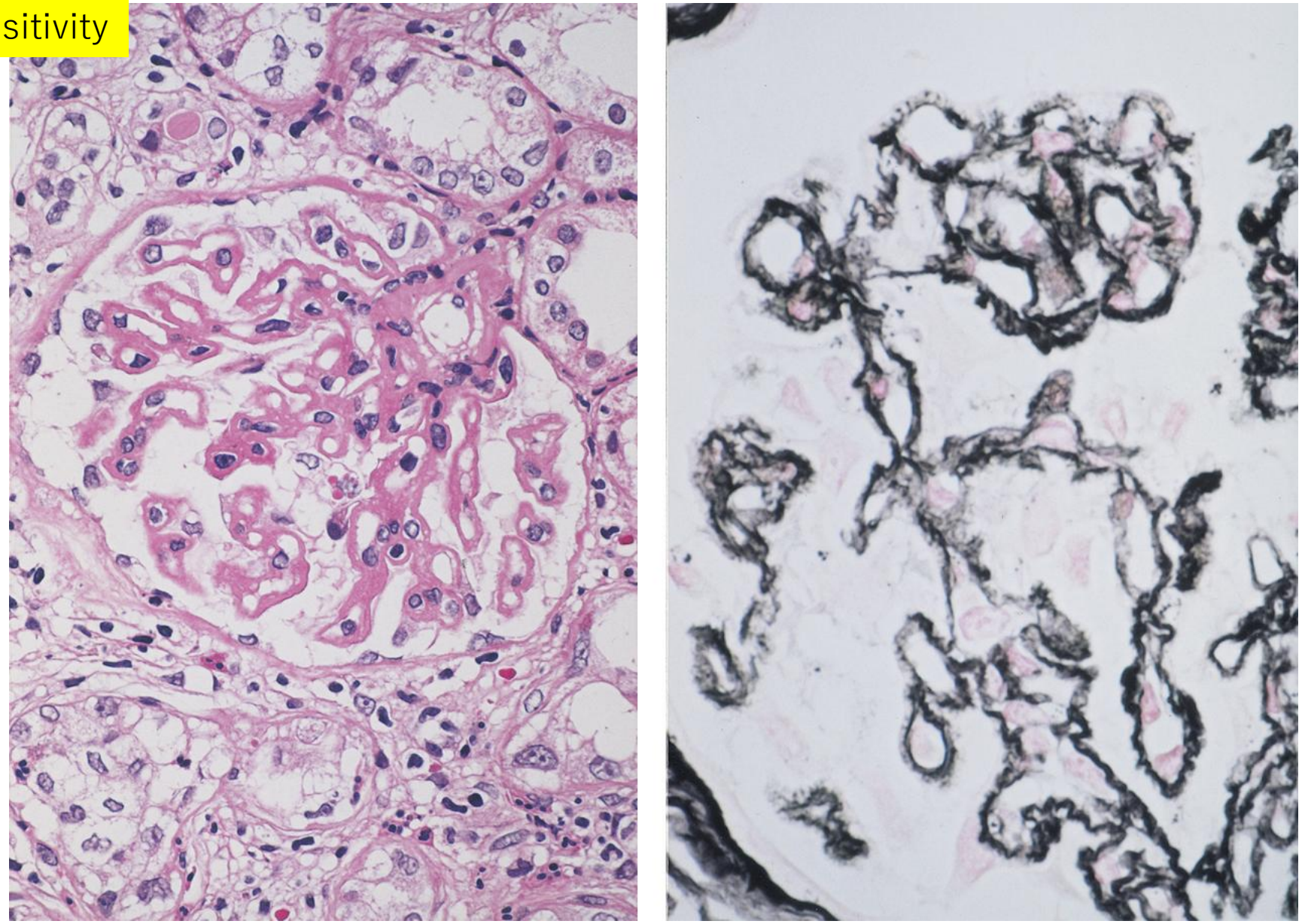
Hashimoto thyroiditis（surgical case, H&E). Marked lymphocytic infiltration, lymphoid follicle formation and oncocytic change (with plump eosinophilic cytoplasm) of the thyroid follicular epithelial cells are observed.



Antigen-antibody complexes formed in the blood deposit in the tissue provoke inflammation and tissue destruction, resulting in dysfunction of the organ involved. Neutrophils secrete proteolytic enzymes.

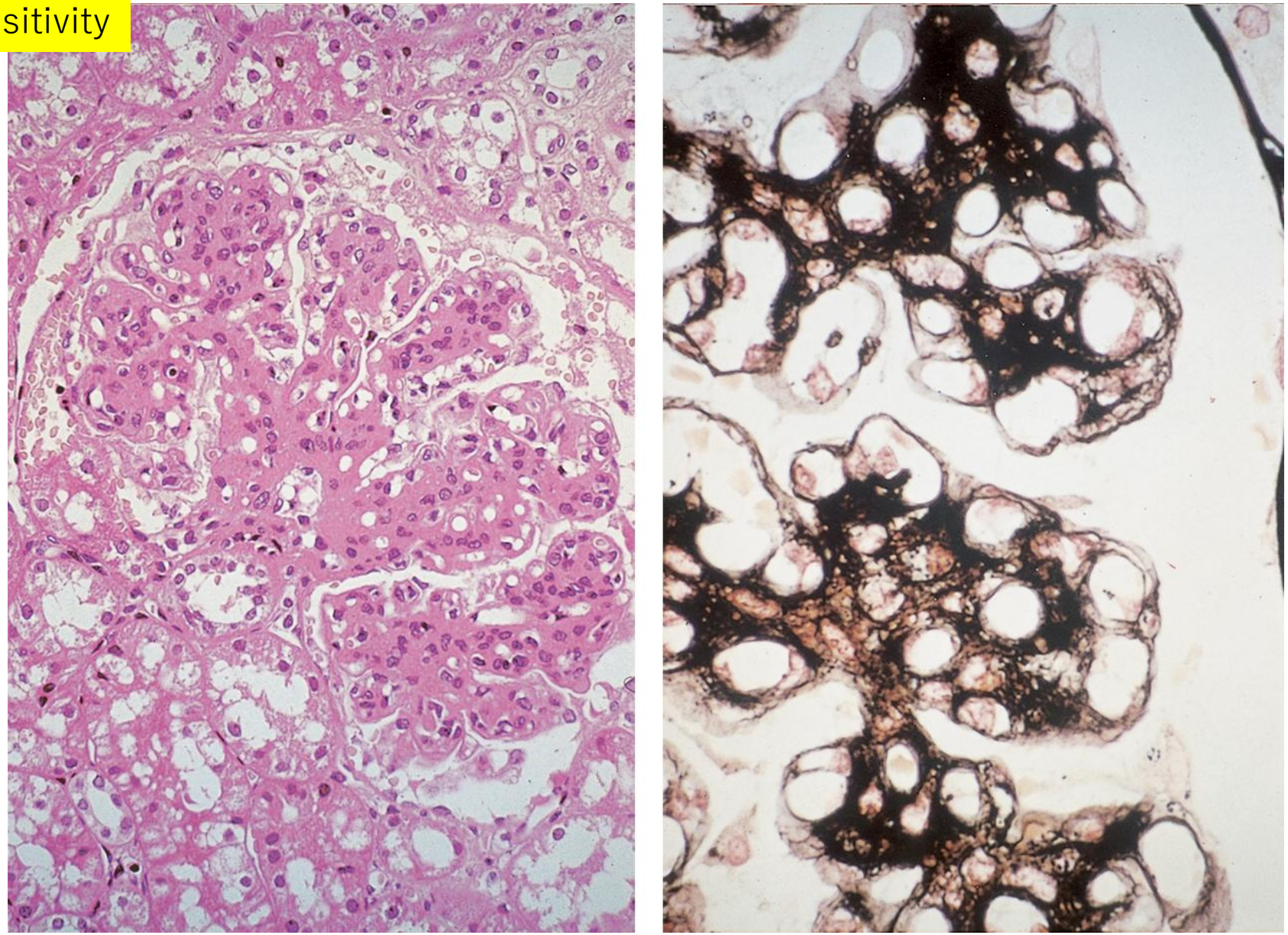
Type III hypersensitivity (immune complex type)

Type III hypersensitivity



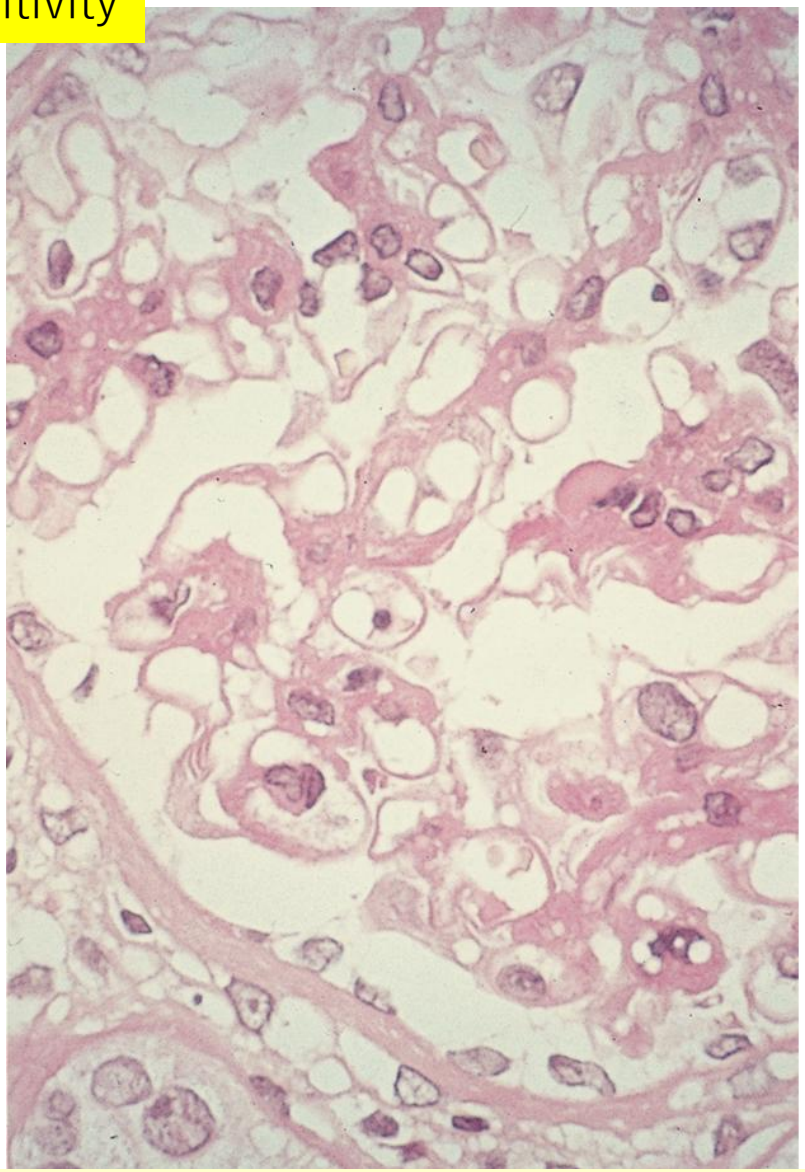
Membranous nephropathy (left: H&E, right: PAM). Capillary tufts are diffusely thickened in H&E, and spike formation is observed along the capillary tufts in PAM staining.

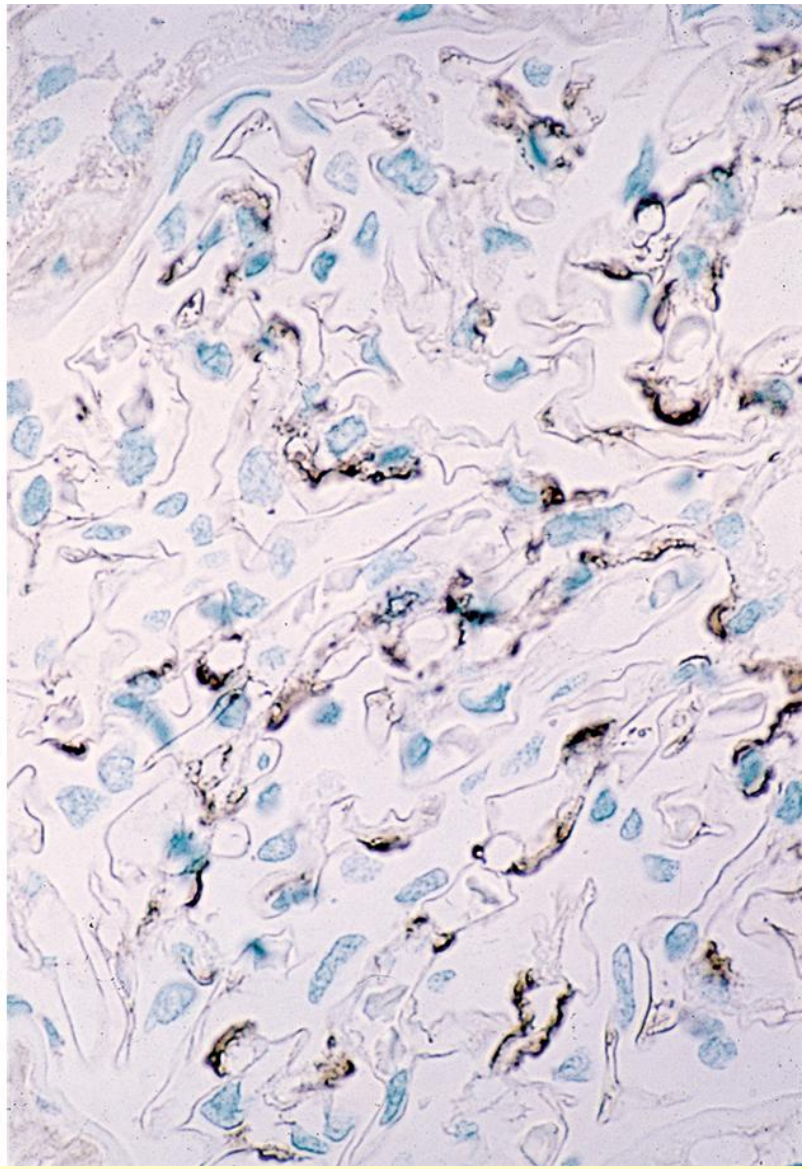
Type III hypersensitivity



Membranoproliferative glomerulonephritis (left: H&E, right: PAM). Active growth of mesangial cells has provoked tram track (double track) formation in the capillary tufts.

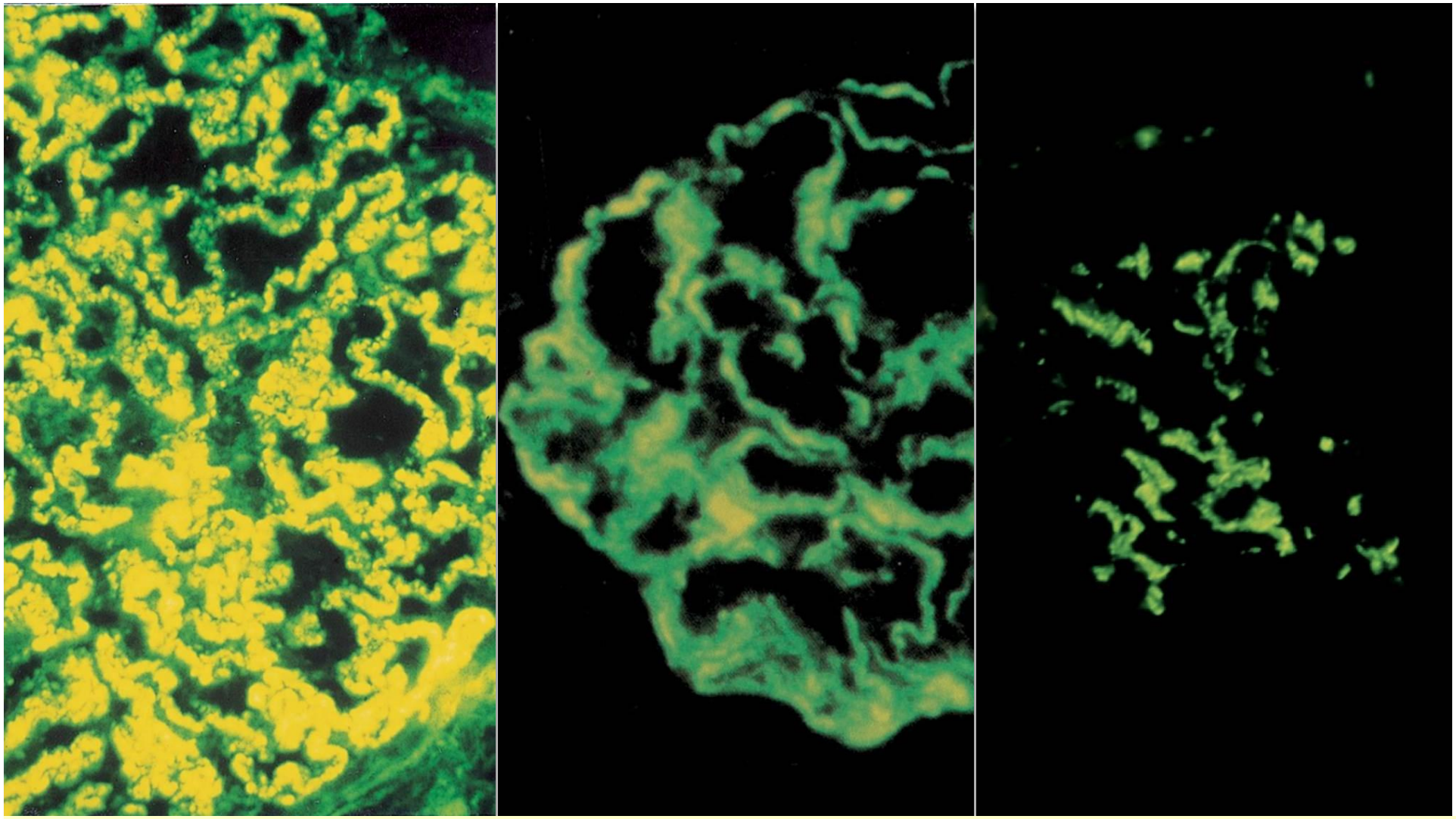
Type III hypersensitivity





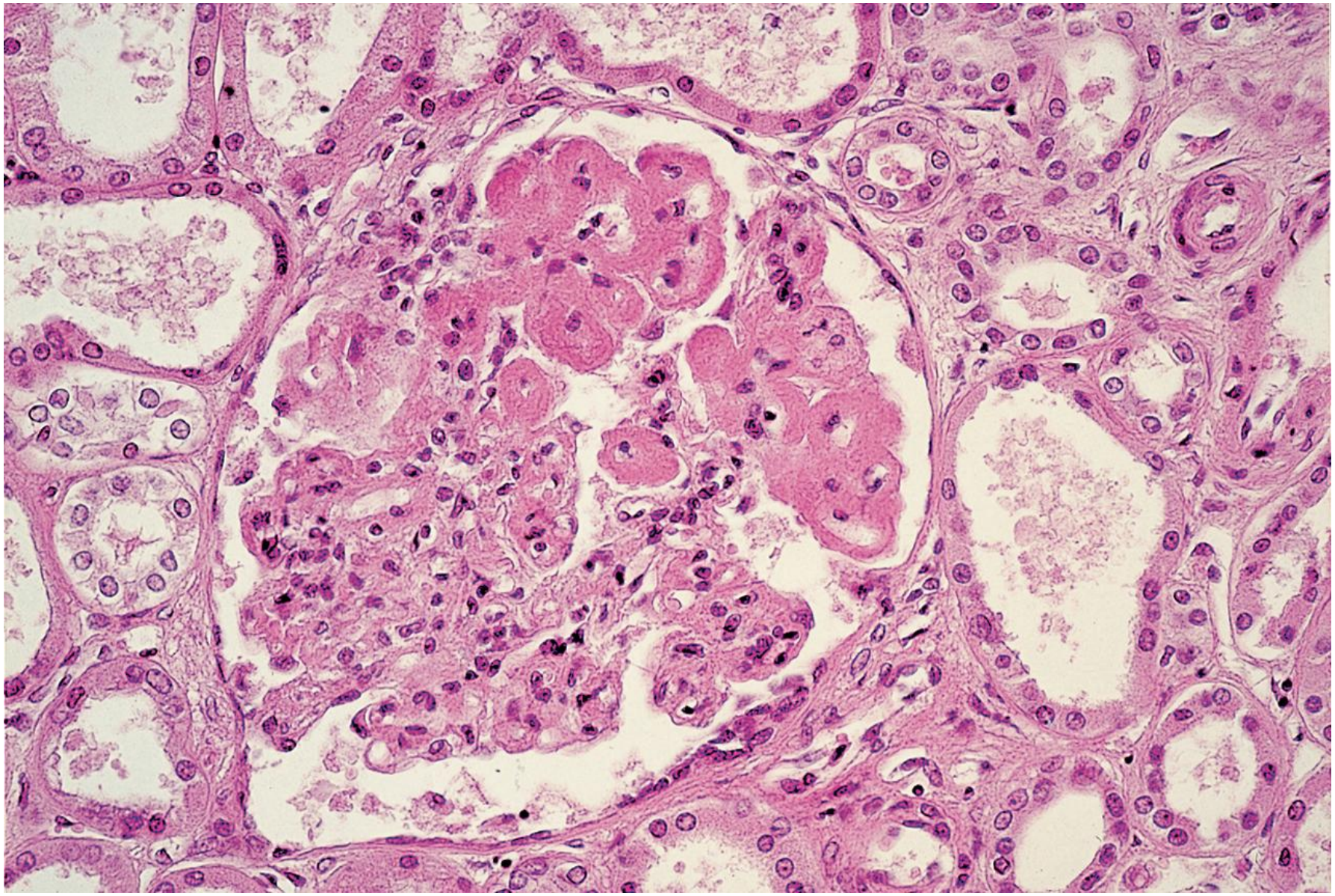
IgA nephropathy (left: H&E, right: immunoperoxidase staining for IgA). H&E preparation demonstrates eosinophilic globular “paramesangial deposits”. Immunostaining discloses mesangial deposition of IgA.

Type III hypersensitivity



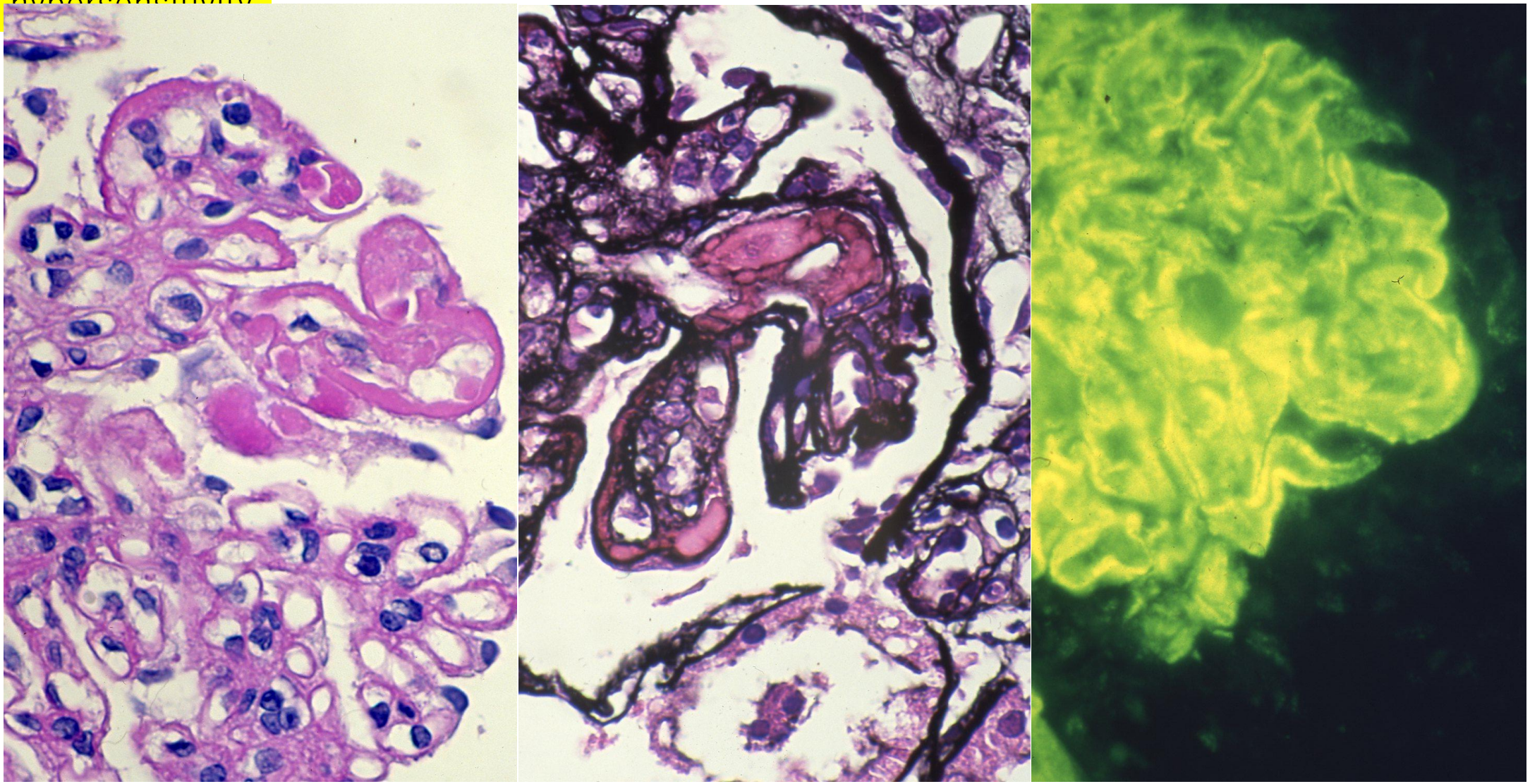
Immunofluorescence study. Left: granular deposition of IgG in membranous nephropathy, center: fringe type deposition of C3 in membranoproliferative glomerulonephritis, right: mesangial deposition of IgA in IgA nephropathy.

Type III hypersensitivity



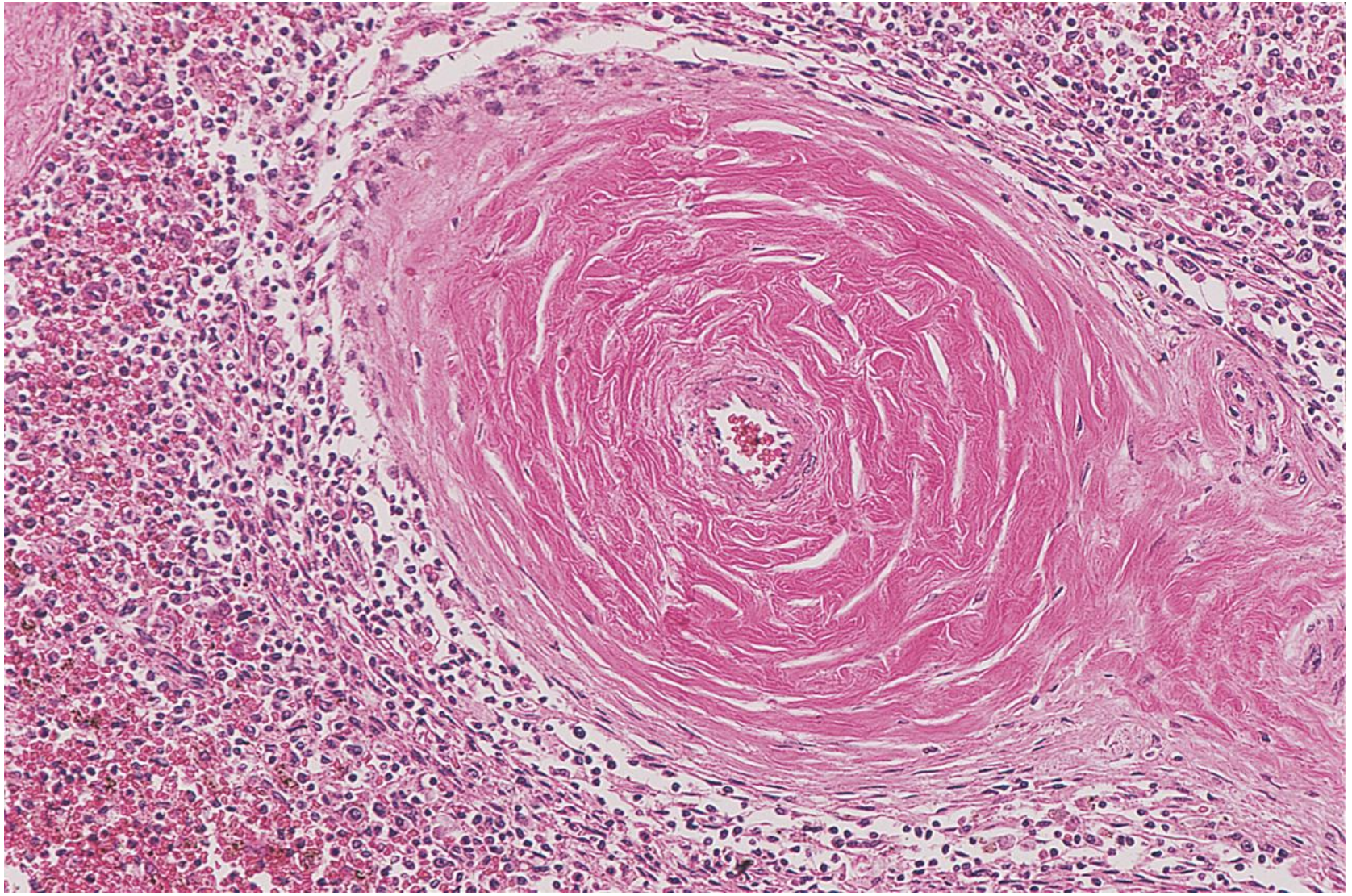
Lupus nephritis (H&E). Formation of the wire loop lesion is characteristic of SLE.

Type III hypersensitivity



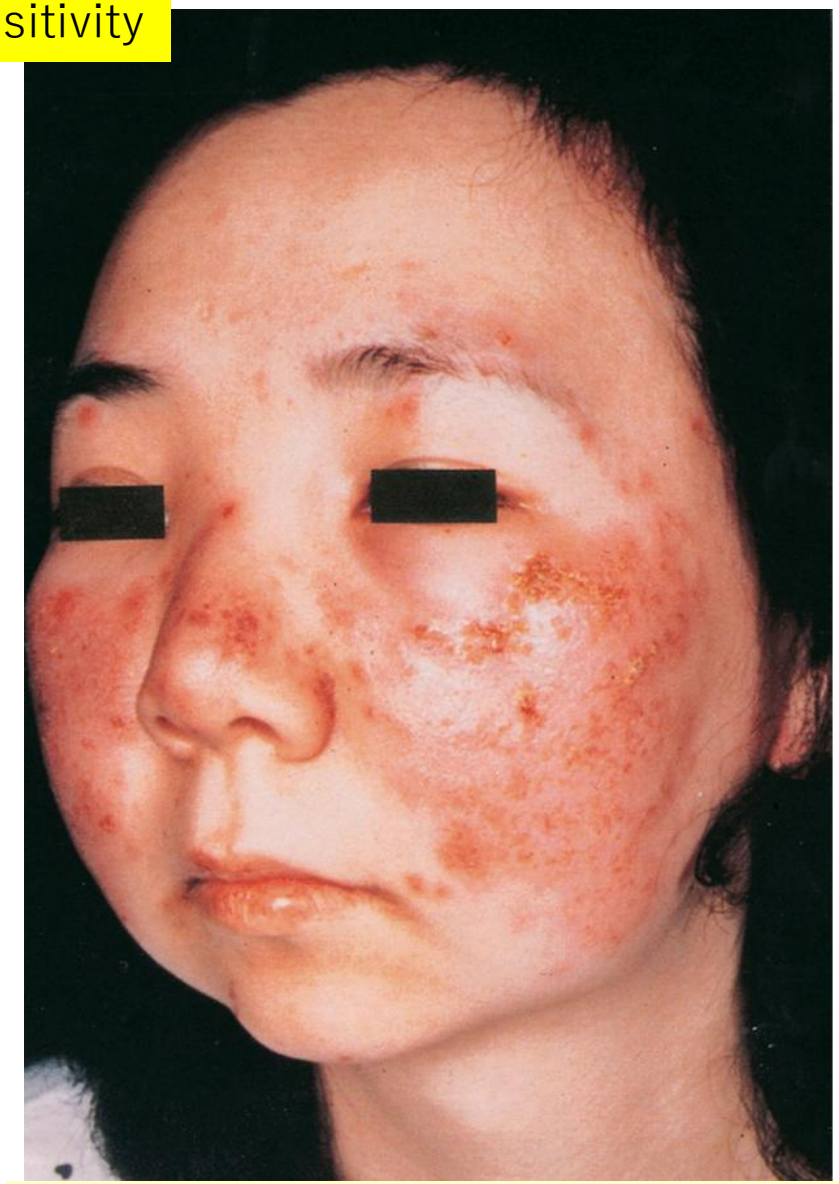
Lupus nephritis (left: PAS, center: PAM, right: immunofluorescence for IgG). The wire loop lesion seen in SLE shows massive subendothelial immune deposits.

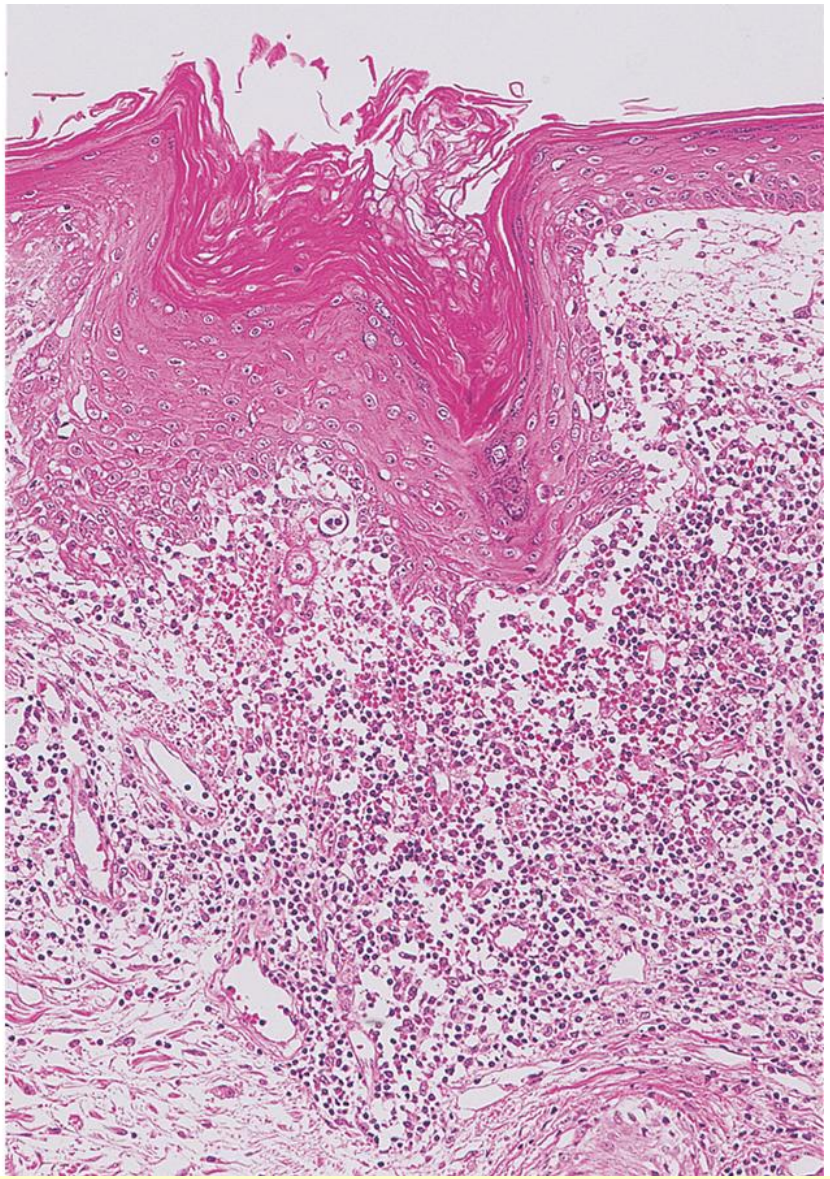
Type III hypersensitivity



Onion skin lesion in the splenic white pulp in SLE (H&E). The onion skin lesion in the spleen corresponds to immune complex deposition.

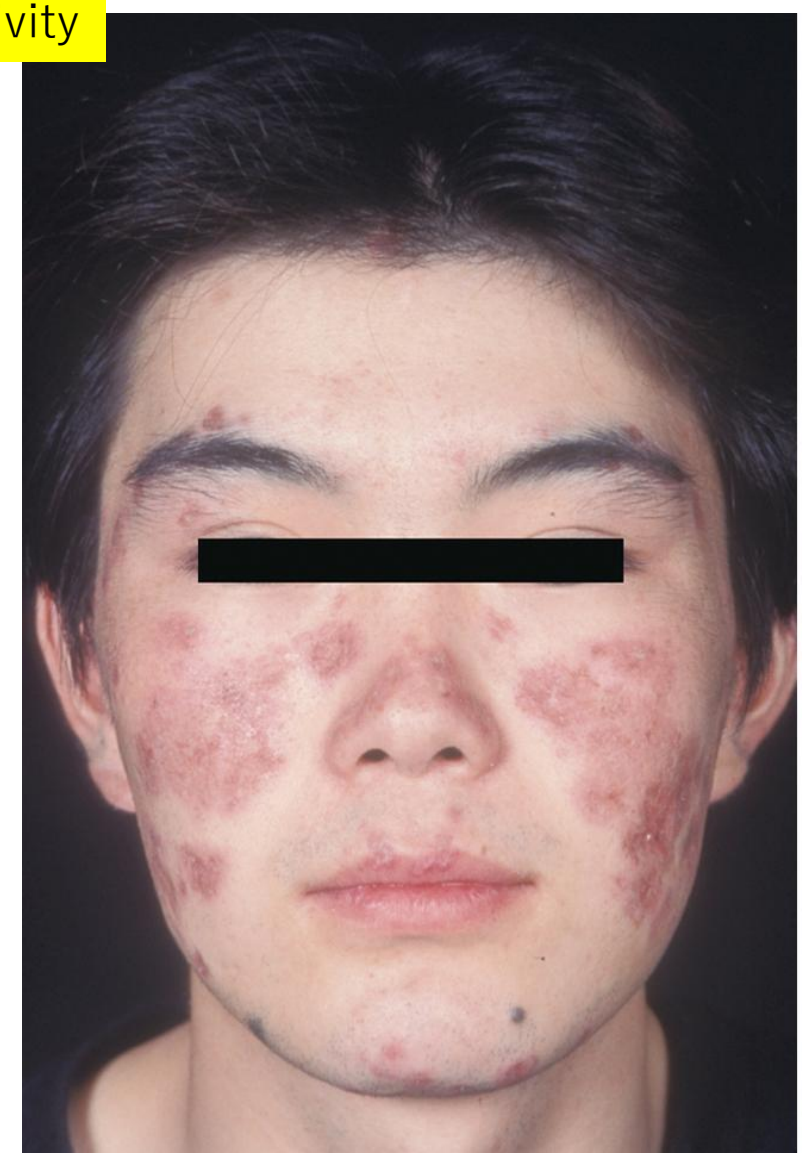
Type III hypersensitivity

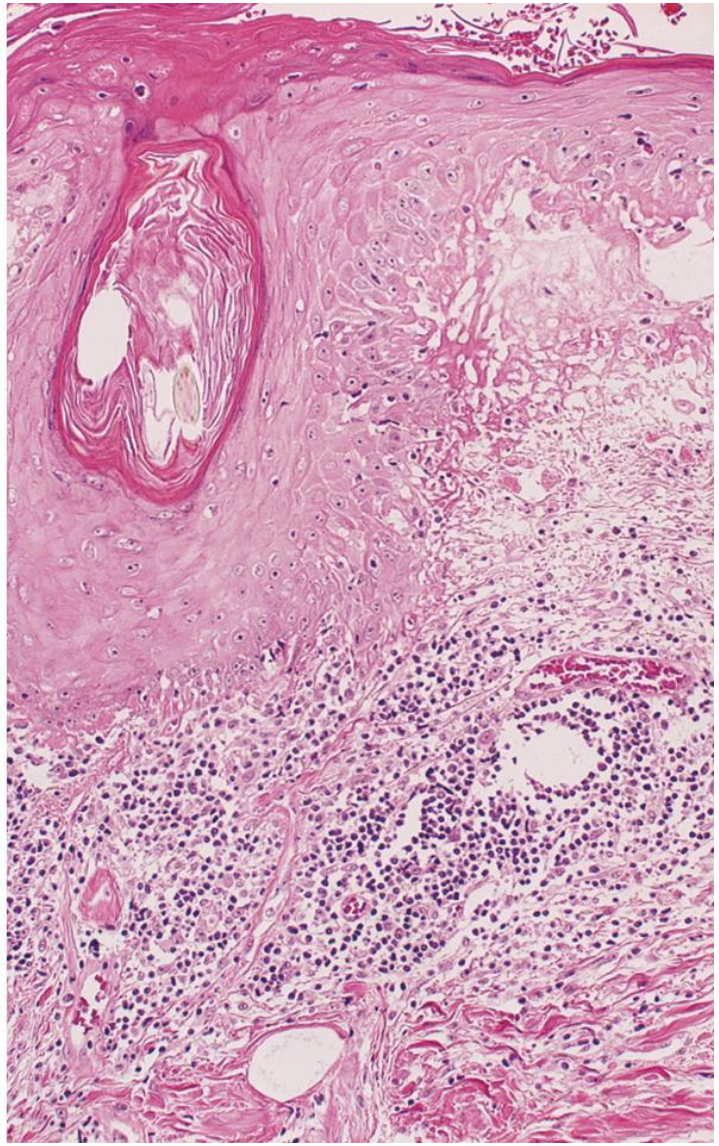




Butterfly rash in SLE (left: gross appearance of the facial skin, right: H&E). Miicroscopically, basal liquefaction, keratotic plugging and dense lymphocytic infiltration in the dermis are observed.

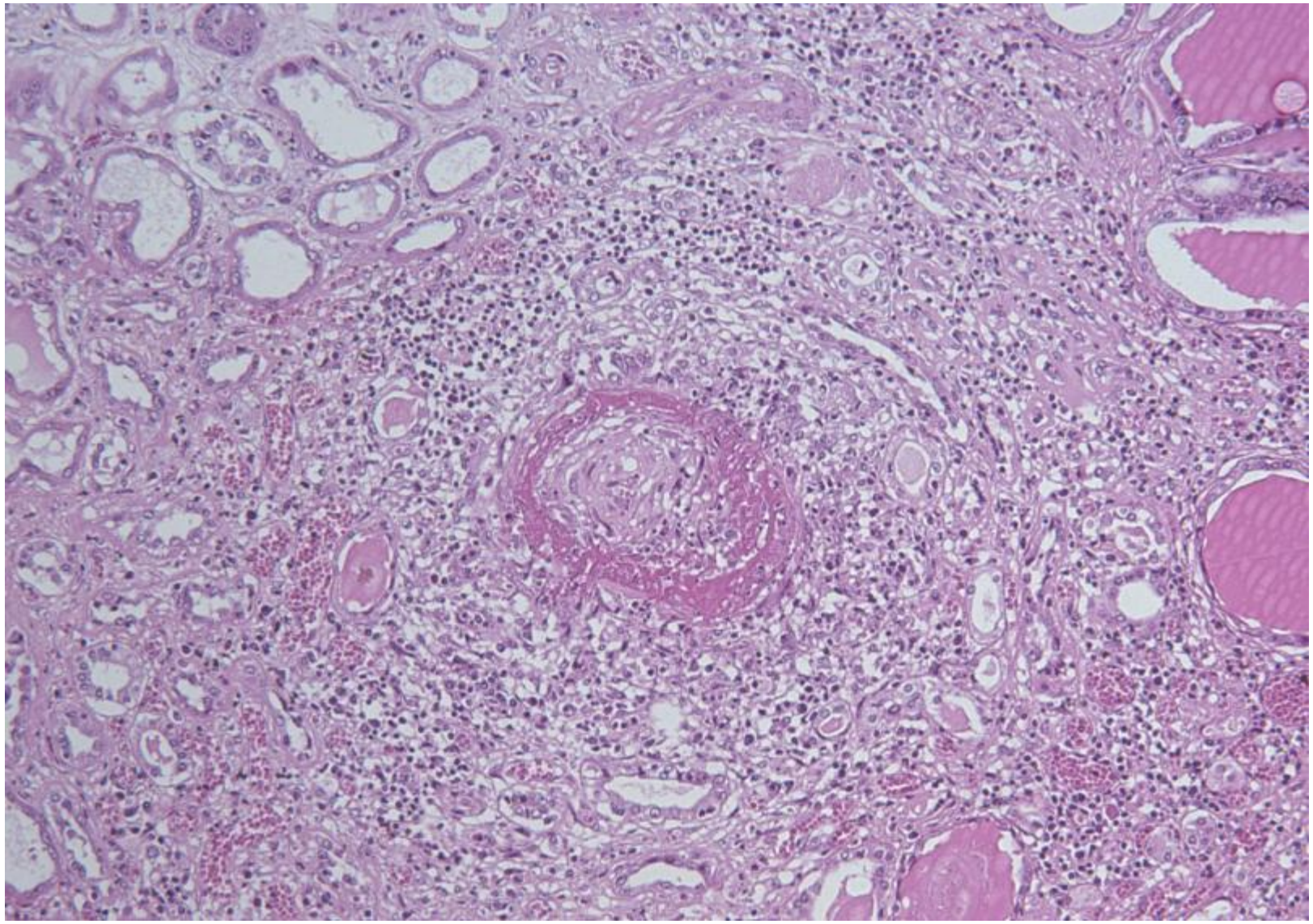
Type III hypersensitivity





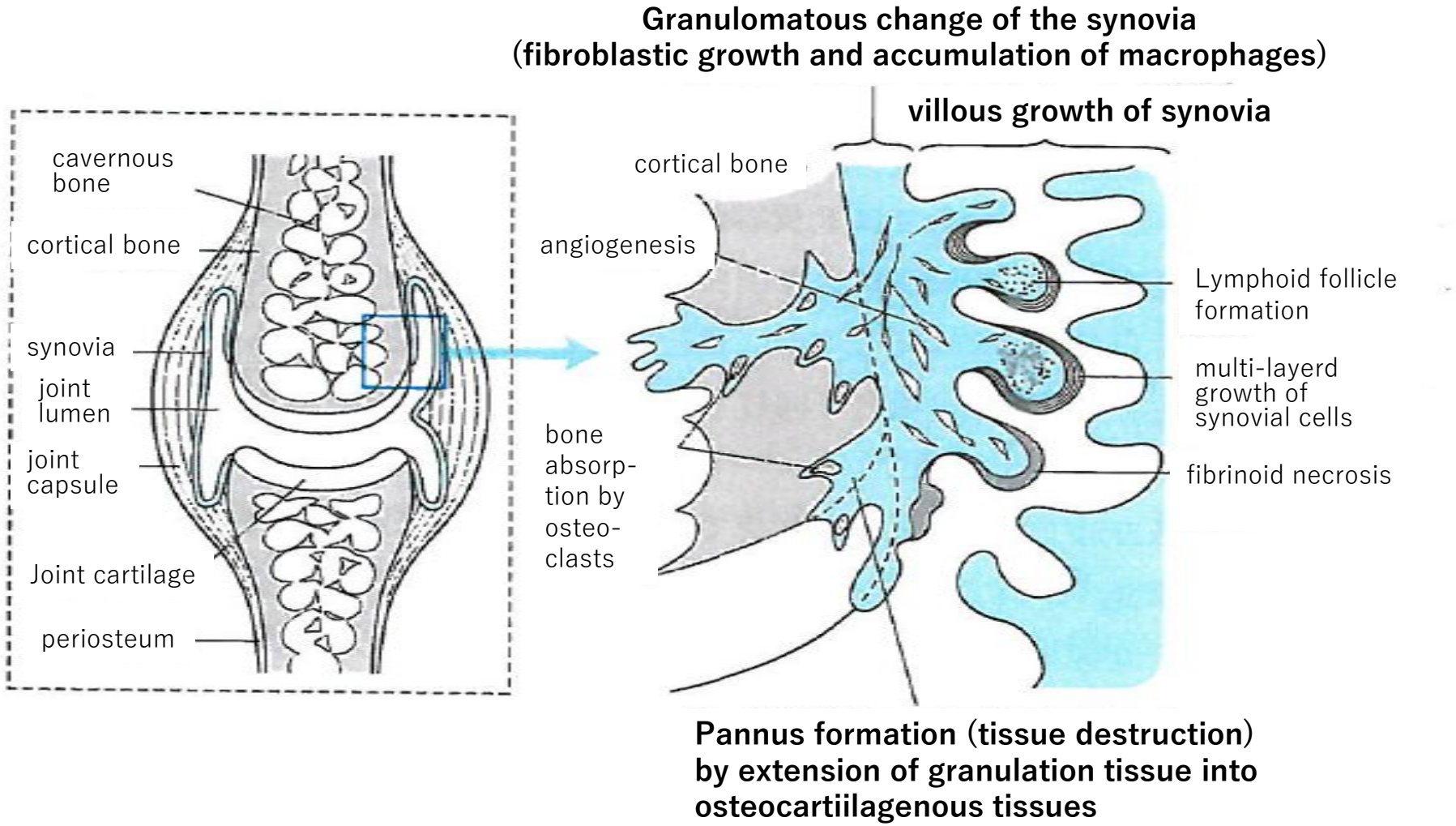
Discoid lupus erythematosus (left: gross appearance of the facial skin, right: H&E). Microscopic features of basal liquefaction, keratotic plugging and dermal lymphocytic infiltration are indistinguishable from SLE, but systemic symptoms are absent in this young male patient.

Type III hypersensitivity

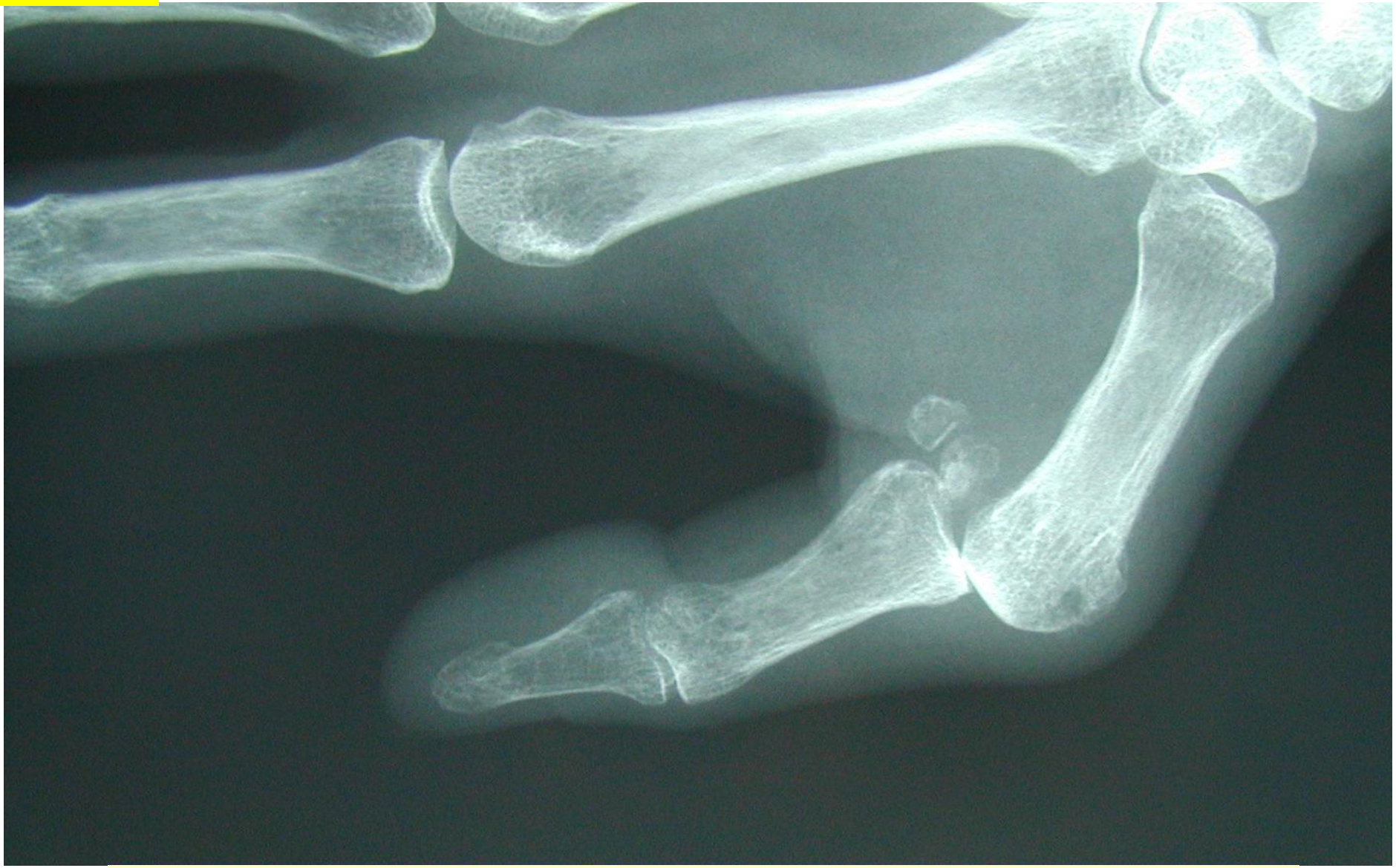


pANCA-positive microscopic polyarteritis nodosa (H&E). A small artery in the kidney reveals necrotizing angiitis with fibrinoid necrosis.

Synovial lesions in rheumatoid arthritis (RA)

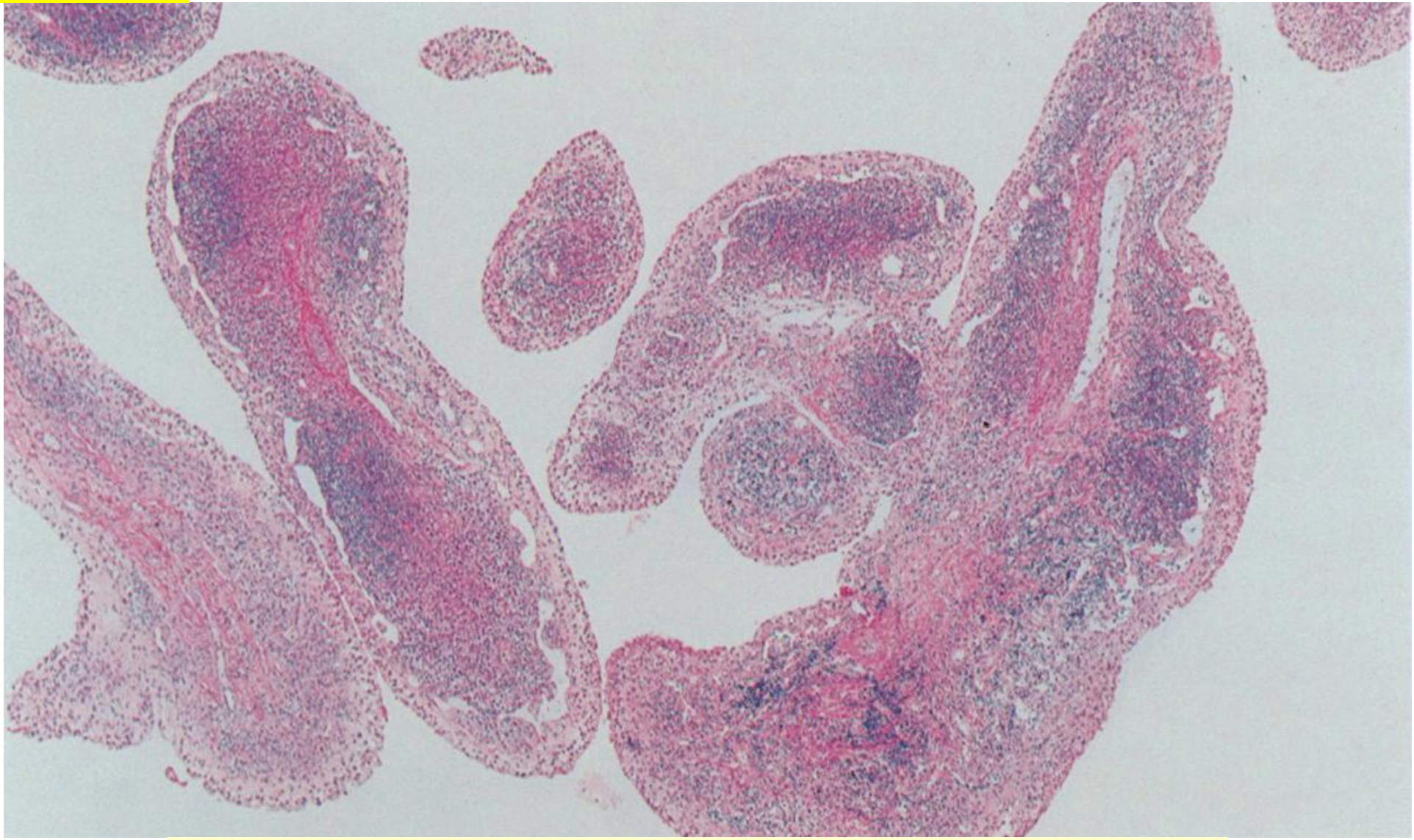


Type III hypersensitivity



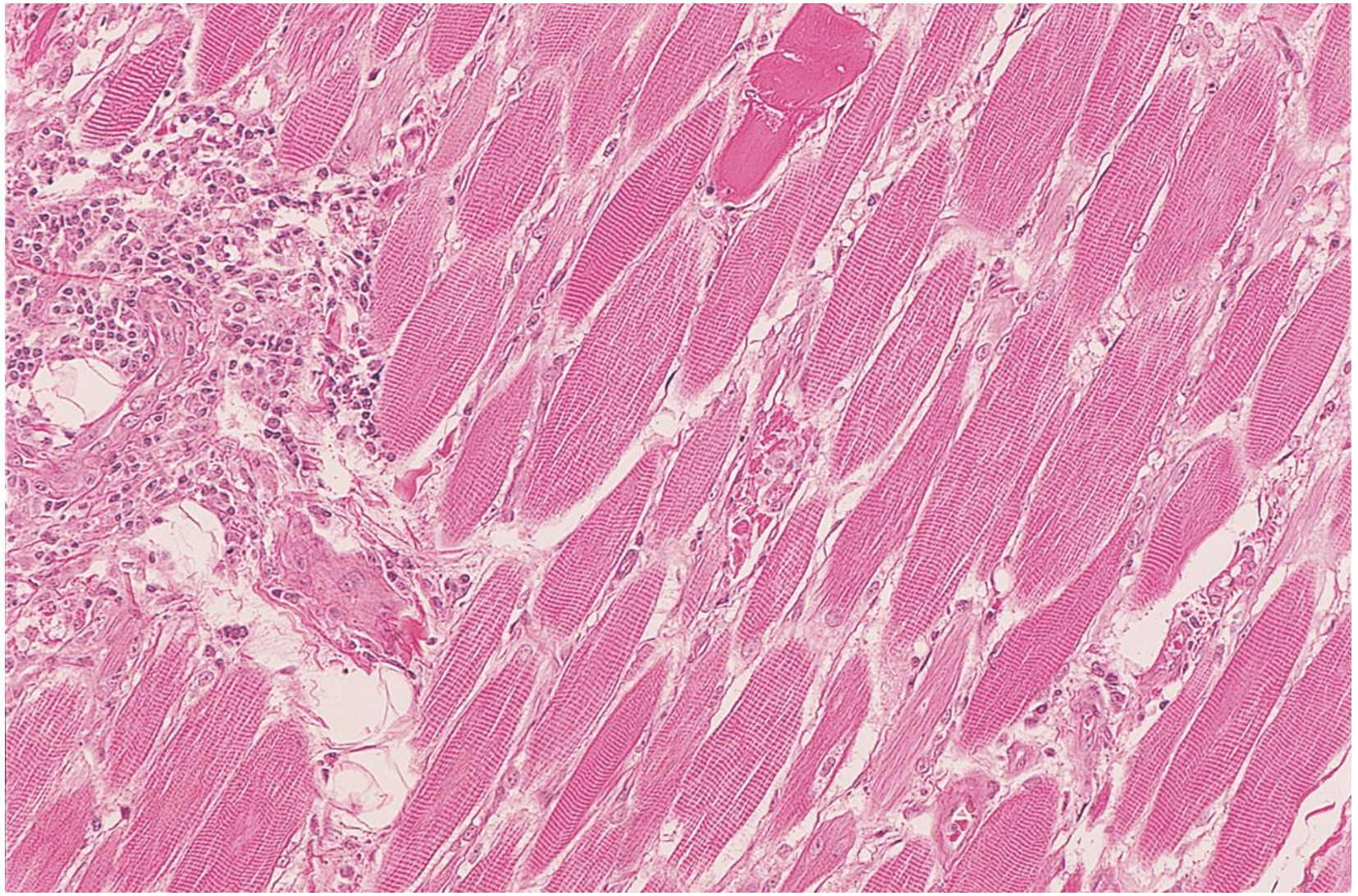
Inflammatory destruction and dislocation of the DIP joint in RA (the 5th finger, X-ray appearance)

Type III hypersensitivity



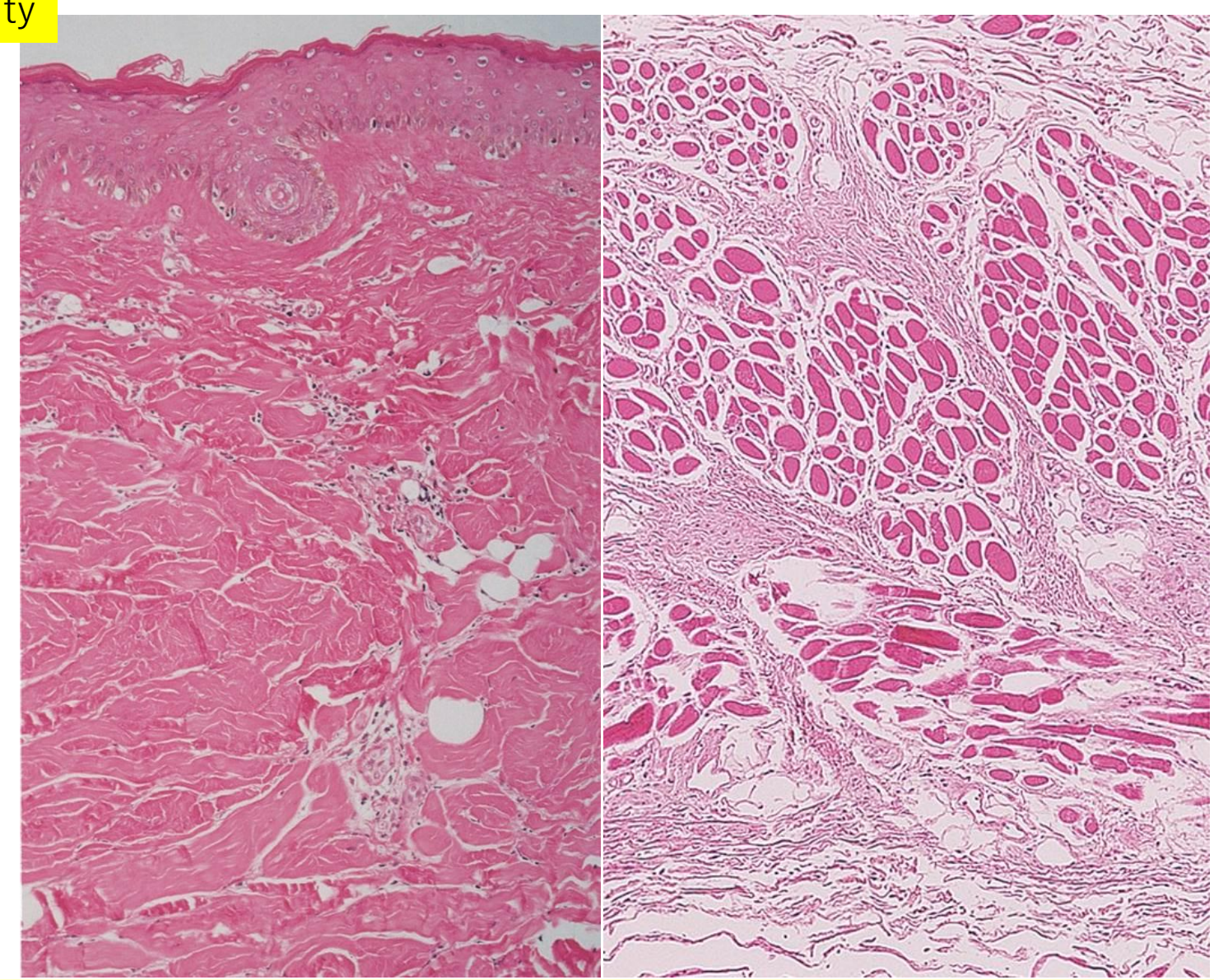
Rheumatoid arthritis (H&E). Pannus formation is shown. Lymphoid follicles are scattered in the inflamed synovia.

Type III hypersensitivity

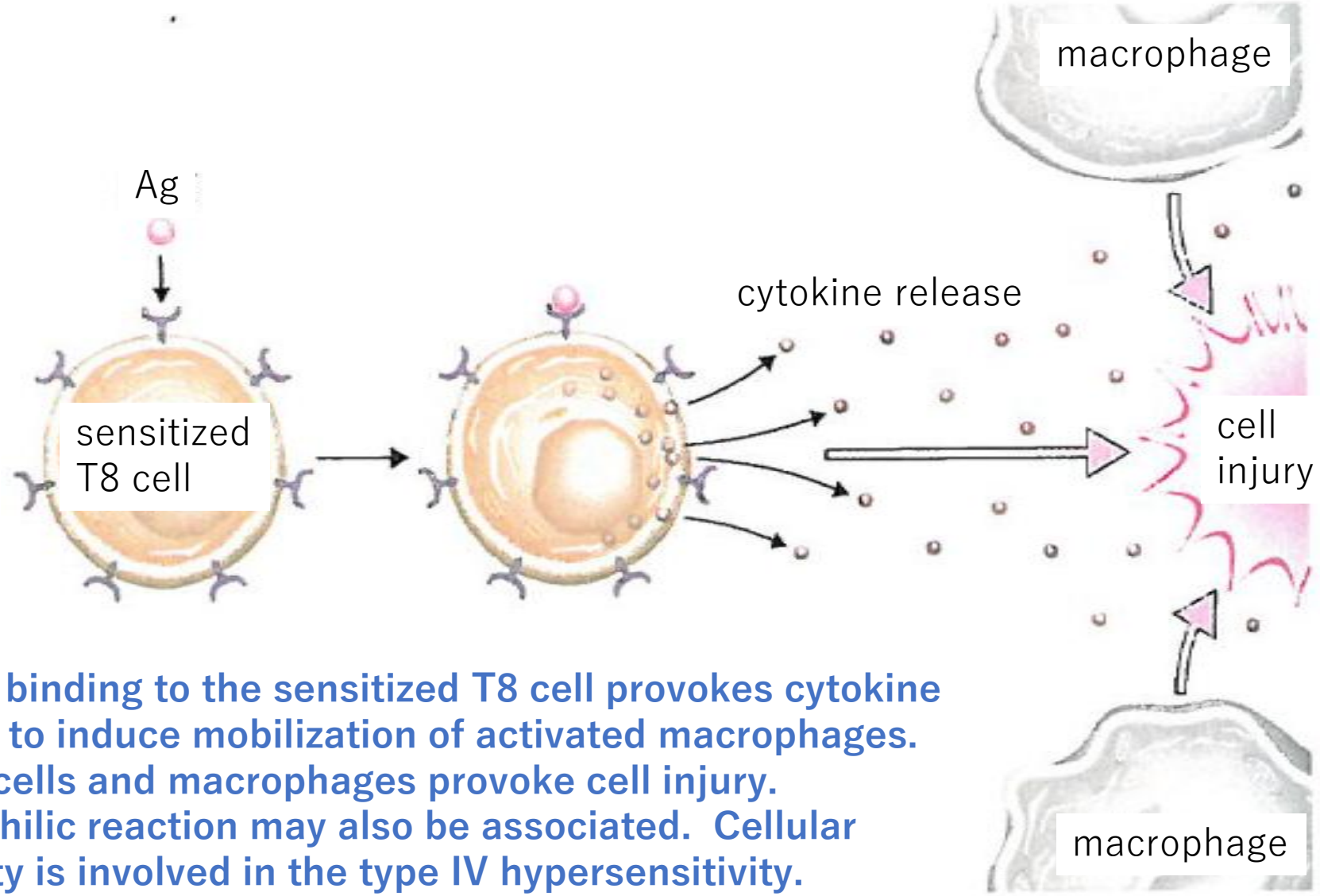


Dermatomyositis (H&E). Lymphocytic infiltration is focally seen in the stroma of striated muscles.

Type III hypersensitivity



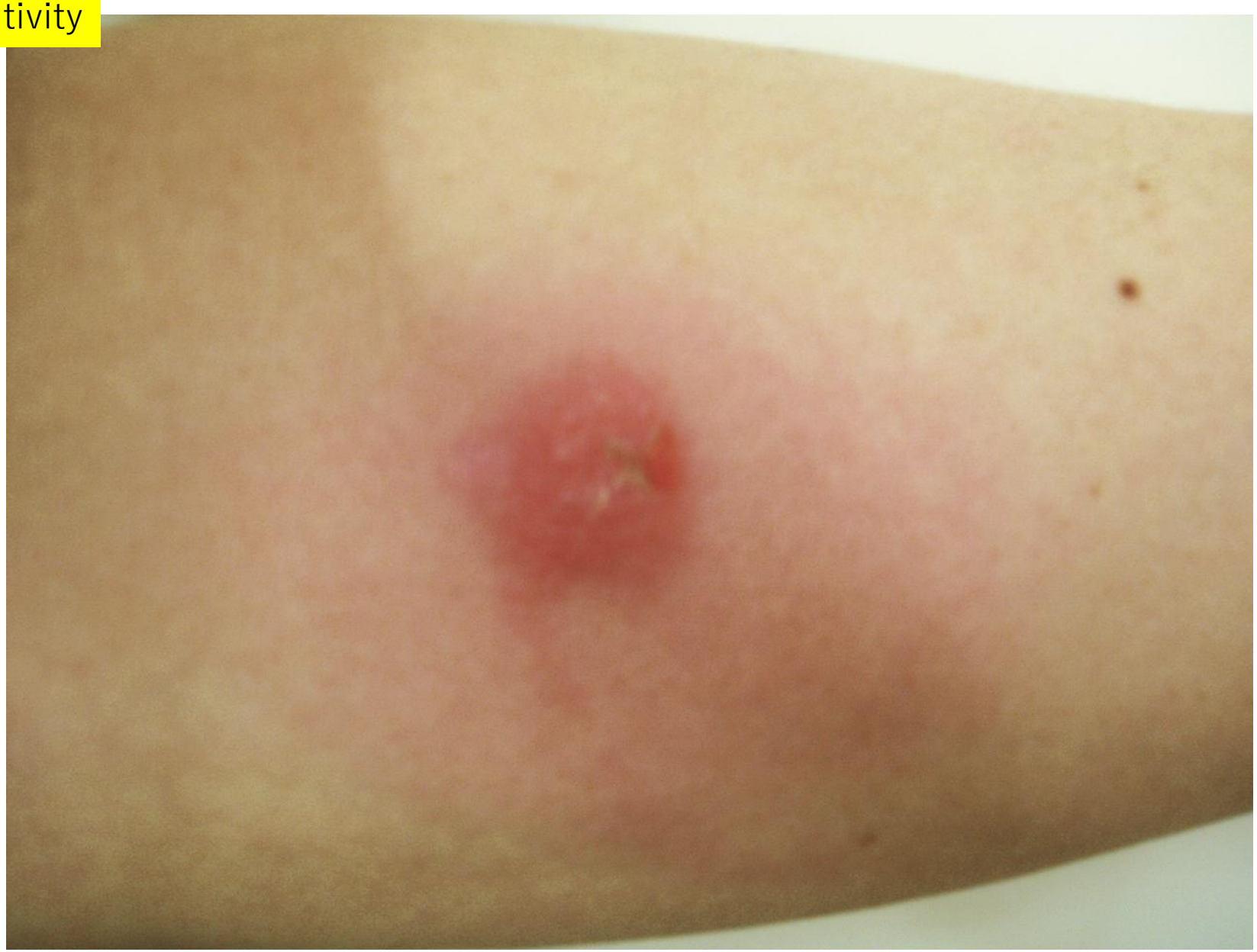
Systemic sclerosis (H&E, left: dermal fibrosis, right: fibrosis in the esophageal wall). In systemic sclerosis, fibrotic processes involve the esophagus and lung in addition to the skin.



Antigen binding to the sensitized T8 cell provokes cytokine release, to induce mobilization of activated macrophages. The T8 cells and macrophages provoke cell injury. Eosinophilic reaction may also be associated. Cellular immunity is involved in the type IV hypersensitivity.

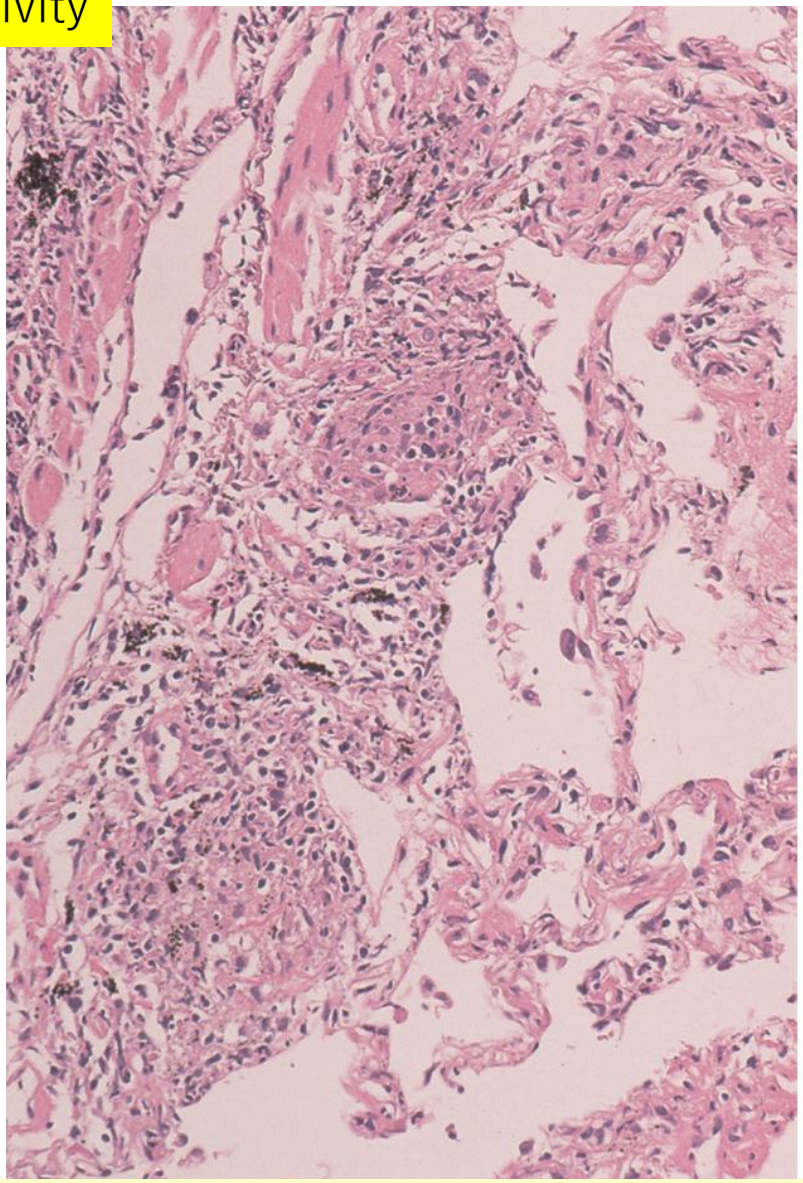
Type IV hypersensitivity (delayed hypersensitivity)

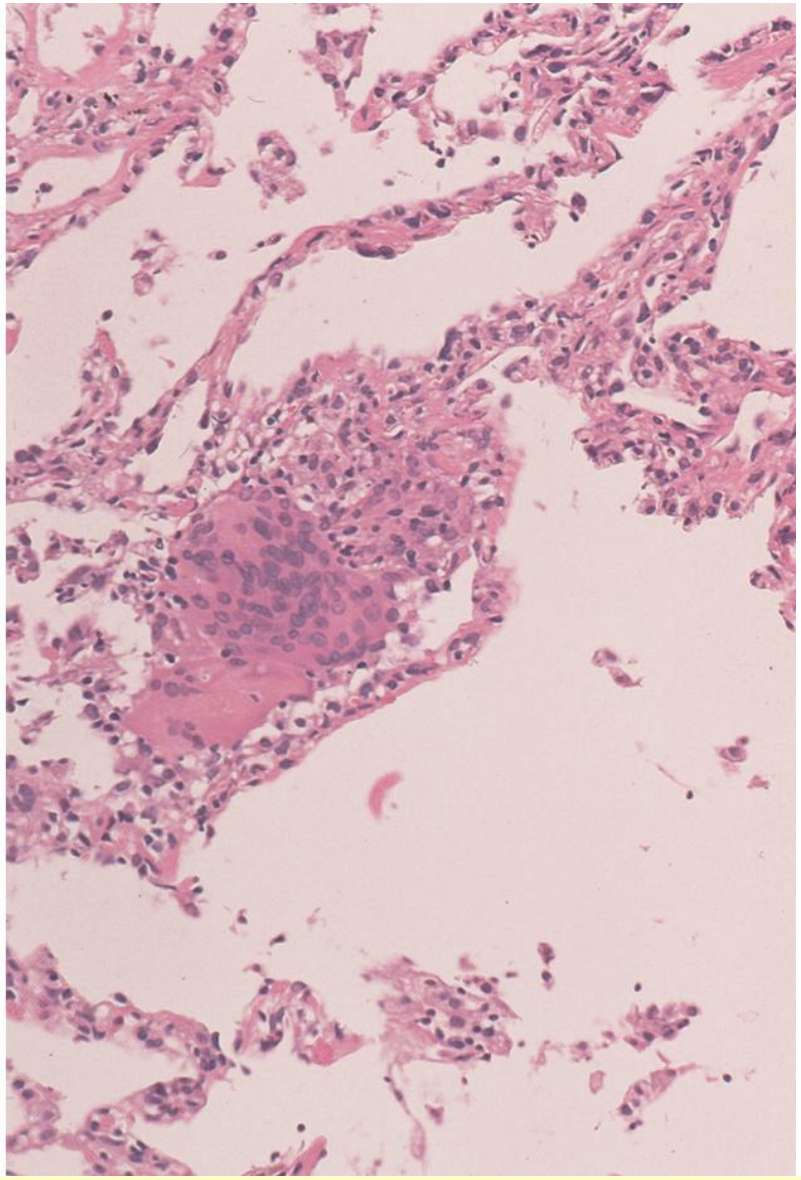
Type IV hypersensitivity



Gross appearance of tuberculin skin reaction: redness and nodule formation

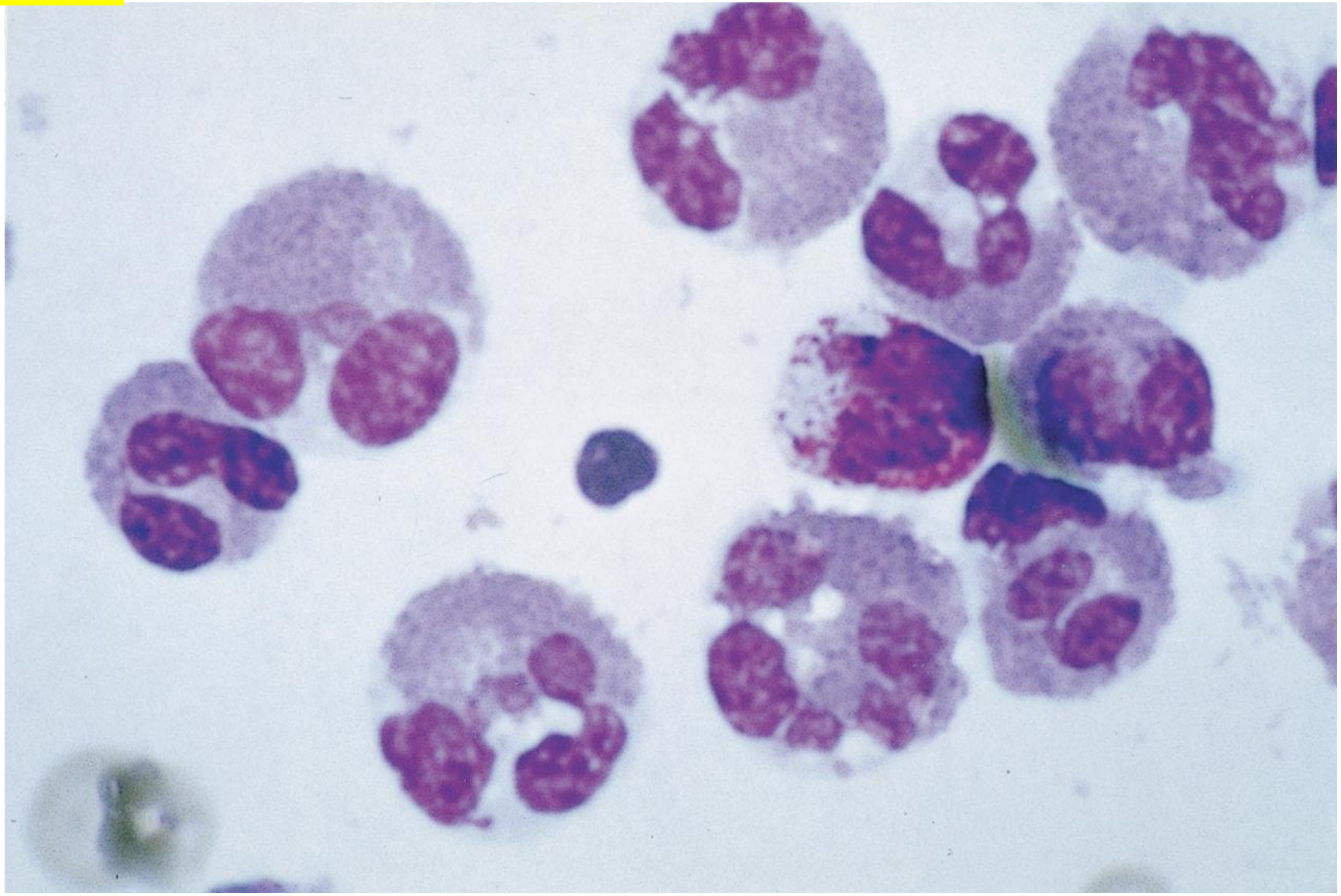
Type IV hypersensitivity





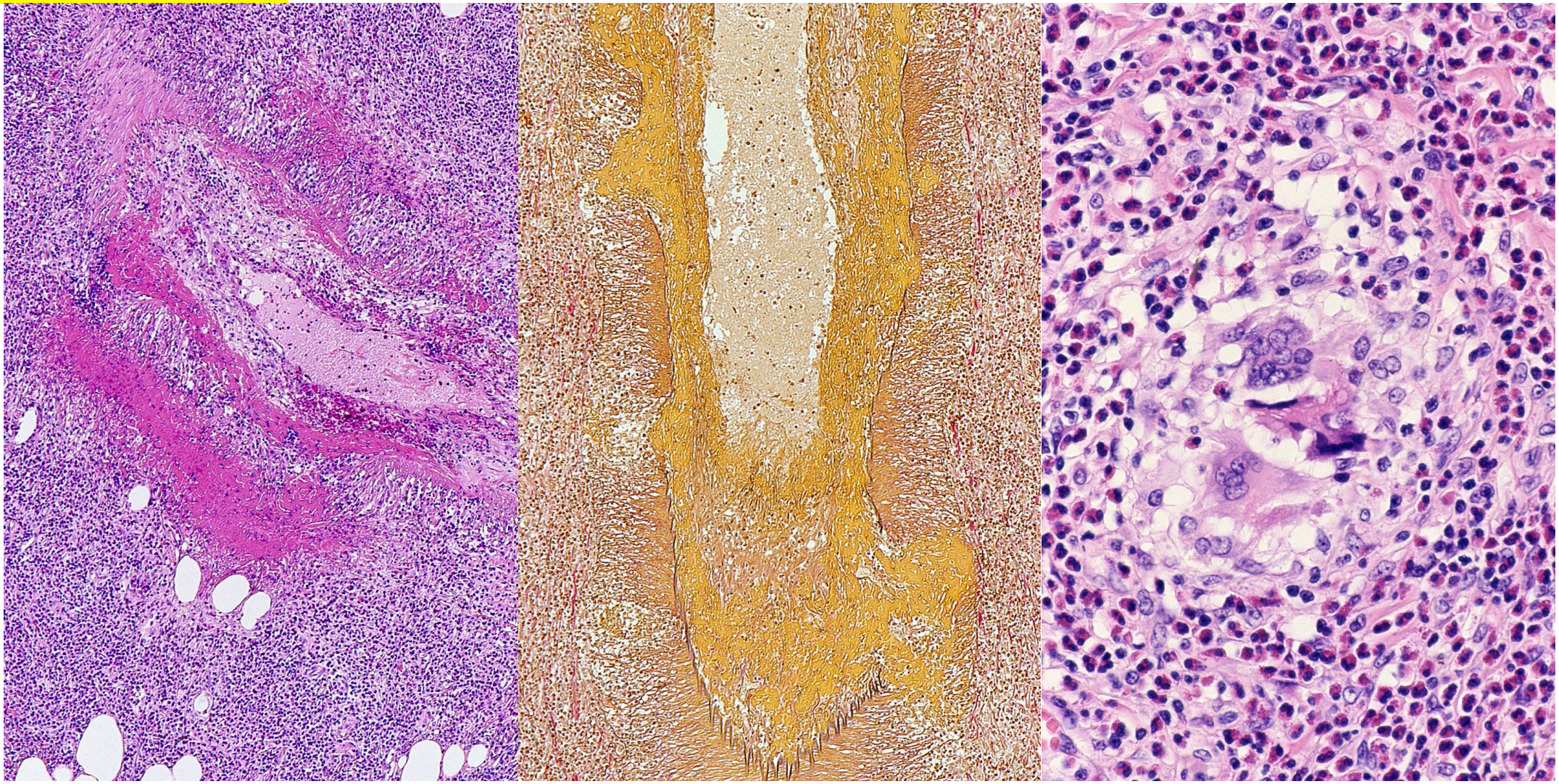
Hypersensitivity pneumonitis (H&E). Hypersensitivity pneumonia is caused by allergic reactions against Trichosporon fungi in the summer time. Small granulomas with multinucleated giant cells are formed in the peripheral lung tissue.

Type IV hypersensitivity



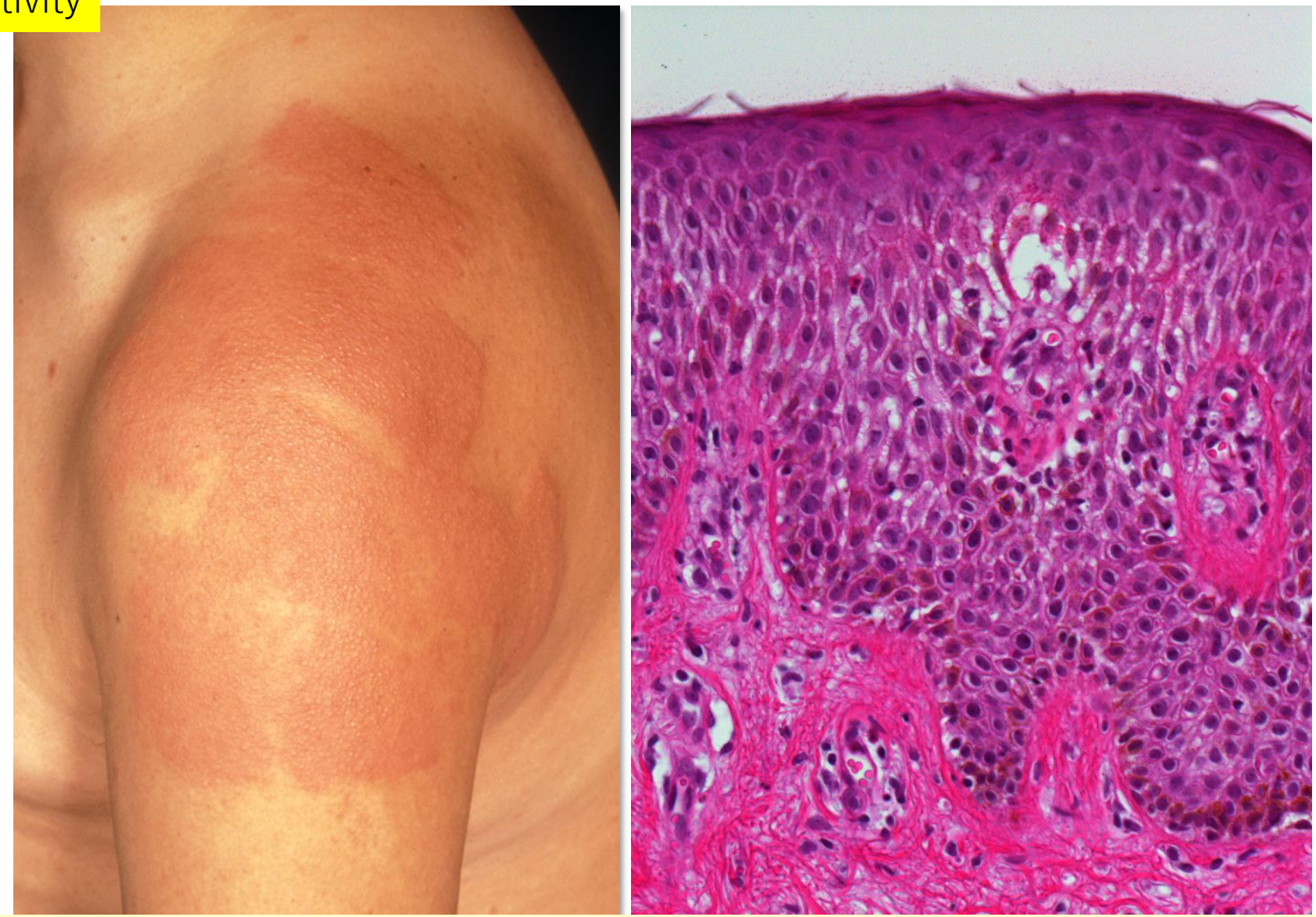
Eosinophilic reaction in the pleural effusion in pleural tuberculosis (May-Giemsa). Eosinophilic reaction may be associated with type IV hypersensitivity.

Type IV hypersensitivity



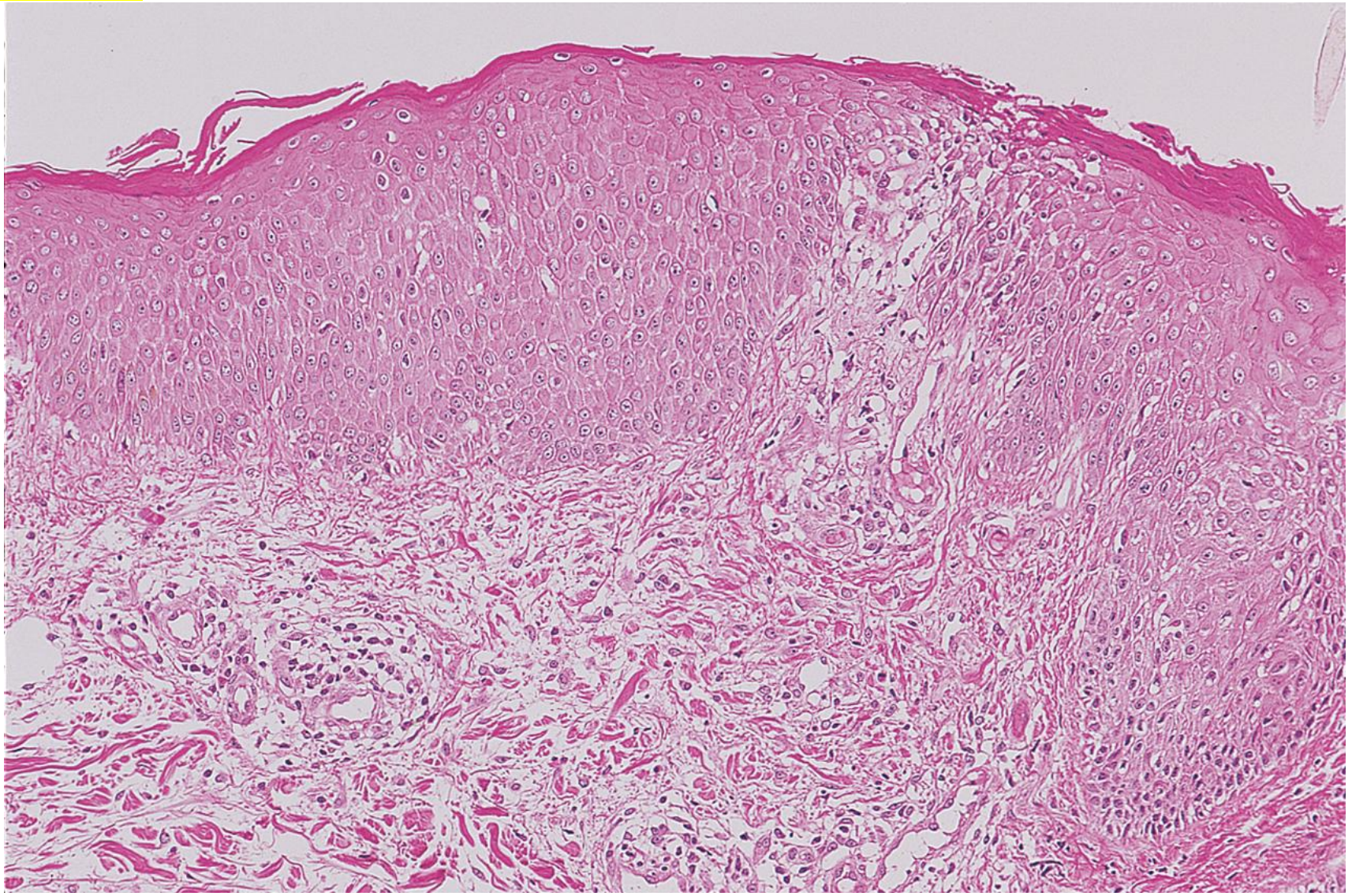
Churg Strauss syndrome (eosinophilic granulomatosis with polyangiitis) manifesting colonic perforation shows necrotizing angiitis of a small mural artery (left: H&E). Disruption of the elastic lamina is evident (center: EVG). Granulomatous reaction with marked eosinophilic infiltration is associated (right: H&E). This is an example of type IV hypersensitivity with eosinophilia.

Type IV hypersensitivity



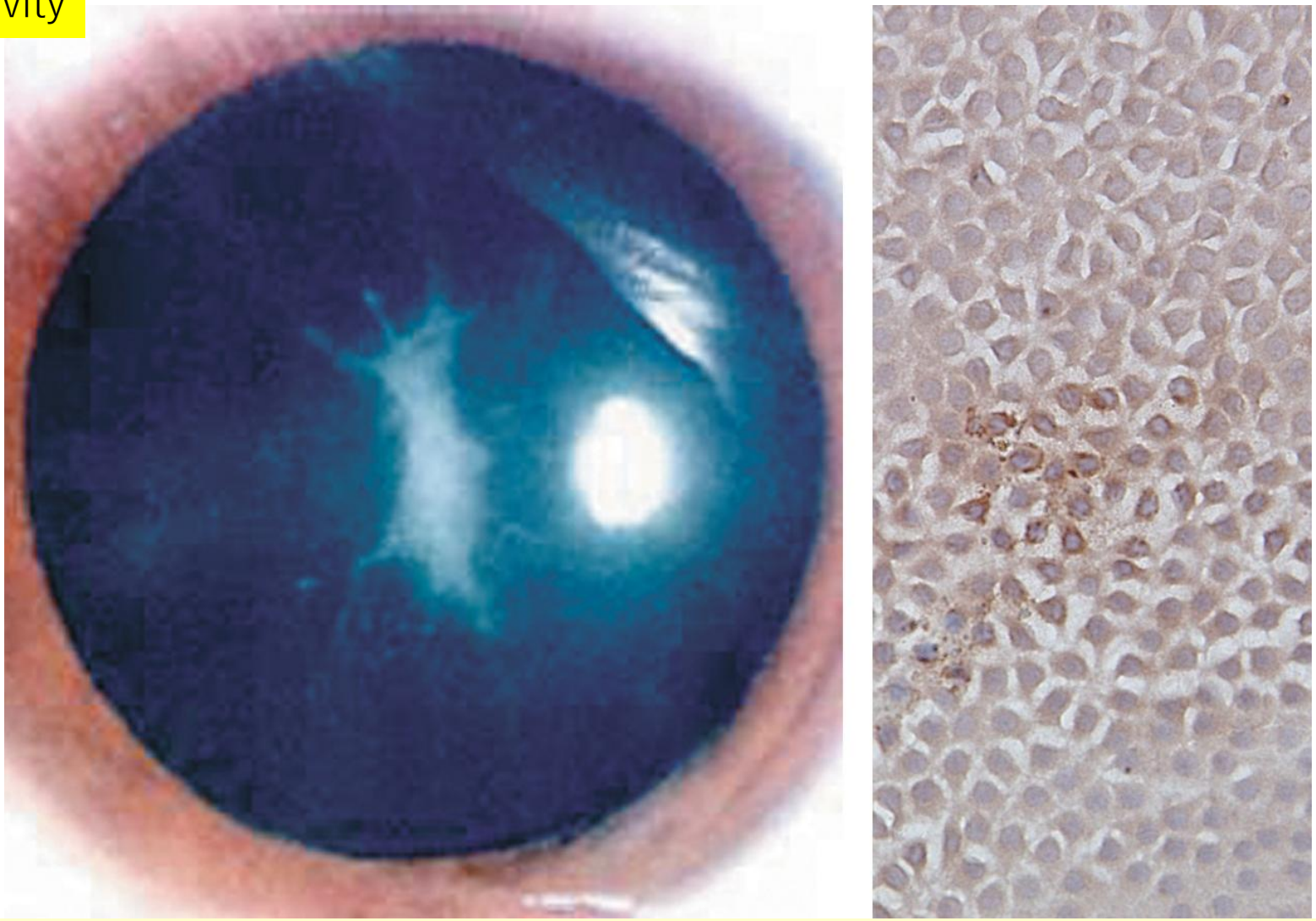
Contact dermatitis against the poultice (Salompas) (left: gross appearance, right: H&E). The shoulder skin pasted with the poultice shows demarcated redness with itching sensation. Microscopically, the epidermis is acanthotic and spongiotic.

Type IV hypersensitivity

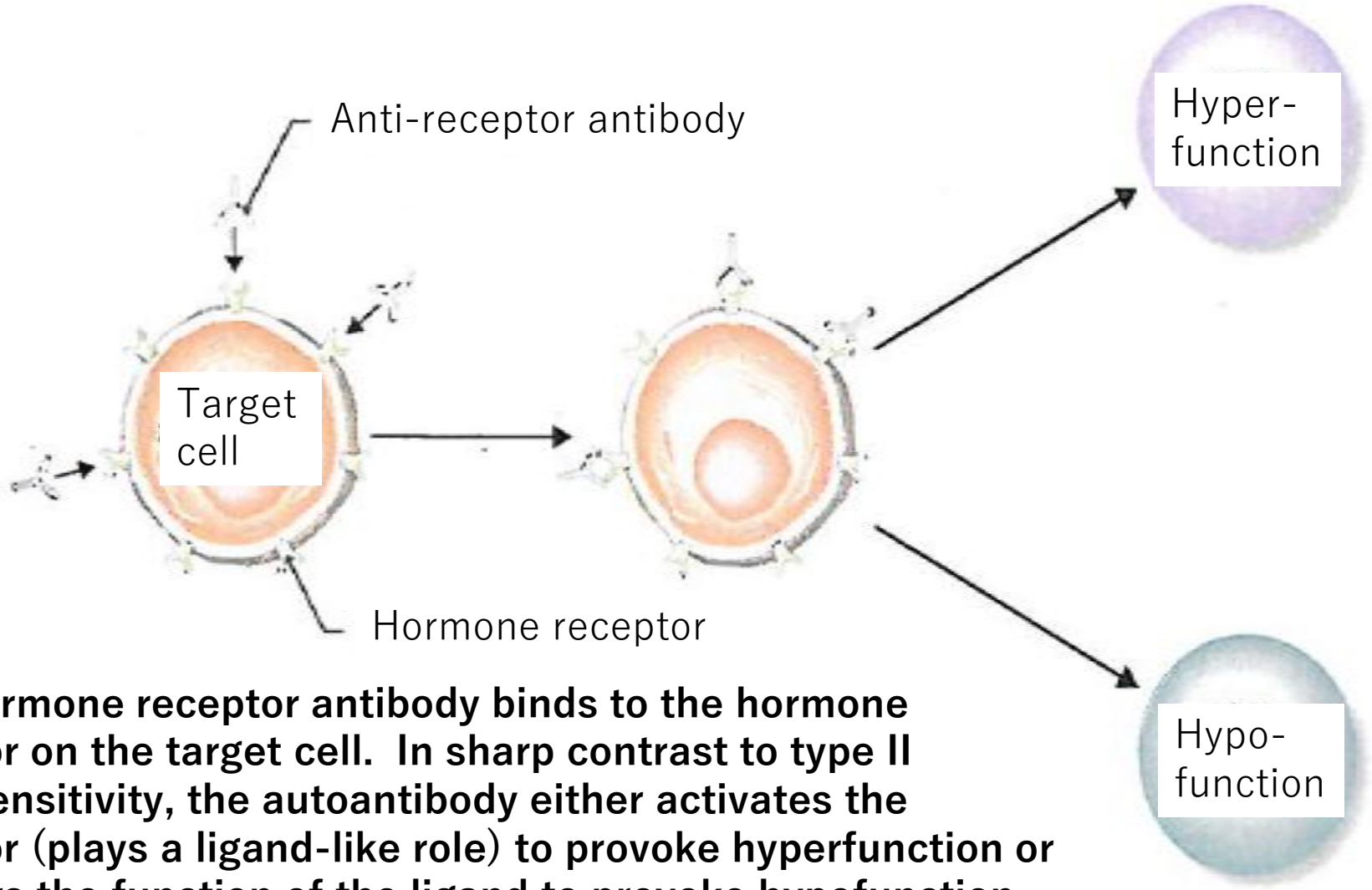


Atopic dermatitis (H&E), a form of type IV hypersensitivity. Irregular acanthosis, spongiosis and parakeratosis are observed microscopically.

Type IV hypersensitivity



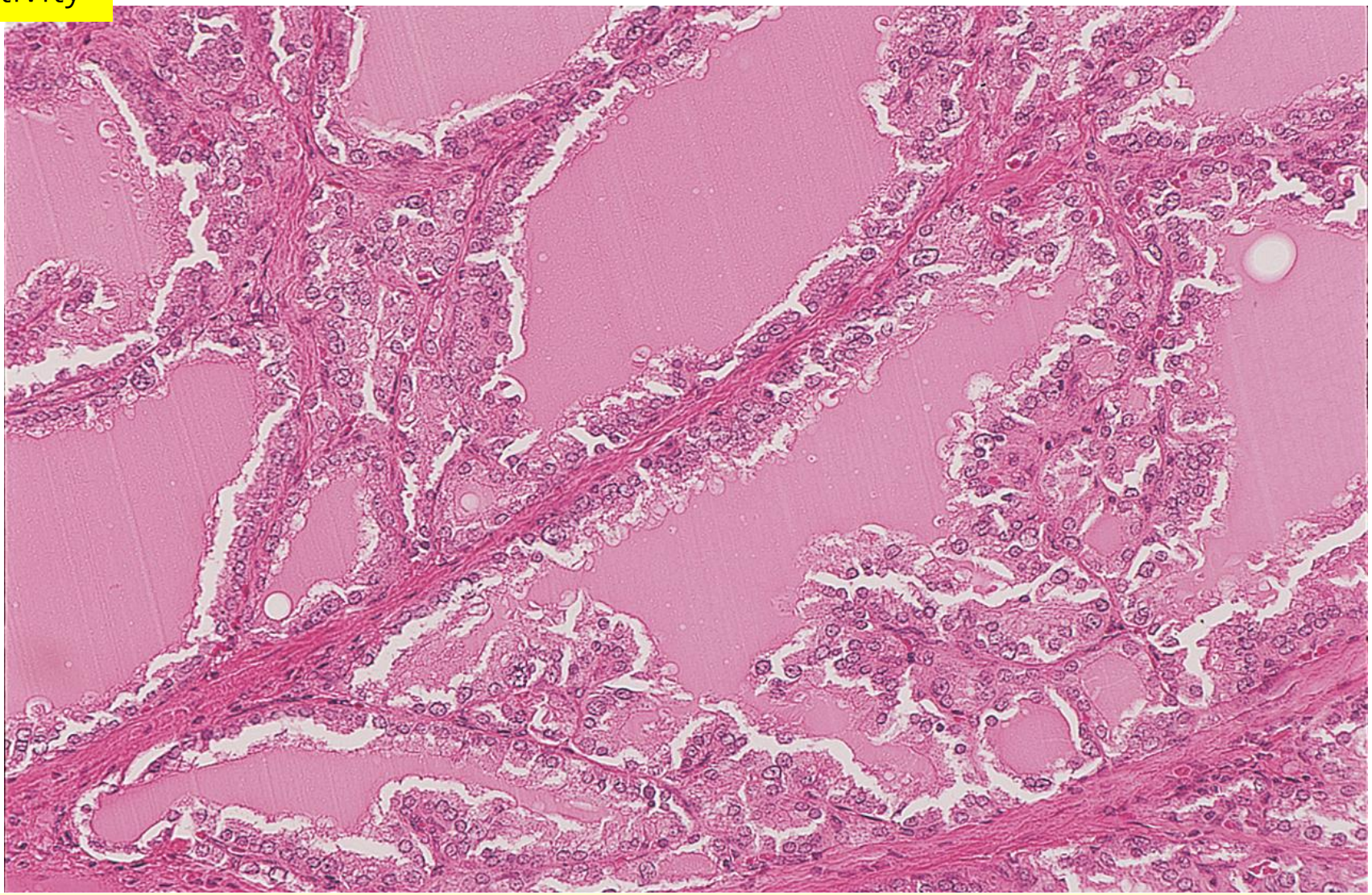
Atopic cataract (left: gross appearance, right: immunostaining for eosinophil-derived major basic protein (MBP) among the cultured lens epithelial cells). Rubbing of the eye due to itching sensation may cause cataract in the central part of the lens. MBP deposition is a potential cause of the cataract.



Anti-hormone receptor antibody binds to the hormone receptor on the target cell. In sharp contrast to type II hypersensitivity, the autoantibody either activates the receptor (plays a ligand-like role) to provoke hyperfunction or hampers the function of the ligand to provoke hypofunction.

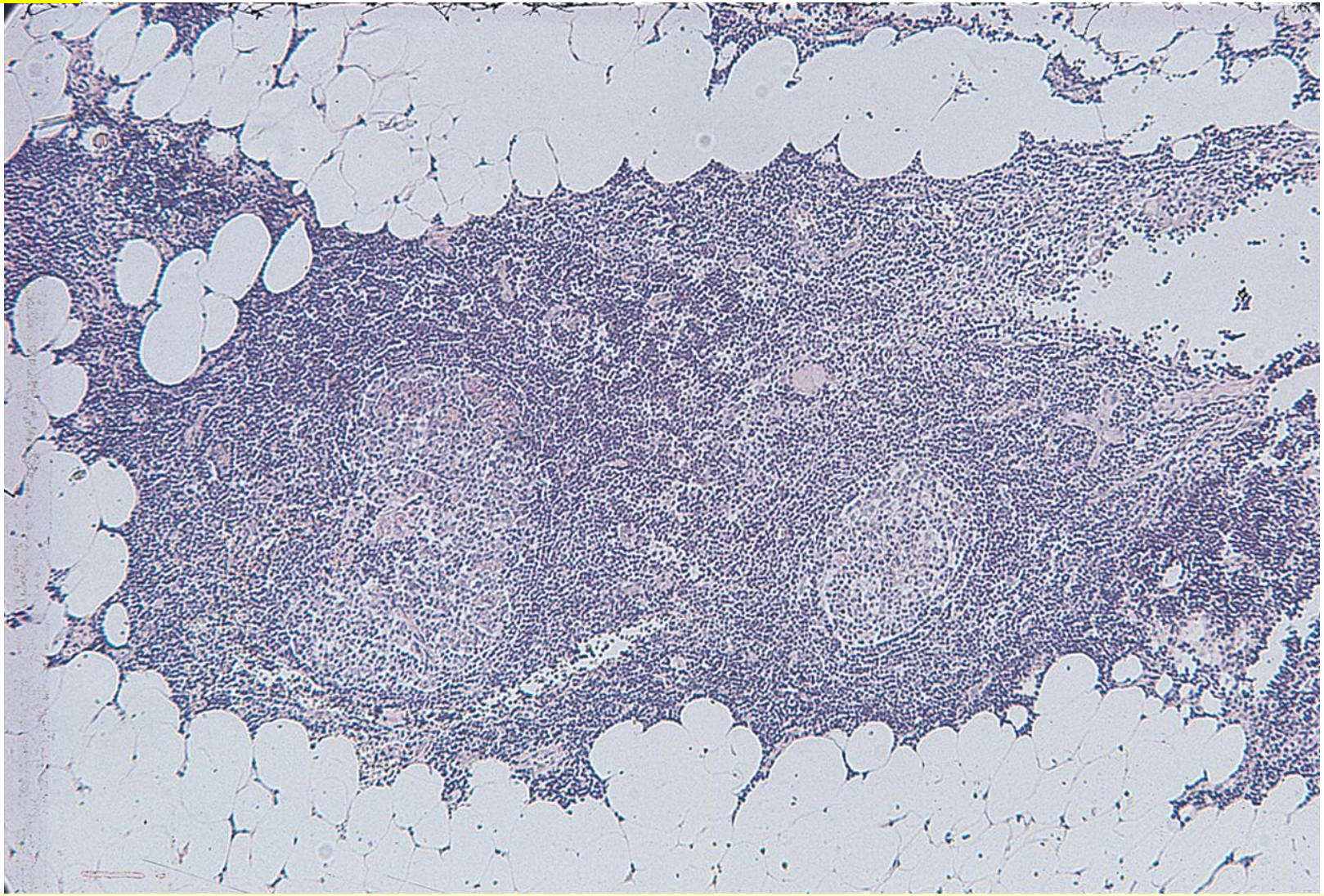
Type V hypersensitivity (anti-receptor type reaction)

Type V hypersensitivity



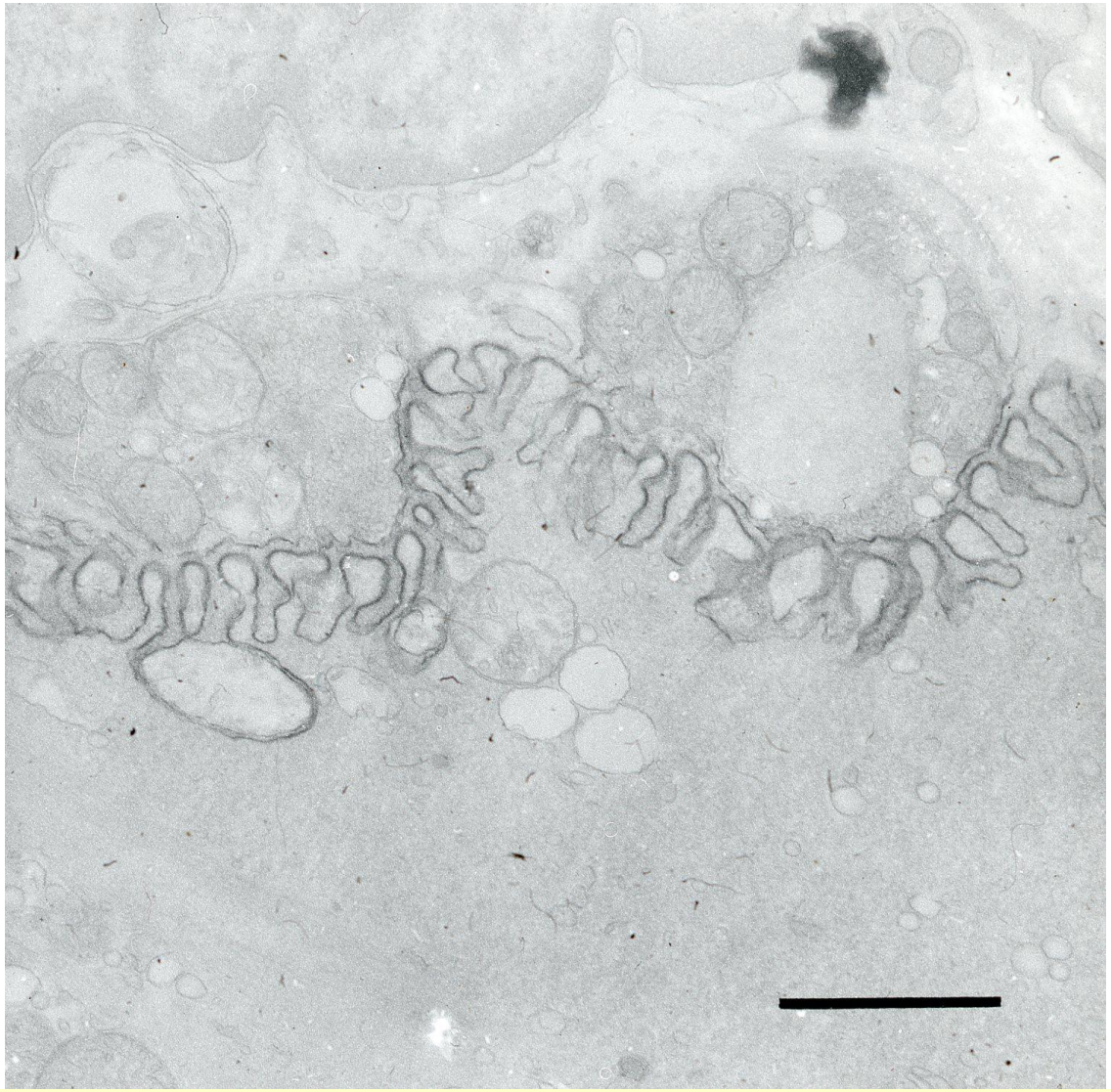
Graves' disease (H&E). In Graves' disease, the autoantibody against TSH receptor activates the thyroid function. Microscopically, the thyroid follicular epithelial cells show papillary infoldings with scalloping in the colloid.

Type V hypersensitivity



Myasthenia gravis (thymus, H&E). In myasthenia gravis, anti-acetylcholine receptor antibody hampers the normal function of neuromuscular junctions. The thymus often reveals hyperplasia of B-cells with lymphoid follicle formation. Thymoma may also be associated.

Type V hypersensitivity



Ultrastructural visualization of neuromuscular junction in normal striated muscle using peroxidase-labeled alpha-bungarotoxin. Nicotinic acetylcholine receptor is visualized. The bungarotoxins are a paralytic venom of venomous snakes. The acetylcholine receptor at the neuromuscular junction is the target of myasthenia gravis.