Transplantation

APPROVED

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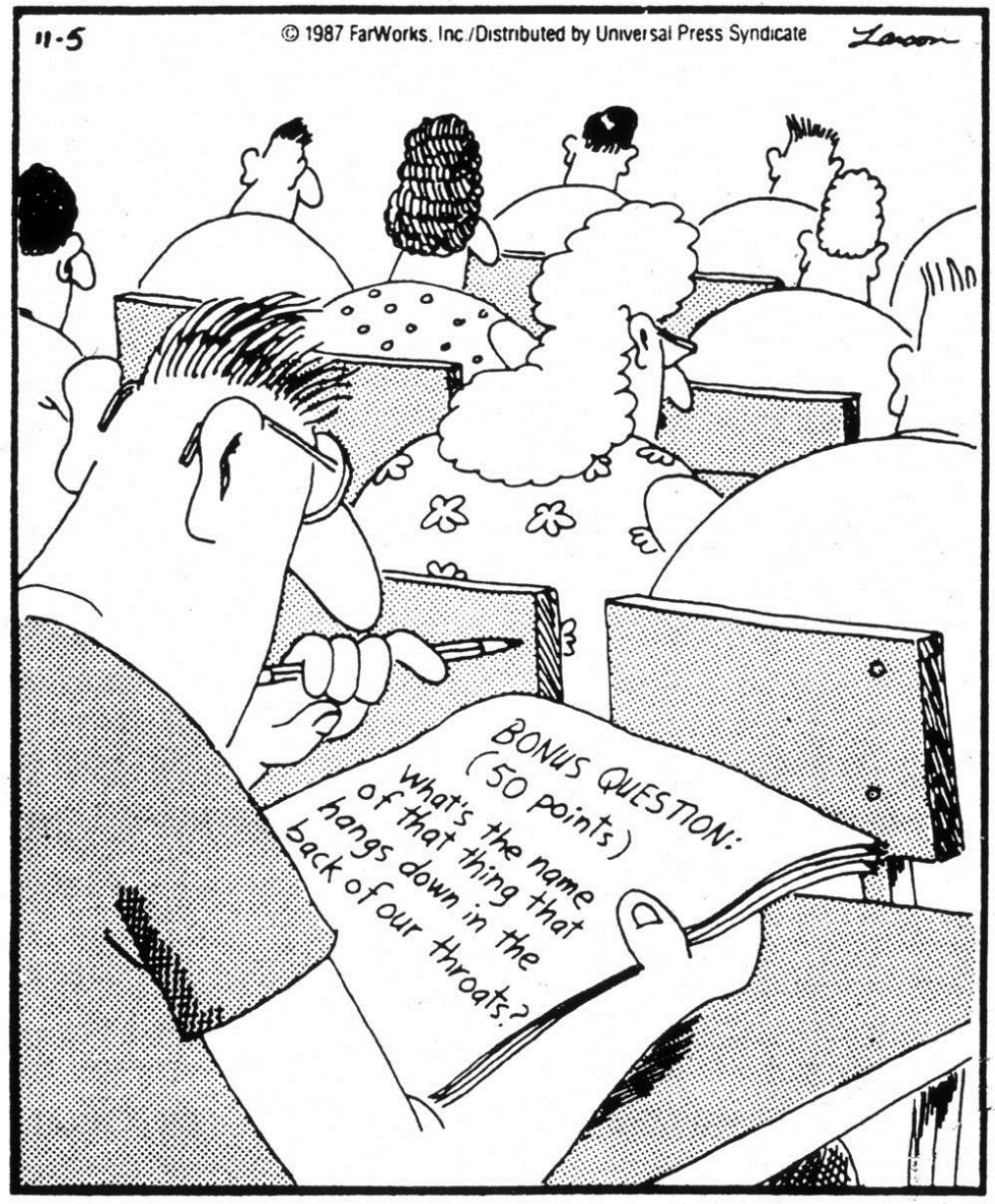
Objectives

He is interested in terminology so I would make sure I know the definitions

- **List and define the various types of donor-recipient organ transplant combinations, organ graft sites, donors and modes of rejection**
- **Recognize signs of rejection and take appropriate action**
- **Identify evidence of rejection from organ biopsies**
- **List the indications for bone marrow transplantation**
- **Describe the procedure for recipient preconditioning prior to bone marrow transplantation**
- **Anticipate acute and chronic problems associated with solid organ and bone marrow grafts**

The Far Side / Gary Larson



Final page of the Medical Boards

Transplantation Definitions
Types of transplant: tissues

Duke has one of the largest lung transplant centers in the country

Vascularized solid organs

- Kidney
- Liver
- Heart
- Lung
- Pancreas
- Small Bowel

Cornea

Skin

Bone Marrow

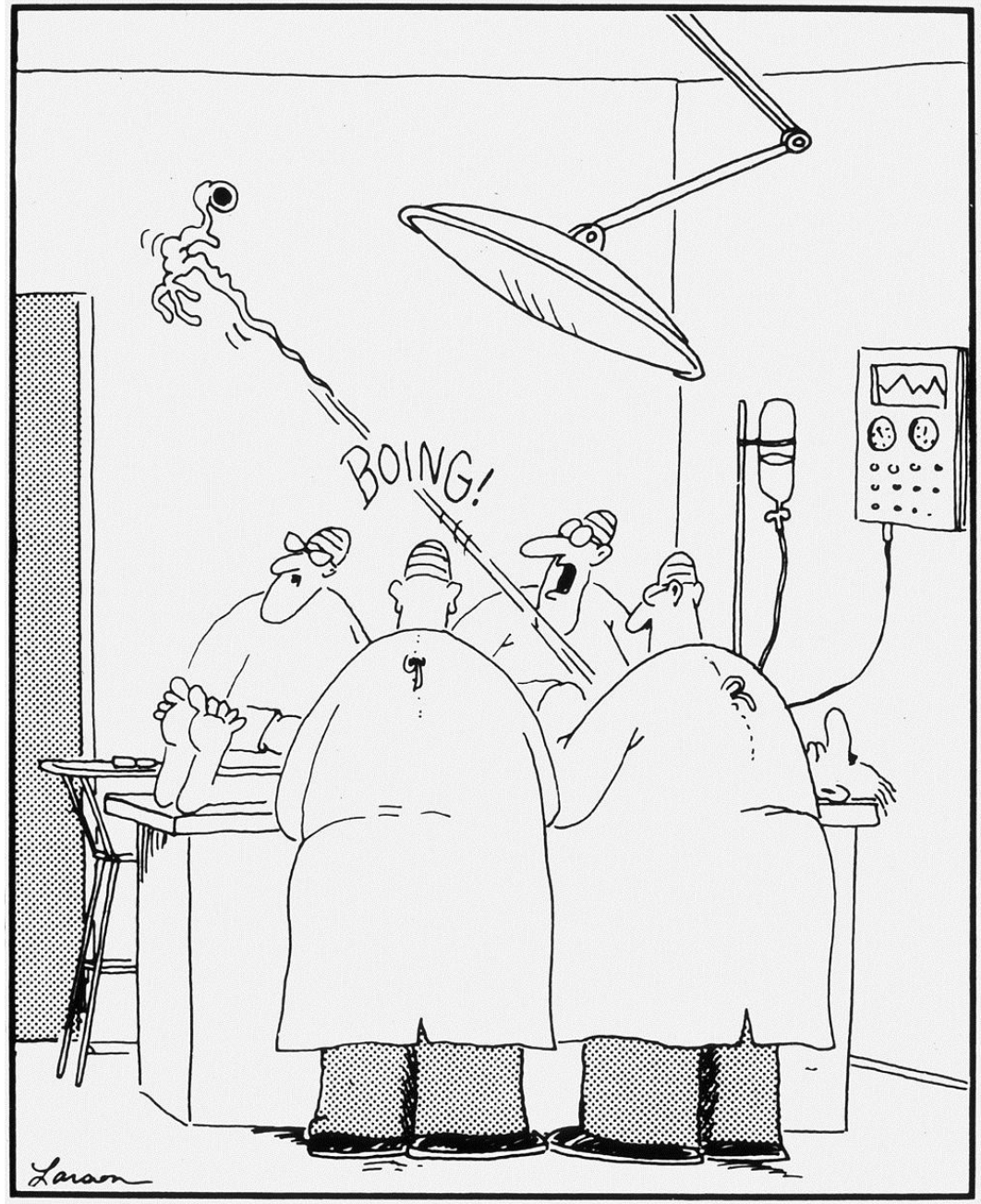
Blood and blood products

Cell suspensions

Pancreatic islet cells

Fetal adrenal cells

can be injected into the brain for Parkinson's disease



"Whoa! Watch where that thing lands — we'll probably need it."

Transplantation Definitions
Donor-recipient combination

Know these they are part of the objectives

can bank your own blood prior to surgery and then have a blood transfusion of your own blood

Autograft: donor and recipient same individual

ex. Burn patient; skin graft from another part of body

Isograft: donor and recipient genetically identical

identical twins

Allograft: donor and recipient genetically disparate individuals of same species

Xenograft: donor and recipient of different species

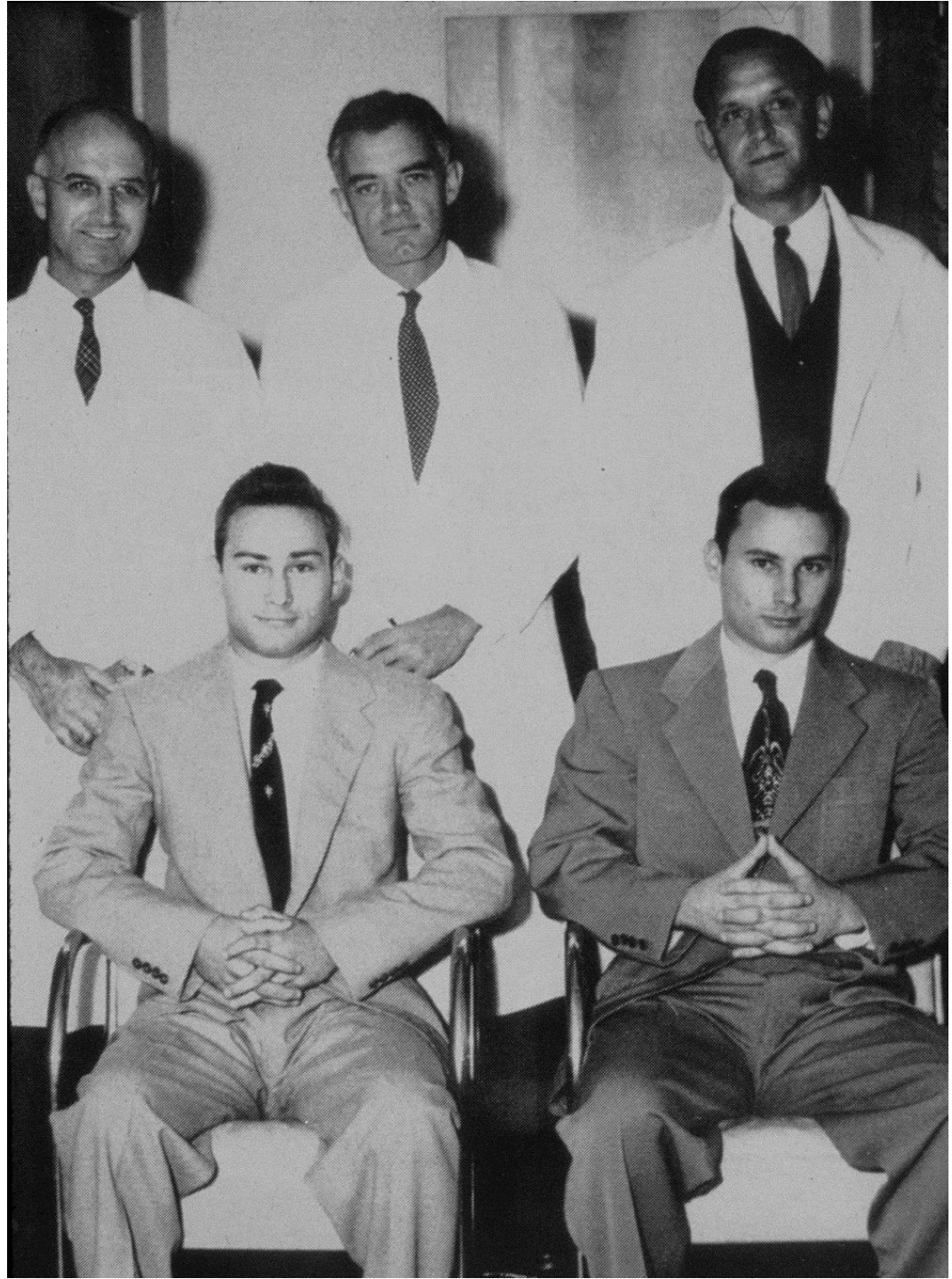
- **concordant:** preformed antibody **absent**
- **discordant:** preformed antibody **present**

humans do not have preformed antibodies to chimpanzee organs

this used to be a hot topic esp. pigs, but pigs are discordant

human do have preformed antibodies to pig organs-- problems for transplanting

Pigs used for heart valve transplants?
Yes, and we also use calf pericardium. The cells that go in are killed so do not have antigens and are incorporated into the endothelium of the heart



Isograft transplant: 1954
The recipient lived 8 yrs after transplant.

Transplantation Definitions

Site of graft

typically done for heart, lung, liver, small bowel transplants

Orthotopic: graft implanted in same site as organ it replaces

Out with the bad-- In with the good. This is what is classically thought of when we think of organ transplantation

Heterotopic: graft implanted in site distinct from organ it replaces

This occurs when new kidneys and pancreas are inserted into host. For example kidneys go into pelvis at a "distinct" site, while old kidneys stay in the retroperitoneum.

Types of allograft: donors

Living related

blood relatives

Living unrelated

non blood relatives; husband and wife pairs or altruistic donations

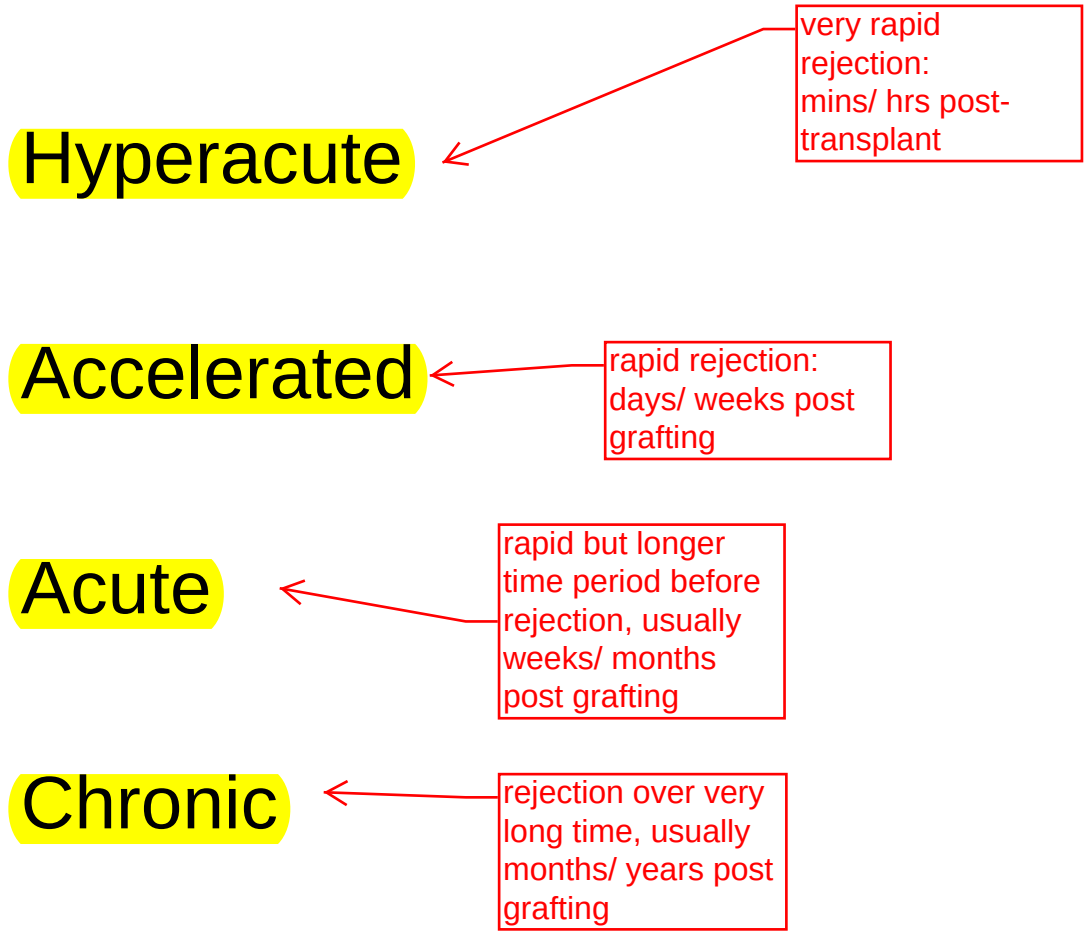
Cadaveric

this constitutes the majority of transplants

Individual usually has died due to trauma. usually the patient is brain dead but still has a beating heart

Modes of allograft rejection

Listed in order of time course



FASTEST

Hyperacute allograft rejection

- Typical scenario:
  - Transplant is put in place, Blood vessels are hooked up, vascular clamps are opened up, organ swells up and quickly turns purple/black & must be immediately taken out

Onset: minutes to hours after anastomosis of graft

Timecourse: minutes to hours

Mechanism: binding of preformed antibodies to graft antigens (HLA, ABO, other), followed by complement fixation, attraction of neutrophils, and tissue damage

(Type II hypersensitivity)

antibodies usually against MHC or blood antibodies

Endothelial damage is mediated by pre-formed antibodies in the recipient

antibody mediated reaction

Hyperacute allograft rejection

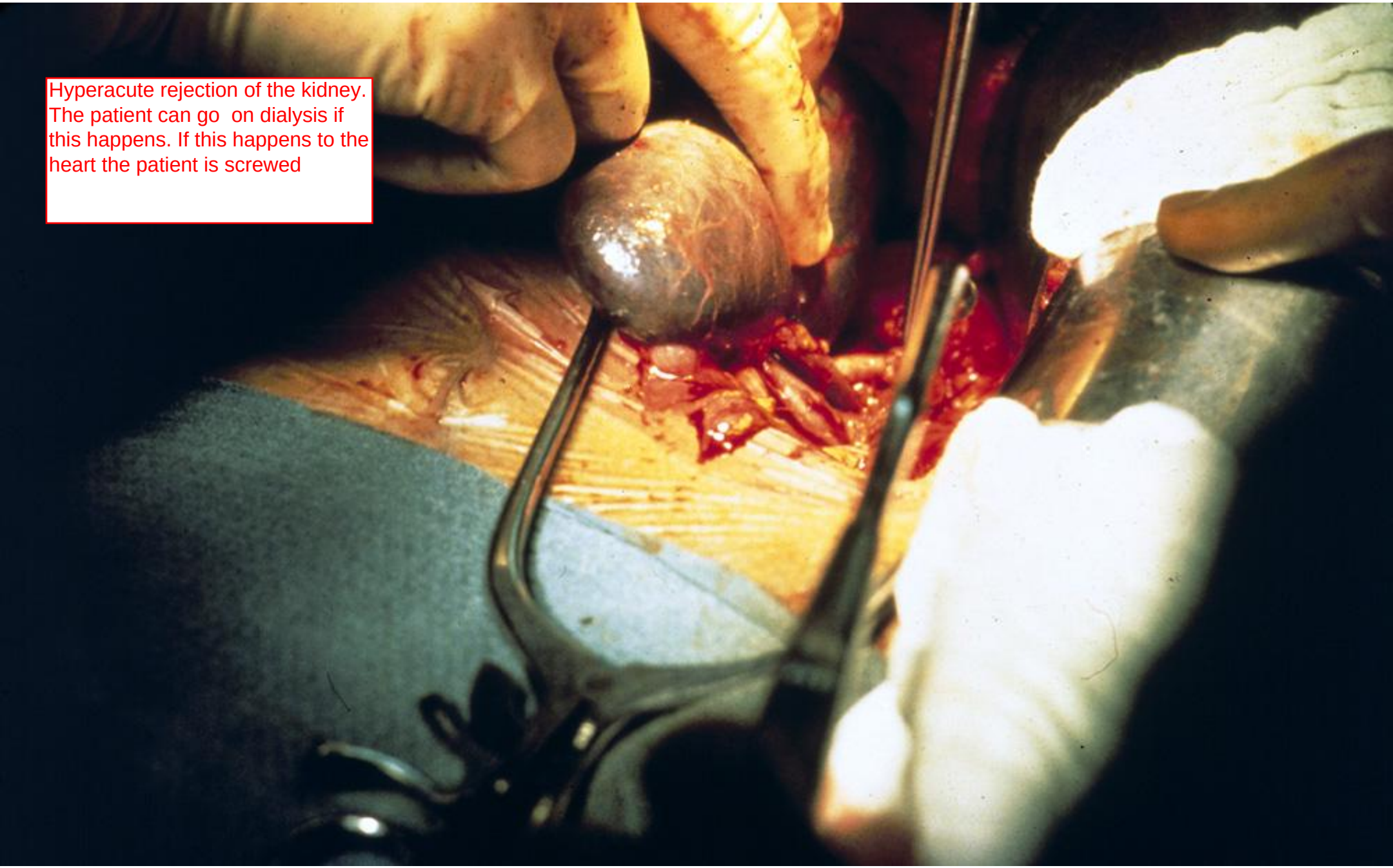
Site of attack: vascular endothelium

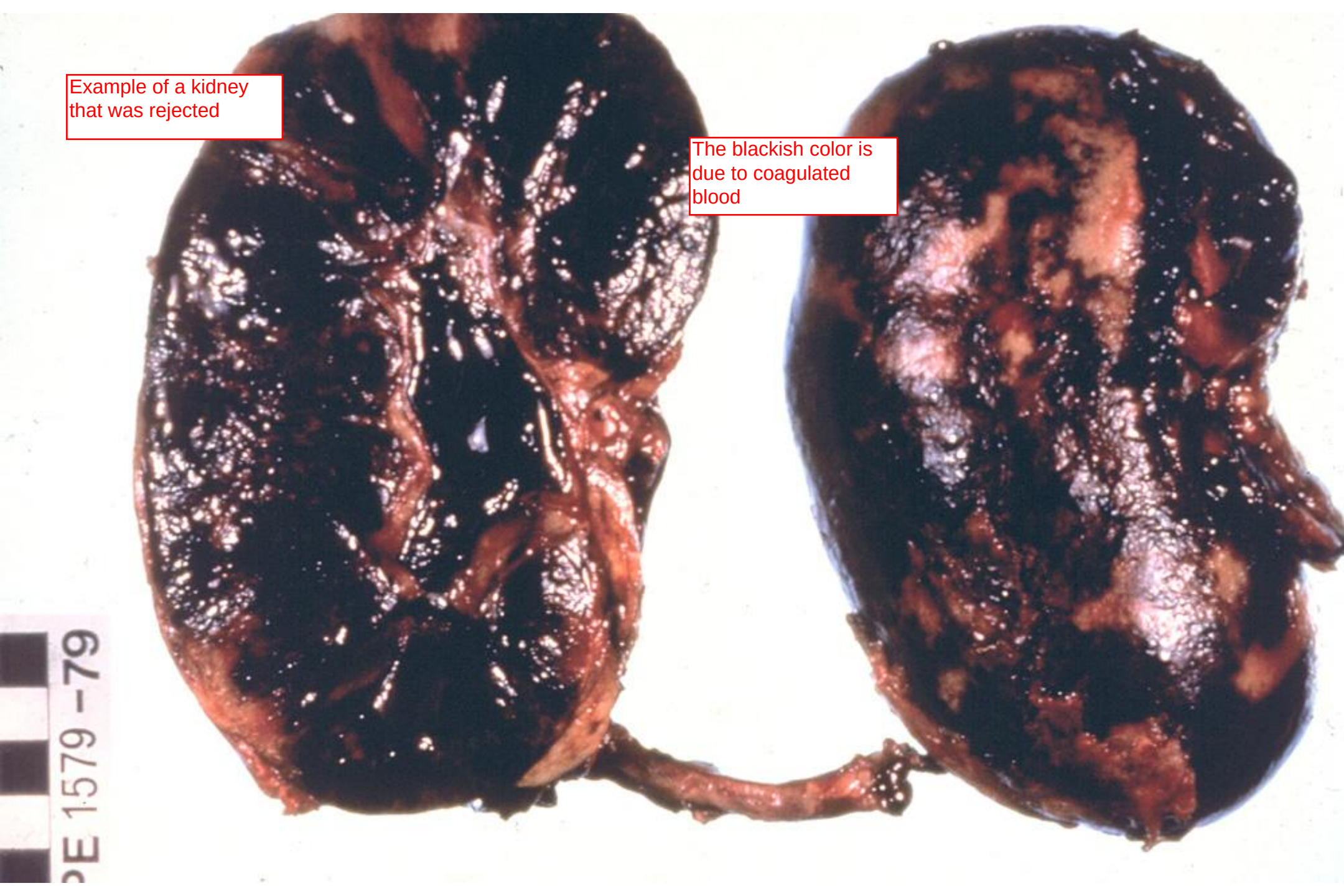
(kidney and heart)

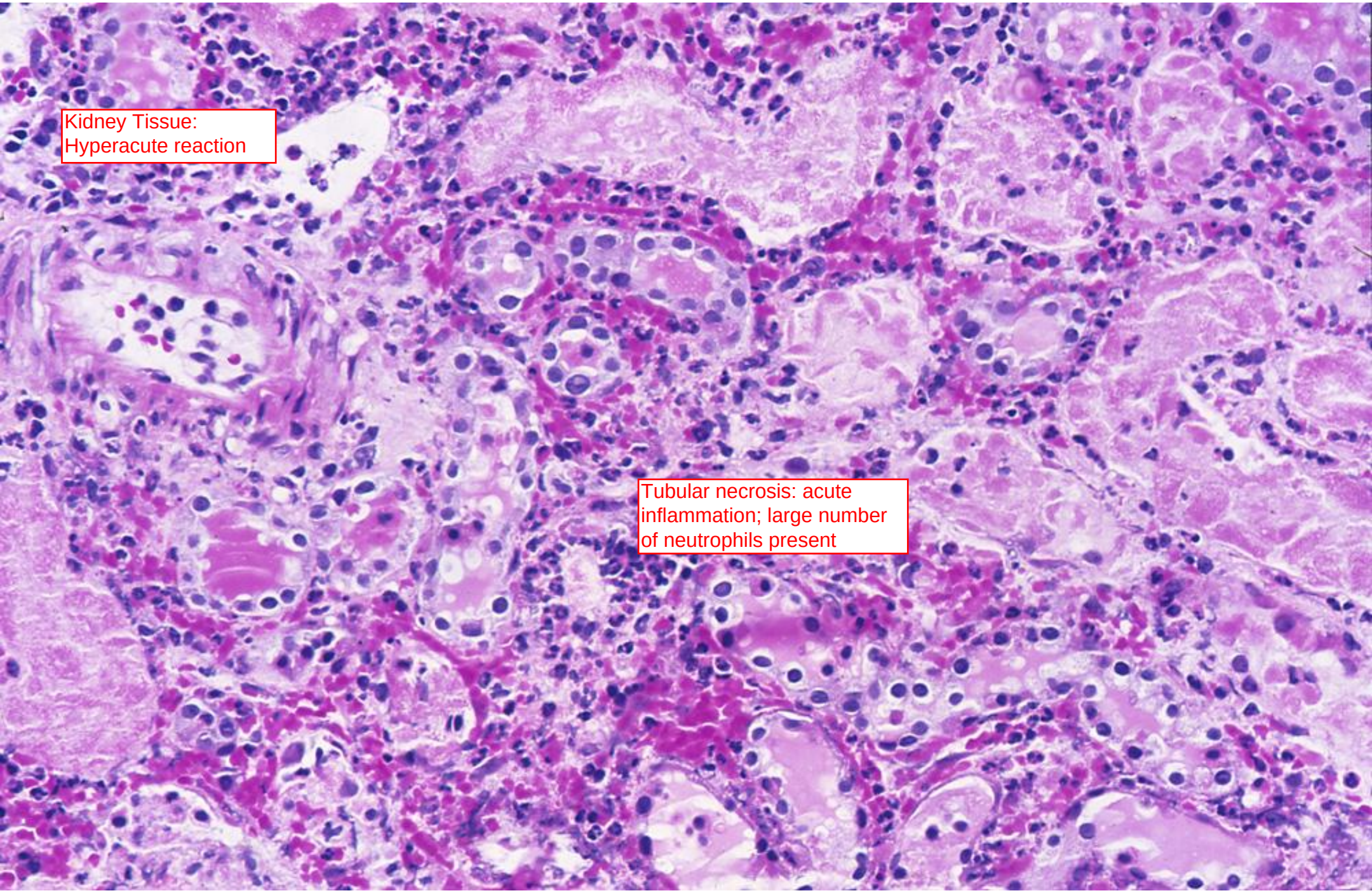
not usually seen in liver, lung, pancreas, small bowel--reasoning unclear. Could be due to the large vascular beds in these organs, so damage is not as severe

Histology: hemorrhage, edema, vascular necrosis, acute inflammation

Therapy: no satisfactory therapy available


Hyperacute rejection of the kidney. The patient can go on dialysis if this happens. If this happens to the heart the patient is screwed


Example of a kidney that was rejected
The blackish color is due to coagulated blood
E 1579 -79


Kidney Tissue:
Hyperacute reaction
Tubular necrosis: acute inflammation; large number of neutrophils present

Causes of prior sensitization to allografts

Blood transfusions

Pregnancy

Previous allografts

Natural immunity (ABO blood group)

-Half of the fetus's antigens will be encoded by father
- If fetus blood becomes apart of the mothers circulation can cause sensitization to fetal HLA antigens
- This is a problem if family member is a donor to mother in future

This is a problem if the second graft shares antigens that were present in the first graft

A person with type O blood does not contain A nor B markers on their Red Blood Cells, however in the gut of this individual there are A and B like carbohydrates so the person makes antibodies against these. Therefore the type O person receiving A/B/AB blood will have an antibody mediated attack against these new RBCs and destroy them very rapidly.

Immunized to HLA complexes occurs thru:
Blood transfusions
Pregnancy
Previous Allografts

Avoidance of hyperacute rejection

use lymphocytes that strongly express HLA complexes

Crossmatch: Testing of recipient serum for antibodies reactive with donor lymphocytes (peripheral blood, lymph node, or spleen).

similar to a test done in blood bank to match blood types

Can be done by:

1. complement mediated cytotoxicity
2. flow cytometry

add complement to cells and if antibody is bound to complement the cells are lysed

FAST

Accelerated allograft rejection

Q:It said the upper limit is several weeks but doesnt it only take a week for lymphocytes to form?
A:It is highly variable and the key is you need the lymphocytes to form on the endothelial lining some could be anergic reactions

Onset: days to weeks after grafting

Timecourse: days

Mechanism: similar to hyperacute rejection, but less fulminant; may involve antibodies produced after grafting or small quantities of preformed antibodies

less aggressive than hyperacute; involves binding of preformed antibodies and antibodies formed after grafting

key difference between accelerated and hyperacute

(Type II sensitivity)

antibody mediated

Class I MHC- CD8+ present on virtually all cells
Class II present on dendritic cells and B cells-- CD4+
Can be upregulated after graft due to a infection and they are exposed to the immune system and an antibody response can be formed

Accelerated allograft rejection

There is therapy for accelerated; this is different than hyperacute

Site of attack: vascular endothelium

Histology: hemorrhage, edema, vascular necrosis, acute inflammation

Therapy: plasmapheresis

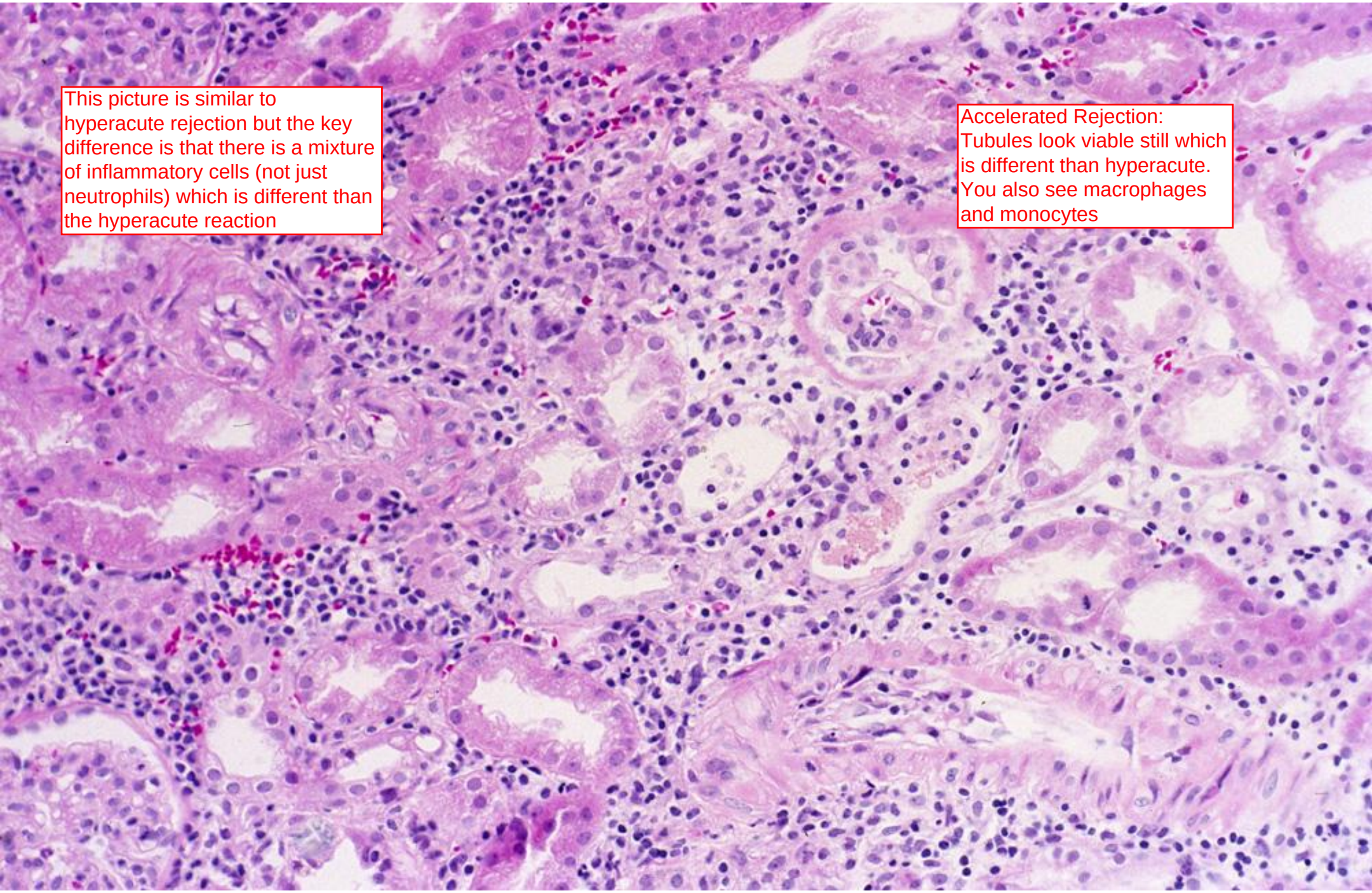
intravenous immunoglobulin

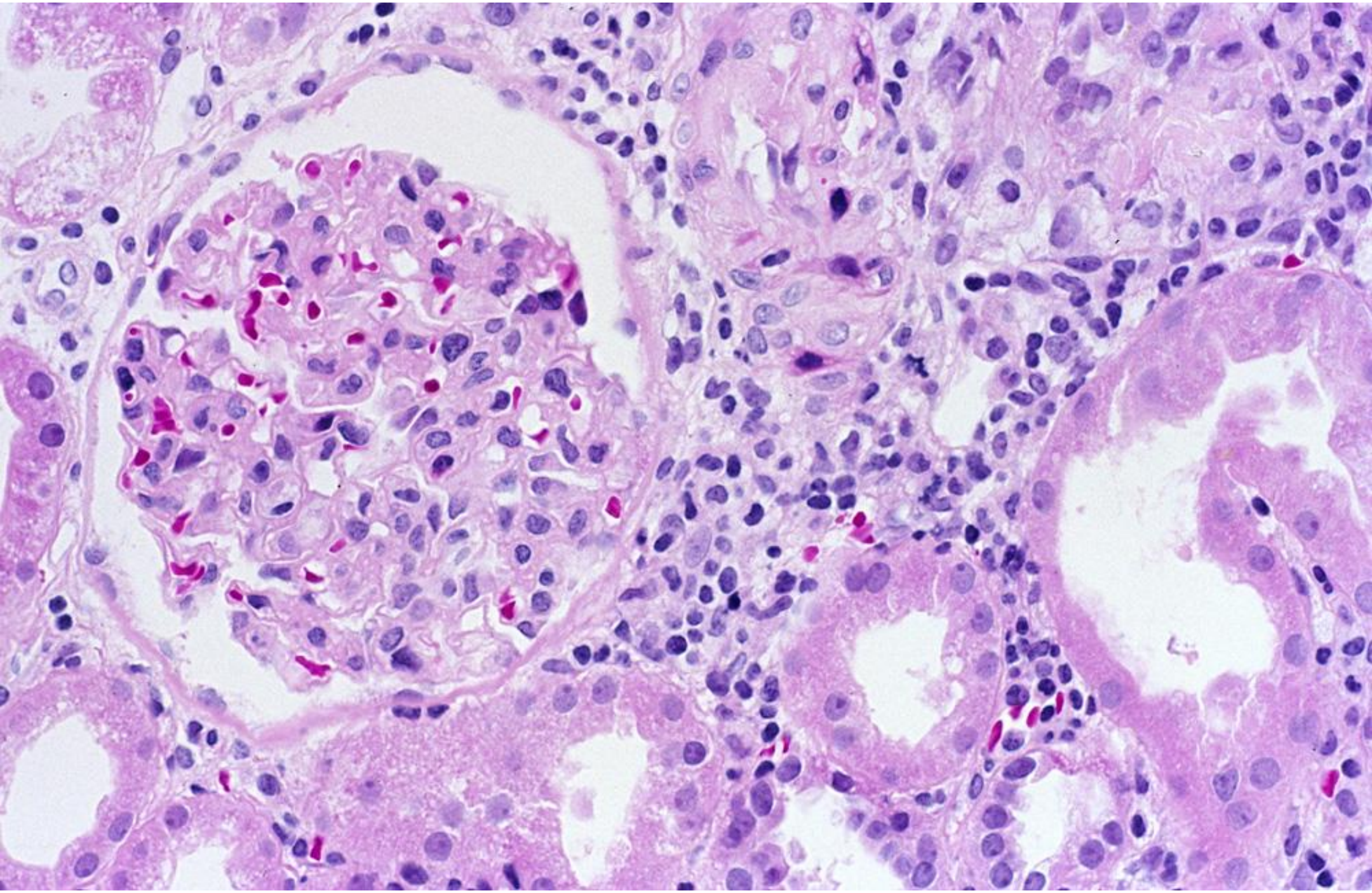
This first involves removing the patients blood and centrifuging out host plasma cells and adding fresh donor plasma to re-infuse into patient. This is done numerous times and is basically "cleaning" the blood of the patient

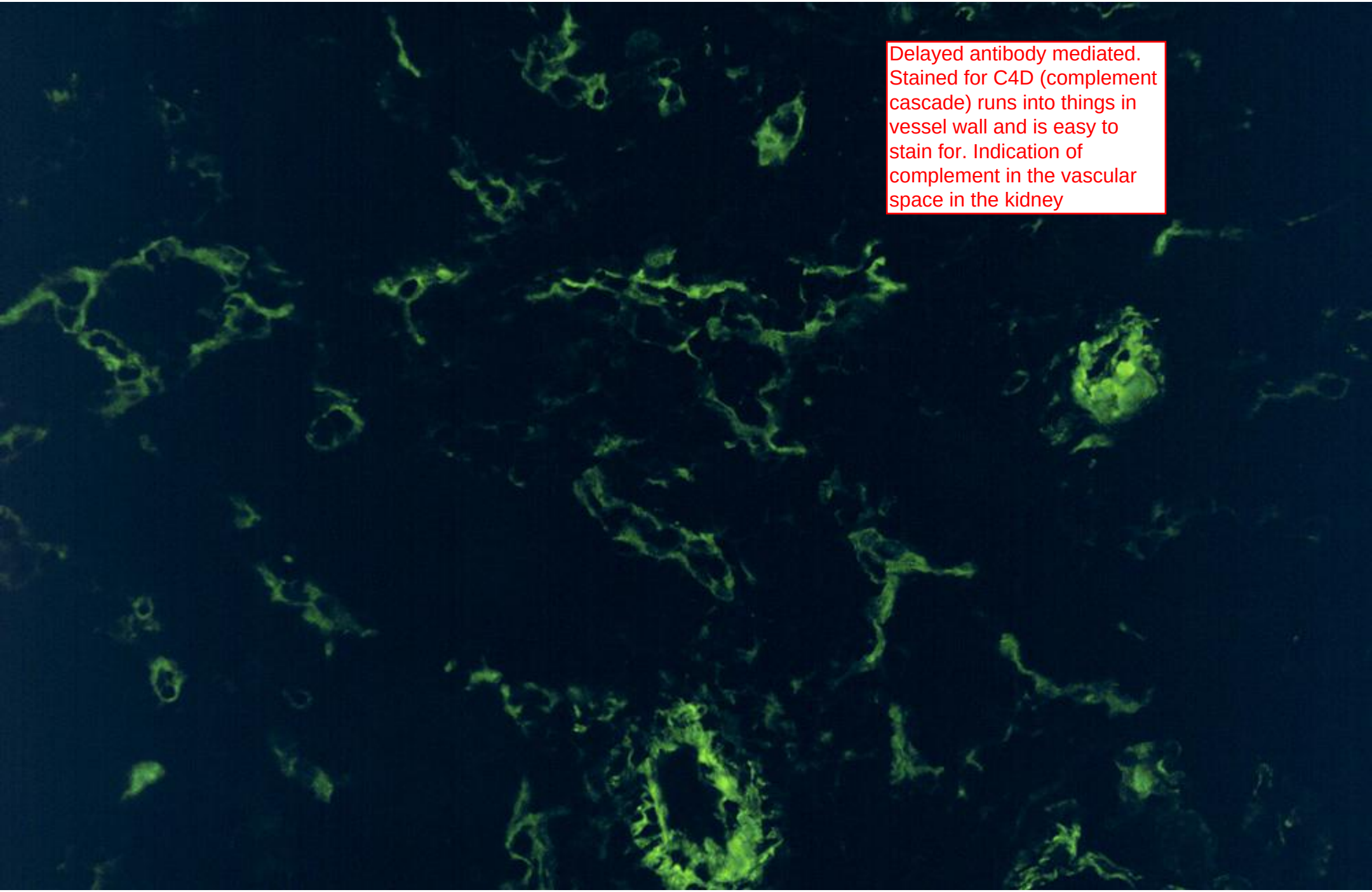
unlike hyperacute there is therapy for accelerated rejection

Rituximab (anti-CD20 monoclonal antibody)-- surface antigen of B cells and try to get rid of the B cells producing antibodies--This is another form of treatment for accelerated allograft

Donor Ig is given to patient to try to downregulate the number of new antibodies the host will make. This is an attempt to prevent create of antibodies that will attack the new organ


This picture is similar to hyperacute rejection but the key difference is that there is a mixture of inflammatory cells (not just neutrophils) which is different than the hyperacute reaction
Accelerated Rejection: Tubules look viable still which is different than hyperacute. You also see macrophages and monocytes




Delayed antibody mediated. Stained for C4D (complement cascade) runs into things in vessel wall and is easy to stain for. Indication of complement in the vascular space in the kidney

Acute allograft rejection

Key to avoiding acute allograft rejection is continuing to take immunosuppressant medicine

Onset: weeks to months after grafting

earliest seen is 5 or 6 days post transplant and can occur a long time after transplant

Timecourse: days

Mechanism: recognition of graft antigens (especially HLA antigens) by allospecific T cells, followed by cytotoxicity (CD8 T cells) or release of inflammation lymphokines (CD4 T cells)

(Type IV hypersensitivity)

Kill graft cells: CD*

CD4:stimulate monocytes and macrophages which damage the graft

This is different than hyperacute and accelerated which were both Type 2 hypersensitivity

This time the recognition of HLA antigens is by T cells and not antibodies

Acute allograft rejection

unlike the first 2 types of rejection; the damage depends on the organ

Site of attack: variable, depending on organ

Know what places are attacked in each organ

Kidney: tubules, interstitum

Liver: venous endothelium, bile ducts

Heart: myocytes

Lung: arterioles

Histology: infiltration of mononuclear leukocytes (lymphocytes, macrophages), tissue damage; in severe cases, hemorrhage and necrosis

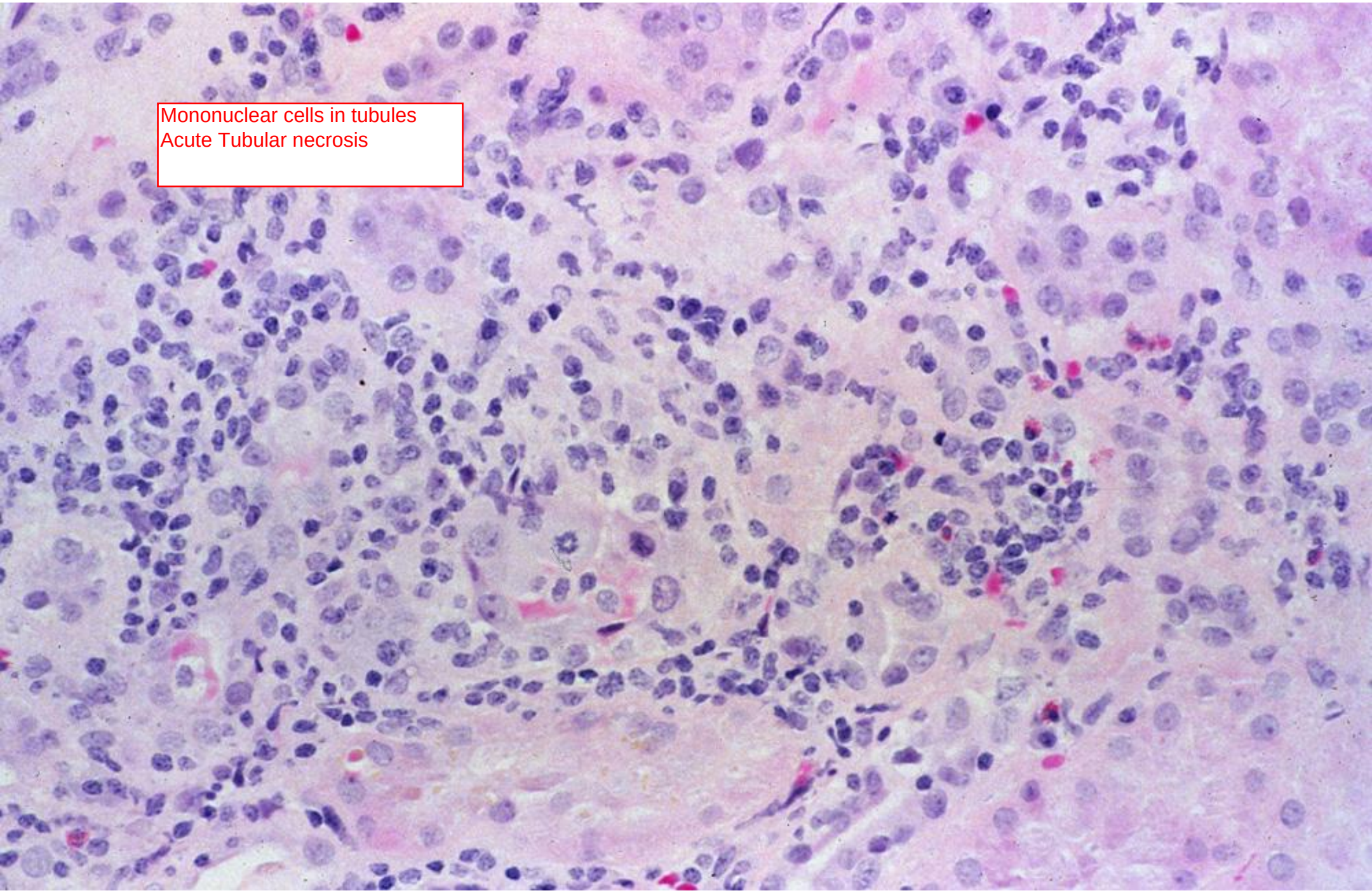
unusual but can occur in severe cases

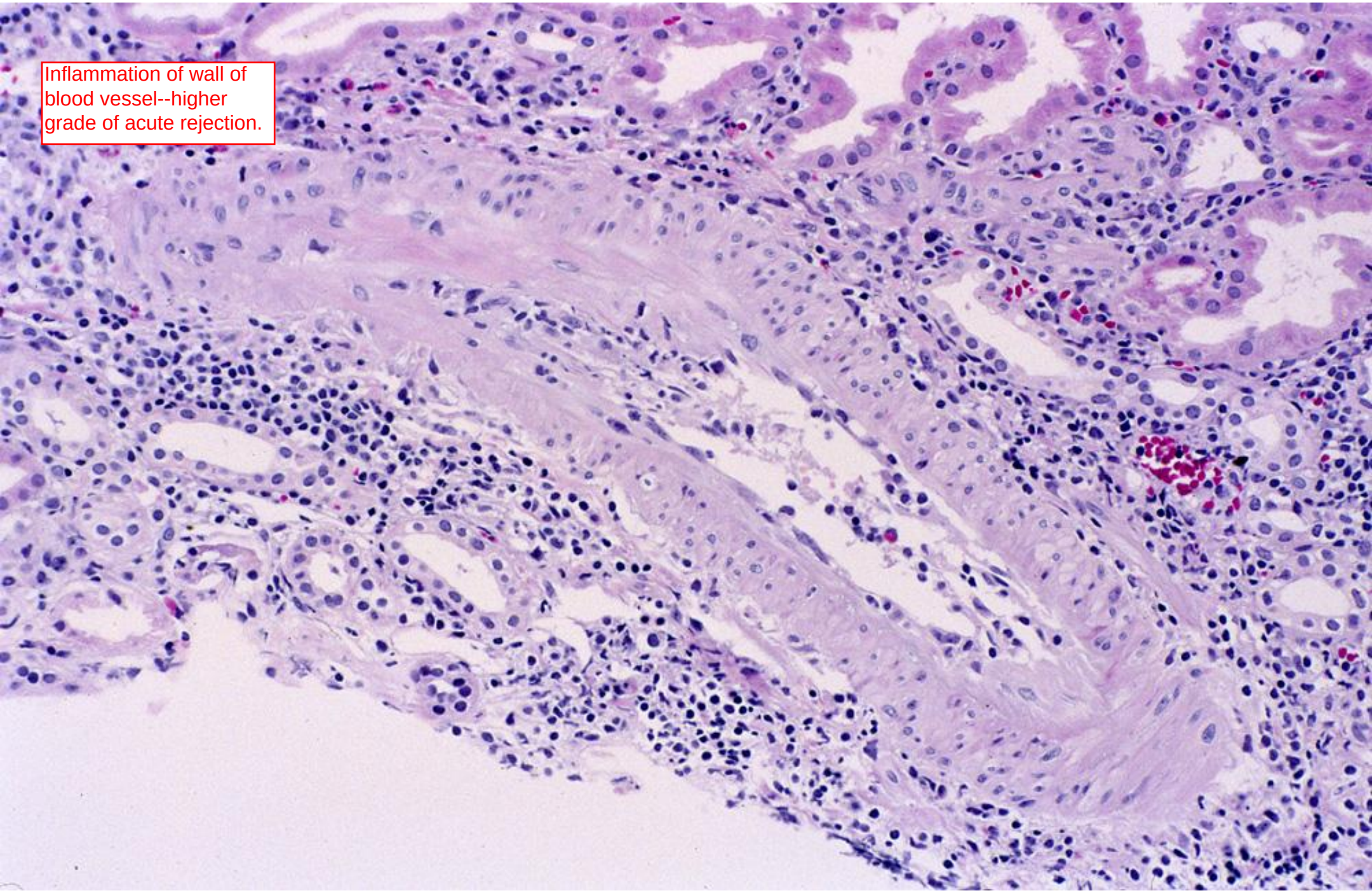
It is possible that the immunosuppressent medicine was at too low of a dose and the physician will initally treat the rejection with steroids and then increase the immunosuppressant medicine dosage

Therapy: pulse steroids

anti-T cell antibodies (e.g., OKT-3)

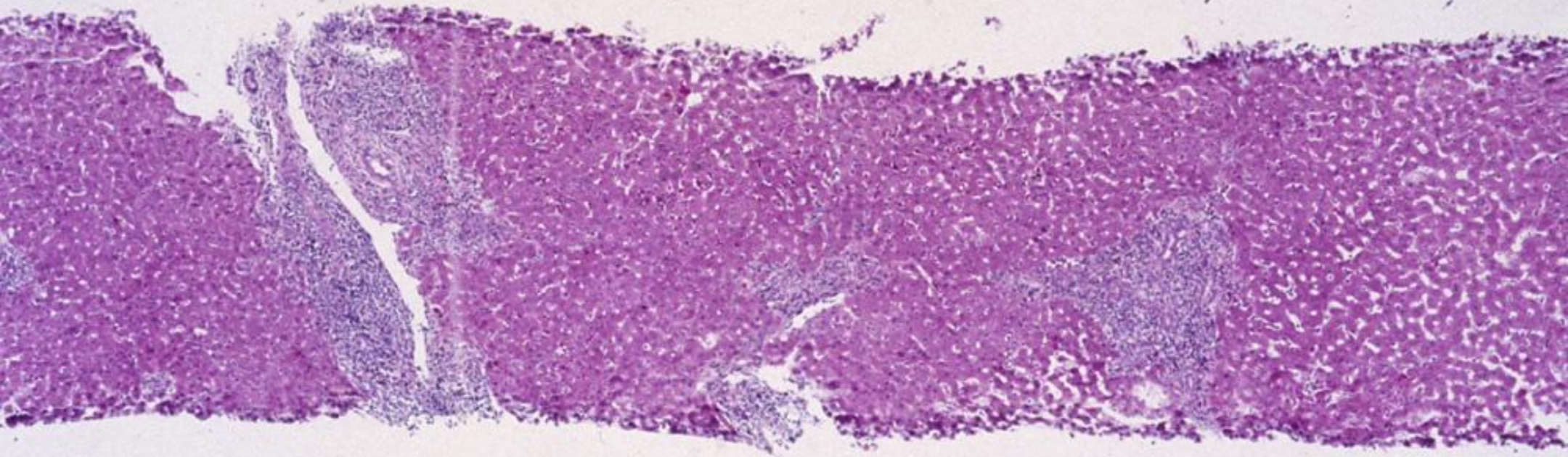
Muromonab- CD3 (OKT3): monoclonal antibody that binds to CD3 on the surface of T cells. Blocks cellular interaction with CD3 protein responsible for T cell signal transduction.

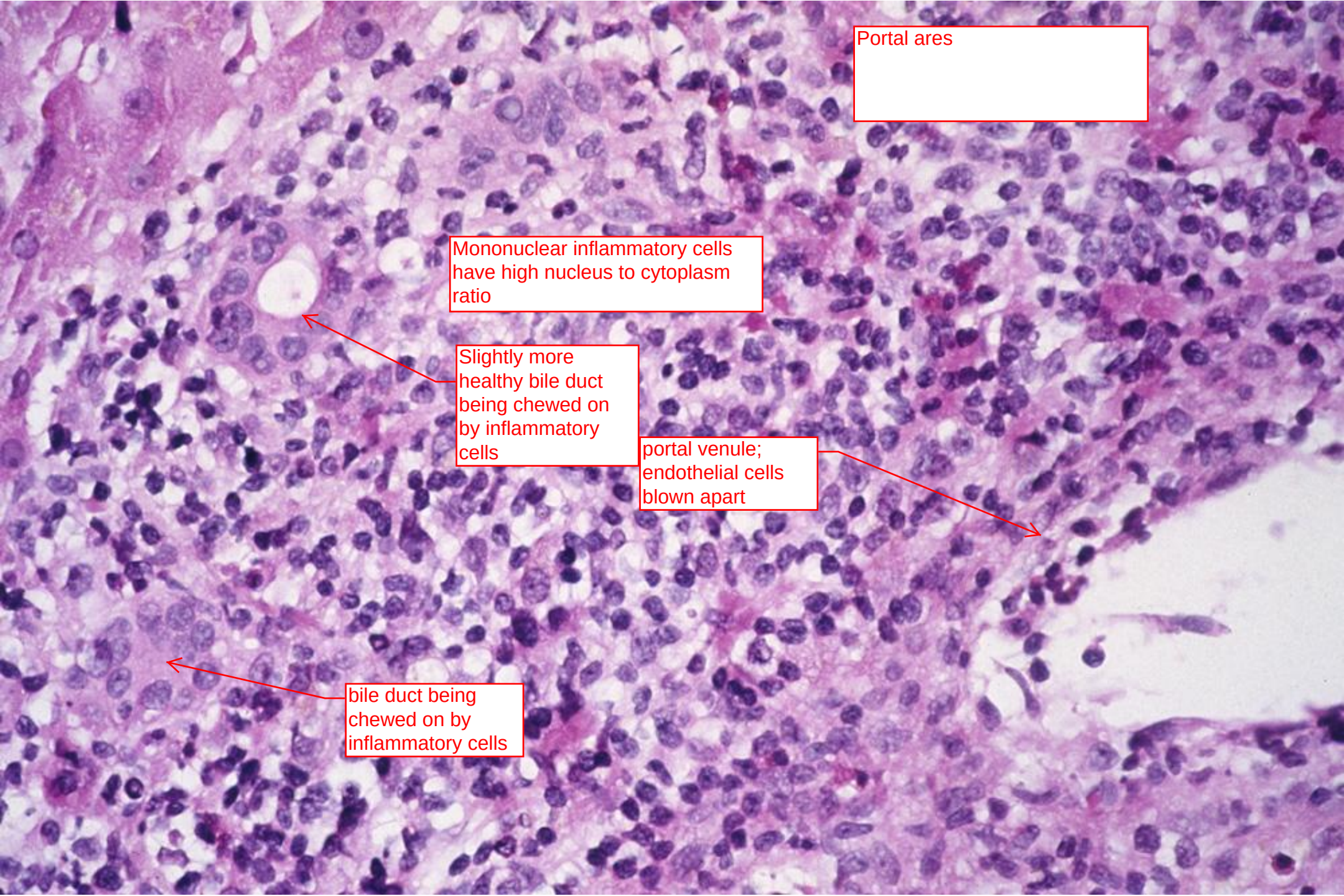

Mononuclear cells in tubules
Acute Tubular necrosis

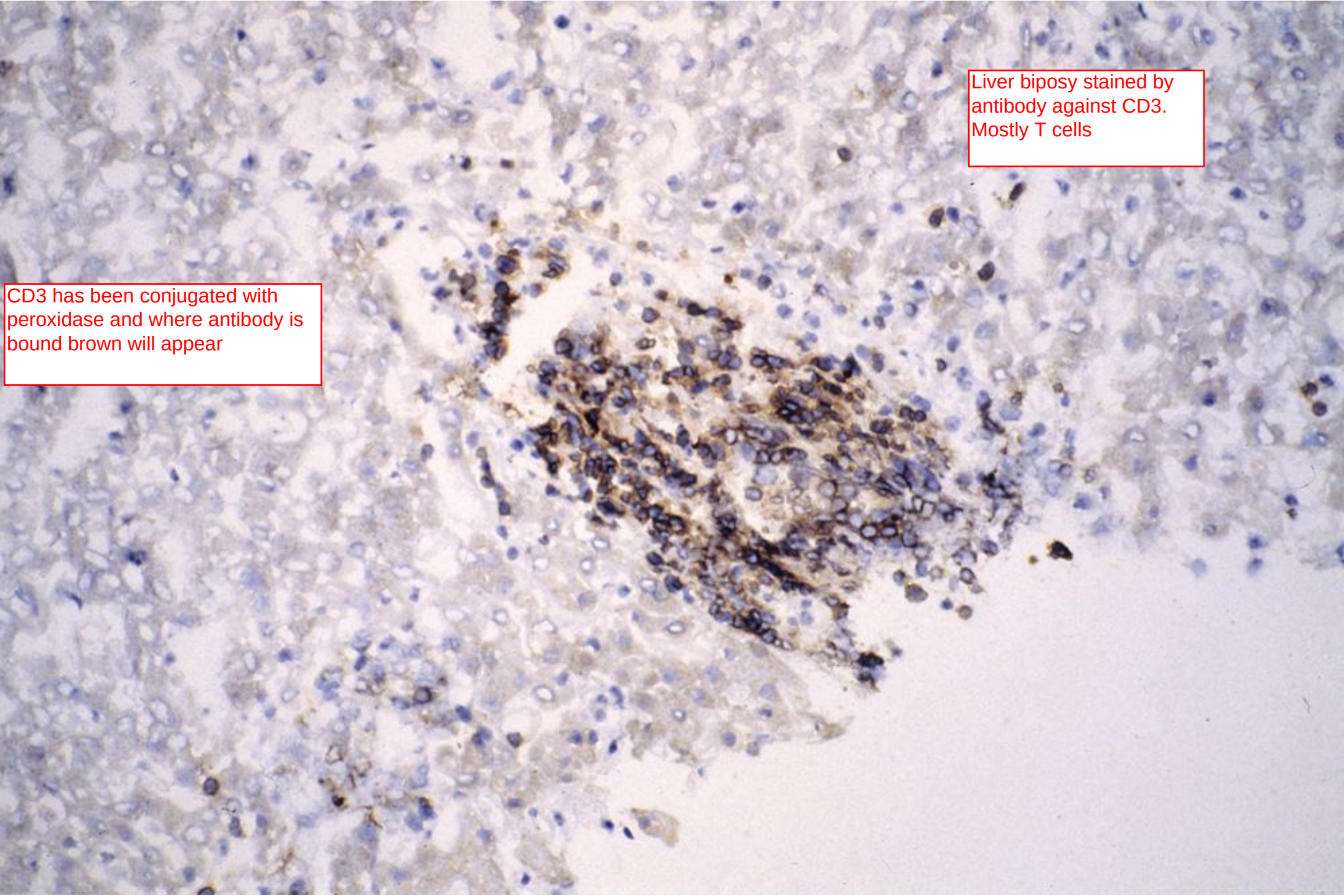

Inflammation of wall of blood vessel--higher grade of acute rejection.

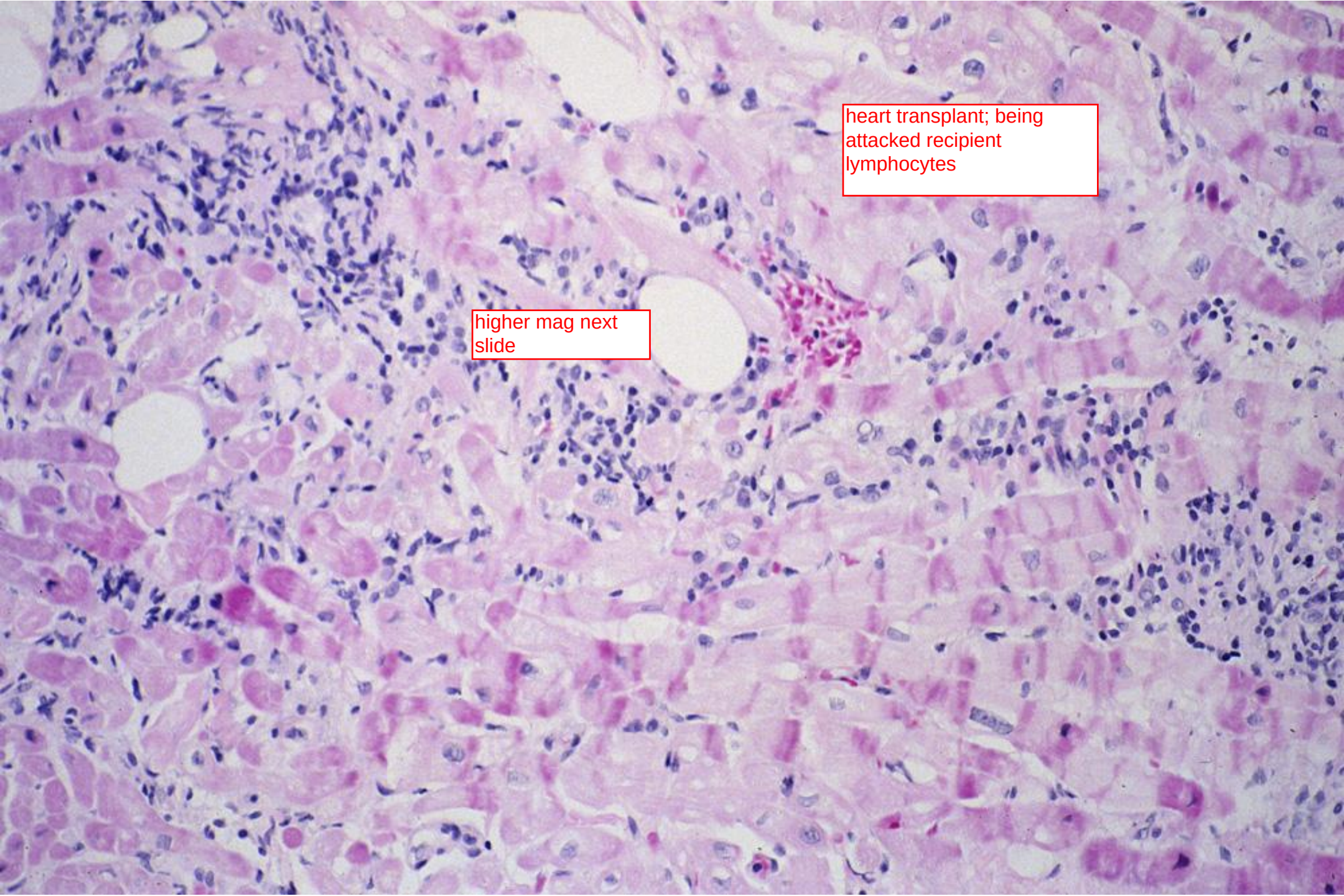
Hepatic parenchyma in purple
Portal areas in blue

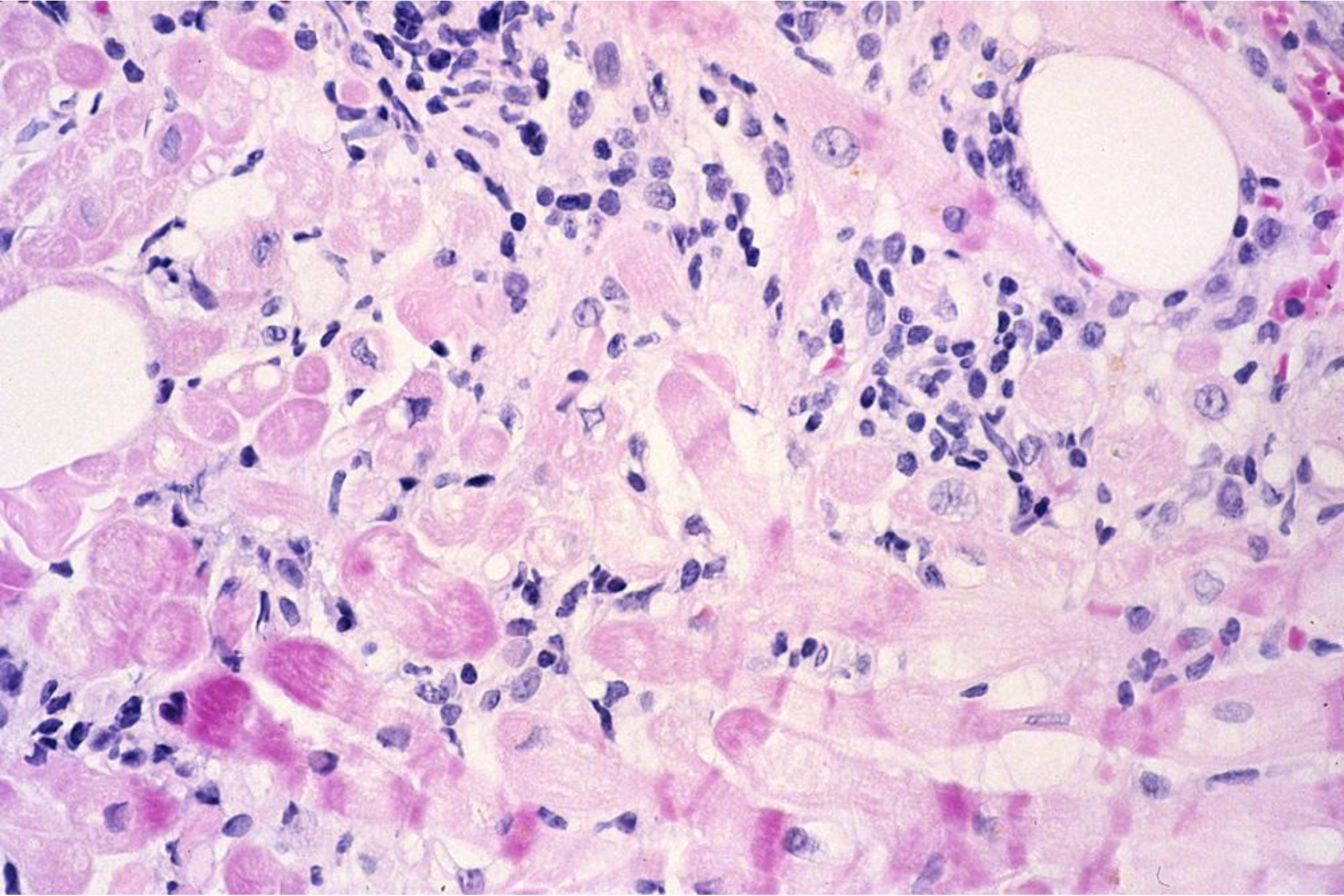
Liver biposy

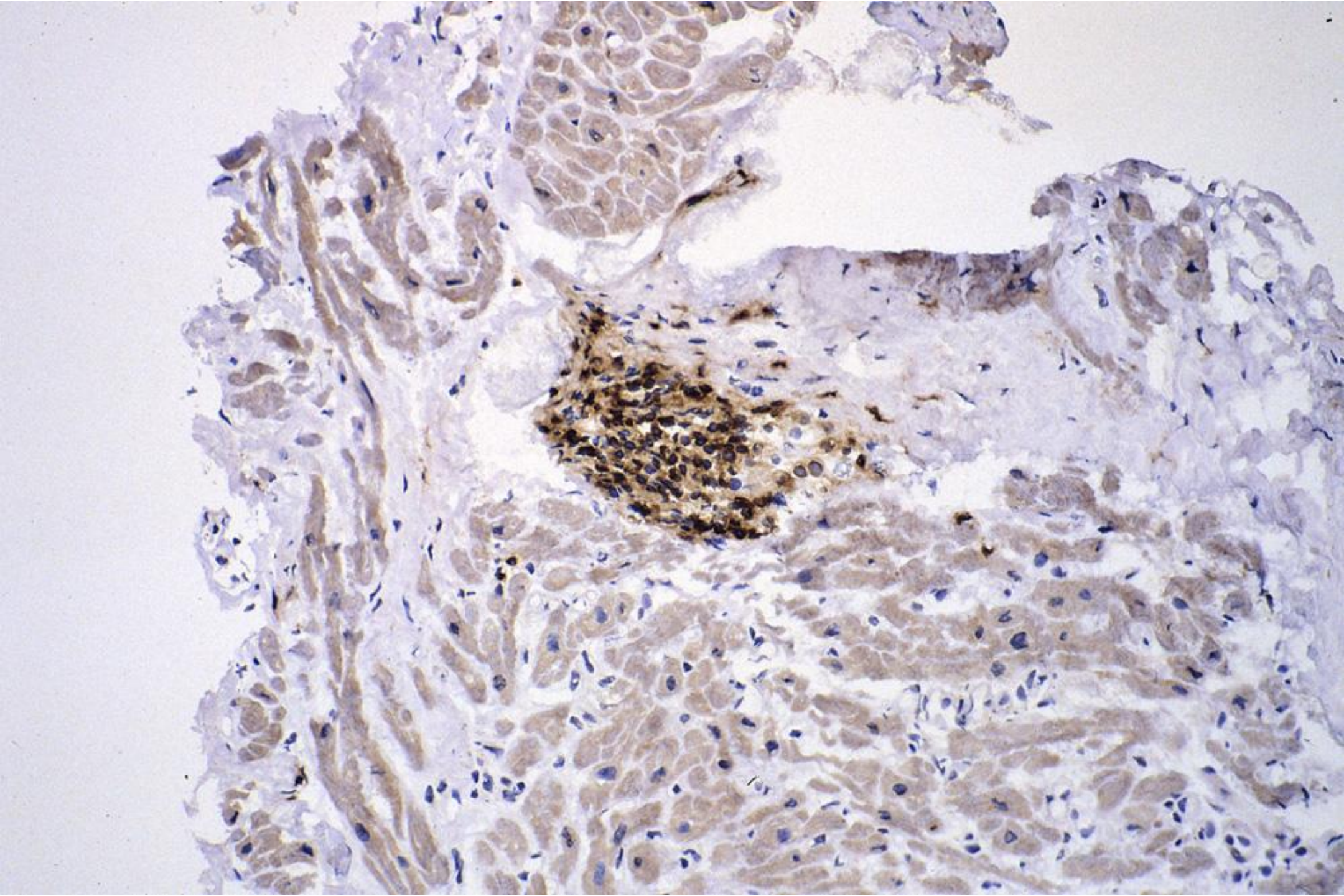


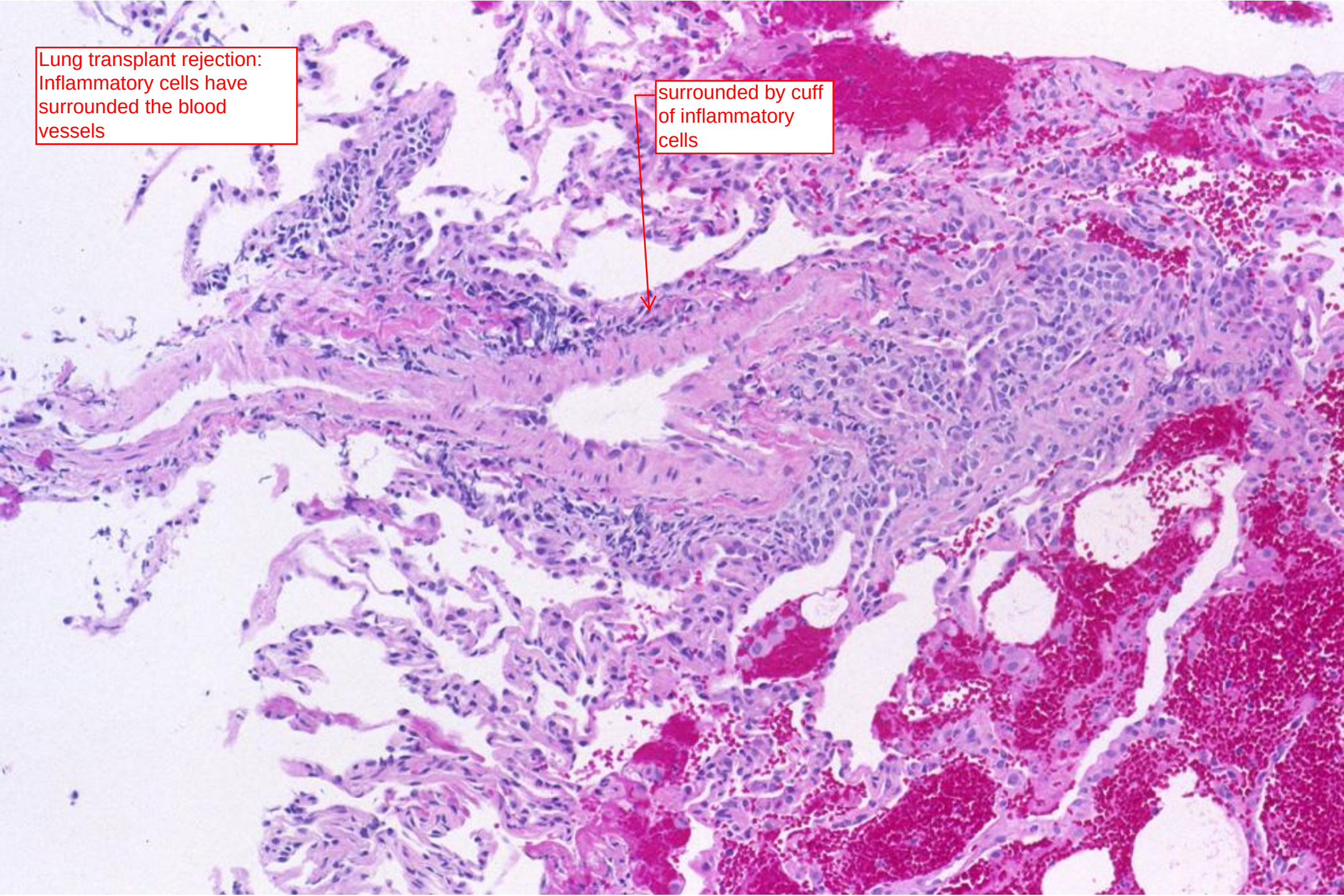

Portal ares
Mononuclear inflammatory cells have high nucleus to cytoplasm ratio
Slightly more healthy bile duct being chewed on by inflammatory cells
portal venule; endothelial cells blown apart
bile duct being chewed on by inflammatory cells


Liver biposy stained by antibody against CD3. Mostly T cells
CD3 has been conjugated with peroxidase and where antibody is bound brown will appear


heart transplant; being attacked recipient lymphocytes
higher mag next slide






Lung transplant rejection: Inflammatory cells have surrounded the blood vessels
surrounded by cuff of inflammatory cells

Avoidance of acute rejection

Donor-recipient matching:

HLA Typing

want as few mismatches as possible

Take lymphocytes from both donor and recipient and culture them together and observe if recipient lymphocytes proliferate in response to donor

Mixed lymphocyte reaction

this is not done much anymore

Pretransplant conditioning:

Blood transfusions

not done anymore

Trying to knock down the patients immune system right before transplant: Done frequently

Immunosuppressive agents (e.g., antilymphocyte globulin)

cyclosporine A inhibits NFAT--prevents T cell production

Posttransplant therapy:

Cyclosporine

Posttransplant therapy is given to all patients except identical twins

Prednisone

block inflammation

Azathioprine

Titrate the dose so that it is just right, many are on gangcyclvir, septa--to prevent other infections

inhibits leukocyte development from bone marrow precursors

Chronic allograft rejection

Bad problem: becoming more common because we are getting good at treating acute rejection

Onset: months to years after grafting

Timecourse: months to years

Mechanism: unknown: probably mixture of cell mediated (Type IV) and antibody mediated (Type II) processes

Both Type 2 and Type 4 hypersensitivity

Chronic allograft rejection

walls of larger arteries is a common theme

Site of attack: variable, depending on organ

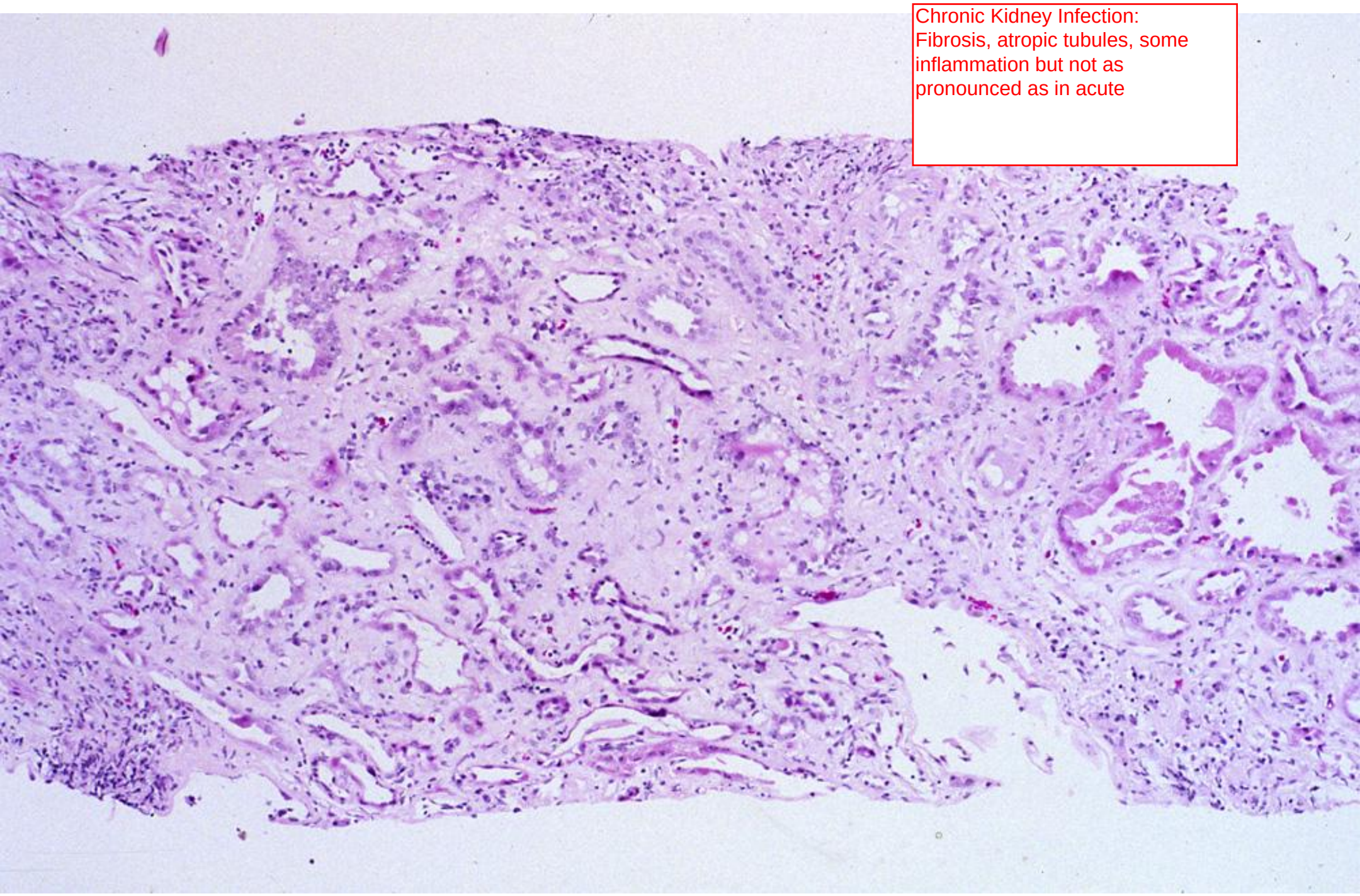
- Kidney: vasculature (especially arteries), tubules, interstitum
- Liver: bile ducts ("vanishing bile duct syndrome")
- Heart: vasculature
- Lung: bronchioles

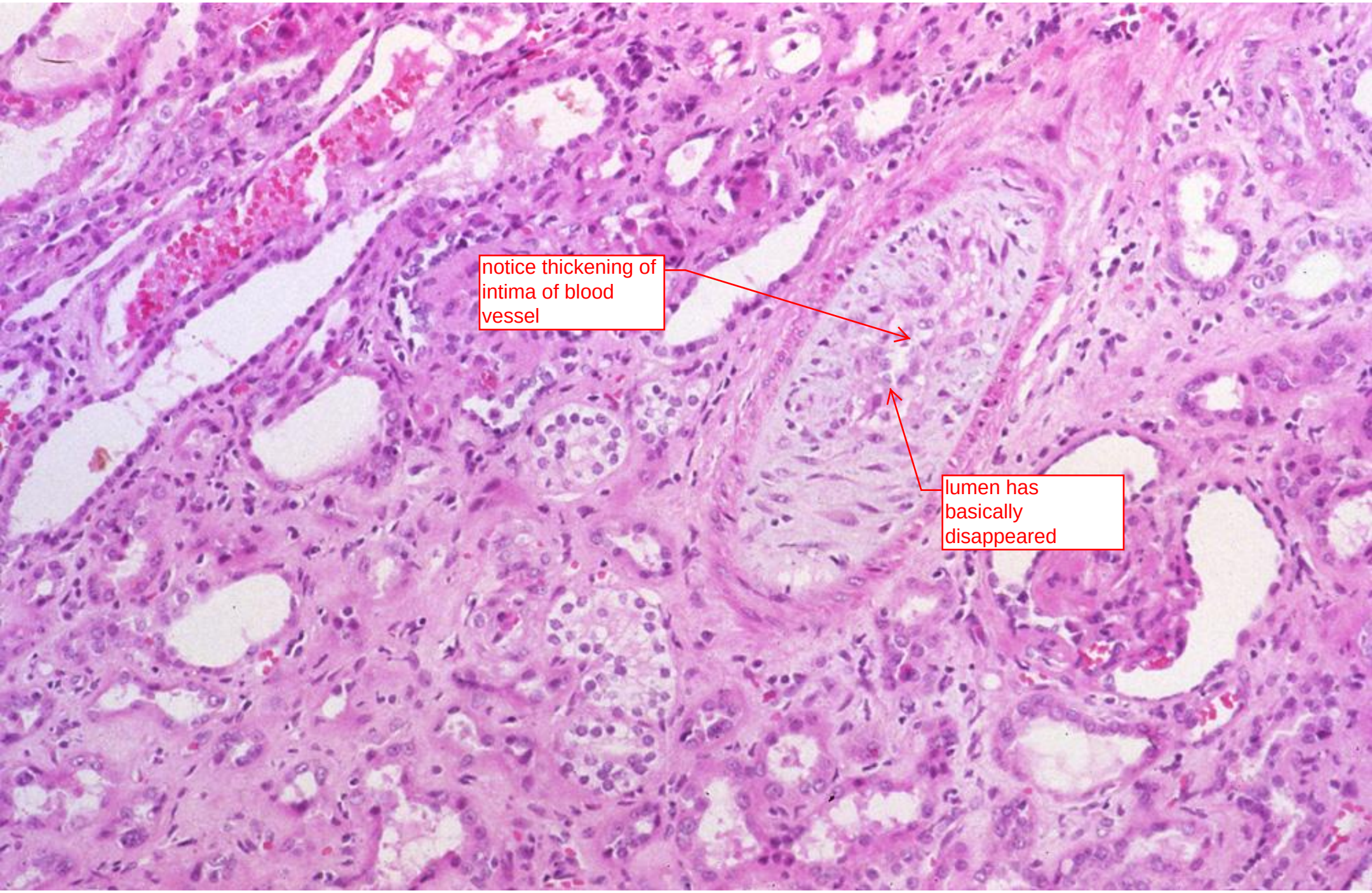
Histology: fibrosis, atrophy, vascular thickening (especially intimal)

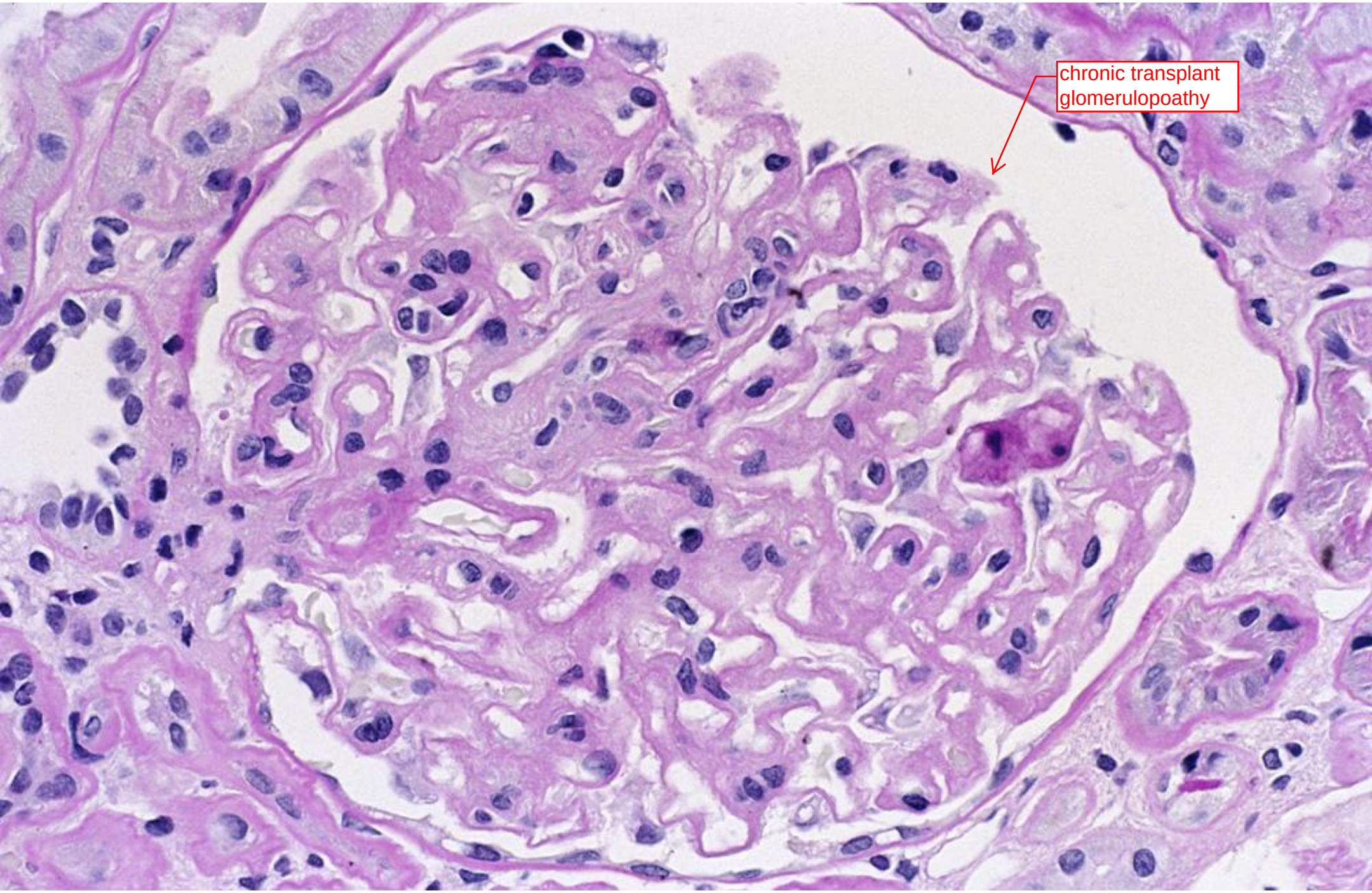
Therapy: no satisfactory therapy available

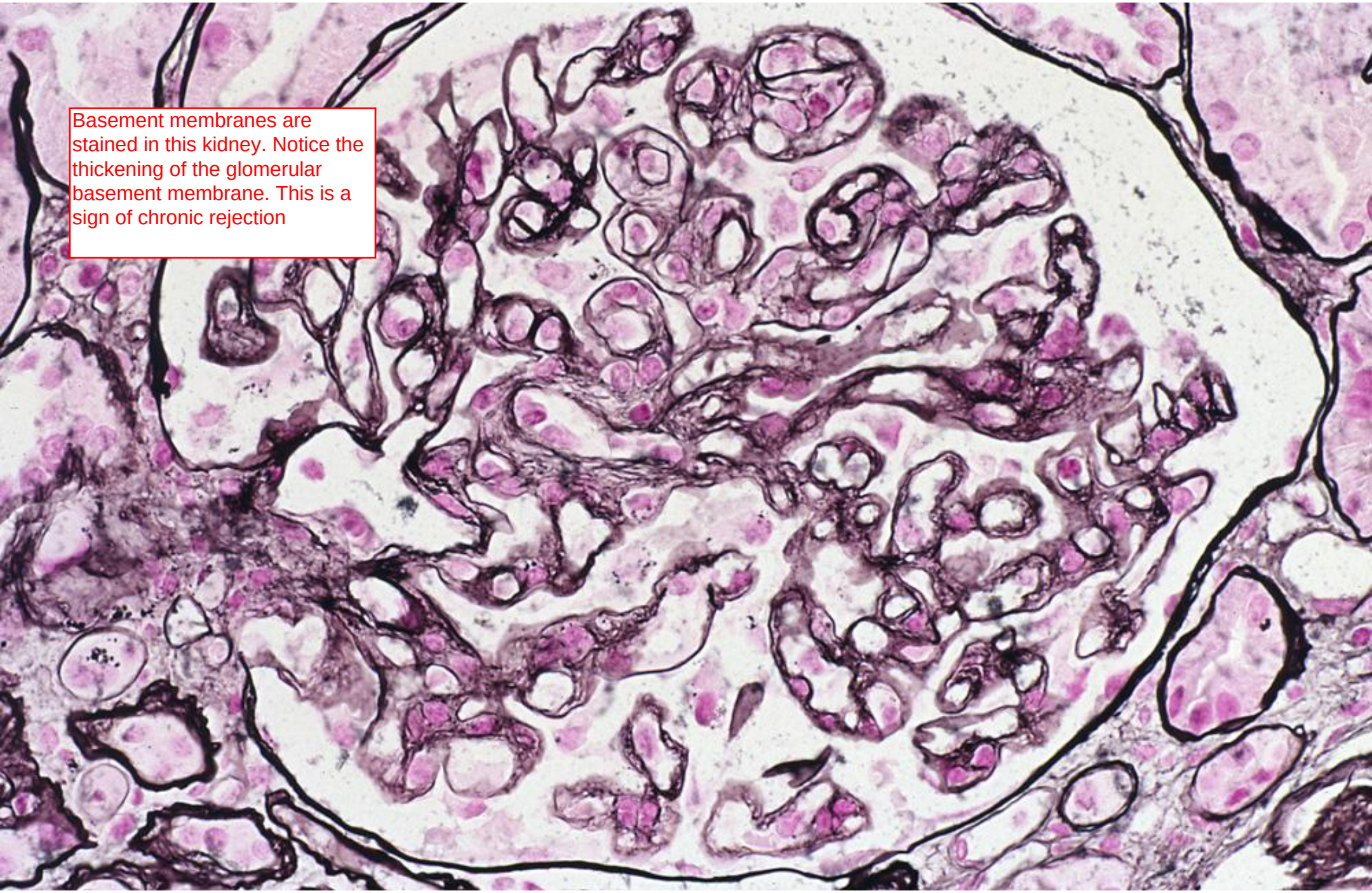
Note that there is no therapy for chronic rejection

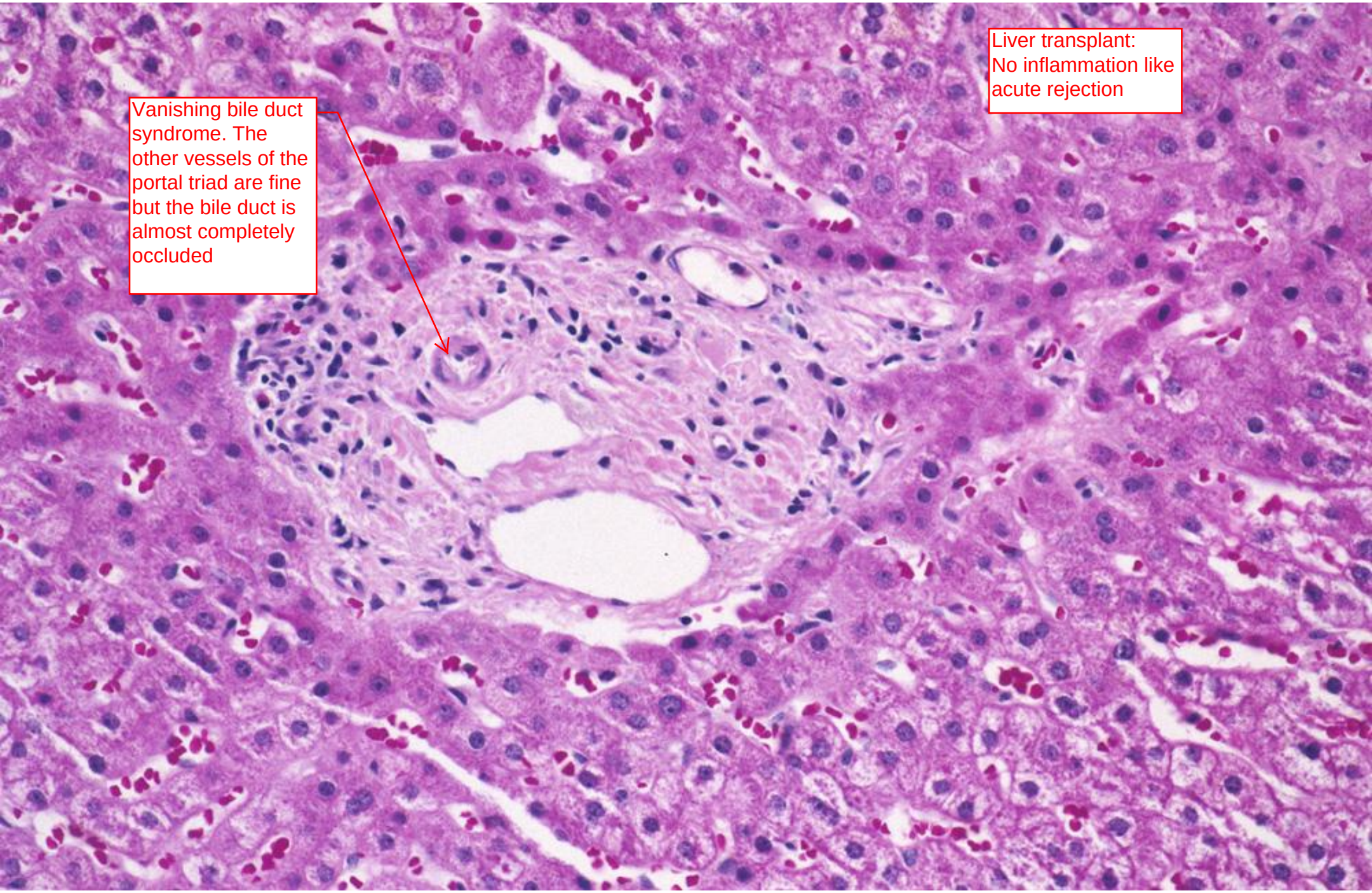
Retransplant is the only real option for these patients

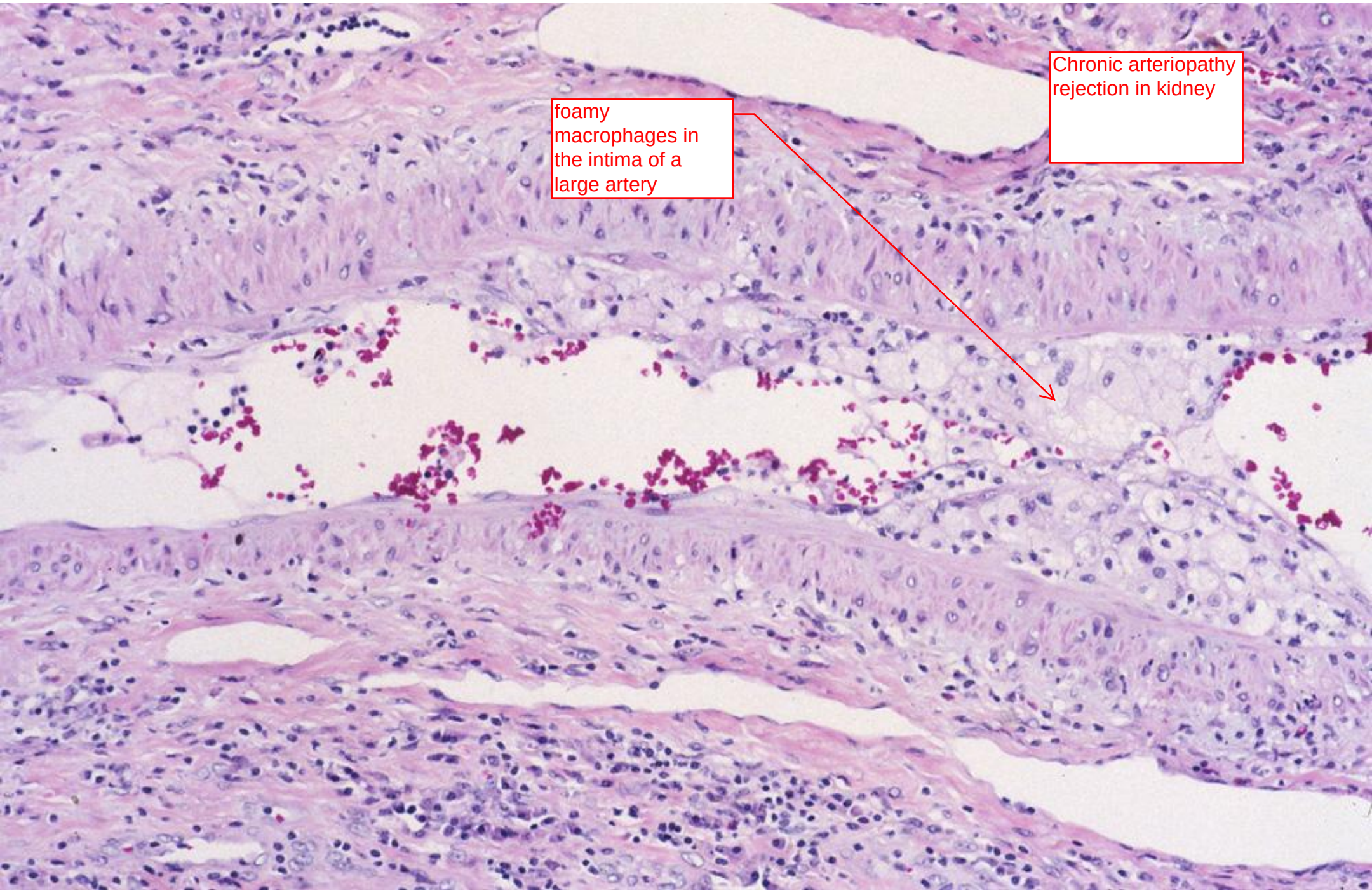

Chronic Kidney Infection:
Fibrosis, atropic tubules, some inflammation but not as pronounced as in acute

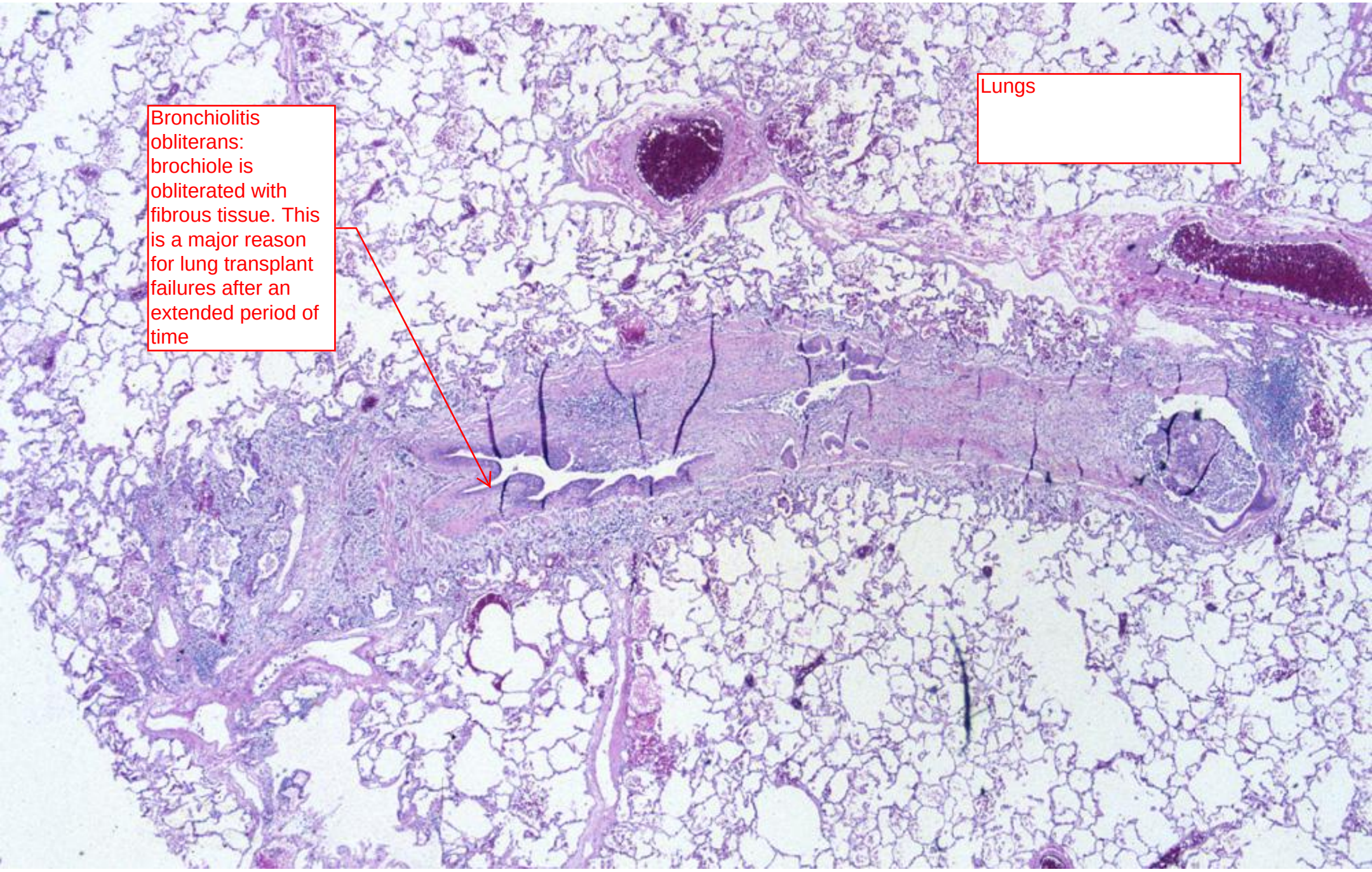

notice thickening of intima of blood vessel
lumen has basically disappeared


chronic transplant
glomerulopoathy


Basement membranes are stained in this kidney. Notice the thickening of the glomerular basement membrane. This is a sign of chronic rejection


Liver transplant:
No inflammation like acute rejection
Vanishing bile duct syndrome. The other vessels of the portal triad are fine but the bile duct is almost completely occluded

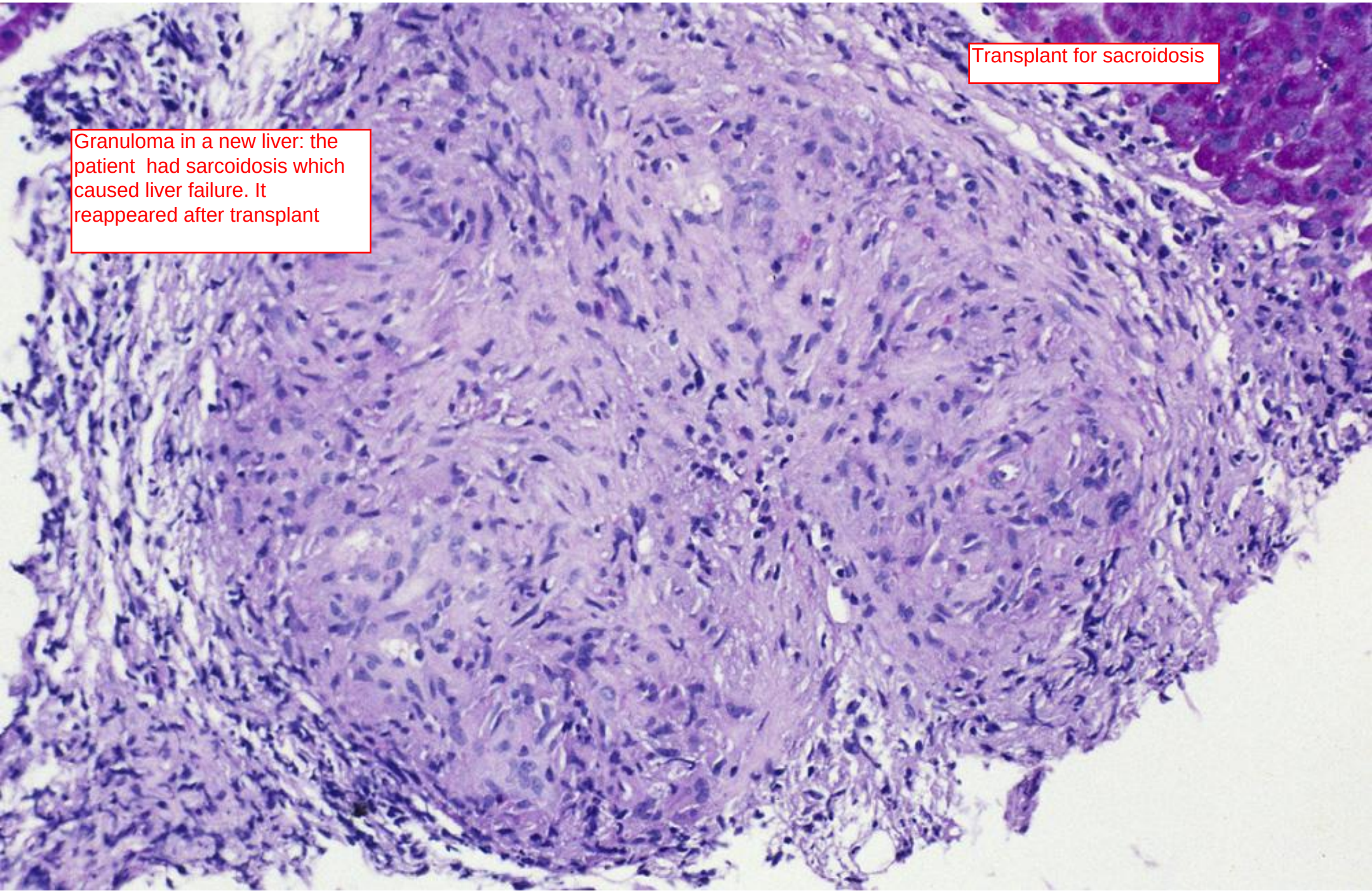

Chronic arteriopathy rejection in kidney
foamy macrophages in the intima of a large artery

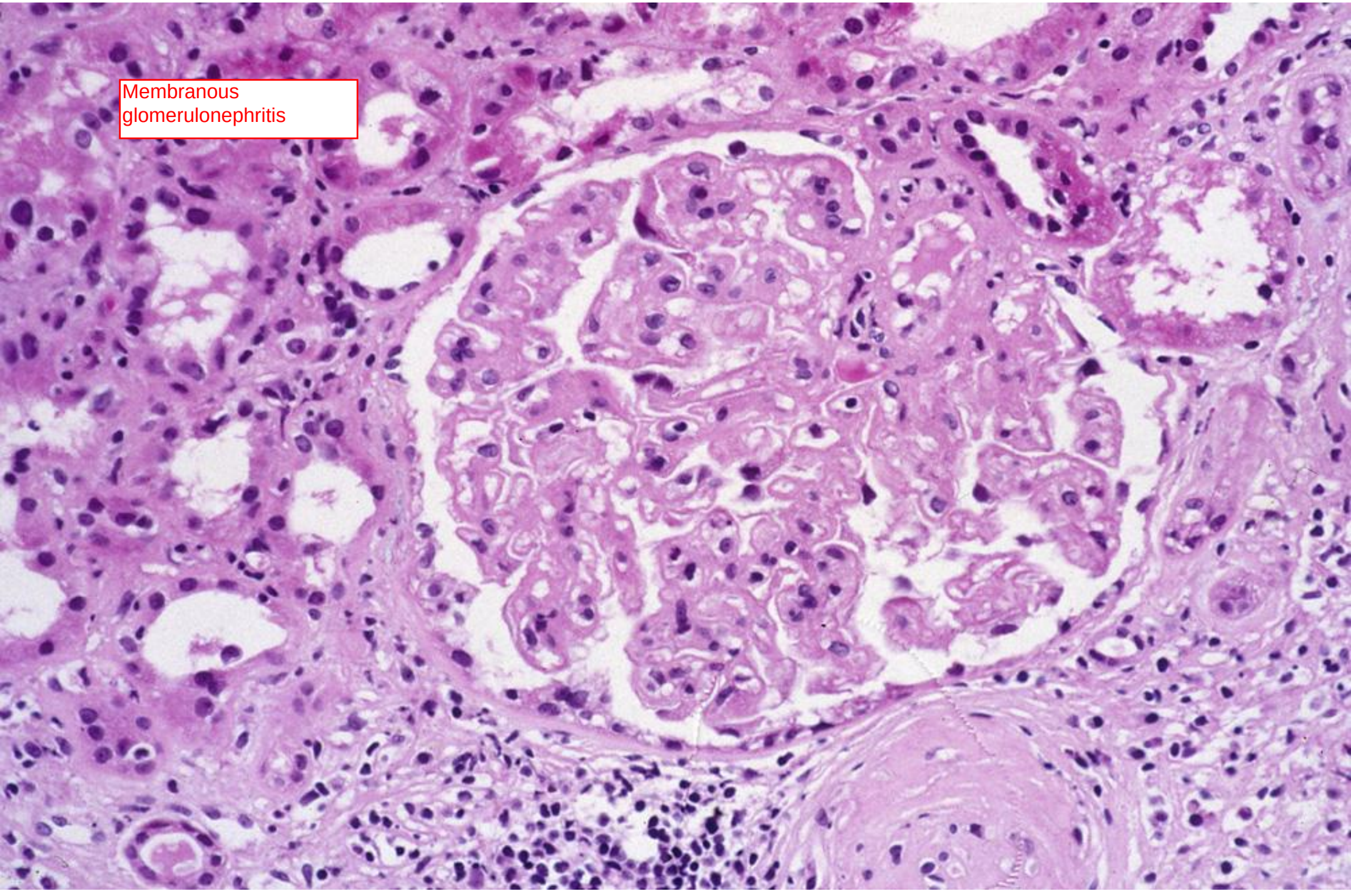

Lungs
Bronchiolitis obliterans: brochiole is obliterated with fibrous tissue. This is a major reason for lung transplant failures after an extended period of time

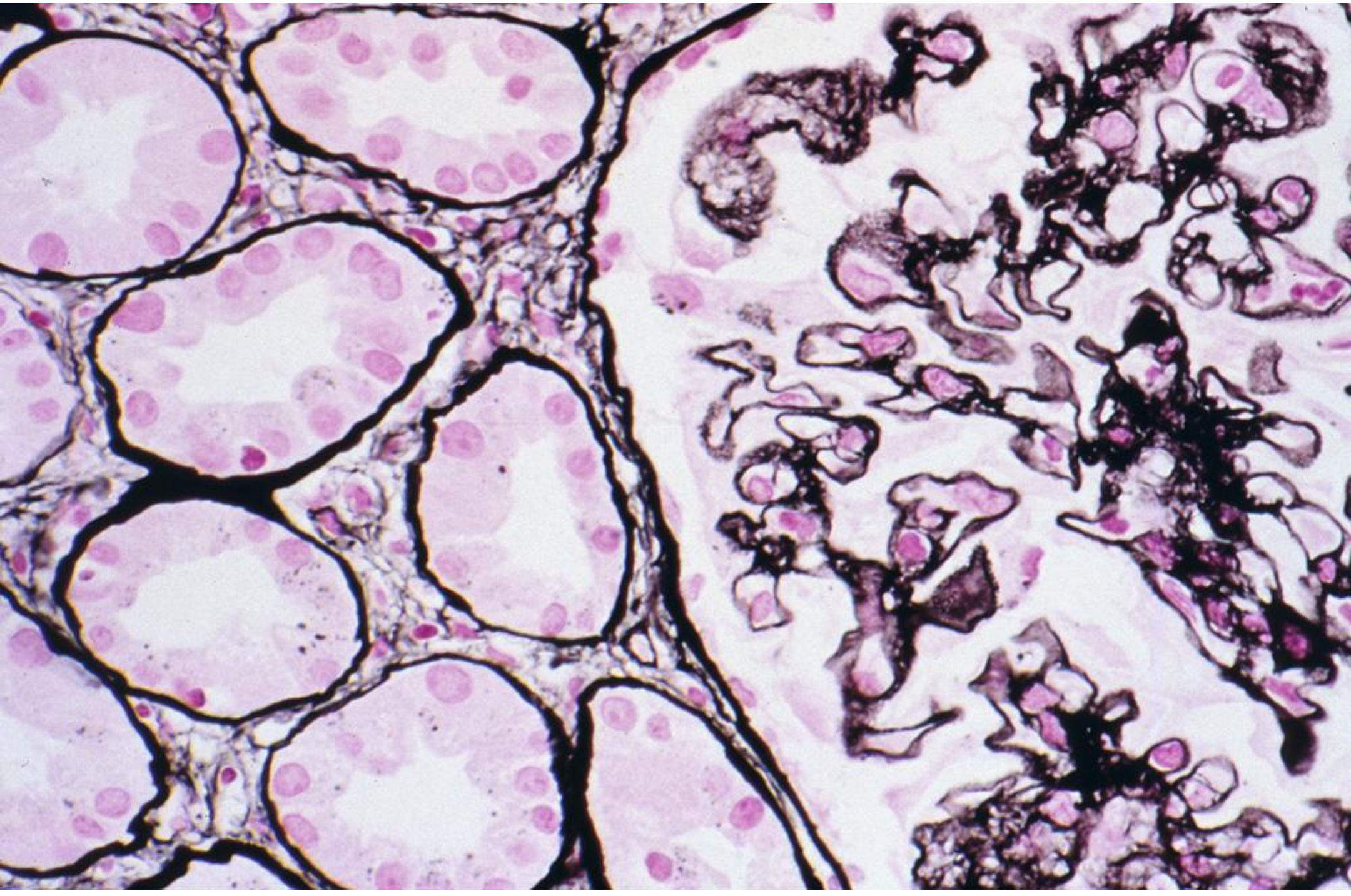
Other problems for solid organ grafts

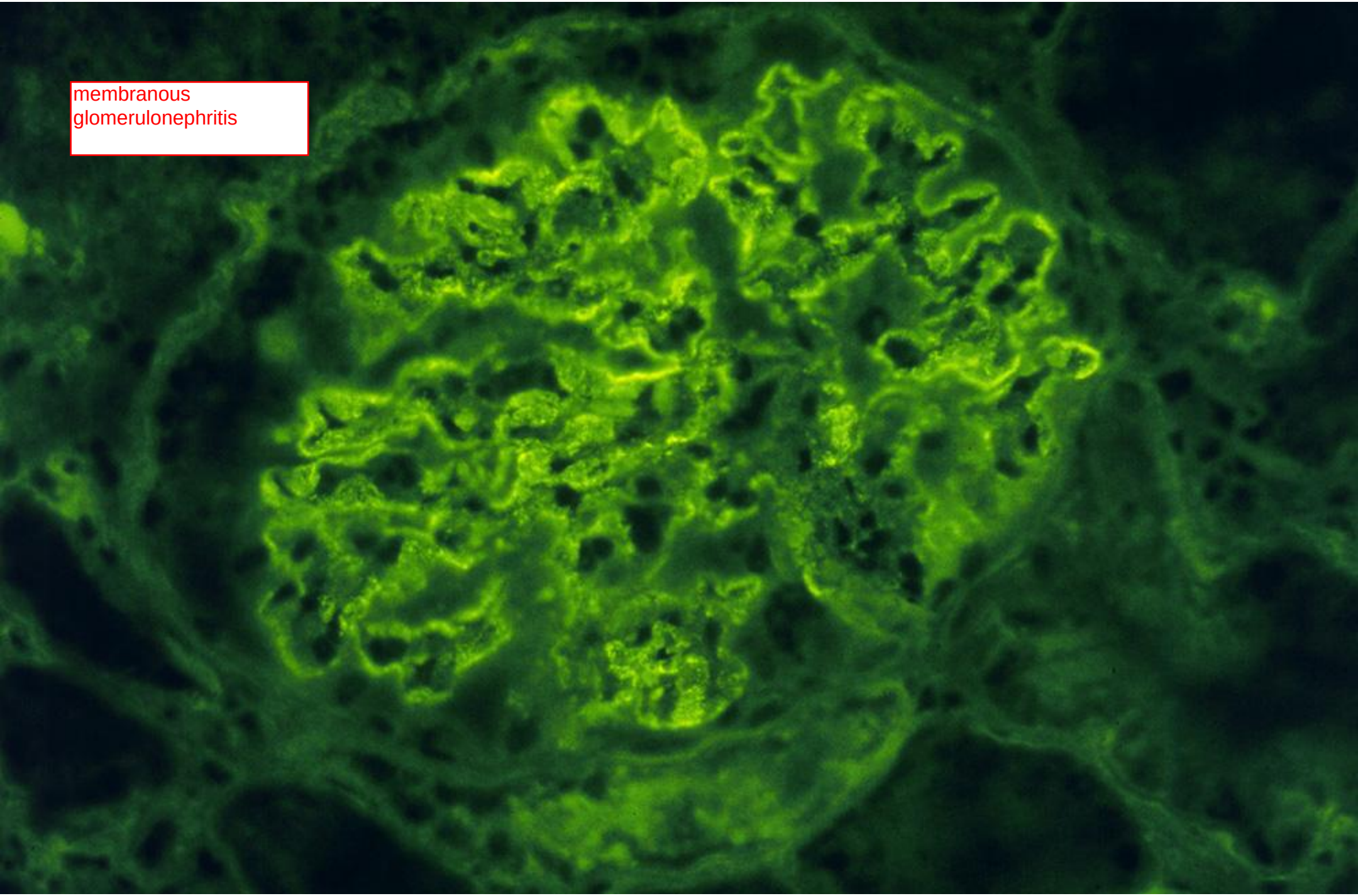
- Recurrence of original disease
- Occurrence of new primary disease in transplant
- Infection (bacterial, viral, fungal, parasitic)
  - Graft
  - Systemic
- Drug Toxicity (e.g., cyclosporine)
- Failure of anastomoses
- Malignancies
  - Lymphoproliferative disorders
  - Skin Cancers

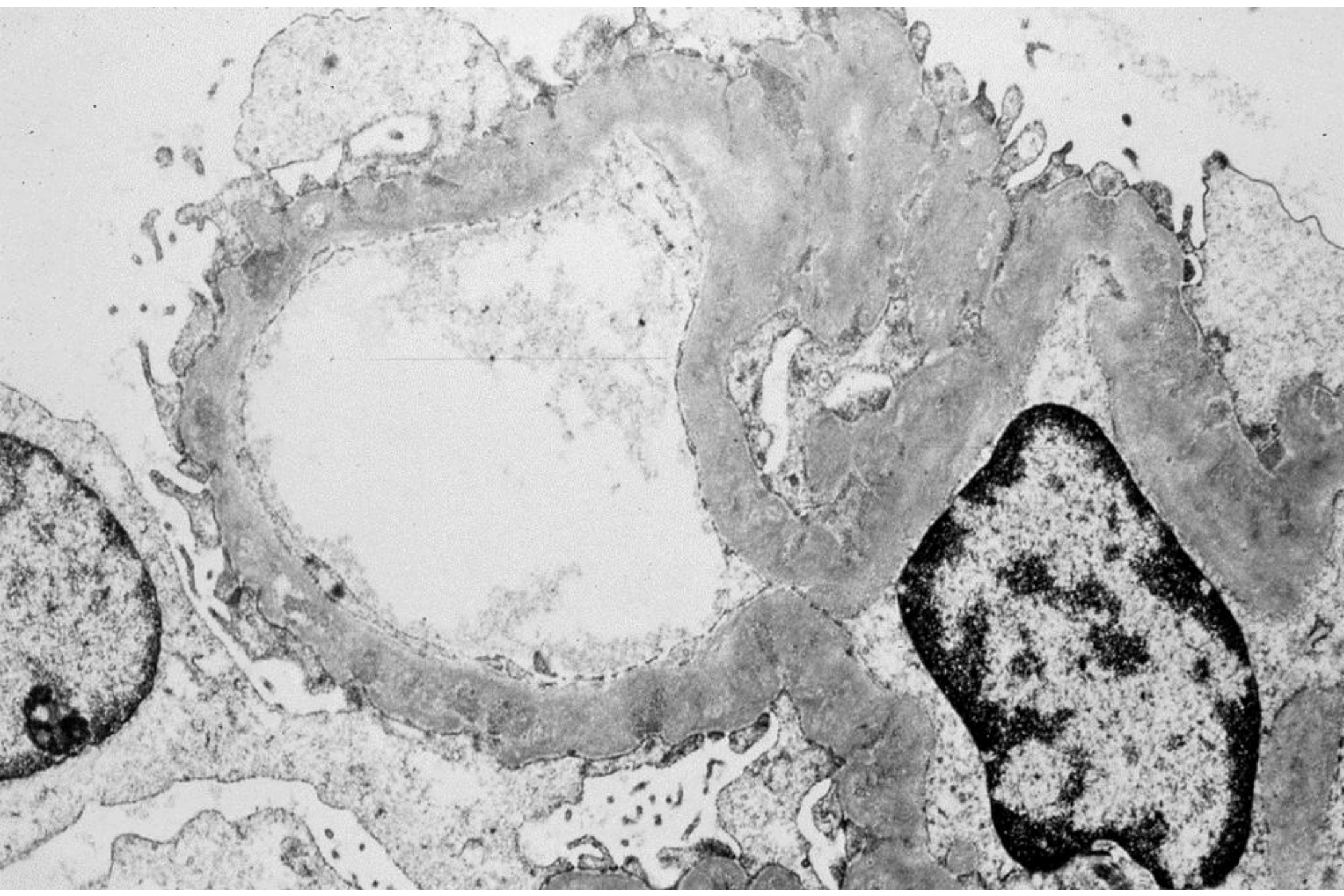
toxic to kidney

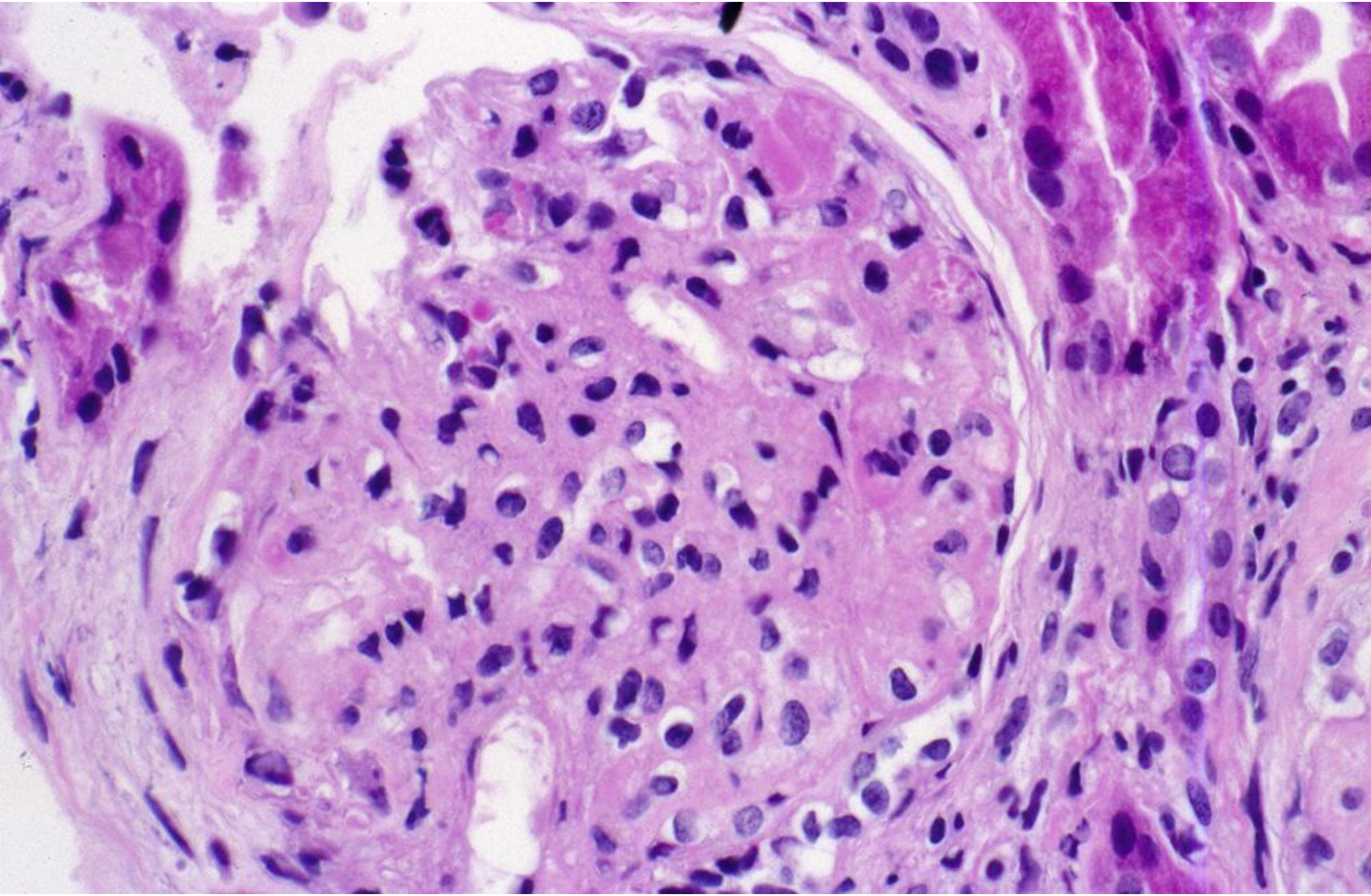

Transplant for sacroidosis
Granuloma in a new liver: the patient had sarcoidosis which caused liver failure. It reappeared after transplant

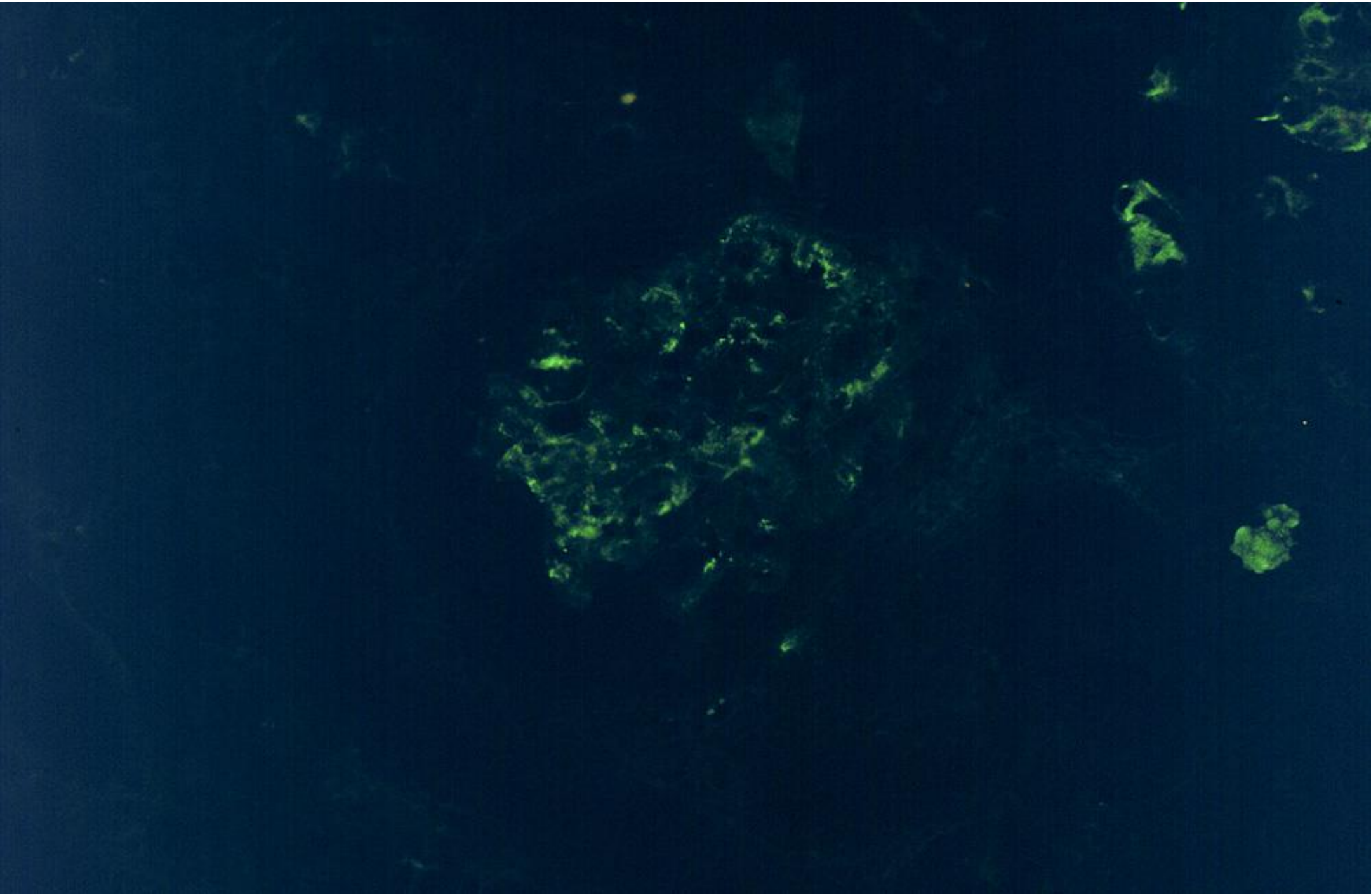

Membranous
glomerulonephritis

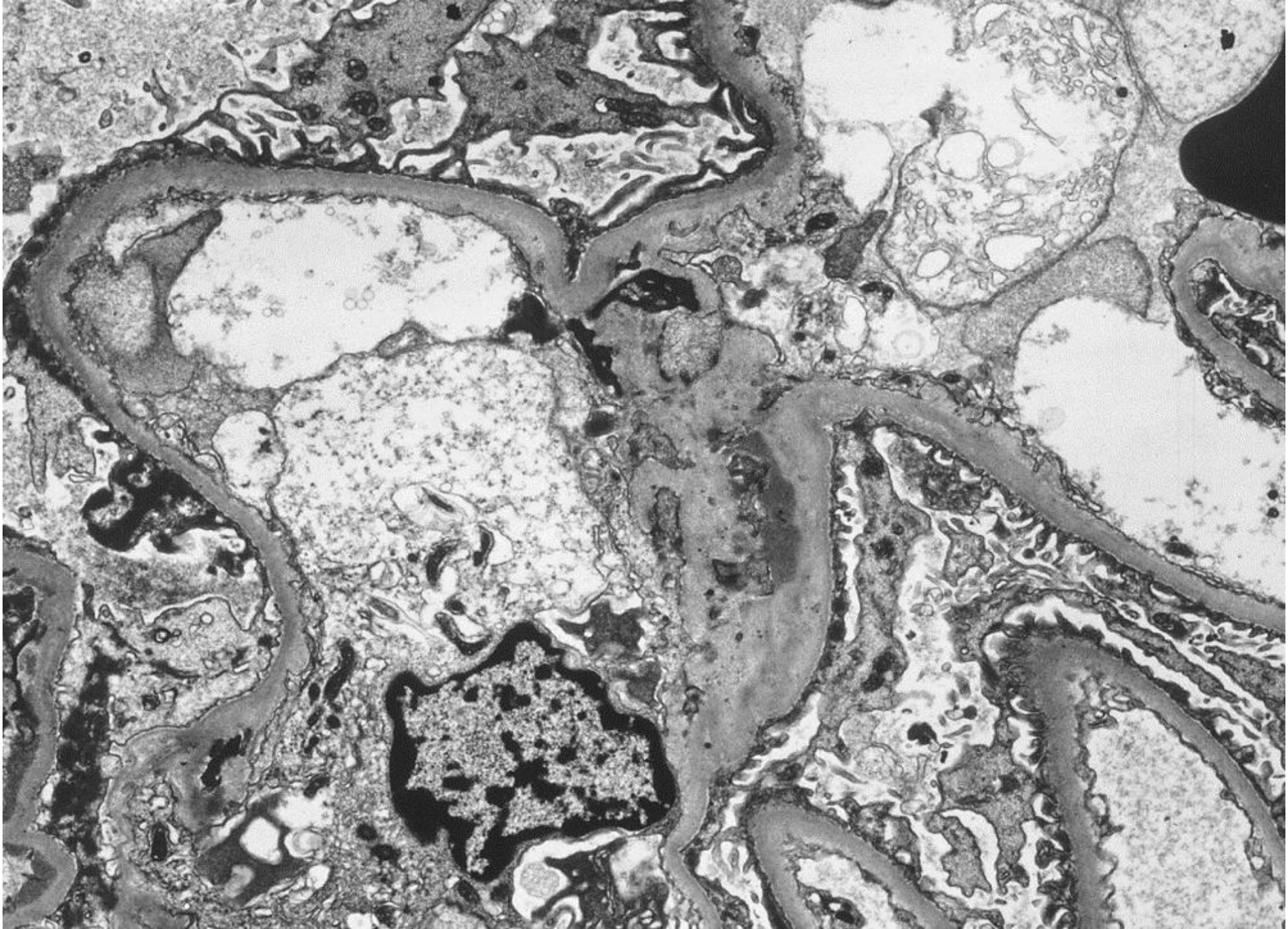


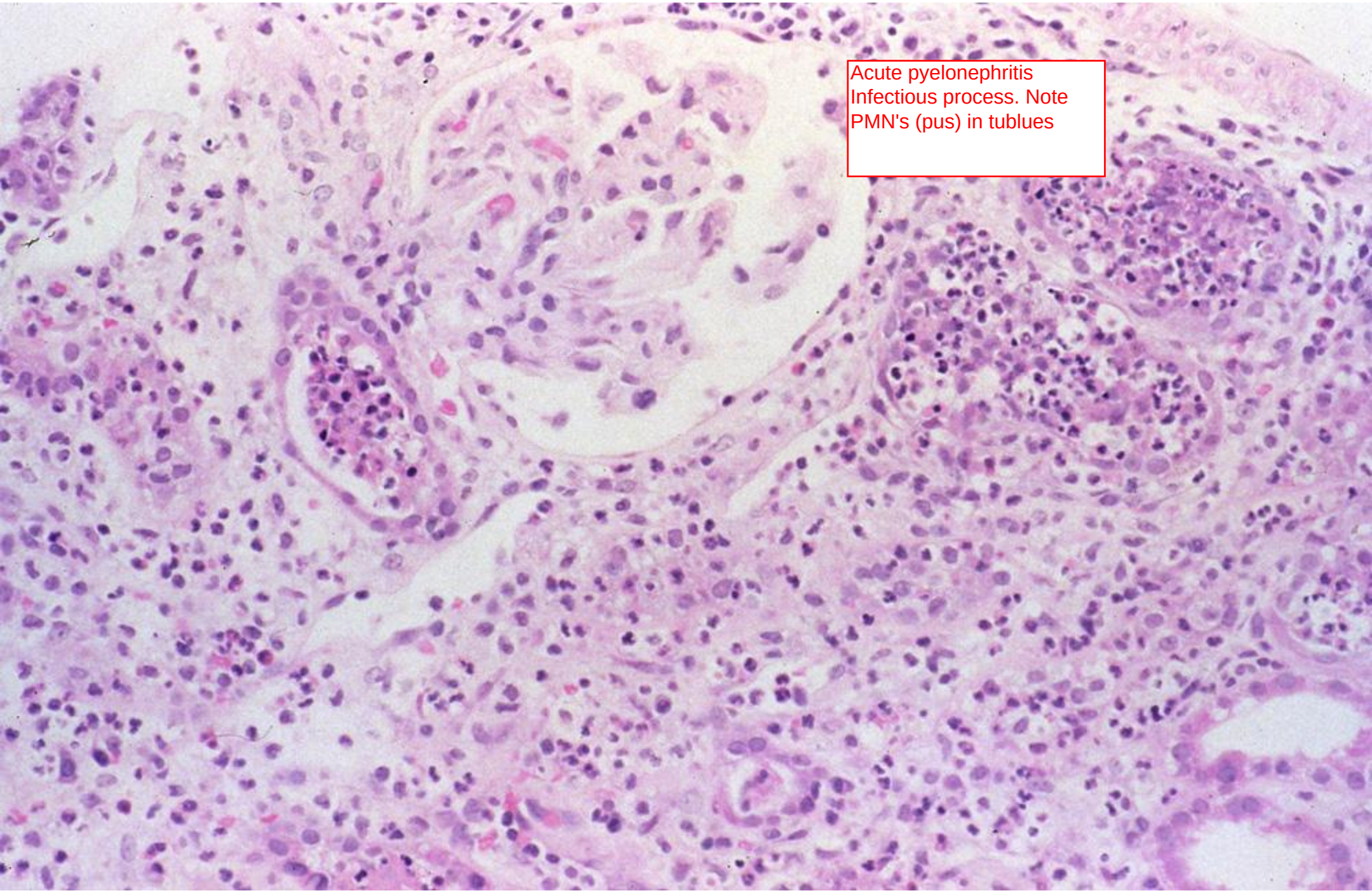

membranous
glomerulonephritis

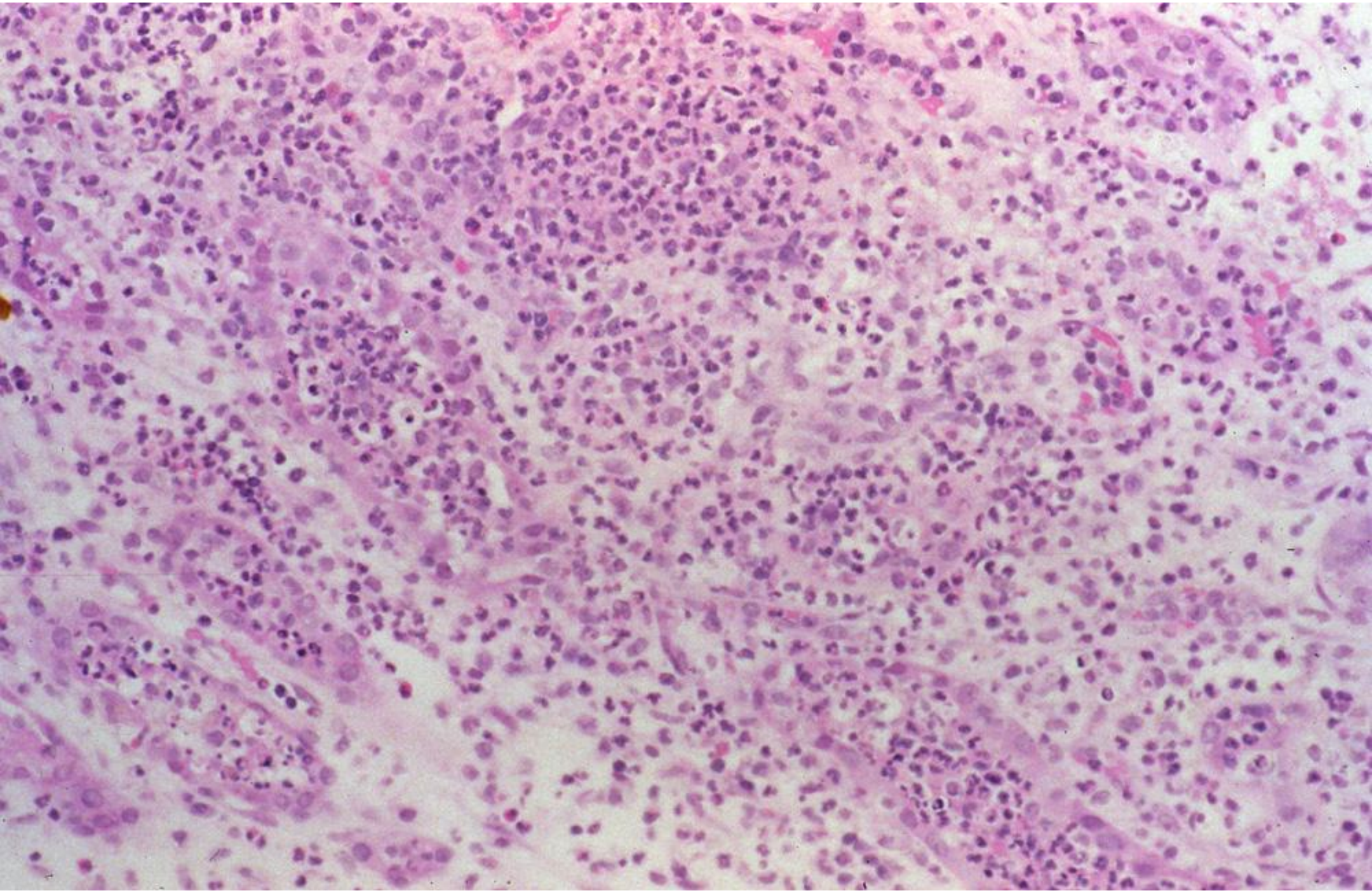


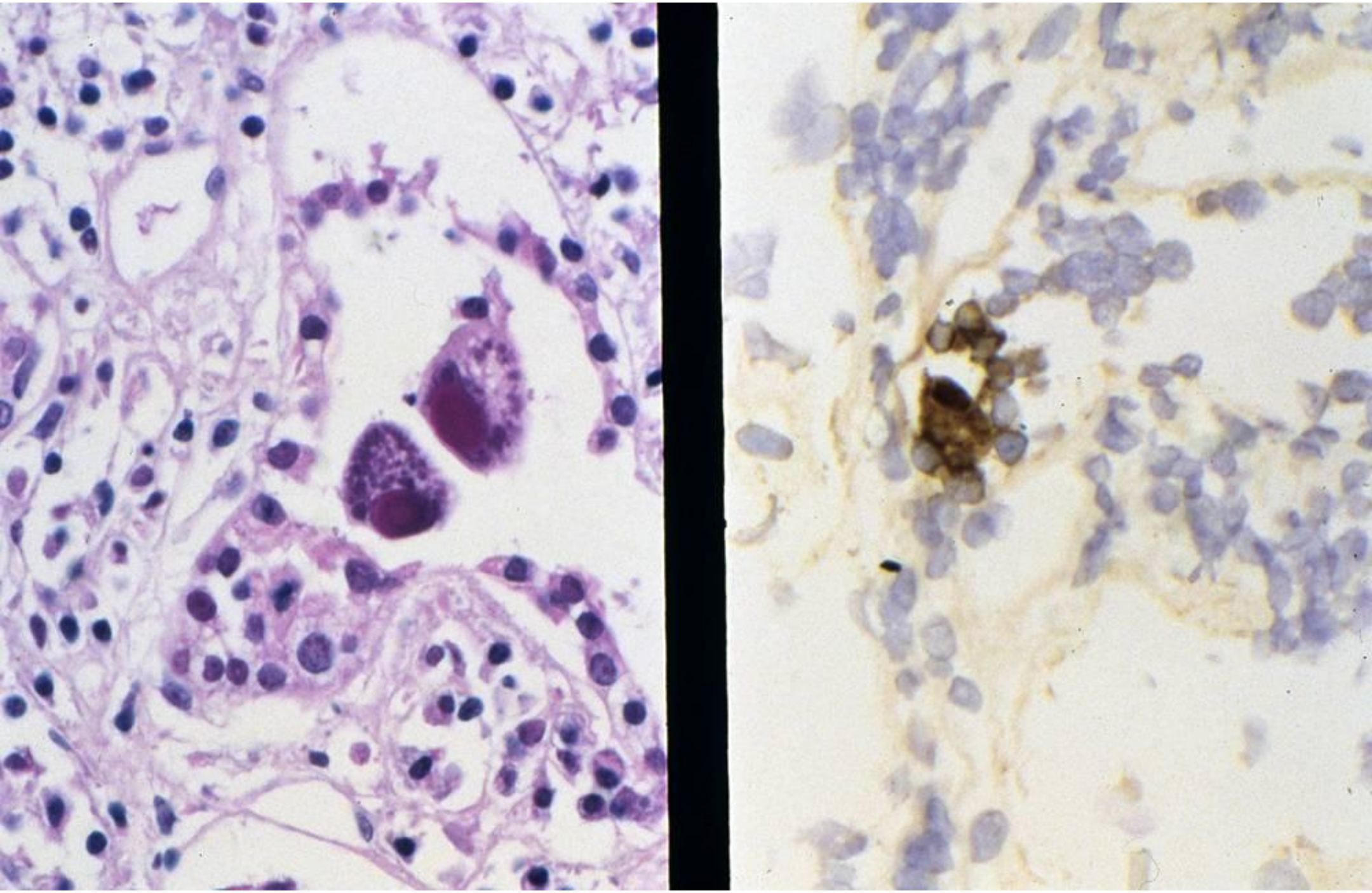


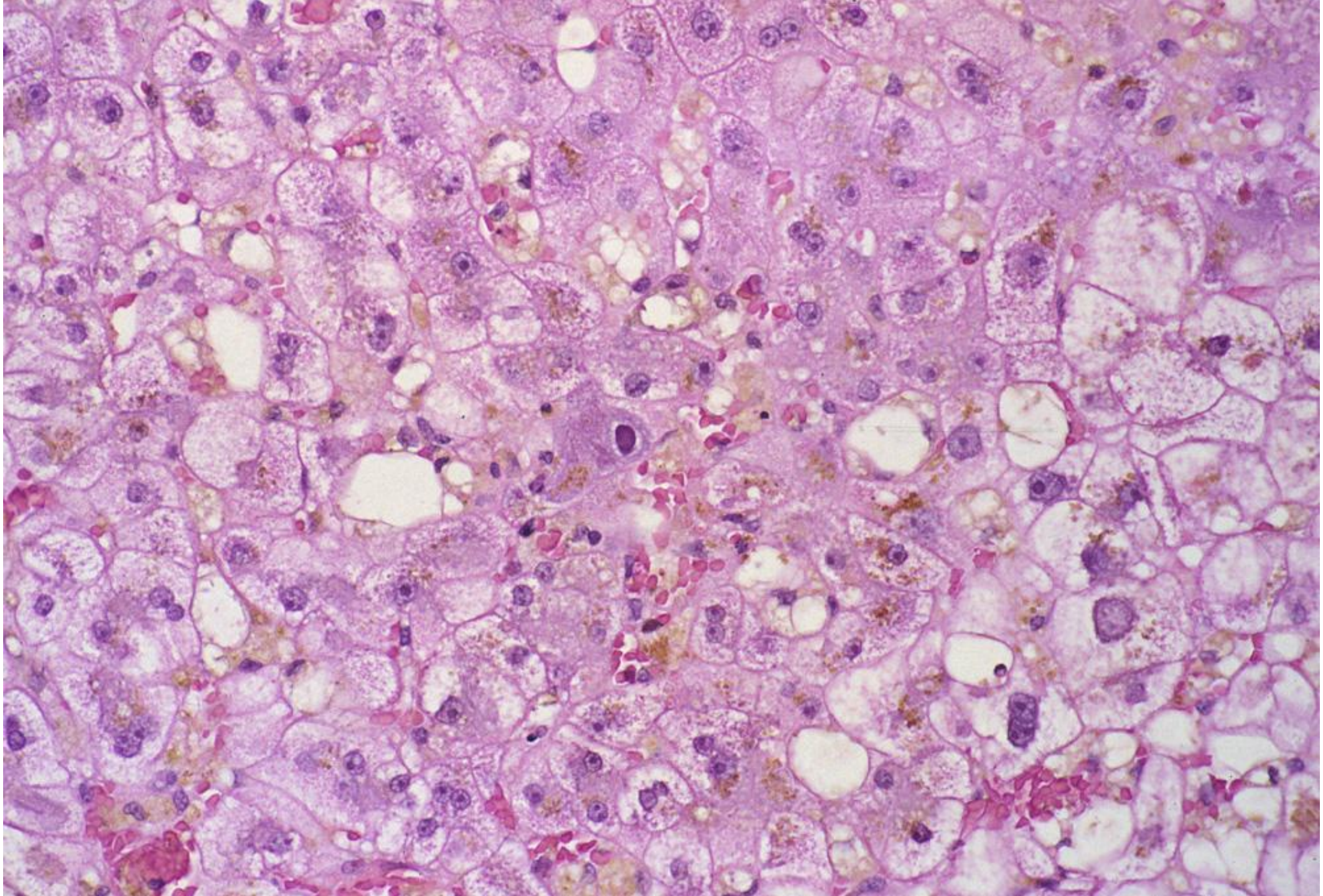


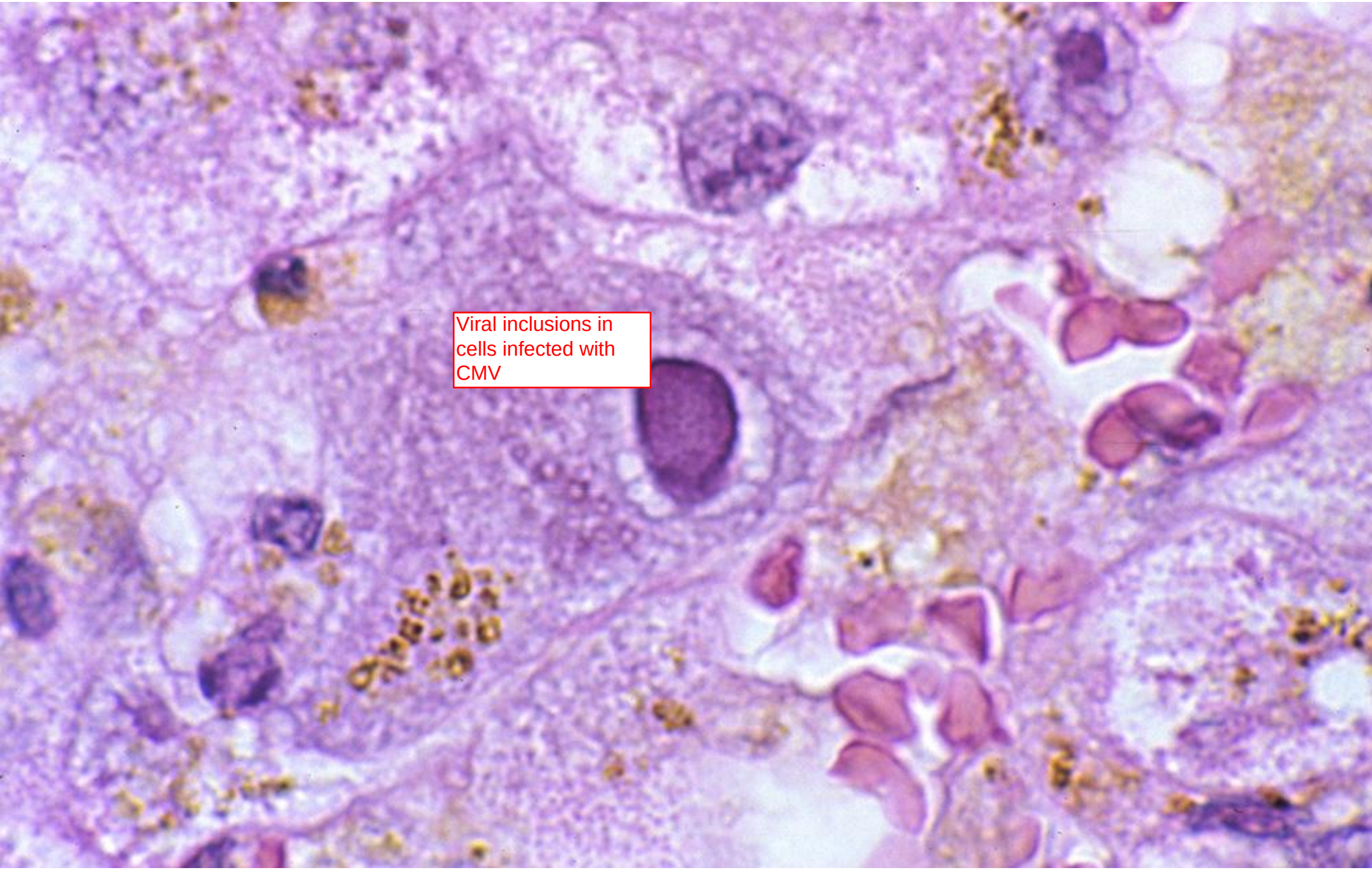


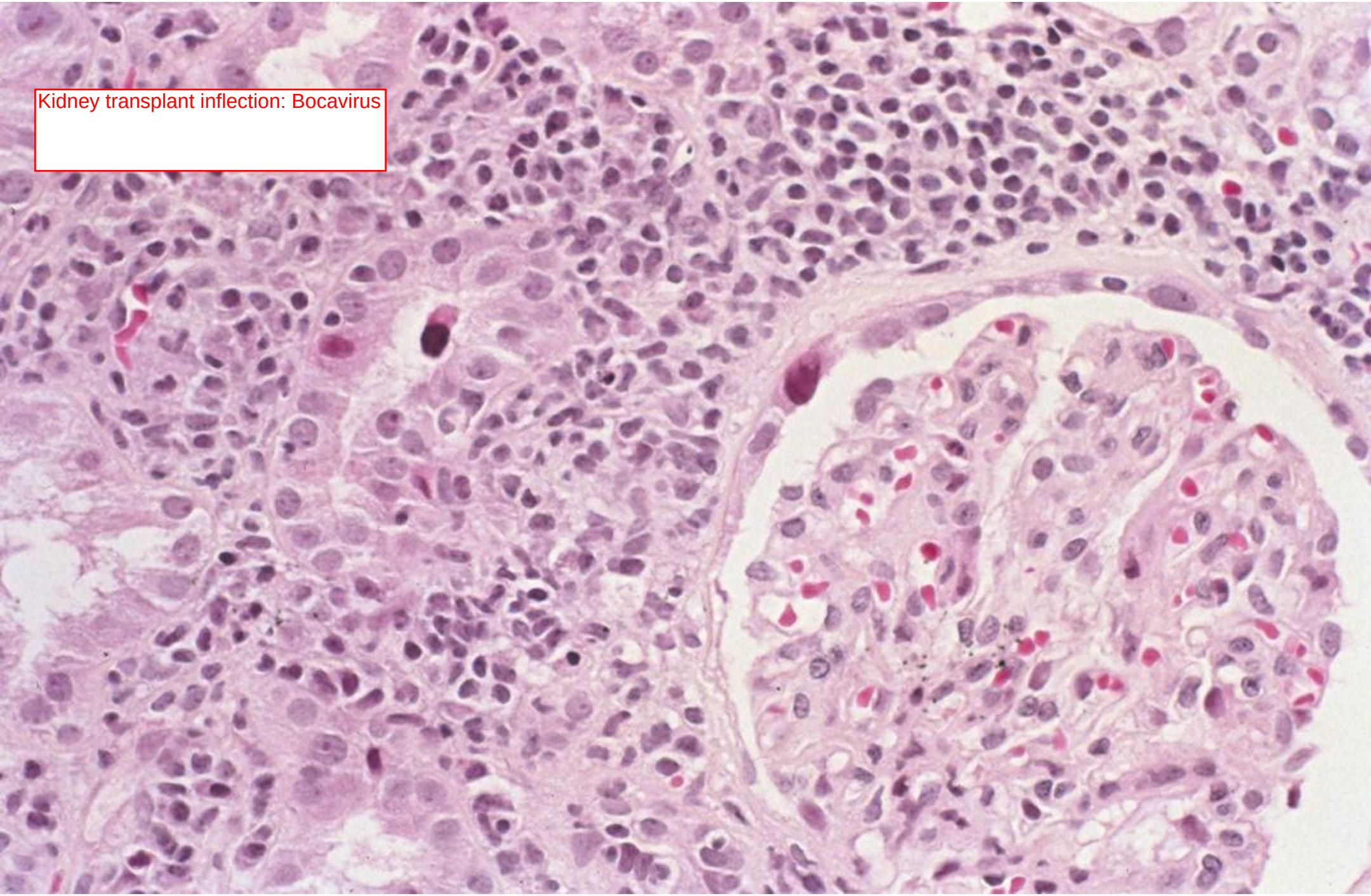

Acute pyelonephritis
Infectious process. Note
PMN's (pus) in tublues

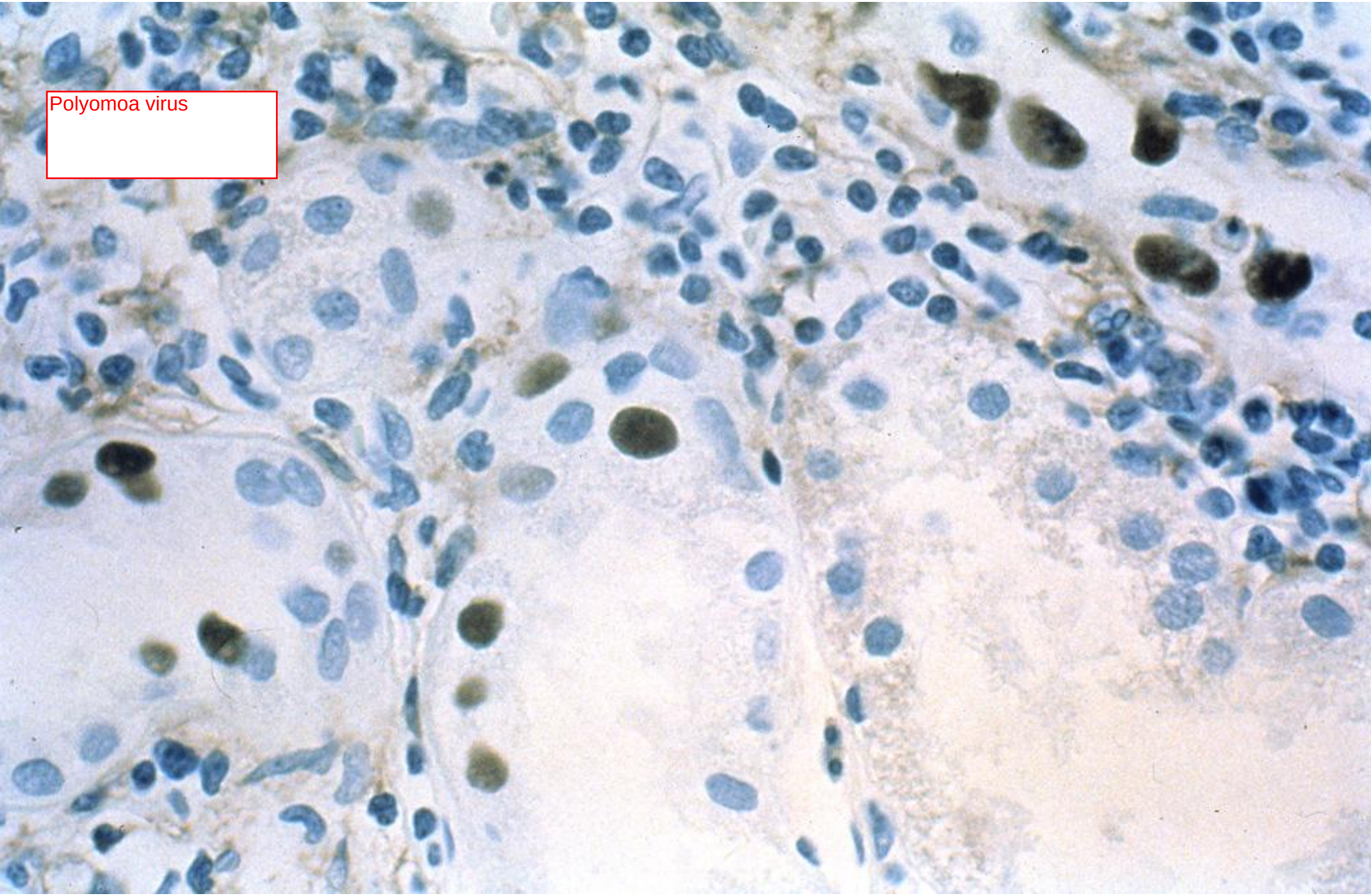


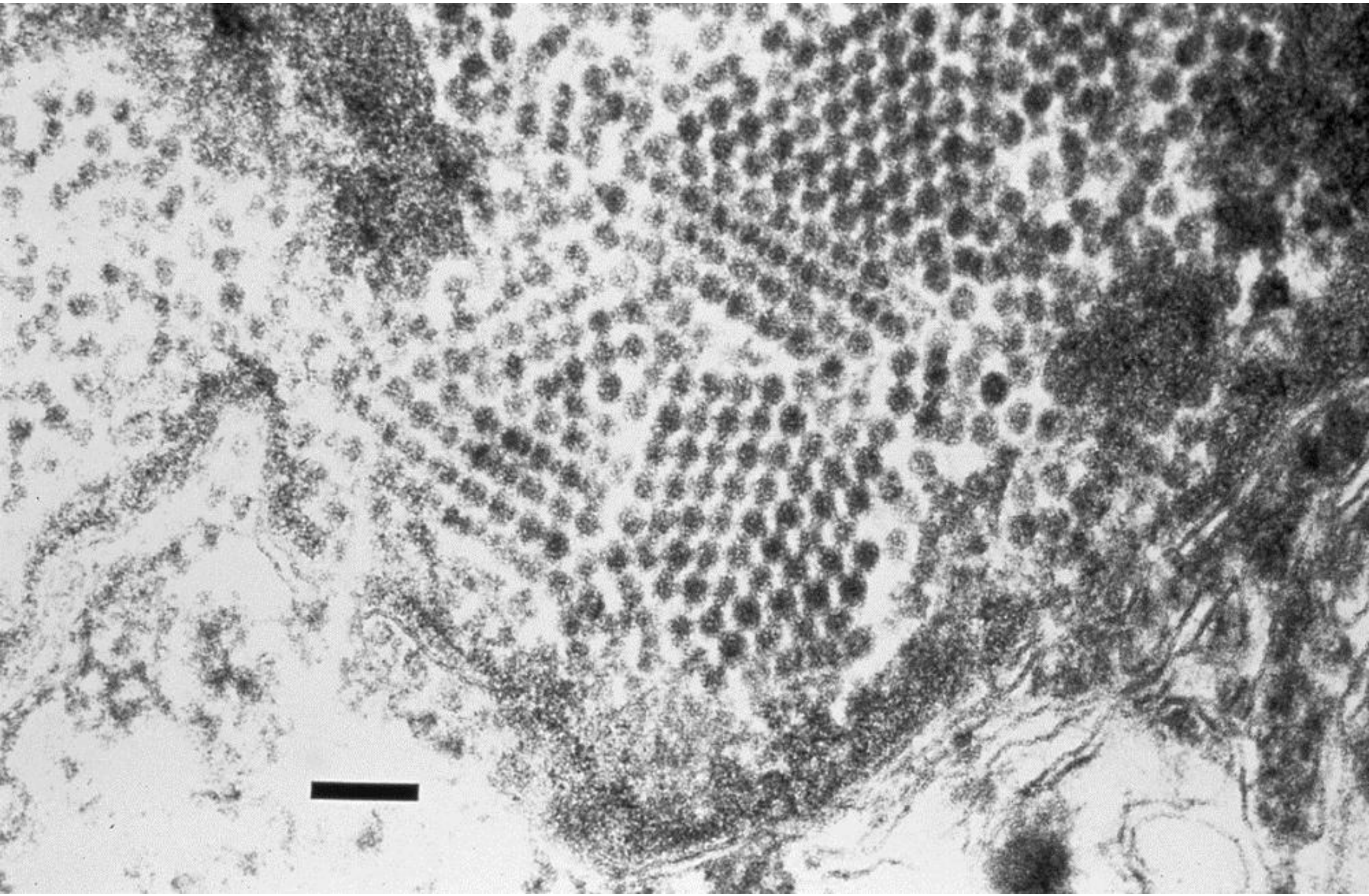


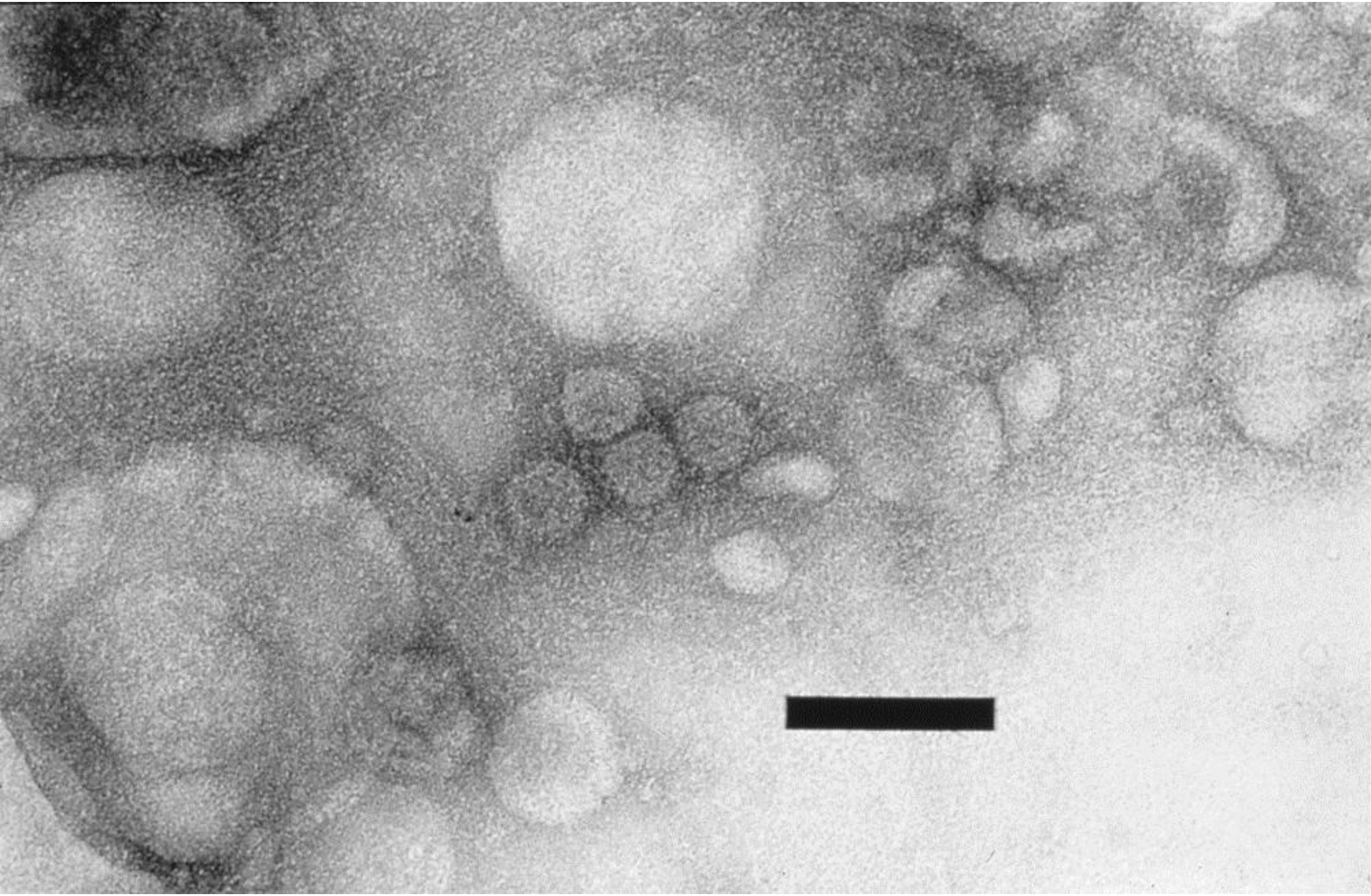


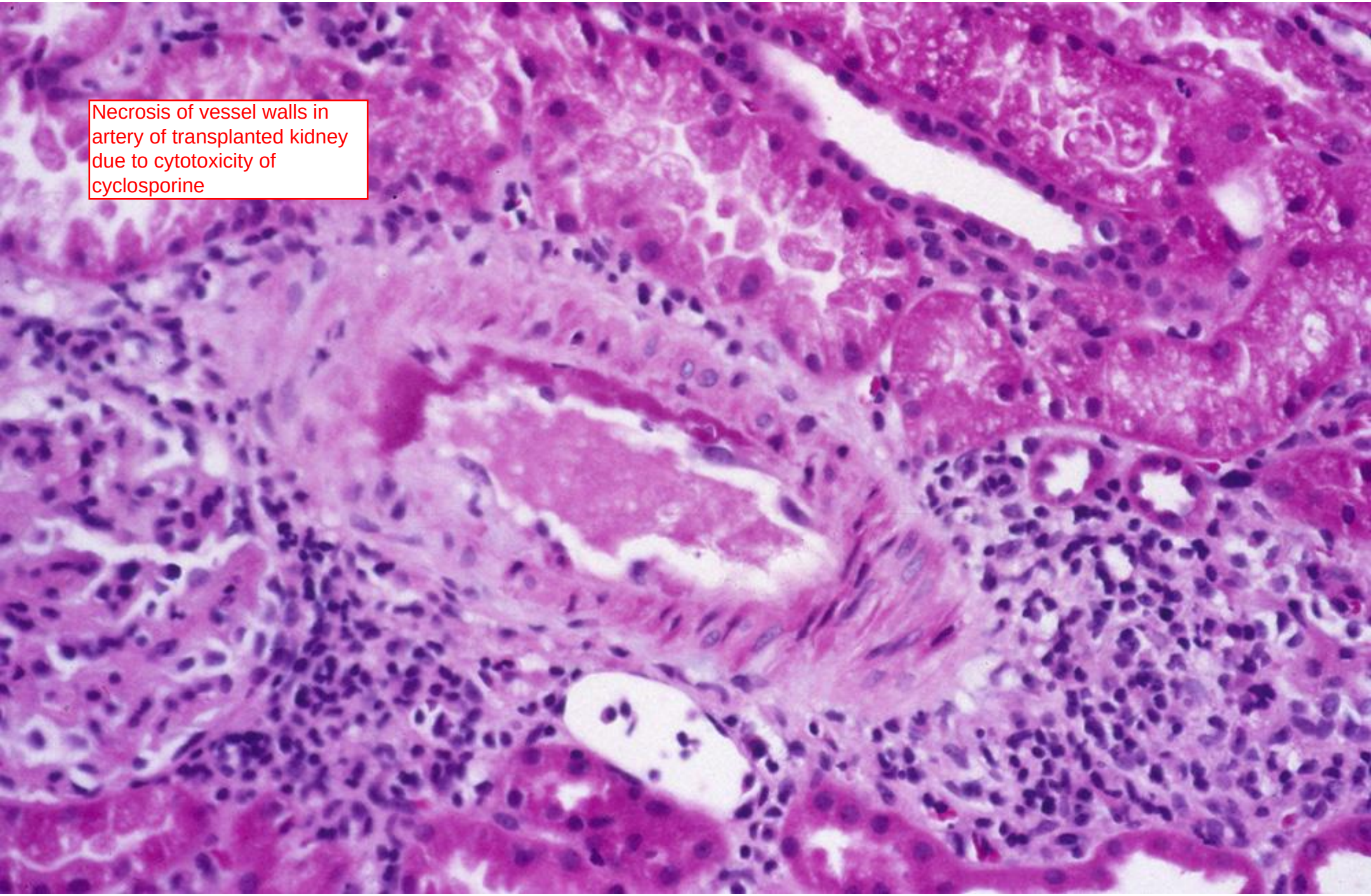

Viral inclusions in cells infected with CMV

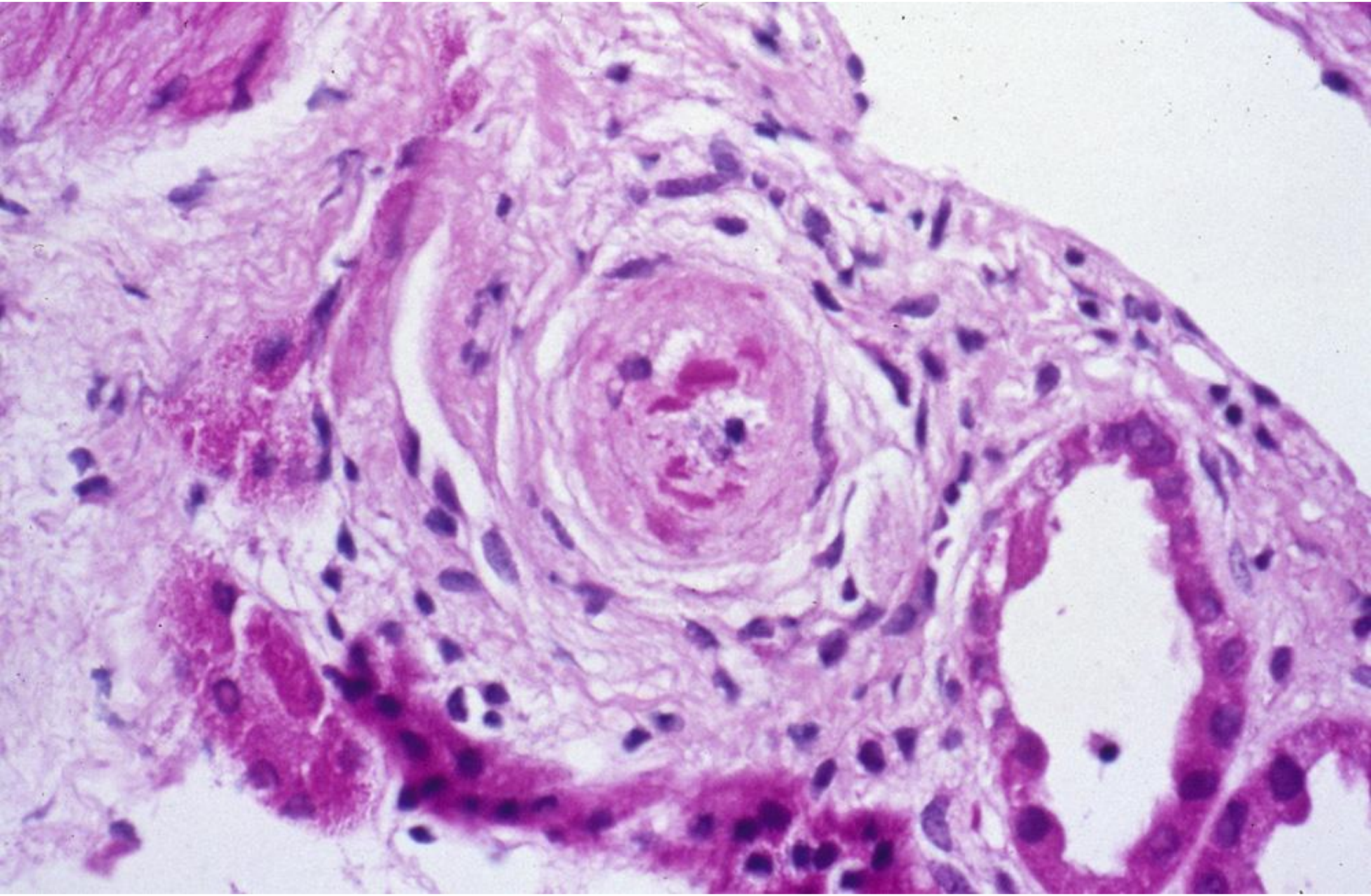

Kidney transplant inflection: Bocavirus

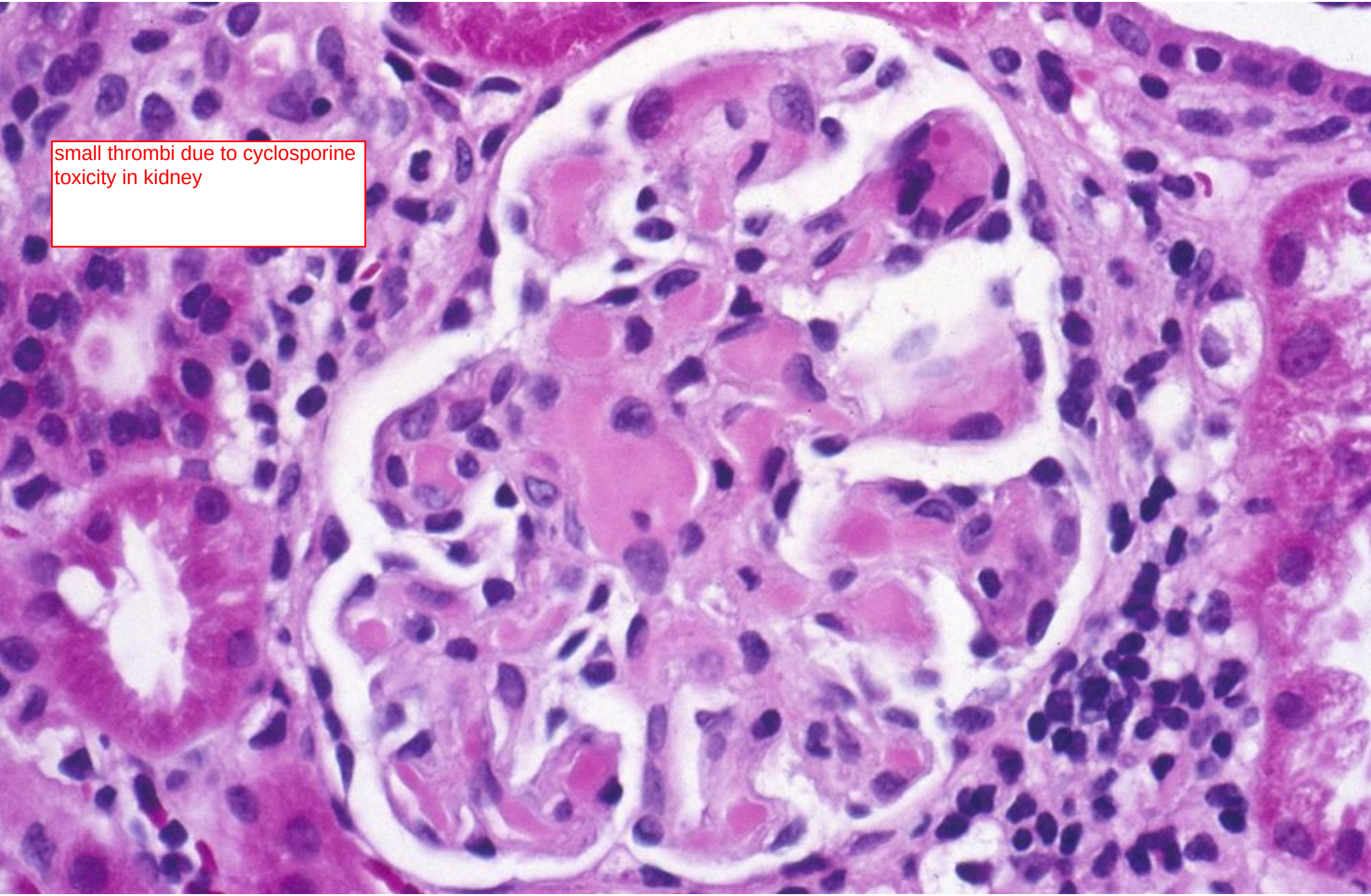

Polyomoa virus

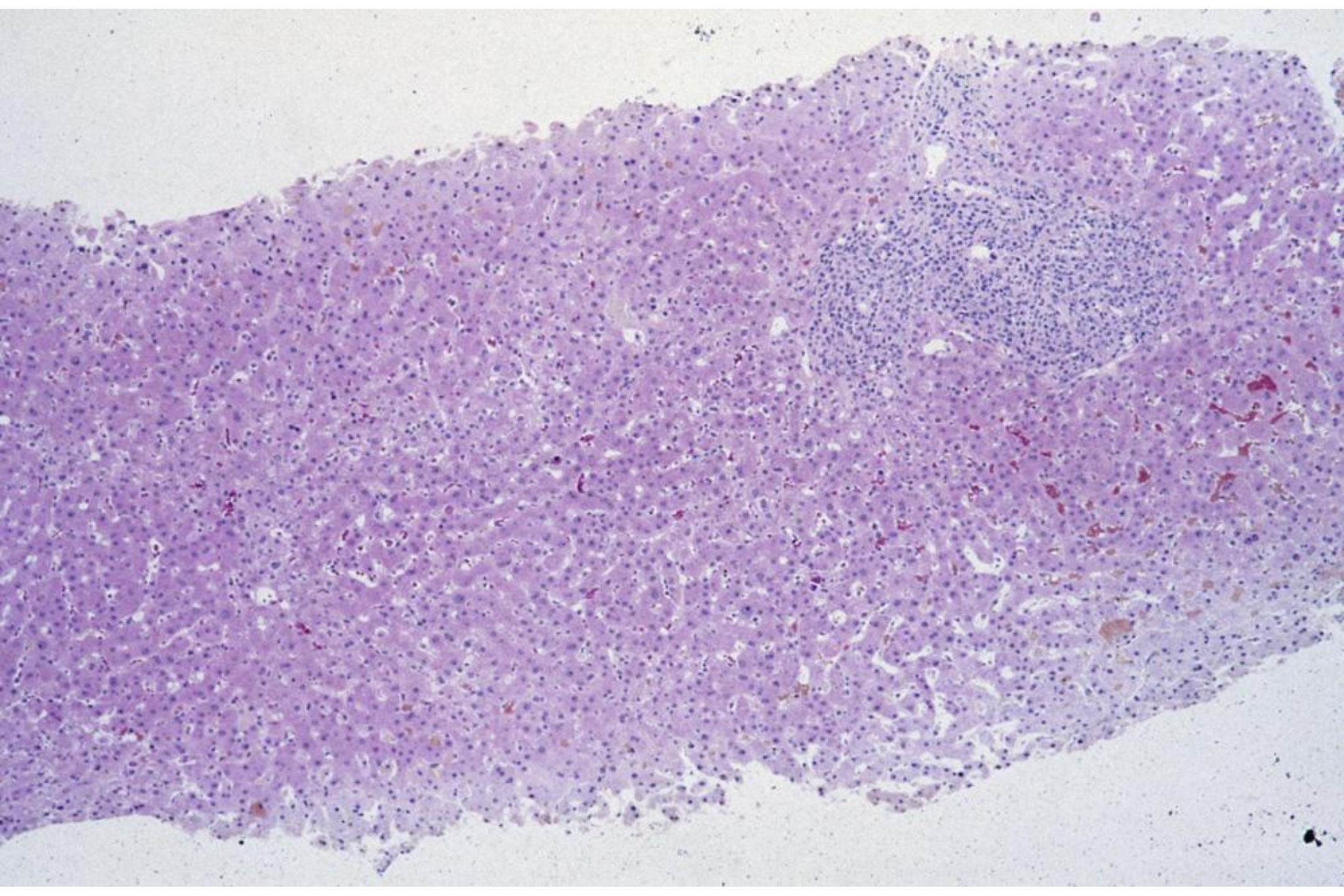


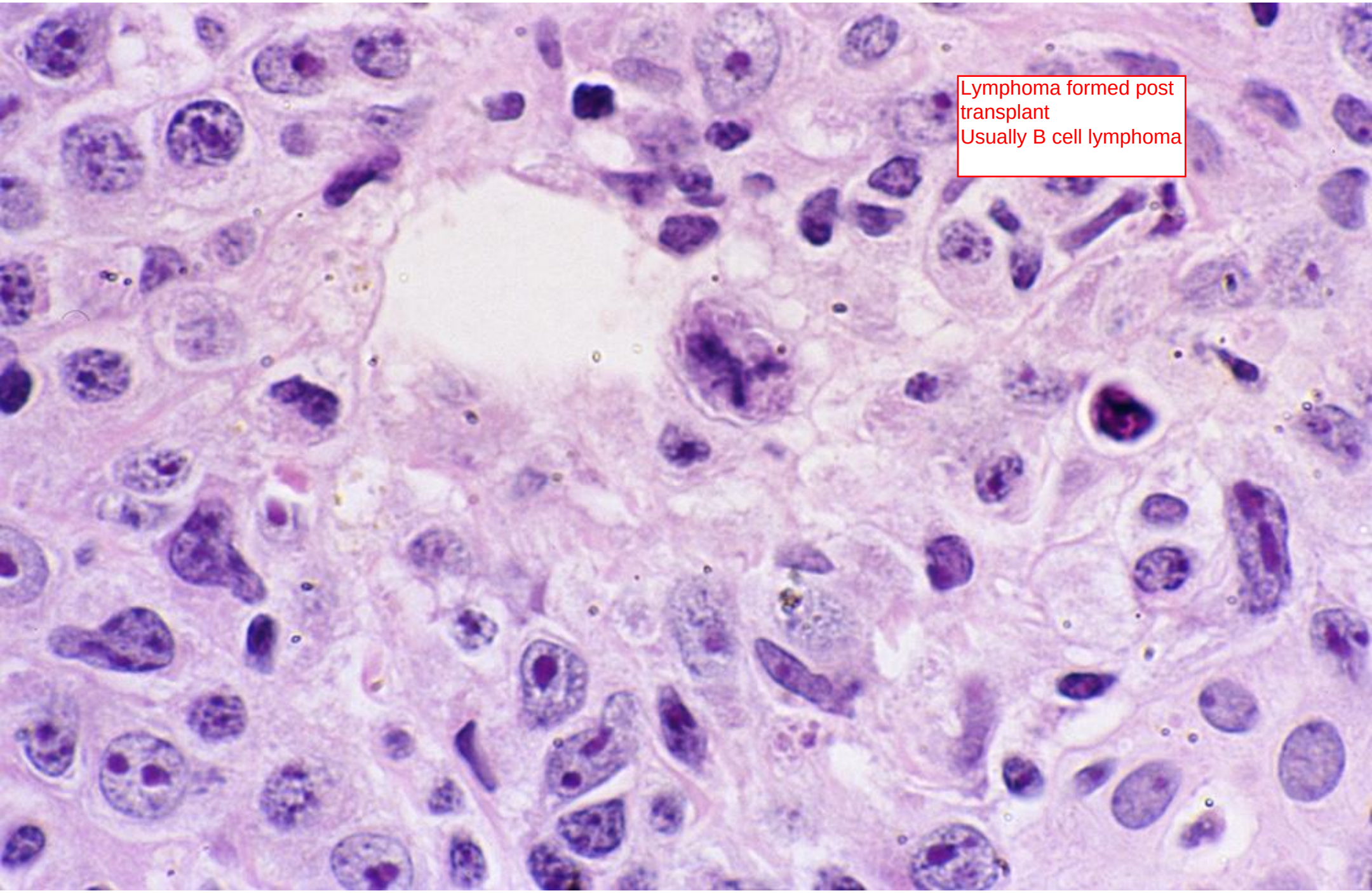


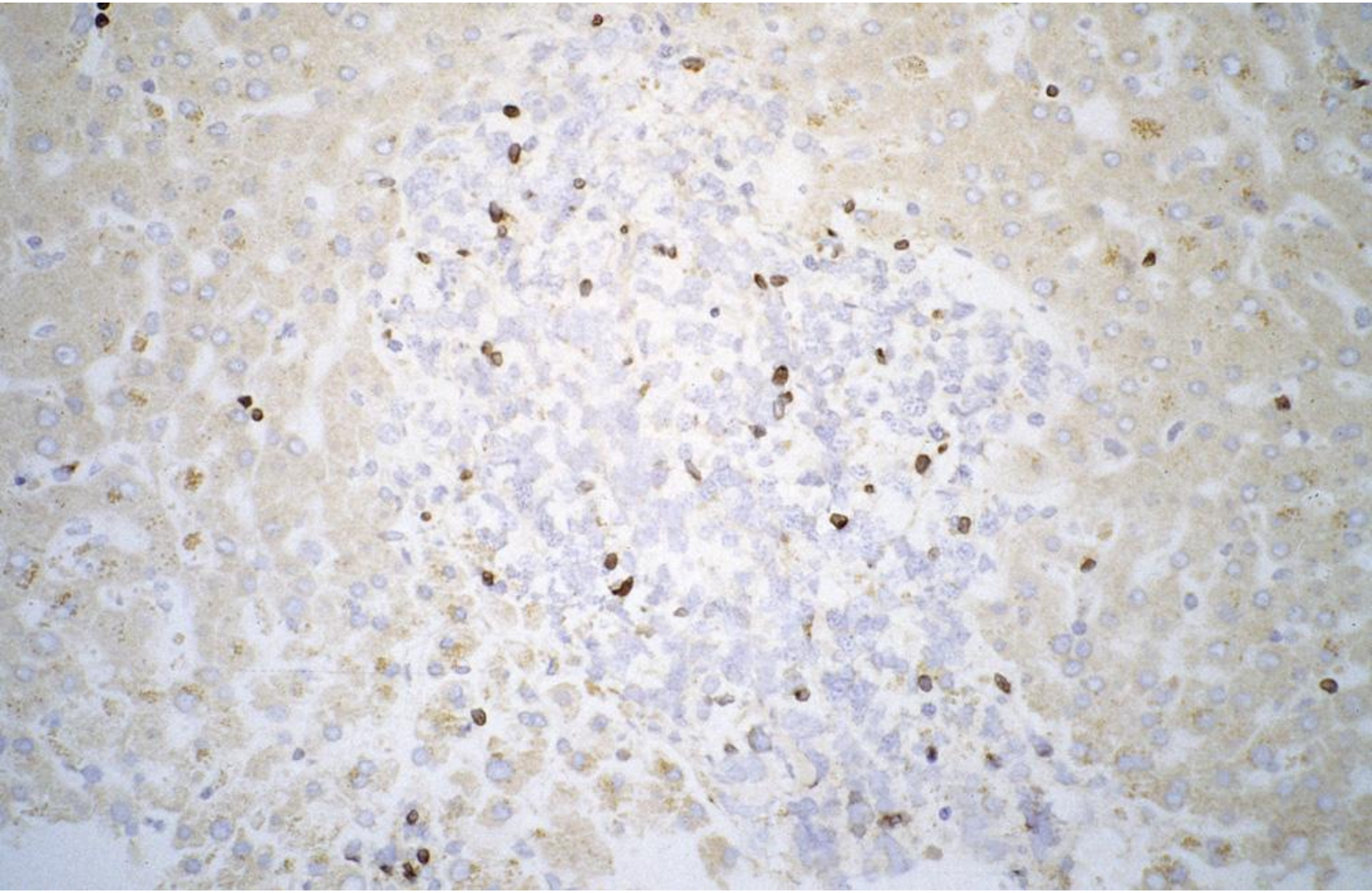

Necrosis of vessel walls in artery of transplanted kidney due to cytotoxicity of cyclosporine




small thrombi due to cyclosporine toxicity in kidney




Lymphoma formed post transplant
Usually B cell lymphoma



Bone marrow transplantation: indications

Heritable or acquired hematopoietic deficiencies

- Severe combined immunodeficiency (SCID) ← patients lack lymphocytes
- Aplastic anemia ← deficiency of red blood cells

Marrow reconstitution following cancer therapy

- Leukemias
- Solid Tumors (e.g., breast carcinoma)

Bone marrow transplantation: recipient preconditioning

Natural immunodeficiency (SCID)

Radiation Therapy

Chemotherapy

Complications of bone marrow transplantation

FOR GVHD the major symptoms are:
maculopapular rash
jaundice
hepatosplenomegaly
diarrhea

Failure to engraft

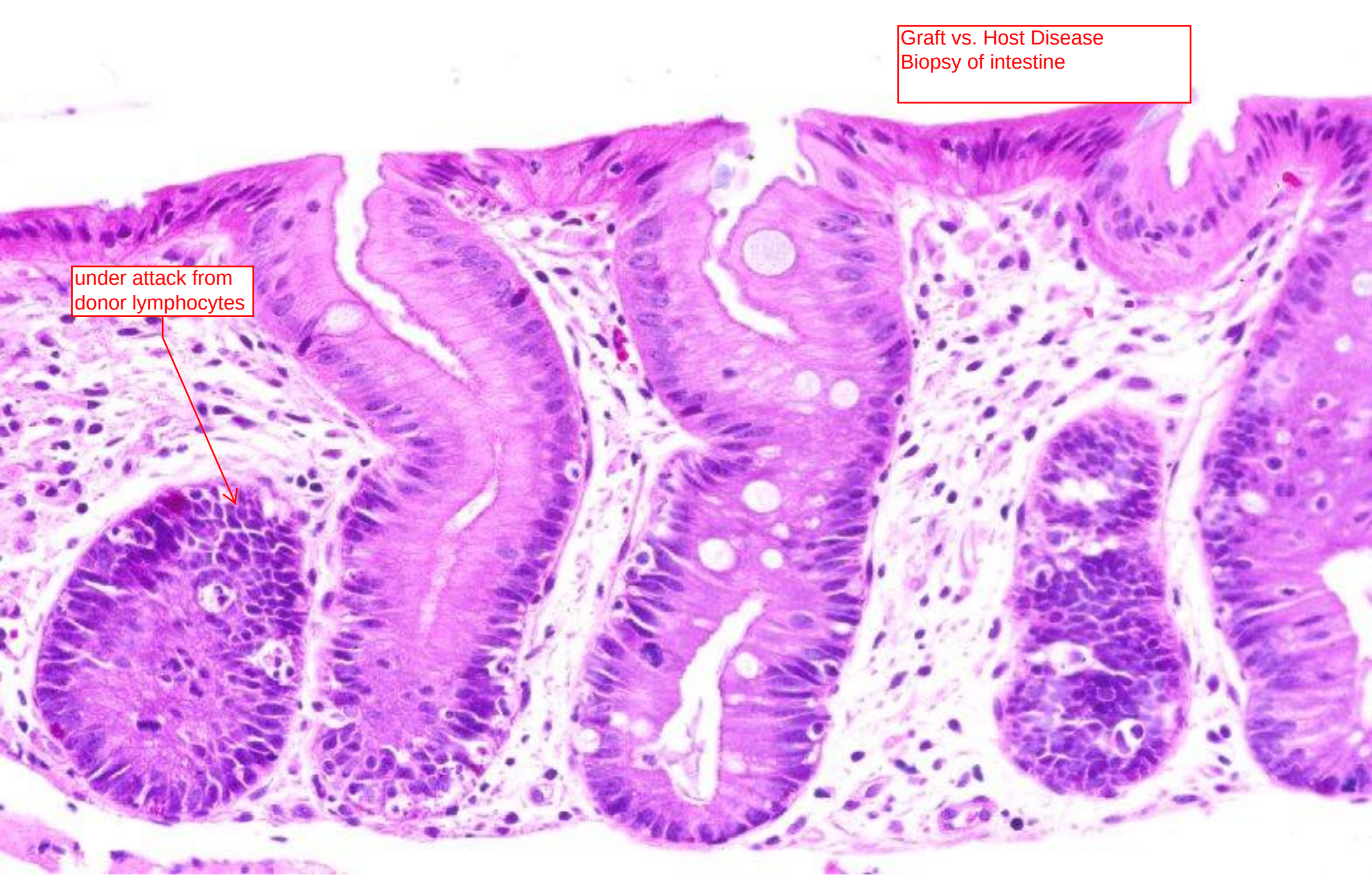
Graft-versus-host disease (GVHD)

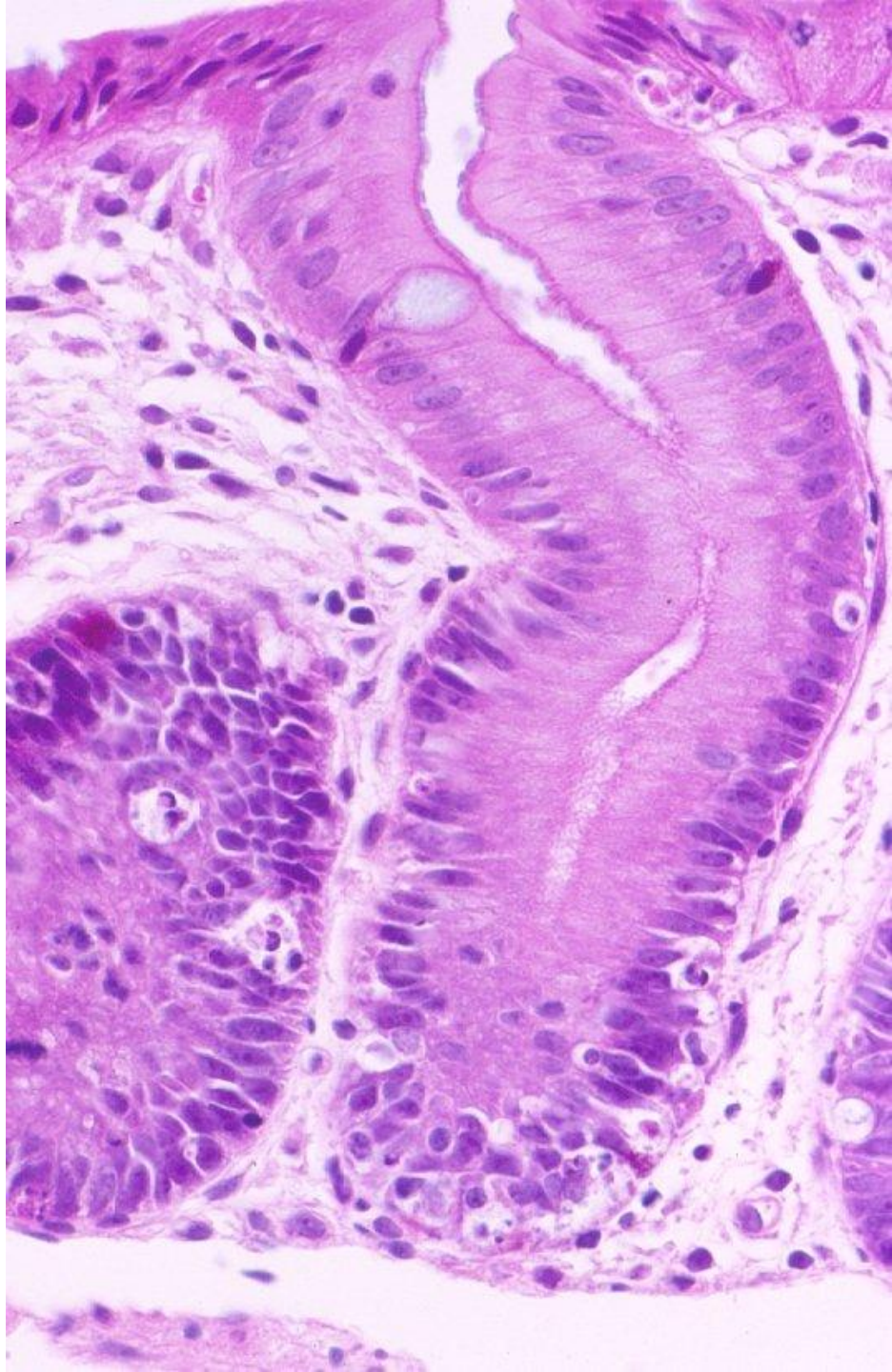
Infection

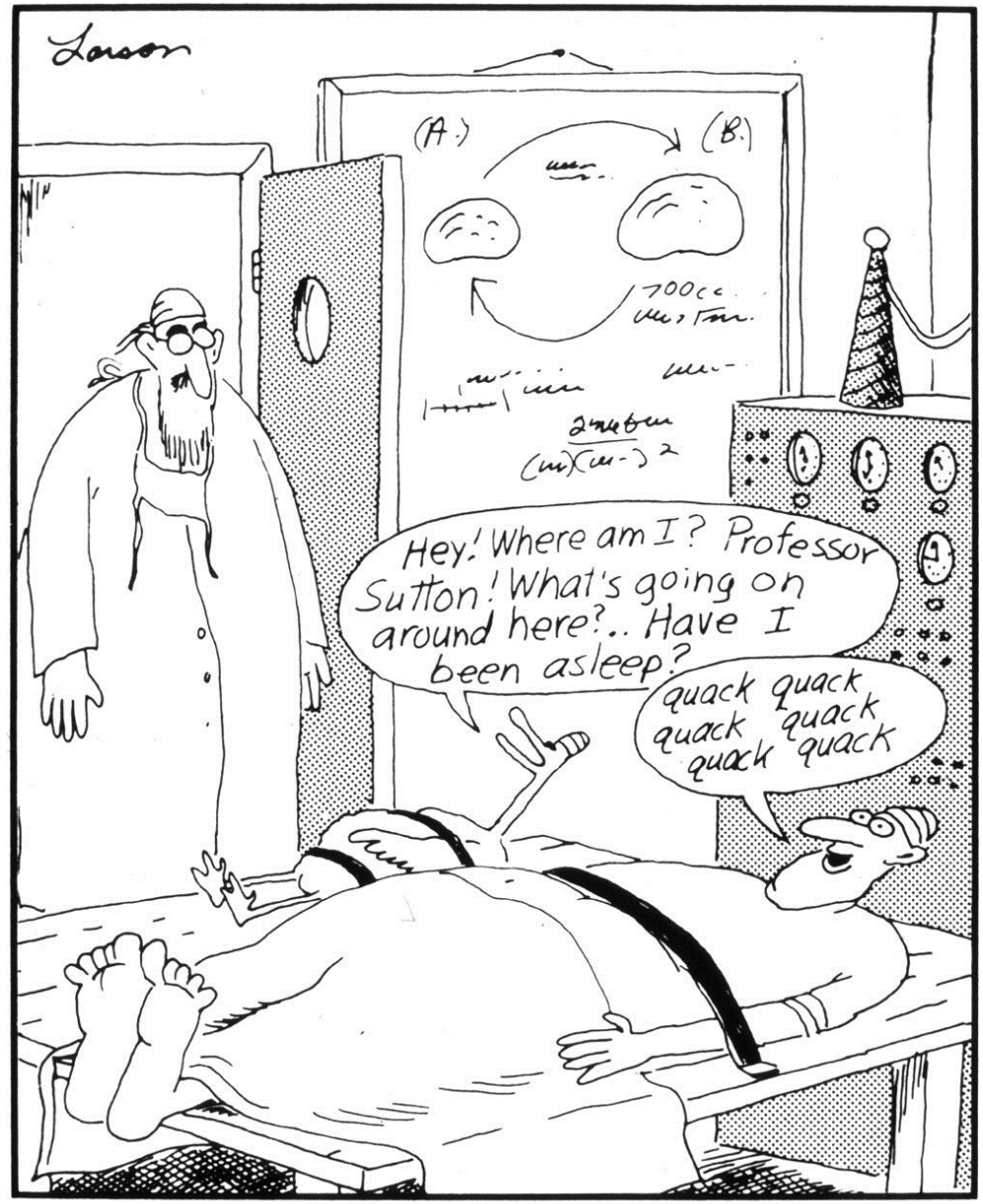
Recurrence of primary tumor

this is a role reversal; where the donor lymphocytes try to reject the recipient because you are transplanting components of the immune system

Acute GVHD results from involvement of the immune system and epithelia of the skin, liver and intestines


Graft vs. Host Disease
Biopsy of intestine
under attack from
donor lymphocytes





The operation was a success: Later, the duck, with his new human brain, went on to become the leader of a great flock. Irwin, however, was ostracized by his friends and family and eventually just wandered south.